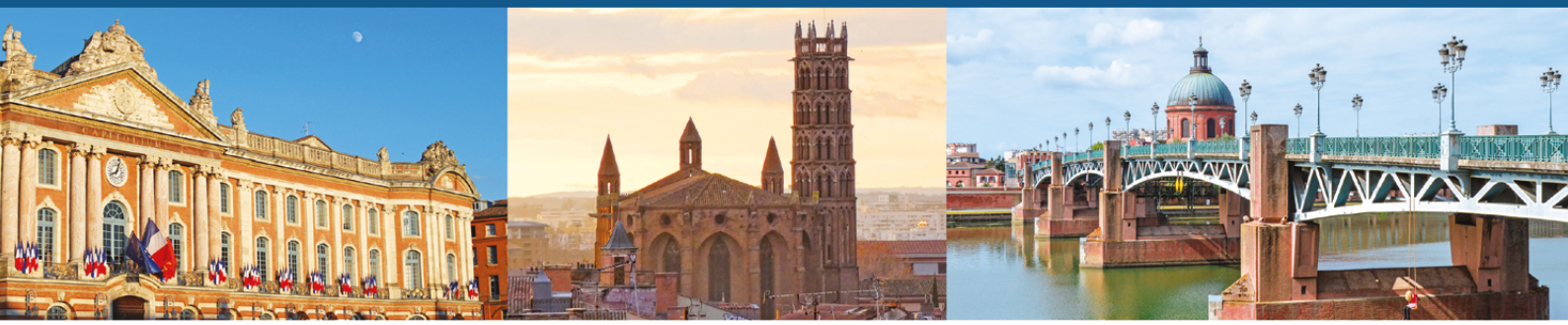
57TH ANNUAL MEETING of the French Society for Immunology



JOINT CONFERENCE of the FRENCH & PORTUGUESE SOCIETIES FOR IMMUNOLOGY

Centre de Congrès Pierre Baudis

TOULOUSE FRANCE

4>6 NOVEMBER 2026

La Région Occitanie Pyrénées · Méditerranée

BOOK OF ABSTRACTS

Société Française d'Immunologie

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WELCOME TO SFI-SPI 2026

The city of Toulouse and the Occitania Region are pleased to host, for the first time, the Joint Annual Meeting of the French Society for Immunology and the Portuguese Society for Immunology. This event will take place on **November 4-6, 2026**, at the **Centre de Congrès Pierre Baudis**, located in downtown **Toulouse, France**.

This year's meeting will notably feature:

Two distinguished keynote speakers:

- **Professor Shimon SAKAGUCHI**, recipient of the 2025 Nobel Prize in Physiology or Medicine (shared with Mary Brunkow and Fred Ramsdell), Professor at Osaka University, Japan;
- **Dr. Pamela SCHWARTZBERG**, Senior Investigator at the National Institute of Allergy and Infectious Diseases (NIAID), NIH, USA;

A plenary session dedicated to Young Immunologists and a parallel session focused on career development, highlighting our commitment to early-career researchers.

The meeting will present recent advancements in fundamental, applied, and medical immunology through plenary and parallel sessions, as well as workshops organized by some of the scientific clubs of the French Society for Immunology and the Fédération d'Immunologie Médicale.

Additionally, several prizes will be awarded for the best oral and poster presentations at the end of the meeting.

The conference welcomes a diverse community from across the immunology field, including students, researchers, engineers, technicians, academic faculty, clinicians, and industry professionals in healthcare or biotechnology.

This conference aims to serve as a dynamic platform for scientific exchanges, promoting fundamental immunology, clinical research and therapeutic development, and facilitating many new collaborations.

The SFI-SPI Organizing and Scientific Committees look forward to welcoming you in Toulouse for what promises to be an exciting scientific event!

On behalf of the Organizing and Scientific Committees - SFI-SPI Toulouse 2026



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- **Nicolas FAZILLEAU**
- **Fatima L'FAQIHI**
- **Julie TABIASCO**

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- **Tiphaine VOISIN**

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ACKNOWLEDGMENT

The Organizers would like to thank **public & private partners and sponsors** for their support of the SFI-SPI 2026.

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The Organizers would like to thank **exhibitors and sponsors** for their suppor of the SFI-SPI 2026.

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PLANNING AT A GLANCE

WEDNESDAY 4 NOVEMBER

08:00 Meeting registration
09:15 Welcome introduction
09:30 Keynote Lecture - *Shimon Sakaguchi*
10:15 PLENARY SESSION 1 Neuroimmunology
11:45 Industry Symposium - BD Biosciences
12:00 Industry Talks - Cytek Biosciences; Meso Scale Discovery - Pixelgen Technologies; StemCell Technologies - Alamar Biosciences
12:36 Lunch - Coffee Visit of exhibition & Posters
14:15 Parallel Sessions
- PS1 Macrophages and dendritic cells
- PS2 Inborn errors in immunity
- PS3 Vaccinology
- CPS4 Immunometabolism and its implications for practical medicine

15:45 Parallel Sessions
- PS5 ILC / NK
- PS6 Immunometabolism
- PS7 T and B cell development and signaling

17:15 Coffee break - Visit of exhibition & Posters
18:00 Parallel Sessions
- PS8 Ageing
- PS9 Young SPI / SFI
- PS10 Autoimmunity and inflammatory diseases

19:30 POSTER SESSION 1 - odd-numbered
Wine & Cheese

THURSDAY 5 NOVEMBER

08:30 Parallel Sessions
- PS11 Innate T cells
- PS12 Women's health/sex bias in immunity
- PS13 T and B cell memory
- CPS14 CAR-T cells in autoimmune diseases

10:00 Coffee break - Visit of exhibition & Posters
10:45 PLENARY SESSION 2 Host-pathogen interactions
12:15 Industry Symposium Sony
12:30 Industry Talks CeGaT- Agilent Technologies
12:42 Lunch - Coffee Visit of exhibition
13:30 POSTER SESSION 2 even-numbered
14:15 Parallel Sessions
- PS15 Neutrophils
- PS16 Gene and cell therapy
- PS17 Germinal Center
- CPS18 Xenotransplantation

15:45 Coffee break - Visit of exhibition & Posters
16:30 Parallel Sessions
- PS19 Mast cells / Basophils
- PS20 Mucosal immunology
- PS21 Tissue homeostasis and dynamics
- CPS22 CEnI General Assembly

18:00 PLENARY SESSION 3 Young investigators
19:30
20:00 Congress Dinner - *Les Espaces Vanel*

FRIDAY 6 NOVEMBER

08:30 PLENARY SESSION 4 Tumor immunity
10:00 Coffee break - Visit of exhibition & Posters
10:45 Parallel Sessions
- PS23 Immunotherapy
- PS24 Glycoimmunology
- PS25 Tolerance and Transplantation

12:15 SFI General Assembly
13:15 Lunch - Coffee Visit of exhibition & Posters
14:15 Parallel Sessions
- PS26 Environmental cues and microbiota
- PS27 System and spatial immunology
- PS28 Antibody

15:45 Closing Keynote Lecture
16:30 Prize awards & Conclusion
17:00

- Clinical session
- *Foyer & Concorde 1&2 - Level -1*
- *Ariane 1 - Level 1 (140)*
- *Cassiopée - Level 1 (300)*
- *Auditorium Saint-Exupéry - Level 2 (500)*
- *Guillaumet 1+2 - Level 2 (200)*



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WEDNESDAY 4 NOVEMBER

08:00-09:15 **Meeting registration** *Foyer & Concorde 1&2 - Level -1*

PLENARY SESSIONS

09:15-09:30 **Welcome Introduction** *Audit. Saint-Exupéry - Level 2*

- **Emmanuelle JOUANGUY** - *SFI President*
- **Bruno SILVA-SANTOS** - *SPI President*

09:30-10:15 **Keynote Lecture** *Audit. Saint-Exupéry - Level 2*

Chairs: Roland LIBLAU (Toulouse, France) & **Luis GRACA** (Lisbon, Portugal)

- **Shimon SAKAGUCHI** *(WPI Immunology Frontier Research Center, The University of Osaka, Osaka, Japan)*
  Regulatory T cells and immune tolerance: therapeutic re-establishment of immune self-tolerance in autoimmune disease by targeting Treg cells

10:15-11:45 **SESSION 1 - NeuroImmunology** *Audit. Saint-Exupéry - Level 2*

Chairs: Julie RIBOT (Lisbon, Portugal) & **Anne ASTIER** (Toulouse, France)

- **Nicolas GAUDENZIO** *(Infinity - Toulouse Institute for Infectious and Inflammatory Diseases, University of Toulouse, Inserm, CNRS, Toulouse, France)*
  A conserved program linking maternal stress to fetal neuroimmune reprogramming
- **Daniela LATORRE** *(Division of Neuroscience, IRCCS San Raffaele Hospital, Milan, Italy)*
  Autoreactive T Cells in inflammatory peripheral neuropathies

Short oral presentations

- **P1-01** - **Lena BOURHY** *(Development and Homeostasis of the Nervous System, The Francis Crick Institute, London, UK)*
  Neural pathways mediating the gut-lung axis CANCELED
- **P1-02 - Nouha SOUFI** *(IPMC, CNRS, Valbonne, Provence-Alpes-Cote d'Azur, France)*
  Splenic nerve stimulation protects against murine experimental autoimmune encephalomyelitis via B cell beta2-adrenergic licensing of Tregs
- **P1-03 - Julien NOVARINO** *(CIMI-PARIS, Paris, France)*
  Cancer-related pain is masked by enkephalins-producing regulatory T cells in mice

11:45-12:00 **Industry Symposium** *Audit. Saint-Exupéry - Level 2*

Chairs: Marc VOCANSON (Lyon, France) & **Fatima-Ezzahra L'FAQIHI-OLIVE** (Toulouse, France)

- **BD Biosciences**
  Seeing Beyond the Spectrum: Exploring biological dimensions through spectral imaging cytometry
  Laurence DELBOS & **Juliette DESFRANÇOIS** *(Cytocell, Nantes, France)*

12:00-12:36 **Industry Talks** *Audit. Saint-Exupéry - Level 2*

Chairs: Marc VOCANSON (Lyon, France) & **Fatima-Ezzahra L'FAQIHI-OLIVE** (Toulouse, France)

- **Cytek Biosciences**
  A New Horizon: Welcome to the Borealis
  Fabien PITOISET *(PhD, Field Applications Specialist, Cytek Biosciences, Amsterdam, Netherlands)*
- **Meso Scale Discovery** (12-min presentation)
  Pushing the Boundaries of Biomarker Quantification: High Sensitivity, Multiplexing and Matrix Flexibility
  Renaud COLISSON *(Field Application Scientist, Meso Scale Discovery, Rockville, United States)*
- **Pixelgen Technologies**
  Immune Cell Surface Protein Architecture in Health and Disease - Publications and Use Case Update
  Peter DJALI *(Business Development Manager, Pixelgen Technologies, Stockholm, Sweden)*
- **StemCell Technologies**
  Automated Tissue Dissociation with STEMprep™
  Christine BARR *(STEMCELL Technologies, Saint-Egrève, France)*

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- **Alamar Biosciences**
  NULISA: An Ultrasensitive, Multiplex Immune Panel for Profiling Inflammatory and Autoimmune Disease Biomarkers
  Véronique BERCHET *(Alamar Biosciences, Segrate, Italy)*

12:36-14:15 **Lunch - Coffee - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

PARALLEL SESSIONS

14:15-15:45 **PS1 - Macrophages and dendritic cells** *Audit. Saint-Exupéry - Level 2*

Chairs: Sandrine HENRI (Tours, France) & **Nathalie BENDRISS-VERMARE** (Lyon, France)

- **Florent GINHOUX** *(Institut Gustave-Roussy, Villejuif, France)*
- **Ana-Maria LENNON-DUMENIL** *(Institut Curie, PSL Research University, INSERM U932, Paris, France)*
  Crypt Engulfment as a Novel Antigen Sampling Mechanism in the Colon

Short oral presentations

- **PS1-01 - Clara TAFFONI** *(IRMB, INSERM U1183, Montpellier, France)*
  VSIG4 licenses resident synovial macrophages to restrain inflammatory arthritis
- **PS1-02 - Donia SAIB** *(CRCL, INSERM, Lyon, France)*
  Macrophage NOTCH1 signaling in pancreatic cancer: immune and stromal remodeling
- **PS1-03 - Sahar SEYED HASSAN TEHRANI** *(Immunoregulation Lab, Champalimaud Foundation, Champalimaud Centre for the Unknown, Lisbon, Portugal)*
  Infection-specific regulation of cDC2 poiesis shapes dendritic cell subset responses

14:15-15:45 **PS2 - Inborn errors in immunity** *Ariane 1 - Level 1*

Chairs: Charline MIOT (Angers, France) & **Emmanuel MARTIN** (Paris, France)

- **Paula VIDEIRA** *(UCIBIO - NOVA School of Science and Technology, Universidade NOVA de Lisboa, Caparica, Portugal)*
  GlycoImmune pathways as determinants of immune variability and disease susceptibility
- **Sylvain LATOUR** *(Inserm - Institut Imagine, Paris, France)*
  Inborn errors of immunity predisposing to severe Epstein Barr infection diseases

Short oral presentations

- **PS2-01 - Dimitra BOZOGLOU** *(INFINITy-INSERM, Toulouse, France)*
  Architecture of actin networks at the T-cell synapse: impact of genetic variants in ACTB and ACTG1
- **PS2-02 - Nhat Duong HO** *(Immunogenetics of Pediatric Autoimmune Diseases, Institute Imagine, Paris, France)*
  Paradoxical Type I Interferon Activation in RELA Haploinsufficiency

14:15-15:45 **PS3 - Vaccinology** *Guillaumet 1+2 - Level 2*

Chairs: Anne-Sophie BEIGNON (Paris, France) & **Jean-Daniel LELIEVRE** (Créteil, France)

- **Laurence ZITVOGEL** *(Institut Gustave-Roussy, Villejuif, France)*
- **Laurent REBER** *(Infinity -Toulouse Institute for Infectious and Inflammatory Diseases, University of Toulouse, Inserm, CNRS, Toulouse, France)*
  Development of therapeutic vaccines for the treatment of allergic diseases

Short oral presentations

- **PS3-01 - Fadel SAYES** *(Unité de Pathogénomique Mycobactérienne Intégrée, Département de Microbiologie, Institut Pasteur, Paris, France)*
  Improved Immune Responses and Tuberculosis Protection by Aerosol Vaccination with rBCG expressing ESX-1 from Mycobacterium marinum
- **PS3-02 - Charlotte HATEB** *(Université Toulouse, INFINITy, Inserm UMR1291, Toulouse, France)*
  Development of an mRNA vaccine encoding the major allergen Bet v 1 to treat birch pollen allergy
- **PS3-03 - Jean-Michel SALLENAVE** *(Immune signaling in cancer and infection, INSERM U1149, Centre for Inflammation Research, Paris, France)*
  A novel cystic fibrosis-mimetic Pseudomonas auxotrophic vaccine is protective *in vivo* and is associated with Th17 and IgA mucosal immunity

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14:15-15:45 **CPS4 - Immunometabolism and its implications for practical medicine** *Cassiopée - Level 1*

Clinical session

Chairs: Guislaine CARCELAIN (Paris, France) & **Olivier TOUTIRAIS** (Caen, France)

- **Antoine MARÇAIS** *(CIRI, Centre International de Recherche en Infectiologie, Université Claude Bernard Lyon 1, Inserm, CNRS, ENS de Lyon, Lyon, France)*
  Metabolic sensors in NK cells: can we move from basic discoveries to clinical applications?
- **Mireille LAFORGE** *(Université Paris Cité, NeuroDiderot, Inserm, Paris, France)*
  Immunometabolism, from diagnosis to treatment: Applications to long COVID and autism spectrum disorders

PARALLEL SESSIONS

15:45-17:15 **PS5 - ILC / NK** *Guillaumet 1+2 - Level 2*

Chairs: Emilie NARNI (Marseille, France) & **Sophie LAFFONT-PRADINES** (Toulouse, France)

- **Sébastien VIEL** *(Centre International de Recherche en Infectiologie, Lyon, France)*
  The TGF-β paradox in NK cells: from immune suppression to context-dependent functional reprogramming
- **Sonja TUGUES** *(Innate Lymphoid Cells and Cancer, Institute of Experimental Immunology, Univ. of Zurich, Zurich, Switzerland)*
  Resident lymphocytes preserve functional integrity of the lactating mammary niche

Short oral presentations

- **PS5-01 - Nathalie BENDRISS-VERMARE** *(CISTAR team, Cancer Research Center of Lyon, Lyon, France)*
  A Polyfunctional IL-33-Responsive ST2$^+$NK Cell State Promotes Antitumor Immunity and Response to Immunotherapy
- **PS5-02 - Juan SIENES BAILO** *(Immunoregulation Unit, Department of Immunology, Institut Pasteur, Université Paris Cité, Paris, France)*
  IL-23 drives a pro-inflammatory state in human group 3 innate lymphoid cells (ILC3)
- **PS5-03 - Mariana CARREIRA** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisbon, Portugal)*
  CXCR3 signaling promotes Delta One T cell recruitment and antitumor efficacy in colorectal cancer

15:45-17:15 **PS6 - Immunometabolism** *Cassiopée - Level 1*

Chairs: Anne DEJEAN (Toulouse, France) & **Ricardo SILVESTRE** (Braga, Portugal)

- **Ricardo SILVESTRE** *(Life and Health Sciences Research Institute (ICVS), Braga, Portugal)*
  Macrophage immunometabolism: shaping pathogen persistence and host protection
- **Anne DEJEAN** *(Infinity -Toulouse Institute for Infectious and Inflammatory Diseases, University of Toulouse, Inserm, CNRS, Toulouse, France)*
  Eomes drives an exhausted T helper cell lineage essential for tumor control and response to immunotherapy

Short oral presentations

- **PS6-01 - Loane JOLY** *(Laboratoire de Biologie et Modélisation de la Cellule, INSERM, CNRS, ENS-Lyon, Lyon, France)*
  Mitochondrial translation is a critical regulator of CD8 T-cell homeostasis and effector responses
- **PS6-02 - Nicolas SOCQUET-JUGLARD** *(INSERM, INFINITy, Toulouse, France; 2 CNRS, IGMM, Montpellier, France)*
  CD8 T cells adjust actin remodeling to nutrient availability during migration and synapse assembly
- **PS6-03 - Diogo ESTÊVÃO** *(Tumour and Microenvironment Interactions Group, Cancer Department, i3S-Institute for Research & Innovation in Health, Porto, Portugal)*
  Lipid Droplets Shield Rectal Cancer from Radiotherapy-Induced Cell Death: A Metabolic–Immune Axis of Resistance

15:45-17:15 **PS7 - T and B cell development and signaling** *Audit. Saint-Exupéry - Level 2*

Chairs: Marion ESPELI (Paris, France) & **Bruno SILVA-SANTOS** (Lisbon, Portugal)

- **Nuno ALVES** *(i3S - University of Porto, Porto, Portugal)*
  Keeping the Thymus Young: ZFP36 RNA-Binding Proteins Sustain Thymic Epithelial Cell Function to Prevent Thymic Involution and Maintain Tolerance
- **Claire LEIBLER** *(Université de Bordeaux, CNRS, ImmunoConcEpT, Bordeaux, France)*
  B Cell Regulation through Nucleic Acid Sensing TLRs

Short oral presentations

- **PS7-01 - Dunja CAPITÁN SOBRINO** *(INFINITy, INSERM U1291, Toulouse, France)*
  HuR sustains immunoregulatory B-cell responses to limit neuroinflammation

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- **PS7-02 - Guilhèn PRUNIER** *(INFINITy, INSERM, Toulouse, France)*
  ICOS, CD226 and CD2 engage non-redundant synapse remodeling programs to optimize CD8+ T cell cytotoxic activity
- **PS7-03 - Ruben PINHEIRO** *(GIMM, Lisboa, Portugal)*
  N-glycosylation controls the thymic development of perinatal gd17 T-cells by dampening TCRgd signal strength

17:15-18:00 **Coffee break - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

PARALLEL SESSIONS

18:00-19:30 **PS8 - Ageing** *Guillaumet 1+2 - Level 2*

Chairs: Nuno ALVES (Porto, Portugal) & **Victorine DOUIN** (Toulouse, France)

- **François TROTTEIN** *(Institut Pasteur, Lille, France)*
  Aging and respiratory infections: cellular senescence, gut dysbiosis, and beyond
- **Almudena RAMIRO** *(CNIC - Spanish National Center for Cardiovascular Research, Madrid, Spain)*
  Understanding the origin of autoreactive antbodies in atherosclerosis

Short oral presentations

- **PS8-01 - David CUNE** *(Service of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland)*
  Autophagy loss in dendritic cells drives inflammatory reprogramming and CD4⁺ T-cell dysregulation during aging
- **PS8-02 - João CARDEIRA DA SILVA** *(RESTORE Institute, Toulouse, France)*
  T-cell programs shaping post-injury outcomes in the zebrafish heart
- **PS8-03 - Inês FARIA** *(Instituto de Investigação e Inovação em Saúde (i3S), Porto, Portugal)*
  Chronic exposure to interleukin-10 drives inflammaging and accelerated tissue senescence

18:00-19:30 **PS9 - Young SPI / SFI** *Cassiopée - Level 1*

Chairs: Fanny HIDALGO VILLEDA (Marseille, France), **Maria LTEIF** (Paris, France), **Catarina RODRIGUES** (Porto, Portugal) & **Rita SILVA-GOMES** (Lisbon, Portugal)

- **Carlos MINUTTI** *(Champalimaud Foundation, Lisbon, Portugal)*
  The Academic Path: The Bad, the Good, and the Pretty

18:00-19:30 **PS10 - Autoimmunity and inflammatory diseases** *Audit. Saint-Exupéry - Level 2*

Chairs: Anne ASTIER (Toulouse, France) & **Nicolas FAZILLEAU** (Toulouse, France)

- **Thomas KORN** *(Institute for Experimental Neuroimmunology, Technical University of Munich School of Medicine, Munich, Germany)*
  Compartmentalized regulation of CNS autoimmunity
- **Rejane RUA** *(Center for Immunology of Marseille-Luminy (CIML), Marseille, France)*
  Brain border myeloid cells: more than immune sentinels?

EMBO

Short oral presentations

- **PS10-01 - Inês ALVES** *(Immunology, Cancer and Glycomedicine, i3S - Instituto de Investigação e Inovação Saude, Porto, Portugal)*
  Glycan mimicry as a key mechanism in the loss of self-tolerance: deciphering novel anti-glycan autoantibodies in lupus
- **PS10-02 - Angélina MIMOUN** *(Infinity U1291, INSERM, Toulouse, France)*
  Eomes Reprograms FoxP3⁺ Regulatory T Cells toward a Cytotoxic and Pro-inflammatory State
- **PS10-03 - Yves-Marie MAGAT** *(UMR7355, CNRS, Orléans, France)*
  NLRP6 promotes inflammation and regulated cell death through activation of the caspase-3/gasdermin E pathway in bleomycin-induced pulmonary fibrosis

19:30 **POSTER SESSION 1 - odd-numbered** *Foyer & Concorde 1&2 - Level -1*

19:30 **Wine & Cheese** *Foyer & Concorde 1&2 - Level -1*

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THURSDAY 5 NOVEMBER

PARALLEL SESSIONS

08:30-10:00 **PS11 - Innate T cells** *Ariane 1 - Level 1*

Chairs: Maria LEITE DE MORAES (Paris, France) & **Julie DÉCHANET-MERVILLE** (Bordeaux, France)

- **Graham OGG** *(University of Oxford, Oxford, United Kingdom)*
  CD1a-reactive T cells and lipid antigens in inflammatory skin diseases: discovery and translation
- **Agnès LEHUEN** *(Institut Cochin, INSERM U1016, UMR 8104, Paris, France)*
  MAIT cells in autoimmune and infectious diseases

Short oral presentations

- **PS11-01 - Youenn JOUAN** *(INSERM U1100, Université de Tours, Tours, Indre et Loire, France)*
  MAIT cells promote lung resilience during severe viral pneumonia by maintaining myeloid balance
- **PS11-02 - Camille KERGARAVAT** *(Saint Louis Research Institute, Paris, France)*
  Developmental waves and genetic regulation of the Human γδ T-cell repertoire
- **PS11-03 - Juan SIENES BAILO** *(Immunoregulation Unit, Dpt of Immunology, Institut Pasteur, Univ. Paris Cité, Paris, France)*
  IL-23 regulates the non-canonical NF-kB pathway in human invariant Natural Killer T (iNKT) cells

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08:30-10:00 **PS12 - Women's health/sex bias in immunity** *Guillaumet 1+2 - Level 2*

Chairs: Ricardo SILVESTRE (Braga, Portugal) & **Anne ASTIER** (Toulouse, France)

- **Nils LANDEGREN** *(Uppsala University, Sweden)*
  Understanding sex differences in human immunity through gender-affirming hormone therapy
- **Sophie LAFFONT-PRADINES** *(Infinity -Toulouse Institute for Infectious and Inflammatory Diseases, University of Toulouse, Inserm, CNRS, Toulouse, France)*
  Hormonal regulation of ILC: consequences on lung immunity

Short oral presentations

- **PS12-01 - Léa FERRAYÉ** *(Toulouse Institute for Infectious and Inflammatory Diseases, Toulouse, France)*
  Tlr7 bi-allelism shapes pathogenic female B cell responses in lupus
- **PS12-02 - Aymeline DEBONLIER** *(INFINITy, Toulouse, France)*
  PI3K/AKT signaling controls sex bias in Tr1 cells and their response to vitamin D
- **PS12-03 - Hélène VANTOMME** *(i3 laboratory, Sorbonne University, Paris, France)*
  Sex-associated differences in human thymic TCR selection

08:30-10:00 **PS13 - T and B cell memory** *Audit. Saint-Exupéry - Level 2*

Chairs: Marion ESPELI (Paris, France) & **Klaas VAN GISBERGEN** (Lisbon, Portugal)

- **Klaas VAN GISBERGEN** *(Champalimaud Foundation, Lisbon, Portugal)*
  T cell diversification in infection and cancer
- **Christina ZIELINSKI** *(University of Cambridge, United Kingdom)*
  TGF-β restricts GSDME-mediated IL-1α Release by Th17 cells to license them for enhanced pathogenicity

Short oral presentations

- **PS13-01 - Maria KERIDON** *(Physiology and Cancer Department, Champalimaud Foundation, Lisbon, Portugal)*
  Clearance of tumor antigen governs the differentiation of bona fide CD8+ tissue-resident memory T cells
- **PS13-02 - Marc VOCANSON** *(Team EIA, Centre International de Recherche en Infectiologie, Lyon, France)*
  Progressive remodeling of pathogenic skin resident memory T cell subsets shapes long-term allergic memory
- **PS13-03 - Andrea PICHLER** *(INFINITY, Toulouse, Midi-Pyrénées, France)*
  PI3Kd promotes T cell effector differentiation during chronic infection

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08:30-10:00 **CPS14 - CAR-T cells in autoimmune diseases** *Cassiopée - Level 1*

Clinical session

Chairs: Roland LIBLAU (Toulouse, France) **& Sébastien VIEL** (Lyon, France)

- **Maxime TEISSEYRE** *(Université Côte d'Azur, CNRS, INSERM, IRCAN, Nice, France)*
  CAR-T cell therapy for refractory autoimmune diseases

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- **Maurine JOURET** *(Pediatric Nephrology, Rheumatology, Dermatology Unit, Hospices Civils de Lyon, Lyon, France)*
  CAR-T cell therapy for juvenile-onset autoimmune diseases: a promising future?

10:00-10:45 **Coffee break - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

PLENARY SESSIONS

10:45-12:15 **SESSION 2 - Host-pathogen interactions** *Audit. Saint-Exupéry - Level 2*

Chairs: Ricardo SILVESTRE (Braga, Portugal) & **Emmanuelle JOUANGUY** (Paris, France)

- **Judi ALLEN** *(Wellcome Centre for Cell-Matrix Research, Lydia Becker Institute for Immunology & Infection, University of Manchester, Manchester, United Kingdom)*
  Immune regulation of the extracellular matrix: at the crossroads of host protection and pathology
- **Etienne MEUNIER** *(Institut de Pharmacologie et de Biologie Structurale, IPBS, Univ. de Toulouse, CNRS, UPS, Toulouse, France)*
  The NLRP1 inflammasome: Scanning the borders

Short oral presentations

- **P2-01 - Vasco RODRIGUES** *(INSERM U932, Institut Curie, Paris, Île-de-France, France)*
  Constitutive macropinocytosis is coupled with reduced rates of protein synthesis to confer intrinsic protection against viral replication in macrophages
- **P2-02 - Léa FROMONT** *(IPBS, Toulouse, France)*
  LiveLung-TB: Intravital imaging reveals $CD4^+$ T-cell dynamics during pulmonary Mycobacterium tuberculosis infection
- **P2-03 - Rute Daniela MATOS GONÇALVES** *(i3s - Instituto de Investigação e Inovação em Saúde, Porto, Portugal)*
  Mycobacterium tuberculosis isolates modulate levels of protective IL-1β *in vivo* accounting for disease severity

12:15-12:30 **Industry Symposium** *Audit. Saint-Exupéry - Level 2*

Chairs: Nicolas FAZILLEAU (Toulouse, France) & **Emmanuelle JOUANGUY** (Paris, France)

- **Sony**
  Clone War: Performance and Interoperability of Two ID7000 Spectral Flow Cytometers
  Hugo GARNIER *(Ingénieur d'Études, Plateau Technique de Cytométrie et Tri Cellulaire, Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity), Toulouse, France)*

12:30-12:42 **Industry Talks** *Audit. Saint-Exupéry - Level 2*

Chairs: Nicolas FAZILLEAU (Toulouse, France) & **Emmanuelle JOUANGUY** (Paris, France)

- **CeGaT**
  Connecting the Pieces of the Immune Response: From T-cell repertoires to cells, tissues and proteins
  Lara EL BAZZAL *(CeGaT, Tuebingen, Germany)*
- **Agilent Technologies**
  Complementary technologies for your fundamental, applied and medical research in immunology/immuno-therapy/immuno-oncology
  Jerome DARAKDJIAN *(Agilent Technologies, Les Ulis, France)*

12:42-14:15 **Lunch - Coffee - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

13:30-14:15 **POSTER SESSION 2 - even-numbered** *Foyer & Concorde 1&2 - Level -1*

PARALLEL SESSIONS

14:15-15:45 **PS15 - Neutrophils** *Guillaumet 1+2 - Level 2*

Chairs: Véronique WITKO (Paris, France) & **Patrice DECKER** (Paris, France)

- **Triantafyllos CHAVAKIS** *(Institute for Clinical Chemistry and Laboratory Medicine, University Hospital and Faculty of Medicine, Dresden, Germany)*
  Trained granulopoiesis in cancer
- **Véronique WITKO** *(Institut Cochin, Paris, France)*
  Proliferating Cell Nuclear Antigen (PCNA): a central signalling scaffold orchestrating neutrophil plasticity in inflammation

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Short oral presentations

- **PS15-01 - Camille DANNE** *(UMRS938, Paris, France)*
  The microbiota-derived metabolite Metab1 prevents neutrophil activation by inducing metabolic quiescence
- **PS15-02 - Patrice DECKER** *(University Sorbonne Paris Nord, Bobigny, France)*
  NETs from rheumatoid arthritis patients trigger a pro-inflammatory response in monocytes through metabolic mechanisms and modulate macrophage differentiation
- **PS15-03 - Aya CHAMAA** *(T-RAIG, TIMC, La Tronche, France)*
  Role of neutrophils in Chlamydia driven Reactive arthritis in the SKG mouse

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14:15-15:45 **PS16 - Gene and cell therapy** — ***Audit. Saint-Exupéry*** *- Level 2*

Chairs: Makoto MIYARA (Paris, France) & **Jacques NUNES** (Marseille, France)

- **Makoto MIYARA** *(Immunology Department, INSERM, Centre d'Immunologie et des Maladies Infectieuses (CIMI), AP-HP, Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France)*
  Human Treg cell therapies for transplantation
- **Alena GROS** *(Vall d'Hebron Institute of Oncology (VHIO), Tumor Immunology & Immunotherapy Group, Barcelona, Spain)*
  Personalized T-cell therapies for solid cancers

Short oral presentations

- **PS16-01 - Sofia MENSURADO** *(Gulbenkian Institute for Molecular Medicine, Lisbon, Portugal)*
  Allogeneic CARγδT-cells recognize CD33 and PVR to target Acute Myeloid Leukemia and suppress tumor progression
- **PS16-02 - Mariana GADELHO GONÇALVES** *(Immune Cell Reprogramming Lab., Centre for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal)*
  A 'Sense-and-Reprogram' Platform for Systemic Cancer Immunotherapy
- **PS16-03 - Annemarie FORTUIN** *(Team 3 - Institute for Regenerative Medicine and Biotherapy, Montpellier, France)*
  Engineering Regulatory T Cells For Rheumatoid Arthritis: Development and Evaluation of CAR Constructs

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14:15-15:45 **PS17 - Germinal Center** — ***Cassiopée*** *- Level 1*

Chairs: Amélie BONAUD (Limoges, France) & **Fréderic MOURCIN** (Rennes, France)

- **Mauro GAYA** *(Center for Immunology of Marseille-Luminy (CIML), Marseille, France)*
  The lung stroma sustains a plasma cell niche for long-term mucosal protection against infection
- **Carole LE COZ** *(Infinity, Toulouse, France)*
  T Follicular Regulatory Cell Homeostasis at the Crossroads of Germinal Center Dysfunction

Short oral presentations

- **PS17-01 - Raphaël JEGER-MADIOT** *(INSERM U1151/CNRS UMR 8253, Université Paris Cité, Institut Necker Enfants Malades, Paris, France)*
  Modeling memory B cell responses in spleen-derived immune organoids
- **PS17-02 - Maya POLKOTYCKI** *(INFINITY U1291 INSERM, Toulouse, France)*
  Type 3 inflammation shapes the Follicular Regulatory T cells (Tfr) into a Tfr17 polarized subset
- **PS17-03 - Audrey AKESSE** *(Control of the immune response B and lymphoproliferation, CNRS UMR 7276, INSERM, University of Limoges, Limoges, France)*
  Plasma cell heterogeneity is imprinted by the type of immune challenge

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14:15-15:45 **CPS18 - Xenotransplantation** — ***Ariane 1*** *- Level 1*

Clinical session

Chairs: Alice KOENIG (Lyon, France) & **Julien ZUBER** (Paris, France)

- **Olivier THAUNAT** *(CIRI, INSERM, Université Claude Bernard Lyon I, CNRS, École Normale Supérieure de Lyon, Université de Lyon, Lyon, France)*
  Breaking Barriers Across Species: The Immunopathological Frontiers of Xenotransplantation
- **Aurélie SANNIER** *(Hôpital Bichat - Claude-Bernard, Paris, France)*
  Lessons from the First Human Xenotransplants

15:45-16:30 **Coffee break - Visit of exhibition & Posters** — ***Foyer & Concorde 1&2*** *- Level -1*

PARALLEL SESSIONS

16:30-18:00 **PS19 - Mast cells / Basophils** *Guillaumet 1+2 - Level 2*

Chairs: Gaël MÉNASCHÉ (Paris, France) & **Nicolas CHARLES** (Paris, France)

- **Sebastien TALBOT** *(Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden)*
  Nociceptor neurons control inflammation
- **Clare LLOYD** *(National Heart and Lung Institute, Imperial College London, London, United Kingdom)*
  It's all about the neighbourhood: regulation of immunity in the allergic lung

Short oral presentations

- **PS19-01 - Céline EL SAMROUT** *(Infinity, INSERM, Toulouse, France; 2 IRSD, INSERM, Toulouse, France)*
  Non-immune function of myenteric mast cells in supporting neuronal plexus homeostasis
- **PS19-02 - Geoffrey CHEMINET** *(Hematology Laboratory, Imagine Institute for Genetic Diseases - U1163 INSERM, Paris, France)*
  Role of mast cells in bone vaso-occlusive crisis and pain of sickle cell disease
- **PS19-03 - Zohra BENMESSAOUD** *(INSERM UMR1291 – CNRS UMR5051 - University Toulouse III, Infinity, Toulouse, France)*
  A new mouse model expressing human IgE and its receptors FcεRI and CD23 predicts a superiority for ligelizumab over omalizumab in anaphylaxis

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16:30-18:00 **PS20 - Mucosal immunology** *Cassiopée - Level 1*

Chairs: Klaas VAN GISBERGEN (Lisbon, Portugal) & **Olivier NEYROLLES** (Toulouse, France)

- **Nicole JOLLER** *(Department of Quantitative Biomedicine, University of Zurich, Zurich, Switzerland)*
  Fungal infections imprint the Th17 pool by establishing a distinct memory Th17 population
- **Andreas DIEFENBACH** *(Laboratory of Innate Immunity, Institute of Microbiology, Infectious Diseases and Immunology (I-MIDI), Berlin, Germany)*
  Regulation of functional adaptation of tissues by innate lymphoid cells

Short oral presentations

- **PS20-01 - Margaux PARADIS** *(IPBS - CNRS, Toulouse, France)*
  A TAK1-Driven NLRP1 Inflammasome Pathway Revealed by Phosphatase Targeting Environmental Toxins
- **PS20-02 - Fabian GUENDEL** *(Microenvironment and Immunity Unit, Institut Pasteur, Paris, France)*
  The Postnatal Stress Response Drives Long-Term Maladaptation of the Intestinal Epithelium via TLR3/TRIF Epigenetic Memory
- **PS20-03 - Ignacio CABALLERO POSADAS** *(INRAE, Toxalim, Toulouse, France)*
  TLR5 signaling amplifies airway epithelial cell responses to type I interferon through MyD88–JAK1 crosstalk during influenza infection in pigs

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16:30-18:00 **PS21 - Tissue homeostasis and dynamics** *Audit. Saint-Exupéry - Level 2*

Chairs: Julie RIBOT (Lisbon, Portugal) & **Meryem ALOULOU** (Toulouse, France)

- **Julie RIBOT** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisbon, Portugal)*
  Stressing the role of γδ17 T cells at the crossroads of tissue communication and pathophysiology
- **Karl BALABANIAN** *(Université Paris Cité, Institut de Recherche Saint-Louis, INSERM, Paris, France)*
  CXCR4 signaling, a gatekeeper orchestrating the bone marrow ecosystem

Short oral presentations

- **PS21-01 - Miguel MESQUITA** *(Gulbenkian Institute for Molecular Medicine (GIMM), Avenida Professor Egas Moniz, Oeiras, Portugal)*
  Ferroptosis is a Physiologic Vulnerability of Iron-Recycling Macrophages
- **PS21-02 - Dan CORRAL** *(INFINITY, Toulouse, France)*
  Let it flow: Maternal immune regulation of lactation
- **PS21-03 - Chloé MICHAUDEL** *(MTS - LIAA, INRAE, Gif sur Yvette Cedex, France)*
  Low-dose perinatal pesticide exposure reprograms immune development in male offspring and increases susceptibility to type-2 airway inflammation

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16:30-18:00 **CPS22 - CEnI General Assembly** **Clinical session** *Ariane 1 - Level 1*

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PLENARY SESSION

18:00-19:30 **SESSION 3 - Young investigators** *Audit. Saint-Exupéry - Level 2*

Chairs: Marie-Astrid BOUTET (Nantes, France)**, Joaquin PELLEGRINI** (Toulouse, France)**,**
Mehdi BENAMAR (Montpellier, France)**, Catarina AZEVEDO** (Porto, Portugal) & **Inês ALVES (Porto, Portugal)**

- **Thomas MARICHAL** *(GIGA Institute, University of Liège, Liège, Belgium)*
  A deep dive into the biology of lung macrophages in health and disease

Short oral presentations

- **P3-01 - Camille CHATELAIN** *(Division of Immuno-oncology, Lund Stem Cell Center, Lund University, Lund, Sweden)*
  Inducing immunogenic lymphoid structures across cancers by tumor-to-dendritic cell reprogramming
- **P3-02 - Ana Carolina VALENTE SANTOS CRUZ DE ARAUJO** *(Department of Immunology, University of São Paulo, São Paulo, São Paulo, Brazil)*
  HIF-1α licenses BCG-induced trained immunity to promote pulmonary and systemic protection against Brucella abortus infection
- **P3-03 - Tomás MACHADO** *(University of Coimbra, Center for Innovative Biomedicine and Biotechnology, Center for Neuroscience and Cell Biology, Cantanhede, Coimbra, Portugal)*
  Retinoic acid modulates invariant Natural Killer T cell development and function in colon cancer

20:00 **Congress Dinner** *Les Espaces Vanel*

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FRIDAY 6 NOVEMBER

PLENARY SESSION

08:30-10:00 **SESSION 4 - Tumor immunity** *Audit. Saint-Exupéry - Level 2*

Chairs: Bruno SILVA-SANTOS (Lisbon, Portugal) & **Fabienne HASPOT** (Nantes, France)

- **Bruno SILVA-SANTOS** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisbon, Portugal)*
  Harnessing gamma-delta T cells for cancer immunotherapy
- **Marisol SOENGAS** *(Melanoma Laboratory, Molecular Oncology Programme, Spanish National Cancer Research Centre (CNIO), Madrid, Spain)*

Short oral presentations

- **P4-01 - YLan BLANCHARD** *(Centre de Recherches en Cancérologie de Toulouse (CRCT), Toulouse, France)*
  Role of intestinal CD8 T cells in the control of colorectal cancer metastases
- **P4-02 - Alexandre LANAU** *(U1330 - Children's Oncology Research Unit, Institut Curie, Paris, France)*
  "Nature vs Nurture" : Understanding How TCR-pMHC history shapes T cell fate during polyclonal response in solid tumors
- **P4-03 - Yenkel GRINBERG-BLEYER** *(Cancer Research Center of Lyon, Lyon, France)*
  NF-kappaB transcription factor c-Rel governs CD8+ T-cell function in cancer

10:00-10:45 **Coffee break - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

PARALLEL SESSIONS

10:45-12:15 **PS23 - Immunotherapy** *Audit. Saint-Exupéry - Level 2*

Chairs: Michel COGNÉ (Rennes, France) & **Nicolas FAZILLEAU** (Toulouse, France)

- **Karin TARTE** *(Inserm, Unité Mixte de Recherche U1236, Université Rennes, EFS, Rennes, France)*
  Is immunotherapy-mediated B-cell depletion the most relevant strategy in autoimmune disease and lymphoma?
- **Bruno SÉGUI** *(INSERM UMR 1037, Cancer Research Center of Toulouse (CRCT), Toulouse, France)*
  TNF blockade with certolizumab improves the efficacy of anti-PD-1 and anti-CTLA-4 combination therapy for melanoma

Short oral presentations

- **PS23-01 - Dalil HANNANI** *(T-RAIG Team - Grenoble Faculty of Medicine - CNRS UMR 5525, TIMC Laboratory, Grenoble, France)*
  Circulating Metabolites Link Gut Microbiota Composition to Clinical Outcomes under Immune Checkpoint Inhibitors in NSCLC
- **PS23-02 - Samad MOHAMMADNEZHADDARYANI** *(U981, Gustave Roussy, Villejuif, France)*
  eIF4F targeting rewires T cell exhaustion and overcomes immunotherapy resistance
- **PS23-03 - Alex PRIGENT** *(Endothelial Cells in Immunity, Inflammation and Cancer, IPBS, CNRS, Toulouse, France)*
  High endothelial venules mediate B cell entry into tumors and tertiary lymphoid structures during PD-1 plus CTLA-4 immunotherapy

10:45-12:15 **PS24 - Glycoimmunology** *Guillaumet 1+2 - Level 2*

Chairs: Salomé PINHO (Porto, Portugal) & **Anne ASTIER** (Toulouse, France)

- **Salomé PINHO** *(i3S - University of Porto, Porto, Portugal)*
  Turning Sweet in Immunity: glycans as master regulators of immune response in chronic inflammation, autoimmunity and cancer
- **Heinz LÄUBLI** *(University of Basel, Basel, Switzerland)*
  Local glycan engineering induces systemic antitumor immune reactions via antigen cross-presentation

Short oral presentations

- **PS24-01 - Yoann ROMBOUTS** *(Univ Toulouse, CNRS, IPBS, Toulouse, France)*
  Polysialylation governs inflammatory monocyte egress from the bone marrow
- **PS24-02 - Beatriz SANTOS-PEREIRA** *(Institute for Research and Innovation in Health (i3S), Porto, Portugal)*
  Complex branched glycosylation as a key regulator of type-3/γδT17 response associated with autoimmunity
- **PS24-03 - Léna ANDRIEUX** *(INFINITy, INSERM UMR1291, Toulouse, France)*
  Role of IgE glycosylation in allergic diseases

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10:45-12:15 **PS25 - Tolerance and Transplantation** *Cassiopée - Level 1*

Chairs: Meryem ALOULOU (Toulouse, France) & **Mathieu CHEVALIER** (Paris, France)

- **Carole GUILLONNEAU** *(Nantes Université, CHU Nantes, INSERM, Center for Research in Transplantation and Translational Immunology, Nantes, France)*
  CD8+ Treg cell therapy in Transplantation and Autoimmunity: from a novel concept to a clinical reality
- **Julien ZUBER** *(Université Paris Cité, INSERM U1151, CNRS 8253, Institut Necker Enfants Malades, Paris, France)*
  Challenges and strategies for translating transplant tolerance into clinical practice

Short oral presentations

- **PS25-01 - Mael SEITE** *(Mononuclear phagocytes, Immunopathology, Immunovirology, Center for Research in Transplantation and Translational Immunology, Nantes, France)*
  Autologous Tolerogenic Dendritic Cells Promote Treg Induction through Lactate Secretion
- **PS25-02 - Sahil ADRIOUCH** *(University Rouen Normandie, INSERM, Normandie University, Rouen, France)*
  Nanoparticles targeting liver sinusoidal endothelial cells improve AAV gene transfer and promote tolerance-spreading to capsid and transgene epitopes
- **PS25-03 - Alice KOENIG** *(INSERM U 1111, Lyon, France)*
  IRE1α-XBP1 inhibitors: a promising approach to treat chronic vascular rejection after organ transplantation

PLENARY SESSION

12:15-13:15 **SFI General Assembly** *Audit. Saint-Exupéry - Level 2*

13:15-14:15 **Lunch - Coffee - Visit of exhibition & Posters** *Foyer & Concorde 1&2 - Level -1*

PARALLEL SESSIONS

14:15-15:45 **PS26 - Environmental cues and microbiota** *Guillaumet 1+2 - Level 2*

Chairs: Dalil HANNANI (Grenoble, France) & **Ilana GABANYI** (Oeiras, Portugal)

- **Thomas GENSOLLEN** *(Institut de Pharmacologie et de Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France)*
  Early-life *Wnt*4 expressing colon stromal cells orchestrate lifelong mucosal homeostasis via BMP-driven iNKT cell imprinting
- **Ilana GABANYI** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisbon, Portugal)*
  Neuronal responses to bacterial signals: the influence of sex hormones

Short oral presentations

- **PS26-01 - Fikir ASFAW** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisboa, Portugal)*
  IL-17 regulates peripheral nerve regeneration in a microbiota dependent manner
- **PS26-02 - Rodrigo DE OLIVEIRA FORMIGA** *(CRSA, Inserm U938, Sorbonne Université, Paris, France)*
  Gut Microbiota Regulates Host Immune Bioenergetics - Role of Proline Metabolism In Monocytes Phenotype
- **PS26-03 - Nicolas BOULADOUX** *(Department of Immunology / Metaorganism Unit, Institut Pasteur, Paris, France)*
  Deciphering the crosstalk between skin commensals and the immune system

14:15-15:45 **PS27 - System and spatial immunology** *Audit. Saint-Exupéry - Level 2*

Chairs: Nicolas FAZILLEAU (Toulouse, France) & **Luis GRACA** (Lisbon, Portugal)

- **Luis GRACA** *(Gulbenkian Institute for Molecular Medicine (GIMM), Lisbon, Portugal)*
  Regulation of humoral responses in health and disease
- **Vera PANCALDI** *(INSERM UMR 1037, Cancer Research Center of Toulouse (CRCT), Toulouse, France)*
  Systems approaches to describe and simulate the tumour microenvironment

Short oral presentations

- **PS27-01 - Fanny LAFOURESSE** *(UMR1037 Inserm - UMR 5071 CNRS - Université de Toulouse, CRCT, Toulouse, France)*
  Spatial characterization of CD8⁺ TRM heterogeneity within B-cell aggregates and tertiary lymphoid structures in triple-negative breast cancer
- **PS27-02 - Miguel MENDES FERREIRA** *(Department of Pathology, Leiden University Medical Center (LUMC), Leiden, Netherlands)*
  Single cell spatial profiling of immune contextures in MMRd colorectal cancer reveals distinct microenvironments associated with HLA-class-I loss

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- **PS27-03 - Keerthi KURMA** *(Laboratoire Cellules Circulantes Rares Humaines, Centre Hospitalier Universitaire de Montpellier, Montpellier, France)*
  Liquid biopsy reveals the immune status and protein profiles linked to CTC burden and clinical outcomes in metastatic breast cancer

14:15-15:45 **PS28 - Antibody** ***Cassiopée*** *- Level 1*

Chairs: Guy GOROCHOV (Paris, France) & **Maria DEL MAR NARANJO GOMEZ** (Montpellier, France)

- **João GONÇALVES** *(Faculdade de Farmácia da Universidade de Lisboa, Lisbon, Portugal)*
  Protein Engineering and Synthetic Biology: New Strategies for Therapeutic Antibody Development
- **Nadia DUARTE** *(Instituto de Biologia Experimental e Tecnológica (iBET), Oeiras, Portugal)*
  Generation of versatile tumour target cell lines using the SpyCatcher/SpyTag system to evaluate antibody-based immunotherapies

Short oral presentations

- **PS28-01 - Stella ROUSSET** *(IPBS, CNRS / University of Toulouse, Toulouse, France)*
  Targeting the C-type lectin receptor DCIR using synthetic single-domain antibodies: a promising strategy for immune modulation in tuberculosis and beyond
- **PS28-02 - Stéphane PINHAL** *(Bruker Dynamic Biosensors, München, Germany)*
  Integrated Biophysical Analysis of Fc–FcR Binding, Affinity, and Avidity in Antibody Therapeutics
- **PS28-03 - Antoine PRAITÉ** *(CRIBL laboratory - UMR CNRS7276 - INSERM U1262, Limoges, France)*
  A comprehensive, transcriptome-wide overview of post-transcriptional control of plasma cell differentiation

PLENARY SESSIONS

15:45-16:30 **Closing Keynote Lecture** ***Audit. Saint-Exupéry*** *- Level 2*

Chairs: Nicolas FAZILLEAU (Toulouse, France) & **Andrea PICHLER** (Toulouse, France)

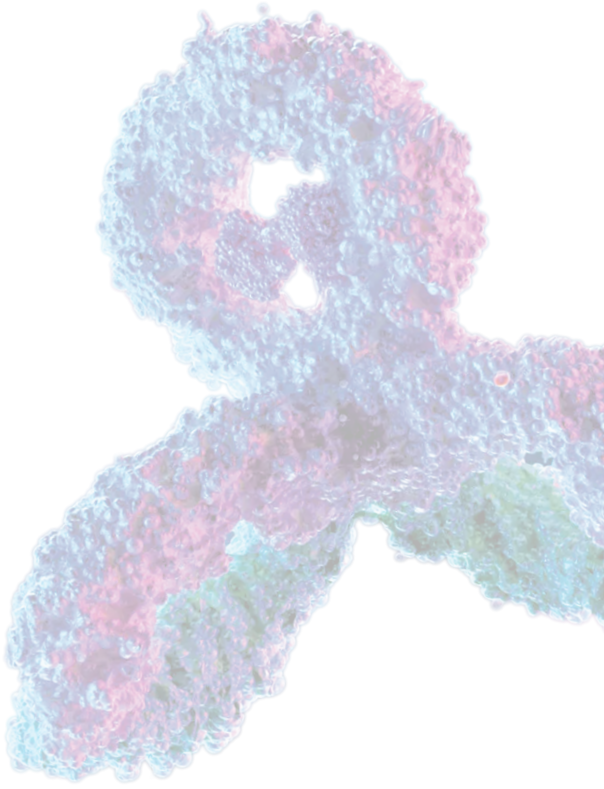
- **Pamela SCHWARTZBERG** *(Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA)*
  Integrating T cells Signals: Lessons from Primary Immunodeficiencies and Tfh cells

16:30-17:00 **Prize awards & Conclusion**

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ABSTRACTS ON WEDNESDAY 4 NOVEMBER

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Regulatory T cells and immune tolerance: therapeutic re-establishment of immune self-tolerance in autoimmune disease by targeting Treg cells

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Regulatory T cells (Tregs), specifically expressing the transcription factor FoxP3 in the nucleus, CD25 and CTLA-4 on the cell surface, are actively engaged in the maintenance of immunological self-tolerance and homeostasis. There are numerous demonstrations mainly from animal models that self-tolerance can be reinstated and autoimmune disease be treated by expanding endogenous natural Tregs (nTregs) or generating Tregs from Tconvs (induced Tregs: iTregs). An outstanding issue for Treg-based therapy of immunological diseases is then how to expand or generate antigen-specific Tregs for disease-specific treatment. Our attempts for this aim have been to convert antigen-specific Tconvs, especially disease-mediating effector/memory-type T cells, into functionally stable FoxP3+ Tregs. We have recently shown that inhibition of CDK8/19, a serine threonine kinase involved in a T-cell signaling pathway, is able to evoke Foxp3 expression in Tconv cells including effector/memory T cells even under *in vivo* and *in vitro* conditions abundant in proinflammatory cytokines. In addition, in the course of *in vitro* generation of iTregs from antigen-specific naive or effector/memory Tconvs, deprivation of CD28 co-stimulatory signal is able to establish Treg-specific epigenetic changes, especially Treg-specific CpG demethylation, at enhancer regions of Treg-signature genes including FoxP3, CD25, and CTLA-4. These findings in mice have enabled *in vitro* generation of functionally stable iTregs from peripheral blood Tconvs in autoimmune disease patients by a combination of a newly developed CDK8/19 inhibitor and CD28 signal deprivation, and by repeating this iTreg induction process. It will be discussed how iTregs akin to nTregs in function and stability can be generated *in vivo* and *in vitro* from the peripheral blood of autoimmune disease patients and how they can be instrumental in treating autoimmune and other inflammatory diseases.

Keywords: Regulatory T cells - Immune tolerance - Autoimmune disease.

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A conserved program linking maternal stress to fetal neuroimmune reprogramming

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Maternal stress during pregnancy is a major risk factor for childhood allergic diseases such as atopic dermatitis (eczema). We recently showed in mice that prenatal stress reprograms fetal skin mast cells and sensory neurons, creating a hyper-reactive neuroimmune unit that predisposes offspring to eczema-like inflammation after birth. Why would such a harmful program exist? In this session we will provide new insights into the developmental origins of allergic diseases.

Keywords: neuroimmunology - stress - mast cell.

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Autoreactive T Cell immunity in inflammatory peripheral neuropathies

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Understanding the immune mechanisms underlying neurological disorders remains a major challenge. Our research integrates *in vitro* T cell screening, single-cell cloning, T cell receptor sequencing, and computational approaches to identify and characterize autoreactive T cells in patients with disorders affecting the central and peripheral nervous systems. This talk will highlight our recent findings on autoreactive T cell immunity in inflammatory demyelinating neuropathies, with a particular focus on Guillain–Barré syndrome and will explore emerging evidence that cross-reactive T cell immunity may provide a mechanistic link between preceding microbial infections and disease onset.

Keywords: autoimmunity.

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P1-01

Neural pathways mediating the gut-lung axis

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Acute respiratory infections, such as Influenza, are highly prevalent in humans, often presenting with a classical 'flu-like' syndrome. However, up to one-third of patients also experience gastrointestinal symptoms like nausea, vomiting, and diarrhoea, which can persist for months post-infection. Despite their clinical significance, the mechanisms underlying gut comorbidity in acute respiratory infections remain elusive. We investigated the hypothesis that airway inflammation triggers neural changes that influence the activity of the enteric nervous system resulting in alterations in gastrointestinal function.

CANCELED

Using viral tracers in mice, we identified a previously unrecognised sensory neural pathway linking the enteric nervous system to the lung mucosa. We demonstrated that this pathway is recruited during respiratory infection, resulting in enteric neuron activation and increased gut motility. Furthermore, through chemogenetic manipulation and immunophenotyping, we revealed that this neural circuit is essential for regulating the pulmonary immune response to infection.

Our findings reveal a novel gut-lung neural circuit that coordinates gastrointestinal and pulmonary responses during respiratory infection. This work highlights a previously underappreciated role for enteric neurons in interorgan communication and immune regulation.

Keywords: Gut-lung axis - Interorgan communication - Neuroimmune interactions.

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P1-02

Splenic nerve stimulation protects against murine experimental autoimmune encephalomyelitis via B cell beta2-adrenergic licensing of Tregs

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Objectives
Vagus nerve (VN) electrostimulation exerts immunomodulatory effects in animal models and clinical trials. However, VN stimulation influences multiple organ systems. Since the splenic nerve (SpN) plays a key role in neuro-immune signaling, we investigated the therapeutic potential and mechanisms of direct arterial splenic nerve stimulation (SpNS) in an experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis, both as a standalone treatment and in combination with fingolimod.
Methods
SpNS was evaluated in wild-type (WT) and B cell-specific beta2-adrenergic receptor knockout (CD19-Cre Adrb2-fl/fl) C57BL/6 mice with EAE, administered at varying frequencies before or after disease onset. Spinal cord demyelination, immune infiltration, and Th1/Th17/Treg responses were quantified. Adoptive transfers of purified B cells or Tregs from SpNS-treated WT or CD19-Cre Adrb2-fl/fl EAE donors into EAE recipients were performed. Additionally, SpNS was compared and combined with daily fingolimod treatment.
Results
Preclinical SpNS treatment reduced EAE severity in a frequency-dependent manner, delayed disease onset, and decreased spinal cord infiltration and demyelination. SpNS inhibited IFN-gamma and IL-17 production by autoreactive Th1 and Th17 cells while enhancing regulatory T cell (Treg) suppressive function and CTLA-4 expression. Crucially, the protective effect of SpNS was completely abolished in CD19-Cre Adrb2-fl/fl mice. Adoptive transfer of B cells or Tregs from SpNS-treated WT EAE mice significantly reduced EAE severity in recipient mice, whereas transfer of B cells or Tregs from SpNS-treated CD19-Cre Adrb2-fl/fl donors failed to confer protection. In established disease, post-onset SpNS halted disease progression with efficacy comparable to fingolimod. Importantly, combining SpNS with fingolimod enhanced the therapeutic efficacy of this drug.
Conclusion
These findings demonstrate that SpNS exerts potent disease-modifying effects in EAE through B cell beta2-adrenergic receptor–dependent licensing of regulatory T cells, positioning SpNS as a promising therapeutic approach for multiple sclerosis.

Keywords: Electrostimulation - EAE - Treg.

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P1-03

Cancer-related pain is masked by enkephalins-producing regulatory T cells in mice

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Objective

Cancer-related pains are a major issue for patients. Pain seriously affects patients' quality of life, causing fatigue, sleep disturbances, anxiety, and social isolation. However, the absence of pain during tumor development can also have dramatic consequences. The early stages of cancer development are rarely painful, which can delay diagnosis, sometimes fatally. Understanding how these pains are masked is a major public health issue. In our previous work, we demonstrated that regulatory T cells (Treg), which are known for their immunosuppressive function, also have analgesic properties through their production of enkephalins (opioid peptides). Since Treg are recruited early in tumor development, we hypothesize that Treg-derived enkephalins mask the pain induced by tumor growth.

Methods

To test this hypothesis, we first examined the analgesic power of Treg during cancer development by depleting Treg with PC61 (an anti-CD25 antibody) and tumor grafts in mice. Next, we examined the production of enkephalins by tumor-infiltrating Treg, as well as the signals responsible for this production. Third, we investigated the direct effect of Treg-derived enkephalins on pain induced by tumor development. We used a transgenic mouse model in which only Treg lack the *Proenkephalin* (*Penk*) gene, the precursor of enkephalins. We then grafted tumors onto these mice and assessed their mechanical sensitivity. For this experiment and the Treg depletion experiment, the test used to assess sensitivity is the vonFrey test.

Results

First, we demonstrated that Treg-depleted mice are more sensitive than control mice, thus validating the initial portion of our hypothesis. Treg mask pain induced by tumor development. Next, we showed *Penk* expression in tumor-infiltrating Tregs using flow-FISH (fluorescent in situ hybridization) and that an *in vitro* treatment of sorted Treg with a 4-1BB agonist enhances *Penk* expression by Treg. Finally, we observed that mice with *Penk*-deleted Treg were more sensitive than control mice, thus validating the second part of our hypothesis that tumor-infiltrating Treg mask cancer-related pain through their production of enkephalins.

Conclusion

Together, these results highlight a novel mechanism by which tumors use our immune system to evade detection. We demonstrated that the Treg-produced enkephalins give them analgesic power within the developing tumor. By recruiting Treg, tumors can inhibit the immune response and mask pain.

Keywords: Neuroimmunology - Treg - Pain.

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Title upcoming

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Crypt Engulfment as a Novel Antigen Sampling Mechanism in the Colon

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Lymphoid cells form aggregates all along the intestine. While Immune cells maintain intestinal homeostasis by promoting tolerance to food antigens and IgA-mediated control of the microbiota, processes that require access to luminal antigens. In small-intestinal Peyer's patches, luminal antigens are sampled by phagocytes or transported across the epithelium by M cells. How this occurs in the colon remains unclear, as colonic lymphoid structures (LS) are separated from the lumen by M-cell-devoid crypts and protective mucus layers. Here, I will present colonic crypt engulfment as a novel mechanism enabling luminal antigen sampling within colonic LS.

Keywords: Phagocytes - Lymphoid structures - Colon.

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VSIG4 licenses resident synovial macrophages to restrain inflammatory arthritis

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Objective
Synovial macrophages comprise distinct resident and recruited populations whose respective functions during arthritis remain incompletely understood. We investigated the fate and transcriptional adaptation of resident synovial macrophages during inflammation and explored the functional role of VSIG4, an immunoregulatory receptor enriched in resident macrophages.
Methods
Resident synovial macrophages were fate-mapped using *Cx3cr1-CreERT2;R26-tdTomato mice*and analysed by flow cytometry and single-cell RNA sequencing at steady state and during K/BxN serum-transfer arthritis. The contribution of VSIG4 was assessed in wild-type and *Vsig4*-deficient mice by clinical, histological and flow-cytometric analyses. Synovial macrophages were further analysed by bulk RNA sequencing. Macrophage-intrinsic effects of VSIG4 were investigated in bone marrow-derived macrophages, including re-expression of VSIG4 in *Vsig4*-deficient cells by mRNA delivery.
Results
Arthritis induced a marked expansion of recruited tdTomato−macrophages, whereas fate-mapped resident macrophages persisted throughout inflammation and displayed remarkable transcriptional stability. Resident macrophages were characterized by a regulatory/homeostatic program including high *Vsig4* expression. VSIG4 deficiency did not substantially alter lining or sublining macrophage abundance but resulted in increased arthritis severity and tissue inflammation. Transcriptomic profiling of *Vsig4*-deficient macrophages revealed enhanced inflammatory, cytokine and chemotactic programs, notably related to neutrophil recruitment. Consistently, restoration of VSIG4 in deficient macrophages reduced inflammatory mediator production, while reinforcing their regulatory phenotype, demonstrating a cell-intrinsic role in shaping macrophage function.
Conclusion: Despite extensive inflammatory cell recruitment, resident synovial macrophages preserve a stable regulatory identity during arthritis. We have identified VSIG4 as a key component of this protective macrophage program, intrinsically restraining inflammatory and chemotactic responses and thereby limiting joint inflammation.

Keywords: Tissue resident macrophages - VSIG4 - Joint inflammation.

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Macrophage NOTCH1 signaling in pancreatic cancer: immune and stromal remodeling

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Objective
Pancreatic ductal adenocarcinoma (PDAC) develops within a highly immunosuppressive and fibrotic microenvironment in which tumor-associated macrophages (TAMs) promote tumor progression. Although NOTCH signaling regulates macrophage fate and activation, the specific contribution of macrophage NOTCH1 to PDAC immune and stromal organization remains poorly defined. We investigated how macrophage-intrinsic NOTCH1 shapes macrophage functions and the tumor microenvironment.
Methods
NOTCH pathway activity was analyzed in public human PDAC single-cell RNA-sequencing datasets. NOTCH1 function was investigated using bone marrow-derived macrophages from *Notch1fl/fl;Lyz2-Cre* mice through phenotypic profiling, phagocytosis, efferocytosis and antigen-specific T-cell activation assays. Tumor cell–macrophage–pancreatic stellate cell co-cultures assessed stromal remodeling. KPC cells were orthotopically implanted into *Notch1* wild-type, heterozygous and homozygous myeloid-deficient mice. Tumor growth and immune composition were assessed by flow cytometry and single-cell RNA sequencing.
Results
Human PDAC analysis revealed increased HES1 expression in tumors versus adjacent tissue and increased RBPJ expression in the myeloid compartment. NOTCH1-deficient macrophages displayed marked phenotypic remodeling and enhanced phagocytic and efferocytic capacities, while antigen-specific OT-I T-cell activation was preserved. In multicellular PDAC cultures, NOTCH1 loss reduced collagen deposition, supporting a role for macrophage NOTCH1 in tumor–stroma crosstalk. Preliminary *in vivo* data showed reduced tumor burden following myeloid *Notch1* deletion. Flow cytometry revealed increased CD45+ immune-cell representation in homozygous and heterozygous *Notch1*-deficient tumors versus controls. Single-cell RNA sequencing further revealed broad remodeling of the immune-cell composition, with increased CD4+ and CD8+ T-cell representation and a trend toward enrichment of cytotoxic CD8+ T cells in *Notch1*-deficient tumors.
Conclusion
These findings position macrophage NOTCH1 as a regulator of macrophage function and the immune–stromal interface in PDAC. Its loss enhances macrophage clearance functions, limits collagen deposition and reshapes intratumoral immunity, concomitant with improved tumor control *in vivo*.

Keywords: Pancreatic cancer - Tumor-associated macrophages - NOTCH1 signaling.

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Infection-specific regulation of cDC2 poiesis shapes dendritic cell subset responses

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Objective
Conventional dendritic cells (cDCs) are critical regulators of immunity, linking innate sensing to adaptive responses. Among them, type 2 cDCs (cDC2s) comprise two ontogenically distinct subsets, cDC2A and cDC2B, which exhibit non-redundant functions in peripheral tissues. However, how their production is regulated in the bone marrow during inflammation remains poorly understood. Here, we investigated whether haematopoiesis dynamically adapts cDC2 subset output to distinct infectious contexts.
Methods
Using viral (Influenza A virus) and helminth (*Nippostrongylus brasiliensis*) infection models in mice, combined with genetic lineage tracing and single-cell transcriptomics, we tracked and analysed the expansion and developmental programming of cDC2 precursors in the bone marrow during distinct inflammatory states.
Results
We demonstrate that early inflammatory cues selectively shape the expansion and mobilisation of cDC2 precursors in an infection-specific manner. Influenza A virus infection preferentially expands and mobilises LysM$^+$ pre-cDC2B cells via type I interferon–dependent signalling. In contrast, *Nippostrongylus brasiliensis* infection induces the rapid egress of T-bet$^+$ pre-cDC2A cells through IL-4–dependent mechanisms.
Conclusion
These results reveal that the bone marrow functions as an early immune-sensing site that tailors dendritic cell output to the inflammatory context prior to antigen encounter. This immunity-matched regulation of cDC2 ontogeny represents a previously unappreciated layer of immune control with implications for the preconditioning of adaptive responses.

Keywords: Conventional dendritic cells - Inflammation - Bone marrow immune sensing.

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GlycoImmune pathways as determinants of immune variability and disease susceptibility

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Objective
Glycosylation is the enzymatic attachment of glycans to proteins, beginning in the endoplasmic reticulum and maturing in the Golgi, and includes N-glycosylation (asparagine-linked) and O-glycosylation (serine/threonine-linked). Because immunoglobulins, cytokines, chemokines, complement, Toll-like receptors, the T-cell receptor and MHC class I are all glycoproteins, glycan remodelling is an integral layer of immune regulation. Using congenital disorders of glycosylation (CDG) as models of immune dysfunction, we aimed to define glycan-dependent immune mechanisms and identify actionable therapeutic nodes. PMM2-CDG, the most common CDG (approximately 1:20,000), is caused by phosphomannomutase 2 deficiency, i.e. loss of conversion of mannose-6-phosphate to mannose-1-phosphate, the precursor of GDP-mannose, depriving dolichol-linked oligosaccharide assembly of mannose.
Methods
Literature curation of immune manifestations across CDG cohorts, combined with patient-derived skin fibroblasts stimulated with TNF-α (10 ng/mL), RNA sequencing , lectin profiling, membrane proteins and cytokines at 24 h, and molecular analysis of sialic acid biosynthesis defects (GNE myopathy).
Results
Of 203 existing CDG, 23 show immunological involvement and 11 are IUIS-recognised primary immune disorders. In PMM2-CDG, 89 patients had immune manifestations spanning 46 genotypes ; 21.3% died, 11.2% of infections, and about half had at least one infection episode, alongside hypogammaglobulinaemia, T lymphopenia and inflammation-triggered SLE. In patient fibroblasts, TNF-α induced IL-6, CCL5 and CXCL1 in controls ($p = 0.004$, 0.002 and 0.024) but not in patients. N-glycans were reduced , Man8GlcNAc2 accumulated ($p = 0.00042$), and ERK1/2 and p38 phosphorylation failed ($p = 0.006$ and 0.02) with JNK2 near-undetectable, consistent with structural TNFR1 alteration. GNE myopathy cells showed upregulated MHC class I, consistent with sialic acid dependence, and altered immune modulators without overt immune disease.
Conclusion
Glycosylation behaves as a rheostat of immune competence: its disruption destabilises receptors and MAPK signalling, driving infection susceptibility and, potentially, and defines glycan-based biomarkers and therapeutic targets.

Keywords: Glycans - TNF-Receptor - MHC-I.

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Inborn errors of immunity predisposing to severe Epstein Barr infection diseases

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Abstract not received.

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Architecture of actin networks at the T-cell synapse: impact of genetic variants in *ACTB* and *ACTG1*

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Objective
Actin remodeling is essential for immune cell dynamics, particularly during immunological synapse (IS) assembly, T-cell receptor (TCR) signal transduction, and polarized cytolytic delivery. Disruptions in these processes lead to inborn errors of immunity (IEIs), underscoring how subtle actin perturbations impair coordinated immune responses. While mutations in actin regulators cause severe immunodeficiencies, mutations within core cytoplasmic actin isoforms (*ACTB* and *ACTG1*) have historically been classified under syndromic and neurodevelopmental headings, such as Baraitser-Winter syndrome. Consequently, their cell-intrinsic immunological consequences remain largely uncharacterized. Moving beyond single-case reports, this project systematically characterizes the multilineage function and morphology of eight *ACTB* and *ACTG1* patient variants to decipher their synaptic and mechanical defects.
Methods
Primary PBMCs from patients are analyzed using a multi-scale functional and morphological pipeline. Immune phenotypes and cellular fitness are evaluated via flow cytometry, proliferation kinetics, cytokine profiling, and cytotoxicity assays. The synaptic architecture is mapped using automated microscopy and 3D cell conjugate analysis. Variants associated with a T cell phenotype will ultimately feed into the workflows of our collaborators for CryoET and *in vitro* biomimetic assays.
Results
Flow cytometry revealed a heterogeneous immune landscape, with lineage-specific perturbations primarily targeting T helper subsets. Remarkably, total cellular F-actin intensity was preserved across all eight variants, demonstrating that actin abundance and global polymerization remain intact. Upon TCR stimulation, patient cells displayed diverse functional outputs, ranging from impaired activation to elevated baseline cytokine secretion. Automated imaging identified synaptic defects in two out of the eight variants, which did not strictly correlate with systemic immunophenotypic abnormalities, uncovering an unexpected disconnect between *in vitro* synaptic architecture and peripheral immune phenotypes.
Conclusion
These findings challenge the hypothesis of a uniform synaptic failure across *ACTB* and *ACTG1* IEIs. With the total F-actin content preserved, immune dysfunction likely arises from discrete perturbations in regulator binding interfaces or non-synaptic dynamics, establishing each mutation as an individualized molecular entity requiring tailored biophysical dissection.

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Paradoxical Type I Interferon Activation in RELA Haploinsufficiency

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Objective
RELA (p65), a core component of canonical NF-κB signaling, controls transcriptional programs governing inflammation, cell survival, and immune homeostasis. Heterozygous RELA deficiency is an emerging monogenic immune disorder with marked clinical heterogeneity, ranging from autoinflammatory manifestations to severe early-onset systemic lupus erythematosus. Strikingly, patients in our cohort (n>30) display increased interferon-stimulated gene (ISG) and pro-inflammatory signatures despite impaired canonical NF-κB signaling. We investigated whether RELA loss of function directly promotes type I interferon responses or whether enhanced TNF-induced cell death contributes indirectly to ISG elevation.
Methods
CRISPR-Cas9 knock-in RELA loss-of-function models were generated in THP-1 monocytes and CAL-1 pDC-like cells. In THP-1 cells, we assessed basal and stimulated IFNB1/ISG expression, TNF- and LPS-induced NF-κB target genes, apoptosis, and cell-free DNA release. CAL-1 cells were used to examine nucleic-acid sensing pathways, including TLR7/8/9 and STING, with p-IRF7 activation and ISG induction used to validate pDC-like responses.
Results
RELA-deficient THP-1 and CAL-1 cells showed no spontaneous increase in ISG expression at baseline, arguing against constitutive cell-autonomous interferon activation. In contrast, RELA-deficient cells displayed impaired induction of NF-κB target genes after TNF or LPS stimulation and increased apoptosis compared with wild-type controls. CAL-1 cells showed robust p-IRF7 activation and ISG induction after TLR7 stimulation, establishing a suitable model to test whether extracellular or intracellular nucleic acids released during cell death amplify type I interferon responses.
Conclusion
Our data support a model in which RELA deficiency does not intrinsically activate the interferon program at rest, but instead weakens NF-κB-dependent survival responses, increasing susceptibility to inflammatory cell death and nucleic-acid release. These danger signals may then engage innate nucleic-acid sensors and promote aberrant type I interferon production, creating a self-sustaining cell death–interferon loop. This mechanism may help explain the paradoxical coexistence of defective NF-κB signaling and elevated ISG signatures in RELA-associated disease and suggests that targeting the cell death–interferon axis could represent a rational therapeutic strategy.

Keywords: NF-κB - ISGs - Monogenic autoimmunity.

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Title upcoming

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Abstract not received.

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Development of therapeutic vaccines for the treatment of allergic diseases

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Monoclonal antibodies (mAbs) have revolutionized the management of chronic inflammatory diseases. However, one limitation of mAbs is the need for frequent reinjection to maintain clinical efficacy. To bypass this limitation, we assessed whether vaccine strategies could be used to induce long-term endogenous production of neutralizing antibodies. We developed conjugate vaccines against IL-4, IL-13 or IgE, three clinically-validated targets in asthma and other type 2 inflammatory diseases. We showed that these vaccines induce sustained specific B cell responses and neutralizing antibodies without breaking T cell tolerance against these inflammatory targets. IL-4/IL-13 vaccination protects against key features of chronic asthma and atopic dermatitis in humanized mice, while IgE vaccination promotes sustained protection against anaphylaxis, the most dramatic clinical manifestation of allergy. We further demonstrated that this vaccine strategy is well tolerated and induces sustained antibody responses in non-human primates. Our data thus pave the way for the development of long-term therapeutic strategies for the treatment of chronic allergic diseases.

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Improved Immune Responses and Tuberculosis Protection by Aerosol Vaccination with rBCG expressing ESX-1 from *Mycobacterium marinum*

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Introduction

The currently licensed anti-tuberculosis (TB) vaccine, *Mycobacterium bovis* BCG, provides limited protection against pulmonary TB in adolescents and adults, the main cause of TB transmission and mortality. A feature of this attenuated live vaccine strain is the partial deletion of the genomic locus encoding the ESX-1 type VII secretion system.

Objective and Methods

To obtain an improved BCG-based vaccine candidate with increased immune signaling but still low virulence, we have previously generated a recombinant BCG Pasteur strain named BCG::ESX-1^{Mmar}, which is heterologously expressing ESX-1 functions of *M. marinum*, a BSL2 organism, and thereby modulates the host innate immune responses via phagosomal rupture-associated induction of type I interferon and enhanced inflammasome activity, leading to superior protection against TB in standard murine infection models.

Results

As protection may also vary with the route of vaccination, here, we have explored aerosol vaccination relative to subcutaneous vaccination, using BCG Pasteur and BCG::ESX-1^{Mmar}. We found that mice vaccinated via the aerosol route with BCG or BCG::ESX-1^{Mmar} both yielded higher frequencies of CD4$^+$ and CD8$^+$ T activated effectors and effector memory cells in the lungs compared to subcutaneously immunised mice, whereas comparable polyfunctional Th1 cytokine-producing subsets were observed in the spleens of all vaccinated mice. Moreover, significantly higher IL-17A responses were induced in the airways of aerosol vaccinated mice associated with transient local inflammatory cytokine responses but without severe lung pathology or any clinical symptoms. In contrast to the subcutaneous route, aerosol vaccination elicited high amounts of humoral IgG and IgA responses and triggered substantial lung CD4$^+$ and CD8$^+$ T cells expressing CD69$^+$ CD103$^+$ tissue-residency markers.

Finally, we show that vaccination of mice with BCG or BCG::ESX-1^{Mmar} via the aerosol route leads to significant improved TB protection and lower lung histopathology compared to subcutaneous vaccination, as judged by mycobacterial loads and tissue score evaluations at one month post virulent *M. tuberculosis* infection.

Conclusion

The live-attenuated BCG::ESX-1^{Mmar} vaccine induced enhanced T-cell immunity and superior TB protection when mice were vaccinated via aerosol or subcutaneous route compared to parental BCG and thereby represents an interesting candidate for defining new promising strategies of vaccination against TB.

Keywords: Tuberculosis - BCG - TB Vaccine.

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Development of an mRNA vaccine encoding the major allergen Bet v 1 to treat birch pollen allergy

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Objectives
Birch pollen is a major seasonal trigger of asthma and allergic rhinitis affecting over 100 million people worldwide. These diseases are characterized by IgE-driven mast cell activation, eosinophilia and impaired respiratory function. Current therapies are symptomatic, and allergen specific immunotherapy (AIT) remains the only treatment able to change the course of the disease. AIT reduces Th2 responses and induces neutralizing allergen-specific IgG. However, AIT is still limited by many side effects and patients rapidly regain allergic symptoms upon cessation of the treatment. We propose a novel mRNA-based vaccine approach to induce long-term protective immunity for the treatment of birch pollen allergy.
Methods
Mice were immunized intramuscularly with mRNA encoding a polyA sequence as control or the major birch pollen allergen Bet v 1 encapsulated in lipid nanoparticles (mRNA-LNPs). Vaccine candidates were optimized and compared based on their humoral and cellular immune responses to select the lead formulation. Antibody responses were measured by ELISA, and their neutralizing capacity was assessed using a human mast cell degranulation assay with plasma from birch-sensitized subjects. Vaccine efficacy was further evaluated in a birch pollen asthma model in Th2-biased mice (IL-4RaF709 mice).
Results
Immunization with Bet v 1 mRNA-LNP induced sustained cellular and humoral responses, notably characterized by induction of Bet v 1-specific IgG responses. These antibodies prevented degranulation of mast cells triggered by IgE from birch pollen-allergic subjects. Prophylactic vaccination reduced allergen-specific IgE and eosinophilia and promoted a shift from a Th2-dominated response toward a Th1 response in the lungs in a birch pollen-induced asthma model.
Conclusion
Bet v 1 mRNA vaccination induces sustained neutralizing antibodies capable of competing with IgE and reducing allergic inflammation. These findings suggest that this mRNA-based vaccine could represent a promising strategy for the long-term treatment of birch pollen allergy.

Keywords: mRNA vaccine - Alergic rhinitis and asthma - Birch allergy.

A novel cystic fibrosis-mimetic Pseudomonas auxotrophic vaccine is protective *in vivo* and is associated with Th17 and IgA mucosal immunity

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Objectives

Pseudomonas aeruginosa (P.a) is a Gram-negative opportunistic pathogen that poses a major global health threat, particularly in immunocompromised individuals, patients with cystic fibrosis, and those with burn injuries or ventilator-associated pneumonia. Despite intense efforts, no vaccine is available for human use. In this context, live attenuated vaccines represent a promising but underexplored approach, offering the potential to elicit robust, long-lasting, and multifaceted immune responses including inducing trained immunity.

Methods

Here, our rationale was to develop, for the first time to our knowledge, an auxotrophic P.a strain phenotypically as close as possible to clinical strains present in sputa secretions from patients with CF (pwCF), with reduced virulence while being robustly immunogenic. To that aim, we developed a live auxotrophic P.a vaccine ('V') by sub-culturing a genetically-modified P.a (*ΔLasB*-PAO1, (a P.a strain we have previously shown to have reduced virulence) in artificial sputum medium (ASM), a culture medium mimicking CF sputum.

Results and Discussion

We show (1) by RNA seq and whole genome sequencing that 'V' up-regulated pathways involved in energy metabolism, redox reaction, cofactor biosynthesis, biosynthetic precursors, stress response and virulence regulation in bacteria, closely mirroring the nutrient-restricted and redox-challenged environment of cystic fibrosis, by shifting metabolic resources from virulence toward a persistence mode of community behavior and survival. Furthermore, we showed that this vaccine was indeed auxotrophic, less virulent, had characteristics of 'small colony' CF-like strain, and had the ability to secrete high amounts of filamentous phages (mainly Pf4). Crucially, 'V' induced *in vivo* in mice both local (IgA) and systemic humoral responses as well as memory Th17 immune responses, and could, when administered in the lung, but not intra-muscularly, fully protect mice against a lethal PAO1-WT infection. Overall, the present study demonstrates that our vaccine formulation, in addition to providing an advantageous auxotrophic phenotype adapted to the CF setting, was efficient, when given mucosally, in preferentially inducing secretory IgA and Th17 pathway at mucosal surfaces, a critical barrier that neutralizes pathogens before tissue invasion.

Keywords: Vaccine - Auxotrophic - Pseudomonas aeruginosa.

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Metabolic sensors in NK cells: can we move from basic discoveries to clinical applications?

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Natural Killer (NK) cells are innate lymphoid cells displaying strong cytotoxic and cytokine secretion capacities endowing them with antitumoural and antiviral functions. The importance of metabolic pathways in regulating immune cells including NK cells is now well established, and the mapping of the bioenergetic metabolism of different immune cell types is under way. To ensure a coordination between nutrients availability, their use in metabolic pathways and the cellular state, a number of metabolic sensors have been selected during evolution. Interestingly, these sensors have been coopted by immune receptors to connect the metabolic cues to the immune state and vice-versa. In this context, we studied the role of the metabolic checkpoint kinase mTOR during NK cell development and activation using mouse models. We showed that this kinase integrates various classes of signals, metabolic and immunologic, to control NK cell development and effector potential. Importantly, we show a bidirectional relationship between NK cell receptors and mTOR activity. This fundamental observation led to clinical studies measuring the impact of mTOR inhibition on NK cell biology in different pathological contexts. We currently investigate the role of other metabolic sensors and the possible application of this knowledge to clinical situations.

Keywords: mTOR - Metabolism - Natural Killer cells.

Immunometabolism, from diagnosis to treatment: Applications to long COVID and autism spectrum disorders

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Immune cell functions depend on their metabolic program and bioenergectics signature that shapes their activation, proliferation, differentiation and polarization. Energy production by cell metabolism mainly involves the mitochondria, which use oxidative phosphorylation or cytosolic glycolysis and is commonly accompanied by the generation of metabolites essential for signaling and cellular function. Dysregulation of metabolic pathways can alter the function of immune cells, creating disruption of immune homeostasis, defect immune response during infection, development of auto-immune diseases or chronic inflammation/neuroinflammation.
Immunometabolic defects can affect immune cells, but also several organs, notably the brain and its functioning; this is why our team has focused on studying immunometabolic dysregulation in a number of conditions, with a view to developing diagnostic biomarkers, as well as understanding the associated pathophysiological mechanisms and proposing targeted therapies based on immunometabolic modulation; One of the conditions studied is Long COVID, a highly complex persistent post-infectious syndrome that can affect several organs, characterised by extreme fatigue, metabolic, immune and neurocognitive impairments affecting several million people of all ages worldwide; however, our team has also focused on neurodevelopmental disorders such as autism, in which immune and metabolic defects have also been described.
Through studies conducted on cohorts of patients with Long COVID or children with autism, we have discovered common pathological mechanisms that place the mitochondria and the bioenergetics at the heart of these defects, with an impact on the functioning of immune cells and the brain. Through these studies, we have identified immunometabolic biomarkers for diagnosis and severity stratification, as well as new targeted therapies for effective precision medicine for patients.

Keywords: Immunometabolism - Mitochondria - Biomarkers.

The TGF-β paradox in NK cells: from immune suppression to context-dependent functional reprogramming

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Natural killer (NK) cells play a central role in antiviral and antitumor immunity. Their responses are shaped by cytokine signals that coordinate metabolic activity, proliferation, and effector functions. Although transforming growth factor-β (TGF-β) is predominantly viewed as a suppressor of NK-cell responses, its contribution to tissue-resident differentiation raises the possibility that its effects depend on the cellular and experimental context. Here, we explore these contrasting roles, from the inhibition of cytokine-driven activation to the ex vivo generation of NK cells with tissue-resident properties.

In the first part, we examine the interplay between TGF-β signaling and the mTOR pathway, a key regulator of IL-15-driven NK-cell activation. Using complementary mouse models with constitutive activation of TGF-β signaling or conditional deletion of TGF-β receptor II in NK cells, together with cytokine stimulation experiments, we investigate how TGF-β restrains metabolic activation and effector responses. These findings highlight the antagonism between TGF-β and IL-15–mTOR signaling and its implications for NK-cell-mediated tumor control.

In the second part, we investigate whether TGF-β can instead be harnessed during ex vivo culture to generate NK cells with properties relevant to adoptive cell therapy. NK cells cultured with IL-2 and TGF-β acquired a tissue-resident-like phenotype, as assessed by flow cytometry. Their cytotoxic activity varied according to the tumor cell line tested, whereas cytokine production was maintained relative to NK cells cultured with IL-2 alone. Seahorse analysis revealed increased extracellular acidification and oxygen consumption rates, indicating enhanced metabolic activity. Moreover, TGF-β-conditioned NK cells exhibited greater in vitro expansion, associated with enrichment of anti-apoptotic pathways identified by proteomic analysis.

Together, these findings support a context-dependent view of TGF-β action in NK cells. Beyond its established inhibitory effects, TGF-β can promote a tissue-resident-like program compatible with maintained cytokine production and enhanced expansion under defined ex vivo culture conditions. This duality provides a framework for investigating how TGF-β signaling might be modulated or harnessed in NK-cell-based immunotherapy.

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Resident lymphocytes preserve functional integrity of the lactating mammary niche

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Abstract not received.

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A Polyfunctional IL-33-Responsive ST2⁺NK Cell State Promotes Antitumor Immunity and Response to Immunotherapy

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Background
Natural killer (NK) cells are key effectors of cancer immunosurveillance, yet the functional diversity of NK-cell states within tumors remains incompletely understood. We investigated the role of the IL-33/ST2 axis in NK-cell biology and antitumor immunity.
Methods
Human NK cells were analyzed using multiparametric flow cytometry, bulk and single-cell RNA sequencing, functional assays, and public cancer datasets. Findings were validated in mouse tumor models and breast cancer patient samples.
Results
IL-33 strongly activated human NK cells only in the presence of IL-12, leading to enhanced IFN-γ production, proliferation, cytokine secretion, and cytotoxicity. We identified a previously unrecognized IL-33-responsive ST2⁺ NK-cell state generated through IL-12/STAT4-dependent induction of the IL-33 receptor ST2. Transcriptomic analyses revealed that ST2⁺NK cells represent an intermediate differentiation state between CD56bright and CD56dim NK cells. These cells combined high proliferative and metabolic fitness with potent effector functions, resulting in marked polyfunctionality. ST2⁺NK cells were enriched within immature CD56dim NK cells and displayed enhanced responsiveness to IL-33. Public single-cell datasets identified ST2⁺NK cells across multiple human and murine tumor types. In orthotopic breast cancer models, combined IL-12 and IL-33 treatment induced potent antitumor activity associated with increased IFN-γ production, reduced tumor growth, and prolonged survival. Therapeutic efficacy required both NK cells and intrinsic ST2 signaling. In breast cancer patients, ST2⁺NK cells were detected in blood and tumors and remained responsive to IL-12 and IL-33 ex vivo. Furthermore, an NKhigh_IL33high signature was associated with improved clinical outcome across several solid tumors, while ST2⁺NK cells were enriched in patients responding to anti-PD-1 therapy.
Conclusions
We identify ST2⁺ NK cells as a previously unrecognized polyfunctional NK-cell state induced by IL-12 and licensed to respond to IL-33. These cells mediate potent antitumor immunity, correlate with favorable clinical outcome, and associate with response to immune checkpoint blockade. Our findings establish the IL-33/ST2/NK-cell axis as a clinically relevant regulator of cancer immunity and a promising target for NK-cell-based immunotherapies.

Keywords: NK cells - Antitumor immunity - Cancer immunotherapy.

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IL-23 drives a pro-inflammatory state in human group 3 innate lymphoid cells (ILC3)

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IL-23 receptor (IL-23R) polymorphisms are associated with chronic inflammatory diseases (CID), including inflammatory bowel disease (IBD), psoriasis and peripheral spondyloarthritis (pSpA). In parallel, evidence from *Il23/Il23r*-deficient mice uncovered the importance of IL-23 in the pathogenesis of experimental models of CID. These findings led to the development of IL-23 blockers.
Recent data suggest the involvement of innate lymphoid cells (ILC) in CID. IL-23R-responsive IL-17-producing ILC accumulate in the intestinal mucosa of patients with IBD. Similarly, NKp44+ ILC3 are increased in lesional skin from psoriatic patients and may arise from IL-23-exposed NKp44- ILC3.
Consistently, we found that NKp44+ ILC3 are approximately 10-fold enriched in synovial fluid from pSpA patients relative to their paired peripheral blood and express high levels of IL-23R.
Nevertheless, the mechanisms underlying the IL-23-induced pathogenic program in humans remain poorly understood. Here, we explored the functional effects of IL-23 signalling in ILC within a human tissue context.
In tonsils, ILC3 displayed the highest frequency of IL-23R-positive cells,followed by Mucosal-Associated Invariant T (MAIT) cells. IL-23R expression varied substantially across ILC3 subsets, with the CD7-NKp44+ ILC3 containing the highest IL-23R frequency.
We next compared the effects of IL-23 signalling in tonsillar ILC3 and MAIT. Bulk transcriptomic analysis revealed that IL-23 significantly regulated 811 genes in ILC3 but only 64 genes in MAIT cells, indicating a markedly stronger responsiveness of ILC3.
Among IL-23-regulated genes in ILC3, we identified a Th17-associated signature (*IL17F*, *IL22*) and pro-inflammatory and cytotoxic mediators (*RELB*, *IFNG* and *GZMB*). Notably, transcript levels of these genes positively correlated with the abundance of NKp44+ ILC3 across donors.
Together, our data suggest that NKp44+ defines a major IL-23-responsive human ILC3 population that may contribute to CID pathogenesis.
Ongoing experiments will address transcriptional and epigenetic differences between NKp44- and NKp44+ ILC3 at steady state and in response to IL-23 stimulation.

Keywords: IL-23 receptor - Group 3 innate lymphoid cells - Peripheral spondyloarthritis.

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CXCR3 signaling promotes Delta One T cell recruitment and antitumor efficacy in colorectal cancer

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Immunotherapy has transformed cancer treatment, yet its efficacy in solid tumors, and particularly in colorectal cancer (CRC), remains limited by insufficient infiltration of endogenous or adoptively transferred immune cells. Our group developed Delta One T (DOT) cells, an allogeneic Vδ1-enriched γδ T-cell product with demonstrated efficacy in CRC models, but the critical mechanisms guiding their tumor homing are unclear. Here we show that DOT cells acquire a specific chemokine receptor profile during expansion to support tumor infiltration, characterized by prominent CXCR3 expression. Importantly, CXCR3 ligands (CXCL9–11) are expressed by CRC cell lines and primary tumors, and correlate with Vδ1 T-cell infiltration and DOT-cell recruitment. CXCR3 signaling is critical for DOT-cell migration *in vitro* and *in vivo*, as pharmacologic blockade reduced tumor homing, whereas enhancing CXCR3 ligand expression increased DOT-cell infiltration and improved tumor control. These findings establish CXCR3 signaling as a key regulator of DOT-cell trafficking and a prime target to boost γδ T cell-based immunotherapies for CRC.

Keywords: Gamma-delta T cells - Immunotherapy - Colorectal cancer.

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Macrophage immunometabolism: shaping pathogen persistence and host protection

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Objective
Metabolic reprogramming is a fundamental feature of macrophage responses to infection, influencing antimicrobial functions, immune cell interactions, and pathogen persistence. However, how distinct metabolic pathways contribute to protective immunity and whether they can be therapeutically manipulated remain incompletely understood. Using *Leishmania* infection as a model, we investigated how macrophage immunometabolism shapes host–pathogen interactions and infection outcomes.
Methods
We combined metabolomic profiling and functional metabolic analyses of infected macrophages with experimental models of leishmaniasis. The contribution of energy metabolism and lipid homeostasis was investigated through metabolic interventions, assessment of intracellular parasite survival, and evaluation of macrophage-mediated T-cell responses. In vivo studies further examined the effects of dietary lipid enrichment, pharmacological inhibition of cytosolic phospholipase A2 (cPLA2), and hormonal manipulation on infection outcomes.
Results
Leishmania infection induced dynamic metabolic adaptations in macrophages, involving pathways associated with energy production and nutrient utilization. Functional studies highlighted the importance of metabolic regulation in determining intracellular parasite survival. Beyond energy metabolism, lipid accumulation increased macrophage susceptibility to infection and impaired antigen-specific CD4+ T-cell activation. Dietary lipid enrichment further influenced disease susceptibility and treatment efficacy. More recently, we identified cPLA2-dependent lipid remodeling as a potential therapeutic vulnerability, with pharmacological inhibition producing sex-dependent reductions in parasite burden. These effects were associated with hormonal status, alterations in myeloid lipid metabolism, and increased lipid peroxidation.
Conclusion
Macrophage immunometabolism is a critical regulator of host–pathogen interactions, extending beyond intracellular antimicrobial mechanisms to influence adaptive immune responses and therapeutic efficacy. Understanding how metabolic pathways are regulated by infection and host-specific factors may reveal new opportunities for host-directed interventions against intracellular pathogens.

Keywords: Macrophage immunometabolism - Host–pathogen interactions - Metabolic reprogramming.

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Eomes drives an exhausted T helper cell lineage essential for tumor control and response to immunotherapy

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Recent studies highlight the importance of $CD4^+$ T helper (Th) cells in tumor immunity, yet the subsets and differentiation programs involved remain unclear. Here, we show that the transcription factor Eomesodermin (Eomes) is essential for Th–mediated anti-tumor immunity by orchestrating the differentiation and maintenance of an exhausted Th cell lineage, which is transcriptionally and functionally distinct from conventional effector or memory Th subsets. This Eomes-dependent program is further enhanced by 4-1BB stimulation, promoting effective Th cell–mediated tumor control. The precursor subset of this lineage (pTh) expresses stemness-associated transcription factors, displays self-renewal capacity, and can differentiate into effector cells capable of controlling tumor growth. At the transcriptional level, Eomes supports the survival, metabolic fitness, and apoptotic resistance of this lineage. Notably, $Eomes^+$ pTh cells are directly relevant to human cancer**,** being detected across multiple tumor types, exhibiting conserved transcriptional features, and representing the most expanded Th cell population upon immune checkpoint blockade therapy.

Keywords: Eomes - Th cells - Tumor immunity.

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Mitochondrial translation is a critical regulator of CD8 T-cell homeostasis and effector responses

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**Contributed equally to the work*

Cytotoxic CD8 T-cells (T-CD8) ensure their anti-viral function and memory potential through metabolic changes that involve a tight coordination between mitochondrial respiration (also known as “OXPHOS”) and glycolysis. While naïve and memory T-CD8 mainly rely on OXPHOS as a source of energy, antigen-driven activation induces a strong increase in glycolysis, although OXPHOS remains essential during effector phase. At the molecular level, proteins of the OXPHOS complex have a double origin: while most subunits are nuclear-encoded and translated by cytosolic ribosomes, 13 proteins are exclusively encoded by the mitochondrial genome and translated by the mitoribosome, a specific translation machinery within mitochondria. In the context of this dual origin and the sustained importance of OXPHOS during effector functions, our results show that both mitochondrial and cytosolic translation are globally stimulated upon T-CD8 activation.
Using transgenic mouse models in which mitochondrial translation is specifically impaired in peripheral, mature T-CD8 (KO T-CD8), we characterized the contribution and regulation of mitochondrial translation during cytotoxic T cell responses. In naïve animals, KO T-CD8 maintain mitochondrial genome copy number and display only limited mitochondrial morphological abnormalities. However, disruption of mitochondrial translation profoundly impacts the T-CD8 compartment, with a substantial loss of naïve T-CD8 in animals older than 6 weeks. Interestingly, proteome analysis of naïve KO T-CD8 shows differential remodeling of individual OXPHOS complexes, accompanied by increased abundance of proteins involved in lipid metabolism, the TCA cycle, and amino acid metabolism. Strikingly, mitochondrial translation deficiency also triggers the accumulation of cytosolic-encoded proteins involved in mitochondrial translation (mitoribosome), suggesting the existence of a feedback mechanism to sustain mitochondrial protein synthesis and some level of coordination between the two translational machineries. However, while those compensatory mechanisms probably allow short-term maintenance of a naïve T-CD8 compartment, activation, proliferation and effector function of KO T-CD8 are greatly compromised both *in vitro,* upon antigen stimulation, and *in vivo,* following lung viral infection.
Together, our findings identify mitochondrial translation as a critical component of T-CD8 metabolic adaptation and function.

Keywords: CD8 T cells - Mitochondrial translation - OXPHOS.

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CD8 T cells adjust actin remodeling to nutrient availability during migration and synapse assembly

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Actin remodeling is essential to sustain CD8 T cell migration and lytic synapse assembly. In neurons, F-actin dynamics are described as an energy-intensive process requiring 50% of ATP resources. In T cells however, ATP allocation to actin remodeling remains elusive, especially during intense actin remodeling activities. We hypothesized that T cell metabolic activity, dependent on nutrient availability, modulates actin remodeling and related T cell functions.

We modulated human CD8 T cell metabolic activity either through acute inhibition of glycolysis and/or OXPHOS, or through prolonged glucose or glutamine deprivation. We monitored actin architecture in migrating and synapse-forming cells by automated confocal microscopy and developed an analysis pipeline to extract 31 parameters pertaining to F-actin staining intensity, texture and spatial distribution. We then performed live imaging and degranulation assays to assess migration properties and cytotoxic potential, respectively. We also initiated proteomic analysis to explore the impact of nutrient deprivation on actin remodeling pathways.

We first induced acute inhibition of glycolysis and OXHOS and revealed that T cells allocate around a third of their ATP content to sustain actin remodeling during synapse assembly. Interestingly, metabolic inhibition affected both actin polymerization and architecture, revealed by the integration of the 31 extracted parameters. Similar observations were made in glucose or glutamine-deprived CD8 T cells. We then measured the impact of nutrient deprivation on actin-dependent T cell functions. Unexpectedly, glutamine deprivation favored T cell migration. We performed proteomics analysis to explore the molecular mechanisms regulating the observed distinct actin architectures and revealed that glucose deprivation enhanced actin bundling pathways. Based on these results, we analyzed the spatial organization of WASP and its effector Arp2/3 and revealed distinct recruitment at the synapse in glucose or glutamine-deprived cells, providing evidence that nutrient restriction shapes actin remodeling by regulating the expression and localization of actin regulators.

This work provides evidence that a significant amount of energy is allocated to actin remodeling dynamics. More than quantitatively affecting F-actin polymerization, acute metabolic inhibition or prolonged nutrient restriction affects F-actin architecture by modulating the expression and/or recruitment of actin regulators.

Keywords: CD8 T cells - Actin remodeling - Nutrient deprivation.

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Lipid Droplets Shield Rectal Cancer from Radiotherapy-Induced Cell Death: A Metabolic–Immune Axis of Resistance

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Objectives
Rectal cancer (RC) remains a significant clinical challenge, where up to 40% of patients fail to respond to radiotherapy (RT).
Methods
To explore the mechanisms underlying this radioresistance, we established an immunospheroid model comprising RC cells (SW837 or SW1463), macrophages, and T lymphocytes and subjected it to the short-course radiotherapy scheme (SCRT, 5 Gy/5 days).
Results
Our data revealed that post-irradiation, T lymphocytes, particularly $CD8^+$ cells, were depleted, accompanied by a significant decrease in CXCL9/10 and CCL5 levels. In contrast, macrophages showed enhanced survival and infiltration, correlating with CCL2 secretion, while RC cells maintained their proliferation status. Additionally, proteomics and metabolomics profiling showed a robust radiotherapy-induced metabolic rewiring, characterised by increased one-carbon metabolism and branched-chain amino acid pathways, suggesting a response to support DNA repair, protein and lipid synthesis. These findings were supported by a significant increase in lipid droplet (LD) accumulation in both RC cells and macrophages, together with increased ATP production and in the number of mitochondria-LD and Golgi-LD contact points, fostering energy transfer. Concomitantly, an increased expression of several antioxidant ferroptosis-evasion markers was observed, suppressing lipid peroxidation levels, leading to stress adaptation rather than cell death. To counteract the RC cell defence pathways, a panel of drugs, specifically targeting LD biogenesis, was used. Our results show that by using sub-lethal drug doses together with RT, a significant increase in cell death in all populations that compose the immunospheroid is observed concomitant with increased levels of lipid peroxidation. Importantly, to validate the clinical relevance of our findings, multiplex analysis was performed on a retrospective cohort of RC patients, comparing biopsies and post-SCRT samples. This analysis revealed treatment-associated shifts in myeloid and lymphoid populations that correlated with patient relapse, aligning with the immune-metabolic alterations observed in our experimental model.
Conclusion
Collectively, our data suggest that RT strongly reshapes the tumour immune microenvironment and metabolic landscape by promoting lipid accumulation and ferroptosis evasion. Targeting these adaptive pathways enhances RT efficacy and represents a promising strategy to overcome radioresistance in rectal cancer.

Keywords: Rectal Cancer - Radioresistance - Lipid Droplets.

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Keeping the Thymus Young: ZFP36 RNA-Binding Proteins Sustain Thymic Epithelial Cell Function to Prevent Thymic Involution and Maintain Tolerance

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The thymus generates immunocompetent T cells, but its function declines with age. Thymic activity relies on proper differentiation of thymic epithelial cells (TECs), which establish unique niches for T-cell development. However, the molecular mechanisms governing the differentiation of functional cortical (c) and medullary (m) TEC subsets from common progenitors remain poorly understood. Through transcriptomic analysis of TEC substs, we became interested in the Zinc Finger Protein 36 (ZFP36) family of RNA-binding proteins (RBPs), which comprises three paralogs: ZFP36/TTP, ZFP36L1, and ZFP36L2. These RBPs bind to AU-rich elements in the 3'-UTR of target mRNAs, regulating their stability and translation and thereby influencing the expression of several key regulatory genes.

Using dual conditional knockout (dcKO) and lineage-tracing mouse models, we demonstrated that RNA-binding proteins ZFP36L1 and ZFP36L2 cooperatively maintain a functional TEC microenvironment. TEC-specific deletion of *Zfp36l1*and *Zfp36l2* in dcKO mouse models led to early-onset thymic hypoplasia and a marked reduction in TEC and thymocyte numbers. Mechanistically, single-cell transcriptomics revealed significant alterations in the composition and transcriptional programs of cTECs, mTECs, and thymic mimetic cells, linking *Zfp36l1* and *Zfp36l2* deficiency to a widespread increase in metabolic gene dysregulation in adult dcKO TECs. The erosion of the TEC compartment and the accumulation of age-associated TECs suggested impaired differentiation of mature lineages from their progenitors. Concordantly, fate-mapping analysis revealed that dual deficiency in *Zfp36l1* and *Zfp36l2* disrupted the canonical developmental trajectory from b5t-expressing TEC progenitors into mature TECs (Cell Death and Differentiation 2026).

Given the high homology among ZFP36 family proteins, we generated TEC-specific triple cKO mice lacking TTP, ZFP36L1, and ZFP36L2, which exhibited an even more severe thymic hypoplasia, severe impairment of T-cell development, and the emergence of autoimmunity (unpublished). We will present further evidence that ZFP36 family members play cooperative yet non-redundant roles in TEC biology. Our findings uncover a previously unappreciated layer of post-transcriptional regulation in TEC biology, identifying a cooperative role for ZFP36 RBPS in orchestrating TEC differentiation to sustain thymic function, prevent premature thymic involution and protect against autoimmunity.

Keywords: Thymus - Tolerance - Thymic Epithelial Cells.

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B Cell Regulation through Nucleic Acid Sensing TLRs

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Abstract not received.

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HuR sustains immunoregulatory B-cell responses to limit neuroinflammation

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B cells protect against neuroinflammation through the production of the anti-inflammatory cytokine IL-10 (Fillatreau et al., 2002; Matsushita et al., 2008). Although RNA-binding proteins (RBPs) tightly control cytokine expression at the post-transcriptional level, how they coordinate the activation and immunoregulatory function of IL-10-producing B cells remains largely unknown.

Objective

Our preliminary findings identified the RNA-binding protein (RBP) HuR as an essential regulator of B-cell immunity. We therefore hypothesized that HuR restrains neuroinflammation by sustaining B-cell activation and immunoregulatory function.

Methods

To address this, we generated mice with a B cell-specific deletion of HuR and evaluated disease progression in experimental autoimmune encephalomyelitis (EAE). Clinical, phenotypic and molecular analyses, including RNA sequencing and iCLIP, were performed to define the intrinsic role of HuR in distinct B-cell subsets.

Results

Conditional deletion of HuR in B cells resulted in a non-remitting EAE phenotype associated with reduced B-cell infiltration into the central nervous system and impaired IL-10 production. Mechanistically, HuR deficiency impaired TLR signaling, resulting in reduced activation of the downstream transcription factors NF-κB and AP-1.Consequently, both the frequency of IL-10^{+} regulatory B cells and the amount of IL-10 produced per cell were markedly diminished. Transcriptomic and RNA-binding analyses further revealed distinct HuR-dependent regulatory programs in B1 and B2 cells, highlighting subset-specific post-transcriptional mechanisms controlling B-cell function.

Conclusion

Our findings identify HuR as a central post-transcriptional regulator of immunoregulatory B-cell responses during neuroinflammation. By coordinating signaling pathways, cytokine production and subset-specific gene expression, HuR promotes the function of IL-10-producing regulatory B cells that restrain central nervous system inflammation. Together, these results reveal a previously unrecognized role for HuR-dependent post-transcriptional regulation in controlling B-cell-mediated immune homeostasis during neuroinflammation.

Keywords: Bregs - RNA binding proteins - neuroinflammation.

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ICOS, CD226 and CD2 engage non-redundant synapse remodeling programs to optimize CD8+ T cell cytotoxic activity

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Cytotoxic CD8+ T cells (CTL) have evolved to recognize and eliminate target cells deploying various resistance mechanisms. The primary mechanism by which CTL eliminate target cells is the polarized secretion of lytic granule content at the lytic immunological synapse. This highly organized structure is the site of sequential molecular and structural events controlling target cell recognition and adhesion, spreading, polarization and exocytosis of lytic granules. We formulated the hypothesis that co-stimulatory receptors (CoR) may engage specific molecular programs to adjust CTL synapse architectures to face the challenges posed by resistant target cells.

To address this question, we conducted a systematic exploration of the relevance of therapeutically relevant Immunoglobulin - ICOS, CD226 and CD2 - and TNF receptor - CD27, OX40, and GITR - superfamily CoR in the tuning of CTL cytotoxicity. High-content cell imaging and phosphoproteomics were combined to both quantify lytic synapse steps and capture the signaling activity of these receptors in primary CTL.

We found that ICOS, CD226 and CD2, but not CD27, OX40, and GITR, acted as strong enhancers of cytotoxicity in CTL and CAR-T cells. High-content cell imaging revealed receptor-specific remodeling of key immune synapse steps, with CD2 stimulating fast lytic granule secretion, CD226 favoring high-affinity LFA-1 belt assembly, and ICOS promoting a unique spreading pattern. Phosphoproteomic analysis uncovered the ability of CD2, CD226 and ICOS to engage partially overlapping signals beyond the TCR signalosome. In particular, signals involved in actomyosin and microtubule dynamics were validated by gene editing as mediators of the synaptic spreading and lytic granule polarization activities evoked by these CoR. Remarkably, engagement of ICOS or CD2 was required for maintaining robust cytotoxicity towards resistant target cells, including ICAM-1 negative cells and cells with reduced stiffness.

Our study reveals that co-engagement of CD2, CD226 and ICOS with the TCR not only reinforces canonical TCR signaling but also triggers receptor-specific signaling events that distinctly remodel the synapse. Such activity endows CTL with capacity to surpass cancer cell resistance. Furthermore, our comparative analysis provides a unique resource to exploit CoR diversity for optimizing T cell synapse function in next-generation immunotherapies.

Keywords: Co-stimulation - Cytotoxicity - Signaling.

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N-glycosylation controls the thymic development of perinatal gd17 T-cells by dampening TCRgd signal strength

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Objective: gdT-cells play a key role in tissue surveillance, differentiating in the thymus where they acquire a mature effector program. Unveiling the underlying molecular mechanisms is then essential to understand how they deploy their functional potential in the periphery. Considering the important role of N-glycosylation in αβ T-cell development, we have addressed how this pathway impacts the thymic differentiation of gd T-cells.
Methods: Here, we used fetal thymic organ cultures as well as mouse models to disrupt N-glycosylation and assess its role in thymic gd T-cell differentiation. Moreover, we employed single-cell RNA-sequencing (scRNA-seq) to investigate how the N-glycosylation machinery of gd thymocytes is regulated during their development and address the impact of disturbing N-glycosylation on the differentiation program of glycoengineered gd thymocytes. Lastly, building on the data generated by scRNA-seq, we took advantage of site-directed mutagenesis to study the specific contribution of TCRgdN-glycosylation for gdT-cell differentiation in the thymus.
Results: We found that IL-17-producing gd (gd17) thymocytes are substantially enriched in genes associated with the *N*-glycosylation pathway when compared to IFN-g-producing (gdIFN) thymocytes. Critically, in the *Rag1creMgat1fl/fl*mouse model, where lymphocytes lack the early glycan-branching enzyme GnT-I, we observed a severe impairment in the thymic differentiation of perinatal gd17 but not gdIFN T-cells, accompanied by a defective induction of the genetic program of the gd17 cell lineage as assessed by scRNA-seq analysis. Conversely, *Rag1creMgat1fl/fl*thymi accumulated gdthymocytes displaying hallmark genes related to TCR activation (e.g. *Cd69*and *Nr4a1*). Notably, N-glycosylation impairment in immature gdthymocytes either by using chemical inhibitors (Kifunensine) or through the ablation of the *Mgat1* gene drastically augments the response to TCR stimulation as measured by the increased expression of TCR downstream targets (e.g. Nur77). By performing site-directed mutagenesis of the TCRgd N-glycosylation sites, we have mechanistically demonstrated that N-glycosylation decreases the TCR activation levels of perinatal gd17 T-cells, promoting their thymic differentiation.
Conclusion: In sum, our data suggests that *N*-glycosylation is a key determinant of the effector differentiation of gd thymocytes by dampening TCRgdsignal strength to enable the differentiation of perinatal gd17 cells.

Keywords: Thymic development - gd T cells - N-glycosylation.

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Aging and respiratory infections: cellular senescence, gut dysbiosis, and beyond

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The global population is aging rapidly, with the proportion of individuals aged 65 years and older increasing substantially worldwide. This demographic shift poses major challenges for healthcare systems and public health, as aging is associated with increased susceptibility to a broad spectrum of diseases, including cardiovascular, metabolic, neurodegenerative, and infectious disorders. Respiratory infections are of particular concern, given their high burden and severity in older individuals. Using relevant preclinical models of aging, we are exploring the contribution of two major age-associated processes, i.e., cellular senescence and gut dysbiosis, to the pathogenesis and outcomes of respiratory viral and bacterial infections. Our recent findings indicate that both processes can contribute to disease severity and/or long-term outcomes following infection. Importantly, targeting age-associated cellular senescence and/or gut dysbiosis through senolytic interventions or microbiota-derived metabolites can mitigate disease outcomes in these experimental models. How these findings may translate to human disease will also be discussed.

This work was supported in part by the ANR (AAP générique 2022), ANR-23-CE15-0014-01, GUTSY.

Keywords: Aging - Respiratory infections - Senescence and dysbiosis.

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Understanding the origin of autoreactive antbodies in atherosclerosis

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Atherosclerosis is a chronic inflammatory disease and a major driver of cardiovascular morbidity and mortality worldwide. Although immune mechanisms are increasingly recognized as important contributors to disease development and progression, the origins and characteristics of autoreactive antibody responses in chronic vascular inflammation remain incompletely understood. A better understanding of how B cell responses are initiated and maintained may provide important insights into disease pathogenesis and reveal new opportunities for therapeutic intervention.

We have investigated the evolution of B cell responses during atherosclerosis and their contribution to autoantibody production. Using approaches that enabled longitudinal analysis of B cell differentiation, we identified multiple immune pathways associated with the generation of autoreactive antibodies over the course of disease. These responses emerged with distinct temporal dynamics and were associated with differences in B cell phenotype, differentiation state, and patterns of antigen recognition.

Our findings demonstrate that chronic vascular inflammation supports diverse B cell programs that contribute to the development of autoreactive humoral immunity. More broadly, this work provides new insight into the relationship between chronic inflammation, B cell fate decisions, and the emergence of self-reactive antibodies.

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Autophagy loss in dendritic cells drives inflammatory reprogramming and CD4⁺ T-cell dysregulation during aging

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Context
As life expectancy increases, individuals spend a greater proportion of their lives in poor health. Healthy aging depends closely on the immune system function. With age, the immune system undergoes immunosenescence, characterized by low grade chronic inflammation, impaired immunosurveillance, and T-cell compartment remodeling. Dendritic cells (DCs), key orchestrators of adaptive immunity, also undergo functional alterations with age, yet the underlying mechanisms remain poorly understood. Autophagy, a lysosomal degradation pathway essential for cellular homeostasis, declines in DCs with age, but its role in regulating DCs function upon aging remains unexplored.
Objectives
To determine whether impaired autophagy in DCs drives immunosenescence, to assess its impact on healthy aging, and to define the underlying molecular and immunological mechanisms.
Methods
We generated mice with autophagy-deficient dendritic cells (DCs) (*Atg14*flox/flox× CD11c-Cre⁺) and monitored aging cohorts (60–80 weeks). We assessed their survival and healthspan, with a characterization of their immune system by serum cytokine profiling, transcriptomics of sorted DCs, single-cell RNA and TCR sequencing of T cells, tissue histology and flow cytometry.
Results
Aged mice mice with autophagy-deficient DCs exhibit reduced lifespan, weight loss, anemia, and elevated circulating proinflammatory cytokine (IL-1β, IL-6, IL-12p40, IFNα) compared with litermate controls. Transcriptomic analysis of autophagy-deficient DCs revealed an increased senescence score together with a pronounced proinflammatory signature. *In vitro*, stimulation with TLR and inflammasome agonists further confirmed their hyperresponsive phenotype. Single-cell analysis uncovered a marked remodeling of the splenic CD4⁺ T-cell compartment, with a proportional shift towards naive cells, an expansion of dysfunctional KLRG1⁺ regulatory T cells, and a loss of EOMES⁺ cytotoxic senolytic CD4⁺ T cells together with an altered TCR repertoire. Solid organ analysis converged on lung pathology — the most affected organ— which displayed lymphocytic infiltration, increased senescence markers (SA-β-galactosidase, p21) and elevated IL-1β.
Conclusion
Autophagy in DCs restrains inflammaging and preserves CD4⁺ T-cell homeostasis. Its loss is sufficient to shorten lifespan and drive an organ-restricted inflammatory and senescent pathology, identifying DC autophagy as a candidate target for sustaining immune function during aging.

Keywords: Immunosenescence - Autophagy - Aging.

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Tcell programs shaping postinjury outcomes in the zebrafish heart

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Objective
Inflammation and adaptive immunity are key determinants of tissue outcomes after injury. However, how these responses support regeneration or promote fibrosis remains poorly understood. T cells, in particular, integrate inflammatory cues and can potentially contribute to regenerative *versus* fibrotic responses. Our work aims to dissect T-cell programs activated after injury in regenerative and poorly regenerative (i.e., aged) conditions, while integrating the inflammatory environment.
Methods
To address our scientific questions, we use the adult zebrafish heart as a model of innate regenerative capacity that declines with aging. We relied on reporter lines to visualize different immune cells, and various knock-out mutant tools to model T-cell depletion and impairment of MHC class II antigen presentation. To modulate the inflammatory environment of the injured heart, we developed granulin overexpression tools. To resolve T-cell heterogeneity, we are applying bulk and single-cell TCR strategies.
Results
We found that T cells respond to cardiac injury and are indeed involved in the regenerative process. Specifically, the absence of T cells leads to exacerbated inflammation accompanied by impaired regeneration. Moreover, regeneration requires MHC class II-dependent antigen presentation. Although regulatory T cells are cardioprotective, they only partially compensate for global Tcell loss, pointing to functional diversity within the Tcell compartment that becomes increasingly relevant in aged animals. TCR sequencing is currently being used to map clonal diversity and T-cell states across regenerative and aging conditions. These adaptive programs are tightly influenced by the inflammatory milieu. In this context, we identified granulin family proteins as strong modulators capable of reshaping this environment and potentially altering Tcell behavior, providing experimental control over the conditions in which T-cell responses act.
Conclusion
Our work focuses on uncovering adaptive immune programs, and their interplay with the inflammatory environment, shaping the outcomes after organ injury, toward identifying immune mechanisms that can be harnessed to limit fibrosis and boost regenerative responses.

Keywords: Zebrafish - Regeneration - Aging.

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Chronic exposure to interleukin-10 drives inflammaging and accelerated tissue senescence

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**Equal contribution*

Interleukin (IL)-10 is a major regulator of the immune system. Paradoxically, IL-10 can also elicit pro-inflammatory activities, which limits the efficacy of IL-10-based anti-inflammatory therapies. We previously showed that *in vivo* exposure to therapeutic doses of IL-10 reprograms T cells, inducing the production of interferon-gamma (IFN-γ) and other inflammatory mediators. In turn, reprogrammed T cells initiate a process of emergency myelopoiesis.

Objective

In this study, we investigated the structural and functional changes caused by IL-10 elevation in the organism beyond emergency myelopoiesis.

Methods

For this, we combined flow cytometry, transcriptomics, and histological analysis to different animal models of IL-10 induction. We have also analyzed a series of bulk and single-cell mouse and human datasets of natural aging.

Results

In mice exposed to therapeutic doses of IL-10, we observed a change in the composition of $CD4^+$ and $CD8^+$ T cell subsets, in the bone marrow and spleen, characterized by a naïve/effector-memory imbalance, accumulation of $CD38^+PD\text{-}1^+$ cells, along with cytotoxic, exhaustion, and senescence transcriptional signatures, and functional evidence of cellular senescence. Physiological and functional alterations were also found in non-lymphoid organs, such as the colon, pancreas, lung, heart, and gonadal white adipose tissue. These alterations are strictly dependent on IL-10 reprogrammed T cells, as elevation of IL-10 in mice lacking $CD3^+$ T cells results in no phenotype, whereas IFN-γ is only partially involved. Interestingly, using publicly available mouse and human RNA-seq datasets, we also found a positive correlation between the expression of *Il10* and the IL-10-induced T cell transcriptional signature across various tissues during physiological aging.

Conclusion

Altogether, we report a novel mouse model of sterile inflammaging and highlight a previously unappreciated role for IL-10 in accelerating aging, which is conserved in mice and humans. Our study opens new avenues on the basic biology and clinical use of IL-10.

Keywords: Interleukin-10 - Inflammaging - T-cell senescence.

The Academic Path: The Bad, the Good, and the Pretty

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An academic career is rarely a linear journey. In this talk, I will share my personal path from undergraduate studies in Spain, through PhD and postdoctoral training across the UK, to establishing my own research group in Portugal. Along the way, I will reflect on the opportunities, failures, difficult decisions, and unexpected turns that shaped both my scientific career and my perspective on academia. Rather than focusing on research results, I will discuss topics such as choosing mentors, dealing with rejection and imposter syndrome, balancing ambition with well-being, navigating career uncertainty, and finding a research environment where I could thrive. I hope this personal account will encourage young scientists to embrace their own strengths, define success on their own terms, and appreciate that there is no single recipe for building a fulfilling academic career.

Keywords: Academic career - Career development - Mentorship.

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Compartmentalized regulation of CNS autoimmunity

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Compartmentalized inflammation in distinct niches in the CNS, including the meninges and the periventricular parenchyma, is considered a driving force for progressive immunopathology in Multiple sclerosis. While the cellular underpinning of relapses, which are initiated by immune cells activated in the peripheral immune system, has been investigated in detail, the biology of compartmentalized inflammatory processes in the CNS, disconnected from the peripheral immune system, is less well understood. Here, I will discuss the autonomous regulation of immune responses in distinct tissue niches of the CNS parenchyma and the meninges in the inflammation-experienced CNS. Also, a novel CD4 T cell-intrinsic pathway of effector T cell differentiation, operational in the inflamed tissue, will be illustrated. The pathway relies on CD96 signaling in T cells and likely controls the development of stemness potential in conventional CD4 T cells in the inflamed CNS.

Keywords: T cell - Multiple Sclerosis - Compartmentalized inflammation.

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Brain border myeloid cells: more than immune sentinels?

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Abstract not received.

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Glycan mimicry as a key mechanism in the loss of self-tolerance: deciphering novel anti-glycan autoantibodies in lupus

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Introduction

Autoimmune diseases are life-threatening disorders with increasing disability, arising when immune stimuli override mechanisms of self-tolerance. Glycans are master regulators of the inflammatory response being important molecules for the discrimination between “self”/“non-self”. Accumulating evidence demonstrate that protein glycosylation is significantly altered in disease development, but it is still largely unclear the mechanisms by which glycans trigger the loss of immunological tolerance and the onset of autoimmune responses.

Objectives

We here explored whether an altered tissue glycosylation exposing abnormal glycan epitopes may contribute to the loss of self-tolerance in autoimmune diseases, such as Systemic Lupus Erythematosus (SLE).

Methods

Mass Spectrometry Imaging was performed on kidney biopsies from SLE patients to identify disease-associated glycan signatures. Mechanistic studies were conducted using lupus-susceptible glycoengineered mice (*Mgat5*$^{-/-}$) to investigate the immunological consequences of abnormal mannose glycan exposure. Serum samples from patients with SLE and other immune-mediated diseases were further analyzed using a glycan microarray comprising an extensive library of glycan epitopes to characterize anti-glycan autoantibody responses.

Results

A comprehensive characterization of tissue glycomics from SLE kidney biopsies revealed a unique glycan signature characterized by an increased abundance and spatial distribution of unusual mannose-enriched glycans that are typically found in lower microorganisms. Mechanistically, we showed that abnormal exposure of these microbial-associated mannose structures in a lupus-susceptible glycoengineered mice, was associated with increased expression of B cell, as well as autoantibody production. Given the fact that autoantibodies are a hallmark of autoimmunity, we then analyzed the presence of anti-glycan autoantibodies in the serum from a variety of immune-mediated diseases, including SLE, in a glycan microarray, designed with an extensive library of glycan epitopes. We have observed that SLE patients display increased levels of serum anti-glycan autoantibodies, correlated with the increased levels of glycan epitopes observed in the kidney. These altered levels of anti-glycan autoantibodies were associate with diagnostic and prognostic factors of lupus disease. Taken together, this work proposes glycan mimicry as a new mechanism of loss of self-tolerance in autoimmunity.

Keywords: Self-tolerance - Autoantibodies - SLE.

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Eomes Reprograms FoxP3⁺ Regulatory T Cells toward a Cytotoxic and Pro-inflammatory State

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Objectives
Eomes is a transcription factor primarily characterized in CD8+ T cells and NK cells, where its expression is associated with cytotoxic functions. Recently, we highlighted the importance of Eomes in T helper cell-mediated anti-tumor immunity. In regulatory T cells (Tregs), Eomes is among the most strongly downregulated genes. However, we identified Eomes-expressing Tregs infiltrating tissues accros several inflammatory condition including tumors. We aimed to investigate the impact of Eomes expression on Treg biology.
Methods
We investigated how Eomes expression affects Treg biology using Eomes-GFP reporter mice and mice with T cell–specific Eomes deficiency. We combined multiparameter flow cytometry, bulk and single-cell RNA sequencing and adoptive T-cell transfer in both tumor and experimental autoimmune encephalomyelitis (EAE) models.
Results
We first demonstrated that Eomes⁺ Tregs accumulate in inflamed tissues and during aging and can be induced under steady-state conditions by 4-1BB stimulation. RNA-seq analysis revealed that Eomes expression profoundly alters the Treg transcriptome. While the Treg-associated transcriptional signature was markedly downregulated in Eomes-expressing Tregs, FoxP3 expression remained unaffected. In contrast, these cells displayed enrichment a leukocyte-mediated cytotoxicity signature. In the EAE model, Eomes+ Tregs were enriched in inflamed tissues and exhibited increased pro-inflammatory cytokine secretion and enhanced cytotoxic activity, while maintaining FoxP3 expression. Moreover, purified Eomes⁺ Tregs exhibited impaired suppressive capacity both *in vitro* and following adoptive transfer *in vivo*.
Conclusions
Our results indicate that Eomes expression in Tregs is associated with the acquisition of cytotoxic and pro-inflammatory features and impaired suppressive functions, while maintaining FoxP3 expression. These findings suggest that Eomes expression may contribute to functional reprogramming of Tregs in inflammatory and tumor contexts. We will further investigate the cytotoxic potential of Eomes+ Tregs *in vitro* and in the tumor context.

Keywords: Eomes - Treg - Cytotoxicity.

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NLRP6 promotes inflammation and regulated cell death through activation of the caspase-3/gasdermin E pathway in bleomycin-induced pulmonary fibrosis

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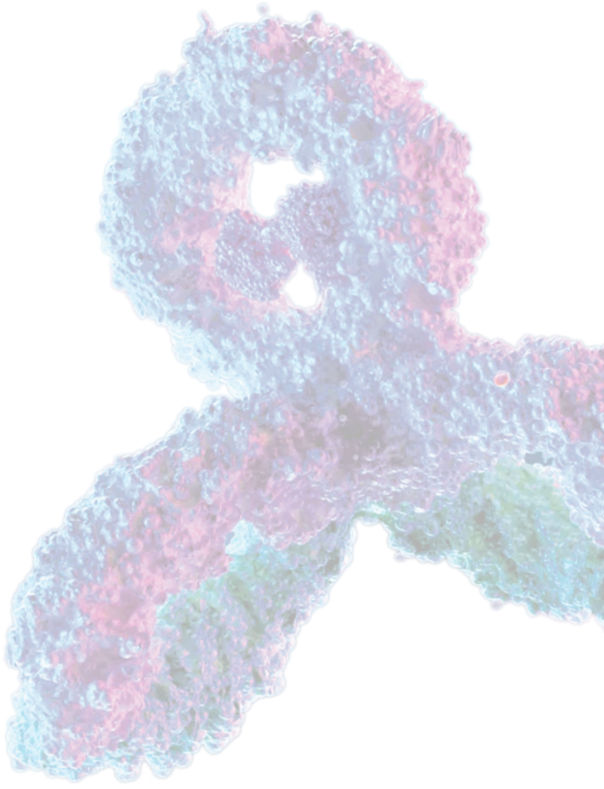
Objectives
Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal interstitial pneumonitis of unknown cause characterized by successive episodes of acute lung injury followed by scarring, ultimately leading to respiratory failure, and there is no effective treatment. Although the mechanisms remain poorly understood, we have previously demonstrated that recurrent lung injury induces pulmonary inflammation through activation of the NLRP3 inflammasome, primarily in immune cells, thereby promoting the development of pulmonary fibrosis. However, the role of the NLRP6 inflammasome, which is predominatly expressed in epithelial cells, remains unknown.
Methods
Using an experimental model of IPF induced by oropharyngeal administration of bleomycin (BLM), we investigated the contribution of the NLRP6 sensor in the context of regulated cell death (RCD) occurring after inflammasome activation, as well as its consequences for the exacerbation of pulmonary inflammation, lung remodeling, and fibrosis. We analyzed the mechanisms by which BLM induces regulated death of alveolar epithelial cell (AEC), focusing on the role of the gasdermins (GSDM) D and E, which are involved in conventional and non-conventional pyroptosis, respectively.
Results
Here, we show that NLRP6 deficiency attenuates airway inflammation, reducing the influx of neutrophils, eosinophils, dendritic cells, T and B lymphocytes into the bronchoalveolar space. Furthermore, we observed reduced collagen deposition and expression of fibrosis-related genes in lung tissue of *Nlrp6*-deficient mice in comparison to wild-type mice. BLM administration triggers the activation of the conventional pyroptosis pathway (caspase-1/GSDMD), as well as a non-conventional pyroptosis pathway (caspase-3/GSDME), in a dose-dependent manner. Furthermore, BLM administration promotes caspase-1/3 and GSDMD/E cleavage in AEC, an effect attenuated in *Nlrp6*-deficient mice suggesting that the NLRP6 inflammasome contributes to pulmonary inflammation and fibrosis through GSDMD/E-dependent pyroptosis. Previous studies showed that BLM leads to the production of reactif oxygen species in lung. Here, we found that BLM administration promotes lipid peroxydation which may underlie AEC pyroptosis, pulmonary inflammation and fibrosis.
Conclusion
Our data indicate that NLRP6 is a key player in BLM-induced pulmonary inflammation and fibrosis in mice, potentially through oxidative stress-induced AEC pyroptosis.

Keywords: NLRP6 - Pyroptosis - Oxidative stress.

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ABSTRACTS ON THURSDAY 5 NOVEMBER

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CD1a-reactive T cells and lipid antigens in inflammatory skin diseases: discovery and translation

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CD1a is an MHC class I-like molecule expressed by Langerhans cells that is capable of presenting lipid antigens to T cells. Recent technological developments have enabled the identification of abundant CD1a lipid antigens and CD1a-reactive T cells in human skin. We employ human *in vivo* skin challenge models to obtain mechanistic insights with spatial and temporal resolution. Our findings demonstrate that these models of skin inflammation are associated with an increase of CD1a-expressing cells in the skin, which can present lipid antigens to CD1a-reactive T cells and induce a broad range of functional responses. Individual T cell receptors are capable of recognising CD1a complexed with remarkably diverse lipids, with important implications for the contribution of CD1a autoreactivity to the pathogenesis of inflammatory skin diseases. Agonist self-lipids can be generated enzymatically during inflammation and may displace naturally occurring antagonist lipids in the skin, which otherwise prevent T cell engagement under healthy conditions. The presence of such natural antagonists suggests therapeutic opportunities through the development of synthetic analogues. In summary, although similarities with the peptide-MHC system exist, growing evidence highlights fundamental differences between these antigen sensing pathways, with important implications for biology, disease pathogenesis and therapeutic development.

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MAIT cells in autoimmune and infectious diseases

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Objective: Mucosal-associated invariant T (MAIT) cells are innate-like T cells expressing an invariant TCR-alpha chain. Their TCR recognize microbial vitamin B-derived metabolites presented by the nonpolymorphic class Ib molecule MR1. MAIT cells harbor an effector memory phenotype and can respond rapidly through TCR activation and/or inflammatory cytokines. Upon activation, they can promote immune response against infectious pathogens as well as participating to tissue homeostasis (1). We have previously shown in patients and mouse models their ambivalent roles, being either protective or deleterious in various autoimmune, metabolic and infectious diseases (1-3). In the present study, we investigated the function of MAIT cells upon viral infection and determine whether MAIT cells are beneficial or deleterious the development of autoimmune disease after such infection in mouse models.
Methods: Mice were infected with the enterovirus CVB4 and MAIT cell activation was analyzed in various tissues including intestine, pancreas,spleen and pancreatic lymph nodes. Viral load was measured in intestine and pancreas on day 3 and 8 post-infection. Several mouse strains and lines were analyzed to determine the function of MAIT cells in the control of viral load and the development of type 1 diabetes upon infection. Extensive flow cytometry and transcriptomic analyses were performed to characterize MAIT cell subsets and function. The role of the microbiota and MAIT cell TCR activation was analyzed in vitro and in vivo.
Results: Our results demonstrate the impact of MAIT cells in promoting inflammation and autoimmunity upon CVB4 infection. Microbiota and MR1 play a key role in inducing MAIT cell activation. In vivo and in vitro experiments highlight the induction of MAIT cells exhibiting regulatory profile and function in the presence of MAIT cell non-agonist ligand.
Conclusion: Microbiota alteration upon enterovirus infection promotes MAIT cell activation, thereby inducing local inflammation and autoimmunity. However, interfering with TCR MAIT cell activation through various mechanisms induces regulatory MAIT cells.

Keywords: MAIT cells - Viral infection - Autoimmunity.

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MAIT cells promote lung resilience during severe viral pneumonia by maintaining myeloid balance

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Objective
Viral pneumonia can progress to acute respiratory distress syndrome (ARDS), a life-threatening form of respiratory failure defined by uncontrolled pulmonary inflammation and failure of tissue-damage control. In this context, mucosal-associated invariant T (MAIT) cells appear as attractive target, given their broad immunomodulatory and tissue-repair functions. However, their role in severe viral pneumonia remains poorly characterized.
Methods
We explored two complementary murine models of severe influenza A virus (IAV) infection (H1N1 and H3N2 strains) in MAIT cell-competent ($Mr1^{+}$) and -deficient ($Mr1^{-}$) mice, using flow cytometry, transcriptomic, and functional analyses.
Results
In both models, $Mr1^{-}$ mice displayed increased lethality independently of viral load, pointing to a role of MAIT cells in immunopathology regulation and tissue damage control / tissue repair. Lung MAIT cells rapidly acquired an activated phenotype, and using $Cd4^{cre} \times Ifnar^{fl/fl}$ and Nur77-GFP reporter mice, this activation was found to be type I IFN-dependent and TCR-independent. MAIT cells also underwent progressive transcriptional and functional reprogramming throughout infection, with early cytotoxic/pro-inflammatory and pro-repair signatures.
MAIT cell deficiency increased alveolo-capillary membrane permeability -a hallmark of ARDS- accompanied by a reduction in ZO-1 tight-junction protein expression and elevated pulmonary inflammatory cytokines. Strikingly, this was paralleled by a myeloid imbalance: accumulation of inflammatory monocytes known to drive alveolo-capillary disruption, and concurrent loss of $Ly6G^{+}$ macrophages, a recently described reparative subset promoting alveolar epithelial repair.
Last, cognate MAIT cell stimulation with 5-OP-RU following infection by influenza conferred significant survival benefit.
Conclusion
These results establish a protective role for MAIT cells in IAV-induced pneumonia, operating through the control of myeloid populations to preserve alveolo-capillary integrity. By positioning the MAIT-myeloid axis as a central regulator of pulmonary tissue-damage control during viral ARDS, these findings identify MAIT cell activation as a potential tractable therapeutic lever to limit injury severity in ARDS.

Keywords: MAIT cells - Viral pneumonia - Immunopathology.

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Developmental waves and genetic regulation of the Human γδ T-cell repertoire

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γδ T cells are an evolutionarily conserved T-cell subset that responds to microbial, viral and tumor stimuli and provides tissue surveillance. They predominate during early gestation and are a minor population from mid-gestation throughout life. Based on the Vδ gene incorporated into their T-cell receptor, human γδ T cells are broadly divided into innate-like effector Vγ9Vδ2 and adaptive-like non- Vγ9Vδ2 populations, mainly Vδ1. During fetal life, γδ T cells emerge in distinct waves starting with innate-like γδ T cells with different effector fates, followed by more adaptive-like populations. Whether waves of innate-like effector γδ T cells are generated after birth remains unclear. Moreover, γδ T-cell subsets show marked inter-individual variation, but the factors determining Vδ1 vs Vδ2 abundance remain poorly understood.

The common polymorphism rs2204985, located within the TCRA–TCRD locus, is associated with variation in thymic output from birth, with GG individuals exhibiting higher thymic output than AA individuals. Whether rs2204985 variant influences γδ T-cell development remains unknown. We therefore investigated γδ T-cell generation from fetal to postnatal life using flow cytometry, repertoire analysis and *in vitro* differentiation systems.

First, our work uncovers a postnatal wave of innate-like effector Vδ2$^+$ γδ T cells emerging between 10 days and 3 months of age. Secondly, we show that rs2204985 genetic variation influences γδ T-cell repertoire. GG infants exhibited increased Vδ2 and reduced Vδ1 γδ thymocyte frequencies. This bias was detectable from the earliest stages of γδ thymocyte development and associated with skewed δ-chain TCR rearrangement. Using humanized mice and *in vitro* T-cell differentiation systems, we reproduced this genotype-dependent Vδ2/Vδ1 bias, supporting an HSC-intrinsic effect. This effect could be observed from fetal γδ T-cell emergence in blood, with increased γδ T-cell frequencies early in gestation in GG fetuses and increased Vδ2$^+$ populations, including Vγ9Vδ2, from mid-gestation onward.

These findings reveal new insights into γδ T-cell dynamics during early life and identify rs2204985 as a genetic determinant of the γδ repertoire. The rs2204985 genotype may influence early-life immunity through baseline differences in Vγ9Vδ2 abundance and could represent a clinically relevant determinant of human γδ T-cell biology.

Keywords: Developmental waves - Gamma Delta Lymphocytes.

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IL-23 regulates the non-canonical NF-kB pathway in human invariant Natural Killer T (iNKT) cells

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IL-23 receptor (IL-23R) polymorphisms are associated with chronic inflammatory diseases (CID), including inflammatory bowel disease, psoriasis and spondyloarthritis. In parallel, evidence from *Il23/Il23r*-deficient mice uncovered the importance of IL-23 in the pathogenesis of experimental models of CID and revealed IL-23R-expressing innate-like T cells as key mediators. However, the mechanisms underlying the IL-23-shaped pathogenic programs in humans remain poorly understood.
Here, we explored the functional effects of IL-23 signaling in iNKT from peripheral blood (PB) of healthy individuals and synovial fluid (SF) of peripheral spondyloarthritis (pSpA) patients.
We found that iNKT cells, but not Vδ2$^+$ or Vδ2$^-$γδ T cells or MAIT cells, were significantly enriched in the SF T-cell compartment of pSpA patients (~3-fold relative to PB) and expressed high levels of IL-23R. In healthy PB, approximately 50% of iNKT cells expressed the IL-23R on their surface, indicating that a substantial fraction of circulating iNKT cells is poised to respond to IL-23.
To assess the role of IL-23 signalling in iNKT cells, we investigated gene expression in CD1d-PBS57-tetramer-isolated cells previously expanded *in vitro* in the presence of α-galactosilceramide. IL-23 stimulation induced a strong NF-κB transcriptional program in iNKT cells, including *RELB, NFKB2,* and *NFKBIA.* These observations were validated in freshly isolated iNKT cells from PB, where we consistently found *RELB* and *NFKB2* among the IL-23-regulated genes.
By revisiting published (1) and recently generated data from our laboratory, we demonstrate that IL-23 treatment strongly activates the NF-κB signalling in iNKT cells, but not in MAIT cells.
Together, these findings identified iNKT cells as IL-23–responsive cells in pSpA and demonstrated that IL-23 triggers an NF-κB program in human iNKT cells, which may contribute to the pathogenesis of IL-23-driven inflammatory diseases.
Our future work aims to elucidate the mechanisms through which IL-23 uniquely regulates the NF-κB pathway in iNKT cells and to compare this transcriptional signature across other innate-like T populations within the synovial fluid of peripheral spondyloarthritis patients.

Keywords: IL-23 receptor - Invariant Natural Killer T cell - Non-canonical NF-kB pathway.

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Understanding sex differences in human immunity through gender-affirming hormone therapy

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Abstract not received.

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Hormonal regulation of ILC: consequences on lung immunity

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Sex influences the incidence and severity of pulmonary diseases, reflecting differences in immune responses between women and men. For example, asthma is more prevalent and often more severe in women after puberty, suggesting a role for sex hormones in shaping pulmonary immunity. In our team, we investigate the mechanisms underlying these sex biases, focusing on how sex biological factors regulate immune responses. In allergic asthma, we identified androgens as potent inhibitors of group 2 innate lymphoid cells (ILC2), key drivers of type 2 inflammation. In mice, androgen receptor (AR) signaling suppresses ILC2 proliferation and function, limiting allergic airway inflammation. Consistent with these findings, our studies in patients revealed higher ILC2 proportions in women than in men, particularly in severe asthma. These results support conserved hormonal regulation of ILC2 in mice and humans and highlight AR signaling as a potential therapeutic target. Building on these findings, we are extending our research to idiopathic pulmonary fibrosis (IPF), a progressive disease that predominantly affects men and involves dysregulated tissue repair and type 2 immunity. We are determining how sex hormones regulate pulmonary immune responses and immune–stromal interactions, particularly macrophage functions, and how these mechanisms contribute to sex differences in fibrotic disease. By defining how sex hormones regulate innate immunity across lung diseases, we aim to foster more precise, effective and equitable healthcare solutions between men and women.

Keywords: Tissue immunity - Asthma - Sex differences.

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Tlr7 bi-allelism shapes pathogenic female B cell responses in lupus

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The incidence of autoimmune diseases, like Systemic Lupus Erythematosus (SLE) is markedly increased in women and in 47 XXY Klinefelter syndrome (KS) men, as compared to 46 XY men, possibly in relationship with differences in X chromosome dosage. While in women, one of the two X chromosomes is inactivated (XCI), some genes can escape XCI, leading to increased expression of these genes in female cells. *Tlr7* gene localized on the X chromosome encodes an endosomal TLR recognizing ssRNA from self and non-self, potentially leading to inflammation or autoimmunity. Indeed, expressed at double dose, *Tlr7* is sufficient to trigger systemic autoimmunity in mice. We have recently demonstrated that *TLR7* evades X silencing in an important proportion of immune cells from healthy women and KS men, resulting in enhanced TLR7 protein expression in female PBMCs. TLR7 bi-allelic B cells exhibited enhanced capacity for class switching into IgG+ B cells and plasmablasts in response to TLR7-specific ligands. This observation supports the notion that TLR7 overexpression through bi-allelism is a candidate contributor to the higher risk of SLE, in women and KS men.
To address the causal relationship between *Tlr7* expression from the inactive X chromosome and the development of dysregulated immune responses involved in disease pathogenesis in SLE, we generated an original dual reporter mouse model in lupus-prone genetic background in order to track *Tlr7* biallelic cells referred as BiA7 B cells *in vivo*.
We will present evidence that BiA7 cells are enriched among ABCs in SLE mice and that their frequency positively correlates with autoantibody levels. BiA7 ABCs display an enhanced capacity to differentiate into plasmablasts in response to TLR7-specific ligands and exhibit a distinct transcriptional profile compared with their mono-allelic counterparts. BCR repertoire analysis further reveals specific clonal expansions among BiA7 ABCs that may contribute to disease development. Finally, we show that BiA7 ABCs display distinct chromatin conformation at the *Tlr7* locus, providing insights into the mechanisms underlying escape from XCI. Together, these findings identify TLR7 biallelic ABCs cells as a distinct and potentially pathogenic B cell population in SLE, and provide a mechanistic link between X chromosome dosage, TLR7 overexpression, and the increased susceptibility of females to systemic autoimmunity.

Keywords: Age-associated B cells - X Chromosome Inactivation - Systemic Lupus Erythematosus.

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PI3K/AKT signaling controls sex bias in Tr1 cells and their response to vitamin D

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system driven by genetic and environmental factors, including vitamin D (VD) deficiency and biological sex. $CD4^+$ T cells play a central role in MS pathogenesis. Among them, type 1 regulatory T (Tr1) cells are impaired in people with MS (pwMS), producing less IL-10 than healthy controls. Although VD can partially restore Tr1 dysfunction in MS, the influence of sex on Tr1 differentiation and VD response remains unclear.

We isolated CD4+ T cells from healthy donors and pwMS and differentiated them *in vitro* into Tr1 cells through either CD46 engagement (anti-CD3/anti-CD46 antibodies + IL-2) or IL-27 stimulation (anti-CD3/anti-CD28 antibodies + IL-27). Tr1 phenotype and cytokine production were assessed by flow cytometry.

In healthy donors, CD46-induced Tr1 cells from females produced less IL-10 and showed reduced c-MAF expression than those from males, whereas no sex bias was observed in IL-27-induced Tr1 cells. As PI3K was shown to regulate IL-10 production in IL-27-induced Tr1 cells in mice, we explored its role in human Tr1 cells. PI3K inhibition revealed pathway-dependent effects on IL-10 production in Tr1 cells, with a sex bias observed only in CD46-induced Tr1 cells. These results support a contribution of PI3K signaling to this difference. This difference was absent in pwMS, consistent with impaired CD46 signaling reported in MS. However, PI3K inhibition elicited a sex-dependent response in IL-27-induced Tr1 cells from pwMS, suggesting a lower dependence on PI3K for IL-10 production in female patients.

We further identified a sex bias in the response of CD46-induced Tr1 cells from healthy donors to VD. Female Tr1 cells showed a greater increase in IL-10 production upon VD treatment. Bulk RNA-seq revealed an overall reduction in PI3K pathway activity with VD, and males exhibited relative activation of this pathway. This activation may limit VD-induced IL-10 production in males. Consistently, VD reduced the phosphorylation of PI3K pathway components in female cells. These findings support a role for PI3K signaling in CD46/VD crosstalk.

Overall, our results identify PI3K signaling as a key regulator of IL-10 production and VD response in CD46-induced Tr1 cells, with effects influenced by biological sex. This mechanism may contribute to sex differences in MS pathophysiology and treatment response, suggesting that the PI3K pathway could represent a potential therapeutic target.

Keywords: Sex difference - Vitamin D - Tr1 cells.

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Sex-associated differences in human thymic TCR selection

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Objective
Women represent about 80% of patients with autoimmune diseases[1]. This may partly result from sex-based differences in T cell receptor (TCR) selection during thymocyte development, potentially influenced by hormones and reduced expression of the Autoimmune Regulator (AIRE) transcription factor in females[2]. To investigate this, we analyzed sex-specific differences in TCR generation and selection by profiling thymic TCRα/β repertoires from male and female deceased organ donors and pediatric cardiac surgery patients.
Methods
Thymocyte populations were sorted into CD3+ CD4+ CD8+ double-positive (DP) cells to assess TCR generation, and single-positive (SP) CD8, CD4 effector (Teffs) and regulatory T cells (Tregs) to assess TCR selection. We analyzed V/J usage, diversity, CDR3 amino acid composition, TCR network structure, generation probabilities and TCR specificity.
Results
Our analyses found that TCR generation at the DP cell stage is largely similar between sexes, showing comparable V and J gene usage, repertoire diversity, and CDR3 amino acid length and composition. No TCR sequences were exclusive to either sex. By contrast, sex-specific differences emerged at the selection stage. Female SP CD8 T cell were enriched for TRB CDR3 amino acid sequences specific for self-antigens associated with autoimmune diseases and for bacterial antigens. Interestingly, a similar trend was observed in CD4 Teff cells. Conversely, female SP CD4 Tregs showed reduced frequencies of these same autoimmunity-associated specificities. These differences were not observed for self-antigens unrelated to autoimmune diseases or for cancer/viral antigens. Additionally, we noted a non-significant trend toward higher usage of polyspecific TRB CDR3 amino acid sequences in female SP CD8 T cells and the opposite trend in female Tregs.
Conclusion
Together, these findings suggest a dual imbalance in females, enhanced selection of autoreactive effector TCRs and reduced selection of regulatory TCRs, that may contribute to diminished immune tolerance and increased susceptibility to autoimmune diseases. Although our analyses were limited to the TRB CDR3 region due to current technical constraints, our results provide evidence that sex-biased TCR selection may underlie the female predominance in autoimmunity. These observations warrant further validation in larger, more detailed datasets.

Keywords: Central tolerance - Immune repertoire profiling - Sex dimorphism.

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T cell diversification in infection and cancer

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Profound understanding of CD8 T cells is highly relevant for the development of novel immunotherapies and vaccination strategies. It has become increasingly clear that CD8 T cells residing inside tumors or at the site of initial pathogen entry are important for protection against tumor growth or secondary infection. For these reasons, the characterization of tissue-resident memory CD8 T cells (Trm) appears of utmost importance. We reported that Hobit together with related Blimp-1 represses expression of tissue-exit receptors, which is crucial for the permanent residence of Trm in peripheral tissues. This work has been important in the recognition of Trm as an independent lineage under the control of a dedicated set of transcription factors. We developed Hobit reporter/deleter mice that allow for the specific identification, elimination and fate-mapping of Trm to tackle important unresolved challenges regarding Trm including how these cells arise, how they are re-activated, and how they develop into effector CD8 T cells that effectively combat viruses and tumor cells. Using these mice, we have shown that pre-existing Trm are essential to repopulate memory T cells in peripheral tissues, blood and lymph nodes after pathogen clearance. These findings suggest progressive increase in the impact of Trm on immune responses after each infection (Nat Immunol, 2020). Furthermore, the Hobit reporter/deleter mice enabled us to identify Trm precursors with strongly biased potential to form Trm rather than circulating memory T-cells, thereby resolving the differentiation pathway of Trm in infection models (Sci Immunol, 2021). We are now applying our Trm toolset for the study of intratumoral T cell differentiation.

Keywords: Tissue resident memory CD8 T cells - T cell exhaustion - T cell differentiation.

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TGF-β restricts GSDME-mediated IL-1α Release by Th17 cells to license them for enhanced pathogenicity

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Transforming growth factor-β (TGF-β) has potent immunosuppressive functions but is also involved in the generation of inflammatory Th17 cells with roles in autoimmunity and clearance of fungal infections. Here, we identify a previously unrecognized function of TGF-β in restraining T cell-mediated inflammation through intracellular sequestration of the unconventional danger signal IL-1α, thereby limiting its extracellular inflammatory bioactivity. This IL-1a entrapment promotes an inflammatory preparedness in Th17 cells, enabling enhanced secretion of stockpiled IL-1a upon secondary TCR stimulation. Mechanistically, we show that TGF-β suppresses cleavage of the membrane pore-forming molecule gasdermin E (GSDME) in T cells via the c-Flip–Casp8–Casp3 axis, thereby blocking the exit route for IL-1α but not for other Th17 cell-associated effector cytokines. Innate IL-1b, but not other cytokines, could abrogate the TGF-β-mediated intracellular sequestration of IL-1a by abrogating TGF-β-mediated suppression of GSDME cleavage, leading to continuous bioavailability of IL-1a. Our findings reveal a novel dimension of TGF-β signaling, in which its anti-inflammatory effects extend to the previously overlooked fundamental regulation of unconventional cytokine release. This has far-reaching implications for Th17 cell-mediated immunopathology and host defense.

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Clearance of tumor antigen governs the differentiation of bona fide CD8⁺ tissue-resident memory T cells

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Objectives
CD8⁺ tissue-resident memory T cells (T_{RM}) have particular spatiotemporal advantages in responding to local threats. Clinically, CD103⁺ T cell infiltration is a positive prognostic marker across diverse tumour types, indicating non-redundant antitumoral roles of TRM. However, their development and function in tumours are largely unknown. Moreover, intratumoral exhausted T cells (T_{EX}) can obtain residency properties, complicating the distinction of T_{RM} and T_{EX}. We hypothesise that despite phenotypic overlap, their formation is driven by distinct developmental programmes and cues. Here, we aimed to elucidate how intratumoral antigen clearance or persistence directs T cell differentiation.

Methods
Using models of pancreatic ductal adenocarcinoma with varying degrees of antigen persistence, we have studied how exposure to cognate antigen affects T cell development in tumours. Additionally, we utilised inducible ovalbumin (OVA) expression in tumour cells and inducible deletion of TCR on T cells to gain a more mechanistic understanding of the effects of antigen abundance and recognition. Flow cytometry was used to analyse persistence of OVA-expressing tumour cells and phenotypes of T cells.

Results
T_{RM} became the dominant population in tumours only after antigen clearance, whilst T cells persistently exposed to antigen obtained exhausted phenotypes, including TOX and TIM-3 expression. Compared to T_{EX}, T_{RM} from tumours with cleared cognate antigen retained superior recall responses as demonstrated by higher production of Granzyme B, IFNγ and TNFα. Recognition of local antigen was found to be important in driving abundant intratumoral T_{RM} formation. However, T_{RM} were permitted to develop only under limited duration of antigen exposure, as elimination of antigen recognition for T cells exposed to chronic antigen in a late stage of tumour development did not result in conversion to T_{RM}.

Conclusions
Altogether, we demonstrate that antigen exposure dictates the divergence of phenotypically and functionally distinct T cell populations, with T_{RM} development only being permitted after antigen clearance. The lack of conversion from T_{EX} to T_{RM} upon TCR deletion late in tumour development suggests an early decision in the lineage divergence of T_{RM} and T_{EX}. Our findings may indicate that T_{RM} maintain a role in preventing re-emergence of previously eliminated tumour clones, but not in actively countering growth of persisting tumours in contrast to T_{EX}.

Keywords: Tissue-resident memory T cells - T cell exhaustion - Cancer immunology.

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Progressive remodeling of pathogenic skin resident memory T cell subsets shapes long-term allergic memory

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Tissue-resident memory T cells (TRM) are major drivers of chronic inflammatory and allergic skin diseases, yet the mechanisms governing their long-term maintenance within tissues remain poorly understood.
Here, using a preclinical model of skin allergy (allergic contact dermatitis (ACD) to the hapten 2,4-dinitrofluorobenzene (DNFB)), we investigated the durability and fate of epidermal $CD8^+CD69^+CD103^+$ TRM generated following sensitization.
We found that, in the absence of further allergen exposure, local allergic memory progressively declined over time and was accompanied by a profound remodeling of the epidermal TRM compartment. Single-cell transcriptomics and spectral cytometry identified three transcriptionally and phenotypically distinct TRMpopulations harboring divergent persistence capacities, ranging from rapidly declining short-term TRM to highly stable long-term TRM persisting in the epidermis for more than two years. Trajectory inference and TCR Vβ repertoire analyses further revealed that these populations were present among both allergen-specific and bystander TRM, shared overlapping clonal features, and aligned along a common transcriptional continuum, consistent with progressive TRM diversification.
Mechanistically, short-term TRM displayed increased proliferative turnover and preferentially underwent spontaneous retrograde migration toward draining lymph nodes, identifying tissue egress as a major driver of TRM attrition. In contrast, long-lived TRM progressively acquired enhanced survival, stress-resistance, and stem-like programs associated with durable tissue persistence. Finally, TCR and IL-15 signaling exerted complementary roles in TRM maintenance, with IL-15 preferentially sustaining short-term TRM once tissue residency was established.
Collectively, our findings demonstrate that the pool of pathogenic TRM in allergic skin constitute a dynamic compartment continuously remodeled through differential persistence, differentiation, trophic dependence and recirculation programs, providing new insights into the mechanisms regulating long-term tissue immunity.

Keywords: Tissue resident memory T cells - Heterogeneity, dynamic, maintenance - Allergic contact dermatitis.

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PI3Kd promotes T cell effector differentiation during chronic infection

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Persistent antigen exposure in chronic infections and cancer leads to a progressive state of T cell dysfunction known as exhaustion, which represents a major barrier to effective immune control, but allows antigen-specific T cells to persist. Understanding signaling pathways that mitigate exhaustion and reinvigorate CD8+ T cell effector function is a key goal for immunotherapeutic strategies. Here, we show that an activating mutant of phosphoinositide-3-kinase d (PI3Kd) led to a reduction of FoxO1-dependent TCF-1+ stem-like progenitor CD8+ T cells that are required for sustaining antigen-specific T cells in response to chronic viral infection. Nonetheless, mice expressing activated PI3Kd maintained CD8+ T cell responses that were skewed instead towards effector-like cells in a FoxO1-independent manner, associated with an amplified IL-21-STAT3 response axis and improved viral control. Activated PI3Kd limited TOX expression, prevented epigenetic changes associated with T cell exhaustion, and promoted effector differentiation and function from both progenitor stem-like cells and cells with an exhausted phenotype. Together, this work uncovers a key role for PI3Kd activation in shaping the balance and plasticity between effector function and exhaustion while promoting T cell persistence during chronic infection, providing insight for immunotherapeutic strategies.

Keywords: T cell exhaustion - CD8+ T cell - PI3Kd.

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Clinical session

CAR-T cell therapy for refractory autoimmune diseases

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Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B-cell malignancies and is now emerging as a promising strategy for severe and refractory autoimmune diseases. By inducing profound depletion of pathogenic B-cell populations, CAR-T cells may achieve an immune “reset” that differs fundamentally from conventional B-cell–depleting therapies.

Initial clinical experience with CD19-targeted CAR-T cells has shown sustained, treatment-free remissions in patients with severe systemic autoimmune diseases, including systemic lupus erythematosus, inflammatory myopathies, and systemic sclerosis. More recently, alternative targets such as BCMA and transient mRNA-based CAR-T approaches have expanded this concept to antibody-mediated diseases and plasma cell–driven autoimmunity.

This presentation will review the biological rationale for CAR-T cell therapy in autoimmune diseases in adults, summarize the main clinical evidence, and discuss current limitations, future perspectives, and the potential place of CAR-T cells within the therapeutic landscape.

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Clinical session

CAR-T cell therapy for juvenile-onset autoimmune diseases: a promising future?

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Objective
Juvenile-onset autoimmune diseases (jAD), including childhood-onset SLE (cSLE), juvenile dermatomyositis (JDM) and juvenile systemic sclerosis (jSSc), carry lifelong morbidity, cumulative treatment toxicity and rare drug-free remission (DFR). CD19 CAR T cell therapy is transformative in adults, giving strong rationale for extension to children.
Methods
Review of published reports on anti-CD19 CAR T therapy in autoimmune disease up to August 2026. Patient-level data were extracted from primary sources and supplementary tables; patients reported more than once were counted once.
Results
We identified 26 unique patients treated before 18 years, in 10 publications. Under European hospital exemption, 8 children (cSLE 4, JDM 3, jSSc 1; median age 15, range 5–17) achieved substantial improvement at median 16.5 months, with organ damage reversal and full immunosuppression withdrawal; toxicity was limited to grade 1 CRS (6/8) and grade 1 ICANS (1/8) (1). A phase 1/2 Chinese trial enrolled 18 SLE patients, 15 of them children: 14/18 reached DORIS remission at 6 months off immunosuppressants, with grade 1 CRS 72%, ICANS 17%, hypogammaglobulinemia 89% and grade ≥3 cytopenias 15/18 (2). Three further children appear as single case reports. Five juvenile-onset patients were treated as adults within an adult series, a population currently dispersed across adult cohorts.
Children differ from adults: more aggressive phenotypes, higher disease activity, greater corticosteroid exposure, and up to 25% of cSLE driven by monogenic innate immune defects, which may modulate efficacy and relapse risk. Pediatric-specific issues include humoral reconstitution, vaccination, fertility preservation and psychosocial burden (3). Cost-effectiveness has been assessed in adults only: in a German cohort CAR T reduced direct costs by over 90% with improved SF-36 at one year. Pediatric care costs about three times adult SLE, so the cost-per-QALY ratio should be more favourable in children, though unmodelled.
Safety requires caution: 26 children worldwide, no controlled trial, CRS and ICANS graded at cohort level only, age-dependent neurotoxicity tools.
Conclusion
CAR T therapy may deliver DFR while sparing decades of immunosuppression in jAD. Prospective pediatric trials with harmonized definitions, precise safety reporting and long-term surveillance are needed.

Keywords: Anti-CD19 CAR-T - Juvenile-onset autoimmune diseases - Immunosuppression withdrawal.

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Immune regulation of the extracellular matrix: at the crossroads of host protection and pathology

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IL-4 and IL-13, which both signal through IL-4Rα, are central mediators of the 'type 2' immune response, promoting control of helminth infection, suppressing inflammation and promoting tissue repair. These functions are in part mediated by macrophages. Much of what we have learned about these cytokines has come from studies of helminth infection, but their functions apply far more broadly. IL-13 regulates how the extracellular matrix (ECM) is modified, broken down, and rebuilt for effective repair. We have been particularly interested in how IL-13 regulates the formation and breakdown of Hyaluronan matrices in the lung. These complex ECM structures are induced in the lung in response to multiple challenges including nematode migration and infection with SARS-CoV2 and influenza. While important for repairing infection-mediated damage, these structures underpin severe disease when poorly regulated.

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The NLRP1 inflammasome: Scanning the borders

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Inflammasomes are intracellular multi-protein complexes that play essential functions in immunity against pathogens. Specifically, inflammasomes both promote a regulated form of cell death termed pyroptosis and trigger the release of the key inflammatory cytokines interleukin (IL)-1β and IL-18, two important processes in controlling microbial infections. Because of their involvement in various pathophysiological conditions, our understanding of inflammasomes has generated an ever-growing interest in the scientific and medical communities over the last 20 years. Yet, most of this knowledge comes either from the use of rodent models, which may lack the specific structural and functional characteristics of human inflammasomes, or from the use of immune cells, which express a wide range of inflammasomes but lack inflammasomes specifically enriched in non-immune cells. In this context, I will discuss about novel findings on the crucial immune function of the human NLRP1 inflammasome, highly expressed in airway, skin and corneal epithelia, in response to a broad range of infections but also environmental threats that converge to a specific stress pathway, the ribotoxic stress response.

Keywords: Genotoxins - Inflammasome - Barrier innate immunity.

References:

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P2-01

Constitutive macropinocytosis is coupled with reduced rates of protein synthesis to confer intrinsic protection against viral replication in macrophages

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Tissue surveillance is a major function of macrophages and requires the constitutive uptake of extracellular fluid via macropinocytosis. However, this process may be exploited by viral pathogens that evolved the ability to enter cells in endocytic compartments. It is unclear how macrophages cope with the need to constantly scan their environment without becoming a vehicle for viral propagation. Our previous work identified Growth Arrest-Specific-7 (GAS7), a plasma membrane-associated cytoskeleton adaptor, as a factor required for constitutive macropinocytosis in macrophages (1). Here, we demonstrate that the expression of GAS7 is also critical for macrophage control of the replication of a wide range of DNA and RNA viruses. Despite their increased internalization of extracellular fluid, GAS7-expressing macrophages demonstrate resistance to productive viral infection. Such protection is constitutive and does not require innate sensing or production of type I IFN. Instead, the expression of GAS7 leads to increased levels of phosphorylated Eukaryotic Elongation Factor-2 (EEF2) ultimately leading to decreased the rates of protein translation and resistance to viral replication. Stimulating macropinocytosis through expression of a constitutively-active RAC1 mutant, also promotes phosphorylation of EEF2 and reduced protein synthesis rates. Our work thus reveals a general mechanism in macrophages wherein active macropinocytosis is coupled to reduced protein synthesis. This limits the risk of increased viral replication that may arise in cells actively engaged in tissue surveillance.

Keywords: GAS7 - Macrophage - Viral infection.

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P2-02

LiveLung-TB: Intravital imaging reveals CD4⁺ T-cell dynamics during pulmonary Mycobacterium tuberculosis infection

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Objective
Protective immunity to *Mycobacterium tuberculosis* (Mtb) depends on the ability of CD4⁺ T cells to reach and stably engage infected macrophages within lung lesions. Histology reveals a persistent spatial segregation of T cells at the lesion periphery, but the dynamic processes underlying this segregation have remained inaccessible, as real-time imaging of a ventilated, infected lung under BSL-3 containment was previously impossible. We aimed to define, *in vivo*, how lesion architecture and antigen recognition shape T cell positioning and engagement.
Methods
We established the first BSL-3-compatible two-photon intravital microscopy platform enabling prolonged imaging of lungs infected with virulent Mtb. Antigen-specific CD4⁺ T cells were adoptively transferred into infected mice and tracked in real time. T-cell motility, positioning, and interactions with infected macrophages were quantified together with vascular organization and extracellular matrix architecture.
Results
LiveLung-TB revealed that most CD4⁺ T cells efficiently infiltrated tuberculosis lesions but accumulated predominantly at the periphery of infected macrophage clusters. Stable interactions with infected macrophages were rare, whereas most cells remained arrested or displayed intermittent migration in collagen-rich regions or around uninfected macrophage aggregates. Surprisingly, T-cell arrest occurred independently of antigen specificity, indicating that local tissue organization rather than TCR recognition primarily determines migratory behavior within lesions. These findings identify vascular remodeling, extracellular matrix organization, and lesion architecture as sequential barriers limiting productive immune surveillance.
Conclusion
Our study provides the first real-time visualization of adaptive immune responses in virulent pulmonary tuberculosis under BSL-3 conditions. By demonstrating that tissue architecture constrains T-cell access to infected macrophages independently of antigen recognition, LiveLung-TB identifies the infected lung microenvironment as a critical regulator of protective immunity. These results suggest that improving T-cell positioning within granulomas may complement strategies aimed at enhancing T-cell effector function, with implications for host-directed therapies and tuberculosis vaccine design.

Keywords: Lung Intravital Imaging - T lymphocytes - Tuberculosis.

References:

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P2-03

Mycobacterium tuberculosis isolates modulate levels of protective IL-1β *in vivo* accounting for disease severity

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Objective
Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), represents a major global public health challenge, accounting for approximately 10 million new cases and over 1.2 million deaths annually. Clinically, TB manifests along a spectrum of severity, depending on both pathogen diversity and host immune responses. We previously demonstrated that distinct Mtb isolates recovered from patients with mild or severe TB manifestations differentially modulate immune responses. Mtb isolated from mild TB patients induce robust macrophage cytokine responses, namely interleukin-1β (IL-1β), whereas Mtb from severe cases evade cytosolic surveillance and trigger weaker IL-1β responses. We aimed to elucidate the molecular mechanisms operating *in vivo* that determine mild or severe TB outcomes following infection with different clinical Mtb isolates.
Methods
C3HeB/FeJ mice were infected with selected clinical isolates causing mild (Mtb 4I2) or severe (Mtb 6C4) TB in humans, and lung bacterial burden, histopathology, and RNA sequencing of infected lungs were obtained to characterize the progression of infection and host transcriptional responses over time.
Results
Aerosol infection with Mtb 4I2 resulted in lower lung bacterial burdens, histopathology and higher IL-1 accumulation than those caused by Mtb 6C4, recapitulating our human data. RNA-seq data revealed a clear transcriptomic separation between Mtb 4I2 and 6C4-infected lungs as early as day 12 post-infection, with convergent signatures at later time points. At day 12, Mtb 4I2 infection showed enrichment of epithelial, $CD8^+$ T-cell, and NK-cell response modules, related to Mtb control. Interestingly, blockade of IL-1R during the first 2 weeks of infection with the high IL-1-inducing Mtb isolate was sufficient to cause increased bacterial burdens and pathology at later time points, highlighting the key early protective role of IL-1. We are now investigating the mechanism underlying early bacterial control and preliminary data suggest differential phagosome maturation following infection with the two clinical isolates.
Conclusion
Our findings highlight the role of Mtb genetic diversity in shaping early host immune responses and ultimately determining TB disease severity and outcome.

Keywords: Tuberculosis - Immune Response - Severity of disease.

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Trained granulopoiesis in cancer

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Abstract not received.

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Proliferating Cell Nuclear Antigen (PCNA): a central signalling scaffold orchestrating neutrophil plasticity in inflammation

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Abstract not received.

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The microbiota-derived metabolite Metab1 prevents neutrophil activation by inducing metabolic quiescence

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Inflammatory bowel disease (IBD) results from genetic predisposition, gut microbiota dysbiosis and environmental factors, leading to intestinal immune alterations and chronic inflammation. Especially, neutrophils are massively recruited to the intestinal lamina propria. Essential to host defense and repair, their overactivation participates in chronic inflammation and tissue damage. Interestingly, the alteration of neutrophil functions also leads to intestinal inflammation, and is associated with pronounced microbiota modifications, highlighting the central role of neutrophils at the host-microbiota interface. However, the interactions of neutrophils with the gut microbiota are nearly undescribed. Microbiota-derived metabolites have been shown to participate to intestinal homeostasis, IBD development and immune modulation, but their specific impact on neutrophils remains largely unknown. Here, we aim at deciphering the impact of microbiota-derived metabolites on murine and human neutrophil functions.
We screened 50 microbiota-derived metabolites for their capacity to regulate neutrophils. Notably, Metab1 inhibits several key effector neutrophil functions, including phagocytosis, ROS production, degranulation and bacterial killing, suggesting a non-targeted effect. Seahorse analysis show that Metab1 induces a metabolic quiescence in neutrophils by inhibiting both mitochondrial respiration and glycolysis, thereby reducing neutrophil activation and mortality upon stimulation. Mechanistically, Metab1 prevents mitochondrial membrane depolarization induced by stimulation.
The microbiota-derived metabolite Metab1, produced by commensal bacteria in the intestinal lumen, is able to prevent neutrophil activation by inducing a quiescence state in the cell. This metabolite could thus promote tolerance in the mucosa toward the microbiota, and participate in the host/microbiota co-evolution. It is crucial to better understand neutrophil roles in host-microbiota interactions in health and disease.

Keywords: Neutrophils - Microbiota-derived metabolite - Intestinal inflammation.

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NETs from rheumatoid arthritis patients trigger a pro-inflammatory response in monocytes through metabolic mechanisms and modulate macrophage differentiation

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Objective
Monocytes, macrophages (MΦ) and polymorphonuclear neutrophils (PMN) are activated in patients with rheumatoid arthritis (RA), a pro-inflammatory disease of unknown etiology. Mechanisms leading to activation of monocytes and those triggering MΦ differentiation are still unclear in RA. Activated PMNs expel neutrophil extracellular traps (NET), DNA/proteins fibers. Described as anti-microbial, NETs can become pro-inflammatory in RA (1). Increased NET formation has been reported in RA. Here, we studied the pro-inflammatory activity of NETs on monocytes, focusing on the effects of RA NETs on monocytes from healthy donors (HD). Moreover, we studied the impact of NETs during monocyte differentiation into MΦ.
Methods
Blood PMNs/PBMCs were isolated from HD and RA patients. Monocytes were purified from PBMCs by CD14-positive selection. NETs were induced *in vitro* by PMA and characterized by fluorescence imaging. Monocytes were cultured with RA NET, in the presence/absence DPI to inhibit reactive oxygen species (ROS) production. Alternatively, monocytes were differentiated into M0 MΦ with M-CSF for 7 days, in the presence/absence of NETs. After differentiation, MΦ were cultured with agonists of TLR4 or TLR9. Cell phenotype were estimated by flow cytometry. Cytokine secretion was measured by ELISA. ROS production was measured by chemiluminescence. Metabolic profiles were analyzed using Seahorse technology.
Results
RA NETs activate monocytes, leading to the secretion of pro-inflammatory cytokines and ROS production. Particularly, NETs triggered the secretion of RA-associated pro-inflammatory cytokines, but not of the immuno-modulatory cytokine IL-10. To better understand the mechanisms involved, monocytes were cultured with DPI; inhibition of ROS production impaired NET-mediated activation. Moreover, monocytes display early modifications of their metabolic profile in response to NETs, as evidenced by increased oxygen consumption rate, indicating that mitochondrial respiration was enhanced. Finally, M0 MΦ differentiated in the presence of NETs have a higher capacity to produce IL-8 after TLR9 stimulation, while they release lower amounts of IL-6 in response to TLR4 stimulation, highlighting a dual response.
Conclusion
Abnormal accumulation of NETs in the extracellular space may be a major trigger capable to activate monocytes within a pathogenic pro-inflammatory response; then NETs interfere with MΦ differentiation and modulate their inflammatory profile.

Keywords: Neutrophil extracellular traps - Inflammation - Rheumatoid arthritis.

References:

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Role of neutrophils in Chlamydia driven Reactive arthritis in the SKG mouse

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Objective
Chlamydia infection triggers reactive arthritis (ReA) in 4% of infected patients. While macrophages systemically disseminate *Chlamydia*, the role of neutrophils in ReA remains poorly understood. We characterized neutrophil involvement in triggering ReA using the SKG mouse model of spondyloarthritis (SpA).
Methods
1- SKG mice were infected with *Chlamydia muridarum* (Cmu) and depleted of neutrophils using anti-Ly6G during early infection (days 0–33), late infection (days 33–55), or treated with isotype control. Disease progression, arthritis incidence, ankle histology (MPO, CD3, H&E), and serum anti-Cmu antibodies (ELISA) were evaluated.
2- SKG and BALB/c mice were infected ± anti-Ly6G and evaluated 7 days post-infection (dpi) for reproductive tract macrophage phenotypes and systemic inflammation. Anti-Cmu IgM levels were measured at 3 and 7 dpi.
3- Bone marrow neutrophils from both strains were infected *ex vivo* with Cmu to evaluate activation and clearance efficiency via flow cytometry.
Results
1 - Early neutrophil depletion significantly increased arthritis incidence and severity in SKG mice compared to isotype controls, whereas late depletion had no effect. Histologically, both early- and late-depleted mice exhibited higher neutrophil joint infiltration, but only early-depleted mice had double the infiltrating T cells. Early-depleted mice also displayed elevated anti-Cmu IgG1 and IgG2a levels.
2 - At 7 dpi, both strains showed increased genital tract neutrophils. Anti-Ly6G treatment efficiently depleted neutrophils and induced pro-inflammatory M1 macrophages (substantially in SKG, modestly in BALB/c). In SKG spleens, Th17 cells doubled following depletion. Anti-Cmu IgM titers rose markedly at 7 dpi exclusively in neutrophil-depleted mice of both strains.
3 - *Ex vivo* Cmu infection of SKG neutrophils induced dose-dependent mortality and $CD62L^-$ activation, while downregulating anti-inflammatory N2 markers (PD-L1, CD206).
Conclusion
Neutrophils exert a protective role during early Cmu infection by restricting subsequent joint T-cell infiltration and curbing arthritis development. The *ex vivo* anti-inflammatory profile of neutrophils and the *in vivo* emergence of pro-inflammatory M1 macrophages upon their depletion further confirm this regulatory role.

Keywords: Neutrophils - Translational medicine - Spondyloarthritis.

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Human Treg cell therapies for transplantation

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Abstract not received.

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Personalized T-cell therapies for solid cancers

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Ex vivo expansion of tumor-infiltrating lymphocytes can lead to durable tumor regression in patients with metastatic melanoma. Accumulating evidence suggests that TIL frequently recognize neoantigens and that neoantigen reactive TIL play an important role in the antitumor responses of patients treated with immune checkpoint blockade and TIL therapy. These are optimal targets for cancer immunotherapy as their expression is exquisitely confined to the tumor site, and T cells targeting these antigens have not undergone negative selection in the thymus. Despite the promising efficacy of TIL therapy against melanoma tumors, current research in the field focuses on trying to extend this efficacy to other tumor types. We will discuss the existing possibilities to develop personalized T-cell therapies targeting neoantigens for solid cancers, with particular emphasis on minimally invasive T-cell therapies.

Keywords: Tumor-reactive TILs - TCRs - Adoptive Cell Therapy.

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Allogeneic CARγδT-cells recognize CD33 and PVR to target Acute Myeloid Leukemia and suppress tumor progression

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Chimeric antigen receptor (CAR)-T-cells hold promise for the treatment of myeloid malignancies, but there is the need to develop safe allogeneic approaches to overcome the limitations of autologous CAR-T-cells. γδ T-cells have gained substantial interest owing to their human leukocyte antigen (HLA)-independent functions, with Vδ1⁺ γδ T-cells demonstrating anti-tumor activity in preclinical models of acute myeloid leukemia (AML). This notwithstanding, therapeutic efficacy requires optimal levels of cytotoxicity and T-cell accumulation in the bone marrow. To promote these traits, we have investigated the utility of engineering Vδ1⁺-enriched T-cells to express a CAR targeting the AML-associated antigen, CD33. So-called "CD33CARγδT-cells" displayed markedly increased cytotoxicity against AML cell lines and primary patient samples when compared to untransduced cells. In an orthotopic (intra-tibia) xenograft AML mouse model, CD33CARγδT-cells displayed robust expansion in the bone marrow and striking suppression of tumor growth and dissemination into the bloodstream and distant organs. Additionally, CD33CARγδT-cells expressed DNAM-1 that binds to its stress-induced ligand PVR on AML cells, offering an additional, CAR-independent mode of tumor recognition that might mitigate the impact of CAR antigen loss or heterogeneity. These findings highlight the potential of CD33CARγδT-cells as a next-generation immunotherapeutic strategy for myeloid malignancies.

Keywords: CAR γδ T cells - Allogeneic therapies - Acute myeloid leukemia.

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A 'Sense-and-Reprogram' Platform for Systemic Cancer Immunotherapy

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Objective

Cell-based cancer immunotherapies are constrained by complex manufacturing and poor efficacy in solid tumors. Although systemic delivery for *in vivo* chimeric antigen receptor (CAR) T-cell therapy is emerging, there remains a critical need for immune engineering strategies that can overcome the immunosuppressive solid tumor microenvironment (TME). *In vivo* direct somatic reprogramming into conventional type 1 dendritic cells (cDC1s) via intratumoral delivery of the transcription factors PU.1, IRF8, and BATF3 (PIB), is an off-the-shelf modality capable of eliciting anti-tumor immunity within suppressive TMEs (1,2). However, clinical translation from intratumoral to systemic delivery requires spatial control. This project proposes a synthetic 'sense-and-reprogram' platform using synthetic Notch (SynNotch) receptors (3) to enable TME-restricted activation of PIB upon tumor-associated antigen recognition. By leveraging the intrinsic tumor-homing capacity of monocytes, this strategy aims to use them as targeted delivery vehicles for in situ immune-cell reprogramming.

Methods

Human monocytic cell lines (THP1 and U937) were engineered with a synthetic Notch receptor (SynNotch) comprising a FLAG-tagged extracellular domain that recognizes human CD19 and the intracellular domain is linked to Gal4. These cells were co-transduced with a construct containing a Gal4-inducible PIB-AzamiGreen and a constitutive BFP reporter. BFP^+FLAG^+ cells were sorted and co-cultured with $CD19^+$ sender cells, both adherent ($T98G\text{-}CD19^+$) and in suspension ($K562\text{-}CD19^+$).

Results

SynNotch activation, evidenced by AzamiGreen expression and HLA-DR upregulation, was triggered by CD19 recognition and abrogated by the gamma-secretase inhibitor DAPT, confirming that reprogramming is SynNotch-dependent. These results were consistent across both conditions at day 5 and day 9 post co-culture. Reprogramming efficiency was significantly improved under 3D spheroid culture conditions compared to standard 2D cultures, likely reflecting enhanced and more sustained cell-cell contact between receiver and sender cells. Furthermore, intratumoral validation in $CD19^+$ tumor models confirmed SynNotch-dependent circuit activation and cDC1 reprogramming *in vivo*.

Conclusion

Collectively, these outcomes provide proof of concept for spatiotemporal controlled monocyte mediated immune reprogramming, highlighting the potential of SynNotch-based platforms for precise, systemically deliverable cancer immunotherapy.

Keywords: Synthetic Notch (SynNotch) receptors - Dendritic cell reprogramming - Cancer immunotherapy.

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Engineering Regulatory T Cells For Rheumatoid Arthritis: Development and Evaluation of CAR Constructs

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Introduction
Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes progressive joint destruction. While treatments aim to control inflammation, they act through broad immune suppression causing significant side effects.
Objective
Regulatory T (Treg) cell-based therapies are an attractive strategy but limitations remain. Antigen (Ag) specific Tregs targeting citrullinated proteins could allow suppression at the site of inflammation while avoiding systemic immunosuppression. Engineering Tregs with Chimeric Antigen Receptor (CAR) is one strategy to produce Ag-specific Tregs. Although CAR designs have been extensively studied in conventional T cells (Tconv), there is no consensus on the optimal CAR construct that would ensure Treg functionality without destabilisation. We aimed to study the effect of second- and third-generation CARs in Tregs.
Methods
Our second (CD28) and third-generation (CD28_4-1BB) CAR constructs contain an scFv derived from a monoclonal ACPA identified from an RA patient. We purified naïve Tregs (nTregs) from healthy PBMC and determined the best MOI to transduce them using a lentiviral vector expressing ZsGreen. Engineered J.RT3-T3.5 JURKAT cells were used to assess CAR-induced activation, using CD69 expression as an activation marker. A third generation anti-CD19 CAR was used as a positive control. In Tregs, we compared the effect of our second- and third-generation CAR, in the absence of CAR-dependent activation. We assessed phenotypic stability by multiparametric flow cytometry and function using an in vitro suppression assay.
Results
Under Ag-independent conditions, nTregs transduced with either the second- (CD28), or third-generation (CD28_4-1BB) CAR construct, displayed a stable phenotype with similar expression of FoxP3, Helios and suppressive molecules like CTLA-4, LAG3 and PD-1. CAR-Treg expansion was comparable to untransduced (UT) nTregs after 23 days of cell culture. Finally, the suppressive function of both CAR-Tregs were similar to UT nTregs on day 10 and day 20.
Conclusion
Our results provide the basis for future studies to use these second and third-generation CAR constructs, as they do not seem to intrinsically destabilize Tregs. This contributes to ongoing efforts to define optimal CARs for Treg-based therapies and provide insight into how CAR signaling can influence Treg stability.

Keywords: CAR-Tregs - Second-generation CD28 CAR - Third-generation CD28_4-1BB CAR.

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The lung stroma sustains a plasma cell niche for long-term mucosal protection against infection

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Long-lived plasma cells (PCs) sustain durable humoral immunity through continuous antibody production. Here, we show that respiratory infection establishes a tissue-resident PC compartment in the lung that persists for at least one year and continuously secretes antibodies into the bronchoalveolar space. Using fate mapping, BCR-seq trajectory analysis, and parabiosis, we show that germinal centers within tertiary lymphoid organs generate a continuum of newly formed and long-lived PCs, with early PC progeny able to seed the bone marrow before established lung PCs become tissue resident. Unlike bone marrow PCs, lung PCs do not require the canonical CXCL12-CXCR4 retention pathway but instead depend on CCR10, with peribronchial fibroblasts providing CCL27 to define a local stromal niche. Selective depletion of lung PCs, while preserving bone marrow PCs and circulating antibodies, accelerates viral invasion. Thus, lung PCs form a distinct arm of tissue-resident humoral memory that provides non-redundant protection against respiratory reinfection.

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T Follicular Regulatory Cell Homeostasis at the Crossroads of Germinal Center Dysfunction

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Germinal centers (GCs) are lynchpins of protective humoral immunity, require complex regulation when impaired may contribute to a spectrum of GC-relevant diseases, including disorders caused by autoantibody production or poor vaccine responses.
The integrity of GCs relied upon T follicular regulatory cells (Tfr), a regulatory subset that ensure antibody affinity for pathogens while decreasing self-recognition. Despite displaying a dual function in GCs reaction, Tfr cells were originally described as affiliated exclusively to Tregs, a population expressing autoreactive T-cell receptors (TCRs). However, this dogma has been challenged, first, by the description, in mice, of a Tfr subset, descending from Tfh cells, expressing vaccine-specific TCRs.
Futhermore, we demonstrated that human tonsillar Tfr cells can be clonally sub-divided into two populations by single cell technologies; one related to Tfh cells lineage (iTfr) and the other to “naturally” derived Tregs (nTfr). Following clonal identification, we found the key genes and proteins distinguishing these two ontogenically distinct populations, including CD38, a reliable tonsillar iTfr cell surface biomarker. Using CD38 as a handle, and a multiplex microscopy approach, we mapped the precise *in situ* locations of iTfr and nTfr cells within the follicle. We discovered that tonsillar iTfr cells preferentially resided in GCs, nearby clonally related Tfh cells whereas nTfr cells are excluded from GCs and stayed closer to Tregs in the follicular mantle. More recently, using the same technical approach, we demonstrated that the ontogeny-related heterogeneity observed in tonsillar Tfr cells is also reflected in the circulating Tfr compartment, where CD38 similarly distinguishes iTfr from nTfr cells. Building on the identification of these circulating Tfr subsets, we investigated their relevance in rheumatoid arthritis, a disease associated with GC dysregulation. Notably, we observed a decreased frequency of iTfr cells alongside an increased frequency of GC-like Tfh cells in the blood of patients experiencing severe flares, suggesting a potential imbalance in Tfr-mediated regulation of Tfh cell differentiation.
Together, these findings highlight Tfr cell heterogeneity as a key dimension of GC regulation and suggest that distinguishing Tfr subsets may provide new insights into the mechanisms underlying humoral immune dysregulation in health and disease.

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Modeling memory B cell responses in spleen-derived immune organoids

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Objective
Much of our understanding of adaptive immunity is derived from mouse studies, which are often difficult to validate in humans. While tonsil-derived organoids have successfully recapitulated some aspects of antigen-specific responses to vaccination, they are prone to bystander activationdue to their chronic inflammatory state. The human spleen, a critical reservoir for memory B cells, currently lacks a similar *in vitro* model. Given its rich microenvironment and high cellular yield, a splenic model could provide a superior platform for studying human memory B cell responses.
Methods
Human splenic tissues were collected from organ donors (post-2021) with documented immunity against SARS-CoV-2. We developed a gel-based 3D culture system designed to mimic the high cellular density of the native splenic tissue. These organoids were stimulated with various formulations of SARS-CoV-2 antigens, and cellular responses were analyzed by flow cytometry.
Results
Stimulation with SARS-CoV-2 spike protein for seven days triggered clear plasmablast (PB) differentiation in 93% of donors (29/31), with Receptor binding domain (RBD)-specific PBs detected in 68% of them (21/31), reaching up to 30% of the PB pool. CD71 staining combined with *in vitro* cell division tracking highlighted efficient activation of most RBD-specific memory B cells in these organoids. And BCR repertoire analyses confirmed a polyclonal plasmablast repertoire at the end of the culture, which further recapitulated interclonal differences in proliferative expansion previously described *in vivo*. Stimulation with mRNA-based SARS-CoV-2 vaccines also led to strong antigen-specific MBC activation, allowing for the fine cartography of preexisting repertoire recall by annual variant-encoding vaccine formulations. Finally, the intrinsic flexibility of the assay and high number of available cells also allowed parallel testing of CD4 T cell help or BCR signaling inhibitors as well as fine tuning of *in vitro* culture parameters, including cellular density and the integration of stroma components such as follicular dendritic cell-like cells for the study of stromal-immune interactions.
Conclusion
Overall, we have developed a novel and versatile spleen-derived immune organoid model effectively recapitulating B cell recall responses *in vitro* to both protein and last generation mRNA-based vaccines. This makes it a valuable tool for addressing both fundamental and translational research questions in human immunology.

Keywords: B cell responses - Organoids - Vaccines.

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Type 3 inflammation shapes the Follicular Regulatory T cells (Tfr) into a Tfr17 polarized subset

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Germinal center (GC) reactions are essential for the generation of high-affinity, long-lived humoral immunity following vaccination or infection[1]. These responses are orchestrated by follicular helper T (Tfh) cells, promoting B cell differentiation, and follicular regulatory T (Tfr) cells, limiting autoantibodies generation[2]. Depending on the inflammatory context, Tfh differentiate into type 1, type 2 or type 3 subsets that shape pathogen-specific B-cell differentiation and antibody class switching[3]. In contrast, whether Tfr exhibit similar functional plasticity to selectively regulate polarized GC responses remains largely unknown.
We hypothesized that Tfr adapt to the inflammatory environment by differentiating into specialized polarized subsets. Unsupervised flow cytometry analysis of human tonsils identified multiple polarized Tfr populations, including a predominant RORγt-expressing subset, termed Tfr17. A homologous population was induced in mice only following type 3 immunization with complete Freund's adjuvant, reaching maximal frequency 14 days post-immunization before declining along with the GC structure. Phenotypic characterization demonstrated that Tfr17 retain, and even enhance, their regulatory and follicular features while acquiring their own signature illustrated by the production of IL-17A in both humans and mice. To investigate their spatial organization, we combined multiplex microscopy with spatial transcriptomics of secondary lymphoid organs. Few Tfr17 were detected throughout the GC (predominantly in the light zone) but most of them were localized outside, at the T-B border and within the B-cell mantle. This specific spatial distribution suggests that Tfr17 might regulate early stages of the GC reaction, potentially by controlling the initiation of class-switch recombination before full GC maturation. Our findings reveal an unexpected degree of functional plasticity within the Tfr compartment and identify Tfr17 as a previously unrecognized type 3-polarized regulatory T-cell subset conserved in humans and mice. The distinct phenotype, cytokine profile and spatial distribution of Tfr17 support the concept that Tfr-mediated regulation is tailored to the inflammatory context, providing a mechanism for selective control of polarized GC responses. These results establish a new framework for understanding Tfr specialization and may offer novel opportunities to modulate humoral immunity during vaccination, infection and autoimmune diseases.

Keywords: Germinal center - Follicular Regulatory T cells - Polarization.

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Plasma cell heterogeneity is imprinted by the type of immune challenge

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Plasma cells are the key players of humoral immunity, through their ability to produce quantities of antibodies. Over the past decade, researchers have documented a range of plasma cell heterogeneity, spanning maturity, cytokine production and immunoglobulin isotype. However, the origin of this heterogeneity remains unclear, and there are no specific surface markers that could be used to investigate its function.
In this study, we characterised five plasma cell subpopulations, named A to E, in human and mouse lymphoid tissues using a protein expression-based approach involving mass cytometry. With a restrained marker list comprising CD62L, CXCR4, FcγRIIB and CD93, these subpopulations could be easily distinguished by flow cytometry based on their differential expression. We showed that specific plasma cell subpopulations were induced according to the type of immune challenge. T-independent immunisation induced the A subpopulation, whereas T-dependent vaccination gave rise to the E subpopulation. However, in an infectious context, the cellular and cytokine environment of plasma cells is modified, leading to the generation of the B subpopulation. Interestingly, the B and E subpopulations express CD93 and exhibit distinct migratory and maintenance capabilities *in vivo*. Subpopulation B has an inherent advantage in terms of persistence in the lymph nodes and migration into the bone marrow. In contrast, subpopulation E is retained less effectively in the lymph nodes, but migrates more slowly into the bone marrow and appears to be more likely to persist there in the long term.
These results have implications for improving plasma cell maintenance in vaccine strategies and suggest that close attention should be paid to the type of plasma cell subpopulation induced. Classifying plasma cell subtypes could facilitate analysis of heterogeneity in other conditions, including autoimmune diseases and malignant transformation, where plasma cells play a key role. Characterising their heterogeneity could aid diagnosis and, in the long term, enable therapies to be adapted according to the plasma cell subpopulations involved.

Keywords: Plasma cell - Heterogeneity - Humoral response.

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Clinical session

Breaking Barriers Across Species: The Immunopathological Frontiers of Xenotransplantation

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Xenotransplantation represents a promising strategy to address the shortage of human donor organs, yet its clinical translation remains limited by complex immunological barriers that are activated immediately upon reperfusion of the graft. This presentation will focus on the mechanisms underlying xenograft hyperacute and acute vascular rejection, driven by preformed “natural” xenoantibodies recognizing conserved endothelial epitopes. These early antibody–antigen interactions rapidly trigger complement activation and endothelial injury, setting the stage for graft dysfunction. In parallel, early innate immune responses involving macrophages, neutrophils, and NK cells amplify vascular inflammation and promote microthrombosis. Finally, intrinsic physiological incompatibilities between donor and recipient endothelium—including dysregulated coagulation and impaired complement regulation—further destabilize vascular homeostasis and contribute to graft failure.

Keywords: Xenotransplantation - Microvascular rejection - Transplantation.

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Clinical session

Lessons from the First Human Xenotransplants

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Abstract not received.

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Nociceptor neurons control inflammation

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Nociceptor neurons detect tissue injury and orchestrate protective responses, yet their influence on antitumor immunity and innate immune adaptation remains incompletely understood. Our work investigates how these sensory neurons shape immune function within tumors and regulate hematopoietic responses associated with trained immunity.

Using complementary genetic and pharmacological approaches in preclinical cancer models, we identify nociceptors as active regulators of the tumor immune microenvironment. In triple-negative breast cancer, sensory fibers innervate tumors and draining lymph nodes, while tumor-derived signals engage a proNGF–NGFR program that promotes neuronal activation and neuropeptide release. Nociceptor silencing or ablation reduces tumor growth, enhances dendritic-cell activation, and strengthens $CD8^+$ T-cell and natural killer-cell effector programs. Distinct sensory neuron populations exert different immunoregulatory effects, with $MrgD^+$ neurons preferentially influencing macrophage-associated programs. Targeting the calcitonin gene-related peptide (CGRP)–RAMP1 pathway further improves responses to PD-1 blockade.

Complementary studies extend this neuroimmune framework to innate immune training. Preliminary findings in β-glucan-treated mice reveal that nociceptor ablation increases hematopoietic stem-cell and myeloid-cell populations, including activated neutrophils and $CCR2^+$ monocytes. Nociceptors also influence subsequent macrophage responsiveness: the reduction in lipopolysaccharide-induced IL-6 production observed in bone-marrow-derived macrophages from neuron-intact, β-glucan-treated mice is absent following nociceptor ablation. These findings suggest that sensory neurons regulate both hematopoietic adaptation and functional responses following innate immune conditioning.

Together, our work positions nociceptor neurons as regulators of local tumor immunity and systemic myeloid adaptation. Defining these neural circuits may reveal opportunities to improve cancer immunotherapy and modulate trained immunity.

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It's all about the neighbourhood: regulation of immunity in the allergic lung

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Many lung diseases are characterized by airway inflammation in conjunction with pathological tissue remodeling. There is growing recognition of the importance of type2 inflammation in tissue healing, with archetypal type2 cells thought to be integral to the tissue repair process. We have determined that the local environment provides directional cues that dictate movement of cells within the lung, and this impacts the course and magnitude of local tissue inflammation. This presentation will focus on the cellular and molecular interactions that govern development of inflammation and remodeling in the lung, with special emphasis on the spatial neighbourhoods that influence cell phenotype and function .

Keywords: Asthma - Remodelling - T2 immunity.

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Non-immune function of myenteric mast cells in supporting neuronal plexus homeostasis

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Mast cells (MCs) are tissue-resident sentinels traditionally studied in the context of IgE-mediated allergy and mucosal immunity. More recently, MCs have emerged as biological hubs capable of integrating immune and neuroendocrine information. Yet whether discrete MC subsets contribute to non-immune facets of tissue physiology remains elusive. Here we identify a rare population of MrgprB2$^+$ myenteric MCs (myMCs) positioned in anatomical association with myenteric plexuses. We demonstrate that myMCs are maintained in a tonic activation state through a bidirectional feedforward loop with *Tac1*$^+$ (substance P-producing) enteric neurons. Genetic ablation of myMCs leads to rapid alterations of enteric neuro-structural functional programs, impacting neuropeptides expression, ileal contractility, glucagon-like peptide-1 (GLP-1) secretion and glucose homeostasis; whereas *Tac1* deficiency prevents local myMCs tonic activation. These findings uncover a previously unrecognized role for myMCs as active components of gut neuro-muscular circuits, extending their function beyond defense toward the direct regulation of organ physiology and metabolic homeostasis.

Keywords: Neuro-immune interactions - Mast cells - Enteric neurons.

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Role of mast cells in bone vaso-occlusive crisis and pain of sickle cell disease

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Objective
Vaso-occlusive crises (VOCs) are a hallmark of sickle cell disease (SCD) and cause severe bone pain, the underlying mechanisms of which remain unclear. The periosteum is densely innervated by nociceptive fibers, richly vascularized, and contains a substantial population of mast cells, being therefore relevant to VOC-associated pain. Mast cells have been implicated in SCD-associated pain, but their contribution within the bone compartment remains unexplored. We investigated periosteal mast cell activation during experimental VOC and assessed whether SCD-associated inflammatory and hemolytic mediators can directly trigger mast cell degranulation.
Methods
Bone VOC was induced in homozygous (HbSS) Townes SCD mice by hypoxia/reoxygenation and outcomes compared with HbAA (healthy) controls and normoxic conditions. Periosteal mast cells and their degranulation were quantified in toluidine blue-stained bone sections, using a custom deep-learning model developed in QuPath. *In vitro*, mouse peritoneum-derived mast cells (pMCs) and the LAD2 human mast cell line were stimulated with SCD-relevant mediators, including hemin (protoporphyrin + oxidized iron) and hemoglobin S (HbS). Degranulation was assessed by β-hexosaminidase and histamine release.
Results
Periosteal mast cell numbers were comparable between HbAA and HbSS mice (n=7 minimum per group). Hypoxia/reoxygenation induced significantly higher periosteal mast cell degranulation in HbSS mice than in HbAA mice (median [IQR] 1412 [688.6-2444] vs 491.9 [344.4-629.9] granules/mm2, p=0.017), with increased degranulation in HbSS mice during VOC compared with normoxic steady-state conditions (1412 [688.6-2444] vs 399.6 [345.1–700.0] granules/mm2, p=0.026). This effect was periosteum-specific, with no corresponding increase in liver, kidney, or skin. *In vitro*, hemin induced dose-dependent degranulation of pMCs, whereas HbS or HbA did not. Hemin-induced degranulation was also observed in LAD2 human mast cells, although at higher concentrations. Hemin concentrations inducing significant degranulation were not cytotoxic.
Conclusion
Our findings identify the periosteum as a site of mast cell activation during experimental VOC and demonstrate that heme, a major product of intravascular hemolysis, directly induces mast cell degranulation, whereas HbS itself does not. These results support a model in which vaso-occlusion-driven local hemolysis promotes a heme-mast cell-nociceptor axis contributing to bone pain during VOC.

Keywords: Sickle cell disease - Bone pain - Mast cell.

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A new mouse model expressing human IgE and its receptors FcεRI and CD23 predicts a superiority for ligelizumab over omalizumab in anaphylaxis

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Allergy affects around 30% of the population worldwide. Upon allergen exposure, binding of the allergen to IgE linked to their high affinity receptor FceRI on the surface of mast cells and basophils activates these cells, and the release of histamine and other mediators responsible for allergic symptoms. In rare cases, this can cause a life-threatening systemic reaction called anaphylaxis. IgE also binds CD23, mainly expressed on B cells and which function in allergy remains poorly understood. Anti-IgE monoclonal antibodies (mAbs) have been developed to neutralize IgE. Omalizumab is approved for asthma, chronic spontaneous urticaria and food allergy. Another anti-IgE, ligelizumab, was developed with a higher affinity for IgE. Surprisingly, this mAb did not provide clinical benefit in asthma compared to omalizumab. However, it showed efficacy in food allergy trials but was discontinued following omalizumab approval.

Objective

To better understand the mechanisms of action (MOA) of the anti-IgE mAbs omalizumab and ligelizumab, and compare their efficacy in a model of anaphylaxis in novel mice humanized for IgE, FceRI and CD23.

Methods

We developed a novel knocked-in (KI) mouse expressing human IgE, FceRI and CD23 in place of the respective mouse proteins. The expression of the transgenes was characterized by flow cytometry and ELISA. We compared the MOA of omalizumab and ligelizumab *in vitro* using mast cells and B cells derived from in hIgE/hFceRI/hCD23KI mice. The efficacy of these mAbs was assessed in a model of hIgE-mediated anaphylaxis *in vivo*.

Results

We confirmed that ligelizumab is more potent than omalizumab at blocking binding of hIgE to hFceRI on mast cells, but less potent at inhibiting binding of hIgE to hCD23 on B cells. *In vivo*, both mAbs markedly reduce circulating hIgE levels as well as hIgE and hFcεRI levels at the surface of blood basophils and peritoneal mast cells. However, ligelizumab is superior to omalizumab at blocking hIgE-mediated systemic anaphylaxis.

Conclusion

This new humanized mouse model represents an interesting preclinical tool to test novel anti-hIgE therapies. Our data suggest that ligelizumab would be more potent than omalizumab at protecting against anaphylaxis, the most severe clinical manifestation of allergy.

Keywords: IgE - anti-IgE - Humanized mouse model.

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Fungal infections imprint the Th17 pool by establishing a distinct memory Th17 population

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T helper (TH) 17 cells exist along a spectrum of states, from homeostatic populations that maintain tissue integrity to pathogenic cells that drive inflammation. They also play a crucial role in antifungal host defense. Understanding the factors that drive this functional heterogeneity could reveal how the protective and pathogenic mechanisms are balanced. Here, we identified infection history a key determinant of heterogeneity within the TH17 compartment. We show that prior infections expand a heterogeneous TH17 pool that displays memory-like features and occupies a distinct transcriptional state that lies in between homoeostatic and pathogenic programs. They exhibit high migratory capacity and rapidly infiltrate the sites of heterologous infection, where they are activated in an IL-23-dependent manner, mounting an early TH17 response. Functionally, these cells accelerate fungal clearance during subsequent heterologous challenges. Overall, we uncovered the ability of prior infections to modulate the functional capacity and heterogeneity of TH17 cells.

Keywords: Th17 - Fungal infection.

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Regulation of functional adaptation of tissues by innate lymphoid cells

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Innate lymphoid cells (ILC) are a recently discovered group of tissue-resident innate lymphocytes, that often take up residency in tissues during embryonal development. A current focus of our research is to obtain a molecular understanding of how the innate immune system and in particular ILC, by integrating environmental signals (such as those from the indigenous microbiota), contribute to tissue physiology. Recent studies have revealed ever more intriguing relationships between ILC and basic developmental and biologic processes that are likely to reveal unsuspected pathways by which the immune system might be plumbed to improve health and healthspan. These lines of research have suggested new paradigms for the immune system and for processes such as tissue homeostasis, tissue resilience, morphogenesis, metabolism, regeneration and growth.

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A TAK1-Driven NLRP1 Inflammasome Pathway Revealed by Phosphatase Targeting Environmental Toxins

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Inflammasomes are multiprotein complexes that control inflammation, host defense, and tissue repair. They assemble in response to pathogenic microorganisms or environmental signals, activating caspase-1, which in turn processes proinflammatory cytokines and induces pyroptotic cell death. While essential for immunity, their dysregulation contributes to inflammatory diseases.
Human NLRP1, the first identified inflammasome sensor, is a prominent innate immune sensor strongly expressed in human epithelial barrier. NLRP1 is highly sensitive to phosphorylation dependent activation, indicating a need for tight phosphatase control to prevent excessive inflammasome activity. In this study, we identified the phosphatases PP1 and PP2A as negative regulators of the NLRP1 inflammasome in human keratinocytes. Accordingly, exposure to the environmental toxins Dinophysistoxin, Okadaic acid, and Cantharidin, which inhibit PP1 and PP2A, triggered NLRP1 inflammasome activation. Notably, this toxin-induced activation process relied on hyperactivation of the MAP3 kinase TAK1. Mechanistically, both TAK1 and its downstream effectors p38 kinases phosphorylated and activated the NLRP1 inflammasome. Further studies underscored that TAK1 also contributed to the NLRP1 inflammasome activation during double-stranded RNA stimulation and viral infection. Finally, human native skins exposed to environmental toxins underlined the role of the PP1/PP2A-regulated TAK1/p38 axis in the development of skin dermatitis. Thus, these findings reveal a novel pathway of phosphorylation driven NLRP1 activation and expand our understanding of its regulation in epithelial immunity.
Paradis et al., under review (2026), pre-print : https://doi.org/10.64898/2026.01.23.70123

Keywords: Innate immunity - Skin.

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The Postnatal Stress Response Drives Long-Term Maladaptation of the Intestinal Epithelium via TLR3/TRIF Epigenetic Memory

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The postnatal period is a critical developmental window during which tissues adapt to the external environment. In the intestinal epithelium, this phase is marked by profound structural and transcriptional maturation. While these developmental transitions are genetically programmed, they are strongly influenced by early environmental cues, including microbial colonization, dietary shifts, and maternal care. Disruptions during this window activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated systemic glucocorticoid levels that alter developmental trajectories.

In this study, we investigated the mechanisms linking early-life stress to heightened intestinal susceptibility to inflammation later in life. Using dexamethasone to simulate stress hormone exposure in one-week-old mice, we evaluated the transcriptomic, epigenomic, and functional consequences on the intestinal epithelium in both neonates and adults.

Our findings reveal that early-life stress response activation induces intestinal epithelial cell depletion accompanied by accelerated maturation, precocious differentiation, and upregulation of endogenous retroviruses (ERVs). Mechanistically, this precocious transition induces TLR3 signaling, establishing a persistent, TRIF dependent epigenetic memory. Pharmacological blockade of TRIF attenuated this epigenetic imprint, restoring stemness profiles and protecting adult mice against experimental colitis.

Together, our data demonstrate that postnatal stress response activation drives maladaptive programming of the intestinal epithelium via TLR3/TRIF mediated epigenetic memory, compromising long-term functional flexibility and environmental resilience. These findings highlight the vulnerability of the early-life developmental window in shaping lifelong epithelial health.

Keywords: Post natal development - Resilience to inflammation - Mucosal immunology.

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TLR5 signaling amplifies airway epithelial cell responses to type I interferon through MyD88–JAK1 crosstalk during influenza infection in pigs

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Objective
Swine influenza A viruses (SIAV) are a persistent threat to animal and public health. Vaccination remains the principal control strategy for influenza, but its effectiveness is limited by antigenic drift of circulating field viruses. On the other hand, antiviral drugs for human influenza, have a narrow therapeutic window, suffer from widespread resistance, and are currently not considered as a suitable option by the livestock sector. An alternative strategy involves the boost the lungs immunity through the activation of Toll-like Receptor 5 (TLR5) with flagellin. While flagellin, a TLR5 agonist, has an established role in shielding against respiratory bacterial infection, its role in shaping antiviral defenses in the airway epithelium remains poorly understood. Our objective was to investigate whether flagellin can modulate the antiviral response in airway epithelial cells (AECs) to SIAV.
Methods
Porcine bronchial epithelial cells were infected with SIAV H3N2 (MOI 0.1) and treated 1 h later with flagellin (100 ng/mL). We evaluated interferon (IFN)-stimulated gene (ISG) expression by RT-qPCR and infectious titer by $TCID_{50}$. CRISPR/Cas9-edited IFNAR1, MyD88 and TRAF6 cells were used to dissect the pathways involved. IFN sensitivity was quantified by STAT2 nuclear translocation across an IFN-α dose range. The association between MyD88 and JAK1 was evaluated by coimmunoprecipitation. *In vivo*, pigs were infected with H1avN2 and received a single dose of FLAMOD or vehicle at 1 h post-inoculation (n=6/group; n=3 mock). Blinded clinical scoring, serum CRP, lung titers and single-nucleus RNA-seq of lung were assessed over 72 h.
Results
TLR5 activation did not induce detectable type I IFN production but instead sensitized cells to its effects. Flagellin lowered the IFN-α concentration required for STAT2 activation (12-fold reduction), amplifying ISG expression and reducing viral titers *in vitro*. Mechanistically, this effect required IFN signaling and MyD88, but not TRAF6 or NF-κB, and was associated with a flagellin-induced interaction between MyD88 and JAK1. In SIAV-infected pigs, a single administration of flagellin heightened ISG expression across most lung cell types and mitigated disease severity.
Conclusion
These findings reveal a novel crosstalk between TLR5 and IFN pathways, offering a strain-independent route to boost antiviral protection.

Keywords: Innate immunity - Influenza - TLR5.

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Stressing the role of γδ17 T cells at the crossroads of tissue communication and pathophysiology

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γδ T cells are enriched at barrier tissues, where they act as rapid responders to environmental perturbations. Among their effector functions, they are the major source of steady-state IL-17, a feature that makes them key regulators of tissue integrity. While traditionally linked to host defense, IL-17-expressing γδ (γδ17) T cells also orchestrate host physiology by integrating signals from the immune system, the nervous system and the microbiota.

Here, we propose a conceptual framework in which IL-17 acts as a dynamic mediator of environmental cues and tissue intercommunication. In steady state, γδ17 T cells contribute to the maintenance of local homeostasis across diverse organs, including the reproductive tract, adipose tissue, brain meninges and peripheral nerves. Upon perturbation, this network is reshaped and reveals context-dependent roles of IL-17 in coordinating adaptive versus maladaptive responses. We show that psychological stress is a critical modulator of this axis, reprogramming γδ17 T cell transcriptional signatures in a tissue-specific manner via glucocorticoid signalling. On the other hand, we use a model of peripheral nerve injury to uncover a bidirectional crosstalk, where IL-17 contributes not only to axonal regeneration but also to the remodeling of distal tissues such as the gut. These processes are further tuned by the microbiota, which both shapes and is shaped by IL-17-driven responses.

Altogether, our work supports a model in which IL-17 acts as a central node connecting local and systemic signals, immune response and tissue pathophysiology. While this network promotes resilience and repair under controlled conditions, its dysregulation may drive chronic inflammation and compromise disease tolerance. A better understanding these interactions will open new avenues for therapies targeting neuroimmune as well as microbiota-related pathways.

Keywords: Psychological stress - Neuroimmunology - Microbiota.

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CXCR4 signaling, a gatekeeper orchestrating the bone marrow ecosystem

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The bone marrow (BM) microenvironment is a dynamic ecosystem that sustains hematopoiesis and immune function through complex interactions between hematopoietic stem and progenitor cells (HSPCs), mesenchymal stromal cells (MSCs), and mature immune cells, including plasma cells (PCs). Aging profoundly alters this ecosystem, leading to myeloid skewing, chronic low-grade inflammation (inflammaging), and declining immune competence. WHIM Syndrome, a rare primary immunodeficiency caused by gain-of-function mutations in *CXCR4*, recapitulates several features of premature BM dysfunction. Our studies in mouse models and patients have revealed that enhanced CXCR4 signaling affects multiple cellular compartments, altering the lympho-myeloid fate of multipotent progenitors (MPPs), the osteogenic potential of MSCs, and the trafficking and maturation of PCs. These findings highlight the multifaceted role of the CXCL12/CXCR4 axis in coordinating cellular fate and function within the BM ecosystem. Building on these observations, our current research aims to unravel how CXCR4 signaling shapes lymphoid cell fate in the BM, using WHIM Syndrome as a disease paradigm. We hypothesize that excessive CXCR4 signaling disrupts the spatial organization of MPPs and PCs within the BM niche, thereby altering their exposure to environmental cues. These changes may reprogram cellular metabolism and epigenetic landscapes, ultimately influencing cell fate and immune output. This talk will present recent advances from our laboratory, providing mechanistic insights into how CXCR4 signaling orchestrates the fate of MPPs, PCs, and MSCs, and exploring broader implications for hematopoietic and immune dysfunction.

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Ferroptosis is a Physiologic Vulnerability of Iron-Recycling Macrophages

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Iron deficiency anemia affects one-third of the global human population. Paradoxically, daily iron required to fuel red blood cell (RBC) production and prevent anemia is provided through recycling, from senescent RBC. This is achieved by splenic red pulp macrophages (RPM) that extract iron from the heme groups of hemoglobin. How these erythrophagocytic macrophages prevent intracellular iron flux from inducing cell death via ferroptosis is unknown. Here we show that SPI-C, the master transcriptional regulator of the erythrophagocytic lineage, orchestrates two redundant anti-ferroptosis pathways. One supports glutathione synthesis, via NF-E2-related factor 2 (NRF2), and the other relies on bilirubin production by biliverdin reductase A (BVRA). Genetic ablation of both pathways, but not either alone, sensitizes erythrophagocytic macrophages to ferroptosis, depletes RPM and increases the severity of iron deficiency anemia in mice. These findings reveal a central physiologic role of ferroptosis in the control of macrophage function, iron homeostasis and iron-deficiency anemia.

Keywords: Macrophages - Ferroptosis - Organismal Homeostasis.

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Let it flow: Maternal immune regulation of lactation

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Breastfeeding is essential for mammalian survival and requires the extensive transformation of the mammary gland into a milk-secreting organ. While tissue immunity is increasingly recognized as a regulator of local physiology, whether and how maternal immunity contributes to mammary gland remodelling and function during pregnancy remains largely unknown. Here, we show that maternal adaptive immunity is an integral component of the physiological programme controlling mammary gland development and lactogenesis. Pregnancy is associated with the establishment of a T-bet-expressing lymphocyte programme within the mammary gland that promotes epithelial differentiation, optimal lactation and neonatal growth. Mechanistically, pregnancy-associated thymic involution is accompanied by a paradoxical enrichment of intraepithelial lymphocyte (IEL) precursors that preferentially accumulate in the mammary gland and differentiate into T-bet-expressing unconventional CD8αα lymphocytes. Mammary IELs promote the differentiation and maturation of contractile and milk-secreting epithelial cells, thereby supporting milk production and offspring fitness. As pregnancy occurs in the context of physiological and pathological stressors, our findings raise the possibility that changes in maternal immune status may influence mammary adaptation. Consistent with this, we find that maternal infections profoundly reshape mammary gland remodelling during pregnancy, with changes in local immunity associated with altered epithelial expansion and differentiation.Altogether, our findings identify maternal adaptive immunity as a key regulator of mammary gland adaptation during pregnancy and reveal an unexpected interface between maternal immune status, tissue remodelling and lactation.

Keywords: Immunophysiology - Pregnancy - Mammary gland.

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Low-dose perinatal pesticide exposure reprograms immune development in male offspring and increases susceptibility to type-2 airway inflammation

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Objectives
Environmental exposure to pesticides during critical windows of immune development may contribute to allergic disease. We investigated whether chronic low-dose exposure to malathion (MAL) and ethoxyquin (ETH) during the maternal period and early life alters immune development and susceptibility to allergic airway inflammation in offspring.
Methods
Female mice were exposed to MAL or ETH in drinking water from preconception through lactation, and offspring remained exposed after weaning. We combined multiparametric flow cytometry, functional T-cell assays and microbiome profiling to characterize immune alterations and their functional consequences one-week after weaning, before inducing allergic inflammation through HDM exposures. Splenic immune compartments were comprehensively characterized before disease induction, and naïve CD4 T cells were isolated to assess their capacity to differentiate into TH1, TH2, TH17 and Treg lineages and investigate potential cell-intrinsic effects. Following sensitization and HDM challenge, type 2 airway inflammation was assessed by evaluating eosinophil recruitment, TH2 cytokine levels (IL-4 and IL-13) in bronchoalveolar lavage fluid, and lung histological scores.
Results
Exposure to both MAL and ETH markedly altered the splenic immune landscape of male offspring, affecting both myeloid and lymphoid compartments, whereas mesenteric lymph nodes were comparatively preserved. Naïve CD4 T cells from exposed offspring displayed impaired differentiation across TH1, TH2, TH17 and Treg programs, accompanied by reduced expression of T-bet, GATA3, RORγt and FoxP3. To a lesser extent, direct pesticide exposure partially reproduced this phenotype in naïve CD4 T cells from unexposed mice. Following HDM challenge, exposed males developed exacerbated type-2 airway inflammation.
Conclusion
Perinatal exposure to MAL and ETH alters immune development in male offspring and impairs the functional differentiation of naïve CD4 T cells. The partial recapitulation by direct pesticide exposure suggests a cell-intrinsic component, whereas the stronger phenotype following developmental exposure points to additional persistent programming mechanisms. These findings led us to investigate the mechanisms underlying this persistent immune reprogramming, including myeloid-lymphoid crosstalk, microbiome alterations and epigenetic regulation.

Keywords: Asthma - Lymphocytes - Pesticides.

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A deep dive into the biology of lung macrophages in health and disease

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Macrophages are essential regulators of tissue homeostasis, inflammation, and repair. In the lung, our understanding of macrophage biology has long been dominated by alveolar macrophages. However, recent advances have revealed a remarkable diversity of interstitial macrophages (IMs), raising fundamental questions about their developmental origins, functional specialization, and interactions with the local microenvironment.
In this lecture, I will discuss how our work has contributed to redefining the biology of lung macrophages in health and disease. I will first highlight the immunoregulatory functions of IMs and our investigations about their heterogeneity, developmental trajectories and transcriptional regulation. I will then explore how local environmental signals, including endothelial-derived TGFβ and metabolic cues, instruct macrophage differentiation and identity, illustrating the central role of tissue niches in shaping macrophage diversity.
Moving from homeostasis to disease, I will discuss how influenza-induced lung injury reshapes the lung macrophage landscape, promoting the emergence of specialized monocyte-derived populations and the acquisition of tissue-repair programs that contribute to epithelial regeneration and recovery.
Finally, I will outline emerging strategies to move beyond descriptive cellular atlases towards a dynamic and spatially resolved understanding of macrophage biology. By integrating genetic fate mapping, longitudinal single-cell profiling, spatial transcriptomics, and computational approaches, we aim to reconstruct and ultimately predict macrophage trajectories within their evolving tissue environment.
Together, these findings highlight macrophage identity as a dynamic property emerging from the interplay between developmental history, local tissue signals, and environmental challenges, opening new perspectives for understanding and manipulating macrophage functions in health and disease.

Keywords: Macrophage - Niche - Developmental trajectories.

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P3-01

Inducing immunogenic lymphoid structures across cancers by tumor-to-dendritic cell reprogramming

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Objective
Tertiary lymphoid structures (TLS) in tumors are associated with improved responses to immunotherapy and provide organized niches for coordinated T and B cell priming against tumor antigens. However, the mechanisms that trigger TLS formation in cancer remain poorly defined. Because dendritic cells (DCs) are present in spontaneous human TLS, and are associated with better outcomes, we tested whether direct reprogramming of tumor cells into type1 conventional DC (cDC1)- like cells could initiate immunogenic TLS (imgTLS) formation.
Methods
Tumor-to-cDC1 reprogramming was induced by overexpressing the minimal cDC1-specific gene regulatory network PU.1, IRF8 and BATF3. We assessed antitumor efficacy and the formation of imgTLS in melanoma, colon, bladder, breast and pancreatic cancer models across different mouse genetic backgrounds. Using spatial transcriptomics, *in vivo* labeling and genetic engineering, we characterized imgTLS maturation kinetics, spatial organization, cellular interactions, molecular pathways, and transcriptional programs. Single cell transcriptomics with paired TCR and BCR sequencing, plasma-transfer assays and *in vivo* cell depletion were used to determine how imgTLS-associated T and B cells contributed to systemic immunity.
Results
cDC1-like cells activated lymphotoxin, TNF, and interferon programs, and rapidly engaged T cells through MHC-I and CD40 signaling to induce mature imgTLS containing $BCL6^+$ germinal centers, independently of endogenous cDC1s. Spatial transcriptomics identified DC-$LAMP^+CCR7^+$ migratory cDC1s nucleating niches enriched in $CD4^+$ T cells, $CD8^+$ T cells, and B cells in mouse and human tumors. ImgTLS sustained T cell and B cell responses and promoted systemic immunity through expansion of shared clonotypes in distant, untreated tumors.
Conclusion
cDC1 reprogramming induces imgTLS across multiple cancers and provides a time-resolved mechanistic framework and translational strategy for remodeling low-immunogenic tumors. By coordinating cellular and humoral immunity, reprogramming offers a controlled platform to interrogate TLS biology and may help overcome therapeutic resistance and broaden the clinical impact of cancer immunotherapy.

Keywords: Tertiary Lymphoid Structures - Cancer Immunotherapy - Cellular reprogramming.

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P3-02

HIF-1α licenses BCG-induced trained immunity to promote pulmonary and systemic protection against *Brucella abortus* infection

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Bacillus Calmette-Guérin (BCG) vaccination can induce trained immunity and heterologous protection, but the contribution of hypoxia-inducible factor-1α (HIF-1α) remains incompletely defined. We investigated whether myeloid HIF-1α coordinates central and peripheral adaptations to systemic BCG immunization and determines protection against respiratory *Brucella abortus* infection. Wild-type and myeloid HIF-1α-deficient mice were immunized intravenously with BCG. Bacterial persistence and myeloid-cell phenotypes were examined in bone marrow (BM), spleen and lung, while bone marrow-derived macrophages (BMDMs) were analyzed for inflammatory, transcriptional, signaling and bioenergetic recall responses. Protection was evaluated after antibiotic treatment, washout and intranasal *B. abortus* challenge. HIF-1α deficiency increased persistent BCG burden in the lung, spleen and BM. Despite increased splenic accumulation of macrophage-enriched populations, deficient cells displayed attenuated iNOS- and CCR7-associated activation and reduced nitrite production. Macrophages generated from BCG-immunized wild-type BM retained enhanced inflammatory and metabolic responsiveness after *ex vivo* differentiation and elimination of detectable viable BCG. Upon *B. abortus* challenge, prior BCG exposure enhanced *Nos2, Ccr7, Hk2* and *Glut1* expression, IL-6 and IL-1β production, nitrite generation and compensatory glycolysis in wild-type macrophages, whereas these responses were diminished or absent in HIF-1α-deficient macrophages. Preserved mTOR-S6K phosphorylation in deficient macrophages was insufficient to restore the complete recall response, and their mitochondrial phenotype showed increased oxygen consumption without a proportional increase in ATP-linked respiration. An independent reanalysis of public ChIP-seq data linked systemic BCG exposure to H3K27ac remodeling at immunometabolic loci in BMDMs. *In vivo*, BCG immunization reduced *B. abortus* burden in the lungs, liver and spleen and limited hepatic granulomatous pathology in wild-type, but not myeloid HIF-1α-deficient, mice. BCG reduced pulmonary inflammatory involvement in both genotypes, dissociating antimicrobial control from tissue inflammation. These findings identify myeloid HIF-1α as a determinant of the immunometabolic quality of BCG-induced trained immunity, linking BM programming, tissue-specific responses and durable heterologous protection against intracellular bacterial infection.

Keywords: BCG - Trained immunity - Brucella abortus.

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P3-03

Retinoic acid modulates invariant Natural Killer T cell development and function in colon cancer

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Objective
Invariant Natural Killer T (iNKT) cells are innate-like T lymphocytes that play a role in anti-tumor immunity. However, how environmental signals regulate their development is poorly understood. Diet is a major risk factor for colon cancer. Vitamin A, exclusively obtained through the diet, is essential for retinoic acid (RA) production. Here we investigated how RA signaling influences iNKT development, the underlying molecular pathways and function.

Methods
Conditional mouse models with impaired RA signaling in thymocytes or thymic epithelial cells were combined with flow cytometry, qPCR and *in vitro* RA stimulation and pharmacological RA inhibition. *Hes1* was further investigated using conditional knockout mice, competitive bone marrow chimeras and retroviral overexpression. iNKT cytotoxicity was explored using MC38 colorectal cancer cell co-culture.

Results
RA signaling-deficient mice showed a marked reduction in total thymic iNKT , particularly in mature stage 3. Transcriptomic analysis of stage 1 iNKT cells identified *Hes1* and *Tbx21* among the transcription factors modulated by RA signaling. *Hes1*/HES1 expression peaked at stage 1 and progressively declined with maturation. RA-deficient iNKT s displayed reduced HES1 and Ki67 expression, phenocopied by pharmacological RA signaling inhibition, whereas RA stimulation upregulated *Hes1*. Canonical Notch signaling components remained unaltered, suggesting Notch-independent *Hes1* modulation by RA. Moreover, thymic epithelial cell-specific deletion of *Rdh10*, essential for RA biosynthesis, impaired iNKT development, supporting local thymic RA supply. Competitive bone marrow chimeras revealed a cell-intrinsic requirement for *Hes1* during iNKT development. *Tbx21*, encoding T-bet, is predominantly expressed by mature stage 3 iNKTs. Consistently, RA signaling stimulation and inhibition modulated *Tbx21* expression, while retroviral *Tbx21* overexpression partially rescued the reduction of mature stage 3 iNKT cells caused by RA signaling deficiency. Finally, stage 3 iNKT cells displayed the highest cytotoxicity against MC38 tumor cells.

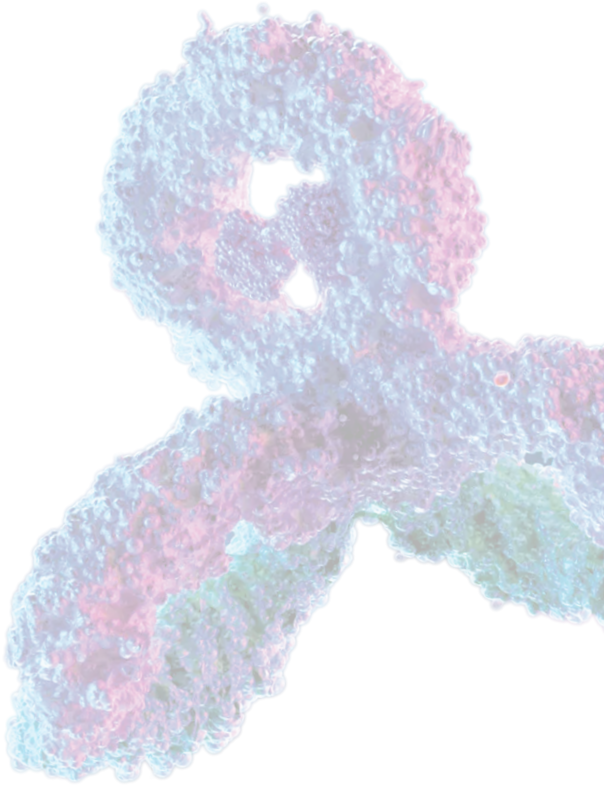
Conclusion
RA signaling is an important regulator of iNKT cell development by modulating *Hes1*-associated early expansion and supporting T-bet-dependent terminal maturation. These data show how diet-derived retinoids shape iNKT-mediated tumor immune surveillance.

Keywords: Invariant Natural Killer T cells - Innate T cells - Retinoic Acid.

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Harnessing gamma-delta T cells for cancer immunotherapy

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In the landscape of upcoming cancer immunotherapies, gamma-delta (γδ) T cells present robust HLA-independent and neoantigen-independent cytotoxic functions, rendering them complementary to conventional (ab) T cells, and especially suited for allogeneic therapies. We have developed a Vδ1+ γδ T cell-based adoptive cell therapy, named Delta One T (DOT) cells, that has been translated to the clinic for hematological malignancies, but has never been applied in solid tumors. Here we demonstrate the therapeutic potential of DOT cells against colorectal cancer (CRC), which remains a major unmet need as only around 10% of CRC displaying microsatellite instability (MSI) respond to current checkpoint (PD-1) inhibition. We demonstrate the capacity of DOT cells to target CRC cell lines (both MSI and MSS) and patient-derived organoids and biopsies in vitro; and to control tumor growth in an orthotopic xenograft model of human CRC. Notwithstanding, we found tumor-infiltrating DOT cells to exhibit a dysregulated balance of cytotoxic and inhibitory receptors that paralleled that of endogenous Vδ1+ TILs and limited their cytotoxic functions. Critically, we were able to revert DOT-cell dysfunction and to fully control tumor growth by blocking the immune checkpoints TIGIT and PD-1. Alternatively, we have engineered DOT cells to express a chimeric antigen receptor (CAR) targeting Guanylyl Cyclase C (GCC CAR) to enhance CRC specificity. Strikingly, a single infusion of GCC CAR-DOT cells resulted in complete tumor suppression, even at advanced stages, without any need of immune checkpoint blockade. Moreover, GCC CAR-DOT cells prevented hematogenous tumor spread and markedly reduced metastatic burden, without any detectable toxicity. These results provide the proof-of-concept for GCC CAR-DOT cells as an allogeneic cell therapy for CRC.

Keywords: Gamma-delta T cells - Cancer immunotherapy.

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Title upcoming

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Abstract not received.

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P4-01

Role of intestinal CD8 T cells in the control of colorectal cancer metastases

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Colorectal cancer (CRC) is a major cause of cancer-related mortality, mainly due to its metastases. We previously demonstrated, in a syngeneic orthotopic mouse model of metastatic CRC (mCRC), that primary colon tumors prime tumor-specific intestinal CD8 T cells capable of circulating and infiltrating distant metastases, contributing to systemic antitumor immunity (Feliu et al., Sci. Immunol., 2023).
However, the mechanisms linking intestinal priming to systemic tumor control remain poorly understood. We aimed to characterize the functional programs of tumor-specific intestinal CD8 T cells and identify the mechanisms regulating their egress from the gut and recruitment into distant tumors.
By single-cell RNA sequencing coupled with barcoded dextramers and TCR repertoire analysis, we fully characterized tumor-specific intestinal CD8 T cells. Using flow cytometry, we monitored their systemic dissemination in blood, while the Kaede photoconvertible mouse model allowed us to track intestinal cells in distant organs and investigate the adhesion pathways involved in their tumor infiltration.
Tumor-rejecting mice were enriched for tumor-specific intestinal CD8 T cells with enhanced cytotoxic programs, whereas progressing tumors accumulated terminally exhausted populations. Blood analyses revealed that early circulation of intestinal CD8 T cells correlated with subsequent tumor rejection and response to anti-PD-L1 therapy. Kaede fate-mapping demonstrated that intestinal CD8 T cells infiltrate distant metastases in different metastatic CRC models, supporting a role for intestinal priming in systemic antitumor immunity.
Our findings identify the gut as a major site of antitumor CD8 T cell priming and reveal its contribution to systemic tumor immune surveillance. Understanding the mechanisms regulating intestinal CD8 T-cell dissemination and tumor infiltration may provide new biomarkers and therapeutic strategies to improve immunotherapy efficacy in mCRC.

Keywords: Tumor-specific - Gut immunity - CD8 T cell.

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P4-02

"Nature vs Nurture": Understanding How TCR-pMHC history shapes T cell fate during polyclonal response in solid tumors

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Tumor-infiltrating lymphocytes (TILs) display a wide spectrum of phenotypes within the tumor microenvironment. While some exhibit potent anti-tumoral activity, others are tumor-permissive. Consequently, the immune system often fails to eliminate neoplastic cells at different stages of oncogenesis. Understanding the factors that regulate CD8⁺ T cell differentiation is therefore essential for the development and optimization of cancer immunotherapies. T cell differentiation is shaped by numerous signals from the microenvironment and lymphoid organs. However, growing evidence suggests that antigen affinity, encoded by the T cell receptor (TCR), also plays a critical intrinsic role in guiding CD8⁺ T cell differentiation[1]. This challenges the previously dominant view that T cell fate is primarily determined by environmental cues. In this study, we leverage large-scale datasets comprising several million paired single-cell RNA/TCR-seq from T cells across human donors to assess generalization of these observations across diverse biological contexts[2,3]. We show that the influence of TCR sequence on T cell fate is largely independent of tissue, is observed in both CD4⁺ and CD8⁺ T cells, and is reproducible across individuals, particularly among shared public clones. Furthermore, T cells carrying similar TCRs can adopt similar functional states both within and across patients. To investigate the dynamics of T cell responses *in vivo*, we generated paired scRNA/TCR-seq of TILs from mice bearing B16-OVA tumors and challenged with OVA peptide variants of different affinities (N4, Q4, and V4). We identified recurrent T cell fate biases across both mice and OVA variants, suggesting that TCR–pMHC interactions can reproducibly shape the functional trajectory of T cells during a polyclonal response. These results demonstrate the feasibility of building a polyclonal-response model of antigenicity and of quantifying the phenotypic biases associated with distinct antigenic signals within tumoral context. To further validate and dissect these observations, we are conducting *in vivo* and ex vivo experiments to systematically screen TCR–peptide combinations across different cancer models, using engineered AAVs that selectively infect T cells. Together, this work aims to clarify how the history of TCR–pMHC interactions influences lineage commitment during T cell activation and differentiation, and to uncover the molecular mechanisms underlying these reproducible fate biases.

Keywords: T cell response - Antigeninicity - System immunology.

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P4-03

NF-kappaB transcription factor c-Rel governs CD8+ T-cell function in cancer

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CD8+T cells are central effectors of the anti-tumor immune response and the main targets of current immunotherapies. Nevertheless, the transcriptional regulators orchestrating their activation, accumulation and cytotoxic function in the tumor microenvironment (TME), are largely unknown. In this project, we aimed at evaluating the roles of the different members of the NF-kappaB family of transcription factors, whose T-cell-intrinsic functions are so far blurry because of the lack of proper study models. We created a library of mouse models and engineered human T cells carrying CD8+ T-cell -restricted ablation of NF-kappaB subunits. We found that ablation of the c-Rel subunit selectively led to increased tumor progression in transplanted models of melanoma. Mechanistically, c-Rel was required for T-cell accumulation in the TME by promoting their re-activation and cytotoxic function *in situ*. At the molecular level, c-Rel promoted Interleukin-2 expression, thus preventing T-cell exhaustion by limiting TOX expression. In line with this, c-Rel-deficiency completely abolished the response to checkpoint-blockade therapies in mice, and c-Rel activity correlated with enhanced response to anti-PD-1 in cohorts of melanoma patients. Conversely, overexpression of c-Rel in endogenous CD8+ T cells, was sufficient to reduce tumor growth in mice; such overexpression also optimized the accumulation and efficiency of engineered TCR-T and CAR T-cell therapy in mice. Together, this work establishes NF-kappaB c-Rel as a prime regulator of CD8+ T-cell function in cancer, and paves the way toward NF-kappaB-modulated adoptive T-cell therapy for solid cancers.

Keywords: T cells - NF-kappaB - Immunotherapy.

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Is immunotherapy-mediated B-cell depletion the most relevant strategy in autoimmune disease and lymphoma?

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Abstract not received.

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TNF blockade with certolizumab improves the efficacy of anti-PD-1 and anti-CTLA-4 combination therapy for melanoma

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Scientific background

Despite the tremendous breakthrough that immune checkpoint inhibitors (ICI) such as anti-PD-1 and anti-CTLA-4 have brought to the treatment of advanced melanoma, 60% of patients do not respond or relapse within 5 years of starting treatment. Moreover, ICI therapy is associated with serious immune-related adverse events (irAEs), such as colitis. This can be treated with tumor necrosis factor-alpha inhibitors (TNFi), such as infliximab. The pharmacodynamic effects of TNFi on the immune response and on the clinical outcome still need to be elucidated.

Results

The phase 1b TICIMEL clinical trial evaluated the safety, tolerability, and anti-tumor activity of combining the immune checkpoint inhibitors (ICI), ipilimumab and nivolumab, with tumor necrosis factor (TNF) blockers, certolizumab or infliximab, to treat advanced melanoma patients. While certolizumab is the monovalent Fab' fragment of a humanized anti-TNF monoclonal antibody, linked to polyethylene glycol, infliximab is a bivalent anti-TNF IgG1 chimeric monoclonal antibody. A higher proportion of responses was observed in patients receiving ICI and certolizumab, while patients treated with ICI and infliximab demonstrated superior tolerability. Moreover, CITE-Seq analyses of circulating CD8 T cells showed that ICI plus certolizumab promoted an IFN signature, whereas ICI plus infliximab reduced the induction of genes associated with T cell activation. In preclinical models, ICI and TNF blockade with certolizumab increased IFN-γ+ CD8 T cells and reduced regulatory T cells in tumors. The IgG1 Fc fragment of infliximab was identified as counteracting the benefits of TNF blockade. These findings underscore the importance of selecting the optimal TNF blocker to combine with ICI to enhance therapy efficacy in melanoma patients.

Conclusion

Overall, our data show that the effect of TNF blockade on immune responses and clinical outcomes varies depending on the type of TNFi. Certolizumab improves the efficacy of ICI therapy, while infliximab is better at improving tolerability. Therefore, the choice of TNFi to combine with ICI therapy depends on medical needs.

Keywords: Immune checkpoint inhibitors - TNF blockers - Melanoma.

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Circulating Metabolites Link Gut Microbiota Composition to Clinical Outcomes under Immune Checkpoint Inhibitors in NSCLC

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Objective
Immune Checkpoint Inhibitors (ICIs), with or without chemotherapy, are a cornerstone of first-line treatment for advanced non-small cell lung cancer (NSCLC), but clinical benefit remains heterogeneous due to several parameters, including microbiota. The limited reproducibility of taxonomic microbiota signatures across cohorts hampers their translation into clinically applicable biomarkers. We hypothesized that despite species heterogeneity, microbiota may converge functionally at the metabolism level, and that this functional imprint can be captured in circulation. Circulating metabolomics could therefore provide a clinically accessible readout of microbiota-host interactions relevant to ICI outcome. We thus launched the METABO-ICI clinical study[1] (NCT04189679) to test this hypothesis.
Methods
Baseline and longitudinal blood and stool samples from 60 patients with lung cancer were prospectively profiled using routine blood tests, immunological assays, untargeted metabolomics and 16S rRNA gene sequencing. Clinical response was assessed by best overall response (BOR, PD, SD or PR) and overall survival (OS) was evaluated. Associations with OS were investigated using Cox proportional hazards models adjusted for relevant confounders. Candidate variables were further assessed by multivariable Cox regression and repeated bootstrap-based LASSO (BOLASSO) selection. A combined score was derived from the selected variables in a training set, validated on the test set, and further evaluated using leave-one-out cross-validation with the concordance index (C-index) as the performance metric.
Results
In addition to relevant microbes, we identified a robust set of 39 circulating metabolites associated with OS. Importantly, microbiota profiles significantly accounted for variance in circulating metabolites. Integration with circulating immunological markers and routine serum parameters further defined a multidimensional signature with prognostic value for patient outcome.
Conclusion
This integrative approach supports the concept that, beyond taxonomic heterogeneity, gut microbiota–host interactions generate a circulating metabolic imprint associated with clinical outcome under first-line ICI-based treatment in NSCLC. Circulating metabolomics may therefore provide a clinically accessible readout of microbiota-related functional signals. Independent validation is now warranted to establish the contribution of microbiota-driven metabolic modulation to ICI response.

Keywords: Immunotherapy - Metabolic signature - Microbiota.

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eIF4F targeting rewires T cell exhaustion and overcomes immunotherapy resistance

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Objective
To define how eIF4F-mediated mRNA translation controls T-cell exhaustion and immunotherapy resistance by regulating immune checkpoints and exhaustion-associated transcription factors in tumor-infiltrating lymphocytes (TILs).
Methods
eIF4F expression was analyzed in bulk RNA-seq from 35 melanoma patients before and during immunotherapy and in a published single-cell RNA-seq dataset. Translational regulation across exhaustion states was assessed by polysome profiling of sorted TIL subsets. eIF4F-regulated transcripts were identified by polysome profiling/RNA-seq and validated by RT-qPCR. TOX dependence on its 5′ untranslated region (5′ UTR) was tested using luciferase reporters and partial UTR deletion. TILs from 12 patients were treated *ex vivo* with eIF4A inhibitors and analyzed by spectral cytometry and single-cell RNA-seq. Functional effects were evaluated in T-cell/tumor co-cultures and by transfer of autologous TILs pretreated *ex vivo* with silvestrol or vehicle into melanoma PDXs. eIF4A inhibition plus anti-PD-1 was tested in patient-derived organotypic melanoma cultures and three syngeneic murine models. Post-treatment tumors were profiled at protein, single-cell transcriptomic, and metabolic levels.
Results
eIF4A1 expression decreased during immunotherapy in responders but increased in nonresponders. TOX translation was enhanced in terminally exhausted TILs, and eIF4F selectively regulated translation of TOX, LAG3, TIM-3, CTLA4, PTP1B, and TGFβ1. Partial deletion of the TOX 5′ UTR abolished sensitivity to eIF4A inhibition, whereas its fusion to a luciferase reporter conferred eIF4A dependence. eIF4A inhibition reduced TOX, LAG-3, TIM-3, and TGFβ1 without broadly suppressing protein synthesis, while increasing IL-2 production, proliferation, and cytotoxicity. Transfer of TILs transiently pretreated *ex vivo* with silvestrol enhanced antitumor efficacy in PDXs. eIF4A inhibition synergized with anti-PD-1, enhancing tumor clearance in organotypic cultures and antitumor responses across all three syngeneic models. Combination therapy shifted TILs from terminally exhausted toward progenitor-exhausted states, enhanced effector programs, and improved metabolic fitness.
Conclusion
eIF4F-dependent selective mRNA translation is a previously unrecognized driver of T-cell exhaustion. Targeting eIF4A reprograms exhausted TILs and sensitizes tumors to PD-1 blockade, revealing translational control as an actionable mechanism of immunotherapy resistance.

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High endothelial venules mediate B cell entry into tumors and tertiary lymphoid structures during PD-1 plus CTLA-4 immunotherapy

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Objective

High endothelial venules (HEVs) are specialized blood vessels mediating lymphocyte entry in lymph nodes (Moussion and Girard, Nature 2011; Girard et al, Nat Rev Immunol 2012)**.** Recently, our team showed that tumor-associated HEVs (TA-HEVs) mediate lymphocyte extravasation into tumors during cancer immunotherapy with anti-PD-1 plus anti-CTLA-4 mAbs (ICB), and predict response to treatment of metastatic melanoma patients (Asrir* et al, Cancer Cell 2022). B cells and tertiary lymphoid structures (TLS) recently emerged as critical for anti-tumor immunity and efficacious immunotherapy. The objective of the project is to analyze the potential role of TA-HEVs in B cell infiltration into tumors and tumor-associated TLS, and the molecular mechanisms involved.

Methods

We combined multidisciplinary approaches: TLS-rich murine tumors models (melanoma, lung cancer…), multiparameter flow cytometry, multiplex IHC, homing assays, function blocking antibodies and *in vivo* imaging using wide-field intravital microscopy. This last technique allows the visualization in real-time of B cells in tumor blood vasculature and TA-HEVs.

Results

We show that TA-HEVs are major sites of B cell entry into TLS-rich tumors during treatment with ICB. ICB therapy promotes the expansion of TLS in tumors, associated with increased frequency of mucosal MECA-79+ MAdCAM-1+ TA-HEVs and B cell infiltration. Interestingly, TA-HEVs are mainly found within or surrounding TLS and are correlated with the homing of B cells into tumors treated with ICB. Intravital microscopy in a TLS-rich model demonstrates that TA-HEVs are the main sites of B cell capture in the blood vasculature of ICB-treated tumors. Function blocking experiments reveal the crucial requirement for CD62L/MECA-79 and α4β7/MAdCAM-1 axes in B cell recruitment and ICB induced expansion of B cell-rich TLS into tumors.

Conclusion

These studies provide critical insights into the mechanisms governing B cell trafficking in cancer immunity and immunotherapy. New therapeutic strategies aiming to promote the formation of TA-HEVs may promote TLS formation/expansion and sensitize refractory tumors to ICBs.

Keywords: High endothelial venule - B cell - Tertiary lymphoid structure.

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Turning Sweet in Immunity: Glycans as Master Regulators of Immune Responses in Chronic Inflammation, Autoimmunity and Cancer

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The nature and the fate of an immune response is written not only in genes and proteins, but also in sugars/glycans. Glycans are complex carbohydrates structures that modify essentially all immune cells and antibodies, and are emerging as fundamental regulators of immune recognition, activation and function both in homeostasis and in disease. Beyond their structural roles, these dynamic molecular signatures constitute an additional layer of immune regulation, shaping the balance between protective immunity and immunopathology.
In this talk, I will highlight discoveries from our laboratory revealing how the immune glycome operates as a molecular switch controlling the nature, the fate and the magnitude of immune responses. We have demonstrated that glycosylation-dependent mechanisms tightly regulate T-cell development, activation and function, with implications in the pathogenesis of chronic inflammatory disorders and cancer. The targeting remodelling of branched N-glycans on T cells can overcome CD8+ T-cell exhaustion and enhance antitumor immunity, opening new avenues for glycoengineered (CAR)T-cell therapies (1).
Extending this glycan-dependent regulation to γδ T-cell, our recent findings identify glycosylation as a critical determinant of γδT-cell functional programming, controlling the balance between inflammatory IL-17-producing and protective immune states, with implications for autoimmunity (2). Besides adaptive immunity, glycans also impact the humoral immune response. We have uncovered how altered IgG Fc glycosylation, together with glycan-specific antibody responses, can promote pathogenic inflammation years before the clinical onset of Crohn's disease (3). We will also discuss emerging evidence showing specific glycan signatures regulating regulatory T-cell identity and immunosuppressive function.
Together, these findings establish the immune glycome as a dynamic regulatory layer of immune-cell programming with impact in many diseases. Deciphering and manipulating this sugar code offers unprecedented opportunities to restore immune homeostasis, intercept chronic inflammation and autoimmunity, and unleash antitumor immunity through next-generation of glycoimmunotherapies.

Keywords: Glycans - Glyco-Immunology - immune glycome.

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Local glycan engineering induces systemic antitumor immune reactions via antigen cross-presentation

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Immune checkpoint inhibitors have revolutionized cancer therapy; however, response rates remain suboptimal across many solid tumors, and key resistance mechanisms-particularly those mediated by glycans-are still incompletely understood. Emerging evidence identifies sialic acid-containing glycans and their interactions with Siglec receptors on tumor-associated macrophages as critical drivers of immune suppression within the tumor microenvironment (TME). Targeting this sialic acid-Siglec axis through glycan engineering, including the use of sialidases and other glycosidases, has demonstrated promising therapeutic potential in preclinical models. Nevertheless, the safe and effective delivery of these enzymes to tumors remains a major translational challenge. Here, we introduce a new strategy based on adeno-associated virus (AAV)-mediated delivery of sialidases (AAVSia) and additional glycosidases, such as fucosidase, directly into the TME. Intratumoral administration of AAVSia in murine tumor models led to significant tumor growth inhibition, prolonged survival, and the induction of systemic antitumor immunity, driven by enhanced cross-presentation and dendritic cell activation. Importantly, combining local sialidase expression with fucosidase treatment and PD-1 blockade resulted in a synergistic effect, further amplifying antitumor responses.
Together, these findings establish glycoengineering of the TME via localized enzyme delivery as a promising therapeutic avenue and provide a strong rationale for combinatorial strategies to overcome glycan-mediated immune resistance. These results and their translational implications will be discussed.

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Polysialylation governs inflammatory monocyte egress from the bone marrow

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Objective
Glycosylation is a fundamental post-translational modification that modulates immune cell migration, intercellular interactions, and activation, thereby shaping immune responses. Polysialylation, a rare and tightly regulated form of glycosylation, is indispensable for neural development and synaptic plasticity. Although expressed on circulating leukocytes, its specific immunological functions remain poorly understood. In this study, we aimed to elucidate the role of polysialylation in immune cell biology.
Methods
We integrated human population genomics with functional *in vivo* studies. Human genomic datasets were analyzed to assess associations between *ST8SIA4* genetic variants, which encode a key polysialyltransferase, and immune cell phenotypes. Complementarily, we employed *St8sia4*$^{-/-}$ mice, which lack polysialylation in immune cells, to dissect its functional role in immune cell dynamics. Experimental approaches included flow cytometry for immune cell profiling, bone marrow egress assays and mixed bone marrow chimera models to evaluate leukocyte mobilization, *Mycobacterium tuberculosis* infection models to assess immune responses under inflammatory conditions, as well as proteomics, advanced microscopy, and biochemical assays to gain mechanistic insights.
Results
Human genomic analyses revealed a significant association between *ST8SIA4* variants and reduced circulating monocyte counts. In *St8sia4*$^{-/-}$ mice, we demonstrated that polysialylation is essential for CCR2-mediated egress of inflammatory monocytes from the bone marrow, both at steady state and during *M. tuberculosis* infection. Consequently, *St8sia4*$^{-/-}$ mice exhibited monocytopenia. NCAM1 was identified as the principal polysialylated protein in these cells, with *Ncam1*$^{-/-}$ mice phenocopying the monocytopenia observed in *St8sia4*$^{-/-}$ animals. Mechanistically, the absence of polysialylation induced cytoskeletal remodeling, disrupted CCR2 surface distribution, and impaired **CCR2 ligand binding and internalization.**
Conclusion
These findings establish polysialylation as a novel regulator of CCR2 function and monocyte trafficking, with profound implications for immune surveillance and inflammatory responses. Furthermore, our preliminary data indicate that polysialylation also regulates the chemotaxis of other immune cells, underscoring the importance of studying this glycosylation motif and, more broadly, glycans in the regulation of immunity.

Keywords: Glycosylation - Inflammatory monocytes - Chemotaxis.

Complex branched glycosylation as a key regulator of type-3/γδT17 response associated with autoimmunity

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Objective
Protein *N*-glycosylation is a post-translational modification, where glycans are added to proteins of essentially all cells, being important fine-tuners of T-cell development and function. Although, the role of glycans on γδT cells biology remains to be unlocked[1,2,3]. In this work, we characterized the γδT cells glycome and how it influences their activity and function, highlighting its impact on immune-mediated inflammatory diseases (IMIDs), such as Lupus, Psoriasis and Inflammatory Bowel Disease (IBD).
Methods
Using healthy human and mouse tissues, we characterized the γδT cells glycome by performing single-cell RNA-seq, which was confirmed at protein level by spectral flow-cytometry. Together, we mapped the γδT glycome in the blood of IMIDs patients, by spatial mass-spectrometry and spectral flow-cytometry. At the mechanistic level, we generated full and conditional (Cre-Lox) glycoengineered mouse models by deleting genes in different steps of *N*-glycosylation pathway. Then, we characterize the γδT cells in each mice model at steady-state, specifically at the transcriptome and protein/glycan level (scRNAseq, scGlycomics and spectral flow-cytometry). We also evaluate the susceptibility and severity of IMIDs-like diseases in those models. Finally, we glyco-reprogramed γδT cells by treating the disease-mice model and patient-derived γδT cells, through glycans supplementation.
Results
At steady-state, in human and mouse, we showed a clear dependency of type-3/IL-17A γδT cells (and not type-1/IFNγ) in complex branched *N*-glycans. This dependency is reflected in an abnormal γδT cells glycosylation in different IMIDs patients. Mechanistically, we found that a deficiency on surface glycocalyx of γδT cells is associated with an autoreactive and IL-17A-driven pro-inflammatory commitment of γδT cells. Moreover, by inducing IMIDs-like diseases (Lupus, Psoriasis and IBD), in the glycoengineered mice models, we observed increased disease activity score and a marked type-3 γδT cells response. Importantly, from the clinical standpoint, we further showed that glycan supplementation can reprogram γδT cells towards a less pathogenic state, in disease-mice model and *ex vivo* patient-derived γδT cells.
Conclusion
Overall, this work highlights *N*-glycans as a novel immune checkpoint for γδT cells response and a new mechanism involved in the immunopathogenesis of IMIDs, proposing the glycoengineering of γδT cells as a new therapeutic target for these chronic diseases.

Keywords: Type-3/γδT17 - Glycosylation - Autoimmunity.

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Role of IgE glycosylation in allergic diseases

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Objective
IgE is the least abundant antibody isotype in circulation, yet it plays a key role in allergic diseases such as asthma and food allergy. In allergic subjects, binding of the allergen to IgE linked to their receptor FceRI on the surface of mast cells (MCs) leads to their degranulation and the release of histamine and other mediators responsible for the clinical manifestations of allergy. Despite its well-established pathogenic functions, total IgE levels correlate poorly with disease severity and around 30% of asthma patients fail to respond to the anti-IgE therapy omalizumab despite high IgE levels. Identifying features that distinguish pathogenic from non-pathogenic IgE could help identify allergic subjects who might benefit from anti-IgE therapies. We hypothesize that IgE pathogenicity is regulated by specific glycosylation patterns, as described for IgG. Indeed, IgE is the most heavily glycosylated immunoglobulin, with seven N-glycosylation sites bearing diverse N-linked glycans, yet the functional role of these glycans remains poorly understood. Notably, a recent report by Plattner et al., indicated that mutation of the N394 site abolishes omalizumab binding, suggesting that IgE glycosylation may influence therapeutic response.
Methods and Results
We purified IgE from a biobank of serum samples from severe asthma or peanut-allergic patients, and non-atopic controls. Compared with non-atopic controls, IgE from asthmatic and peanut-allergic subjects displayed increased sialylation and induced significantly more MC degranulation. Enzymatic desialylation of IgE reduced MC degranulation and anaphylaxis in mice humanized for FceRI. We then obtained full IgE glycosylation profiles by MALDI-MS, and identified specific patterns enriched in IgE from severe asthma patients compared to non-atopic controls. Finally, we compared the glycosylation profiles, affinity for FcεRI and omalizumab, and ability to induce MC degranulation in purified IgE from responders and non-responders to omalizumab, and found no significant differences between the two groups.
Conclusion
We identified specific glycosylation patterns in IgE from subjects suffering from allergic disorders, and confirmed the pathogenic potential of these glycan structures by modulation of mast cell activation. However, these glycan signatures are unlikely to predict clinical response to omalizumab.

Keywords: Antibody - Glycosylation - Asthma.

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CD8+ Treg cell therapy in Transplantation and Autoimmunity: from a novel concept to a clinical reality

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Regulatory T cells (Tregs) are essential for maintaining immune tolerance and represent a promising therapeutic strategy for transplantation and autoimmune diseases. While most efforts have focused on CD4+ Tregs, our research has established CD8+ Tregs as a distinct and potent regulatory population with unique immunosuppressive properties and considerable therapeutic potential.

Building on the initial discovery of CD8+CD45RClow/− Tregs as key mediators of transplantation tolerance in preclinical models, we progressively characterized their phenotype, mechanisms of action, and capacity to control alloimmune responses. We demonstrated that human CD8+ Tregs can be isolated, expanded under GMP-compatible conditions, and retain potent suppressive activity. Their therapeutic efficacy was further established in humanized models of graft-versus-host disease and skin transplantation, providing the foundation for clinical translation.

These advances led to the development of the Eight-Treg clinical trial, a first-in-human Phase I study evaluating the safety and feasibility of autologous polyclonal CD8+ Treg adoptive cell therapy in living-donor kidney transplantation. This milestone represents a major step toward translating a novel regulatory cell concept into a clinically applicable therapeutic approach.

Beyond transplantation, the ability of CD8+ Tregs to modulate pathogenic immune responses offers exciting opportunities for autoimmune diseases. Current research aims to better understand their heterogeneity, stability, and antigen specificity, while developing next-generation therapies based on engineered, antigen-specific, and universal allogeneic CD8+ Tregs.

Together, these findings illustrate the journey from fundamental immunological discovery to clinical application and highlight the potential of CD8+ Treg-based therapies to promote durable immune tolerance while reducing the need for conventional immunosuppression.

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Challenges and strategies for translating transplant tolerance into clinical practice

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The induction of donor-specific immune tolerance remains a major unmet goal in organ transplantation. Achieving stable graft acceptance without maintenance immunosuppression would represent a paradigm shift, sparing transplant recipients the cumulative toxicity of immunosuppressive drugs. Beyond improving long-term patient and graft outcomes, tolerance induction could fundamentally redefine the balance between immunological protection and immune competence after transplantation.

Despite remarkable advances in experimental transplantation, translating tolerance-inducing strategies from rodents to humans remains a formidable challenge. Laboratory mice typically exhibit limited exposure to environmental antigens and a relatively restricted memory T-cell compartment compared with adult humans. In clinical transplantation, pre-existing alloreactive memory T cells, shaped by previous infections and heterologous immunity, constitute a major barrier to tolerance induction.

To date, approaches based on donor hematopoietic chimerism have provided the most compelling clinical evidence that durable, robust donor-specific tolerance can be achieved. By establishing coexistence between donor and recipient hematopoietic cells, these strategies can promote profound and sustained immune unresponsiveness to donor antigens. However, their broader clinical implementation remains constrained by the toxicity of conditioning regimens, the risks of cytopenias, infections and graft-versus-host disease.

An alternative, increasingly pursued avenue is to harness peripheral immune regulation and targeted immunomodulation. Rather than relying on hematopoietic replacement or profound immune depletion, these strategies seek to selectively restrain donor-reactive immunity while preserving protective responses against pathogens and tumors. Approaches under investigation include regulatory T-cell therapies, manipulation of costimulatory pathways, and strategies designed to promote regulatory networks within the graft.

The central challenge is to translate these promising concepts into safe, reproducible and clinically scalable interventions capable of overcoming pre-existing alloimmune memory. Achieving this goal will require a deeper understanding of human immune heterogeneity, robust biomarkers of operational tolerance, and clinical trial designs that distinguish durable donor-specific tolerance from pharmacologically controlled graft acceptance.

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Autologous Tolerogenic Dendritic Cells Promote Treg Induction through Lactate Secretion

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Objective
Kidney graft survival remains limited by chronic rejection and the adverse effects of long-term conventional immunosuppression. Tolerogenic dendritic cell-based therapies have emerged as a promising strategy to promote immune tolerance. Autologous Tolerogenic Dendritic Cells (ATDC), generated from monocytes cultured with low concentrations of GM-CSF, display a glycolytic profile and produce lactate, which inhibits $CD4^+$ T-cell proliferation. A first-in-human Phase I clinical trial demonstrated the feasibility and safety of ATDC administration in kidney transplant recipients, with no major safety concerns, and was associated with an increased proportion of regulatory T cells (Treg) in treated patient. Previous *in vitro* studies showed that ATDC mediate their immunomodulatory effects primarily through secreted metabolites rather than cytokines. We therefore investigated how the ATDC secretome promotes Treg accumulation.
Methods
ATDC were generated from monocytes cultured with low concentrations of GM-CSF. Total and naïve $CD4^+$ T cells were stimulated in the presence or absence of ATDC secretome. Treg induction and proliferation were assessed by flow cytometry. The role of lactate was investigated using pharmacological inhibition of lactate production. Metabolic changes in Treg were evaluated using mitochondrial and lipid probes. Treg induction and suppressive capacity were further assessed in a conventional iTreg model.
Results
The ATDC secretome increased Treg frequency among activated $CD4^+$ T cells independently of lactate and classical cytokine-mediated mechanisms. In isolated naïve $CD4^+$ T cells, this effect primarily resulted from *de novo* Treg induction and was dependent on lactate. Metabolic profiling revealed increased mitochondrial polarization, mitochondrial ROS, and lipid content in Treg generated from total $CD4^+$ T cells, whereas only mitochondrial polarization was increased in Treg generated from naïve $CD4^+$ T cells, indicating a broader metabolic effect in the presence of other $CD4^+$ T-cell subsets.Finally, using a conventional induced Treg (iTreg) model, the ATDC secretome enhanced iTreg induction and their suppressive capacity.
Conclusion
The ATDC secretome promotes Treg induction, with lactate playing a key role in naïve $CD4^+$ T cells, while broader effects in total $CD4^+$ T cells suggest additional mechanisms. These effects are associated with metabolic changes and enhanced iTreg function, providing new insights into ATDC-mediated tolerance.

Keywords: Regulatory T cells - Lactate - Tolerogenic dendritic cells.

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Nanoparticles targeting liver sinusoidal endothelial cells improve AAV gene transfer and promote tolerance-spreading to capsid and transgene epitopes

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Viral-vector-mediated gene therapy is impeded by deleterious immune responses against capsid- and transgene-derived antigens, limiting transgene expression. Therefore, clinical situations such as adeno-associated viral (AAV) gene transfer would benefit from simultaneous tolerance induction to multiple epitopes/antigens. An innovative approach to induce antigen-specific tolerance has been developed using peptide-coupled nanoparticles, designed to preferentially deliver antigenic peptides to liver sinusoidal endothelial cells (LSECs), thereby exploiting their natural potential of cross-presenting antigens and tolerizing T cell responses. Different mouse models of AAV-mediated gene transfer to muscle and liver were used to assess whether nanoparticles coupled to capsid- and transgene-derived peptides can effectively inhibit vector- and transgene-specific immune responses and improve transgene persistence. For that, LSEC-targeting peptide-coupled nanoparticles were intravenously administered at predefined timepoints in the context of muscle- and liver-directed AAV-gene transfer and T- cell responses were analysed overtime. Our results show that treatment with nanoparticle-peptide-conjugates abrogated CD4+ and CD8+ T cell immune responses towards the targeted peptide-epitopes and significantly improved transgene persistence in liver and muscle. Furthermore, we report here for the first time that LSEC-targeting nanoparticles coupled to a single transgene-related peptide epitope promoted extension of tolerance to multiple relevant epitopes/antigens and simultaneously tolerized both CD4+ and CD8+T cell responses. This tolerance spreading, which we termed «Tspread,» remained specific to the transgene- and capsid-derived antigens conveyed by the administered AAV vector and did not impair immune responses to an unrelated vaccine antigen. These findings delineate a novel LSEC-mediated extension of tolerance with important clinical implications for viral-vector gene therapy, where tolerance to multiple epitopes/antigens is essential for long-term expression of therapeutic genes.

Keywords: Nanoparticles - Liver sinusoidal endothelial cells (LSECs) - Immune tolerance, tolerance spreading.

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IRE1α-XBP1 inhibitors: a promising approach to treat chronic vascular rejection after organ transplantation

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Background
Chronic vascular rejection (CVR) is the leading cause of graft loss following organ transplantation. Natural Killer (NK) cells play a pivotal role in CVR, being activated through two main mechanisms: missing-self (MS) recognition, which detects the absence of self-HLA molecules, and antibody-dependent cellular cytotoxicity (ADCC) in the presence of donor-specific antibodies (DSA). NK cell activation requires an initial “priming” signal, commonly provided by cytokines such as interleukin 15 (IL-15). Recent studies have shown that IL-15 activation induces the IRE1α-XBP1 pathway in NK cells, which regulates their effector functions and survival. This study aimed to confirm the involvement of the IRE1α-XBP1 pathway in NK activation during CVR and explore whether blocking this pathway could be a potential therapeutic approach.
Methods & results
We first analyzed single-cell RNA sequencing data from biopsies of CVR patients and found that most intragraft NK cells highly expressed XBP1s. *In vitro*, we confirmed that IL-15 priming significantly increased XBP1s expression, validating the activation of the IRE1α-XBP1 pathway in NK cells. Furthermore, we demonstrated that IL-15 priming was essential for NK cell activation through both MS recognition and ADCC mechanisms. Only IL-15-primed NK cells were capable of degranulation and IFN-γ production in response to DSA or MS when co-cultured with allogeneic endothelial cells. Notably, two distinct IRE1α inhibitors effectively blocked NK cell activation by both mechanisms involved in CVR. Ongoing experiments in murine *in vivo* models will further validate these findings.
Conclusions
These results underscore the critical role of the IRE1α-XBP1 pathway in NK cell activation during chronic vascular rejection. Targeting this pathway with specific inhibitors may provide a novel therapeutic strategy for managing chronic vascular rejection in transplant recipients.

Keywords: Transplantation - Rejection - NK cells.

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Early-life *Wnt4* expressing colon stromal cells orchestrate lifelong mucosal homeostasis via BMP-driven iNKT cell imprinting

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Early-life intestinal signals shape immune development with lasting consequences for mucosal homeostasis. We previously identified an early-life developmental pathway in which embryonic macrophages regulate the establishment of colonic invariant natural killer T (iNKT) cells for the long-term (1). Building on these findings, we identify a neonatal niche of Wnt4^{+} stromal cells, spatially associated with macrophages and iNKT cells, that promotes iNKT cell proliferation through BMP-MAPK signaling (2). These stromal cells are shaped by microbial signals, as germ-free and early-life antibiotic- treated mice exhibit increased Wnt4+ stromal cell abundance and elevated Bmp2 expression, with excessive iNKT cell accumulation that lasts into adulthood. These persistent changes in iNKT cells due to early-life perturbations are associated with altered susceptibility to later-life mucosal disorders. Importantly, similar stromal cells are present in fetal and neonatal human colon, and human rBMP2 promotes iNKT cell growth. Together, our findings reveal a neonatal colonic stromal niche, orchestrated by microbial cues, that regulates colonic immune homeostasis in later-life (1,2).

Keywords: iNKT - Microbiota - Imprinting.

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Neuronal responses to bacterial signals: the influence of sex hormones

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The microbial community of the gastrointestinal tract and the central nervous system communicate via a bidirectional network of signaling pathways known as the gut-brain axis. This axis has emerged as a complex regulator of system-wide physiology, playing essential roles in the outcomes of metabolic and neurological diseases. Thus far, most gut-brain axis mechanisms are described as indirect, via bacterial interaction with, for example, the immune system or the vagus nerve. However, microbe-derived compounds are found in the brain, where these compounds can interact directly with neurons, a direct gut-brain axis mechanism. My work was one of the first to highlight that brain neurons responded via a direct mechanism to microbe-derived compounds in an interaction that was sex- and age-dependent (1). However, the limited knowledge of how the gut-brain axis is affected by the individual's physiological state (e.g., hormonal status) and its impact on the host impairs advances in understanding host-microbe interactions and translational approaches. Therefore, we set out to dissect how physiological factors influence microbe-induced neuronal activation. Using gain- and loss-of-function approaches and 3D brain imaging, we have shown that estrogen influences how brain neurons perceive bacteria-derived muropeptides, highlighting the impact of sex hormones and the individual's physiological state on bacterial sensing in the brain. This new knowledge will be a major step towards understanding novel aspects of host-microbial symbiotic relationships, opening new possibilities for developing individual-specific treatments for neurometabolic diseases and beyond.

Keywords: Gut-brain axis - Estrogen - Muropeptides.

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IL-17 regulates peripheral nerve regeneration in a microbiota dependent manner

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Objective
Infiltration of immune cells following nerve injury regulates neuroinflammation and axon regeneration. Tissue-resident IL-17 producing γδ (γδ17) T cells display pro-repair roles in tissues and contribute to the central nervous system function by regulating cognition and anxiety. However, their role in peripheral nerve regeneration remains unexplored. Here, we investigate the role of IL-17 and its interplay with the gut microbiota in functional recovery after sciatic nerve injury.
Methods
We crushed mouse sciatic nerve as a model of peripheral nerve injury and analysed by flow cytometry the phenotype of immune cells accumulating in situ across time. Additionally, we employed the mouse-walker platform and *in vivo* electrophysiology to assess motor recovery in singly- or co-housed IL-17-deficient (IL-17^{-}/$^{-}$) mice and their wild-type (WT) (IL-17^{+}/$^{+}$) littermates. We profiled gut microbial composition from animal feces by 16S rRNA sequencing and characterized proteome landscape from sciatic nerve and associated dorsal root ganglia (DRG) through an unbiased proteomics approach.
Results
We found that IL-17 was mostly produced by γδ T cells, which accumulated in WT nerve early after injury. This process was triggered by microbiota-derived cues, as it was abolished in mice treated with broad-spectrum antibiotics. IL-17 appeared crucial for nerve repair, as IL-17^{-}/$^{-}$ mice showed an incomplete motor recovery and abnormal nerve activity compared to their littermate controls. Mechanistically, our proteomic data are suggesting a key role for IL-17 in the regulation of neuronal apoptosis, immune activation, cytoskeletal remodelling and oxidative phosphorylation. These processes were seemingly dependent of gut microbial cues, as the impaired nerve regeneration observed in IL-17^{-}/$^{-}$ mice was restored upon co-housing with their littermate controls. Our 16S rRNA sequencing analysis further confirmed distinct gut bacterial colony enrichment between both genotypes after nerve injury, identifying a regenerative IL-17 dependent microbiota signature, which is being validated by fecal transplantation.
Conclusion
By revealing a bidirectional IL-17-microbiota crosstalk that regulate the outcome of sciatic nerve injury, our findings pave the way to a better understanding of the molecular mechanisms involved in peripheral nerve regeneration.

Keywords: IL-17 - Microbiota - Nerve regeneration.

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Gut Microbiota Regulates Host Immune Bioenergetics - Role of Proline Metabolism In Monocytes Phenotype

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While the gut microbiota is a key regulator of host physiology, its specific influence on immune cell bioenergetics and effector functions remains incompletely understood[1]. Here, we systematically investigate how the gut microbiota shapes immune cell energy metabolism across compartment-specific and systemic immune populations in mice and humans. Antimicrobial-induced depletion of the gut microbiota in mice induced a profound, global energy-deficient state in isolated intestinal immune cells from both the small intestine and colon, assessed by SCENITH[2]. This phenotype was characterized by markedly diminished mitochondrial respiration and ATP production, loss of metabolic plasticity, and a compensatory heightened reliance on glycolysis. To evaluate translational relevance in humans, we analyzed peripheral blood mononuclear cells from patients with recurrent *Clostridioides difficile* infection (rCDI) undergoing fecal microbiota transplantation (FMT). Antibiotic treatment in pre-FMT patients similarly compromised systemic immune cell mitochondrial fitness, whereas successful FMT in the same patients restored oxidative phosphorylation capacity and basal ATP synthesis. Serum transfer experiments from conventional or germ-free mice, or from rCDI patients (before and after FMT) to healthy donors' peripheral cells, confirmed that gut-derived circulating factors are sufficient to dynamically tune distant immune cell bioenergetics. Integrative multi-omics profiling combining serum metabolomics and SCENITH parameters identified a positive correlation between proline metabolism and mitochondrial oxidation. Supplementation with either proline or its related metabolite N-methylproline directly sustained basal and maximal mitochondrial oxygen consumption rates in primary human monocytes in a context-dependent manner. Notably, N-methylproline specifically enhanced monocyte phagocytic capacity through this bioenergetic support, linking metabolic fueling directly to host defense functions. Finally, oral administration of proline or N-methylproline to microbiota-depleted mice rescued metabolic deficits and improved mitochondrial mass in both circulating and tissue-infiltrating monocytes. Together, these findings establish the gut microbiota as an essential orchestrator of host immune bioenergetics in mice and humans, uncovering a functional microbial proline metabolic axis impacting monocyte fitness, representing a novel targetable pathway for immunometabolic interventions.

Keywords: Gut microbiota - Immunometabolism - Proline and monocytes.

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Deciphering the crosstalk between skin commensals and the immune system

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The mechanisms underlying the crosstalk between the microbiota and the immune system remains largely unknown. We previously established that skin colonization with *Staphylococcus epidermidis* results in the induction of T cell responses that control tissue function in a way that both enhances cutaneous immunity and promotes tissue repair.
To uncover the molecular determinants of *S. epidermidis* that promote T cell responses, we engineered a library of *S. epidermidis* mutants with defined cell envelope alterations. We found that *S. epidermidis* cell envelope mutants elicit marked changes in the composition and function of the T cell populations induced in the skin after physiological cutaneous colonization. In particular, the removal of cell envelope lipoproteins and the loss of D-alanylation of teichoic acids almost completely abrogated CD8+ T cell induction while having no significant effect on CD4+ T cell stimulation.
Similarly, deletion of *Tlr2* gene also strongly reduced the CD8+ T cell response after *S. epidermidis* colonization, while the CD4+ T cell response remained unchanged. This phenotype mirrored that observed following the removal of cell envelope lipoproteins and D-alanylation of teichoic acid in *S. epidermidis*. Notably, these microbial determinants were dispensable for T cells responses induced by intradermal infection.
Mechanistically, we found that TLR2-mediated sensing of *S. epidermidis* molecular determinants specifically by keratinocytes is required for the induction of CD8+ T cell responses following cutaneous colonization. Altogether, these findings reveal a mode of communication between the immune system and a dominant member of the skin microbiota, and provide a basis for the exogenous modulation of host pathways governing immune modulation by skin commensals.

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Regulation of humoral responses in health and disease

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It has long been known that CD4 T cells are necessary for effective antibody responses to provide help to B cells, triggering a germinal centre (GC) reaction where affinity maturation and isotype switching occur. However, the nature of the dedicated CD4 helper T cells, known today as T follicular helper (Tfh), was only recently described. A population of Foxp3+ regulatory cells with unique access to the follicle – T follicular regulatory (Tfr) cells – represent the counterpart of Tfh cells. In addition, Tfh cells also specialize according to the inflammatory environment, acquiring different properties under type-1 or type-2 conditions. The interplay between different specialized subsets of Tfh and Tfr cells can determine the outcome of humoral responses, including the formation of tertiary lymphoid structures that can occur in chronic inflammatory conditions and cancer. The detailed knowledge of regulatory mechanisms controlling T cell- B cell interactions offers an opportunity for therapeutic modulation, namely in autoimmune diseases or to achieve more effective vaccination.

Keywords: Tfh cells - Treg cells - Autoimmunity.

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Systems approaches to describe and simulate the tumour microenvironment

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Given the recent discoveries about the importance of specific interactions between immune and cancer cells, understanding the spatial properties of tumors at single-cell resolution becomes crucial. We have recently developed computational tools to describe spatial patterns and clustering of specific cell types in tissues using network theory. These approaches allow us to extract statistical properties from imaging or spatial-omics datasets that can be used as biomarkers. We will describe software to extract cellular networks in tissues (*tysserand*) and analyze spatial patterns (*mosna,* Coullomb et al. 2026*)*. Some of the identified patterns can constitute biomarkers and are predictive of response to immunotherapy.
We will then discuss our planned strategy to achieve an understanding of the dynamics of cellular interactions and phenotype transitions that can help us better target and personalise therapies, via a combination of agent-based (Verstraete et al. 2023) and logic modeling to represent processes at play in tumors at different levels. A major challenge remains in bridging the gap between literature based model construction and data-driven approaches, which are necessary to make the models patient-specific and clinically relevant. We will discuss our recent attempts to construct data-driven models of immune dynamic phenotypes in simplified in-vitro models of the tumour microenvironment of Chronic Lymphocytic Leukemia (Marku, Chenel et al. 2026), and particularly ongoing work based on single-cell transcriptomics time courses produced from these in-vitro cultures.
Finally, we will describe our ongoing work on integrating these dynamic modeling approaches in solid cancers to obtain personalised simulations of the tumour microenvironment and ultimately control their trajectories.

Keywords: Mathematical models - Spatial omics - Tumour microenvironment.

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Spatial characterization of CD8⁺ TRM heterogeneity within B-cell aggregates and tertiary lymphoid structures in triple-negative breast cancer

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CD8+ tissue-resident memory T cells (TRM) are a population of non-recirculating T cells that reside in peripheral tissues and tumors, where they are strategically positioned to rapidly respond to local threats. In breast cancer (BC), CD8+TRM are associated with favourable clinical outcomes, but their phenotypic heterogeneity and spatial organization within the tumor microenvironment remain poorly characterized.
Our flow cytometry analyses revealed a marked heterogeneity among CD8+TRM in BC and our tissue analysis showed that CD8+TRM are frequently located within or in close proximity to B-cell aggregates and tertiary lymphoid structures (TLS). These structures are known to positively impact clinical outcomes and immunotherapy responses in BC, making the investigation of CD8+TRM within such aggregates particularly relevant.
To investigate whether CD8+TRM phenotype vary according to their local tissue context and TLS maturation, we developed a multiplex imaging approach. Whole frozen tissue sections from 10 triple-negative breast cancer (TNBC) patients, pre-selected for a high density of B-cell aggregates/TLS, were stained using an 18-plex panel and imaged with the PhenoCycler-Fusion. The panel combines markers for CD8+TRM phenotyping, B-cell aggregates/TLS maturation stage characterization, and tumor cell identification.
The resulting images are being analyzed using a spatial analysis pipeline combining cell segmentation, phenotypic identification and spatial quantification of CD8+TRM. We will assess whether CD8+TRM phenotypes differ according to their localization within or around B-cell aggregates and TLS, and according to TLS maturation stage. We will present the complete imaging-to-analysis workflow, the main challenges encountered during image analysis, and preliminary findings on CD8+TRM heterogeneity and localization within the TNBC tumor microenvironment. The study aims to identify markers that will uniquely characterize CD8+TRM within TLS, shedding light on their potential roles in local immune responses. These findings will contribute to a better understanding of CD8+TRM biology in TNBC and may ultimately help identify tissue-based biomarkers relevant to patient prognosis and response to immunotherapy

Keywords: Tissue-resident memory T cells - Spatial imaging - Breast cancer.

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Single cell spatial profiling of immune contextures in MMRd colorectal cancer reveals distinct microenvironments associated with HLA-class-I loss

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Objective
Strong CD8+ T cell-mediated immunological pressure in mismatch repair-deficient (MMRd) colorectal cancers (CRC) drives tumour evolution and the selective outgrowth of clones with immune-evasive properties, including loss of HLA-class-I expression, observed in over 75% of MMRd CRCs. Despite impaired recognition by cognate CD8+ T cels, MMRd CRCs remain highly responsive to immunotherapy, suggesting that other immune cells or HLA-class-I-independent mechanisms contribute to antitumour immunity. Here, we investigate the immune landscape and cancer–immune cell dynamics of MMRd CRCs across distinct HLA-class-I phenotypes to better understand the mechanisms underlying ICB efficacy following HLA-class-I loss.

Methods
Treatment-naïve primary tissues from 28 MMRd CRC specimens (10 HLA-class-I positive, 10 HLA-class-I negative without B2M defects, and 8 HLA-class-I negative with B2M defects) were profiled using spatial transcriptomics with a tailored 480-gene Xenium panel to spatially characterize tumour immunophenotypes and assess local immune microenvironments.

Results
We found strong infiltration of $CD8^+$ T cell subsets in HLA-class I-negative tumours, particularly those retaining B2M expression. In contrast, γδ T cell/innate lymphoid cell (ILC) subsets were strongly associated with HLA-class I-negative tumours with B2M loss. Both populations displayed increased expression of cytolytic enzymes, including granzymes, perforin and granulysin, and were enriched near the tumour mass, either within the intraepithelial compartment or at the tumour–stroma interface. These findings indicate the presence of cytotoxic immune subsets in HLA-class I-negative tumours despite impaired antigen presentation. Gene processes analysis further supported a cytotoxic, Th1-driven program, including T cell activation and regulation of ILC cytotoxicity. Conversely, HLA-class I-positive tumours showed an immunosuppressive signature, characterized by increased IL-10 signalling and a Th2-skewed response, suggesting the adoption of distinct mechanisms of immune escape by tumours that retain HLA-class-I expression.

Conclusion
We show that antitumour activity is maintained in HLA-class-I-deficient MMRd CRCs through distinct immune mechanisms: CD8+ T cells predominate in tumours that retain B2M expression, whereas innate lymphocytes drive activity in B2M defective tumours. In contrast, HLA-class-I-positive tumours exhibit immunosuppressive features that may promote immune escape.

Keywords: Colorectal cancer - Spatial transcriptomics - Immune landscape.

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Liquid biopsy reveals the immune status and protein profiles linked to CTC burden and clinical outcomes in metastatic breast cancer

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Background
Metastatic breast cancer (mBC) remains a major therapeutic challenge. Growing evidence indicates that metastatic progression and treatment resistance are supported by systemic immune dysfunction and vascular remodeling, although the underlying mechanisms remain incompletely understood. We therefore applied a multilayered liquid biopsy approach to characterize the systemic immunovascular landscape of mBC and identify circulating biomarkers associated with disease progression and prognosis.

Methods
Peripheral blood was prospectively collected from 60 patients with newly diagnosed stage IV mBC before treatment initiation. Circulating tumor cells (CTCs) were enumerated using CellSearch®. Immune profiling was performed by flow cytometry and plasma proteins were analyzed using the Olink® 96 Immuno-Oncology panel. Progression-free survival (PFS) was assessed using Kaplan–Meier and Cox proportional hazards models, including multivariate analysis.

Results
Most tumors were $HR^+/HER2^-$ (83.3%). Median follow-up was 31.5 months and median PFS 19.9 months. CTCs were detected in 58.3% of patients (1–962 CTCs/7.5 mL). Compared with age-matched healthy donors, patients showed reduced total leukocytes and $CD3^+$ T cells, increased regulatory T cells (Tregs), and enhanced expression of inhibitory receptors including PD-1, CTLA-4, TIGIT and LAG-3. Co-expression of these checkpoints on $CD4^+$ and $CD8^+$ effector T cells indicated an exhausted phenotype. Circulating monocytes/macrophages were shifted toward an immunosuppressive $CD163^+CD206^+$ phenotype. Proteomic profiling revealed an inflammatory and angiogenic signature characterized by increased IL-6, IL-8, HGF, ANGPT2, NOS3, CSF1 and galectin-9, with reduced FASLG and TWEAK. Treg proportion and levels of IL-8, HGF, galectin-9 and TNFRSF12A were higher in CTC-positive patients. Liver metastases, triple-negative status and high CTC counts were associated with shorter PFS. Multivariate analysis identified IL-8 (HR=1.49, p=0.004) and NOS3 (HR=4.72, p=0.003) as independent predictors of PFS.

Conclusion
This integrated cellular and proteomic liquid biopsy analysis identifies mBC as a systemic immunovascular disease characterized by T-cell exhaustion, Treg expansion, immunosuppressive monocyte polarization, pro-angiogenic inflammation and CTC-associated immune escape. Circulating IL-8 and NOS3 may represent promising blood-based prognostic biomarkers and potential therapeutic targets.

Keywords: Liquid biopsy - Circulating immune cells - Circulating proteins.

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Protein Engineering and Synthetic Biology: New Strategies for Therapeutic Antibody Development

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Protein engineering and synthetic biology enable the development of biological medicines with properties tailored to therapeutic needs. This presentation explores strategies for discovering, selecting and optimising antibodies and their fragments, with applications in oncology, infectious diseases and inflammatory disorders.
Examples include the development of nanobodies targeting nucleolin to promote tumour cell recognition, cellular internalisation and recruitment of immune effector functions. Directed evolution, library construction and functional selection illustrate how these molecules can be refined to enhance their therapeutic potential.
The presentation further highlights platforms for antibody diversification in mammalian cells using CRISPR/Cas9 and zinc-finger nucleases, alongside intracellular selection methods. Finally, approaches to improving pharmacokinetics through albumin binding will be explored, including experimental applications in inflammation.
Together, these studies demonstrate how integrating molecular engineering, functional selection and preclinical validation can support the development of innovative therapeutic approaches. They also illustrate opportunities to expand antibody diversity, improve molecular targeting and optimise biological activity, while recognising that clinical translation requires further research and development.

Keywords: Antibody - Synthetic.

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Generation of Versatile Tumour Target Cell Lines Using the SpyCatcher/SpyTag System to Evaluate Antibody-Based Immunotherapies

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Objective
Immunotherapies such as monoclonal antibodies and CAR-T cells have shown remarkable success against hematological cancers but remain less effective in solid tumours due to multiple escape mechanisms, including antigen downregulation and heterogeneity. Current in vitro analytical platforms used to evaluate immune therapeutics lack the flexibility to rapidly generate target cells with tunable antigen expression levels. To address this limitation, we developed a cell-based platform enabling flexible antigen display to assess effector cell potency during immunotherapy development.

Method
We generated versatile tumor target cell lines, named SpyTarget cells, based on the SpyTag/Catcher system derived from the fibronectin-binding protein (FbaB) of *Streptococcus pyogenes*. SpyTag and SpyCatcher were engineered as separate peptides that spontaneously form a covalent isopeptide bond upon interaction. Leveraging this protein ligation technology, SpyTarget cells can be post-translationally decorated with tumour antigens allowing precise control over antigen selection, density, and the simultaneous presentation of multiple antigens within the same cell line.

Results
To generate SpyTarget cells, we engineered HEK293T and MDA-MB-231 to express SpyCatcher on the cell membrane. As a proof of concept, we selected HER2, a clinically relevant antigen overexpressed in various solid tumours, as a target antigen and produced SpyTag-HER2 fusion protein. Flow cytometry analysis revealed that incubation with defined concentrations of SpyTagHER2, generated HER2 surface densities ranging from around 20,000 molecules per cell to levels comparable to naturally HER2-high tumors (1,000,000 molecules). We then functionally tested SpyTarget cells displaying varying HER2 densities in Antibody-Dependent Cell Cytotoxicity assay (ADCC) using a reporter cell line. Titration of a therapeutic anti-HER2 antibody (trastuzumab) showed a SpyTag-HER2 dose-dependent activation of effector cells. Additional studies with primary NK cells and HER2-specific CAR-T cells further validated the functionality of the platform.

Conclusions
We are expanding the evaluation of this platform by biophysical measurements and incorporation of additional functional assays using different CAR cell and antibodies. We propose that the SpyTarget system serves as a versatile and robust platform for quantifying effector cell responsiveness, offering a powerful tool for the development of immune therapeutics.

Keywords: Immunotherapies - SpyTarget - ADCC.

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Targeting the C-type lectin receptor DCIR using synthetic single-domain antibodies: a promising strategy for immune modulation in tuberculosis and beyond

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Objective
The dendritic cell immunoreceptor (DCIR) is a myeloid inhibitory C-type lectin receptor involved in the pathophysiology of several autoimmune, chronic inflammatory, and infectious diseases, making it a therapeutic target of interest. In 2017, my team demonstrated its role in regulating immune responses and bacterial elimination during tuberculosis (TB), one of the leading causes of death worldwide. Recently, we identified the low density lipoprotein receptor related protein 1 (LRP1) as an endogenous ligand for DCIR, and further demonstrated that DCIR recognizes the galactose-terminated biantennary N-glycans carried by LRP1. Our objective was to develop agonistic or antagonistic antibodies targeting DCIR for potential host-directed therapies in TB and other immune-mediated diseases.
Methods
We generated synthetic single-domain antibodies (sdAbs) targeting human (hDCIR) or murine DCIR (mDCIR1). Using several rounds of ribosome and phage display, we screened three synthetic libraries of sdAbs (named sybodies) on recombinant lectins and live cells. We assessed sdAb effects on DCIR-glycan interactions via competitive lectin binding assays. Four candidates were selected for further optimization, epitope mapping, and evaluation of immunomodulatory properties *in vitro* and *in vivo* in a murine TB model.
Results
We identified 16 sybodies specifically binding to either hDCIR or mDCIR1 at the surface of myeloid cells. Interestingly, most sybodies blocked DCIR-glycan interaction. Two anti-hDCIR and two anti-mDCIR1 sybodies were fused to human or murine IgG hinge and Fc domains and optimized via Fc engineering. Their epitopes were mapped using AlphaFold 3 interaction models and hydrogen-deuterium exchange mass spectrometry. *In vitro*, the anti-mDCIR1 sybodies-IgG fusions enhanced TNFα production in TLR9-stimulated bone marrow-derived dendritic cells. *In vivo*, the anti-mDCIR1 sybodies-IgG fusions differentially modulated immune cell recruitment and bacterial burden in the lungs of *M. tuberculosis*-infected *Sp140*$^{-/-}$ mice, suggesting one acts as a mDCIR1 agonist and the other as an antagonist.
Conclusion
These findings provide a first proof of concept of the interest of targeting DCIR in host-directed TB therapy. These anti-DCIR sybodies may advance our understanding of DCIR's role in immunity, and serve as future therapeutics to modulate immunity in TB and other diseases.

Keywords: Single-domain antibody - c-type lectin receptor - Tuberculosis.

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Integrated Biophysical Analysis of Fc–FcR Binding, Affinity, and Avidity in Antibody Therapeutics

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Fc–receptor (FcR) engagement is a key determinant of an antibody's therapeutic potential, influencing effector functions such as ADCC, ADCP, and immune modulation. As antibody formats grow more complex - from monoclonals to bispecifics and Tcell engagers - robust analytical strategies are needed to fully characterize how Fc regions interact with their corresponding receptors. We present an integrated biophysical workflow for systematic evaluation of Fc–FcR interactions, complemented by affinity and avidity analysis.
Using multiplexed highthroughput SPR, we quantified FcR binding capacities across antibody variants and identified the impact of Fc subclass, Fc glycoengineering, receptor polymorphisms, and pH on binding kinetics. To dissect affinity versus avidity contributions in bispecific formats, we applied a DNAnanotechnology–based assay capable of distinguishing monovalent recognition from multivalent engagement. Finally, singlecell Interaction Cytometry (scIC) enabled realtime measurement of antibody and FcR interactions directly on living cells, preserving native membrane context to capture the influence of receptor density, membrane mobility, and coreceptors.
Together, this workflow provides a comprehensive and physiologically relevant framework for characterizing antibody interactions and guiding datadriven therapeutic antibody design.

Keywords: Fc Receptors - Therapeutic Antibodies - Binding Kinetics.

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A comprehensive, transcriptome-wide overview of post-transcriptional control of plasma cell differentiation

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Differentiation of B lymphocytes into antibody-secreting cells (ASCs) is accompanied by extensive genomic, transcriptomic, and morphological remodeling required to sustain immunoglobulin (Ig) synthesis and secretion. Although many cellular adaptations have been extensively characterized, the post-transcriptional mechanisms orchestrating ASC differentiation remain largely unexplored. However, accumulating evidence highlights post-transcriptional regulation as a major determinant of cell identity and function. To address this gap, we developed complementary approaches to generate a comprehensive map of the post-transcriptional regulatory events driving human ASC differentiation, with a particular focus on Ig transcripts.

To our knowledge, this study represents the first application of transcriptome-wide Direct RNA Sequencing (DRS; Oxford Nanopore Technologies) to primary human B cells undergoing activation and differentiation into ASCs. This unique dataset simultaneously captures transcript isoforms, poly(A) tail length, and the epitranscriptomic landscape throughout the early stages of differentiation. After establishing the high quality of our sequencing data, we identified extensive remodeling of Ig transcript polyadenylation, which was independently validated using a complementary single-transcript assay. Furthermore, analysis of RNA base modifications revealed a global decrease in m6A methylation levels in plasmablasts compared with activated B cells, suggesting that epitranscriptomic remodeling constitutes a key regulatory event during the acquisition of the antibody-secreting phenotype.

To further dissect the molecular mechanisms controlling plasma cell differentiation and survival, we are currently integrating complementary analyses of the RNA-binding proteome using Orthogonal Organic Phase Separation (OOPS) and translatome profiling. Together, these multi-omics approaches will provide an integrated view of post-transcriptional regulation during plasma cell differentiation.

Ongoing studies aim to elucidate these regulatory networks and identify alterations specific to malignant plasma cells.

Collectively, this work should provide new insights into the mechanisms governing ASC differentiation and reveal potential therapeutic vulnerabilities in plasma cell dyscrasias, including multiple myeloma.

Keywords: Plasma cell differentiation - Post-transcriptional - Direct RNA Sequencing.

Integrating T cells Signals: Lessons from Primary Immunodeficiencies and Tfh cells

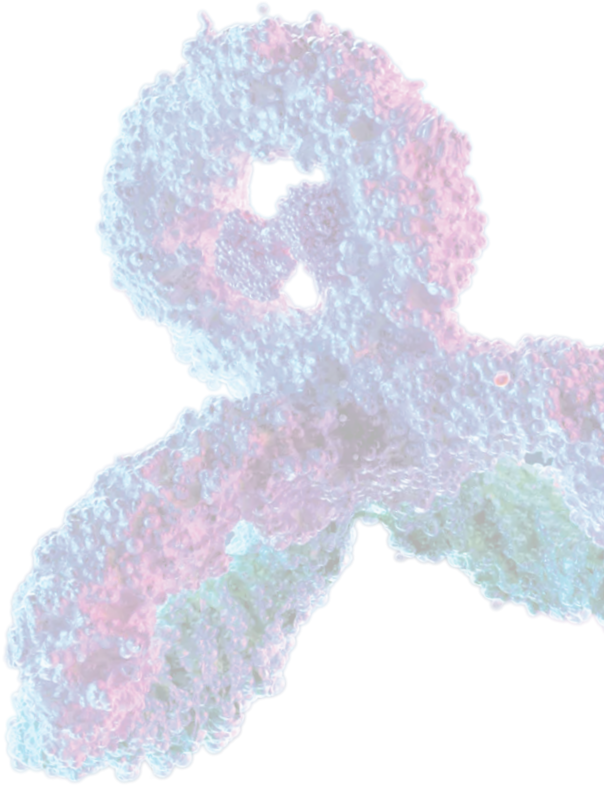
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Abstract not received.

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CADOT	Romane	The role of neuroinflammation in toxic epidermal necrolysis	**S1-P02**
CALVENTE	Julien	Role of immune checkpoints PD-1 and BTLA in the regulation of T-cell responses during central nervous system (CNS) inflammation	**S1-P03**
CUNNINGHAM	Kyle	Neuro-immune Control of Dendritic Cell-poiesis in Type-2 Immunity	**S1-P04**
DUFOURD	Eloïse	Brain barrier-specific tissue-resident memory CD8+ T cells alleviate EAE severity	**S1-P05**
FOHRER	Tiphaine	Tissue-specific neuroimmune regulation of antiviral immunity during HSV-1 infection	**S1-P06**
GARNIER	Nathan	Macrophages promote human sensory neuron progenitor proliferation in a developing dorsal root ganglia model	**S1-P07**
GOPINATH	Gayathri	Therapeutic targeting of JAK2 signaling and microglia to limit pathogenic tissue-resident $CD8^+$ cells in the brain	**S1-P08**
HÄMÄLÄINEN	Klaus	A new transcription factor regulates microglial activation and restrains neuroinflammation	**S1-P09**
JORDÃO	Inês	Stress derived glucocorticoids regulate γδ17 T cell transcriptomic signature in tissues	**S1-P10**
KHAYARI	Soufiane	CITE-seq reveals inhibition of NF-κB pathway in B cells from vitamin D-treated multiple sclerosis patients	**S1-P11**
MOREIRA	Diogo	Impact of IL-17 on gut immune homeostasis upon peripheral nerve injury	**S1-P12**
NINNEMANN	Justus	Chronic systemic inflammation imposes critical thresholds in energy metabolism	**S1-P13**
PIGNATA	Aurora	A $CD8^+$ T cell-mediated model of retinal neuroinflammation and ganglion cell degeneration	**S1-P14**
RIO	Lucie	Intrathecal Mesenchymal Stromal Cell administration improves EAE severity by inducing B cell reprogramming	**S1-P15**
ROUX	Camille	Immune checkpoint control of autoimmune inflammation in the eye	**S1-P16**
SAMPAIO	Yasmim	Zika virus targets human Schwann cells	**S1-P17**
SIMON	Thomas	Electrical stimulation of the arterial splenic nerve has durable therapeutic efficacy on murine collagen-induced arthritis by promoting regulatory B cells	**S1-P18**
STYM-POPPER	Grégoire	Functional subsets of regulatory T cells predict the rate of cognitive decline in Alzheimer's disease	**S1-P19**

POSTERS PS1 - Macrophages and dendritic cells

Last name	First name	Title of poster	# poster
AMANO	Mariane	Immunometabolic Reprogramming and Mitochondrial Remodeling in LPS-Induced Tolerized Macrophages	**PS1-P01**
DELLACASAGRANDE	Jérôme	Integrating monocyte-derived dendritic cells in the dermal compartment of a full-thickness skin model to confer a functional cytokine response	**PS1-P02**
FRYDER	Margot	Characterization of IL-23 producing cells during Klebsiella pneumoniae pulmonary infection	**PS1-P03**
GRAVERON	Guilhem	Uncovering endogenous pro-resolving macrophage programs in skin fibrosis	**PS1-P04**
GUILLIN	Marie	The role of FOLR2+ macrophages in anti-tumor immunity	**PS1-P05**
HIDALGO VILLEDA	Fanny	Epigenetic regulation of tumor-associated macrophage states by TET2 in pancreatic cancer	**PS1-P06**
HOSMALIN	Anne	Divergent pDC trajectories induced by HIV-infected T cells toward IFN production, T cell stimulation or cytotoxicity	**PS1-P07**
HUTTEAU	Tom	Characterisation of blood monocytes by scRNAseq and multiparametric flow cytometry in adult patients with isolated pulmonary Langerhans cell histiocytosis	**PS1-P08**
LE MERCIER	Mathilde	Development of a personalized and targeted therapeutic strategy for pathogenic synovial macrophages in osteoarthritis	**PS1-P09**
MANRIQUEZ	Valeria	Peritumoral HMOX1+ macrophages promote CD8+ T-cell infiltration through iNOS-dependent matrix remodeling	CANCELED

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MASCHALIDI	Sophia	Metabolic regulation of antigen presentation via MHC Class II.	**PS1-P11**
QUINTAS	Sofia	Uncovering the therapeutic potential of dendritic cell-derived extracellular vesicles for immunotherapy in triple-negative breast cancer	**PS1-P12**
REVERENDO	Marisa	Exploring RNA Biology and RNA Polymerase III Regulation During Dendritic Cell Activation	**PS1-P13**

POSTERS PS2 - Inborn errors in immunity

Last name	First name	Title of poster	# poster
MALAYE	Marie Olive	Multiparametric Flow Cytometric Profiling of Regulatory T and B Cells in Pediatric Inborn Errors of Immunity	**PS2-P01**
		Characterizing STAT1 Deficiency and the IL-12/IFN-γ Signaling Pathway in Four Moroccan Kindreds with Mendelian Susceptibility to Mycobacterial Disease	**PS2-P02**
		Kindreds with Mendelian Susceptibility to Mycobacterial Disease	**PS2-P03**

POSTERS PS3 - Vaccinology

Last name	First name	Title of poster	# poster
AMOIA	Charlie	Newcastle Disease Control: Do Perception Structures Drive Vaccine Adoption among Smallholder Poultry Farmers in Tanzania?	**PS3-P01**
BALSINHA PEDROSO	Rodrigo	Dissecting the contribution of T cells to protection against WNV-infectious mosquito bite induced by an EV-based vaccine	**PS3-P02**
CADENAT	Isabelle	Preclinical evaluation of Fel d 1 mRNA vaccine for the treatment of cat allergy	**PS3-P03**
CHARTOIRE	Dimitri	Monovalent mRNA Influenza Hemagglutinin Vaccine Sparks Potent Cellular Immunity Relative to Recombinant Protein Comparator in Humans	**PS3-P04**
CHEN	Hsin-Wei	Harnessing Neutrophil-Driven Innate Immunity for Antigen-Agnostic and Broad-Spectrum Vaccine Development	**PS3-P05**
EL HAJJ	Marwa	CD40 targeting sustains germinal centre activity and broadens antibody responses to SARS-CoV-2 variants	**PS3-P06**
HAIGH	Oscar	Early immunity determines how HSV-1 persists: programming latent reservoir reactivation competence	**PS3-P07**
MAMBELLI SILVA	Fabio	T cell-associated immunity induced by heterologous recombinant BCG and purified protein vaccination confers cross-variant protection against SARS-CoV-2	**PS3-P08**
RICHARD	Alexandre	Distinct innate immune programs induced by five HIV-1 vaccine platforms shape the magnitude and durability of adaptive immunity	**PS3-P09**
YALAOUI	Maria	HPV16 tumor control in mice through anti-CD40 targeting HPV16.E6/E7 vaccine combined with anti-PD-1	**PS3-P10**

POSTERS PS5 - ILC / NK

Last name	First name	Title of poster	# poster
DUMOLARD	Lucile	HBV-induced modulations in DC subsets reprogram NK cell responses	**PS5-P01**

POSTERS PS6 - Immunometabolism

Last name	First name	Title of poster	# poster
BROUQUE	Hugo	Metabolic profiling of circulating and tumor-infiltrating T cells uncovers bioenergetic checkpoints linked with immune and clinical skewing in melanoma patients	**PS6-P01**
DEWALLE	Caroline	Identifying metabolic requirements for Treg and CD8+ T cell intratumoral motility	**PS6-P02**
F. MENDES	Luís	Impact of pyruvate availability and ER-stress on the crosstalk between plasmacytoid dendritic cells and fibroblasts	**PS6-P03**
HAKIM	Nawad	Impact of RNA modifications in CD4+ T cell differentiation and function	**PS6-P04**

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HERRMANN	Arthur	Deciphering the antitumor activity of P. distasonis: Impact of its metabolites on tumor and T cells	**PS6-P05**
KERN COQUILLAT	Nicolas	Deciphering the Metabolic Programs Underlying Eomes$^+$ Th Cell Adaptability	**PS6-P06**
RODRIGUEZ	stephane	Molecular and metabolic profiling of cerebrospinal fluid EOMES expressing CD4$^+$ T cells in early multiple sclerosis	**PS6-P07**

POSTERS PS7 - T and B cell development and signaling

Last name	First name	Title of poster	# poster
ALVES-FILHO	Jose	Control of regulatory T cell stability during inflammation by adenosine signaling	**PS7-P01**
BERZINS	Stuart	Mapping the development pathways of human unconventional T cells	**PS7-P02**
BORIES	Cyrielle	GDE3 controls splenic marginal zone B cells positioning and plasmablast differentiation	**PS7-P03**
CARDOSO	João	LAMP2 controls autophagy-lysosomal pathway for selfpeptide–MHC II processing in thymic epithelial cells to tune CD4 T-Cell Selection	**PS7-P04**
INACIO	Daniel	MicroRNA-Mediated Post-Transcriptional Regulation of Peripheral γδ T Cell Effector Functions	**PS7-P05**
LOFFREDA	Iliana	Mapping and pharmacological targeting of CISH intracellular signaling checkpoint interactions in CD8+ T cells to improve immunotherapy	**PS7-P06**
MAIRE	Kilian	Genetic Traits Underpin T Cell Antigen Recognition	**PS7-P07**
MARTIN	Bruno	Foxo1 restrains naive CD4 T cell differentiation into type 1 and type 2 effector cells bysuppressing early cytokine production	**PS7-P08**
NGUYEN	Trang-My	The RNA-Binding Proteins TIA1 and TIAL1 shape T cell activation and function	**PS7-P09**
OSMA-GARCIA	Ines Claire	Post-transcripitonal regulation shapes Tregs development	**PS7-P10**
ROBARDEY	Anaïs	T cell fate is controlled by the functional interplay between the Ikaros and Foxo1 transcription factors	**PS7-P11**
RODRIGUES	Pedro M.	KLF15 is a novel regulator of thymic epithelial cell microenvironments that sustain T cell development	**PS7-P12**
SOBRAL	Francisco	Post-transcriptional control of key signalling pathways by ZFP36 RNA-binding proteins sustains thymic epithelial cell differentiation and thymic function	**PS7-P13**

POSTERS PS8 - Ageing

Last name	First name	Title of poster	# poster
DURAND	Aurélie	Impact of biological sex and inflammatory cytokines on T-cell exhaustion during aging	**PS8-P01**
LOPEZ	Léna	Emergence of an atypical immunosuppressive and pro-inflammatory monocytic subset linked to age-related frailty	**PS8-P02**
NOGUEROL	Julie	Inhibition of PTPN2/N1 by the small molecule inhibitor CLS-484 overcomes age-related immune deficiencies to enhance the efficacy of Flu vaccine in aged mice	**PS8-P03**
TORRES	Romain	Consequences of aging on naive CD4 T cell heterogeneity	**PS8-P04**
VUILLIER	Sylvia	Multiple Myeloma Progression and Treatment Drive Premature Ageing of Bone Marrow CD8+ T Cells	**PS8-P05**
AUTAA	Gaëlle	Optimized flow cytometry detection of p16INK4a reveals its differential expression across T cell differentiation subsets and age groups	**PS8-P06**

POSTERS PS10 - Autoimmunity and inflammatory diseases

Last name	First name	Title of poster	# poster
DIALLO	Mariama Sadjo	Profile of Autoantibodies and Clinical Symptoms in Guinean Patients with Connective Tissue Diseases	**PS10-P01**
BONNEFOY	Francis	Treatment of chronic inflammatory bowel diseases using intrarectal UVA radiation	**PS10-P02**
BOUILLE	Alice	c-Maf regulates age-associated B cell responses and limits autoimmune inflammation	**PS10-P03**

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BRUCHON	Adeline	Deciphering the role of regulated cell death by PANoptosis in neutrophilic asthma	**PS10-P04**
CARDON	Anaïs	Immunophenotyping of human synovial tissue using spectral flow cytometry	**PS10-P05**
CARRASCO G.	D. Giovana	Inflammatory skin-gut crosstalk in psoriasis progression	**PS10-P06**
CHAMY	Lea	The ASB2α-filamin A/B axis as a new therapeutic opportunity in type 2 immune pathologies	**PS10-P07**
CHAPEROT	Laurence	Innate Immunity, Microbiota, and Inflammation in Endometriosis: Understanding the Immunopathology to Develop Innovative Treatments	**PS10-P08**
CHERIEF	Valentin	Single-Cell Trajectory-Analysis Identifies Early Transcriptomic Imprinting of Type 1 Diabetes Risk Genes in Developing NOD Thymocytes	**PS10-P09**
COLLETTE	Lisy	PTK7 expression by dendritic cells regulates T-cell responses and the Treg/Th17 balance	**PS10-P10**
COURNEZ	Lucie	Development of a humanized murine model of lupus for preclinical evaluation of innovative therapies	**PS10-P11**
FRUTOSO	Marie	Natural Killer cells phenotypic and functional signature in Sjögren's Disease	**PS10-P12**
		Autoreactive SSA+ B cells phenotypic and functional signature in Sjögren's Disease	**PS10-P13**
HOPSOMER	Grégoire	Impact of a STING gain-of-function on B Cell Phenotype and Development of Autoimmunity	**PS10-P14**
LABROSSE	Mathilde	BMP9 and BMP10 Limit IL-6/STAT3 signaling in Endothelial Cells by Inducing SOCS3 and Suppressing Inflammatory Activation	**PS10-P15**
LAGO	Claire	Immunomic Characterization of Circulating B and T Cells in Autoimmune Hepatitis	**PS10-P16**
LANAU	Alexandre	Understanding thymic selection and central tolerance defects in thymoma patients	**PS10-P17**
LEITE-DE-MORAES	Maria	Resolution of pediatric cow's milk allergy is associated with low Tfh cell frequencies and elevated IL-17 and IL-22 levels	**PS10-P18**
LOUREIRO	Inês	Thapsigargin enhances STING-dependent activation in a pDC cell line	**PS10-P19**
LOURENÇO ALVES	Mathieu	The human PERK p.P649T variant synergizes with STING signaling to drive enhanced type-I IFN and inflammatory cytokines expression in monocytes.	**PS10-P20**
MACHADO	Mariana	ER stress and matrix stiffness promote pDC-mediated fibroblast activation	**PS10-P21**
MAGAT	Yves-Marie	NLRP6 senses ozone-induced oxidative stress, triggering the activation of pyroptotic pathways in type 1 alveolar epithelial cells	**PS10-P22**
MALAYE	Marie Olive	Autoimmune Cytopenias : A frequent manifestation in patients with Autoimmune Lymphoproliferative Syndrome (ALPS)	**PS10-P23**
MARMONT	Ninon	Molecular determinants of TYPE-2 CD4+ tissue resident memory T Cells in atopic dermatitis	**PS10-P24**
MIREY	Emilie	From Mouse to Clinic: Non-Invasive Swab-Based Profiling of Inflammatory and Barrier Markers in Atopic Dermatitis	**PS10-P25**
ORLHAC	Elisa	Complement fractions in cryoglobulinemia: a study of their biological distribution and clinical correlation	**PS10-P26**
PEYROT	Charline	Role of the DNA sensor STING in immune responses to infection and lung inflammation: a One Health perspective	**PS10-P27**
PFEIFER	Romain	A novel lncRNA modulates Th cell identity and inflammatory responses	**PS10-P28**
PIERRE	Philippe	A human eIF2AK3 (PERK) variant synergizes with STING to drive enhanced type-I IFN and inflammatory cytokines expression in monocytes of a SAVI patient	**PS10-P29**
PLUCHART	Chloé	Characterization of Factor VIII-specific regulatory and conventional CD4+ T cells using TCR tranfer in Jurkat cells by microfluidics	**PS10-P30**
SHAH	Nainisha	Inflammation-Driven Treg Adaptation Reveals a Distinct Effector State in Rheumatoid Arthritis Synovial Fluid	**PS10-P31**
TAVARES-GOMES	Leticia	Intestinal mucosal glycosylation as a regulator of the gut-joint axis	**PS10-P32**
VILLENEUVE ADESSI	Maud	Characterization of pathogenic autoreactive B cells in antiphospholipid syndrome	**PS10-P33**
ZECO	Faris	Beyond platelets: ACTN1 variants drive immune dysregulation at the thrombocytopenia-autoimmunity interface	**PS10-P34**

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ZHU	Yixiang Y.J.	Dynamic type I IFN signature, monocyte bias and impaired TLR7/8 response in SITRAME syndrome	**PS10-P35**
		Dysregulated dsRNA sensor signaling and viral infection during onset of pediatric autoimmune interferonopathy	**PS10-P36**
ZITOUNI HUTCHINS	Sihem	Targeting the MyDDosome: SPM001, a Stapled Peptide Inhibitor of IRAK4/IRAK2 interactions for NF-κB-Driven Inflammation	**PS10-P37**

POSTERS PS11 - Innate T cells

Last name	First name	Title of poster	# poster
CAILLENS	Vivien	Control of SARS-CoV-2 replication by activated Delta One T Cells	**PS11-P01**
MENARD	Margaux	Understanding MAIT cell function in Neisseria meningitidis pathogenesis	**PS11-P02**
STEVENS	Georgia	Decoding Vδ1 T Cell-Acute Myeloid Leukemia Interactions	**PS11-P03**

POSTERS PS12 - Women's health/sex bias in immunity

Last name	First name	Title of poster	# poster
LANGLAIS	Antonin	Influence of estrogen receptor ligands on NK Cell functions: consequences on anti-tumour immunity	**PS12-P01**

POSTERS PS13 - T and B cell memory

Last name	First name	Title of poster	# poster
LENIEF	Vanina	Emerging function of tissue-resident memory T cells in chronic allergic contact dermatitis	**PS13-P01**
RASCLE	Marie	Elucidating the mechanisms controlling the persistence of brain resident memory T cells during chronic T.gondii infection	**PS13-P02**
WENCKER	Melanie	Gain-of-function mutation in CXCR4 chemokine receptor controls the pool size of memory CD8 T-cells	**PS13-P03**

POSTERS S2 - Host-pathogen interactions

Last name	First name	Title of poster	# poster
DIALLO	Mariama Sadjo	Immunovirological Discordance and AssociatedFactors among People Living with HIV underAntiretroviral Treatment at Hôpital de Jour de Donka, Guinea	**S2-P01**
BOITTELLE	Gwendoline	Cardiometabolic disorders exacerbate bacterial pneumonia and reshape lung neutrophil states in a murine model	**S2-P02**
CARDOSO	Marcos	Integrative transcriptomic analysis reveals early host response programs associated with divergent tuberculosis outcomes	**S2-P03**
CARNOY	Christophe	Flagellin enhances innate immune responses in human airway epithelium during bacterial infection	**S2-P04**
DE ARAUJO	Ana Carolina	HIF-1α licenses BCG-induced trained immunity to promote pulmonary and systemic protection against Brucella abortus infection	**S2-P05**
JEAN	Baptiste	Development of a Simoa-Based Assay for virokine cmvIL-10 quantification	**S2-P06**
JNEID	Bakhos	Elucidating the endothelial transcriptional landscape during Neisseria meningitidis infection by using single-cell and spatial profiling	**S2-P07**
MARTIN	Aurore	Development of a Rapid Automated Functional Assay to Assess Innate Immune Function in Septic Shock Patients	**S2-P08**
RAVON KATOSSKY	Léa	Bacterial Genotoxins Trigger Schlafen11-Dependent Ribotoxic Stress Response	**S2-P09**
ROUX	Fanny	Deciphering the microbiota-lactate-macrophage axis in pneumonia: the protective role of Streptococcus mitis and signalling via the host GPR81 Receptor	**S2-P10**

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SCHNELLER	Anaïs	Characterizing CMV-Specific Immune Signatures to Predict Post-Transplant Infection Risk	**S2-P11**
SILVA	Maria	SSC5D as an Immunological Mediator in Pregnancy-Associated and Neonatal Infections	**S2-P12**
SILVA FOLHAS DAMAS	Marcelo	Ex vivo HIV latency reversal combined with shingrix leads to enhanced hiv reservoir reactivation and immune restoration	**S2-P13**
TANTET	Léa	Dissecting MHC-II-restricted endogenous antigen presentation using viral proteins: the influence of HTLV-1 Tax	**S2-P14**
TONNERRE	Pierre	Sensitive detection of pathogen-specific T cells after antigen stimulation comes with phenotypic trade-offs	**S2-P15**
		Cellular and spatial features of the liver microenvironment associated with chronic hepatitis B disease progression	**S2-P16**
YANG	Haiyi	Distinct interactions of Tropheryma whipplei with intestinal epithelial cells	**S2-P17**
		Investigating the Interaction Between Tropheryma whipplei and Epithelial Cells	**S2-P18**

POSTERS PS15 - Neutrophils

Last name	First name	Title of poster	# poster
CAVADA	Sofia	Optimizing Immunotherapies in rhabdoid tumors (RTs) by targeting tumor-associated neutrophils	**PS15-P01**
LABAYE	Quiterie	Circulating neutrophil state mapping reveals phenotypic and functional heterogeneity in rheumatoid arthritis	**PS15-P02**
RODRIGUEZ	André	MYELOTRACKER®: a peptide-based tool for specific detection and functional analysis of neutrophils	**PS15-P03**
ROMERO	Sebastian	Neutrophils dynamically orchestrate the myeloid inflammatory network in arthritis	**PS15-P04**

POSTERS PS16 - Gene and cell therapy

Last name	First name	Title of poster	# poster
FORTUIN	Annemarie	Engineering Regulatory T Cells For Rheumatoid Arthritis: Development and Evaluation of CAR Constructs	**PS16-P01**
ROUX-PORTALEZ	Vincent	Identification of TCRs targeting neogene-derived neoantigens for immunotherapy of Ewing sarcoma	**PS16-P02**

POSTERS PS17 - Germinal Center

Last name	First name	Title of poster	# poster
CAVACO	Maria	Exploring human T follicular cell subsets in allergic disease	**PS17-P01**
CHAKRABARTI	Lisa	Leveraging a human lymphoid organ-on-chip reveals help-dependency in B cell responses to mRNA vaccines	**PS17-P02**
CULIE	Louis	Peripheral induction of regulatory T cells seeds the follicular regulatory T cell compartment	**PS17-P03**
SEITE	Fanette	Ins and outs of HIV antigen presentation by HIV-specific B cells	**PS17-P04**

POSTERS PS19 - Mast cells / Basophils

Last name	First name	Title of poster	# poster
ABDULLAH	Nasser	Ontogeny Matters: How Primitive Mast Cells Drive Eczema After Birth	**PS19-P01**
HUSSEIN	Hind	Single cell transcriptomics reveal mast cell heterogeneity in the human gut in health and Irritable Bowel Syndrome	**PS19-P02**

POSTERS PS20 - Mucosal immunology

Last name	First name	Title of poster	# poster
DE OLIVEIRA NERY NETO	José Arimatéa	Humanized animals for IgA1 and FcαRI (CD89) exhibit increased susceptibility to intestinal inflammation and microalbuminuria following DSS-induced colitis	**PS20-P01**

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GOMES	Andréa	Function of novel inflammasome sensor in keratinocytes in the frame of contact dermatitis	**PS20-P02**
HEREDIA	Maud	LIGHT+ memory CD4+ T cells have an inflammatory phenotype and their infiltration in the intestine relates to histological disease severity in CD patients	**PS20-P03**
RITEAU	Nicolas	STING Regulates Pulmonary Remodeling and Immune Responses in Experimental Hypersensitivity Pneumonitis	**PS20-P04**

POSTERS PS21 - Tissue homeostasis and dynamics

Last name	First name	Title of poster	# poster
LUGO-VILLARINO	Geanncarlo	Identification of a Unique TUBB3^{+} Pericyte-like Cell Population Associated with Tuberculosis Granulomas	**PS21-P01**
MATIZ	Luisamaria	Injury-triggered HA degradation modulates immune responses to promote cardiac valve regeneration	**PS21-P02**

POSTERS S4 - Tumor immunity

Last name	First name	Title of poster	# poster
ALBANET	Sylvain	Role of the transcription factor ChREBP in modulating the immune function of tumor-associated macrophages during HCC development	**S4-P01**
ALMANSA	Julie	Paraneoplastic Ovarian Tumors Reveal Cellular and Spatial Features of Naturally Effective Antitumor Immunity	**S4-P02**
ANTOLOVIC	Clara	Treg stability in cancers	**S4-P03**
BAABDATY	Elissa	High-dimensional spatial profiling of the immune microenvironment in human uveal melanoma according to BAP1 status	**S4-P04**
BEJJANI	Christina	Intravenous BCG vaccination promotes early onset of mature tertiary lymphoid structures forming a local protective barrier against lung tumors	**S4-P05**
BRESSAN	Silvia	Unraveling mechanisms of immunotherapy resistance through biomarker profiling in triple-negative breast cancer	**S4-P06**
BRUGIERE	Line	Understanding the molecular antitumor mechanisms downstream of testosterone in the treatment of adrenocortical carcinoma	**S4-P07**
CAPRON	claude	Imaging of tumor recruitment of CD8-T cells induced by tumor irradiation: is there any abscopal effect?	**S4-P08**
CERDEIRA	Alexis	Loss of IL4I1 restrains pancreatic cancer growth and reshapes the tumor microenvironment	**S4-P09**
CHAVES	Beatriz	Role of THEMIS on CD8^{+} T cell mediated anti-tumoral response	**S4-P10**
COURAU	Tristan	Differential assembly of mouse and human tumor microenvironments	**S4-P11**
DEREDEC	Nicolas	Pro-inflammatory role of granzyme K producing bystander CD8+ T cells in acute myeloid leukemia	**S4-P12**
		Characterization of T cells phenotype and specificity in pediatric acute myeloid leukemia	**S4-P13**
FERNANDES	Jason	Perforin pore formation autonomously triggers pyroptotic cell death in target cells following attack by cytotoxic T lymphocytes	**S4-P14**
HAZARD	Calypso	Impact of tumor microenvironment on the response to radio- and immunotherapy of pediatric glioma cells	**S4-P15**
HUARD	Emma	Impact of the Glioblastoma microenvironment on the differentiation of immunosuppressive myeloid cells	**S4-P16**
LAFOURESSE	Fanny	Uncovering the molecular determinants of APC-CD8+TRM interactions in cancer	**S4-P17**
LAURENT	Adrien	MAP3K8 controls CD8 T cells fate	**S4-P18**
LTEIF	Maria	Bright side of the dark genome: lncRNA expression is dysregulated in colorectal precancer lesions	**S4-P19**
MARQUES	Rui	CCL18-expressing macrophages may drive an immunosuppressive and pro-invasion colorectal tumor microenvironment	**S4-P20**
MICHEA	Paula	Tumor heterogeneity shapes distinct immune landscapes and therapeutic responses in triple-negative breast cancer	**S4-P21**

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MOODY	Rhiane	Focused Antibody Responses Against Tumour-Associated Antigens Emerge from Dominant Extrafollicular B-Cell Differentiation in Ovarian Cancer	**S4-P22**
NATUREL	Marie	The costimulatory molecule ICOSLG promotes Treg-mediated immunosuppression in human models of triple-negative breast cancer	**S4-P23**
NGUYEN	Huong Giang	KLRG1 Identify Tumor-Associated T-Cell Populations in Colorectal Cancer	**S4-P24**
PACINI	Maria F.	Characterization of the Immune Landscape in the Novel Prss56 Rhabdoid Tumor Model	**S4-P25**
PAYEN	Alexandre	Exploring the interplay between PD-1 and BTLA in regulating T-cell antitumor responses	**S4-P26**
RICHARME	Thomas	BCL6 acts as a regulator of T cell exhaustion in cancer	**S4-P27**
SAKANWI	Joy	Prenatal maternal stress durably impairs CD8 T cell antitumour immunity through a microbiota-derived bile acid	**S4-P28**
SALVIONI	Anna	T-cell exhaustion and immune landscapes differ between peritoneal and ovarian lesions in ovarian cancer patients	**S4-P29**
SOUMOY	Laura	Translation reprogramming of melanoma persister cells drives MIF secretion and an immunosuppressive tumor microenvironment	**S4-P30**
TEIRLINCK	Mathilde	A Dual CSF-1/IL-34 Trap Suppresses CSF-1R Signaling and Targets the Myeloid Compartment	**S4-P31**
VALITUTTI	Salvatore	Stenocytosis a mechanism for supramolecular attack particle transfer at the CTL lytic synapse	**S4-P32**
VIGNES	Marina	Microneedle-Mediated Intratumoral Delivery of Immune Checkpoint Inhibitors in Melanoma: Antitumor Activity and Biodistribution in Murine Models	**S4-P33**

POSTERS PS23 - Immunotherapy

Last name	First name	Title of poster	# poster
ALEXIA	Catherine	Dimethyl fumarate sensitizes solid tumor cells to expanded NK-cell cytotoxicity and enhances antibody-guided targeting	**PS23-P01**
BELBEZIER	Aude	Metal Exposure and Immune Activation in Sarcoidosis: Combining LIBS Elemental Imaging and Functional Immunological Assays	**PS23-P02**
BERROZPE	Blanca	IL-2-variant-based immunocytokines improve Diffuse large B-cell lymphoma outcomes in mice by promoting long-term immune surveillance	**PS23-P03**
BLANCO-DOMINGUEZ	Rafael	Combined CAR- and innate receptor-mediated cytotoxicity of GCC-CAR γδ T cells limits antigen escape and curbs advanced colorectal cancer	**PS23-P04**
CAMPOS	Najla	Engineering CAR-T Cells to enhance tumor infiltration and antitumor function in renal Cell Carcinoma	**PS23-P05**
CAPRON	Claude	Role of CD47/SIRPαcheckpoint in resistance to immune checkpoint inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC)	**PS23-P06**
CHAPEROT	Laurence	The allogeneic plasmacytoid dendritic cell line PDC*line: an off-the-shelf therapeutic cancer vaccine platform	**PS23-P07**
COUTO-MOREIRA	Hugo	Retinoic Acid Signaling Biphasically Regulates PIB-mediated cDC1 Reprogramming	**PS23-P08**
DEREDEC	Nicolas	Integration of clinical and T-cell immune profiling to predict early response to CD3xBCMA bispecific antibody immunotherapy in Multiple Myeloma	**PS23-P09**
KAZEMIMANESH	Monireh	From Reinvigoration to Exhaustion: Tumor-Infiltrating Lymphocyte Responses to PD-1 Blockade in Melanoma	**PS23-P10**
LENOGUE	Kevin	From Target to Therapy – A Validated Workflow for Selecting the Right TCR	**PS23-P11**
MARCOUX	Paul	Patient-Derived Lymphoma Spheroids (PDLS) Reveal Predictive Markers of Glofitamab Resistance in Relapsed/Refractory B-cell non-Hodgkin lymphomas (R/R B-NHL)	**PS23-P12**
MAROTEL	Marie	SpyTag/Catcher based Universal Platform for Evaluating the Responsiveness of CAR-NK cells	**PS23-P13**
MENA OSUNA	Rafael	Circulating effector regulatory T cells define a systemic immunosuppressive state associated with resistance to immune checkpoint blockade	**PS23-P14**
PERSCH	Mathilde	Multimodal Analysis of Immunotherapy Responses in Patient-Derived Tumor Slices	**PS23-P15**
RODRIGUES	Catarina A.	Early Immunotherapy-driven peripheral immune modulation in melanoma: preliminary findings from multiparametric flow cytometry analysis	**PS23-P16**

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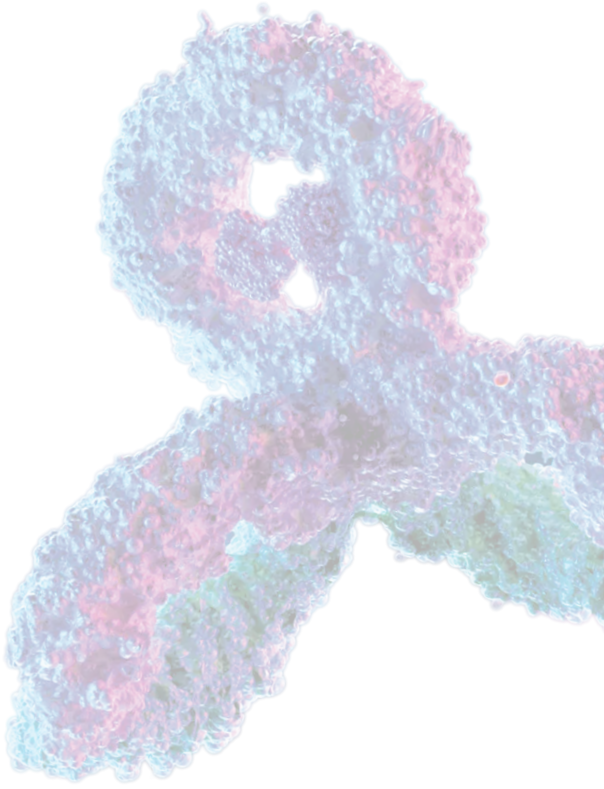
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ROUSSEL	Anaëlle	A single-domain antibody-based anti-CD20 bi-modular fusion protein redirects endogenous anti-EBV antibodies to trigger potent complement-dependent cytotoxicity	**PS28-P09**
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ABSTRACTS POSTERS

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S1-P01

Neuro-immune interactions in breast cancer: contribution of nociceptors to the antitumor response and therapeutic efficacy

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Frequently observed in human tumors and often associated with poor prognosis, nerve fibers are important components in the tumor microenvironment, modulating tumor development and anti-tumor immunity. Among these fibers, nociceptors expressing the Nav1.8 sodium channel mediate pain perception and, upon activation, release neuropeptides such as CGRP or substance P, which modulate immune cell functions. Numerous studies have demonstrated close interactions between nociceptors and the immune system, with important roles in pain, inflammation and host defenses. Their role has been investigated in several cancer types but remains largely unexplored in breast cancer, a major public health burden.

The aim of this project is to determine the influence of nociceptors on tumor growth and on the anti-tumor immune response in breast cancer, using two complementary murine models: the spontaneous MMTV-PyMT model, which recapitulates multistage tumor progression and displays features of both human luminal B and triple-negative breast cancer, and a transplanted model derived from tumor cells purified from MMTV-PyMT tumors.

Quantification of sensory innervation across these tumor models showed that sensory fibers were less abundant in the tumor core than in healthy mammary tissue, being mainly concentrated in peritumoral regions and in the adjacent intact gland. We next investigated whether tumor affects these neurons. In vitro, tumor cells sensitized sensory neurons without directly activating them. In vivo, bulk RNA-seq of tumor-innervating DRG revealed transcriptional changes dominated by an inflammatory signature. Despite these effects, genetic and chemical depletion of nociceptors affected neither tumor growth or the baseline anti-tumor immune response. In contrast, in mice treated with breast cancer chemotherapies (cyclophosphamide or taxol) nociceptor depletion improved tumor control, in association with increased intratumoral infiltration of cytotoxic lymphocytes, including $CD8^+$ T cells and NK cells. Thus, nociceptors do not control mammary tumor growth per se but limit the efficacy of chemotherapy and the associated cytotoxic immune response. Consistently, DRG transcriptomics revealed a neuronal excitability program induced by the combination of tumor and chemotherapy.

Ongoing work aims to identify the underlying neuro-immune mechanisms involved and to determine how the tumor and chemotherapy modulate sensory neuron activity, at the peripheral and central levels.

Keywords: Sensory neurons - Breast cancer - Chemotherapy efficacy.

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The role of neuroinflammation in toxic epidermal necrolysis

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Toxic epidermal necrolysis (TEN) is a severe cutaneous delayed drug allergy characterized by massive epidermal detachment, preceded by skin pain. It is driven by drug-specific cytotoxic CD8+ T cells that induce widespread keratinocyte death. Early skin pain suggests activation of cutaneous sensory neurons (nociceptors), whose role in TEN remains unknown. In other inflammatory conditions, nociceptors actively regulate immune responses, including CD8+ T cell activity. We therefore hypothesize that nociceptors interact with CD8+ T cells and contribute to TEN pathophysiology.

To address this question, we used K5-mOVA transgenic mice expressing ovalbumin (OVA) in keratinocytes to establish a model of epidermal necrolysis (EN), induced by transfer of OVA-specific OT-1 CD8+ T cells and anti-CD4 treatment to suppress regulatory responses. It recapitulates pathological and immune features of TEN. EN mice exhibit pain 48h before epidermal detachment, suggesting early nociceptor activation and enabling the study of neuroinflammation in TEN.

Neuroinflammation was investigated using complementary approaches: (1) confocal microscopy to assess spatial proximity between CD8+ T cells and nociceptors, (2) TRPV1+ nociceptor depletion to evaluate their role, (3) single-nucleus RNAseq of dorsal root ganglia to characterize neuronal responses, and (4) calcium imaging to test neuronal activation by CD8+ T cells. Translational relevance was explored using patient samples.

CD8+ T cells localize in close proximity to sensory neurons in skin, supporting neuro-immune interactions. TRPV1+ neuron depletion significantly exacerbates EN, suggesting a protective role for nociceptors. We showed that CD8+ T cell mediators directly activate neurons *ex vivo*, and found inflammation-associated transcriptomic changes in sensory neurons during EN progression. Interactome analysis from published scRNAseq data (TEN skin/blister fluid, healthy sensory neurons) reveals candidate ligand-receptor pairs between nociceptor and CD8+ T cells, some detected in patient samples.

Altogether, our preliminary data support a role for nociceptor-CD8+ T cell interactions in the EN pathophysiology in both mice and patients.

Keywords: Toxic epidermal necrolysis - Nociceptors - Neuroinflammation.

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Role of immune checkpoints PD-1 and BTLA in the regulation of T-cell responses during central nervous system (CNS) inflammation

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Immune checkpoint (IC) receptors PD-1 and BTLA are key negative regulators of T-cell activation, limiting immune responses and maintaining tissue homeostasis. Although they are structurally and functionally related, it remains unclear whether they play similar or distinct roles *in vivo*. Previous studies have shown that germline deletion of either PD-1[1] or BTLA[2] exacerbates experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS). As PD-L1 and HVEM are expressed by central nervous system (CNS) resident cells, both pathways may regulate local T-cell responses in the CNS. Given their close relationship, we therefore compared the physiological roles of PD-1 and BTLA during EAE to define their distinct functions in neuroinflammation. To address this question, we generated two conditional mouse models with T cell-specific deletion of PD-1 or BTLA after T-cell development prior to EAE induction. Immune cell infiltration and characterization were assessed using high-dimensional flow cytometry, single-cell RNA (scRNA-seq) and TCR sequencing (scTCR-seq). The deletion of BTLA in T cells does not affect disease development. BTLA is expressed at low levels on CNS-infiltrating T cells and is maintained in an inactive state by the protein THEMIS, which restricts its signaling activity. In contrast, PD-1 deletion strongly enhances disease severity. Unexpectedly, the loss of PD-1 in T cells has limited impact on the generation of encephalitogenic T cells or on inflammatory cytokines production. Instead, PD-1 deficiency promotes the accumulation of a distinct population of CD8+ T cells in the CNS, characterized by high expression of the transcription factors TOX[3], EOMES, and c-MAF, which have been associated with T-cell-driven neuroinflammation. Interestingly, this population is almost absent in PD-1-sufficient mice and, based on scRNA-seq analysis, displays an aging-associated inflammatory profile. Moreover, scTCR-seq analysis reveals that these cells are clonally expanded within the CNS, suggesting that recognition of local antigens may drive their accumulation. Our findings reveal distinct roles for BTLA and PD-1 in T cell-mediated neuroinflammation. BTLA is dispensable during EAE, likely due to its low expression in the CNS and to THEMIS-mediated inhibition. In contrast, PD-1 limits CNS neuroinflammation by restraining the accumulation of clonally expanded CD8 T cells with an aging-associated inflammatory program in the CNS.

Keywords: T-cells - Immune checkpoints - Neuroinflammation.

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Neuro-immune Control of Dendritic Cell-poiesis in Type-2 Immunity

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Objective
Conventional dendritic cells (cDCs) are essential for the robust induction of innate and adaptive inflammatory responses. This process is highly dependent on the rapid differentiation, activation and mobilization of the precise cDC subsets required for each infection. To achieve this, at the onset of inflammation, progenitor cells in the bone marrow (BM) are activated by various mediators to rapidly differentiate and traffic to the site of inflammation. During infection with parasitic worms, host factors and parasite-derived molecules were shown to play a role in the induction of hematopoiesis. Of note, neurotransmitters have been implicated, indirectly, in hematopoietic stem cell quiescence and egress. Here, we aim to investigate the role of neurotransmitters in the selective expansion of cDC subsets upon infection.
Methods
Using single cell RNA sequencing, we show that cDC precursor subsets (pre-cDCs) have differential expression of the β2 adrenoreceptor (ADRB2) in the BM, one of the key receptors for the sympathetic neurotransmitter noradrenaline (NA). Through the integration of *in vitro*assays, confocal imaging, spectral cytometry, and *in vivo* manipulation of NA signaling, we aimed to identify a role for NA in cDC differentiation during type-1 and type-2 inflammation.
Results
We found a rapid release of NA in the BM after infection with the helminth parasite *Nippostrongylus brasiliensis*. This early release coincides with expansion of cDC2A and their progenitors (pre-cDC2A). Notably, this does not occur during infection with the type-1 pathogen influenza, indicating a helminth-specific response. Mice which lack ADBR2 on the cDC lineage, cannot mount a successful anti-helminthic response, with increased parasite burden, tissue damage, and weight loss compared to controls. Furthermore, we have found that the *in vitro* co-culture with sympathetic neurons, or stimulation with NA, preferentially expands the cDC2A lineage. This effect was found to be mediated by ADBR2 signaling-induced proliferation.
Conclusions
We have found that sympathetic innervation of the BM provides early, direct NA signaling to pre-cDCs during helminth infection. Our data suggest that this early signaling allows for the robust induction of the appropriate innate and adaptive immune responses to combat infection. This constitutes a novel and specific mechanism for the induction of type-2 immune responses, focused on the direct sensing of NA by cDC progenitors in the BM.

Keywords: Dendritic Cells - Noradrenaline - Parasitology.

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Brain barrier-specific tissue-resident memory CD8+ T cells alleviate EAE severity

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Objective
Tissue-resident memory T cells (TRM) mostly emerge in a tissue following local encounter with their cognate antigen. Endothelial cells from the blood brain barrier (BBB-EC), at the interface between the central nervous system (CNS) and the periphery, can interact in many ways with circulating CD8+ T cells. Our studies aim at understanding whether antigen-specific interactions between BBB-EC and CD8+ T cells can shape a residency profile of CD8+ T cells, promoting their persistence in the CNS, and how it can further impact CNS inflammation. Indeed, the active contribution of TRM to inflammatory processes is debated since they have been shown to have pro-inflammatory as well as anti-inflammatory potential.
Methods
We use an original mouse model in which BBB-EC can conditionally and inducibly express the influenza virus hemagglutinin (HA) as a neo-antigen. Additionally, we employed a TCR-transgenic mouse line in which ~95% of CD8+ T cells specifically recognize the HA512-520:Kd complex. HA-specific CD8+T cells were thus transferred to mice expressing HA at the BBB surface. The contribution of TRM to CNS inflammation was then tested using the MOG peptide-induced Experimental Autoimmune Encephalomyelitis (EAE) model.
Results
The antigen-specific interaction between CD8+ T cells and BBB-EC allows the CD8+ T cells to persist in the CNS of the mice up to day 30, regardless of their prior activation state, in an otherwise non-inflammatory CNS environment. The accumulating CD8+T cells express classical TRM markers (CD69, CD103) at their surface, and harbor a TRM transcription profile. Remaining relatively silent in term of clinical signs at day 30 following T cell transfer, the presence of HA-specific CD8+ TRM in the CNS of mice surprisingly decreases the clinical signs of further neuroinflammation induced by EAE. The enrichment of a CD8+ regulatory signature in the TRMpopulation motivates us to test for a direct role of the HA-specific CD8+T cells in the protection from subsequent EAE.
Conclusion
Our study demonstrates that antigen-specific interactions between CD8+ T cells and BBB-EC can generate long-lived CNS-resident memory T cells. Remarkably, these resident CD8+ T cells provide robust protection against neuroinflammatory disease in the EAE model, highlighting the ambivalent functional properties of TRM cells.

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Tissue-specific neuroimmune regulation of antiviral immunity during HSV-1 infection

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Neuroimmune interactions are increasingly recognized as essential regulators of tissue homeostasis, inflammation and host defense. Sensory neurons can directly communicate with immune cells in peripheral tissues, while immune signals can in turn modulate neuronal activity and pain. Although such interactions have been extensively studied in bacterial infection, allergy and tissue injury, their contribution to antiviral responses remains less understood. Here, we focus on herpes simplex virus type 1 (HSV-1) infection, a dermo-neurotropic virus capable of infecting both epithelial cells and sensory neurons. We investigate neuroimmune interactions across the skin, the sensory ganglia (DRG) and spinal cord and especially their contribution to inflammation and pain.

Using a mouse model of cutaneous HSV-1 infection, we characterized neuronal activity, viral replication and immune cell recruitment in the skin, DRG and spinal cord by plaque forming assays, immunofluorescence and flow cytometry analysis. Mechanical hypersensitivity was monitored using Von Frey assays.

We identified two mediators produced by different populations of sensory neurons that regulate the immune response against HSV-1 in a tissue-specific manner. Substance P (SP), produced by TRPV1+ sensory neurons in the skin, limits neutrophils infiltration through its interaction with MRGPRA1 receptor to reduce tissue damage and promote CD8 T cell response. In infected DRG, TAFA4, a neurokine produced by C-LTMRs sensory neurons, limits the recruitment of immune cells without affecting viral clearance. More specifically, our data suggest that TAFA4 acts on DRG macrophages to promote the resolution of inflammation after viral clearance in this tissue. Extending these findings, we detected immune recruitment in the spinal cord that persisted at time points when infectious particles are no longer detectable in the DRG and spinal cord, suggesting that neuroimmune interactions can also play a regulatory role in the central nervous system. Finally, we observed that a TAFA4 deficiency was associated with increased mechanical hypersensitivity after viral clearance, suggesting a potential link between immune recruitment in these neuronal tissues and HSV-1-induced pain perception.

Future work aims to characterize the nature and origin of the spinal cord immune response and determine whether and how immune cell recruitment contributes to pain following HSV-1 infection.

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S1-P07

Macrophages promote human sensory neuron progenitor proliferation in a developing dorsal root ganglia model

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Beyond their crucial contribution in innate immunity, mononuclear phagocytes play a key role in regulating embryogenesis. Indeed, macrophages colonize embryonic tissues at early stages and are involved in brain development. They are also closely associated with the peripheral nervous system, which consists of sensory nerve fibers that extend from dorsal root ganglia (DRG). Several macrophage subsets have been found in both human embryonic and adult DRG, but their functions remain unknown. As suggested by mouse models, we hypothesized that DRG macrophages may promote neuronal progenitor proliferation.
To investigate this, we set up an *in vitro* culture model where induced pluripotent stem cells (iPSCs) were differentiated into sensory neurons. Single-cell RNA sequencing demonstrated the presence of neural crest cells, neuronal progenitors and differentiated neurons, which altogether resembled the populations present in developing DRG. We observed that the proliferation of neuronal progenitors increased upon coculture with monocyte-derived macrophages, and this was concomitant with augmented cell numbers by the end of the coculture.
To determine the pathway involved in this interaction, we performed an *in-silico* analysis that included transcriptomic datasets from the literature on *ex vivo* DRG and from our iPSC-derived sensory neuron differentiation. This highlighted the potential role of the IGF1/IGF1R pathway. To investigate this pathway, we first set a physical separation between differentiating neurons and macrophages, which confirmed that a soluble ligand was requested to promote neuronal progenitor proliferation *in vitro*. Moreover, interfering with the IGF1/IGF1R pathway with specific inhibitors abrogated the increase in cell numbers associated with macrophages. Preliminary data have been showed that the modulation of this pathway have an impact on neuronal proliferation *in vitro*.

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S1-P08

Therapeutic targeting of JAK2 signaling and microglia to limit pathogenic tissue-resident CD8⁺ cells in the brain

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Objective
Pathogenic tissue-resident memory CD8⁺ T (CD8⁺ TRM) cells can persist in the central nervous system (CNS) and contribute to chronic neuroinflammation and neuronal damage or death. However, the molecular and cellular cues supporting CD8⁺ TRM persistence remain poorly understood. Using the Orex-HA mouse model of antigen-specific CD8⁺ T cell mediated orexin neuron loss, we investigated the roles of JAK2-associated signaling, microglia and of CNS monocyte-derived cells in CD8⁺ TRM maintenance and neuronal damage.
Methods
In vitro-activated hemagglutinin (HA)-specific CD8⁺ T cells were adoptively transferred into Orex-HA mice, expressing HA selectively in orexin-producing neurons. JAK2 signaling was inhibited using AZD1480 following depletion of circulating CD8⁺ T cells, allowing preferential targeting of established CNS-resident T cells. In distinct sets of experiments, microglial cells were depleted using the CSF1R inhibitor PLX5622, while inflammatory monocytes were depleted using an anti-CCR2 antibody. CD8⁺ TRM cells and myeloid populations were analyzed by flow cytometry, and orexin neuron survival was assessed by immunohistochemistry.
Results
JAK2 inhibition reduced the persistence of HA-specific CD8⁺ TRM in the hypothalamus, decreased the frequency of activated MHC II⁺ microglia and attenuated orexin neuron loss. Similarly, efficient microglial depletion with PLX5622 reduced the persistence of hypothalamic CD8⁺ TRM cells. Preliminary data showed a trend toward preservation of orexin neurons following microglial depletion. In contrast, CCR2-dependent depletion of CNS monocyte-derived cells did not significantly affect HA-specific CD8⁺ T-cell infiltration into the hypothalamus nor did it prevent orexin neuron loss.
Conclusion
Our findings identify JAK2-associated signaling and microglia as potential regulators of pathogenic CD8⁺ TRM persistence in the CNS and highlight their role in the destruction of neurons in our reductionist model of CNS autoimmunity. These findings, therefore, point to JAK2-associated signaling and microglia as potential therapeutic targets for limiting CNS-resident pathogenic T-cell responses, notably in the context of subacute or chronic T-cell mediated autoimmune encephalitis.

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S1-P09

A new transcription factor regulates microglial activation and restrains neuroinflammation

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Microglia are Central Nervous System (CNS)-resident macrophage-like cells that modulate neurodevelopment and maintain neural homeostasis by sensing changes in the CNS. Therefore, their inflammatory responses must be tightly controlled. Uncontrolled activation of these cells can disrupt myelin, compromise neural function, and contribute to neurodegenerative diseases. This underscores the importance of identifying mechanisms that modulate microglial inflammation.

We demonstrated that the expression of a new transcription factor is upregulated in activated microglia, supporting the hypothesis that this factor limits microglial inflammatory responses. To investigate its role in CNS inflammation, we generated mice with microglia-specific deletion of this factor, as well as a human microglia cell line depleted of this factor. Using these models, we demonstrated that its loss shifts microglia toward a pro-inflammatory phenotype, characterized by enhanced inflammatory and type I interferon signatures, and that this factor's deficiency exacerbates disease severity in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS).

To gain mechanistic insight, we performed antibody-targeted chromatin profiling (CUT&RUN) in human and mouse microglia. This analysis revealed binding of this factor to genes involved in the nonsense-mediated mRNA decay (NMD) pathway, which is an RNA surveillance mechanism that limits the abundance of specific transcripts by promoting their degradation. Our results indicate that it controls the inflammatory response by promoting the degradation of inflammatory transcripts through NMD. By identifying this factor as a regulator of NMD-dependent inflammatory gene expression, this work reveals a previously unrecognized mechanism that controls microglial inflammation and contributes to our broader understanding of immune gene regulation.

Keywords: Microglial activation - Neuroinflammation - CNS homeostasis.

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Stress derived glucocorticoids regulate γδ17 T cell transcriptomic signature in tissues

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Objectives

Stress is a powerful modulator of physiology, it activates the hypothalamic-pituitary-adrenal axis, releasing glucocorticoids that not only act on the brain but also modulate immune responses. Here, we investigated the impact of physiological stress on IL-17 producing γδ (γδ17) T cells, a subset of lymphocytes that contribute to immune surveillance, as well as tissue homeostasis and functions.

Methods

Mice were subjected to prolonged restraint stress (PRS) and γδ T cell phenotype was analysed in lymphoid (lymph nodes) and non-lymphoid tissues (meninges, testis and adipose tissue). Single-cell RNA sequencing (scRNA seq) of γδ T cells was performed to characterize stress-induced transcriptional changes. The role of glucocorticoid receptor (Nr3c1, encoding GR) signalling was assessed using GR agonist (dexamethasone) and antagonist (RU486). We also deleted Nr3c1 in γδ17 T cells by breeding Il17a-Cre mice to Nr3c1fl/fl mice, thus generating GRΔIL-17mice.

Results

We observed that mice subjected to PRS exhibit a reduction of IL-17 expression by γδ T cells selectively in the meninges, adipose tissue and testes, but not in the lymph nodes. scRNA seq analysis further revealed organ-adapted subsets and distinct transcriptional profiles between stressed and control animals. PRS induced a decrease in type 17 program and TCR signaling scores, as well as an increase in exhaustion related genes, with key hallmarks being validated at the protein level. Mechanistically, the administration of dexamethasone reproduced the stress-induced decline of IL-17 expression by γδ T cells in a tissue-dependent manner, and this phenotype was rescued with RU486. Using GRΔIL-17mice, we validated GR as a key molecular determinant of γδ17 T cell stress-sensing mechanism in some particular tissues. We are currently using this mouse model to address the physiological consequences of stress-induced IL-17 reduction by analyzing behavioral outcomes and thermogenic response.

Conclusions

Stress reveals tissue-adapted γδ T cell responses, selectively affecting γδ17 T through GR signalling in a tissue-specific manner. Understanding how psychological stress impairs immune responses is critical to uncover novel neuroimmune crosstalks, which may inform the development of therapeutic strategies for stress-related disorders.

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CITE-seq reveals inhibition of NF-κB pathway in B cells from vitamin D-treated multiple sclerosis patients

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Background
Vitamin D deficiency is strongly associated with multiple sclerosis (MS), yet the molecular mechanisms underlying its immunomodulatory effects remain incompletely understood. Here, we combined single-cell transcriptomics and surface proteomics to characterize the impact of vitamin D supplementation on peripheral immune cells in MS patients and validated candidate modulated pathways.
Methods
We conducted a multi-omic study combining single-cell transcriptomics and surface proteomics (CITE-seq) to characterize the impact of high dose vitamin D supplementation versus placebo on peripheral immune cells from MS patients aged 18-55 years-old. B cells were purified from peripheral blood by negative selection. Lysates were prepared from B cells and peripheral blood mononuclear cells, and Western blotting was performed using antibodies against phosphorylated p65 (Ser536), total p65, phosphorylated IKKβ, NFKB1, and GAPDH, followed by densitometric quantification. Fas ligand (FasL/CD95L)–induced apoptosis in memory B cell subsets was measured by flow cytometry using annexin V and propidium iodide (PI) staining.
Results
Vitamin D reduced cytotoxic $CD8^+$ T cell subsets, particularly TC1 ($GZMB^+$) and TEMRA populations, and expanded activated regulatory $CD4^+$ T cells, indicating a shift toward an anti-inflammatory immune profile. B cell composition remained largely unchanged. Across immune populations, NF-κB–associated genes (NFKB1, FOS, FOSB, JUN) were consistently downregulated, with the strongest effects in naïve T and B cell subsets. In T cells, the interferon (IFN) pathway was activated following vitamin D supplementation. In B cells, vitamin D altered differentiation pathways, including IL-2–STAT5 signaling, and decreased expression of activation markers CD83 and CD69. These findings were validated at the protein level by reduced activation of core NF-κB components, including phosphorylated p65, IKKβ, and NFKB1. Vitamin D–mediated NF-κB modulation selectively sensitized switched memory B cells to extrinsic apoptosis induced by Fas ligand.
Conclusion
Vitamin D suppresses NF-κB signaling and promotes a coordinated shift away from cytotoxic and inflammatory immune states in MS, together with an enhanced IFN response in T cells. Given the role of NF-κB in supporting B cell survival under Epstein–Barr virus (EBV) influence, these findings suggest that vitamin D may partially counteract EBV-associated survival mechanisms.

Keywords: Multiple sclerosis - Vitamin D - CITE-seq.

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Impact of IL-17 on gut immune homeostasis upon peripheral nerve injury

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Objectives

Traumatic peripheral nervous system (PNS) injury affects 3% of the population[1], often causing consequences beyond local neuropathies, involving multisystem comorbidities like gastrointestinal dysfunctions[2,3]. This study aims to elucidate the immune mechanisms by which nerve inflammation provokes these changes.

Methods

We used a mouse model of nerve injury (sciatic nerve crush, SNC), in which we previously demonstrated that γδ T cells accumulate at the lesion and promote nerve regeneration through IL-17 in a microbiota-dependent manner. Here, we analysed intestinal immune homeostasis upon SNC by flow cytometry in C57Bl/6 wild-type (WT), as well as in IL-17-deficient (*Il17a-/-*) mice and their littermate controls (*Il17a+/+*). We also optimized gut-nerve transwell migration *in vitro* assays and depleted the gut microbiota by delivering broad spectrum antibiotics *in vivo*.

Results

Five days post-injury, we observed a decrease of intestinal γδ T cell numbers in the ileum of nerve crushed mice, mirroring their accumulation in the injured nerve. Hypothesizing that these cells migrate from the gut to the nerve, we performed migration assays which showed that intestinal lymphocytes are indeed attracted by nerve-derived factors. We then identified IL-17 as a key regulator of the gut immune homeostasis after SNC by showing that IL-17- deficient mice displayed an exacerbated accumulation of intestinal hematopoietic cells when compared to their littermate controls. Interestingly, the microbiota affects selective region and subset, with CD4+ αβ T cell frequencies increasing in the small intestine following SNC, and their reduced activation state in the colon being partially restored upon antibiotic treatment.

Conclusions

Together, these results suggest that nerve injury shapes the gut immune landscape in an IL-17- and microbiota-dependent manner. Understanding this neuroimmune link is crucial to uncover novel strategies for the treatment of neuropathy-associated intestinal comorbidities.

Keywords: Inter-organ communication - IL-17 - Gut homeostasis.

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Chronic systemic inflammation imposes critical thresholds in energy metabolism

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Objective

The brain senses inflammatory signals upon infection and responds by inducing sickness behaviour, which is characterized by fever, lethargy, social withdrawal and reduced appetite. This coordinated response of the immune system and the brain is necessary to allocate energy expenditure to the immune response[1]. Mostly described upon acute immune challenge, we determined how behaviour and metabolism are affected during chronic inflammation.

Method

We developed a model of chronic inflammation utilizing programmable, refillable micro-infusion pumps, delivering the inflammatory cytokine IL-1ß. Physiological and behavioural parameters were measured in real time by activity monitoring cages and temperature probes. Neuronal activity was determined and manipulated by *in vivo* fibre photometry.

Results

Prolonged systemic inflammation increases the energy expenditure to critical threshold levels. To preserve a viable metabolic balance, the inflamed mice reduced their physical activity while their food and water intake remained largely unaffected. Upon chronic inflammation the body temperature circadian rhythm (36 to 38 °C) was lost and remained constant at approximately 36 °C, while occasionally falling to ambient temperature levels (~23 ºC) in a hypometabolic state (torpor).

The sustained inflammation resulted in a hepatic shutdown characterised by depleted glycogen and glucose storages, that rendered animals susceptible to stress induced hypothermia. This inflammation-dependent hypometabolic state was orchestrated by the preoptic area (POA) of the hypothalamus, a central hub for thermoregulation and fasting-induced hypometabolism[2,3], as photometric activation of POA neurons projecting to the dorsomedial hypothalamus (DMH) was sufficient to induce torpor, but only in inflamed animals.

Conclusion

Our data show that chronic inflammation imposes critical energetic thresholds by depleting hepatic energy reserves, that force the POA to induce new states of equilibrium (allostasis) in order to maintain vital body functions and thereby renders the organism susceptible to psychogenic stress-induced metabolic shutdown.

Keywords: Chronic inflammation - Torpor - Preoptic Area.

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A CD8⁺ T cell-mediated model of retinal neuroinflammation and ganglion cell degeneration

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Ocular immune privilege physiologically limits inflammatory responses that may compromise visual function. However, its disruption during uveitis and inflammatory disorders affecting the visual system can lead to irreversible neurodegeneration. While CD4⁺ T cells are central to classical experimental autoimmune uveitis models, CD8⁺ T cells are frequently detected in human ocular inflammatory infiltrates, including in certain forms of uveitis and optic neuritis. Their direct contribution to retinal inflammation and neuronal damage remains incompletely understood.

Here, we developed a controlled mouse model of antigen-specific cytotoxic CD8⁺ T cell-mediated inflammation of the visual system. Mice received a unilateral intravitreal injection of an AAV2 vector encoding hemagglutinin (HA) and GFP. Thirty days after injection, vector expression was preferentially detected in retinal ganglion cells (RGCs), without evidence of spontaneous ocular inflammation. In vitro-generated HA-specific effector CD8⁺ T cells (Tc1) were then adoptively transferred into recipient mice.

Flow cytometry and immunofluorescence analyses revealed a marked and antigen-dependent accumulation of CD8⁺ T cells, predominantly transferred Tc1 cells, in HA-expressing retinae and associated optic nerves. This response remained largely restricted to visual system compartments, with no comparable increase in the spinal cord or cervical lymph nodes. Between days 10 and 30 after transfer, Tc1 cells persisted locally and showed progressive enrichment of a CD69⁺CD103⁺ population, consistent with acquisition of a tissue-resident memory-like phenotype. Tc1 infiltration was associated with rapid and sustained loss of HA-expressing Brn3a⁺ RGCs, detectable by day 10 and maintained at day 30. Importantly, retinal neurodegeneration was not observed in contralateral eyes or in eyes injected with a control vector expressing GFP alone.

This original model complements conventional CD4⁺ T cell-driven models of experimental autoimmune uveitis. It provides a tractable system to dissect the mechanisms governing CD8⁺ T cell infiltration, cytotoxicity, and tissue residency in the retina, and to evaluate strategies aimed at limiting inflammation and neurodegeneration within the visual system.

Keywords: Retina inflammation - Autoreactive CD8+ T cells - Tissue resident memory cells.

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Intrathecal Mesenchymal Stromal Cell administration improves EAE severity by inducing B cell reprogramming

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Objective
Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). In the progressive form of MS (PMS), pathogenic mechanisms involve both compartmentalized inflammation and neurodegeneration. Owing to their immunomodulatory and trophic properties, mesenchymal stromal cells (MSC) have emerged as a promising therapeutic strategy in this disease. In parallel of an ongoing phase I clinical trial (NCT06592703),we evaluated the therapeutic efficacy and mechanisms of action of clinical-grade intrathecal human ASC infusion in experimental autoimmune encephalomyelitis (EAE).
Methods
EAE was induced in female C57BL/6 mice by MOG35−55 immunization. Clinical-grade human ASCs (2.10^5 cells) or PBS were administered intrathecally at Day 10 (clinical onset). Weight and clinical scores were monitored longitudinally. ASC persistence was assessed by bioluminescence imaging. Spleen and CNS immune cell populations were analyzed at Day 18 and Day 40 by flow cytometry. CSF and serum cytokines were analyzed by multiplex immunoassay.
Results
ASCs remained detectable within the CSF/CNS for at least 9 days after administration. ASC treatment significantly improved EAE severity, mainly by improving clinical remission ($p<0.001$, n=15 mice PBS vs n=33 mice ASC, 3 independent experiments). Immunophenotyping revealed CNS-specific immune remodeling, characterized by a significant increase in the total number of $CD4^+$ T cells without major changes of the relative frequencies of CD4 T cell subsets. Conversely, we observed a significant increased frequency of T-Bet+ CD11b+ age-associated B cells, recently shown to be regulatory in EAE-context (Gauthier, Immunity 2026). No significant changes were observed in the spleen of ASC-treated compared with control mice. At the chronic stage of disease, ASC-treated mice displayed significantly higher levels of IL-10, IL-4, and IL-5 in the CSF compared with control mice, supporting the establishment of a regulatory CNS immune environment.
Conclusion
Intrathecal ASC administration provides significant therapeutic benefit in EAE and induces local immune reprogramming within the CNS associated with clinical improvement. These findings support intrathecal ASC therapy as a promising strategy for PMS and provide mechanistic insights for its clinical translation.

Keywords: ASC treatment - EAE - B cell reprogramming.

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Immune checkpoint control of autoimmune inflammation in the eye

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In non-infectious autoimmune uveitis (NIU), the breakdown of retinal immune privilege leads to autoreactive T cells targeting retinal antigens and infiltration of proinflammatory mononuclear phagocytes (MP). Paired immunoglobulin-like receptors (PIRs) are murine immunoglobulin-like cell surface receptors expressed on immune cells, regulating immune responses through interactions with ligands, particularly MHC class I molecules. Among these, PIR-A acts as an activator, while PIR-B functions as an inhibitory counterpart. Although PIR-B has been implicated in regulating humoral immunity, its impact on retinal homeostasis and T cell–mediated autoimmunity remains poorly defined. Here, we aimed to define its contribution to local immune regulation during retinal inflammation.
To investigate this, we examined the consequences of PIR-B deficiency on the development of experimental autoimmune uveitis (EAU), a mouse model of NIU. scRNA-sequencing of retinal immune cells revealed that PIR-A and PIR-B are expressed in infiltrating MPs, but not in T or NK cells. In addition, resident microglia only expressed high levels of PIR-B. Using PIR-B-deficient mice, we observed an exacerbation of EAU severity compared to WT controls, as assessed by fundus photography and analysis of cellular infiltration in the retina via flow cytometry. Importantly, a clear overactivation of microglia was detected in PIR-B-deficient mice during EAU. RNA-sequencing results further demonstrated that this hyperactivated state was already present in naive PIR-B-deficient mice. Moreover, local injection of a PIR-B ligand, MHC-I, during EAU showed a decrease in inflammation one day post-injection, suggesting an early modulatory effect.
Overall, our study identifies PIR-B as a key regulatory checkpoint maintaining microglial quiescence and limiting excessive inflammatory responses within the retina. By restraining microglial activation through potential interactions with neuronal MHC-I molecules, PIR-B emerges as a promising therapeutic target to control pathological immune responses in NIU.

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Zika virus targets human Schwann cells

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Objectives

The 2016 Zika virus (ZIKV) outbreak was associated with neurological disorders, including Guillain-Barré syndrome (GBS). Despite the existing knowledge regarding the autoimmune response underlying GBS, further studies are needed to understand how Schwann cell biology is affected when GBS is preceded by a transient infection. To better explore the underlying mechanisms of ZIKV-related GBS development we used an *in vitro* model to investigate the effects of ZIKV infection in human schwannoma cells.

Methods

The human schwannoma cell line ST88-14, which retains key features of primary Schwann cells were infected with the RIO-U1 strain of Zika virus in a MOI of 1 during 72h, and the consequences of this infection were accessed by immunofluorescence, cytometry, transcriptomic and proteomic analysis.

Results

Flow cytometry and immunofluorescence analyses confirmed approximately 40% of infected cells, and that infection was accompanied by cytoskeletal alterations. Transcriptomic analysis identified 170 upregulated and 3 downregulated genes (adjusted $p < 0.05$; $|log2FC| > 0.5$). Enrichment evaluation revealed modulation of “interferon-mediated signaling pathways,” “antigen processing and presentation,” and “T-cell–mediated immunity,” suggesting strong activation of antiviral responses and potential modulation of T-cell activation. By a proteomic approach we identified 459 upregulated and 249 downregulated proteins (adjusted $p < 0.05$). Pathway enrichment indicated modulation of processes related to “generation of precursor metabolites and energy,” “G1/S transition,” “lamellipodium,” and “actin filament,” reflecting impacts on energy metabolism, cell proliferation, and cytoskeletal integrity and motility. The modulation of “neurodegeneration pathways” points to the involvement of molecular events common to several highly debilitating neurological diseases. Additionally, infected shwannoma cells exhibited higher adhesion to activated T lymphocytes (Jurkat cell line) compared with uninfected controls.

Conclusion

Collectively, our findings provide evidence that Schwann cells may act as a reservoir for ZIKV and active participants in the peripheral nervous system immune response, undergoing alterations that potentially contribute to ZIKV-associated GBS pathogenesis.

Keywords: Zika - Guillain-Barré - Transcriptome.

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S1-P18

Electrical stimulation of the arterial splenic nerve has durable therapeutic efficacy on murine collagen-induced arthritis by promoting regulatory B cells

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Objectives
Vagus nerve (VN) electrostimulation has demonstrated anti-arthritic effects in both animal models and patients with rheumatoid arthritis (RA). However, VN stimulation influences multiple physiological functions. Since the splenic nerve (SpN) plays a key role in VN-mediated immunomodulation, we investigated the therapeutic potential of direct arterial splenic nerve stimulation (SpNS) in a collagen-induced arthritis (CIA) mouse model, both as a standalone treatment and in combination with bariticinib.
Methods
SpNS was evaluated in male DBA mice with CIA, either before or after disease onset, and administered one or six times daily. Alternatively, mice were treated daily with propranolol or baricitinib.
Results
Preclinical SpNS treatment in CIA mice prevented disease onset in a β1/β2-adrenergic receptor-dependent manner. Following SpNS treatment, reductions were observed in splenic inflammatory monocytes, autoantibody-secreting cells, and serum levels of TNF and anti-collagen antibodies. Adoptive transfer of B cells from SpNS-treated, CIA-protected mice significantly reduced CIA severity in recipients, indicating that chronic SpNS induces regulatory B cells. Additionally, the number of IL-10+ B cells was significantly increased in the spleen of electrostimulated CIA mice. In established disease, SpNS treatment resulted in significantly reduced clinical scores compared to sham controls. Importantly, combining SpNS with baricitinib enhanced the therapeutic efficacy of this drugs.
Conclusion
These findings suggest that SpNS exerts potent anti-arthritic effects and promotes the induction of regulatory B cells, positioning it as a promising therapeutic approach for arthritis.

Keywords: Electrostimulation - Arthritis - Regulatory B cells.

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Functional subsets of regulatory T cells predict the rate of cognitive decline in Alzheimer's disease

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Objective
Besides neuroinflammation, accumulating evidence now supports that peripheral adaptive immunity and peripheral-central immune crosstalk also play an instrumental role in the pathophysiology of Alzheimer's disease (AD), although the impact of different T cell subsets, including regulatory T cells (Tregs), remains poorly defined. Whereas previous studies suggested altered frequencies and/or functionality of Tregs according to disease stages, different studies reported contradictory results and the potential impact of Tregs on the rate of disease progression remains unclear. Here, we assessed variations of functional subsets of Tregs according to not only different stages of AD, but also to the rate of cognitive decline.
Methods
Based on stringent clinical inclusion criteria to avoid any potential misdiagnosis, we included 59 patients with strict clinico-biological diagnosis of AD and 33 age-matched healthy controls from the IMABio3 longitudinal study. Using multiparametric flow cytometry, transcriptomic studies and regression modeling, we investigated the potential impact of functional subsets of Tregs on the rate of disease progression in AD.
Results
We observe decreased frequencies of PD1+ and/or CD39+naive Tregs in fast-decliner AD patients at the prodromal stage. Transcriptomic studies on sorted Treg subsets support that PD1 expression in naive Tregs is associated with a distinct phenotype, suggestive of potential higher immunosuppressive activity. Predictive modeling shows that selected Tregs immunophenotypes could predict the rate of cognitive decline in prodromal AD patients. Further combining these parameters with [18F]DPA-714 PET imaging of brain neuroinflammation allows distinguishing slow- and fast-decliners among all AD patients, independently of their initial disease stages.
Conclusion
These results suggest that altered homeostasis of selected PD1+and/or CD39+ functional subsets of Tregs may be associated with faster cognitive decline in patients with AD. If confirmed in an independent validation cohort, such peripheral Tregs immunophenotypes may constitute promising candidate prognostic biomarkers for refining patient stratification according to their predicted rate of disease progression. Further studies remain needed to better characterize the functionality of such functional Tregs subsets and their mechanistic implication in disease pathophysiology, which could open new immunomodulatory therapeutic avenues in AD.

Keywords: Tregs - Alzheimer's disease - Biomarker.

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PS1-P01

Immunometabolic Reprogramming and Mitochondrial Remodeling in LPS-Induced Tolerized Macrophages

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Inflammatory disorders such as sepsis are characterized by an initial hyperinflammatory phase followed by prolonged immunosuppression. Sustained exposure to inflammatory stimuli, including lipopolysaccharide (LPS), induces a Tolerized Macrophage (TM) phenotype distinct from classical M1 and M2 phenotypes that contributes to limiting excessive inflammation. Although M1/M2 immunometabolic programming has been investigated, the metabolic features of TM remain poorly understood. Characterizing these adaptations may provide new insights into inflammatory diseases. Our objective was to investigate whether LPS-induced TM is associated with metabolic modulation and its impact on signalling pathways. Monocytes were isolated from healthy human PBMCs using CD14+ beads and differentiated with M-CSF. TMs were generated by LPS stimulation (50 ng/mL) on day 0, washing on day 1, and LPS restimulation on day 2. Unstimulated macrophages (M0) and macrophages stimulated once with LPS (M1) served as controls. Macrophages were co-cultured with CFSE-labelled PBMCs for four days. RT-qPCR and Western blotting were performed 6 h after the final LPS stimulation, and FACS analyses 24 h later. Inflammatory markers, metabolic enzymes, mTORC1 signalling, mitochondrial dynamics, and mitochondrial function were evaluated. Tolerance was confirmed by reduced TNFα, IL-12, and IL-6 expression and diminished lymphocyte proliferation. TMs exhibited immunometabolic reprogramming, with 2.2-fold higher HK2 expression than M1, 1.7-fold higher LDHA expression than M0, and elevated lactate production, indicating enhanced glycolysis. Mitochondrial fission genes FIS1 and DNM1L were increased 1.4-fold compared with M1. Despite these changes, mitochondrial mass and function were preserved. Total ROS production was transiently increased, suggesting preserved oxidative stress responsiveness and bactericidal potential. Reduced S6K phosphorylation (2.9-fold lower than M1) indicated decreased protein synthesis. Human LPS-induced TM involves adaptive mitochondrial remodelling alongside glycolytic reprogramming and reduced mTORC1 activity, without evidence of mitochondrial dysfunction. These findings provide new insights into the mitochondria–immunometabolism interface in macrophage tolerance.

Keywords: Macrophages - Tolerance - Mitochondria.

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PS1-P02

Integrating monocyte-derived dendritic cells in the dermal compartment of a full-thickness skin model to confer a functional cytokine response

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Full-thickness skin models are widely used to study skin biology but often lack a resident immune compartment, which can limit their relevance to studies of skin sensitization, inflammation, and immune modulation.
We developed a full-thickness skin immunocompetent (FTSKi) model incorporating monocyte-derived dendritic cells (MoDCs) into the dermal compartment and assessed whether the integrated cells retain a functional, pharmacologically modulable response to a pro-inflammatory challenge.
MoDCs were seeded into the dermal compartment during FTSKi reconstruction. Integration and distribution were confirmed by immunofluorescence staining for HLA-DR and CD209 (DC-SIGN). MoDC-containing and MoDC-free tissues were challenged with 1µg/mL lipopolysaccharide (LPS), with or without dexamethasone co-treatment (1 µM). Cytokine release (IL-6, IL-8, TNF-α, IL-10, IL-12/IL-23p40) was quantified in culture supernatants by cytometric bead array.
Following LPS challenge, MoDC-containing tissues released approximately 10-fold higher levels of IL-6 and IL-8 than MoDC-free tissues under identical conditions. TNF-α, IL-12/IL-23p40, and IL-10 were quantifiable only in MoDC-containing tissues, remaining below the assay detection limit in MoDC-free tissues under the same challenge. Dexamethasone co-treatment reduced LPS-induced release of all five cytokines, with inhibition ranging from approximately 55% to 95% depending on the cytokine, most pronounced for IL-12/IL-23p40 and TNF-α.
Together, this demonstrates that MoDC integration confers a functional, quantifiable, and pharmacologically reversible cytokine response onto the FTSKi model. This model may offer a tractable in vitro platform for dendritic cell-mediated responses in skin, alongside classical full-thickness skin endpoints, supporting non-animal assessment of topical immunomodulation with the option to integrate endpoints relevant to skin irritation.

Keywords: Full thickness skin model - Dendritic cells - Dermatology development.

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PS1-P03

Characterization of IL-23 producing cells during *Klebsiella pneumoniae* pulmonary infection

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Yearly mortality rates from pneumonia remain alarming worldwide. This underscores the need for a deeper understanding of the mechanisms involved in pneumonia pathogenesis, which could be harnessed to develop novel therapies. Dendritic cells detect microbial signals and convert them into immunological signals, thus playing a central role in controlling the anti-infectious immune response, particularly the production of interleukin-17 (IL-17) and interleukin-22 (IL-22). These interleukins play a key role in the lung's defense against extracellular pathogens such as *Klebsiella pneumoniae*. Despite the establishment of the crucial role of Interleukin-23 (IL-23) in the modulation of IL-17 and IL-22 production, the cellular source of IL-23 remains unclear, especially in the lung. Using a murine model of *K. pneumoniae* lung infection, we observe a peak in the expression of inflammatory mediators implicated in the initiation and/or maintenance of the Th17 axis, including *Il1b*, *Il6*, *Il12b* and *Il23a* in the lung tissue at 21h post-infection. This transcriptional response is associated with an increased number of inflammatory dendritic cells in the lungs during the early stages of *K. pneumoniae* infection. Furthermore, a single-cell RNA sequencing analysis identified a distinct population of dendritic cells characterized by an inflammatory transcriptional profile (*Fcgr1*, *Itgam*, *Il1b*, *Il6*, *Tnf*) and expressing *Il23a* mRNA. Then, transcriptomic analysis of lung dendritic cells subsets demonstrated that inflammatory dendritic cells express *Il23a* and *Il12b* during *K. pneumoniae* lung infection. Consistent with these findings, *ex vivo* cultures of bone marrow-derived dendritic cells confirmed that inflammatory DCs produce IL-23p19 and IL-12p40 in response to *K. pneumoniae* infection. Our findings delineate a subset of lung inflammatory dendritic cells that promote antimicrobial immunity, presenting a promising target for the development of innovative immunotherapy strategies to combat infections.

Keywords: Dendritic cells - IL-23 - Lung infection.

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PS1-P04

Uncovering endogenous pro-resolving macrophage programs in skin fibrosis

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Objective
Skin fibrosis has long been regarded as irreversible, yet it can regress after intensive immunosuppressive treatment, indicating that fibrotic tissue retains an endogenous capacity for repair. Macrophages are established drivers of fibrogenesis, but their contribution once fibrosis regresses remains unexplored. We investigated the origin and transcriptional adaptation of the skin macrophage compartment during the establishment and spontaneous resolution of fibrosis.
Methods
Skin fibrosis was induced in mice by repeated intradermal injections of hypochlorous acid, and analysed at successive timepoints after cessation. Macrophages were fate-mapped using Ccr2-CreERT2;R26-tdTomato mice and analysed by flow cytometry and single-cell RNA sequencing. Their spatial distribution was mapped by imaging mass cytometry. Macrophage function was addressed by depletion in Cd64-DTR mice during resolution, with clinical and transcriptional readouts of fibrosis.
Results
Fibrosis induced a marked expansion of a Clec4e+ macrophage population, scarce in healthy skin and retaining monocytic markers, whereas an MRC1+ population present at steady state followed comparable kinetics. MRC1+ macrophages were characterized by an endocytic and lipid catabolic program, Clec4e+ macrophages by an inflammatory one. A third interferon-responsive population was identified. To trace their origin, macrophages were fate-mapped: the pool was almost entirely of CCR2 lineage at the peak of inflammation and remained predominantly monocyte-derived throughout resolution, indicating that regression relies mainly on a functional switch of the macrophages already present in the injured skin rather than on their replacement. Spatially, macrophages were dispersed across the fibrotic dermis and hypodermis, with CD206 predominating in the dermis, suggesting that their function is shaped by anatomical location. Functionally, macrophage depletion during resolution increased skin thickening and sustained collagen gene expression, pointing to an antifibrotic role.
Conclusion
Spontaneous regression of skin fibrosis proceeds in a tissue whose macrophage compartment remains largely monocyte-derived. Rather than being replaced, these macrophages appear to switch towards an MRC1+ pro-resolving program, and their depletion compromises regression. These data point to a macrophage contribution to defibrosis, and position them not only as drivers of fibrogenesis but as candidate effectors of its reversal.

Keywords: Macrophages - Fibrosis resolution - Systemic sclerosis.

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PS1-P05

The role of FOLR2+ macrophages in anti-tumor immunity

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Tumor-associated macrophages comprise functionally diverse subpopulations playing key roles in tumor immunity. Understanding this diversity is crucial to design effective macrophage-targeted therapies. The lung contains three distinct tissue-resident macrophage populations with specific localization: alveolar, perivascular and nerve-associated macrophages[1]. In lung cancer, a fourth population derives from recruited circulating monocytes. We recently identified folate receptor 2 (FOLR2) as a specific marker for perivascular macrophages, found in healthy mammary gland and breast tumors. FOLR2+ macrophages localize within lymphoid aggregates, and their abundance correlates with increased CD8+ T cell infiltration[2]. Thus, we hypothesized that FOLR2+ macrophages contribute to anti-tumor immunity via the activation and/or recruitment of lymphocytes. Importantly, FOLR2+ macrophages have been also found in lungs[3].
In this study, we investigate the role of FOLR2+ macrophages in lung tumor immunity, using the pre-clinical *K-ras, p53* KP lung cancer model.
First, we characterized the spatial distribution of FOLR2+ macrophages and their cellular interactions. FOLR2+ macrophages localize around bronchovascular bundles and in subpleural regions, but are largely excluded from tumor islets. These two distinct localizations of FOLR2+ macrophages suggest that they might be an heterogenous population. Using a published scRNAseq dataset of murine lung macrophages, we found that FOLR2+ macrophages are a heterogeneous population comprising distinct subsets (CX3CR1+FOLR2int and TIM4+LYVE1+FOLR2+ (TLF)). We found that the TLF subset was located around bronchovascular bundles, whereas CX3CR1+FOLR2int subset was in subpleural regions. In addition, FOLR2+ macrophages formed cellular aggregates with CD3+ T cells and MHCII+ antigen-presenting cells, suggesting a potential role in local immune regulation.
To assess their contribution to tumor immunity, we developed a genetic model allowing inducible depletion of FOLR2+ macrophages. Depletion of FOLR2+ macrophages in KP tumor-bearing mice led to an increase in activated/exhausted CD4+ T cells and towards exhaustion of tissue resident memory CD8+ T cells, suggesting that FOLR2+ macrophages contribute to the maintenance of tumor-infiltrating T cell fitness.
In sum, our findings reveal spatially restricted heterogeneous subsets of FOLR2+ macrophages with potential roles in shaping the immune microenvironment via the control of T cell activation.

Keywords: Perivascular macrophages - Lymphocytes - Lung cancer.

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PS1-P06

Epigenetic regulation of tumor-associated macrophage states by TET2 in pancreatic cancer

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Objective
Pancreatic ductal adenocarcinoma (PDAC) is characterized by a profoundly immunosuppressive tumor microenvironment in which tumor-associated macrophages (TAMs) represent a major barrier to effective anti-tumor immunity (1). TET2 is an epigenetic regulator of myeloid cell differentiation and function, but its contribution to TAM heterogeneity in PDAC remains poorly understood (2-3). We investigated whether TET2 supports TAMs states in PDAC and whether transient pharmacological TET inhibition (TETi) could remodel the tumor immune microenvironment.

Methods
Orthotopic PDAC tumors were established in Tet2 wild-type (WT) and Tet2-deficient (KO) mice. Tumor progression and immune composition were characterized using histopathology, spectral flow cytometry and single-cell RNA sequencing. Complementary experiments using a small-molecule TET inhibitor (TETi) were performed both *in vitro* in BMDMsand *in vivo* in tumor-bearing mice.

Results
Tet2 deficiency reduced orthotopic PDAC tumor burden and was associated with increased tumor necrotic areas and enhanced immune infiltration. Spectral flow cytometry revealed remodeling of the tumor immune compartment, with Tet2-deficient, TAMs displaying increased expression of CD64, CD86 and MHC-II, consistent with a shift toward a more activated and antigen-presenting phenotype. These changes were accompanied by enhanced T-cell responses, including increased Ki67 expression in $CD4^+$ T cells and increased CD107a expression in $CD8^+$ T cells.
Single-cell RNA sequencing further revealed a reduced abundance of TREM2 macrophage populations in Tet2 KO tumors, accompanied by increased representation of inflammatory, interferon-responsive and antigen-presenting macrophage programs.
Pharmacological TET inhibition reproduced key features of the genetic model, reducing tumor burden and remodeling the immune landscape. *In vitro*, TET inhibition altered macrophage expression of genes associated with activated and antigen-presenting phenotypes, similar to what we observed in our Tet2 deficiency model.

Conclusion
Our findings identify TET2 as an epigenetic regulator of macrophage heterogeneity in PDAC. Genetic or pharmacological targeting of TET activity remodels the myeloid compartment, including a reduction in pro-tumor macrophage states, toward a more inflammatory and immune-permissive tumor microenvironment. These findings support targeting TET activity as a potential strategy to enhance anti-tumor immunity in pancreatic cancer.

Keywords: TAMs - TET2 - Pancreatic cancer.

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PS1-P07

Divergent pDC trajectories induced by HIV-infected T cells toward IFN production, T cell stimulation or cytotoxicity

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Objective
Plasmacytoid dendritic cells (**pDC**) are major interferon (IFN) producing-cells in response to viral stimulation. After maturation, we found that human pDC cross-present HIV antigens from infected T cells to specific cytotoxic T lymphocytes1,2. However, pDC can become **heterogeneous**: diversification into IFN-alpha-producing (PD-L1+) or T-cell stimulating (CD80+) populations was found by unsupervised multiparametric flow cytometric analysis after stimulation by free influenza virus or SARS-Cov23. To understand their functional evolution, and as HIV is rarely free, **we stimulated pDC by HIV-1 or -2-infected cells**.
Methods
Human pDC purified from cytapheresis residues by immunomagnetic depletion and BD Aria III **sorting**were stimulated for 16h by the **CD4+ T cell line H9, infected or not by HIV-1 or-2**. They were tested by unsupervised multiparametric **spectral cytometry** (Cytek Aurora, Omiq) and single-cell RNA sequencing (**scRNAseq**, Chromium Next Gem-X Flex 10xGenomics, Illumina NextSeq2000, Human genome GRCh38-2024-1, R v4.05, Seurat, DGE, UMAP, Louvain, GOE, Monocle 3). Sub-populations were **FACS**-sorted for **functional** analysis.
Results
After stimulation by **uninfected H9 cells**, 15% of pDC left their initial immature stage to evolve into a cluster expressing the surface negative **costimulatory** molecule PD-L1 and CD107a, a sign of **cytotoxicity**, and expressing RNA coding for **TLR-7 and -9 and signaling pathway molecules**. After stimulation by **HIV-1-infected H9 cells**, pDC diversified into **7 discrete clusters** identified by scRNAseq, expressing either genes coding for **IFN-alpha and -lambda**, **TLR7/9 signaling pathway**, and T cell positive or negative **costimulatory molecules** or **IFN-stimulated genes**. Pseudo-trajectory analysis indicated **divergent** evolution toward these clusters. Spectral cytometry analysis and FACS-sorting identified clusters either **producing IFN alpha and/or-lambda,** exerting **cytotoxicity**, or **stimulating positively or negatively T cell** proliferation and differentiation. Differences between the stimulating effects of HIV-1 or -2 infected cells is interpreted in relation to the different clinical outcomes of these two infections *in vivo*.
Conclusion
Targeting selectively these new pDC clusters will help develop appropriate **therapeutic strategies** against HIV infection, other infections or tumors.

French Government's Investissement d'Avenir program, Laboratoires d'Excellence «Integrative Biology of Emerging Infectious Diseases» (ANR-10-LABX-62-IBEID) and ANRS.

Keywords: Dendritic Cells - Interferons - Antigen presentation.

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PS1-P08

Characterisation of blood monocytes by scRNAseq and multiparametric flow cytometry in adult patients with isolated pulmonary Langerhans cell histiocytosis

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Background
Pulmonary Langerhans cell histiocytosis (PLCH) is a rare clonal lung disease affecting young smokers, characterised by the infiltration of the wall of distal bronchioles by $CD1a^+/CD207^+$ mononuclear cells.
Aims and objectives
To unravel the origin of PLCH cells.
Methods
Peripheral blood mononuclear cells (PBMC) from 5 healthy smokers (HS) and 11 PLCH patients were analysed by single cell RNA sequencing (RNAseq) and multiparametric spectral flow cytometry, blinded to patients' clinical features.
Results
No statistical difference was evidenced in the proportion of PBMC subtypes between HS and PLCH patients. UMAP projection showed a clearly distinct profile between PLCH patients and HS, particularly for classical monocytes (cMo). Differentially expressed genes (DEGs) analysis confirmed highly different cMo transcriptomic profiles between HS and PLCH patients. PLCH cMo profiles were heterogeneous and could be clustered into 2 groups (Grp) of 7 and 4 samples, respectively. U-cell score algorithm showed that Grp2 cMo had highest similarity scores with LCH cells derived from in vitro Jagged2 stimulated cMo and with the 77 top DEGs identified from non-pulmonary LCH lesions. At flow cytometry, HLA-$DR^{high}CD80^+CCR7^-CD163^+$ cMo were increased in Grp2 PLCH samples compared to HS and Grp1 PLCH. Grp2 samples corresponded to patients with active PLCH.
Conclusion
Blood cMo appear to be involved in PLCH pathogenesis. In active disease, their profile is reminiscent of that of LCH cells in the lesions.

Keywords: Lung Cancer - Neoplastic disease - Monocyte.

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PS1-P09

Development of a personalized and targeted therapeutic strategy for pathogenic synovial macrophages in osteoarthritis

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Osteoarthritis (OA) is the most prevalent joint disease, affecting nearly 600 million people worldwide. Despite its considerable socio-economic impact, OA remains incurable, notably due to difficulties in addressing patient heterogeneity. Characterized by cartilage degradation and bone remodelling, OA is also driven by synovial tissue (ST) inflammation playing a key role in disease onset and progression. As previously described in our group, histological and transcriptomic analyses of the ST revealed 3 OA synovial endotypes, each characterized by distinct immune cell profiles and molecular pathways. The marked infiltration of synovial macrophages, and the enrichment of distinct subsets in specific groups of patients led us to hypothesize that a precise characterization and targeting of macrophage subsets could enable the development of personalized therapeutic approaches.
OA synovial tissues from patients who underwent total knee replacement were analysed by single-cell RNA sequencing and spatial transcriptomics to characterize macrophage diversity, spatial organization and crosstalk with other joint cells. 2D *in vitro* models were established to decipher the pathogenic roles of macrophages subsets in OA, notably through phagocytosis assays and co-cultures with other joint cells. A targeting strategy using a combination of relevant siRNA is being optimized to specifically modulate the phenotype of macrophage subpopulations and a lipoplex-based vectorization system has been developed in parallel on synovial explant ex vivo and OA mouse knees in vivo using light sheet imaging technology.
Single-cell RNA sequencing and spatial transcriptomics identified that a deep-lining macrophage subset, previously described as TREM2low macrophage, was enriched in the lympho-myeloid OA patient subgroup. The role of TREM2low macrophages, was investigated in vitro using a relevant model previously validated by high-throughput transcriptomic approach. TREM2low macrophages presented a reduced phagocytic activity and were able to influence synovial fibroblasts phenotype. Lipoplexes-mediated vectorization of siRNA demonstrated highly efficient uptake by macrophages, good penetration within ex vivo synovial tissue and effective targeting of the synovial tissue following intra-articular injection into mouse knees. Further experiments will evaluate the therapeutic benefits of the siRNA combination on the development of OA in a relevant murine model.

Keywords: Osteoarthritis - Macrophages - Synovitis.

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Metabolic regulation of antigen presentation via MHC Class II

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Presentation of exogenous antigens through major histocompatibility complex class II (MHC II) molecules by antigen-presenting cells is central to adaptive immunity and immune tolerance. Previous elegant studies have delineated many key components of this pathway. Here, while investigating the role of solute carrier transporters in phagocytes, we serendipitously discover a link between cysteine metabolism and MHC Class II (MHC II) antigen presentation. Specifically, genetic and pharmacological inhibition of the cystine-glutamate antiporter SLC7A11 in antigen presenting cells markedly impaired the MHC II presentation of antigens: this includes antigen derived from apoptotic cells, soluble proteins, and synthetic peptides, and analyzed under *in vitro*, *ex vivo*, and *in vivo* contexts. Mechanistic studies revealed that loss of cystine import through SLC7A11 compromises the processing of invariant chain that occupies the peptide-binding groove, peptide loading, and MHC II maturation. Strikingly, restoring cysteine levels in the antigen presenting cells rescued these defects. The underlying impairment in antigen presentation was linked to lysosomal dysfunction, including alterations in morphology, pH, redox balance, and proteolytic activity.
Collectively, these data uncover an immunometabolic axis linking cysteine homeostasis to lysosomal function and MHC II antigen presentation, positioning SLC7A11 as a potential modulator of immune tolerance.

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Uncovering the therapeutic potential of dendritic cell-derived extracellular vesicles for immunotherapy in triple-negative breast cancer

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Dendritic cells (DCs) are antigen-presenting cells involved in tumor antigen presentation to naive T cells. DC-derived extracellular vesicles (DC-EVs) promote tumor antigen-specific responses, present MCH complexes at the surface and resist to immunosuppression. Nevertheless, DC-EVs immunotherapeutic potential is not fully explored. We propose to unveil DC-EVs role as an immunotherapy for triple-negative breast cancer, orphan of effective therapies.
Two strategies were developed to do MDA-MB-231 TNBC lysates: freeze/thaw plus sonication (FT+S) and sonication (S). Monocytes from healthy blood donors were cultured with IL-4 and GM-CSF. FT+S and S lysates with MPLA were added at day 4 to induce DCs activation. DC-EVs were isolated by size exclusion chromatography (SEC) and characterized by Western Blot, NTA and TEM. Pre-educated DCs, conditioned media (CM) from pre-educated DCs and DC-EVs potential to activate T cells was evaluated by flow cytometry.
Tumor cell lysates expressed immunological cell death markers (HMGB1, HSP90, Calregulin). DCs phenotype was confirmed by flow cytometry (CD11c, CD86, CD40, HLA-DR), suggesting DCs activation with cell lysates with MPLA, with increased expression of CD86 and HLA-DR. ELISA of CM revealed an increase of IL-6 and IL-12p40 expression. Pre-educated DCs induced T cells activation, with increase in CD8+CD69+T cells expression and IFN-γ production in CM. Moreover, CM from pre-educated DCs activated T cells, with increase in CD8+CD69+ T cells expression. CM of pre-educated DCs reduced MDA-MB-231 cell viability, which did not happen when given to MDA-MB-468, showing specific pre-education of DC by the tumor cell lysates. We also observe a peak corresponding to EVs size (~130.5 ± 13.0 nm) by NTA, cup shaped particles by TEM, and expression of EVs and DC-EVs markers (CD9, CD81, CD63, Alix, CD86, HLA-DR), suggesting successful EVs isolation. Studies to evaluate DC-EVs potential to activate T cells are being conducted, together with proteomics, as well as toxicity assays to evaluate TNBC cell death upon exposure to pre-educated DC-EVs.
Our data shows that tumor cell lysates with MPLA pre-educated DCs and both DCs and their CM were able to induce CD8+ T cell activation. Their CM was able to reduce MDA-MB-231 viability in a specific manner. However, DC-EVs immunomodulatory potential is still not clear. Further studies will dissect the immunomodulatory potential of DC-EVs, opening doors for new immunotherapeutic approaches for TNBC.

Keywords: Dendritic Cells - Immunomotherapy - Extracellular Vesicles.

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Exploring RNA Biology and RNA Polymerase III Regulation During Dendritic Cell Activation

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Objectives
Dendritic cells (DCs) are professional antigen-presenting cells essential for initiating adaptive immune responses and maintaining immune tolerance. Upon activation, DCs rapidly remodel gene expression and protein synthesis to process and present antigens via MHC-I and MHC-II, produce cytokines, and prime naive T cells. Since tRNAs are essential for protein synthesis, we investigated the role of RNA Polymerase III (Pol III)-dependent tRNA transcription during DC activation.
Methods
Complementary approaches were used to investigate the role of Pol III in DC activation. Pharmacological inhibitors of Pol III and mTOR were used to dissect signaling pathways regulating Pol III activity. tRNA transcription was analyzed using tRNA arrays and validated by Northern blotting, while global protein synthesis was measured by SUnSET. Functional consequences were assessed using antigen presentation assays in which ovalbumin-loaded DCs were co-cultured with OT-II $CD4^+$ T cells.
Results
Stimulation with the TLR ligands lipopolysaccharide (LPS) and polyinosinic acid (poly(I:C)) strongly induced Pol III-dependent transcription, increasing tRNA expression. This response was mediated by phosphorylation and nuclear export of the Pol III repressor Maf1. Enhanced tRNA synthesis was required to sustain global protein translation and efficient translation of DC-specific mRNAs. Inhibition of de novo tRNA transcription impaired protein synthesis and compromised DC activation, including cytokine production, antigen presentation, and T-cell priming. These findings demonstrate that tRNA expression is dynamically regulated during immune activation and supports the immune gene expression program induced by TLR and interferon signaling.
Conclusions
Pol III-dependent tRNA transcription is a critical component of the translational program underpinning DC activation. Regulation of protein synthesis and tRNA abundance is vital for DC activation, cytokine production, and T-cell priming. Dynamic tRNA synthesis enables efficient protein production required for optimal antigen presentation and immune function, indicating that protein synthesis quality can affect DC fitness and function.

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Keywords: DCs - tRNA - Protein synthesis.

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PS2-P01

Multiparametric Flow Cytometric Profiling of Regulatory T and B Cells in Pediatric Inborn Errors of Immunity

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Background
Immune dysregulation is a major feature of Inborn Errors of Immunity (IEIs), yet the contribution of regulatory lymphocyte subsets remains incompletely understood, particularly for regulatory B cells (Bregs). Characterizing both regulatory T cells (Tregs) and Breg subsets may improve our understanding of the immunological mechanisms underlying different pediatric IEIs.
Objectives: To characterize the phenotypic distribution of regulatory T cells and regulatory B-cell subsets in pediatric patients with different Inborn Errors of Immunity using multiparametric flow cytometry.
Methods
Peripheral blood samples were obtained from 18 pediatric patients, including chronic granulomatous disease (CGD) with gastrointestinal involvement (n = 6), CGD without gastrointestinal involvement (n = 6), and other IEIs (n = 6), together with 25 healthy controls. Tregs were identified as $CD3^+CD4^+CD25^{high}CD127^{low}$cells, while memory and transitional Bregs were defined as $CD19^+CD24^{high}CD27^+$ and $CD19^+CD24^{high}CD38^{high}$ cells, respectively. Immunophenotyping was performed using a BD FACSLyric flow cytometer.
Results
Significant differences in regulatory lymphocyte frequencies were observed among the study groups ($p < 0.001$). Treg frequencies were increased in patients with CGD and gastrointestinal involvement (median 8.09%) compared with healthy controls (4.89%), whereas patients with other IEIs exhibited markedly reduced Treg frequencies (0.88%). In contrast, both memory and transitional Breg subsets were consistently decreased across all patient groups. Median memory Breg frequencies declined from 11.24% in healthy controls to 2.59%, 4.90%, and 3.73% in CGD with gastrointestinal involvement, CGD without gastrointestinal involvement, and other IEIs, respectively. Similarly, transitional Bregs decreased from 10.13% in controls to 2.99%, 5.88%, and 3.78% across the corresponding patient groups. These findings reveal disease-specific alterations in Treg frequencies together with a consistent depletion of regulatory B-cell subsets in pediatric IEIs.
Conclusion
These findings identify regulatory B-cell deficiency as a potential shared immunological feature across pediatric IEIs, while revealing disease-specific Treg alterations that may contribute to distinct mechanisms of immune dysregulation. This work provides a foundation for future functional characterization of regulatory lymphocytes and may support the development of immune biomarkers for patient stratification.

Keywords: Inborn Errors of Immunity - Regulatory T cells - Regulatory B cells.

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PS2-P02

Characterizing STAT1 Deficiency and the IL-12/IFN-γ Signaling Pathway in Four Moroccan Kindreds with Mendelian Susceptibility to Mycobacterial Disease

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Mendelian Susceptibility to Mycobacterial Disease (MSMD) comprises rare inborn errors of IFN-γ–mediated immunity causing selective susceptibility to mycobacterial infections. More than 44 genetic defects involving 22 genes have been identified, converging mainly on the IL-12/IFN-γ axis. In Morocco, a cohort of 22 patients from 15 kindreds identified six genetic etiologies, with partial autosomal dominant (AD) STAT1 deficiency emerging as the second most frequent cause.

To characterize the clinical, genetic, and functional features of partial AD STAT1 deficiency in four Moroccan kindreds.

MSMD patients followed at Ibn Rushd University Hospital, Casablanca, were investigated retrospectively and prospectively. Genetic diagnosis was established by Sanger sequencing and/or whole-exome sequencing. The IL-12/IFN-γ axis was functionally assessed by whole-blood stimulation with BCG alone, BCG + recombinant IL-12p70, or BCG + recombinant IFN-γ, followed by ELISA quantification of IFN-γ and IL-12p40.

Seven patients from four unrelated non-consanguineous kindreds harbored four distinct heterozygous loss-of-function STAT1 mutations: p.E157K (Exon 7), p.L498V (Exon 18), p.Y701C and p.I707T (Exon 23). No consanguinity was found in any kindred, consistent with the AD mode of inheritance. Median age of diagnosis was 10 years. Clinical manifestations ranged from locoregional BCGitis and cutaneous tuberculoid disease to severe multifocal osteomyelitis and fatal multifocal tuberculosis with cerebral abscess, illustrating marked variable expressivity. Incomplete penetrance was demonstrated in one kindred, where a father and one son carrying the pathogenic variant remained asymptomatic. Functional assays in three symptomatic patients revealed preserved IFN-γ production in response to IL-12, and impaired response to IFN-γ. STAT1 is a transcription factor implicated in both IFN-γ (type II) and IFN-α/β (type I) signaling pathways. Partial AD STAT1 deficiency impairs IFN-γ signaling while largely preserving IFN-α/β responses, thereby producing an isolated predisposition to mycobacterial infections. On the other hand, AR STAT1 deficiency impairs both IFN-γ and IFN-α/β signaling, causing a syndromic MSMD with predisposition to both viral and mycobacterial infections.

Partial AD STAT1 deficiency is a frequent MSMD cause in Morocco, with variable clinical expression and incomplete penetrance. Functional testing helps identify impaired IFN-γ responses and supports genetic diagnosis.

Keywords: MSMD - Tuberculosis - STAT1 deficiency - IL-12/IFN-γ axis - Inborn errors of immunity.

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PS2-P03

Hereditary Angioedema Associated with a SERPING1 Variant in a Moroccan Family: Clinical and Molecular Findings

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Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by deficiency or dysfunction of C1 esterase inhibitor (C1-INH), a key regulator of the kallikrein–kinin system. It affects approximately 1 in 50,000–60,000 individuals and is characterized by recurrent, non-pruritic angioedema involving the skin, gastrointestinal tract, and upper airways due to bradykinin-mediated increased vascular permeability (1). Most cases of HAE types I and II are linked to pathogenic variants in the *SERPING1*gene, with over 700 variants reported. While 75–80% of cases are familial, 20–25% result from de novo mutations, and clinical expression is highly variable (2,3). In Morocco, HAE remains underdiagnosed, leading to delays in diagnosis and management. We report two related patients carrying a *SERPING1*variant, highlighting the role of genetic testing in diagnostic confirmation.

Case Report

We describe a familial case of HAE involving a mother and her son. The proband developed symptoms at the age of 21 years, presenting with recurrent angioedema affecting the extremities, genital region, and larynx, along with abdominal attacks, respiratory discomfort, and dysphonia. Episodes were triggered by stress, trauma, cold exposure, and emotional factors, with partial response to tranexamic acid. Complement testing revealed low C4 levels, decreased C1-INH antigen, and reduced functional activity, consistent with HAE type I.

The mother reported symptom onset at 16 years, with recurrent abdominal and cutaneous angioedema and possible laryngeal involvement. Triggers included stress, trauma, cold, and pregnancy, with no response to tranexamic acid. A deceased brother with suspected laryngeal involvement further supports a strong familial pattern.

Genetic analysis identified the NM_000062.3(*SERPING1*) : c.551-1G>A splice-site pathogenic variant in both patients using a targeted panel (*SERPING1*, *ANGPT1*, *F12*, *PLG*).

Conclusion

This case illustrates significant intrafamilial variability in hereditary angioedema despite a shared *SERPING1* pathogenic variant and points out the potential for delayed diagnosis within affected families. It emphasizes the necessity of early recognition and molecular testing to ensure accurate diagnosis and optimal management.

Keywords: Hereditary angioedema (HAE) - SERPING1 - Genetic testing.

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PS3-P01

Newcastle Disease Control: Do Perception Structures Drive Vaccine Adoption among Smallholder Poultry Farmers in Tanzania?

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Newcastle disease (ND) remains a major constraint on smallholder poultry production in sub-Saharan Africa, causing high flock mortality and deepening rural poverty. Despite high vaccine awareness, vaccine adoption rates remain persistently low. This study investigates whether latent perception structures drive ND vaccine adoption among smallholder poultry producers in the Morogoro Region of Tanzania. Using a two-stage analytical approach, we apply exploratory factor analysis (EFA) on a tetrachoric correlation matrix to identify latent perception dimensions, then link derived factor scores to adoption outcomes via binary logistic regression. EFA identifies two orthogonal perception structures reflecting an institutional access factor (proximity to livestock officers, agrovet shops, and physical accessibility), and a cultural constraint factor (traditional medicine use, slaughter-if-sick behavior, and vaccine avoidance). Results reveal that perception structure related to the institutional access only influences ND vaccine adoption (β = 0.431; OR = 1.539), increasing adoption probability by 9.4 percentage points. Socio-economic characteristics such as education level and prior ND outbreak experience by farmers are also associated with ND vaccine adoption. Beyond reinforcing the centrality of institutional access to vaccine adoption, these findings suggest that cultural constraints should be addressed through complementary strategies rather than treated as a separate barrier. Policy interventions may prioritize strengthening veterinary extension networks, community vaccination outreach, and last-mile service delivery over behavioral messaging alone.

Keywords: Newcastle disease - Vaccine adoption - Tanzania.

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PS3-P02

Dissecting the contribution of T cells to protection against WNV-infectious mosquito bite induced by an EV-based vaccine

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Mosquito-borne Orthoflaviviruses, including West Nile (WNV), dengue, Zika, and yellow fever viruses, cause over 500 million infections annually and are now encroaching on Europe, representing the top epidemic threat. Current vaccines targeting Orthoflaviviruses have limited efficacy and safety issues, underscoring the urgent need for innovative strategies. Extracellular vesicles (EVs) present in mosquito saliva enhance bite-initiated skin infection for all Orthoflaviviruses by modulating the cutaneous immune and metabolic profile, amplifying transmission and aggravating disease outcome. EV-immunization was previously shown to protect mice against WNV infection by mosquito-bite, reducing disease severity and improving survival, thereby establishing the proof-of-concept for a novel, safe and broad-spectrum vaccine. However, a clear understanding of the underlying immune mechanism is still lacking. This work aimed to determine the immune correlates of protection of this vaccine in a mosquito-to-mouse transmission model to enable future efficacy improvement studies, as well as to support clinical development. Since passive immunization failed to recapitulate the protection observed, suggesting a T-cell-dependent mechanism, we focused on assessing the contribution of T cells to the immune response in EV-immunized mice during the early stages of infection. To this end, we quantified WNV RNA levels 9 h post-infection by qPCR in 2 mm skin biopsies from the bite site and draining lymph nodes in T-cell-depleted EV-immunized mice. Moreover, complementary experimental approaches were used to characterize EV-mediated protection and assess the potential role of T-cells in early control of infection. Overall, this work represents a first step towards elucidating the immune mechanisms underlying protection conferred by EV immunization, with particular emphasis on the contribution of T cells, and may help identify immune correlates to guide future vaccine optimization.

Keywords: Orthoflavivirus vaccine - Extracellular vesicles - T-cells.

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PS3-P03

Preclinical evaluation of Fel d 1 mRNA vaccine for the treatment of cat allergy

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Objectives

Cat allergens are among the most frequent indoor allergens inducing allergic rhinoconjunctivitis and asthma symptoms, with 10-30% of people sensitized to cat dander in Western countries. These diseases are characterized by eosinophilia, impaired respiratory functions and IgE-driven mast cell activation. 95% of cat allergic subjects have IgE antibodies directed against the dominant cat allergen Fel d 1. Current therapies are mainly symptomatic, and allergen specific immunotherapy (AIT) which consists of giving low doses of allergens over a long period of time remains the only treatment capable of changing the course of the disease. AIT has been shown to induce allergen-specific IgG which can compete with IgE. However, AIT is still limited by many side effects and many patients rapidly regain allergy upon cessation of AIT. Here, we propose a novel mRNA-based vaccine approach to induce long-term protective immunity for the treatment of cat allergy.

Methods

Mice were immunized intramuscularly with mRNA encoding Fel d 1 or a polyA sequence as control encapsulated in lipid nanoparticles (mRNA-LNP). Antibody responses were measured by ELISA. Neutralizing capacities of the induced antibodies were assessed with a competitive bioluminescent IgE detection assay (LuLISA) and with a human mast cell degranulation test using sensitization with plasma from cat allergic subjects.

Results

Immunization with Fel d 1 mRNA-LNP induces strong and long-lasting specific IgG responses (over 5 months, the longest time-point analyzed). Binding of human IgE present in the serum of cat-sensitized subjects to Fel d 1 was significantly reduced after preincubation of the allergen with serum from mice immunized with Fel d 1 mRNA-LNP. This inhibitory effect is abrogated upon depletion of IgG from the serum of vaccinated mice. Moreover, antibodies induced by Fel d 1 mRNA-LNP prevented degranulation of mast cells sensitized with IgE from cat allergic subjects.

Conclusion

Vaccination with Fel d 1 mRNA-LNP induce sustained neutralizing IgG which can compete with IgE from cat allergic subjects and thereby block mast cell degranulation. Our data thus suggest that vaccination with Fel d 1 mRNA-LNP could be a promising approach for the long-term treatment of cat allergy.

Keywords: Allergy - Vaccine - mRNA-LNP.

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PS3-P04

Monovalent mRNA Influenza Hemagglutinin Vaccine Sparks Potent Cellular Immunity Relative to Recombinant Protein Comparator in Humans

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Emerging evidence indicates that immunity to Influenza is complex with the orchestration of different immune compartments such as innate, antibodies and cell mediated immune (CMI) responses. To analyze the impact of various mRNA vaccine candidates on CMI and compare it with that of analogous recombinant antigens, key cell subpopulations were characterized following immunization with both types of vaccination platforms. The clinical protocol included healthy adults (130 subjects 18 to 59 years old and 130 subjects ≥60 years old) were randomized to receive one intramuscular injection of a modified mRNA vaccine encoding A/Tasmania/503/2020 H3N2 hemagglutinin (HA) at a dose of 5, 15, 45, 75, and 130 µg of mRNA and the corresponding HA recombinant protein delivered at a dose of 45 µg of protein . We assessed intracellular cytokines and cell surface markers induced in Tasmania H3 restimulated PBMCs before and after vaccination. Additionally, plasmablasts and T follicular helper cells (Tfh) were analyzed before and after vaccination by ex vivo labelling using high resolution spectral flow cytometry. In mRNA vaccinated groups, we observed a significant increase of Th1 cytokines (IFN ɣ , IL2 and TNF α) in CD4+ T cells from Day 0 to Day 9. Moreover, activation induced markers (CD40L and CD69) were correlated with cytokine production. Regardless of mRNA vaccination dose, the CD4+ response was more pronounced compared to the recombinant vaccinated group. Regarding the CD8+ response, significant increases in IFN ɣ + and Granzyme B+ were noted in higher mRNA dosing groups, while no significant response was detected in the recombinant HA vaccinated group. Plasmablasts and Tfh showed a significant increase after 45 µ g dose in mRNA vaccinated group , comparable to the recombinant HA vaccinated group. Overall, these findings indicate that an mRNA influenza candidate vaccine can induce a robust Th1 response, increase plasmablasts and Tfh, and elicit specific CD8+ lymphocyte responses. lymphocyte responses. The impact, reflected as a correlation with antibody production, remains to be determined.

Keywords: mRNA vaccine - Cellular immunity - Influenza.

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PS3-P05

Harnessing Neutrophil-Driven Innate Immunity for Antigen-Agnostic and Broad-Spectrum Vaccine Development

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Objective
Rising risks from respiratory pandemics and drug-resistant pathogens highlight the urgent demand for host-directed, broad-spectrum prophylactic solutions. This study investigates whether intranasal administration of recombinant lipidated FLIPr (rLF), a novel TLR2 agonist, can induce antigen-independent protective immunity against diverse viral and bacterial respiratory infections.
Methods
Mice were prophylactically treated with rLF via intranasal delivery and subjected to lethal challenge models using H7N9 influenza virus, *Streptococcus pneumoniae*, and carbapenem-resistant *Acinetobacter baumannii*. Immunological mechanisms were evaluated by mapping bone marrow hematopoiesis and signaling pathways, performing selective cell-depletion experiments, and executing transcriptomic profiling during secondary immune challenges.
Results
Intranasal rLF administration stimulated the TLR2/IFN-γ/STAT1 signaling axis, leading to enhanced secondary innate immune responsiveness and the expansion of myeloid-biased progenitor cells in the bone marrow. Prophylactic rLF treatment significantly reduced local pathogen loads and enhanced survival across lethal H7N9, *S. pneumoniae*, and multidrug-resistant *A. baumannii* infection models. Anti-H7N9 protective immunity persisted for at least six weeks post-administration. Selective cell-depletion assays revealed that neutrophils are essential mediators of this cross-pathogen defense. Furthermore, transcriptomic analysis during secondary challenges highlighted a distinct neutrophil gene expression profile predominantly enriched for cell migration, degranulation, and inflammatory signaling pathways.
Conclusion
Mucosal delivery of rLF acts as an effective host-directed immunoprophylactic strategy. By activating the TLR2/IFN-γ/STAT1 axis and driving neutrophil-mediated defense mechanisms, rLF establishes durable, antigen-independent protection against emerging viral and antibiotic-resistant bacterial respiratory threats.

Keywords: Neutrophil - Innate immunity - Vaccine.

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PS3-P06

CD40 targeting sustains germinal centre activity and broadens antibody responses to SARS-CoV-2 variants

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Objective
SARS-CoV-2 variant immune escape has reduced vaccine effectiveness, highlighting the need for boosters inducing broad and durable antibody (Ab) responses. We previously showed that CD40.Pan.CoV, a CD40-targeted vaccine designed to address variant diversification, induces strong variant-directed Ab responses. Here, we evaluated its long-term booster efficacy and mechanisms supporting B-cell response durability.
Methods
CD40.Pan.CoV consists of a partial agonist anti-human CD40 mAb fused to a mutated RBD (K417N, L452R, T478K, E484Q, N501Y) and a nucleocapsid fragment. Human CD40-transgenic mice primed with two BNT162b2 doses were boosted at month 8 with BNT162b2, original/BA.4-5 BNT162b2, or CD40.Pan.CoV plus poly-ICLC. Sera were collected monthly until month 16. Binding and neutralising Abs, and $Ki67^{+}BCL6^{+}$ germinal-centre (GC) B cells, were assessed. Mathematical modelling estimated the contributions of SLPC and LLPC to Ab kinetics. In mechanistic studies, GC permissivity to naïve B cells was assessed by adoptive transfer, while anti-CD40L-mediated GC disruption and anti-CD20 depletion examined the contribution of CD40L-dependent and $CD20^{+}$ B-cell responses to Ab maintenance.
Results
In BNT162b2-primed mice, CD40.Pan.CoV induced broader and more durable binding and neutralising Ab responses than mRNA boosters. Mathematical modelling predicted a greater LLPC contribution to sustained Ab responses after CD40.Pan.CoV boosting. This response was associated with prolonged proliferative GC activity, as shown by sustained $Ki67^{+}BCL6^{+}$ GC B cells. At day 7 post-boost, GCs were more permissive to naïve B-cell recruitment after CD40.Pan.CoV than after mRNA vaccination. CD40L blockade abrogated GCs and selectively reduced Ab levels in CD40.Pan.CoV-immunized mice, supporting a sustained requirement for GC-dependent B-cell responses. Conversely, CD20 depletion reduced Ab levels after mRNA vaccination but not after CD40.Pan.CoV boosting, indicating distinct requirements for $CD20^{+}$ B-cell populations in maintaining serum Ab responses.
Conclusion
CD40.Pan.CoV induces broader and more sustained antibody responses than mRNA boosting in BNT162b2-primed mice. This phenotype is associated with prolonged proliferative GC activity, naïve B-cell recruitment into recall GCs, and sustained sensitivity to CD40L blockade. Together, these findings support a distinct post-boost B-cell response profile that may contribute to durable humoral immunity against SARS-CoV-2 variants.

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PS3-P07

Early immunity determines how HSV-1 persists: programming latent reservoir reactivation competence

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HSV-1 establishes lifelong latent reservoirs in neurons, but latent genomes are not functionally equivalent. During early reservoir establishment, persistent virus enters different trajectories that later prove to be reactivation-prone or reactivation-resistant, despite comparable viral gDNA burdens. We asked if this early divergence is instructed by the immune environment in which latency forms.

Using a BALB/c oro-ocular model, we combined timed immune-cell depletion, multiparameter flow cytometry and tissue proteomics to resolve immune conditions associated with these divergent reservoir states. Priming with a thymidine kinase-deficient HSV-1 (TKdel) mutant before contralateral wild-type (WT) challenge permitted persistent WT genome establishment in trigeminal ganglia (TG), but abolished detectable explant reactivation. Transient AGM1$^+$-cell depletion immediately before WT challenge restored reactivation to ~98% without increasing latent genome burden, whereas matched CD8α depletion did not.

Flow cytometry associated reactivation-resistant trajectory with early mature CD11b$^+$CD27$^+$ NK cell responses, and a redistribution of effector activity toward the peripheral infection site rather than the TG. In parallel, draining lymph node proteomics identified highly overlapping global infection responses between TKdel and WT, but they were organised differently: WT favoured IFN/innate-effector amplification, whereas TKdel favoured regulated APC–stromal and RNA/chromatin-associated architecture.

Together, cellular and proteomic data identified an early immune-programming checkpoint that determined later HSV-1 reservoir fate. We propose that transient early immune history becomes encoded in the architecture of latent HSV-1 genomes, thereby setting their future threshold for reactivation. These findings suggest that vaccinology strategies should be aimed not only at limiting infection, but also at altering the functional quality of the persistent viral reservoirs to prevent reactivation.

Keywords: Herpes - Reactivation - Immunity.

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PS3-P08

T cell-associated immunity induced by heterologous recombinant BCG and purified protein vaccination confers cross-variant protection against SARS-CoV-2

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We have developed a recombinant BCG-based vaccine (rBCG) expressing a chimeric protein with spike and nucleocapsid immunodominant epitopes (here termed rChimera) to combine BCG's innate immune training capacity with SARS-CoV-2-specific adaptive immune responses. As a heterologous prime-boost consisting of one dose of the rBCG and one dose consisting of the purified rChimera in association with Alum, we were able to induce strong humoral and cellular immunity, conferring protection against the ancestral Wuhan strain in K18-hACE2 mice. By using knockout mice lacking functional B cells, CD4+ or CD8+T lymphocytes but also expressing hACE2, we evaluated the mechanisms of anti-viral immune protection, while also evaluating vaccine efficacy against the omicron sublineage JN.1. Vaccination induced high titers of anti-rChimera antibodies with modest neutralizing capacity against the Wuhan SARS-CoV-2 strain. Nonetheless, vaccinated B lymphocyte KO mice still showed reduced viral loads, suggesting that humoral immunity may not represent the predominant protective mechanism in this model (at least regarding neutralizing activity). Vaccinated mice displayed a strong Th1-biased cellular profile characterized by increased IFN-γ production and multifunctional $CD4^+$ T cell responses, alongside activated $CD8^+$ T cells responses. CD4+ and CD8+ T cell-deficient animals exhibited loss of vaccine-associated protection, supporting an important contribution of T cells to viral control. Additionally, immunized IFN-γ knockout mice revealed only partial protection, suggesting that IFN-γ contributes to, but is not strictly required, for vaccine-induced immunity. We also observed that macrophages derived from vaccinated animals displayed enhanced inflammatory responsiveness following heterologous stimulation. Remarkably, vaccination conferred cross-protection against JN.1, despite lack of neutralization antibodies. These findings indicate that rBCG/rChimera+Alum vaccination induces an integrated innate and predominant T cell protective immunity cross-reactive with JN.1, supporting the rBCG-based platforms as a promising approach for COVID-19 vaccine development.

Keywords: COVID-19 - SARS-CoV-2 - BCG.

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PS3-P09

Distinct innate immune programs induced by five HIV-1 vaccine platforms shape the magnitude and durability of adaptive immunity

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Objective
An effective HIV vaccine requires the coordinated induction of broadly neutralizing antibodies, potent CD8⁺ T-cell responses, durable immune memory and mucosal immunity. While innovative vaccine platforms have expanded the possibilities for antigen delivery, how they differentially engage innate immunity to shape long-term adaptive responses remain poorly understood. We sought to define the early innate immune signatures induced by distinct HIV-1 vaccine platforms and determine their relationship with the magnitude, quality and persistence of adaptive immunity.
Methods
Five vaccine platforms delivering the same HIV-1 Envelope (Env) gp140 (ZM96) immunogen were evaluated in mice: three poly-ICLC-adjuvanted protein: soluble Env, CD40-targeted Env (CD40.Env, previously evaluated in humans), and Env nanoparticles (NP.Env), together with mRNA.Env (Moderna Access Program) and MVA.Env. Animals were immunized on days 0 and 21 and followed until month 8. Early innate responses were assessed by serum cytokine/chemokine profiling 6h post-immunizations and phenotypic analysis of myeloid cells in draining lymph nodes 24 h after priming. Adaptive responses were assessed longitudinally through Env-specific IgG subclass profiling, GC B-cell responses, and Env-specific CD4⁺ and CD8⁺ T-cell responses by IFN-γ ELISpot and ICS.
Results
Despite delivering the same antigen, vaccine platforms elicited distinct immune trajectories. CD40.Env and NP.Env induced strong early antibody responses with distinct IgG subclass profiles, while CD40.Env, NP.Env and mRNA. Env generated robust Env-specific GC B-cell responses. All platforms elicited Env-specific CD4⁺ T-cell responses, whereas only mRNA.Env induced detectable CD8⁺ T-cell immunity. CD40.Env, NP.Env and MVA.Env maintained durable antibody responses through month 8. Early innate responses also differed markedly between subunit vaccines, mRNA and MVA vaccines, with distinct systemic cytokine/chemokine profiles and activation of myeloid cells within draining lymph nodes.
Conclusion
Vaccine platforms are not passive antigen delivery systems but establish distinct innate immune programs that shape the quality and durability of HIV-specific adaptive responses. Ongoing integrative systems immunology analyses seek to identify innate immune signatures predictive of adaptive immune magnitude and durability, providing mechanistic insights into vaccine-induced immunity and guiding the rational design of next-generation HIV vaccines.

Keywords: Vaccines - Vaccine platforms - HIV.

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PS3-P10

HPV16 tumor control in mice through anti-CD40 targeting HPV16.E6/E7 vaccine combined with anti-PD-1

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Objective
Persistent high-risk Human papillomavirus (HPV) infections are responsible for approximately 5% of global cancers, particularly cervical, anogenital, and oropharyngeal (OPC). Therapeutic options for established HPV-associated malignancies remain limited. The CD40.HPV16.E6/E7 vaccine targets E6/E7 oncoproteins to antigen-presenting cells through a monoclonal anti-CD40 antibody. Phase 1/2a clinical trial demonstrated a good safety and immunogenicity profiles in patients with OPC after curative therapy (NCT 2022-502930-25-00). Further development would combine CD40.HPV16.E6/E7 with an immune checkpoint inhibitor (anti-PD-1). We aimed to evaluate antitumoral effect of this combination in a murine model of HPV-induced cancer.
Methods
Human CD40 Transgenic C57BL/6 mice (hCD40Tg) were subcutaneously engrafted with TC-1 tumor cells expressing HPV16.E6/E7. Five days post-graft, mice received CD40.HPV16.E6/E7+poly-ICLC at d0, d7, d14, d21 and d28 +/- anti-PD-1 (every 2 days). Control mice received either PBS, poly-ICLC adjuvant alone or anti-PD-1 alone (every 2 days). Tumor growth and survival were monitored. Splenic and tumor infiltrating T cell responses were characterized by IFN-γ ELISpot and E7-specific $CD8^+$ T cells H-2Db/HPV16 E7 tetramers.
Results
The vaccine alone slowed tumor growth and improved mice survival compared with the control groups. Control mice reached a tumor volume of 700 mm^3 by approximately day 16, whereas this threshold was delayed to day 29 in both vaccinated groups (vaccine alone and vaccine + anti-PD-1). All control animals were euthanized by approximately day 28, compared with day 46 for the vaccine-alone group. Combining the vaccine with anti-PD-1 further enhanced antitumor efficacy, resulting in complete tumor regression in 20% of the animals. Systemic and intratumoral anti-E6/E7 IFNg-secreting T cell responses were detected in vaccine + aPD1 group, with predominant responses against E7 in tumors. Up to 60% of total CD8+ T cells were E7 specific CD8+ T cells in tumors with no improvement with anti-PD-1 treatment.
Conclusion
The CD40.HPV16.E6/E7 vaccine was immunogenic inducing systemic and tumor E6/E7 specific CD8+ T cells, tumor control growth and improved survival. Anti-PD1 combination enhanced tumor regression. These findings, and previous clinical data, support further combination of CD40.HPV16.E6/E7 with anti-PD-1 in clinical trials for HPV-positive cancer patients.

Keywords: CD40.HPV16.E6/E7 vaccine - Anti-PD-1 immunotherapy - HPV-associated cancer.

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PS5-P01

HBV-induced modulations in DC subsets reprogram NK cell responses

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Objective
Infection with hepatitis B virus (HBV) is a significant global health concern, often progressing to chronic infection in individuals unable to mount an effective immune response. Natural Killer (NK) cells and Dendritic cells (DC) are a prominent arm of innate immunity and defence against viral infections, but their functions are compromised in HBV patients. The mechanisms through which HBV disrupts the DC-NK cell interactions remain unclear. We aimed to address this gap by exposing distinct DC subsets to HBV and examining the subsequent effects on NK cell cytokine, chemokine and ICM secretion, their phenotype, activity, and functionality.
Methods
We investigated how human HBV influences the interplay between cDC1, cDC2 and pDC subpopulations and NK cells. Blood-derived DC subsets from healthy donors were exposed to HBV, then co-cultured with NK cells under different stimulation conditions. NK cell phenotype, function and secreted factors were analysed. In parallel, serum from patients with acute and chronic HBV, as well as healthy donors, was assessed for immune mediators.
Results
HBV-exposed DCs altered NK cell phenotype without affecting degranulation, and significantly changed cytokine and soluble immune checkpoint secretion in a subset-specific manner. Preexposure of cDC1 to HBV enhanced NK cell secretion of MCP-1, MIP-1α, MIG, and IP-10 through TLR3-dependent pathways, while reducing sCTLA-4, sLAG-3, and sGITR release. Similarly, cDC2 pre-exposure promoted NK cell production of MCP-1, MIP-1α, and MIP-1β *via*TLR7/8-dependent mechanisms. HBV-conditioned pDCs reduced NK cell secretion of IFN-γ, sCTLA-4, sLAG-3 and sGITR. Serum analysis demonstrated a systemic increase in cytokine levels during acute HBV infection, with MIG levels showing a positive correlation with viral load.
Conclusions
These findings reveal novel mechanisms by which HBV disrupts DC–NK cell communication, contributing to immune evasion.

Keywords: DC-NK crosstalk - Hepatitis B virus - Immunophenotyping.

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PS6-P01

Metabolic profiling of circulating and tumor-infiltrating T cells uncovers bioenergetic checkpoints linked with immune and clinical skewing in melanoma patients

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Metabolism is critical for immune cell functions. Tumors shape their microenvironment to render it metabolically hostile for infiltrating immune cells. While targeting immunometabolism emerges as a promising way to reinvigorate anticancer immunity, a deeper understanding of the metabolic disturbances of immune cells is needed. Here, we explored how the metabolic status of T cells governs immune skewingfrom circulating and tumor-infiltrating CD4$^+$ and CD8$^+$ T cells of melanoma patients at a single-cell level using the SCENITH method and targeted metabolomics. Circulating and tumor-infiltrating T cells from patients displayed a decreased mitochondrial dependency associated with an enhanced glycolytic capacity and a skewed metabolic reprogramming upon stimulation. Such metabolic disturbances were linked to the activation status, immune checkpoint profile and functional orientation of T cells, underlining critical connections between T-cell features and metabolic patterns. Targeted metabolomics within sorted CD4$^+$/CD8$^+$T cells identified a decrease in citrulline, cysteine and threonine within all subsets in patients, together with a sharp rise in sterol cholesterol CE(20:2) and ceramide dhCer(d18:0/22:0) within tumor-infiltrating CD4$^+$ T cells, and in glycerolipid DG(16:0/16:0) within CD8$^+$ T cells in blood and tumor. We further outlined a metabolic-checkpoint-based signature composed of six genes coding enzymes/transporters connected to the imbalanced metabolites found within tumor-infiltrating T cells (*LIPA*, *DGKA*, *GLUL*, *SLC38A1*, *SLC7A7*, *GCH1*) that shape patients' clinical outcome. These findings outline the skewed bioenergetic profiles of T cells and depict metabolic checkpoints associated with immune subversion. Harnessing metabolic pathways is promising for developing innovative therapies to restore optimal anti-tumor responses and improve clinical success.

Keywords: Immunometabolism - Melanoma - T cells.

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PS6-P02

Identifying metabolic requirements for Treg and CD8+ T cell intratumoral motility

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Objectives
T cell infiltration and migration within the tumor microenvironment (TME) are major determinants of efficacy of T cell-based immunotherapies. The team previously showed that cytotoxic CD8+ T cell (CD8+) intratumoral motility depends mainly on mitochondrial metabolism[1]. Unfortunately, the TME can be infiltrated by immunosuppressive T cells too, notably regulatory T cells (Tregs). These cells directly interact with and suppress cytotoxic T cells, preventing tumor eradication. Of note, metabolic requirements for Treg motility in solid tumors remain poorly characterized, with previous studies mainly performed in 2D models. Therefore, our aim is to characterize Treg motility in a solid tumor mass in comparison with that of CD8+ T cells. Addressing this point is important, as the identification of unique metabolic preferences regulating Treg *vs*. CD8+ T cell intratumoral motility would allow us to develop more precise metabolic intervention to restore cytotoxic T cell activity and tumor eradication.
Methods
Tregs and CD8+ T cells were isolated by magnetic sorting, activated with TransAct (anti-CD3/CD28) and expanded with IL-2. Treg purity and suppressive capacity were assessed by flow cytometry and a Treg-CD8+ suppression assay. Motility was analysed by live-imaging microscopy following Calcein green/red labelling in presence of nutrients and drugs targeting main metabolic pathways using (*i*) a 3D collagen gel and (*ii*) viable tumor slices derived from preclinical human xenograft tumor model.
Results
After protocol optimization, we obtained Tregs with 80–85% purity up to 10 days of *in vitro* culture and confirmed suppressive capacity. Nicely, Tregs and CD8+ T cells displayed a differential dependence on glucose and glutamine utilisation to migrate in a 3D collagen gel. This was confirmed also through the use of specific inhibitors of glycolysis and glutaminolysis pathways. In addition, Tregs seems to depend more on fatty acid oxidation to support their 3D motility. Preliminary data using viable tumor slices from a preclinical human xenograft tumor model confirmed these results.
Conclusion
Our initial results indicate distinct metabolic requirements for Treg and CD8+ T cell motility. Further experiments will determine whether these differences can be exploited to promote CD8+ T cell infiltration while limiting Treg infiltration in solid tumors, thereby opening new avenues for the optimization of immunotherapies.

Keywords: T cell motility - T cell metabolism - Tumor microenvironment.

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PS6-P03

Impact of pyruvate availability and ER-stress on the crosstalk between plasmacytoid dendritic cells and fibroblasts

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Objectives

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by immune dysregulation, vasculopathy, and fibrosis. Plasmacytoid dendritic cells (pDCs) are key players in fibrotic progression in SSc, and recent studies found that pDCs from patients with SSc display altered ER-stress responses [1]. In addition, pDC metabolism has been suggested to play a role in SSc [2] and pyruvate availability is crucial for optimal IFN response in human pDCs.[3] Importantly, previous work from our lab showed that CAL-1 pDCs co-cultured with IMR-90 fibroblasts and exposed to SubAB, an ER stress inducer, promoted fibroblast activation. [4] Thus, our goal was to analyze the role of nutrient availability and metabolic modulation in the pDC – fibroblast crosstalk under ER stress.

Methods

In this work, we used a human pDC cell line (CAL-1) and a human lung fibroblast line (IMR-90). CAL-1 cells were pre-treated with HA-15 (a BiP/GRP78 inhibitor) before co-culturing with IMR-90 for 24h or 48h. To assess the impact of metabolic modulation, experiments were performed with and without pyruvate supplementation. mRNA expression and protein levels of fibronectin, α-SMA and FAP (fibroblast activating protein) were analyzed by qPCR and Western blot. NMR-based metabolomics was also performed on CAL-1 treated with HA-15 for 24h to characterize their endo- and exometabolomic profiles.

Results

Pyruvate deprivation on its own promoted a fibrotic phenotype in co-cultures, even in the absence of ER stress induction, particularly affecting α-SMA expression and protein levels. In the presence of pyruvate, HA-15-induced ER-stress resulted in a clear increase in fibronectin, α-SMA and FAP at both the mRNA and protein levels. Importantly, the same effects were not observed in IMR-90 monocultures, where neither HA-15 nor pyruvate deprivation resulted in significant increases in fibrotic markers. Metabolomics analysis of CAL-1 pDCs showed a distinct metabolic profile following HA-15 treatment, including changes in amino acid metabolism, energy/redox homeostasis and one-carbon metabolism.

Conclusion

These results suggest that pDC–fibroblast interactions are metabolically regulated, with pyruvate availability and ER stress shaping the outcome of these cultures. NMR-based metabolomics further highlights metabolic alterations associated with HA-15 treatment in CAL-1 pDCs and may help identify potential new targets against pDC-mediated tissue fibrosis under ER stress.

Keywords: Fibrosis - ER-stress - Immunometabolism.

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Impact of RNA modifications in CD4⁺ T cell differentiation and function

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Objectives
CD4⁺ T cells differentiate into specialized T helper (Th) subsets in response to different immune challenges. This process is orchestrated by complex rearrangements of gene expression, regulated in particular by epigenetic mechanisms. Furthermore, epitranscriptomic mechanisms also contribute to this regulation by modulating gene expression via post-transcriptional modifications on RNAs. Similarly to epigenetic modifications, these epitranscriptomic modifications are regulated by "writers" that imprint the mark, "erasers" that remove it, and "readers" that translate this signal into biological functions. Although epitranscriptomic regulation has emerged as an important layer controlling CD4⁺ T cell activation and differentiation, the roles of most epitranscriptomic enzymes remain poorly understood. We therefore aimed to identify and characterize novel epitranscriptomic regulators of CD4⁺ T cell differentiation and function.
Methods
We combined analysis of epitranscriptomic enzyme expression across different Th subsets with targeted CRISPR/Cas9 screening in naïve CD4⁺ T cells, followed by Th differentiation and phenotypic analysis. Native long-read RNA sequencing using nanopore technology was further used to identify potential target transcripts. The role of the identified enzyme was subsequently investigated in vivo using a transgenic mouse model.
Results
We identified a novel methyltransferase as a key regulator of Th17 and Treg differentiation. Its deletion impaired Th17 differentiation, as evidenced by reduced RORγT expression and IL-17 production, while promoting Treg differentiation, with increased expression of Treg-associated markers, including the master transcription factor FoxP3 and CD25 subunit. Loss of this enzyme also altered the metabolic program of Treg cells, increasing translation and mitochondrial activity while reducing glycolytic pathways and enhancing serine-glycine-one-carbon metabolism. Its critical role was confirmed in vivo by using a transgenic mouse model.
Conclusion
We identified a novel epitranscriptomic regulator of Th cell differentiation and function in vitro and in vivo. This methyltransferase regulates T cell metabolism and translation and controls the balance between Th17 and Treg differentiation. Our findings uncover a previously unrecognized link between epitranscriptomic regulation, cellular metabolism, and T cell fate.

Keywords: CD4+ T cells - Epitranscriptomic - Metabolism.

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PS6-P05

Deciphering the antitumor activity of *P. distasonis*: Impact of its metabolites on tumor and T cells

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Metabolic dysregulation plays a critical role in shaping the tumor immune microenvironment and microbiota. Our team recently demonstrated that IL4I1, a phenylalanine-catabolizing enzyme, promotes tumor-associated dysbiosis and alters the bacterial composition in mice transgenic for the RET oncogene, thereby contributing to tumor aggressiveness in this spontaneous metastatic melanoma model. Notably, administration of *P. distasonis,* a bacterium markedly enriched in IL4I1-deficient RET mice, controlled more efficiently the growth of cutaneous as well as lung metastases in RET mice and was associated with remodeling of the tumor-infiltrating T-cell compartment.
P. distasonis appears to exert its antitumor effect through multiple mechanisms. First, bacterial treatment failed to delay tumor growth in immunodeficient CD3KO and NSG mice transplanted with melanoma cells derived from a RET metastasis, highlighting a critical role for the lymphoid compartment, and more specifically T cells. Treatment with heat-killed *P. distasonis* significantly delayed melanoma growth to a lesser extent than alive bacteria, suggesting that part of its antitumor mechanism comes from bacteria-derived metabolites. Targeted HPLC-MS metabolomic analyses revealed increased relative abundances of fatty acids and purine pathway metabolites in serum and metastases from RET mice treated with *P. distasonis* compared to control RET mice. We next assessed immuno-regulatory and antitumor properties of one metabolite from each pathway using complementary readouts. Our preliminary data show that the fatty acid directly impairs the viability of melanoma cell lines and that its exposure decreased the exhaustion of T cells chronically stimulated with anti-CD3/anti-CD28 to mimic the tumor microenvironment. Using real-time imaging, we further observed that both metabolites potentiate T-cell cytotoxicity against melanoma cells. Finally, their *in vivo* administration significantly delayed melanoma outgrowth, associated with remodeling of dendritic cells and T cell subsets within the tumor microenvironment as shown by spectral cytometry analysis.
Collectively, these results suggest that *P. distasonis*-mediated tumor control involves metabolites contributing to both direct tumor cell inhibition and enhanced T-cell function and pave the way for the development of novel treatments combining metabolites and immune checkpoint targeting.

Keywords: Metabolites - Anti-tumor Immunity - T cells.

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PS6-P06

Deciphering the Metabolic Programs Underlying Eomes⁺ Th Cell Adaptability

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Our recent work identified Eomes as a key regulator of progenitor Th cells that give rise to a distinct exhausted-like CD4⁺ Th cell lineage that differs transcriptionally and functionally from conventional Th cells (1). This program is reinforced by 4-1BB signaling and promotes tumor control. Eomes⁺ Th cells accumulate in tumors following immunotherapy and maintain effector functions despite severe metabolic stress, suggesting exceptional metabolic fitness (2). We aim to identify the metabolic pathways and sensors underlying their enhanced adaptability and link them to the Eomes transcriptional program.
Eomes⁺ Th cells were expanded in Eomes-GFP reporter mice following anti-4-1BB treatment, and Eomes+ and Eomes- CD44hi CD4⁺ T cells were isolated for in vitro analyses. Targeted metabolomics and lipidomics using mass spectrometry and NMR were performed to characterize Eomes⁺ and Eomes⁻ Th cells under control and mitochondrial stress conditions. In parallel, multi-omic analyses, including ATAC-seq and CUT&RUN, DNA footprinting identified Eomes-regulated metabolic genes. Next, stable isotope tracing of glucose, glutamine and palmitate will next define metabolic fluxes and candidate enzymes and metabolic sensors will be validate by CRISPR-Cas9 .
Our results demonstrated that Eomes⁺ Th cells showed increased resistance to mitochondrial stress induced by rotenone and antimycin A in a glutamine-dependent manner. RNA-seq revealed increased expression of glutaminolysis enzymes, suggesting enhanced anaplerosis. Preliminary metabolomics identified specific metabolic reprogramming under mitochondrial stress, including increased glycerol-3-phosphate, a metabolite of the glycerol-3-phosphate shuttle involved in redox control and linked to glycerophospholipid metabolism. scRNA-seq further revealed upregulation of glycerophospholipid-related genes, including LPIN1, AGPAT, FAR1 and lipid transporters FABP4 and LRP8. LPIN1 produces DAG, a key lipid second messenger downstream of TCR signaling.
Our data suggest that Eomes⁺ Th cells acquire metabolic flexibility through coordinated glutamine-dependent anaplerosis, mitochondrial shuttles, lipid uptake and glycerophospholipid metabolism. These pathways may enable them to withstand tumor-associated metabolic stress while maintaining effector functions. Integrating metabolic, multi-omic and genetic approaches will identify key metabolic regulators and potential therapeutic vulnerabilities.

Keywords: Eomes - Metabolism - Mitochondrial stress.

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PS6-P07

Molecular and metabolic profiling of cerebrospinal fluid EOMES expressing CD4+ T cells in early multiple sclerosis

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Background and Objectives
Disability worsening in multiple sclerosis (MS) involves new lesion formation, compartmentalized inflammation, and neurodegenerative processes. Early recruitment of immune populations into the central nervous system (CNS) may contribute to persistent inflammation through tissue adaptation and long-term survival. EOMES-expressing CD4 (EOMES CD4) T cells have been implicated in pathogenicity and enhanced persistence in experimental models of neuroinflammation (EAE), yet their role within the CNS at MS diagnosis remains poorly defined. We aimed to characterize key features of EOMES CD4 T cells at MS onset and identify mechanisms potentially supporting their persistence in the CNS.
Methods
Single-cell RNA sequencing (scRNA-seq) was performed on i) paired peripheral blood mononuclear cells (PBMCs) and cerebrospinal fluid (CSF) collected locally at diagnosis from patients with MS (n = 6) or viral meningitis (n = 4), ii) CD4 T cells infiltrating the CNS of EAE mice, and iii) publicly available datasets from individuals with neurological diseases. EOMES CD4 T cells frequencies were compared across human neurological disease cohorts. Their transcriptional and metabolic features were characterized in MS and EAE and validated ex vivo using human PBMCs. EOMES CD4 T cells clonality and cellular interactions were also investigated.
Results
EOMES CD4 T cells were heterogeneous and comprised distinct CCR5-positive and CCR5-negative subsets, both enriched in the CSF of individuals with neurological diseases. Their CSF enrichment was associated with enhanced migratory features, clonal expansion, and stronger interactions with B cells, including atypical B cells (ABCs). EOMES CD4 T cells also displayed a metabolic shift from glycolysis toward lipid metabolism and increased mitochondrial activity, observed in both MS and EAE and reproduced ex vivo in human PBMCs, suggesting metabolic adaptation compatible with enhanced persistence.
Conclusion
EOMES CD4 T cells represent heterogeneous, clonally expanded, and metabolically adapted CD4 T cell subset that accumulate in the CSF at MS diagnosis. Their interaction with ABCs and metabolic adaptation may contribute to their persistence within the CNS and sustained inflammation. Targeting mechanisms underlying EOMES CD4 T cells recruitment or metabolic adaptation may therefore represent a therapeutic strategy to limit early CNS inflammation and potentially subsequent disease progression.

Keywords: Multiple sclerosis - EOMES CD4 T cells - Metabolism.

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Control of regulatory T cell stability during inflammation by adenosine signaling

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Objective
Regulatory T (Treg) cells generate extracellular adenosine, which contributes to immune suppression through activation of the adenosine A2A receptor (A2aR) on effector cells. Whether adenosine also acts directly on Treg cells to control their function and stability remains unclear. We investigated the Treg-intrinsic role of A2aR signaling in immune homeostasis and autoimmunity.
Methods
We generated mice with Treg-specific deletion of A2aR (Adora2a-ΔTreg) and assessed immune homeostasis during aging and susceptibility to experimental autoimmune encephalomyelitis (EAE). Treg phenotype, suppressive function and stability were investigated by flow cytometry, single-cell RNA sequencing and lineage tracing. A2aR-dependent signaling pathways were examined in Treg cells.
Results
While young Adora2a-ΔTreg mice showed no major abnormalities at steady state, aged mice spontaneously developed systemic lymphoproliferation and lupus-like autoimmunity, characterized by T- and B-cell activation and increased anti-dsDNA antibodies. Adora2a-ΔTreg mice also developed more severe EAE, with impaired Treg suppressive function and increased IL-17- and IFN-γ-producing CD4 T cells in the central nervous system. Single-cell RNA sequencing revealed that A2aR-deficient Treg cells acquired a Th17-like transcriptional program during autoimmune inflammation. Lineage tracing confirmed loss of Foxp3 expression and generation of ex-Treg cells producing IL-17 and IFN-γ. Mechanistically, A2aR signaling sustained intracellular cAMP and CREB phosphorylation, promoting SOCS3 expression and restraining acquisition of the Th17 program.
Conclusion
A2aR signaling has a previously unrecognized Treg-intrinsic role in maintaining Treg stability. By preventing conversion of Treg cells into pathogenic effector cells, the adenosine-A2aR pathway preserves immune tolerance during inflammation and aging.

Keywords: Regulatory T cell - Signaling - Inflammation.

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PS7-P02

Mapping the development pathways of human unconventional T cells

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Unconventional T cells (UTCs) including Natural Killer T (NKT) cells, Mucosal-Associated Invariant T (MAIT) cells, gamma delta (γδ) T cells, and group 1 CD1-restricted T cells, represent up to 10% of T cells in human blood and tissues. They are known for rapid, potent cytokine and cytotoxic responses that collectively bridge innate and adaptive immunity. Defects and deficiencies in UTCs are associated with increased incidence and severity of many diseases, including cancers and infections. It has long been hypothesized that some of these defects originate during UTC development in the thymus, but a poor understanding of this process has hampered efforts to target these pathways to increase UTC frequency and function.
Our group has published a series of influential papers, including in *Nature Immunology* and *Science Immunology,* defining the development of human MAIT cells and Vδ2+ γδ T cells, revealing a pivotal role for the thymus and identifying the gene networks underpinning UTC development in humans. Extending this work, and that of our earlier studies characterizing human NKT cell development, we have now used a range of cutting-edge technologies to enrich NKT cells from human thymus and delineate a four-stage, unidirectional developmental pathway. The earliest immature thymic iNKT cells expressed CD1a, with maturation to later stages marked by sequential upregulation of CD27 and then CD161. As seen for MAIT and γδ T cell development pathways, PLZF expression increased with maturation, coinciding with the acquisition of TNF, IL-2, and Granzyme A/K expression. Strikingly, we unexpectedly find that human iNKT cells primarily adopt a Th1 phenotype, in contrast to mouse iNKT cells, which display Th1, Th2, or Th17 subsets.
Together, this work sheds new light on the developmental pathways of human UTCs and identifies new opportunities to specifically target these cells for the treatment or prevention of conditions associated with UTC disorders.

Keywords: Unconventional T cell - thymus - T cell development.

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PS7-P03

GDE3 controls splenic marginal zone B cells positioning and plasmablast differentiation

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Splenic marginal zone (MZ) B cells are a subset of B lymphocytes involved in T cell-independent immune responses. They play an important role in the early defense against blood-borne pathogens through the rapid production of low-affinity IgM antibodies upon differentiation into plasmablasts. Although mainly located in the splenic MZ, MZ B cells continuously shuttle between the MZ and the follicle, a process controlled by CXCR5/CXCL13-mediated attraction to the follicle and S1P/S1P1-dependent return to the MZ.
Cannabinoid receptor 2 (CB2) also contributes to MZ B cell positioning[1,2]. Its ligand, 2-arachidonoylglycerol (2-AG), helps retain MZ B cells within the MZ of the spleen and prevents their loss into the circulation. CB2 is part of the endocannabinoid system, a key regulator of immune responses. 2-AG, the most abundant endocannabinoid, acts as a full CB2 agonist. Recently, we have discovered a new 2-AG biosynthetic pathway involving glycerophosphodiesterase 3 (GDE3) which converts lysophosphatidylinositol (LPI), the agonist of GPR55 into 2-AG, thereby acting as a switch between the GPR55 and CB2 signaling pathways[3]. Notably, GDE3 is highly expressed by splenic red pulp fibroblasts located near MZ B cells, suggesting a potential role in regulating local endocannabinoid signaling and MZ B cell function.
To investigate the role of GDE3 in the spleen, we used GDE3-deficient (GDE3-KO) mice, characterized by impaired 2-AG synthesis and LPI accumulation. We assessed the impact of GDE3 deficiency on splenic B cells at steady state and during T-independent immune responses. Flow cytometry analysis revealed a strong decrease of MZ B cells and an expansion of plasmablasts in GDE3-KO mice compared with wild-type (WT) controls. Consistently, *in vitro* stimulation of WT B cells showed that LPI promotes plasmablast differentiation.
Following NP-Ficoll immunization, GDE3-KO mice displayed increased NP-specific antibody production associated with enhanced plasmablast expansion. *In vitro*, LPI also synergized with NP-Ficoll to further promote plasmablast differentiation.
Together, these results suggest that GDE3 deficiency leads to LPI accumulation, which promotes B cell differentiation into plasmablasts through GPR55 signaling, thereby enhancing antibody production during T-independent immune responses.
To conclude, our study highlights a physiological role for GDE3 in regulating MZ B-cell positioning and plasmablast differentiation.

Keywords: Marginal zone B cell - Spleen - Endocannabinoid.

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LAMP2 controls autophagy-lysosomal pathway for selfpeptide–MHC II processing in thymic epithelial cells to tune CD4 T-Cell Selection

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Objective

Thymic epithelial cells (TECs) provide unique microenvironments for T-cell selection by presenting unique self-peptide-MHC complexes to developing thymocytes. However, the molecular mechanisms that govern the generation of these selecting ligands remain elusive. Although the autophagy-lysosomal pathway has been implicated in CD4 Tcell selection, how it contributes to the production of the self-peptide repertoire that calibrates T cell selection remains unknown. Our previous findings identified LAMP2, a lysosomal membrane protein essential for autophagosome-lysosome fusion, as a strong candidate in thymic stromal cells for coupling autophagy to self-peptide:MHC II processing in TECs and CD4 T cell development (Autophagy 2023). Because LAMP2 is highly expressed by TECs, which directly mediate CD4 T-cell selection, we sought to define its cell-intrinsic role in coupling autophagosome-lysosome fusion to self-peptide–MHC class II processing during CD4 T-cell selection.

Methods

We generated a novel conditional Lamp2 floxed allele and Lamp2 conditional knockout (LAMP2 cKO) mice by crossing with TEC-specific Foxn1Cre mice. LAMP2 cKO were analyzed in polyclonal setting and combined them with TCR transgenic models to investigate the role of LAMP2 in TEC-mediated thymocyte selection across polyclonal and monoclonal TCR repertoires. Autophagy, lysosomal function, and self-peptide-MHC class II processing were assessed using LC3 dual-reporter mice and biochemical assays. TEC differentiation, thymocyte development, TCR signaling, and TCR repertoire diversity were analyzed by high-dimensional flow cytometry and TCR sequencing.

Results

In LAMP2 cKO mice, elective deletion of LAMP2 in TECs impaired CD4 T cell selection. Analysis of MHC class II-restricted OT-II TCR transgenic mice further demonstrated that LAMP2 is required for efficient positive selection of CD4 thymocytes. Moreover, analysis of LC3 dual-reporter mice revealed impaired autophagic flux in LAMP2deficient cortical TECs, which was associated with defects in MHC class II antigen processing. We will further present mechanistic data demonstrating how LAMP2 regulates autophagolysosomal activity and self-peptide–MHC II processing in TECs.

Conclusion

Our findings identify LAMP2 as a key regulator linking the autophagylysosomal pathway to self-peptide–MHC II processing in TECs, thereby tuning TCR signaling during CD4 T-cell selection and promoting the establishment of a diverse TCR repertoire.

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PS7-P05

MicroRNA-Mediated Post-Transcriptional Regulation of Peripheral γδ T Cell Effector Functions

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Objectives
γδ T cells are unconventional lymphocytes able to rapidly produce large quantities of interleukin-17A (IL-17A) or interferon-γ (IFNγ), which often have major effects on the pathophysiology of diseases such as cancer or infections. Yet, we do not fully understand how the thymic-derived effector γδ T cell subsets making either IL-17A (γδ^{17} cells) or IFNγ (γδ^{IFN} cells) are activated and function in peripheral tissues. Here, we aimed at analysing at unprecedented depth the microRNA (miRNA) transcriptomes of pure γδ^{17} versus γδ^{IFN} cell substes from peripheral lymph nodes, uncovering new mechanisms of miRNA-mediated post-transcriptional regulation of γδ T cell effector functions.
Methods
To do so, we established an *Il17a-GFP:Ifng-YFP* double-reporter mouse strain in order to purify γδ^{17} and γδ^{IFN} cell subsets from which we extracted RNA in order to perform RNA- and small RNA-seq. We performed functional validation of candidate miRNAs *in vitro*, which included retroviral overexpression of candidate miRNAs in peripheral γδ T cell subsets, and *in vivo*, analysing the γδ T cell repertoire of gene-deficient mouse models for selected miRNAs both under homeostasis and *Plasmodium* infection.
Results
We found 103 differentially expressed miRNAs between γδ^{17} and γδ^{IFN} cells, from which we selected 10 candidates likely to target members of the transcriptional networks underlying IL-17A of IFN-γ production, to test their effects on γδ T cell differentiation or effector functions. Retroviral gain-of-function approaches *in vitro* highlighted a plethora of context-dependent miRNA-specific effects on the differentiation or expansion of γδ^{17} or γδ^{IFN} cells, and respective cytokine production. Furthermore, a detailed analysis of each candidate miRNA expression throughout ontogeny showed that in some cases it was imprinted in the thymus, whereas in others it was peripherally induced. This led to the observation that miR-181a-5p promotes peripheral γδ^{IFN} activation and proliferation in response to TCR stimulation *in vitro*, as well as upon malaria infection *in vivo*.
Conclusion
In conclusion, γδ^{17} and γδ^{IFN} cells present different miRNA profiles, with individual miRNAs presenting distinct expression dynamics and regulatory roles. In particular, miR-181a-5p acts as a promotor of γδ^{IFN} cell response both *in vitro and in vivo*. These findings unravel a new layer of regulation of γδ T cell effector functions, which we are further characterizing with additional molecular assays.

Keywords: γδ T cells - microRNAs.

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PS7-P06

Mapping and pharmacological targeting of CISH intracellular signaling checkpoint interactions in CD8+ T cells to improve immunotherapy

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Objectives

Despite the clinical success of immunotherapies, refractory patients highlight the need for new strategies. We previously identified CISH (Cytokine Inducible SH2-containing protein) as a key intracellular immune checkpoint in CD8⁺ T cells (*1*) and NK cells (2). Recently, the first phase I clinical trial targeting CISH genetically in tumor-infiltrating lymphocytes from metastatic gastrointestinal cancer resulted in a complete response in a stage IV colon cancer patient (3). Our aim is to better understand CISH biology in T cells to target it pharmacologically and improve T cell functions.

Methods

We developed a novel CISH-OST K*nock-In* mouse model and performed pull-down assays to identify CISH interactors by mass spectrometry (MS) analysis. OT-I expressing Cas9 mice were used to knock out genes of interest and test T cell functions. We performed a high-throughput screening of protein-protein interaction (PPI) inhibitors targeting the most promising CISH interaction.

Results

CISH-OST mice exhibit the same T cell development and phenotype as WT mice. By performing a time-course stimulation with high-dose IL-2, we mapped the first physiological CISH interactome, allowing us to visualize the dynamic assembly of the protein complex around CISH. This analysis revealed four previously known partners and four new partners of interest. The main interactions were further validated by immunoprecipitation and western blot. Furthermore, CISH KO T cells showed increased production of TNF-α, IFN-γ, and GZMB, one partner KO regulating CISH favored T cell inhibition. We then pharmacologically targeted a CISH interaction favoring T cell inhibition using a high-throughput screen and identified 9 promising PPI inhibitors.

Conclusion

This study characterizes the physiological CISH interactome and the functional impact of its partners on T cell activity. Furthermore, the identification of PPI inhibitors disrupting CISH function offers a promising avenue to reinforce CD8⁺ T cell-based immunotherapies.

Keywords: Cytotoxic T cells - Intracellular immune checkpoint - Signaling.

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Genetic Traits Underpin T Cell Antigen Recognition

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Antigen recognition by CD4 T cells is central to allergic inflammation, yet the molecular rules governing clonal selection and immunodominance of allergen-reactive T cells remain elusive. Classical models posit that antigen specificity is primarily encoded within the CDR3 region of the T cell receptor (TCR), a stochastically generated element unique to each clone. However, whether germline TCR segments contribute to shaping allergen-specific CD4 T cell responses has not been systematically addressed.
Using a murine house dust mite (HDM) allergy model, we discovered that allergen-specific CD4 T cell responses are unexpectedly dominated by stereotyped clonotypes relying on defined germline-encoded V and J gene segments. These biases were reproducible across independent cohorts and immunization protocols, suggesting that single germline TCR alleles may exert non-redundant control over CD4 T cell immunodominance, a concept well established for invariant NKT or MAIT cells, but largely unexplored for conventional helper T cells in disease settings. Beyond this tetramer-defined population, unbiased scRNA-seq of airway-infiltrating CD4 T cells revealed dominant clonotype families representing up to 12% of total bronchoalveolar lavage CD4 T cells across six mice. We are now leveraging CRISPR-Cas9 mouse genetics to establish causality between specific germline alleles and allergen-driven CD4 T cell responses, combined with structural characterization of dominant TCR–pMHC-II interactions. On the human translational side, we developed and validated an activation-induced marker (AIM) assay to identify HDM-reactive CD4 T cells and their TCR clonotypes in an HLA-dependent manner. This pipeline is being deployed in a family and homozygotic twin-based cohort of HDM-allergic patients to investigate whether heritable germline TCR usage patterns shape human allergen reactivity. We are also extending our observations beyond HDM to antigens derived from viral, fungal and other environmental sources.
This project sits at the interface of TCR repertoire biology, structural immunology, and translational allergology. By redefining how genetic traits shape CD4 T cell antigen recognition, our work opens perspectives for clonotype-directed immunotherapies that could selectively target pathogenic allergen-reactive T cells while preserving protective immunity, a paradigm shift from broad immunosuppression toward precision immune modulation in allergic diseases.

Keywords: Acquired immunity - Mice & Humans - TCR repertoire.

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PS7-P08

Foxo1 restrains naive CD4 T cell differentiation into type 1 and type 2 effector cells bysuppressing early cytokine production

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Foxo1 is a critical transcription factor for T cell survival, trafficking, and memory responses. However, its role in naive CD4 T cell differentiation remains unclear. Here, we show that Foxo1 restrains naive CD4 T cell differentiation into TH1/TH2 effector cells by suppressing early cytokine production. Foxo1TKO mice exhibit increased TH1/TH2 effector cells in secondary lymphoid organs and elevated plasma IFN-γ/IL-5 levels. Foxo1-deficient naive CD4 T cells readily differentiate in vitro into TH1/TH2 cells, even in the absence of polarizing cytokines.
Mechanistically, this bias arises from rapid and robust early production of IFN-γ, IL-4, and IL- 13 upon activation, which establishes a positive feedback loop amplifying their polarization potential. Neutralizing IFN-γ or IL-13 reduces TH1/TH2 differentiation, while IFN-γ supplementation enhances TH1 differentiation in Foxo1-sufficient cells. Enhanced STAT3 phosphorylation in response to IL-4 underlies the increased TH2 potential of Foxo1-deficient cells. These findings reveal Foxo1 as a global gatekeeper, preventing premature and uncontrolled naive CD4 T cell differentiation into effector lineages, ensuring immune responses align with environmental cues.

Keywords: Foxo1 - CD4 T cells - Th1/Th2 differentiation.

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PS7-P09

The RNA-Binding Proteins TIA1 and TIAL1 shape T cell activation and function

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T cell recognition of an antigen triggers extensive transcriptional and post-transcriptional remodelling, shaping T cell activation and differentiation for effective vaccines and immunotherapies. Emerging evidence shows the prominent role of post-transcriptional mechanisms mediated by RNA-binding proteins (RBPs) in fine-tuning T cell function. Our recent studies uncovered the RBPs T-cell antigen 1 (TIA1) and like 1 (TIAL1) as essential players for B-cell expansion and selection in germinal centres[1], but their roles in T cells remain largely unexplored. We hypothesise that TIA1 and TIAL1 are components of a post-transcriptional regulatory program essential for T cell signalling and activation.
To validate this hypothesis, we used conditional knockout mice to evaluate the cell-intrinsic roles of TIA1 and TIAL1 in different models of T cell activation, such as vaccination with model antigens, and syngeneic tumour models. We further combined in vitro functional assays, including calcium influx and phospho-protein analyses by flow cytometry, to dissect the impact of TIA1 and TIAL1 deficiency in TCR signalling. To identify the molecular mechanisms regulated by TIA1 and TIAL1, we integrated state-of-the-art techniques such as Individual Crosslink Immunoprecipitation (iCLIP), LC-MS-based Proteomics and RNA Sequencing.
Phenotypic characterisation of T lymphocytes revealed a critical role for TIA1 and TIAL1 in early T cell activation. Consequently, the absence of TIA1 and TIAL1 in T lymphocytes resulted in defective germinal centre responses and uncontrolled tumour growth, highlighting the importance of those RBPs for effective adaptive immunity and anti-tumour responses. At the molecular level, conditional knockout of TIA1 and TIAL1 altered the expression of MYC, SKAP1, FYB and PKC-θ, which are key TCR modulators for thorough activation. Together, these findings identify TIA1 and TIAL1 as important post-transcriptional regulators of T cell function, linking RNA regulation to the control of TCR-driven responses. Understanding the crucial functions of TIA1 and TIAL1 in T cells may uncover new regulatory nodes that could be exploited in developing innovative immunotherapies.

Keywords: RNA Binding Proteins (RBPs) - T cell activation - TCR signalling.

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PS7-P10

Post-transcripitonal regulation shapes Tregs development

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Regulatory T cells (Tregs) have an essential role in maintaining immune homeostasis and prevent autoimmune diseases. Their development occurs through a two-step process involving T-cell receptor (TCR) activation followed by Interleukin-2 (IL2) signaling. This complex development of Tregs make them susceptible to suffer transcriptional and post-transcriptional regulation where RNA-binding proteins (RBPs) play a main role.
We hypothesize that the RBPs TIA1 and TIAL1 regulate systemic and mRNA target-specific changes in gene expression during Treg development. To investigate this hypothesis, we used conditional TIA1/TIAL1 knockout (KO) mice to clarify how post-transcriptional regulation contributes to Treg development and functions.
TIA1 and TIAL1 are progressively expressed upon TCR recognition of self-MHC, and in their absence results in a significant reduction in thymic Tregs progenitors and mature Tregs, potentially compromising the immune response. Interestingly, TCR activation and downstream signaling were not affected in the absence of TIA1 and TIAL1, suggesting that the TCR signal threshold required for Treg linage commitment remains normal. By contrast, sc-RNA seq analyses revealed impaired progression toward mature, IL2-responsive Tregs; suggesting that TIA1 and TIAL1 contribute to the transition of Treg progenitors into mature IL2-responsive Tregs.
Identification of RNA targets by TIA1 and TIAL1 is necessary to understand how post-transcriptional regulation shapes Tregs development. Bulk RNAseq combined with iCLIP-seq identified *Il2ra*(CD25) mRNA as a target of TIA1 in Tregs, indicating that upon TCR stimulation, IL2 response is at least partially dependent on TIA1 and TIAL1. In fact, the absence of TIA1 and TIAL1 resulted in a significant reduction in IL2Rα (CD25) protein expression in mature Tregs as measure by FACs, without affecting *Cd25* mRNA levels in Tregs, suggesting that TIA1 and TIAL1 might regulate Treg development by controlling the translation of *Il2ra*.
To summarise, our data highlight an important role of the RBPs TIA1 and TIAL1 in the regulation of Tregs development and immunity. Defining the functions and mRNA targets of TIA1 and TIAL1 in Tregs cells may uncover novel post-transcriptional mechanisms governing immune regulation which could be exploited in the development of innovative immunotherapies against disease.

Keywords: Tregs - IL2 - Post-transcriptional regulation.

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PS7-P11

T cell fate is controlled by the functional interplay between the Ikaros and Foxo1 transcription factors

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T lymphocytes are central actors that orchestrate the immune response. There are two major types of T cells, helper CD4 T cells and cytotoxic CD8 T cells. T cell fate is finely regulated by a network of transcription factors. Among these, Ikaros is a key regulator, that maintains the quiescent state of CD4 T cells while limiting their activation and pro-inflammatory function. Nevertheless, the mechanisms by which Ikaros regulates T cell homeostasis remain poorly understood. Previous results from the team have shown that among the genes overexpressed upon loss of Ikaros, a high proportion possess binding sites for the transcription factor Foxo1. This led us to hypothesize that these two transcription factors may act coordinately to control the transcriptional program of CD4 T cells. To study the functional interaction between Ikaros and Foxo1 during CD4 T cell activation, we used mouse models based on the Cre-LoxP recombination system to inactivate their genes. We found that CD4 T cells lacking both Ikaros and Foxo1 lose their naive phenotype and adopt an effector phenotype. In addition, transcriptomic studies revealed that upon activation via the T Cell Receptor and the co-stimulatory protein CD28, mutant CD4 T cells express genes that are part of the signature of cytotoxic T cells. Together, our data highlight a functional cooperation of Ikaros and Foxo1 as key factors, not only for maintaining the naive T cell homeostasis, but also for repressing the programming of CD4 T cells toward a CD8- like cytotoxic phenotype. This finding places Ikaros and Foxo1as guardians of CD4 T cell fate.

Keywords: CD4 T cells - Transcription factors.

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PS7-P12

KLF15 is a novel regulator of thymic epithelial cell microenvironments that sustain T cell development

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Thymic epithelial cells (TECs) orchestrate T cell development and selection, ensuring the generation of a functional diverse, self-MHC-restricted and self-tolerant T cell receptor (TCR) repertoire capable of responding to foreign antigens[1]. Yet, the TEC microenvironment is vulnerable to ageing and cytoablative therapies[2], underscoring the need to identify key regulators that can be harnessed to preserve or restore TEC function *in vivo*. Guided by transcriptomic analyses, we identified the transcription factor Krüppel-like factor 15 (KLF15), an essential metabolic regulator, as a candidate determinant of TEC homeostasis and central tolerance.

Using TEC-specific conditional knockout ($KLF15^{cKO}$) and fate-mapping models combined with single-cell transcriptomics, we show that KLF15 controls medullary TEC (mTEC) maintenance and functional composition, and sustains long-term thymic function. TEC-intrinsic KLF15 inactivation predominantly disrupts the integrity of the mTEC niche, markedly reducing mTEC abundance, including CCL21+ mTECs and specific post-Aire mimetic subsets. These alterations impaired regulatory T (Treg) cell differentiation and drove a progressive postnatal decline in thymopoietic activity, reducing peripheral T cell numbers. Defective embryonic mTEC maturation pointed to potential changes in TEC progenitors. Accordingly, fate mapping analysis revealed that KLF15 deficiency alters the canonical mTEC differentiation from *B*5t-expressing progenitors, and thymic organotypic cultures showed that mutant TEC progenitors have an impaired capacity to respond to mTEC-inducing signals. Mechanistically, KLF15 deletion reshapes the transcriptional landscape of the thymic epithelium, including TEC progenitors, with a shift in their metabolic programmes. Consistently, bioenergetic profiling demonstrated metabolic reprogramming of mutant TECs towards increased glycolytic ATP production. We will further present analyses addressing how these thymic defects affect peripheral immune tolerance in models of spontaneous autoimmunity.

Overall, our findings establish KLF15 as a new determinant of TEC diversification and function, with consequences for T cell immunity and tolerance, opening new avenues for understanding TEC biology and developing thymic regenerative therapies.

Keywords: Thymus - Thymic Epithelial Cells - KLF15.

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PS7-P13

Post-transcriptional control of key signalling pathways by ZFP36 RNA-binding proteins sustains thymic epithelial cell differentiation and thymic function

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Objective

The thymus generates immunologically competent T cells. Deficits in thymic activity are linked to alterations in thymic epithelial cells (TECs), which create unique thymopoietic niches. Yet, the genetic network governing the differentiation of functionally diverse TECs from common TEC progenitors remains elusive. In particular, the role of post-transcriptional mechanisms in regulating TEC turnover and lineage specification is still poorly defined. The Zinc Finger Protein 36 (ZFP36) family of RNA-binding proteins (RBPs), comprises ZFP36, ZFP36L1, and ZFP36L2. Here, we sought to define the role of ZFP36 family RBPs in TEC differentiation, and how this post-transcriptional regulatory network shapes thymic activity.

Methods

We integrated complementary Foxn1Cre and β5tCre TEC-specific conditional knockout (cKO) and fate-mapping models with single-cell transcriptomics and high-dimensional phenotypic analyses to study the cell-intrinsic function of ZFP36 RBPs in TEC biology

Results

We showed that TEC-specific deletion of *Zfp36l1* and *Zfp36l2* in two complementary dcKO mouse models led to early-onset thymic hypoplasia and a marked reduction in TEC and thymocyte numbers. Mechanistically, single-cell transcriptomics revealed significant alterations in the composition and transcriptional programs of cTECs, mTECs, and thymic mimetic cells, with a notable accumulation of age-associated TECs, and linking *Zfp36l1*:*Zfp36l2* deficiency to a widespread increase in metabolic gene dysregulation in adult dcKO TECs. The accelerated aging phenotype of TECs and abnormalities in TECs as early as embryonic life suggest a defect in TEC progenitors. Fate-mapping analysis showed that *Zfp36l1*:*Zfp36l2* deficiency caused an erosion in the canonical route of differentiation from b5t-expressing TEC progenitors (Cell Death and Differentiation 2026). More recently, recognizing the extensive homology and potential functional redundancy within the ZFP36 family, we generated TEC-specific triple conditional knockout (cKO) and showed that ablation of all RBPs resulted in a more profound thymic hypoplasia, severe impairment of T-cell development, and the emergence of autoimmunity (unpublished).

Conclusion

Our findings uncover a previously unappreciated layer of post-transcriptional regulation in TEC biology, identifying a cooperative role for ZFP36 RBPS in orchestrating TEC differentiation to sustain thymic function, prevent premature thymic involution and protect against autoimmunity.

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PS8-P01

Impact of biological sex and inflammatory cytokines on T-cell exhaustion during aging

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Objective
Aging profoundly impacts immune function, including T-cell biology. We previously showed in female mice that aging is associated with attrition of the naïve T-cell compartment, compensated by expansion of memory T cells expressing high levels of immune checkpoint receptors such as PD-1, TIGIT, and TOX, leading to functional exhaustion. These alterations are driven, at least in part, by the chronic low-grade inflammation that develops with age, a process known as inflammaging. Sex-based differences in immune responses have been well documented, especially in the context of inflammatory conditions. The aim of this project was to investigate how biological sex and inflammatory cytokines influence T-cell aging.
Methods
Flow cytometry and transcriptomic analyses.
Results
When comparing 18-month-old male and female mice, we found that the T-cell compartment of males was less affected by aging than that of females. Male mice maintained a higher proportion of naïve T cells and expressed lower levels of exhaustion markers. Notably, male castration abolished these sex-dependent differences. Transcriptomic analyses of memory CD4 and CD8 T cells revealed significant enrichment of TNF-α and type I interferon signatures in aged female mice compared with males. However, while T cells from aged Ifnar-KO mice displayed reduced exhaustion marker expression and an expanded naïve T-cell pool relative to wild-type controls, male mice still retained a comparatively “younger” T-cell phenotype than females. By contrast, in aged TNF-α-KO and Ifnar/TNF-α double KO mice, sex-biased differences were largely abolished, as T cells from old female mutants exhibited low exhaustion marker expression and an enlarged naïve compartment, closely resembling their male counterparts.
Conclusion
Our findings demonstrate a sex bias in T-cell aging and identify TNF-α as a key mediator of these sex-dependent differences.

Keywords: T-cell exhaustion - Inflammation - Sex differences.

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PS8-P02

Emergence of an atypical immunosuppressive and pro-inflammatory monocytic subset linked to age-related frailty

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Research on aging and the underlying mechanisms led to the well-recognized concept that one individual's biological rather than chronological age is linked to their decreased intrinsic capacities. Among the main biological dysfunctions associated with aging, « Inflammaging », a chronic low-grade inflammation that gradually develops with age, represents a major risk factor for the development of frailty.

Objective

Identifying the cellular actors that participate to functional decline in this context remains a major challenge. Inflammaging is known to be associated with a myeloid differentiation bias, suggesting that the emergence of particular cells within this lineage could be linked to age-related decline.

Methods

We explored myelopoiesis in the bone marrow and blood of aged individuals and characterized frailty associated monocytic cells and the molecular mechanisms controlling their emergence.

Results

We identified in mice and human a subset of age-associated monocytic cells with an atypical phenotype, displaying both immunosuppressive function and pro-inflammatory gene expression, and featuring an unique combination of surface markers. Interestingly, we also positively correlated the frequency of this monocytic subset in blood and bone marrow with decreased functional capacities of the mice evaluated by measuring muscular strength, cognitive functions and by scoring clinical frailty.

Mechanistically, activation of a specific nuclear receptor in the myeloid lineage was involved in the differentiation, during aging, of this monocytic subset. Impaired ligand production for this nuclear receptor decreased frequency of this monocytic subset and alleviated functional decline of aged mice which increased health span.

Conclusion

This work has evidenced for the first time the accumulation with aging of an atypical monocytic cell subset in humans which correlates, in aged mice with declined functional capacities.

We propose that this new monocytic cell subset could drive frailty status of aged individuals by exerting a dual function during aging, both supporting Inflammaging through production of pro-inflammatory mediators whilst hindering effective immunity due to their immunosuppressive function, participating to age-related decline.

Keywords: Inflammaging - Myelopoiesis - Frailty.

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PS8-P03

Inhibition of PTPN2/N1 by the small molecule inhibitor CLS-484 overcomes age-related immune deficiencies to enhance the efficacy of Flu vaccine in aged mice

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Objective
Upon aging, both the innate and adaptive immune system undergo alterations that profoundly affect the health and well-being of older individuals. This decline significantly compromises vaccine-induced immune responses, leading to increased susceptibility to infectious diseases. PTPN2 and PTPN1 are key negative regulators of the immune response, dampening the JAK-STAT pathway and T/B-cell receptor signaling. Recently, the small-molecule inhibitor of PTPN2/N1, CLS-484, has demonstrated the ability to unleash robust anti-tumor immunity. Building on this pre-clinical context, we hypothesized that pharmacological inhibition of PTPN2/N1 could enhance immune cell activation and overcome age-related deficits in vaccine responses.
Methods
To test this hypothesis, young and aged C57BL/6 mice were immunized with Flu-mRNA LNP vaccines and treated with PTPN2/N1 inhibitor CLS-484, or vehicle control, for 5 days following vaccination. Immune dynamics, including innate cell activation, T cell expansion, and memory formation, were assessed using flow cytometry and transcriptomic analysis. Protective efficacy was subsequently evaluated via an *in vivo* Influenza challenge in aged mice.
Results
While mRNA-LNP vaccine activated innate cells similarly across age groups, aged T cells exhibited a weaker baseline response. CLS-484 treatment successfully enhanced dendritic cell and macrophage activation in both young and aged mice. Furthermore, PTPN2/N1 inhibition boosted early CD4+ and CD8+ T cell activation, significantly amplifying the effector program. By Day 28, CLS-484 left a marked pro-inflammatory memory imprint in CD8+ T cells, and improved antigen-specific antibody response. Importantly, CLS-484 treatment provided vaccinated aged mice with significantly better protection against Influenza infection.
Conclusion
Here, we show that administering PTPN2/N1 inhibitor CLS-484 following vaccination, enhances innate and adaptive immunity in aged hosts, effectively restoring protective responses. This pharmacological approach has the potential to serve as a powerful systemic adjuvant, potentiating next-generation mRNA-LNP platforms to provide robust, long-lasting prophylactic protection against infectious diseases tailored for aging populations.

Keywords: Vaccine - Aging.

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Consequences of aging on naive CD4 T cell heterogeneity

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Objective
Aging is a complex and multifactorial biological process resulting from the progressive accumulation of molecular and cellular alterations that impair the organism's ability to maintain tissue functional integrity and to respond effectively to endogenous and exogenous stressors. It is characterized by a gradual decline in vital functions, ultimately leading to the development of age-related diseases and death. Aging is influenced by both genetic factors and environmental stimuli encountered throughout life. It is therefore not a linear process and does not manifest uniformly across individuals. Consequently, it is essential to be able to track this process in order to identify and manage individuals undergoing premature aging. The immune system, positioned at the interface between the host and its environment, represents an ideal candidate to define individual aging trajectories. In particular, T lymphocytes (T cells), due to their central role in coordinating immune responses and contributing to systemic aging, may exhibit hallmarks of biological aging.
Methods
In this context, we investigated age-related alterations in the T cell compartment by multiparametric flow cytometry in a cohort of 750 individuals, with the aim of developing a predictive tool for healthy aging. We next calculted a biological age based on age-associated T cell parameters to identify aging trajectory for each individuals.
Results
Our analysis enabled the identification of an aging signature within the T cell compartment used to calculate a biological age. Among all T cell parameter, we identified an accumulation of naive CD4+ T cells expressing CXCR3 as a key parameter to modelize aging. Functionally, next-generation sequencing (NGS) analyses and *in vitro* experiments show that these cells display a predisposition toward a Th1 phenotype. Additional analyses suggest that they may arise from the reprogramming of unbiased precursors, driven by the combined effects of homeostatic proliferation and inflammageing. Thus, we generated a comprehensive dataset that now serves as a foundation for the development of an algorithm to predict individual aging trajectories.
Conclusion
Overall, our analyses led to the identification of a novel biomarker of aging. With advancing age, a subset of naïve CD4+ T cells emerges, biased toward a pro-inflammatory phenotype, which may contribute to inflammageing and/or enhance host defense against viral infections or tumor-related pathologies.

Keywords: Immunosenescence - T cell.

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PS8-P05

Multiple Myeloma Progression and Treatment Drive Premature Ageing of Bone Marrow CD8⁺ T Cells

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Objective

Multiple myeloma (MM) is an age-related hematologic malignancy characterised by clonal expansion of plasma cells in the bone marrow (BM). The immune microenvironment is increasingly recognised as an important determinant of tumour control and MM evolution[1]. More particularly, T cells are central to anti-tumour immunity and key effectors of bispecific antibody (BsAb)-based therapies[2]. However, T cells are among the immune populations most profoundly affected by ageing[3], with impairments in their differentiation, proliferative capacity, and effector function. This age-related vulnerability could therefore have an impact on T-cell-mediated MM control and on the efficacy of T-cell engaging immunotherapies. However, the interplay between disease progression, MM treatments and T-cell ageing remains poorly understood.

Methods

To assess the relationship between MM progression and T-cell ageing, 8- or 45-week-old mice were transplanted or not with Vk12653 MM cells and analysed by flow cytometry 4.5 weeks after injection. To investigate potential treatment-induced T-cell ageing, BM immune cells from MM patients treated with isatuximab, carfilzomib, lenalidomide and dexamethasone were analysed by single-cell RNA sequencing, at diagnosis and after treatment.

Results

Younger mice showed a higher tumour burden than older mice. The frequency of exhausted CD8⁺ effector memory T cells (PD-1⁺TIM3⁺ T_{EM}) and the expression of ageing-related markers (p53, p21 and CD38) by BM CD8⁺ T_{EM} showed a positive correlation with tumour burden, suggesting premature T-cell ageing associated with MM progression. In MM patients, BM-derived CD8⁺ T cells displayed an enhanced expression of senescence-related transcriptomic signatures following treatment. These ageing CD8⁺ T cells exhibited a pro-inflammatory phenotype, with increased *IFNG* and *TNFA* expression following treatment.

Conclusion

Our results identify MM-associated and treatment-induced ageing of BM CD8⁺ T cells, characterized by a senescent, an exhausted and pro-inflammatory phenotype. This premature T-cell ageing may compromise subsequent BsAb-based immunotherapy. Identifying the molecular mechanisms underlying this process could reveal new therapeutic strategies for restoring T-cell function and improving immunotherapy efficacy.

Keywords: T-cell ageing - Anti-tumour immunity - Multiple Myeloma.

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PS8-P06

Optimized flow cytometry detection of p16INK4a reveals its differential expression across T cell differentiation subsets and age groups

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Objective
The cyclin-dependent kinase inhibitor p16INK4a (p16) plays a central role in inducing and maintaining permanent cell cycle arrest in senescent cells. While p16 is widely recognized as a pivotal biomarker of senescence, robust intracellular detection of p16 in human peripheral blood immune subsets using flow cytometry remains challenging due to technical limitations. In peripheral T lymphocytes, immunosenescence is typically marked by phenotypic changes, including loss of costimulatory molecules and acquisition of CD57. Here, we describe an optimized overnight intracellular staining protocol for p16 and characterize its co-expression with CD57 across CD4+ and CD8+ T-cell differentiation subsets in young and elderly individuals.
Methods
We established an optimized overnight (ON) staining protocol for intracellular p16 detection in human CD4+ and CD8+ T lymphocytes and compared its sensitivity against standard protocols. We evaluated p16 percentages and median fluorescence intensity (MFI) across T-cell maturation stages (Naive [CD45RA+ CCR7+], Central Memory [CD45RA- CCR7+], Effector Memory [CD45RA- CCR7-] and Terminally Differentiated Effector Memory [CD45RA+ CCR7-]) and assessed its relationship with the senescence marker CD57 across young and old individuals.
Results
The optimized staining protocol markedly enhanced signal resolution compared to the standard method, increasing p16 expression detection from background levels (~0.19–0.21%) up to ~27.5–28.3% in CD4+ and CD8+ T cells, while increasing MFI values (385 vs. 208 for CD4; 425 vs. 224 for CD8). Analysis across subsets demonstrated a progressive increase in p16 expression alongside T-cell differentiation (N < CM < EM < TEMRA) correlated with CD57 expression. Furthermore, p16 expression is higher in elderly individuals compared to young individuals particularly in EM and TEMRA subsets of CD8 T cells. Based on CD57high T cells, p16 expression does not differ among the CM, EM and TEMRA subsets, supporting the fact that its expression clearly depends on the CD57 marker with a percentage of p16 strongly higher in CD57high T cells compared to CD57neg population.
Conclusion
Our optimized staining protocol enables reliable quantification of intracellular p16 in T cells by flow cytometry. These findings confirm that p16 expression tracks with human T-cell differentiation, senescence markers, and aging, providing a reliable tool for immunosenescence studies.

Keywords: Immunosenescence - p16INK4a - Flow Cytometry.

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PS10-P01

Profile of Autoantibodies and Clinical Symptoms in Guinean Patients with Connective Tissue Diseases

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Connective tissue diseases (CTDs) are Autoimmune diseases (AIDs) characterized by the appearance of autoantibodies, which are diagnostic markers. Investigations of these autoantibodies play a major role in the management of several autoimmune diseases. The objective of this study was to describe the profile of anti-ENA antibodies according to the clinical symptoms of mixed CTDs in Conakry teaching Hospital. We performed a cross-sectional study during six months. A total of 20 patients was recruited and we measured antibodies using the ELISA technique. The mean age of our patients was 36.5 years, with a predominance of females. Cutaneous and rheumatological signs were the main clinical manifestations. SLP was the most frequent CTDs; the threshold of ENA antibodies positivity was higher in scleroderma with and SLP. Anti-ENA identification reveals the frequency of anti-SSA (83.33%), anti-U1RNP (66.66%) and anti-histone (50%) antibodies. Antinuclear antibodies (ANA) react with various components of the cell nucleus. Their detection
is of major interest in the diagnosis of CTDs. Our results highlight the importance of determining the specificity of these antibodies to guide differential diagnosis.

Keywords: Autoantibodies - Extractible Nuclear Antigen (ENA) by ELISA - Connective Tissue Diseases.

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PS10-P02

Treatment of chronic inflammatory bowel diseases using intrarectal UVA radiation

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The resolution phase is a critical process that limits inflammatory responses while promoting tissue repair and the restoration of tissue integrity. The induction of apoptosis, together with the efficient clearance of apoptotic cells by macrophages, plays a central role in orchestrating this process. Defects in apoptosis induction have been widely reported in a variety of chronic inflammatory diseases. Therefore, restoring apoptosis at sites of inflammation represents a promising therapeutic strategy to resolve chronic inflammation and address the underlying causes of inflammatory diseases.
That is why we have developed a therapy in a murine model of chronic inflammatory bowel disease based on UV irradiation of the damaged areas. A DSS-induced chronic intestinal disease model is used. Following the onset of the first signs of the disease, the animals are treated with UVA via endoscopy and subsequently monitored both clinically and endoscopically. At the end of the experiment, the organs are harvested and analyzed.
First, we demonstrated the ability of various intestinal cell types (epithelial, endothelial, immune, etc.) to undergo apoptosis following UVA irradiation, as well as the capacity of macrophages to phagocytose these apoptotic cells of diverse origins. Subsequently, we demonstrated *in vivo* that *in situ*UVA therapy has a highly beneficial effect on improving clinical and endoscopic scores in a DSS-induced model of chronic intestinal disease, and also leads to changes in the distribution of immune cells within the colon. These improvements are dose-dependent.
Our data demonstrate that restoring apoptosis enables the re-initiation of inflammation resolution and reduces the clinical signs of the disease. The ultimate goal of this work is to provide an effective treatment for patients with conditions refractory to conventional therapies.

Keywords: Resolution of inflammation - Inflammatory diseases.

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PS10-P03

Deciphering the role of regulated cell death by PANoptosis in neutrophilic asthma

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Due to climate change, extreme weather events have become more frequent and intense, leading to increased exposure to allergens and pollutants. The increased damage to the epithelial barrier caused by these environmental toxins is responsible for the rise in chronic diseases, including respiratory conditions such as allergies and allergic asthma. Damage to the airway epithelium and pulmonary inflammation may result from the interaction between environmental stressors, genetic factors and epigenetic regulatory mechanisms. Severe asthma is a complex and heterogeneous form of asthma, characterized by uncontrolled chronic inflammation and resistance to standard treatments. Recent studies[1,2,3] suggest that inflammatory programmed cell death mechanisms, such as PANoptosis, may play a key role in the pathogenesis of this condition. Building on our previous *in vivo* findings in a mouse model of house dust mite (HDM)-induced severe allergic lung inflammation, we demonstrated the expression of key PANoptosis-associated molecular components.[2] Here, we are investigating the role of PANoptosis in severe asthma by identifying the molecular pathways involved in PANoptosome activation in airway epithelial cells. To characterize this complex, we established *in vitro* human airway epithelium by using air liquid interface (ALI) cultures of primary nasal and bronchial cells. ALI cultures were chronically exposed to clinically relevant allergens, including HDM, birch pollen (BP) and *Aspergillus fumigatus* (ASP) under type 2 inflammatory medium induced by IL-13 alone or in combination with IL-4. ALI cultures exposure to allergens under type 2 conditions seems to increase the release of lactate deshydrogenase (LDH), the damage-associated molecular pattern (DAMP) HMGB1, and NINJ1, a mediator of plasma membrane rupture. Further analyses are ongoing to characterize the PANoptosome assembly components and define its allergen-specific contribution to epithelial cell death and airway inflammation.

Keywords: Allergy - Asthma - Cell death.

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PS10-P04

Immunophenotyping of human synovial tissue using spectral flow cytometry

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Objective
Osteoarthritis (OA) is increasingly recognized as a heterogeneous disease in which distinct patterns of synovial immune cell infiltration, including lymphocyte-rich inflammatory infiltrate, define clinically relevant patient subsets. Based on histological features, OA synovitis can be classified into three major pathotypes, namely pauci-immune (PI), diffuse-myeloid (DM), and lympho-myeloid (LM), the latter characterized by prominent macrophage infiltration and ectopic lymphoid structures (ELS), some exhibiting a fully mature phenotype ($CD21^+CD23^+$). However, comprehensive characterization of lymphocyte diversity in OA synovium remains limited by the lack of high-dimensional flow cytometry approaches specifically adapted to synovial tissue. This study aimed to develop and optimize a spectral flow cytometry panel enabling in-depth profiling of lymphocyte subsets in OA synovial tissue.
Methods
A high-parameter spectral flow cytometry panel comprising 30 antibodies was designed to characterize T- and B-cell phenotypic diversity as well as the myeloid compartment in human synovial tissue. Following validation of the enzymatic dissociation protocol, antibody selection, fluorochrome assignment, and spectral unmixing parameters were optimized using peripheral blood mononuclear cells and dissociated synovial tissues. Data were analyzed using conventional gating strategies and unsupervised dimensionality reduction approaches.
Results
The optimization phase revealed enzymatic dissociation influenced antigen expression and should be carefully considered. The optimized spectral flow cytometry panel enabled robust identification of lymphocyte subsets within OA synovium, including naive and memory T-cell populations, regulatory T cells, helper T-cell subsets, B-cell maturation stages, and innate-like lymphocytes, together with myeloid subsets, such as monocytes, macrophages and dendritic cells. The panel enabled distinction between tissues lacking ELS, displaying immature ELS, or harboring mature ELS.
Conclusion
We report the development of a robust spectral flow cytometry panel for high-dimensional analysis of lymphocyte and myeloid diversity in OA synovium. This tool provides a valuable framework for dissecting immune heterogeneity within the synovial tissue and supports future studies investigating the relationship between immune cell phenotypes, histological features, disease activity, progression, and therapeutic response.

Keywords: Synovium - Immunophenotyping - Flow cytometry.

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PS10-P05

c-Maf regulates age-associated B cell responses and limits autoimmune inflammation

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Introduction
C-Maf is a key regulator of immune cell differentiation and cytokine expression and has been implicated in shaping B-cell fate decisions, including plasma cell differentiation and germinal center responses. While c-Maf-dependent regulatory programs in B cells may contribute to tumor progression in cancer models, and to immune tolerance and protection from autoimmune inflammation, the role of c-Maf in controlling Aged associated B cells (ABCs) functional polarization during chronic inflammation remains poorly understood.
Objective
Our work aims to define how c-Maf regulates the differentiation, regulatory programming, and inflammatory functions of ABCs during autoimmune diseases.
Methods
A B cell-specific c-Maf-deficient C57BL/6 mouse model (MafΔB) was used to investigate the role of c-Maf in two preclinical models of autoimmunity: the Experimental Autoimmune Encephalomyelitis (EAE) model of neuroinflammation and an aging-based model of Sjögren's syndrome (SS). ABC populations were characterized by flow cytometry and immunofluorescence in peripheral organs (spleen) and at disease sites, including the central nervous system (CNS) and salivary glands (SG). Their phenotype and function were assessed by cytokine production and transcriptomic analyses. In parallel, cytokine profiling was performed in fluids collected from inflamed tissues, including cerebrospinal fluid (CSF) and saliva.
Results
Preliminary results indicate that MafΔB mice develop more severe disease than wild-type controls in both models. In EAE, MafΔB mice exhibited an earlier disease onset and higher clinical paralysis scores. In the SS model, aged MafΔB mice showed reduced saliva production consistent with impaired salivary gland function.
Both models displayed increased B-cell infiltration within inflamed tissues, associated with an expansion of T-bet+ and CXCR3+ ABCs. Consistently, c-Maf-deficient B cells exhibited an enhanced capacity to differentiate into ABCs in vitro, suggesting that c-Maf restrains ABC differentiation. Moreover, ABCs lacking c-Maf expressed lower levels of CD25 consistent with a reduced regulatory phenotype.
Conclusion
In aged MafΔB mice, salivary cytokine profiling revealed an inflammatory signature characterized by increased IL-1b, TNFa, IL-6 and IFNg together with reduced IL-4 levels compared with age-matched controls, supporting a role for c-MAF in limiting tissue inflammatory responses.

Keywords: c-Maf - ABCs - Auto-immunity.

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PS10-P06

Inflammatory skin-gut crosstalk in psoriasis progression

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Psoriasis is an immune-mediated skin disorder characterized by blood vessel dilation, epidermal hyperplasia and increased oxidative stress and inflammation, mainly orchestrated by T cells. In addition, psoriasis patients present comorbidities such as intestinal dysfunctions, potentially triggered by the bidirectional connection of the skin-gut axis. However, factors regulating this interplay are not fully known. We observed that deprivation of TGFb signalling in T lymphocytes leads to spontaneous psoriasis associated with gut inflammation.

Objective

To investigate the interplay between the skin and gut modulated by TGFb.

Methods

To this end, we used CD4-Cre mice with double knockout of components from the TGFb pathway (DKO), that present chronic inflammation in the gut and scaly lesions in the skin, and characterised skin architecture and environment as well as microbial composition in the skin-gut axis.

Results

We observed psoriasis-like features gradually appearing in DKO mice from 6 months old, along with increased alterations in the skin-gut microbiota and high production of cytokines such as IFNg, TNFa and IL1b. Treatment of animals with anti-IFNg decreased the psoriasis-like features observed and modified cytokine expression in the skin of DKO mice. Ongoing experiments are providing an input on the potential migration of immune cells from the gut to the skin using photoconverted mice.

Conclusions

Overall, these findings established the first link between skin and gut immunity through T lymphocytes regulated by TGFb by observing that inflammation in the intestine affect the skin environment. Future studies will aim to further characterize these changes to address key pathological features that can be tackled for the development of potential treatments.

Keywords: Psoriasis - Chronic inflammation - Skin-gut axis.

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PS10-P07

The ASB2α-filamin A/B axis as a new therapeutic opportunity in type 2 immune pathologies

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Type 2 immune-mediated diseases such as allergic asthma and atopic dermatitis (AD) are prevalent chronic disorders marked by inflammatory cell recruitment and tissue remodeling associated with airway hyperresponsiveness or skin barrier dysfunction, respectively. Th2 lymphocytes drive pathology development through type 2 cytokines. In clinics, treatments targeting type 2 cytokines or their receptors are used to decrease the inflammation. A therapy would be to inhibit the recruitment of Th2 lymphocytes to the inflamed site. We showed that the ASB2a ubiquitin ligase is a positive regulator of Th2 lymphocyte functions that triggers degradation of filamins A and B (FLNa/b). Loss of ASB2a in Th2 lymphocytes reduces their migration and their recruitment in inflamed lungs and attenuates airway inflammation in preclinical models of asthma[1].

The objectives of the study is to show that increasing the levels of FLNa/b in Th2 lymphocytes using small molecules is a benefit in reducing type 2 airway inflammation and to decipher the role of the ASB2a-FLNa/b axis in AD.

First, we screened a compound library to identify small molecules that increase FLNa/b levels in Th2 lymphocytes. Using *in vitro* studies including live microscopy and cytometry, and *in vivo* mouse models of airway inflammation, we evaluated the impact of FLNa/b accumulation in Th2 lymphocytes on lung inflammation and airway hyperresponsiveness. Next, *ASB2* knockout mice were used to investigate the role of ASB2a on skin inflammation in mouse models of AD.

We identified two compounds, thiostrepton and oxibendazole, that increase the levels of FLNa/b in Th2 lymphocytes with no impact on Th2 identity. We show that Th2 lymphocytes treated with the compounds present reduced migratory properties. Using *in vivo* model of airway inflammation, we showed a reduction of type 2 inflammation and airway responsiveness of the mice that received Th2 lymphocytes treated with the compounds[2]. We also showed a reduced thickening of the epidermis and a diminished recruitment of skin homing T cells in *ASB2*KO mice submitted to an AD protocol, in agreement with the fact that *ASB2* is one of the most deregulated gene in AD patients[3].

These results indicate that increasing FLNa and FLNb in Th2 lymphocytes may represent a therapeutic opportunity to mitigate pathogenic type 2 immune responses. Overall, we propose that targeting the ASB2α-FLNa/b axis might be considered as a potential therapeutic opportunity in type 2 immune-mediated diseases.

Keywords: Allergic Asthma - Atopic Dermatitis - Ubiquitine Ligase.

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PS10-P08

Single-Cell Trajectory-Analysis Identifies Early Transcriptomic Imprinting of Type 1 Diabetes Risk Genes in Developing NOD Thymocytes

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Regulatory T cells (Treg) are essential for the maintenance of immune tolerance and the prevention of autoimmunity. In non-obese diabetic (NOD) mice, the primary murine model of type 1 diabetes (T1D), Treg display *in vivo* functional impairments linked to genetic susceptibility loci (*Idd*). However, beyond these functional defects, our recent data indicate that *Idd5* promotes the intrathymic development of a notably high frequency of strongly autoreactive Treg in neonatal NOD mice, as compared to several non-susceptible strains, suggesting that atypical Treg development may influence T1D susceptibility. To further investigate differences in the thymic development of conventional and regulatory T lymphocytes between NOD and control mice, we performed a comparative analysis of single-cell RNA sequencing (scRNA-seq) data, generating a transcriptomic atlas of over 59,000 NOD and C57BL/6 thymocytes. Data-integration using the Harmony algorithm and pseudotime-analysis (Slingshot/tradeSeq) revealed that, as compared to B6 cells, NOD thymocytes exhibit higher expression of T1D-associated genes, starting as early during development as at the CD4/CD8 double-positive (DP) stage. Interestingly, while the DP stage shows a broad transcriptomic shift in T1D-associated genes, this enrichment only becomes directionally consistent with GWAS risk (*i.e.*, coordinated upregulation of risk alleles) within the Treg lineage. Gene Ontology (GO)-based functional analysis of the genes consistently upregulated throughout NOD Treg differentiation demonstrated an enrichment in pathways governing the positive regulation of alpha-beta T cell activation. Within this NOD genetic signature, we identified several upregulated conserved genes during Treg development, notably that encoding the co-stimulatory receptor CD226. The significant overexpression of CD226 in NOD mice, persisting from the DP stage through to mature Treg, was validated by flow cytometry (FACS). Given that CD226 has been reported to dysregulate Treg stability and suppressive function, these results suggest that the loss of tolerance in T1D may take root during the earliest stages of thymic development, driven by the premature, activation-induced expression of molecular players such as CD226 that heighten T1D susceptibility.

Keywords: Treg - NOD - Autoimmunity.

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PS10-P09

PTK7 expression by dendritic cells regulates T-cell responses and the Treg/Th17 balance

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Objective
Protein Tyrosine Kinase 7 (PTK7) is a transmembrane protein involved in cell adhesion, polarity and migration (1). PTK7 overexpression is associated with tumor progression, metastasis and poor prognosis in several cancers (2), that led to the development of therapeutic strategies targeting PTK7, including antibody-drug conjugates. PTK7 expression has been reported in plasmacytoid DCs (pDCs) from blood and non-small cell lung cancer (3), suggesting a potential role in immune regulation. However, its role in dendritic cell (DC)-mediated immunity remains unknown.
Methods
We aimed to characterize PTK7 expression in DCs and investigate its role in T-cell responses at steady state and in pathological situations. To do so, we used CD11c-Cre PTK7flox/flox mice, in which PTK7 is selectively deleted in DCs. PTK7 expression was analyzed across DC subsets in mice and humans, at steady state and in the tumor microenvironment. The functional consequences of PTK7 expression were assessed by co-culturing WT or PTK7-deficient DCs with antigen-specific $CD4^+$ or $CD8^+$ T cells and analyzing T-cell proliferation, activation and differentiation. T-cell responses were further investigated *in vivo* in aged mice.
Results
PTK7 expression by DCs was conserved between mice and humans. At steady state, PTK7 was mainly expressed by Langerhans cells, whereas conventional DCs acquired PTK7 expression in the tumor microenvironment, indicating that PTK7 expression is regulated according to tissue context. Functionally, $PTK7^+$ DCs had a reduced capacity to induce antigen-specific $CD4^+$ and $CD8^+$ T-cell proliferation and activation, while promoting Treg differentiation *in vitro*. Consistent with these findings, DC-specific PTK7 deficiency altered helper T-cell differentiation *in vivo* in aged mice, resulting in a shift from Treg toward Th17 responses.
Conclusions
These results identify PTK7 as a regulator of DC-mediated T-cell responses. PTK7 expression is associated with a tolerogenic DC phenotype that limits effector T-cell responses while promoting Treg differentiation. Its induction in tumor-associated DCs may therefore contribute to immune suppression and suggests a role for PTK7 in the regulation of immune tolerance during aging and cancer.

Keywords: PTK7 - T-reg - Immunity.

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PS10-P10

Development of a humanized murine model of lupus for preclinical evaluation of innovative therapies

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Objective

Systemic lupus erythematosus (SLE) is a severe autoimmune disease characterized by the production of pathogenic autoantibodies causing inflammation and organ damage. Current treatments limit inflammation but present important side effects and are not curative, highlighting the need for new therapeutic approaches.

Several mouse models of SLE exist, but even if they partially reproduce the symptoms of the human disease, their non-human immune system leads to an autoreactive B-cell and autoantibody response that does not fully mimic the human situation. Therefore, the development of humanized models is necessary to validate new human-specific immunomodulatory agents.

As well, several humanized mouse models exist, based on the engraftment of hematopoietic stem cells (HSC) or peripheral blood mononuclear cells (PBMC), but, in any case, B cells are not fully functional, i.e. affinity maturation/class switching and differentiation into plasma cells secreting high affinity antibodies is limited.

As 17β-estradiol is known to support the differentiation of HSC and many immune cells, this project aims to develop an experimental humanized mouse model based on a recently established model of immunodeficient mice, the THX mice (NOD.Cg-KitW-41JTyr+PrkdcscidIl2rgtm1Wjl/ThomJ) engrafted with CD34+ HSC and treated with 17β-estradiol, designed to faithfully replicate human myeloid and lymphoid compartments with functional B cells, and carried out on a closely related genetic background.

Methods

Female NRG-cKit mice (NOD Rag2tm1-Il2rgtm1-Kitem1/Rj) were humanized by engraftment of CD34+ HSC at 5 weeks of age and supplemented with 17β-estradiol in their drinking water starting 14 weeks after humanization. Humanization was assessed by flow cytometry detection of human cells in blood and lymphoid organs and by ELISA quantification of human antibodies. Estradiol treated mice were compared to non-estradiol control mice to assess the effect of the estradiol on humanization.

Results

Early results showed the presence of human cells in the blood of humanized mice (B cells, CD4+ and CD8+ T cells, NK cells, monocytes), along with production of human IgG and IgM.

Conclusion

This model will subsequently be used to develop a pristane-induced SLE model in order to evaluate the efficacy of new immunotherapies targeting autoreactive B cells.

Keywords: Lupus - Humanized mice - 17β-estradiol.

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Innate Immunity, Microbiota, and Inflammation in Endometriosis: Understanding the Immunopathology to Develop Innovative Treatments

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Background/Objective
Endometriosis is a polygenic and multifactorial inflammatory disease, for which understanding pathogenesis and developing innovative treatments still remain a challenge. This disease affects approximately 10% of women of reproductive age. We propose to deeply explore innate immunity, apoptosis and microbiota composition in a cohort of patients with endometriosis, in comparison with endometriosis-free patients and to test a pro-resolutive approach therapeutic efficacy in *in vitro* models.

Methods
A prospective, controlled, interventional, single-center, non-randomized, open experimental study allowing access and analysis of blood, biopsies (extra-uterine endometriotic lesion, surrounding tissue, and non-lesional endometrium), and stools samples. For this project, 20 symptomatic women and 20 control endometriosis-free (permanent contraceptive surgery) women (18 and 42 years) undergoing surgery during the 2nd phase of the menstrual cycle (NCT07078435). We will characterize (phenotype and function) innate immune cells using flow cytometry in tissue biopsies and peripheral blood (focusing on Dendritic cells (cDC2, cDC1, pDC, CD16+DC), Natural killer cells, MAIT, gdT cells, macrophages). Immunogenetic characterization of KIR and HLA class I alleles by Next-Generation Sequencing (NGS) technologies will be assessed. We will also characterize apoptosis in endometriotic versus normal endometrial cells. The intestinal bacterial microbiota profile (16S genomic analysis) will be characterized and compared between endometriosis patients and controls at T0 and followed from T0 to M12 for endometriosis patients to determine a correlation with disease stage evolution and immune status. Finally, we plan to investigate efferocytosis and pro-resolutive factors.

Results
Sampling procedures have been optimized to improve sample yield; flow cytometry panels and gating strategy have been developed. Preliminary results show the presence of various subtypes of dendritic cells in the endometrium at low frequencies, including AS-DC 123−, cDC1, and pDC populations, and the presence of innate effector cells.

Conclusion
This project, by characterizing immunological signature of endometriosis, looking for connections between this signature and the microbiota composition, will allow better understanding of pathophysiology and identification of new therapeutic targets.

Keywords: Endometriosis - Dentritic cell - MAIT cells.

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PS10-P12

Natural Killer cells phenotypic and functional signature in Sjögren's Disease

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Objective
Sjögren's disease (SjD) is a chronic systemic auto-immune disease which affects predominantly women, characterized by lymphocytic infiltration of exocrine glands. B cells are primary drivers of the pathology, and several strategies are based on their depletion. These rely on antibodies that target B cells for depletion via Natural Killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC). This highlights the importance of characterizing NK-cell functionality. This study aims to evaluate the function and phenotype of NK cells in SjD.
Methods
We leveraged the DIAPSS cohort (NCT03681964), providing access to both confirmed SjD and Sicca patients (patients experiencing symptoms of SjD, but with no signs of autoimmunity); as well as healthy donors from the French blood bank. To evaluate the phenotype of NK cells, we first performed spectral flow cytometry analysis on thawed peripheral blood mononuclear cells (PBMC) from SjD patients (n = 16), sicca donors (n = 18) and healthy donors (n = 4), using a panel of 30 markers combining lineage markers to discriminate NK cell subsets, their activation and maturation states, the presence of activating, inhibitory receptors and migration markers. In parallel, NK cell functionality was assessed through cytokine and chemokine production after 24 hours of stimulation with IL-12/IL-15/IL-18 on sicca patients (n = 6) and SjD patients (n = 4).
Results
Among NK cells, frequencies of CD16-, CD16+ and CD16+ CD57+ subsets were comparable across SjD patients, Sicca and healthy donors. Overall, we observe a large heterogeneity in expression for all markers in SjD and Sicca. However, we observed some significant changes in expression of Granzyme B which was higher in SjD compared to Sicca while CD11b was lower in SjD in CD16- NK cells. Meanwhile, CD38 was higher and NKG2D was lower in SjD in CD16+ and CD16+ CD57+ NK subsets. No differences were detected regarding cytokine and chemokine (IFNg, TNFa, GM-CSF, CCL5, FLT3L) production on 10 patients tested.
Conclusion
Activation, maturation and functionality of NK cells from SjD patients resembled those of sicca patients, despite subset-specific protein expression variations. Preliminary data indicates that NK-cell subsets were functional, supporting B-cell depletion potential. Single-cell analyses and functional assays will help further characterize these differences and determine the specific NK-cell subsets potentials in depletion strategies.

Keywords: NK cells - Sjögren's Disease.

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PS10-P13

Autoreactive SSA+ B cells phenotypic and functional signature in Sjögren's Disease

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Objective
Autoreactive B cells targeting TRIM21/Ro52 and TROVE2/Ro60 antigens are thought to contribute to Sjögren's disease (SjD) pathogenesis. Circulating anti-SSA antibodies can be detected months to years before clinical onset. However, the phenotype and functional role of these autoreactive B cells (SSA+ B) in the pre-disease state or in healthy individuals remain poorly understood. To address this gap, this study aims to develop a flow cytometry-based method to identify autoreactive B cells in peripheral blood mononuclear cells (PBMCs).
Methods
Healthy donor PBMCs from the French blood bank (EFS) were co-incubated with Ro52 antigen conjugated to biotin revealed by Streptavidin-RB613 and Ro52 antigen conjugated to AF488 to specifically identify double positive Ro52-autoreactive B cells by spectral flow cytometry. Ro52+ B cell distribution was assessed across B cell subpopulations (Live, CD19+) using a panel of 8 markers to detect transitional (CD38+, CD24+), naïve (CD27-, IgD+), unswitched memory (CD27+, IgD+), switched memory (CD27+, IgD-), double-negative (CD27-, IgD-) as well as plasmablast (CD27+, CD38+).
Results
Most B cells were negative for either of the Ro52 antigen (95% (+/- 2%) but a small fraction were positive for Ro52-biotin and Ro52-AF488 (4% (+/- 2%) confirming the presence of SSA-autoreactive B cells in healthy donors (n = 6). Interestingly, we did not observe any single positive population for Ro52-biotin or Ro52-AF488 indicating that even single staining allows for specific detection of B Ro52+. B Ro52+ cells were more specifically found in transitional cells (8% +/- 4%) and at lower frequency in naive (3% +/- 1%), unswitched memory (2% +/- 0,5%) and switched memory cells (1% +/- 0,5%), double negative (1% +/- 0,5%), plasmablasts (<0,5%).
Conclusion
Our method allows for detection of specific Ro52+ autoreactive B cells and our preliminary findings suggest that Ro52+ B cells are more present in transitional and naive populations in healthy individuals. Moving forward, we aim to apply this approach to Ro60 and further characterize the SSA+ B-cell compartment using an expanded spectral flow cytometry panel. We also plan to sort and culture SSA+ B cells to assess their capacity to produce anti-SSA antibodies. These protocols will subsequently be applied to PBMCs from SjD patients. By investigating these differences, we seek to better understand the pathogenic role of the autoreactive B cells in SjD.

Keywords: Autoreactive B cells - Sjögren's Disease.

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Impact of a STING gain-of-function on B Cell Phenotype and Development of Autoimmunity

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STING (Stimulator of Interferon Genes) is a central adaptor of cytosolic DNA-sensing pathways [1]. Gain-of-function (GOF) mutations in the STING-coding gene cause SAVI (STING-associated vasculopathy with onset in infancy), a type I interferonopathy characterized by systemic inflammation, vasculopathy and severe lymphopenia. Beyond innate immunity, STING activation also affects lymphocyte development and function, but its impact on B cells remains poorly understood.
We investigated how chronic STING activation affects B cell phenotype, signaling and function, and whether it may contribute to impaired B-cell tolerance.
We used heterozygous STING GOF V154M and N153S knock-in mice, carrying murine counterparts of SAVI-associated mutations [2]. B cell phenotype, responses to *in vitro* stimulation and proliferation were assessed in splenocytes by flow cytometry. Downstream signaling pathways were analyzed by Western blot. To investigate B cell tolerance, STING GOF mice were crossed with 56R transgenic mice expressing an autoreactive anti-DNA BCR [3].
We found that STING GOF B cells displayed a constitutively hyperactivated phenotype, with increased expression of several activation markers at baseline. Upon *in vitro* stimulation, they showed stronger activation responses to CD40, TLR7 and TLR9 agonists, together with increased proliferative capacity. Preliminary results further suggest that TLR7 and TLR9 stimulation promotes plasmablast differentiation and increased IgG and IgM secretion. In addition, STING GOF B cells showed increased CD40 surface expression and enhanced ERK1/2 phosphorylation following CD40 stimulation, suggesting that altered CD40 signaling contributes to their hyperactivated state.
Chronic STING activation alters B cell phenotype and function, leading to constitutive hyperactivation and enhanced responses to multiple pathways (TLRs, CD40).
As persistent B cell hyperactivation is often associated with defective B cell tolerance and autoreactive B cells, these findings suggest that STING GOF may contribute to B cell tolerance breakdown. Enhanced TLR/CD40 signaling in STING GOF B cells provides an additional indication supporting this hypothesis, further reinforced by accumulating evidence from the literature. Ongoing studies using the 56R model will determine whether chronic STING activation promotes the survival and activation of self-reactive B cells and contributes to the development of autoimmune manifestations.

Keywords: STING - B cells - Autoimmunity.

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PS10-P15

BMP9 and BMP10 Limit IL-6/STAT3 signaling in Endothelial Cells by Inducing SOCS3 and Suppressing Inflammatory Activation

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The endothelium is known as an active regulator of immune responses, controlling leukocyte recruitment and secreting cytokines within tissues. Beyond its vascular functions, endothelial signaling pathways may therefore contribute directly to the regulation of inflammation. BMP9 and BMP10 are circulating molecules that signal through the endothelial ALK1 receptor. Mutations in the BMP9/BMP10/ALK1 pathway are associated with two vascular diseases, pulmonary arterial hypertension (PAH) and hereditary hemorrhagic telangiectasia (HHT), both characterized by increased inflammation. However, whether endothelial BMP/ALK1 signaling directly regulates inflammatory responses remains largely understudied. Our team previously observed inflammatory phenotypes in mouse models deficient for ligands *Bmp9*and/or *Bmp10*. Here, we show that mice lacking both *Bmp9* and *Bmp10*, as well as mice with endothelial *Alk1* deletion, develop lung inflammation associated with increased circulating IL-6 levels and enhanced STAT3 phosphorylation in lung tissue. We therefore investigated a direct interaction between BMP/ALK1 and IL-6 signaling in endothelial cells. We found that BMP9 and BMP10 significantly attenuated IL-6-induced STAT3 phosphorylation. Mechanistically, BMP9 and BMP10 rapidly induced expression of the negative regulator of cytokine signaling SOCS3, providing a molecular link between BMP/ALK1 activation and inhibition of IL-6/JAK/STAT3 signaling. Consistent with this regulatory mechanism, BMP9 and BMP10 reduced the IL-6-induced expression of the inflammatory mediators CCL2 and HGF in endothelial cells.
This work demonstrates, for the first time, that the BMP9/BMP10-ALK1 pathway inhibits endothelial IL6/JAK/STAT3 inflammatory signaling via induction of the negative regulator SOCS3. This molecular mechanism could explain the spontaneous inflammatory phenotypes previously described in mouse models. These findings offer a novel mechanistic basis from inflammation-driven pathogenesis in HHT and PAH and reveal potential anti-inflammatory therapeutic targets for these diseases.

Keywords: Inflammation - ALK1 - IL-6.

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Immunomic Characterization of Circulating B and T Cells in Autoimmune Hepatitis

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Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by hypergammaglobulinemia, circulating autoantibodies, and lymphoplasmacytic liver infiltration. Despite effective immunosuppressive therapies, frequent relapses after treatment withdrawal suggest the persistence of lymphocyte populations sustaining the autoimmune response. Circulating auto-antigen-specific $CD4^+$ T cells expressing PD-1 and TIGIT have been identified in AIH. They share transcriptional features with intrahepatic clones and display a B-helper phenotype. However, the B-cell populations involved, their antigen specificity, and their interactions with T cells remain poorly characterized. Our project aims to characterize T- and B-cell populations involved in AIH by integrating single-cell transcriptomic profiles with TCR/BCR repertoires and comparing circulating and liver-infiltrating lymphocytes, with particular attention to tertiary lymphoid structures.

Peripheral blood from 21 newly diagnosed, treatment-naïve AIH patients was analyzed. $CD3^+CD4^+PD\text{-}1^+TIGIT^+$ T cells and $CD19^+IgD^-$ B cells were isolated by flow cytometry and analyzed by single-cell RNA sequencing. Libraries were prepared in pools of four samples and sequenced at 25,000 reads/cell. Cell Ranger, Seurat v5, and scRepertoire were used to analyze transcriptional profiles and clonal diversity. Liver biopsies from the same patients were collected in OCT for upcoming spatial immunomics analyses aimed at comparing clonotypes between blood and liver.

Approximately 140,000 T and B lymphocytes were processed. T-cell analysis identified previously described populations, including subsets enriched for B-helper, cytotoxic and autoreactivity-associated signatures. Some of these populations showed clonal expansion with a relatively dispersed distribution across patients. B-cell analysis notably identified memory B cells and plasmablasts and revealed distinct patterns of clonal expansion. One B cell subset showed limited clonal expansion broadly distributed across AIH patients, whereas another was dominated by highly expanded clones from just two patients.

This study provides a single-cell resource combining transcriptomic and TCR/BCR repertoire data from treatment-naïve AIH patients. Upcoming integrated blood-liver analyses will help identify lymphocyte populations involved in disease persistence and guide functional characterization of candidate B-cell clonotypes through recombinant antibody production and testing.

Keywords: Autoimmune hepatitis - Lymphocytes - Transcriptomics.

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PS10-P17

Understanding thymic selection and central tolerance defects in thymoma patients

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T lymphocytes undergo critical selection steps during their development in the thymus, ensuring the reduction of autoreactive clones. This process is largely mediated by thymic epithelial cells (TECs), which present a broad repertoire of peripheral tissue antigens to developing T cells. Defects in thymic selection can therefore lead to the escape of autoreactive T cells and contribute to autoimmune disease or inappropriate "non-self" responses[1].
Thymomas are rare thymic epithelial tumors containing variable proportions of lymphocytes, and approximately one-third of patients present with autoimmune manifestations[2].
In order to better understand thymopoiesis in thymoma, we performed scRNA/TCR-seq on thymocytes and thymic epithelial cells from thymoma patients and healthy donors[3]. T cells at all developmental stages, from immature to mature, were detected within tumors, suggesting active thymopoiesis. However, multiple approaches identified a maturation blockade at the transition from the double-negative to the double-positive stage. Among mature T cell subsets, regulatory T cells were markedly reduced. scRNA-seq showed that tumoral TECs (tTECs) most closely resembled medullary TECs from healthy individuals, but displayed defective expression of key molecules involved in positive and negative selection. To validate these findings across a larger cohort, we performed bulk RNA-seq on 150 thymoma patients and 30 paired healthy distant thymic tissues. Similar alterations were observed across all histological subtypes. Autoimmune status did not correlate with either Treg reduction or the extent of defects in the negative selection machinery, supporting the hypothesis that rare autoreactive thymocytes may escape deletion. Finally, to assess the clinical relevance of these findings, we analyzed the French national SNDS database to identify patients with thymoma and evaluated the occurrence of autoimmunity according to time to surgery. Patients with a longer delay to surgery were more likely to have autoimmune manifestations, supporting a model in which prolonged exposure to thymoma-associated defective thymic selection increases the release of autoreactive T cells and, consequently, the incidence of autoimmunity.
Altogether, these results indicate that thymopoiesis in thymomas is active but abnormal and may contribute to the high prevalence of autoimmunity observed in this disease.

Keywords: Auto-immunity - Thymic selection - Thymoma.

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PS10-P18

Resolution of pediatric cow's milk allergy is associated with low Tfh cell frequencies and elevated IL-17 and IL-22 levels

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Background
IgE-mediated cow's milk allergy (CMA) is one of the most common food allergies in childhood. Although many children tolerate baked milk and most eventually develop tolerance to raw milk, the immune mechanisms underlying allergy persistence or resolution remain incompletely understood. We investigated whether distinct T-cell subsets and circulating cytokine profiles are associated with clinical tolerance to cow's milk.
Methods
Fifty-eight children with confirmed IgE-mediated CMA were enrolled at the time of an oral food challenge (OFC) with baked or raw cow's milk. Children were classified according to OFC outcome into baked milk-allergic (BMA, n=9), raw milk-allergic (RMA, n=20), baked milk-tolerant (BMT, n=12), and raw milk-tolerant (RMT, n=17) groups, reflecting a continuum from persistent allergy to complete tolerance. Peripheral T-cell subsets and intracellular cytokine production were assessed by flow cytometry. Plasma levels of 49 cytokines and chemokines were measured before OFC.
Results
Frequencies of IL-4-, IL-13-, and IL-17-producing $CD4^+$ T cells did not differ significantly between groups. In contrast, IFN-γ- and TNF-α-producing $CD8^+$ T cells and TNF-α-producing $CD4^+$ T cells were enriched in tolerant children, with significantly lower frequencies in BMA than in RMT. Naïve $CD4^+$ T cells were reduced, whereas regulatory T (Treg) and T follicular helper (Tfh) cells were increased in BMA compared with RMT. Tfh cells correlated positively with Treg frequencies and cow's milk-specific IgE levels. Plasma IL-17A, IL-17F, IL-22, and IL-2 were significantly lower in BMA than in RMT. IL-33 and soluble ST2 levels differed according to tolerance status, while CCL17 was increased and CXCL12 decreased in BMA compared with RMT.
Conclusion
Clinical tolerance to cow's milk was associated with distinct T-cell and circulating cytokine signatures. In particular, reduced Tfh and Treg frequencies and increased IL-17A, IL-17F, and IL-22 levels characterized children with complete tolerance. These findings highlight the immunological heterogeneity of CMA and suggest that Tfh/Treg populations and type 17-associated cytokines may represent candidate biomarkers of disease trajectory. Longitudinal studies in larger cohorts are warranted to validate their predictive value for natural tolerance and therapeutic responses.

Keywords: Cow's milk allergy - Pediatric patients - T cells.

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Thapsigargin enhances STING-dependent activation in a pDC cell line

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Introduction

The cGAS–STING pathway is crucial for innate immunity by detecting cytosolic DNA and inducing type I interferon (IFN-I) production. Plasmacytoid Dendritic Cells (pDCs) are specialized in IFN-I production upon innate sensing. STING is located in the endoplasmic reticulum (ER), and thus its activation may be affected by ER stress. However, the impact of ER stress on STING activation and IFN-I production in pDCs is unclear. This study aims to investigate how thapsigargin (Tg)-induced ER stress affects STING in a pDC cell line, focusing on the unfolded protein response (UPR) and calcium (Ca^{2+}) signalling pathways.

Methods

The human pDC line CAL-1 was treated with Tg to induce ER stress and stimulated with 2'3'-cGAMP to activate the STING pathway. To identify STING proximal interactors, we employed TurboID-based proximity labelling with streptavidin enrichment and quantitative mass spectrometry. To characterize signalling and trafficking, we used immunofluorescence microscopy, co-immunoprecipitation, Western blotting, RT-qPCR and ELISA/LegendPlex. Cells were also treated with pharmacological inhibitors for the UPR and for CaMKII.

Results

cGAMP prompted STING to move from the ER to the Golgi apparatus, leading to changes in its interactome. Tg treatment enhanced 2'3'-cGAMP-induced STING activation and IFN-I production, unaffected by UPR inhibition. Proteomic analysis revealed known trafficking components and new proteins associated with STING, such as the ubiquitin-editing enzyme A20, TAX1BP1, and MAVS. Co-immunoprecipitation confirmed that A20 is recruited to STING in a stimulus-dependent manner, suggesting regulation through dynamic ubiquitination. Since Tg induces ER stress by inhibiting SERCA and raising cytosolic Ca^{2+} levels, we tested if CaMKII signaling played a role by treating cells with KN-93. When CaMKII was inhibited, TBK1 and IRF3 phosphorylation levels were maintained, but STAT1 activation and IFN-β secretion were reduced, indicating that IFN-I production relies on CaMKII.

Conclusions

Inducing ER stress with Tg in CAL-1 cells enhances STING signalling independently of canonical UPR pathways. Our findings suggest that STING activation involves regulatory proteins A20, TAX1BP1, and MAVS, with ER stress promoting STING's transition to endosomal signalling compartments. Also, Calcium-dependent pathways modulate IFN secretion. This research provides new insights into the regulation of innate immune signalling.

Keywords: cGAS–STING - ER stress - A20 (TNFAIP3).

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The human PERK p.P649T variant synergizes with STING signaling to drive enhanced type-I IFN and inflammatory cytokines expression in monocytes

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Objective

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is a rare autoinflammatory disease characterized by early-onset skin lesions, vasculopathy, and lung damage. Gain-of-function mutations in *STING1* cause constitutive activation of the STING pathway and aberrant interferon (IFN) production by immune cells. Single-cell RNA sequencing of PBMCs from a family carrying the STING^{V155M} mutation revealed a monocyte-enriched Unfolded Protein Response (UPR) gene signature, with elevated PPP1R15A/GADD34 expression indicative of Integrated Stress Response (ISR) induction downstream of endoplasmic reticulum (ER) stress and EIF2AK3/PERK activation. The ISR mitigates stress by globally reducing protein synthesis and engaging antioxidant responses via the NRF2 pathway. Notably, one STING^{V155M} patient lacked the UPR signature and presented with atypical, systemic lupus erythematosus-like immune symptoms and clinical features [1]. Genetic analysis identified in this patient an additional heterozygous missense variant, p.P649T, in EIF2AK3, encoding the UPR kinase PERK. Given emerging evidence, including our own, that PERK and STING signaling are intertwined to support optimal type-I IFN production [2], we aim to dissect how the PERK^{P649T} mutation impacts STING signaling in the human monocytic THP-1 cell line model.

Methods

RNA sequencing was performed to characterize the effect of the PERK^{P649T} mutation on THP-1. We took advantage of our new Single-Nuclei Analysis of the Unfolded Protein Response (SNUPR) technique [3] to determine how the mutation influences the UPR process, and performed established molecular biology techniques to analyze several signaling pathways.

Results

We observed that PERK^{P649T} triggers ISR activation. Moreover, the mutation impairs UPR activation upon ER stress induction with thapsigargin. PERK^{P649T} also reduces reactive oxygen species (ROS) levels. Following stimulation with the STING agonist diABZI, PERK^{P649T} amplified the expression of several pro-inflammatory genes (IFN-β and TNF-α) and two type-III IFNs (IFN-λ1 and IFN-λ2). These data indicate that PERK^{P649T} modulates IFN production, likely through effects on STING, NF-κB, and/or TLR signaling pathways.

Conclusion

Together, our findings suggest that PERK influences SAVI disease severity by modulating IFN and cytokine output and highlight PERK as a potential therapeutic target to attenuate pathological IFN production in this interferonopathy.

Keywords: Auto-inflammation - Unfolded protein response - SAVI.

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PS10-P21

ER stress and matrix stiffness promote pDC-mediated fibroblast activation

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Objective
Plasmacytoid dendritic cells (pDCs) are key contributors to fibrosis in Systemic Sclerosis (SSc), a systemic autoimmune disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis of the skin and internal organs. In murine models, depletion or inhibition of pDCs alleviates fibrosis. In SSc, pDCs contribute to a strong type I IFN (IFN-I) signature, infiltrate fibrotic tissues, and exhibit dysregulated endoplasmic reticulum (ER) stress responses. Thus, we are exploring how ER stress and tissue stiffness affect the pDC-fibroblast crosstalk.
Methods
We established an *in vitro* co-culture model using CAL-1 pDCs and IMR-90 lung fibroblasts. Cells were stimulated with the ER stress inducers HA-15 and SubAB and a TLR7 agonist and cultured on substrates mimicking healthy (1 kPa) or fibrotic (50 kPa) tissue stiffness. Cellular activation was assessed by RT-qPCR, Western blotting and ELISA. PERK, STING and cGAS involvement was investigated using genetically modified CAL-1 cells. Some experiments were performed in the presence of clinically relevant inhibitors.
Results
ER stress promoted fibroblast activation in pDC-fibroblast co-cultures. Culture on stiffer substrates amplified both IFN-I production and ER stress-induced fibrotic responses. pDC-mediated fibroblast activation required direct cell-cell contact. Pre-conditioning of CAL-1 cells with ER stress inducers before co-culture was sufficient to induce fibroblast activation, indicating that ER stress imprints a transmissible pro-fibrotic phenotype in pDCs. Mechanistically, this response required PERK in CAL-1 cells but was independent of cGAS and STING. TLR7 stimulation in conjunction with ER stress had a synergistic effect on IFN-I production but did not further increase fibroblast activation in co-cultures. Moreover, pharmacological inhibition of IFN-I signaling did not affect pDC-mediated fibroblast activation.
Conclusion
ER stress promotes a PERK-dependent pro-fibrotic phenotype in a pDC cell line, promoting fibroblast activation through direct cell-cell interactions. While ER stress enhances IFN-I responses, these are unlikely to be the primary drivers of pDC-mediated fibroblast activation. Importantly, a fibrotic-like mechanical environment enhances these effects, suggesting that tissue stiffness may contribute to fibrosis persistence in SSc. Further understanding of this pathway may contribute to the development of novel therapeutic strategies to limit fibrosis in SSc.

Keywords: Systemic Sclerosis - Plasmacytoid Dendritic Cells - Endoplasmic Reticulum Stress.

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PS10-P22

NLRP6 senses ozone-induced oxidative stress, triggering the activation of pyroptotic pathways in type 1 alveolar epithelial cells

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Objective
Tropospheric ozone is a major gaseous air pollutant resulting from the photochemical interaction between nitrogen oxides and volatile organic compounds in the presence of solar radiation. It contributes significantly to the exacerbation of pulmonary inflammation in respiratory diseases such as chronic obstructive pulmonary disease (COPD), promoting disease progression and mortality.
Methods
In this context, we investigated the role of the NOD-like receptor pyrin domain-containing 6 (NLRP6) in chronic pulmonary inflammation to ozone in mice, as well as NLRP6 expression in COPD and in murine models mimicking the pathology.
Results
Analysis of public RNA-seq data revealed NLRP6 overexpression in the lung parenchyma, both in COPD and murine models of COPD. In mice chronically exposed to ozone, *Nlrp6* deficiencyattenuated airway and lung inflammation, tissue remodeling and damage. Mechanistically, ozone exposure induces oxidative stress, resulting in a decrease in glutathion peroxydase 4 (GPX4), an antioxidant defense enzyme with detoxifying properties, and an increase in 4-hydroxy-2-nonenal (4-HNE), a toxic aldehyde produced through the peroxidation of polyunsaturated fatty acids. In *Nlrp6*-deficient mice, we observed an enhanced antioxidant response, with elevated GPX4 and cysteine/glutamate exchanger (xCT/SLC7A11) levels, and reduced lipid peroxidation in alveolar epithelial cells following ozone exposure. Interestingly, ozone exposure triggers the translocation of nuclear Erythroid Factor 2 (NRF2), a key player in the antioxidant response required for the transcription of antioxidant gene, from the cytoplasm to the nucleus in *Nlrp6*-deficient mice, but not in wild-type mice. These results suggest that NLRP6 senses oxidative stress and promotes inflammation and lung epithelial injury. Furthermore, we show that ozone induces NLRP6-dependent caspase-1, caspase-11 and gasdermin D activation in type 1 alveolar epithelial cells suggesting NLRP6-inflammasome- and non-canonical inflammasome-dependent pyroptosis of these cells. These results were confirmed using mice with tissue-specific Nlrp6 deficiency.
Conclusion
Overall, we identify NLRP6 as an innate sensor of ozone-induced oxidative stress that triggers the activation of pyroptotic pathways in alveolar epithelium, potentially exacerbating COPD. Therapeutic strategies targeting NLRP6 could prove beneficial in reducing pollutant-induced cell death and mitigating the severity of chronic lung diseases.

Keywords: NLRP6 - Oxidative stress - Pyroptosis.

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PS10-P23

Autoimmune Cytopenias: A frequent manifestation in patients with Autoimmune Lymphoproliferative Syndrome (ALPS)

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Background
Autoimmune lymphoproliferative syndrome (ALPS) is a rare disorder caused by defective lymphocyte apoptosis, leading to lymphoid proliferation and autoimmune manifestations, notably autoimmune cytopenias, which represent a major complication associated with significant morbidity in patients. The aim of this study is to characterize the clinical, immunological, and genetic profiles of ALPS patients, with a particular focus on autoimmune cytopenias.
Methods
In this study, we report 13 cases of ALPS, all presenting with autoimmune cytopenias, diagnosed and followed in the Pediatric Infectious Diseases and Clinical Immunology Department at the mother and Child Hospital A. Harouchi.
Results
Thirteen ALPS patients (9 males, 4 females) with autoimmune complications, mainly autoimmune cytopenias, were included. The median age at symptom onset was 12 months, and the median age at diagnosis was 48 months. Clinically, all patients presented with autoimmune cytopenias, while 13/13 patients (100%) showed lymphoproliferation (splenomegaly, hepatomegaly, and/or polyadenopathies). Immunologically, double-negative T lymphocytes (DNTs) were elevated in 11/13 patients (85%), and vitamin B12 was increased in 8/13 patients (62%). Genetically, 4 patients (31%) were confirmed: 2 with Casp10 mutation, 1 with NFKB1 mutation, and 1 with NCF2 mutation, while no Fas/FasL pathway mutations were identified.
Conclusion
ALPS frequently presents with autoimmune manifestations. In the presence of autoimmune cytopenias accompanied by lymphoproliferation, screening for this syndrome is strongly recommended to ensure optimal management of these patients.

Keywords: ALPS - Autoimmune cytopenias - Pediatries.

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PS10-P24

Molecular determinants of TYPE-2 CD4⁺ tissue resident memory T Cells in atopic dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disease driven by type-2 immune responses and epidermal barrier dysfunction. In contrast to CD8⁺ tissue-resident memory T cells (TRMs), the mechanisms governing the differentiation and maintenance of IL-4/IL-13-producing CD4⁺ TRMs (TRM2) remain poorly understood. Single-cell transcriptomic studies in human AD have revealed disease-associated stromal and immune programs, suggesting that tissue context and skin microanatomy may influence the establishment of a TRM2 residency program.

To address this question, we leveraged preclinical models of skin inflammation representing distinct immune endotypes: type 2 inflammation induced by repeated exposure to calcipotriol (MC903), type 1 inflammation induced by the hapten DNFB, and type 17 inflammation induced by the TLR7 agonist imiquimod. Using these models, combined with single-cell RNA sequencing, spectral cytometry and lineage-tracing approaches, we performed comparative phenotypic and functional analyses of skin CD4⁺ TRM subsets associated with each inflammatory context and assessed their persistence over time.

Our preliminary data reveal that CD4⁺ TRMs arising in these three inflammatory settings display distinct transcriptional programs and that the persistence of CD4⁺ TRM2 in the skin is limited, not exceeding three months in total ear tissue. Ongoing studies aim to determine the fate of CD4⁺ TRM2 during the resolution of AD-like inflammation. In parallel, we are testing the contribution of several candidate regulators that may control the acquisition of the TRM2 program in AD skin.

Together, this work will delineate the molecular circuits that govern the formation and persistence of CD4⁺ TRM2 cells in the skin. These insights may pave the way for the development of novel therapeutic strategies aimed at modulating pathogenic TRM populations in allergic skin diseases.

Keywords: Atopic dermatitis - TRM CD4+ - Skin.

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PS10-P25

From Mouse to Clinic: Non-Invasive Swab-Based Profiling of Inflammatory and Barrier Markers in Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disease driven by immune dysregulation and impaired barrier function, including altered ceramide composition. In clinical practice—especially in children—non-invasive tools such as epidermal curettage, microneedle patches, and tape stripping are widely used to monitor skin biomarkers and predict therapeutic efficacy. However, these techniques remain underused in preclinical models, where invasive biopsies are still standard, limiting longitudinal monitoring and translational relevance.
This study assessed the feasibility, safety, and translational value of a non-invasive skin surface sampling strategy to monitor immune dysregulation and barrier alterations in two murine AD models. AD-like lesions were induced by chronic oxazolone application on the back or repeated MC903 treatment on the ear.
Weekly samples were collected using cotton-tipped swabs for multiplex cytokine assays and ceramide profiling, while glass beads were rolled over the skin for lipid extraction and LC-MS/MS quantification. Data from non-invasive samples were compared with full-thickness biopsies analyzed at endpoint by immunoassays and lipidomics.
Repeated sampling over 20 days caused no visible damage, distress, or interference with disease progression. Key cytokines (IL-4, IL-6, TNF, IL-1β) and ceramides were consistently detectable on the skin surface and correlated with tissue levels. Ceramide profiles reflected barrier dysfunction and inflammation, supporting their value as non-invasive biomarkers.
This dual-parameter, minimally invasive approach enables longitudinal monitoring of both immune and barrier markers in preclinical AD models. It aligns with clinical strategies, supports the 3Rs principles and enhances the translational value of murine studies.

Keywords: Atopic dermatitis - Non-invasive sampling - Skin biomarkers.

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PS10-P26

Complement fractions in cryoglobulinemia: a study of their biological distribution and clinical correlation

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Objectives
Cryoglobulins (CGs) are immunoglobulins that precipitate at temperatures below 37°C and redissolve upon warming. Decreases in complement fractions, particularly C4, are associated with the presence of CG and appear to be involved in its pathogenesis; however, the link to the clinical presentation of the disease remains poorly defined. The objective of this study was to investigate the various complement profiles in the presence of CG and to correlate them with clinical outcomes.
Methods
An experimental part aimed to measure the levels of C1q, C2, C3, C4, and C5 in plasma, cryoprecipitate (purified CG), and serum supernatant after CG precipitation using two different precipitation techniques. A second part consisted of a retrospective study (January 2023–June 2026) of a cohort of patients with cryoglobulinemia, to investigate the relationships between complement profile (C3, C4, CH50) and the clinical manifestations of the disease (vasculitis, arthralgia, peripheral neuropathy, glomerulonephritis).
Results
The complement fractions studied in 35 patients were most often undetectable in the cryoprecipitate. In 7 patients, at least one of the fractions (C2, C3, C4, or C1q) was detected in the cryoprecipitate, suggesting possible but inconsistent coprecipitation. The clinical study of a cohort of 210 patients revealed an association between complement abnormalities and the clinical impact of cryoglobulins. A profile characterized by an isolated decrease in C4 was more frequently associated with a definite clinical impact of the disease, whereas normal complement levels were observed in patients without clinical impact. A score was developed, taking into account C4 and CG concentrations, to categorize the clinical impact attributable to CG.
Conclusion
This study suggests that the coprecipitation of complement fractions is not the primary mechanism explaining the decrease in certain fractions in cryoglobulinemia. Furthermore, a profile characterized by an isolated decrease in C4 (≤0.06 g/L) associated with a CG concentration (≥198 mg/L) constitutes biological markers of definite clinical manifestations of CG with a specificity of 94%.

Keywords: Cryoglobulin - Complement fractions - Vasculitis.

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PS10-P27

Role of the DNA sensor STING in immune responses to infection and lung inflammation: a One Health perspective

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Humans and livestock are increasingly facing significant health challenges due to environmental changes, rising pollutants, and close contact with both wild and domestic animals that may transmit pathogens. To address these global challenges, health agencies advocate for a «One Health» approach, integrating human, animal, and environmental health. These factors contribute to a considerable disease burden, particularly lung-associated conditions such as lower respiratory infections, asthma, and chronic obstructive pulmonary disease (COPD). Lung damage caused by infections or air pollutants often results in the presence of pathogen DNA and/or self-DNA in the cytoplasm, which activates the STimulator of INterferon Genes (STING) pathway. This activation triggers the production of cytokines, including type I and III interferons, and regulates cell death and autophagy, modulating the immune response. Recent literature and our data indicate that targeting STING activity could yield significant therapeutic benefits, highlighting the urgent need for new drugs that modulate the STING pathway in both humans and livestock. Here, we aimed to investigate the therapeutic potential of modulating the STING pathway across multiple species, including humans, mice and livestock species such as chickens and pigs. First, we assessed the kinetic and dose-dependent effects of selected STING agonists on primary human bronchial airway epithelial cells (hAECs). We evaluated STING pathway activation kinetics, cell death through LDH release, IFNb and IFNl production, as well as the production of pro-inflammatory cytokines. Bronchial hAECs stimulated with either natural STING agonist cGAMP or the synthetic agonist diABZI, showed increased expression of pSTING/STING and pTBK1/TBK1 proteins at 6h time point, followed by the production of IFN-β and IFNl. In addition, activation of the STING pathway induced the secretion of IL-6, IL-8, and CXCL10. Stimulation of Bronchial hAECs with 2'3'-cdiAMP and poly(dG:dC) resulted in IFNb production at later time point (24h). These findings provide a basis for selecting an optimal time point for future studies and will facilitate the characterization of novel STING agonists and antagonists.

Keywords: STING - One Health - Immunity.

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PS10-P28

A novel lncRNA modulates Th cell identity and inflammatory responses

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Objectives

CD4⁺ T cells integrate molecular signals to differentiate into effector and regulatory subsets (Th), a plasticity essential for appropriate immune responses. Long non-coding RNAs (lncRNAs) have emerged as important regulators of T cell identity and function, but their contribution to Th cell differentiation remains poorly understood. We aimed to identify and characterize novel lncRNAs involved in Th cell identity and function.

Methods

We analyzed RNA-seq datasets from different Th subsets to identify lncRNAs selectively expressed during T cell differentiation. Functional characterization was performed by CRISPR/Cas9-mediated deletion in naïve CD4⁺ T cells before Treg and Th2 in vitro differentiation. The role of the identified lncRNA in inflammatory diseases was investigated using mouse models of colitis and asthma. Finally, antisense oligonucleotide (ASO)-mediated depletion was used to investigate its mechanism of action.

Results

RNA-seq analysis identified an uncharacterized lncRNA within the *Lrrc32* locus. HiChIP revealed chromatin interactions between the lncRNA and the *Lrrc32* promoter in Tregs, suggesting a potential *cis*-regulatory relationship. *Lrrc32* encodes GARP, a membrane protein involved in TGF-β activation and Treg-mediated immunosuppression. The lncRNA was also highly expressed in Th2 and Th9 cells, suggesting a broader role in Th cell differentiation.

CRISPR/Cas9-mediated deletion of this *Lrrc32*-associated lncRNA in naïve CD4⁺ T cells increased *Lrrc32* and *Foxp3* expression and TGF-β concentration in the supernatant following Treg differentiation. In Th2 cells, its deletion similarly increased *Lrrc32* expression but impaired Th2 identity, reducing Th2 cytokine levels. Moreover, iTregs deficient in this lncRNA displayed enhanced immunosuppressive activity in a mouse model of colitis, while lncRNA-deficient Th2 cells induced reduced Th2 response in a mouse model of asthma. Finally, ASO-mediated depletion of the lncRNA recapitulated *Lrrc32* upregulation, showing that the lncRNA transcript itself contributes to this regulation.

Conclusion

We identified an *Lrrc32*-associated lncRNA as a novel regulator of Th cell identity and function, with distinct effects on Treg and Th2 responses. This lncRNA regulates *Lrrc32* expression and, at least in part, exerts its effects through its transcript. The ability to modulate Treg and Th2 responses *in vivo* highlights this lncRNA as a potential target for ASO-based therapeutic approaches in immune-mediated diseases.

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PS10-P29

A human eIF2AK3 (PERK) variant synergizes with STING to drive enhanced type-I IFN and inflammatory cytokines expression in monocytes of a SAVI patient

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Endoplasmic reticulum (ER) stress triggers the integrated stress response (ISR) by activating EIF2A kinase 3 (PERK) and phosphorylating eukaryotic initiation factor 2α, reducing global protein synthesis and promoting cellular adaptation and survival. Recent studies indicate that the stimulator of interferon genes (STING) can also activate PERK, preceding type I interferon (IFN) production in response to viral DNA. Conversely, we have shown that selective ER stressors, such as bacterial Subtilase cytotoxin (SubAB) or the small BIP inhibitor HA-15, activate PERK and in turn stimulate STING and IFN production in human plasmacytoid dendritic cells (pDCs), with strong synergy upon TLR7 activation. The identification of a patient with STING-associated vasculopathy in infancy (SAVI) carrying mutations in both Sting1 and eif2ak3, and exhibiting distinct autoimmune features compared to affected relatives lacking the PERK mutation, underscores the importance of PERK-STING crosstalk in innate immunity. Using cell biology approaches combined with bulk and single-cell RNA sequencing, we further demonstrate that the patient's PERK mutation impairs monocyte differentiation, robustly amplifies STING signaling, and greatly increases transcription of IFN-β, IFN-λ, and pro-inflammatory mediators such as IL6 and CXCL10. Notably, this PERK variant strongly activates the NRF2/HO-1 pathway and enhances NF-κB pathway activation following STING stimulation. Importantly, while cytokine mRNA expression is markedly upregulated, translation into functional proteins remains tightly controlled until additional stress signals arise, revealing a previously unrecognized level of translational regulation mediated by the PERK-STING interaction. Our findings provide novel insights into the dual roles of the ISR in regulating monocyte differentiation and STING activation, with significant implications for the pathogenesis of interferonopathies and autoimmune diseases.

Keywords: UPR - STING - SAVI.

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PS10-P30

Characterization of Factor VIII-specific regulatory and conventional CD4+ T cells using TCR tranfer in Jurkat cells by microfluidics

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Objective

Up to 30% of Factor VIII (FVIII)-treated *Hemophilia A* patients develop antibodies against FVIII resulting in loss of treatment efficacy. Anti-FVIII antibodies are also detectable in healthy donors (HD), suggesting incomplete immune tolerance toward this endogenous protein. CD4+ conventional T cells (Tconv) are thought to drive this response through T-cell receptor (TCR) recognition of FVIII-derived peptides, whereas regulatory T cells (Treg) contribute to immune tolerance. Thus, the FVIII-specific Tconv/Treg balance is thought to be crucial for immune tolerance toward FVIII. We previously identified the most immunogenic FVIII-derived peptides in HD. Here, we aimed to better understand the loss of immune tolerance to FVIII by comparing the TCR repertoires of specific Tconv and Treg and their cognate epitopes within the same healthy individuals. Because of the limited number of FVIII-specific T cells, we therefore developed a new microfluidic-based approach allowing TCR repertoire transfer into a Jurkat reporter cell line.

Methods

CD4+ Tconv and Treg isolated from HD were stimulated for three weeks with autologous dendritic cells loaded with immunogenic FVIII-derived peptides. About 10,000 specific Tconv and Treg cells were sorted based on their CD137 expression and encapsulated as single-cells in semi-permeable capsules using a microfluidic instrument. Complete FVIII-specific TCR repertoires were next sequenced using NGS and re-expressed using CRISPR–Cas9 engineering in Jurkat cells. Thus, TCR-mediated activation can be detected through the expression of reporter fluorescent proteins.

Results

From three HD, FVIII-specific Tconv and Treg were detected at mean frequencies of 2.1 and 0.33 cells per million total CD4+ T cells, respectively. Comparison of FVIII-specific TCR clonotypes between Treg and Tconv revealed no shared clonotypes within individual donors. Moreover, NGS sequencing performed before and after TCR transfer confirmed the successful immortalization of the 20 most abundant TCRs which represent, at least, 87% of the total TCRs sequenced.

Conclusion

Despite the low frequency of FVIII-specific Tconv and Treg in healthy donors, FVIII-specific TCRs have been immortalized in Jurkat reporter cells to assess TCR avidity, HLA restriction, and antigen specificity. This approach should provide new insights about T cell tolerance to FVIII and could be applied to other T cell specificities.

Keywords: Tolerance - Immunogenicity - Microfluidic.

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PS10-P31

Inflammation-Driven Treg Adaptation Reveals a Distinct Effector State in Rheumatoid Arthritis Synovial Fluid

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Objective
Regulatory T cells (Tregs) accumulate in inflamed Rheumatoid Arthritis (RA) joints but fail to restore immune homeostasis. However, the effects of synovial fluid (SF) on Treg plasticity remain poorly understood. We investigated how CCP^+ and CCP^- RA SF differentially affects Treg phenotype, suppressive function and adaptation to the inflammatory microenvironment.
Methods
SF (CCP^+ or CCP^-) was collected from 12 RA patients. We evaluated the effects of SF CCP^+ and SF CCP^- on proliferation, phenotype (FoxP3, Helios and activation marker expression), and suppressive function of Tregs from healthy donors. To further map heterogeneity, multiparametric immunophenotyping and scRNA-seq was performed on paired synovial and peripheral $CD4^+$ T cells, enriched in Tregs, from RA patients.
Results
CCP^+ SF was associated with IL-17A and disease activity, whereas CCP^- SF with increased IFN-γ, IL-6, IL-8, and TNF-α. Purified effector Tregs (eTregs) cultured with CCP^+ RA SF showed a significant reduction in the $FoxP3^{high}Helios^{high}$ population. Despite this, suppressive function was maintained, suggesting that Tregs adapt to inflammatory environments while preserving regulatory capacity. Transcriptomic analyses revealed distinct signaling programs, with CCP^+ SF treated eTreg characterized by reduced IL-2 signaling and CCP^- SF treated eTreg skewed toward Th2-like pathways.
ScRNA-seq analysis of PB and SF samples from RA patients further mapped Treg functional states, and differentiation trajectories. Compared to PB, SF contained increased frequencies of peripheral helper, exhausted, and cytotoxic T-cells. We identified an activated Treg state enriched in RA SF and characterized by LAG3 expression within a heterogeneous $CXCR6^+$ compartment comprising $CXCR6^+BATF^+$ and $CXCR6^+CCR6^+$ states. These cells retained FOXP3 transcripts despite reduced FoxP3 protein expression, suggesting altered regulation. Trajectory analysis positioned $LAG3^+$ Tregs along a path toward terminal differentiation, consistent with SF-effector state.
Conclusion
We demonstrate that inflammatory RA synovial fluid promotes substantial Treg plasticity, shaping Tregs toward persistent effector states without necessarily abolishing their suppressive function. Despite reduced FoxP3 protein expression, these cells may retain regulatory capacity through FoxP3-independent mechanisms. This highlights the role of Treg adaptation in tolerance and autoimmunity, and its potential implications for Treg therapies in RA

Keywords: Rheumatoid Arthritis (RA) Synovial Fluid - Regulatory T cell (Treg) Plasticity - $LAG3^+$ Tregs.

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PS10-P32

Intestinal mucosal glycosylation as a regulator of the gut-joint axis

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The "Epithelial Barrier Theory" proposes that disruption of epithelial barriers contributes to the rising prevalence of autoimmune and chronic inflammatory diseases, including i**nflammatory bowel disease** (IBD) and **rheumatic disorders**. We have shown that alterations in intestinal mucosal glycosylation reshape the microbiota and influence intestinal inflammation[1]. Furthermore, changes in the circulating IgG glycome precede the clinical onset of Crohn's disease (CD)[2], supporting a role for glycosylation in early disease development. However, whether alterations in the intestinal mucosal glycome impair barrier integrity and promote gut-derived antimicrobial immune responses capable of driving inflammation at distant sites remains unknown.

We hypothesize that disruption of the intestinal mucosal glycome acts as an upstream trigger of epithelial barrier dysfunction, microbial alterations and intestinal inflammation, ultimately promoting **circulating antimicrobial antibodies** that contribute to joint inflammation.

Using a glycoengineered mouse model with intestinal epithelial-specific truncation of N-glycans, we assessed intestinal barrier integrity and permeability, together with circulating antimicrobial and anti-glycan antibodies. To investigate the contribution of mucosal glycosylation to the gut-joint axis, mice were subjected to DSS-induced colitis and collagen antibody-induced arthritis (CAIA). Disease phenotypes and immune responses were characterized using histological, cellular, serological and glycomic approaches. The relevance of these mechanisms is also being evaluated in a clinical cohort of patients with concomitant IBD and spondyloarthritis (SpA).

Disruption of intestinal mucosal glycosylation led to increased anti-glycan/antimicrobial antibody titers, enhanced intestinal permeability and greater systemic exposure to pro-inflammatory microbial products. We also successfully established CAIA in this model, revealing genotype-dependent differences in disease phenotype and distinct immune profiles between wild-type and glycosylation-truncated mice.

Together, these findings identify intestinal mucosal glycosylation as a potential upstream regulator of epithelial barrier integrity, antimicrobial antibody responses and systemic inflammation, providing initial mechanistic evidence for a role of the intestinal glycome in the gut-joint axis.

Keywords: Glycosylation - Gut permeability - Inflammatory Disease.

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PS10-P33

Characterization of pathogenic autoreactive B cells in antiphospholipid syndrome

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Objective

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disorder characterized by vascular thrombotic events and/or pregnancy complications, mediated by pathogenic antiphospholipid antibodies (aPL) targeting β2-glycoprotein I (β2GPI). Among these, antibodies directed against domain I (DmI) of β2GPI are strongly associated with thrombotic APS and represent a particularly pathogenic aPL subset. However, the B cells giving rise to anti-DmI antibodies remain poorly characterized, and the mechanisms allowing their escape from immune tolerance are largely unknown. We previously showed that aPL-producing B cells are present in the natural repertoire, display polyreactivity and a restricted BCR repertoire, and show dysregulation of the mTORC1 and MYC pathways in primary APS patients (PAPS). Here, we sought to define the cellular and molecular features of DmI-specific B cells, from BCR repertoire to antibody pathogenic potential.

Methods

DmI-specific B cells were identified using tetramerized DmI probes and phenotyped by flow cytometry in healthy donors (HD) and PAPS, then isolated by single-cell sorting and cultured in a Nojima-like system for BCR analysis. DmI specificity was then revalidated in culture supernatants, which were assessed for polyreactivity. Selected sequences are being cloned and recombinantly expressed for specificity and functional characterization, including lupus anticoagulant activity. Epitope mapping of selected anti-DmI antibodies will subsequently be performed. Single-cell Sort-seq analyses are ongoing.

Results

DmI-specific B cells were enriched within the unswitched memory compartment in PAPS. In HD, their frequency decreased between the naive and switched memory compartments, whereas this reduction was not observed in PAPS. DmI-specific antibodies recovered from single-cell cultures were polyreactive, consistent with our previous findings on the aPL-producing B-cell repertoire. BCR repertoire analysis showed no clear IGHV restriction, but CDR3 regions were enriched in positively charged amino acids, a feature associated with autoreactivity. Functional characterization of selected recombinant antibodies and single-cell Sort-seq analyses are ongoing.

Conclusion

Altogether, these findings extend our previous observations to DmI-specific B cells and support an altered selection of autoreactive B cells in PAPS. Ongoing analyses will further define these cells' molecular characteristics and contribution to APS pathogenesis.

Keywords: Antiphospholipid syndrome (APS) - Autoreactive B cells - Immune tolerance breakdown.

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PS10-P34

Beyond platelets: *ACTN1* variants drive immune dysregulation at the thrombocytopenia-autoimmunity interface

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Background

ACTN1, encoding an actin-binding protein critical for cytoskeletal organization, underlies inherited thrombocytopenia[1], yet its potential role in immune homeostasis remains unexplored. Cytoskeletal dynamics govern both platelet function and lymphocyte activation, and actinopathies have recently emerged as a distinct class of immune dysregulation disorders.

Methods

We studied a cohort of 4 patients with immune thrombocytopenic purpura (ITP) carrying heterozygous *ACTN1* variants. Functional analyses included lymphocyte and platelet phenotyping, actin remodeling assessment by microscopy, cell migration and deformability assays, and surface expression of immunoregulatory molecules.

Results

Patients presented with autoimmune cytopenias and immunological abnormalities. Microscopy revealed altered cell morphology consistent with impaired actin remodeling, likely disrupting intracellular trafficking and cell activation. Lymphocytes showed increased migration speed and reduced deformability. Strikingly, patient platelets overexpressed CD40L, a key driver of loss of immune tolerance[2], suggesting that platelet-mediated immune activation may contribute to autoimmunity in these patients.

Conclusions

ACTN1 joins a growing family of platelet-disease genes, including *NBEAL2*[3], whose loss-of-function engages a dual thrombocytopenic and autoimmune program. These findings reveal a previously unrecognized role for ACTN1 at the interface between platelet biology and immune tolerance and highlight the power of genetic dissection to reframe ITP as a mechanistically heterogeneous disorder amenable to targeted intervention.

Keywords: Immune thrombocytopenia - Autoimmunity - Actin cytoskeleton.

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Dynamic type I IFN signature, monocyte bias and impaired TLR7/8 response in SITRAME syndrome

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Objectives

Systemic Inflammatory Trunk Recurrent Macular Eruption (SITRAME) syndrome is a recently discovered autoinflammatory disorder [1] characterized by recurrent flares of macular eruptions on the trunk, associated with elevated C-reactive protein [2]. Association of flares with viral infections history or messenger Ribonucleic Acid (mRNA) vaccination suggests the involvement of type I interferon (I-IFN) signaling in the disease. Absence of efficient therapeutic options in this condition reflects the need for a better comprehension of its pathogenesis. The aim of the study is to identify the inflammatory pathways involved in SITRAME syndrome.

Methods

A multi-omic approach was adopted, incorporating cellular, plasmatic cytokine, transcriptomic, and genomic analyses. 15 patients were prospectively included, with paired basal and flare samples for four individuals. Genetic origin of the disease was investigated by whole exome sequencing in blood and skin. Inflammatory profile in active and inactive patients was evaluated using bead-based conventional or digital ELISA on plasma and targeted transcriptomic analysis on whole blood. Circulating immune cells distribution and activation was evaluated by mass and flow cytometry. Whole blood was stimulated with oligodeoxynucleotide (ODN), resiquimod (R848) and polyinosinic-polycytidylic acid (poly(I:C)) using Truculture assays and cell activation was analyzed by digital ELISA .

Results

No pathogenic genetic variants were found. Transcriptomic profiling demonstrated a common innate immunity activation in patients at baseline. During flares, patients demonstrated an upregulation of C-X-C motif chemokine ligand 10 ($p = 0.0384$) and interferon-α ($p = 0.00159$) protein levels versus healthy donors. Patients experiencing flares showed increased circulating monocytes, with a bias towards CD14++CD16+ monocytes. Stimulation with a TLR 7/8 agonist resulted in decreased I-IFN production in patients compared to HD.

Conclusion

Together our finding identified: i) a basal subclinical activation of innate immunity in patients and ii) altered type I interferon signaling in SITRAME patients, paving the way for evaluation of type I interferon targeted treatment strategies in this condition.

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Keywords: Translational research - Type I interferon - Autoinflammatory.

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PS10-P36

Dysregulated dsRNA sensor signaling and viral infection during onset of pediatric autoimmune interferonopathy

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Objective
Juvenile dermatomyositis (JDM) is characterized by a type I interferon (IFN-I) signature associated with disease activity. We aim to valuate the link between viral infections, nucleic acid sensor responses and JDM onset.
Methods
Blood from controls and JDM patients at diagnosis was used to study circulating inflammatory cytokines levels using bead based conventional and digital ELISA. Circulating cells phenotyping was evaluated by mass cytometry. Whole blood was stimulated with R848 and poly I:C using True culture tubes and cell activation was analyzed using bead based conventional and digital ELISA and BRB sequencing. Single cell RNAseq and ATACseq were performed on PBMC from an active new onset patient and 2 controls. SARS-CoV-2 RNA in muscle biopsies was seek using RNAscope technology. Plasmatic IgG against 27 common childhood infections were measured by multiplex ELISA.
Results
Newly diagnosed JDM patients display an overexpression of *IFIH1* (encoding MDA5 protein) at baseline, coupled with an altered response to dsRNA stimulation at proteomic and transcriptomic levels. We identified a myeloid-specific enrichment of interferon-stimulated genes (ISGs) and preferential disruption of chromatin accessibility in genes from the Type I IFN pathway at disease onset. SARS-CoV-2 RNA was present in muscle biopsies of Covid-19 pandemic-onset JDM patients. Increased exposure to RSV B was confirmed in two independent cohorts.
Conclusion
Together, these findings integrate systemic, single-cell, and tissue-level analyses implicating RNA viral infection and biased antiviral sensing in shaping IFN-I responses at JDM onset, providing mechanistic insight into environmentally triggered pathogenesis.

Keywords: Dermatomyositis - Interferon - Infection.

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PS10-P37

Targeting the MyDDosome: SPM001, a Stapled Peptide Inhibitor of IRAK4/IRAK2 interactions for NF-κB-Driven Inflammation

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Objective
The MyDDosome, a multiprotein complex recruited downstream of TLR/IL-1R receptors, is a central hub for NF-κB activation and pro-inflammatory cytokine production. Its assembly is physiologically restrained by IRAK-M (IRAK3), the endogenous TLR-signalling brake that becomes underexpressed during inflammation. Unlike catalytic IRAK4 inhibitors or IRAK4 degraders, we designed a hydrocarbon-stapled peptide, SPM001, that mimics IRAK-M to block MyDDosome assembly downstream of TLR1/2/4/5 by directly disrupting the IRAK4-IRAK2 protein-protein interaction, offering a novel mechanism to modulate inflammation.
Methods
Target engagement of SPM001 on the IRAK4-IRAK2 complex was assessed by conformational assay, while downstream impact was characterised via a 199-target NF-κB phosphoprotein array (TAK1-IKK-p65 cascade) and RNA-seq in LPS-stimulated THP-1 cells. Cytokine suppression was profiled across a SPM001 dose range in THP-1 cells and primary PBMCs using a 250-analyte NULISA panel, benchmarked against IRAK4 degrader KT474. Efficacy was evaluated in vivo in caerulein-induced pancreatitis and DSS-induced ulcerative colitis, alongside a 7-day subcutaneous tolerability study.
Results
Conformational assay confirmed specific binding of SPM001 to the IRAK4-IRAK2 complex. Functional inhibition was validated by suppression of the TAK1-IKK-NF-κB p65 phosphorylation cascade and significant down-regulation of IL-6 and TNF secretion in LPS-stimulated cells ($Q<0.05$). SPM001 dose-dependently reduced key NF-κB cytokines (TNF, IL-6, IL-12B, IL-12p70, IL-23) by 50-94% at 20 µM, outperforming KT474 (1-22% at 500 nM) in THP-1 cells and primary PBMCs. In vivo, SPM001 dampened caerulein-induced pancreatitis, reducing systemic and pancreatic inflammatory markers and histopathological injury in a regimen-dependent manner. In DSS-induced colitis, SPM001 (15 mg/kg SC BID) significantly lowered colonic IL-6, TNF-α and myeloperoxidase activity (40-49% vs vehicle, $p<0.05$) and a 46% improvement in histopathology score ($p=0.037$), matching the efficacy of the 5-ASA standard of care. SPM001 was well tolerated over 7 days of subcutaneous dosing (up to 25 mg/kg BID).
Conclusion
SPM001 represents a promising preclinical candidate for MyDDosome-targeted anti-inflammatory therapies, with superior NF-κB pathway suppression compared to existing IRAK4 inhibitors. Its selective mechanism and favorable safety profile support further development for chronic inflammatory diseases (e.g. psoriasis).

Keywords: MyDDosome - Stapled peptide - Inflammation.

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PS11-P01

Control of SARS-CoV-2 replication by activated Delta One T Cells

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Objective

Unconventional γδ T cells play a major role in immunity due to their vast TCR diversity, secretory abilities, and their activation in an MHC-independent manner, leading to faster mobilization upon viral infection. Our work search to identify if γδ1 T cells, which are the γδ T cells enriched in mucosal tissue, can be directly activated by SARS-COV-2 infection and participate to the viral clearance.

Methods

We employed a clinically relevant model of expanded γδ T cells, called Delta One T (DOT) cells, enriched in Vδ1+ T cells, to explore their role in SARS-CoV-2 infection. We co-cultured this DOT cells with human lung epithelial Calu-3 cells infected with SARS-CoV-2. We then assessed the ability of DOT cells to secrete IFN-γ by ELISA and inhibit viral replication by quantifying viral load using RT-qPCR.

Results & Discussion

We demonstrated that DOT cells secrete high levels of IFNγ in the presence of infected human pulmonary cells in vitro, confirming their activation upon SARS-CoV-2 infection. Moreover, DOT cells led to a significant reduction of viral replication. Our observation suggests a direct anti-SARS-CoV-2 activity of γδ1 T cells, which could partially be mediated by IFNγ. Our findings are essential to better characterize the involvement of γδ T cells, especially Vδ1+ T cells in the host immune response to SARS-CoV-2 and their participation in viral clearance.

Keywords: Gamma delta T-cell - SARS-COV2 - Viral clearance.

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PS11-P02

Understanding MAIT cell function in *Neisseria meningitidis* pathogenesis

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Mucosal-associated invariant T (MAIT) cells are innate-like T lymphocytes that rapidly respond to bacterial infection at barrier sites, exerting both antibacterial and tissue-reparative functions. This plasticity positions them at the intersection of host defense and tolerance, balancing pathogen clearance with tissue preservation.
Here, we investigated the role of MAIT cells during infection with *Neisseria meningitidis* (*Nm*), a bacterial pathogen responsible for meningitis and fulminant sepsis. Invasive *Nm* strains interact with human microvasculature, inducing vascular dysfunction, thrombosis, and tissue injury, particularly in the skin. This interaction is mediated by type IV pili, dynamic filamentous structures that generate high mechanical forces upon retraction, which are sensed by the host. Unexpectedly, endothelial infection with a retraction-deficient mutant (Δ*pilT*) triggered a tolerance response, preserving vascular integrity despite inflammation and reducing pathology in a humanized mouse model of invasive meningococcal disease (mice grafted with human skin).
To identify tolerance-related modifications, we performed comparative transcriptomics between skin grafts infected by the wild strain (WT) and Δ*pilT* strain. Interestingly, Δ*pilT*-infected grafts showed upregulated MAIT cell signature genes. We then analyzed MAIT cell frequency and phenotype after bacterial supernatant exposure using multiparameter flow cytometry. We quantified MAIT-activating ligands and used multiplex imaging to study MAIT cells spatial relationships with endothelial and immune cells in infected tissue.
Our results confirmed that *Nm* activates MAIT cells. *In vivo*, MAIT cells localize at the epidermis–dermis interface in both uninfected skin and skin infected with the WT strain. However, in skin infected with the Δ*pilT* strain, MAIT cells accumulate near infected vessels, suggesting that tolerance mechanisms induced by Δ*pilT* infection promote MAIT cell chemoattraction, potentially via CCL20, CXCL16, or CCL5, which are upregulated in Δ*pilT*-infected endothelial cells. Ongoing experiments are assessing differences in MAIT cell frequency, activation, and ligand production between WT and Δ*pilT* conditions.
In the context of *Nm* infection, this work may identify MAIT cells as contributors to vascular and tissue tolerance mechanisms and highlight the MAIT–endothelium axis as a potential therapeutic target to mitigate tissue damage during invasive meningococcal disease.

Keywords: MAIT cells - Tolerance - Bacterial infection.

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PS11-P03

Decoding Vδ1 T Cell-Acute Myeloid Leukemia Interactions

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Gamma delta (γδ) T cells recognise tumour cells through a mechanism distinct from conventional T cells, sensing conserved stress signals on transformed cells independently of MHC class I antigen presentation. Our group has previously demonstrated that Delta One T (DOT) cells, a Vδ1+ γδ T cell-based therapy, can recognise acute myeloid leukaemia (AML) cells via the NK receptor DNAM-1, with tumour susceptibility to DOT cell-mediated killing dependent on expression of its ligand, PVR. However, the broader molecular mechanisms governing tumour discrimination and targeting by DOT cells remain poorly understood. To address this, we performed a genome-wide CRISPR-Cas9 knockout screen in an AML cell line co-cultured with DOT cells, aiming to systematically identify novel molecular determinants of tumour cell targeting beyond NK receptor ligands. Characterising these determinants may have important implications for understanding DOT cell biology and optimising their clinical application.

Keywords: Gamma delta (γδ) T cell.

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PS12-P01

Influence of estrogen receptor ligands on NK Cell functions: consequences on anti-tumour immunity

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Breast cancer is the leading cause of cancer-related mortality among women, accounting for 12,500 deaths and 60,000 new cases annually. Various subtypes of breast cancer exist, classified according to their expression of HER2 and hormone receptors, specifically estrogen receptors (ER) and progesterone receptors (PR). For hormone receptor-positive breast cancers, the first-line treatment relies on the administration of synthetic molecules acting as estrogen receptor agonists or antagonists, namely Selective Estrogen Receptor Modulators or Degraders (SERMs/SERDs)[1].
However, estrogen receptors are also expressed by numerous immune cells, including dendritic cells[2], macrophages, and T cells. Several studies have demonstrated that estrogens exert a direct effect on these immune cells, which can be either stimulatory or inhibitory depending on the cell type, the tissue microenvironment, and the inflammatory context. Among the immune cells expressing estrogen receptor alpha ERa are Natural Killer (NK) cells, which are strongly involved in the immune response against breast cancer, particularly in controlling metastasis[3].
Nevertheless, the effects of ERa ligands on NK cells remain poorly characterized, whether concerning endogenous estrogens or synthetic SERMs and SERDs. Therefore, we sought to investigate the impact of ERa and its ligands under steady-state conditions and within an NK-dependent breast cancer context. To address this, we developed a murine model featuring a conditional deletion of ERa specifically in NK cells (NKp46Cre+ ERa Flx/Flx). This model allowed us to demonstrate that ERaexpression in NK cells directly impacts tumor control, specifically, the deletion of the receptor enables better control of tumor growth. Furthermore, our data suggest that intrinsic ERasignaling in NK cells dampens their anti-tumoral functions. We are now seeking to investigate the effect of clinically relevant ERa ligands on NK cells features.

Keywords: Estrogen receptor - NK cells - Breast cancer.

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PS13-P01

Emerging function of tissue-resident memory T cells in chronic allergic contact dermatitis

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Allergic contact dermatitis (ACD) is a $CD8^+$ T cell-driven inflammatory skin disease that often progresses to chronic forms due to repeated exposure to allergens. Chronic ACD is characterized by profound tissue remodeling, including epidermal hyperplasia and dermal fibrosis, yet the immunological mechanisms underlying this transition remain poorly understood.
Here, we explored whether repeated hapten exposure drives a functional reprogramming of $CD8^+$ T cells, uncoupling effector function from pathogenic activity.
Using a chronic DNFB-induced ACD model combined with adoptive transfer, spectral cytometry, histological analysis, and single-cell RNA sequencing, we demonstrate that hapten-specific $CD8^+$ T cells progressively acquire a hyporesponsive state marked by sustained expression of inhibitory receptors (TIM-3, PD-1, CTLA-4, LAG-3) and impaired production of effector molecules (IFN-γ, CCL3, CCL4, XCL1, granzyme B). Despite their accumulation in the tissue, these cells are dispensable for the maintenance of chronic inflammation.
Strikingly, chronically stimulated $CD8^+$ T cells adopt non-canonical functions and actively contribute to tissue remodeling, promoting dermal fibrosis through collagen III deposition. These findings identify a previously unrecognized functional switch in $CD8^+$ T cells, from cytotoxic effectors to tissue-remodeling cells.
Collectively, our results redefine the role of $CD8^+$ T cells in chronic ACD and highlight their contribution to fibrotic remodeling, providing new insights into disease chronicity and paving the way to the discovery of new therapeutic targets.

Keywords: CD8 Tcells - Chronic inflammation - Tissue remodeling.

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PS13-P02

Elucidating the mechanisms controlling the persistence of brain resident memory T cells during chronic *T. gondii* infection

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Tissue-resident memory T cells (Trm) are a subset of memory T cells that can persist long-term in non-lymphoid tissues and provide rapid local protection against re-infection or tumor development through cytokine production and cytotoxic activity. However, the molecular mechanisms underpinning their prolonged survival in non lymphoid tissues remain poorly understood.
Here, we investigated the role of the pro-survival Bcl2 family member A1 in Trm survival during chronic *Toxoplasma gondii (T.gondii)* infection. Using single-cell RNA sequencing (scRNAseq) of brain-infiltrating CD8 T cells from *T.gondii*chronically infected mice, our data revealed that A1 expression was strongly increased in brain Trm compared with their circulating splenic counterparts. Using a strain of *T.gondii* expressing the model antigen ovalbumin (OVA) and OT-I OVA-specific TCR transgenic CD8+ T cells expressing constitutive shRNA targeting A1 (shA1), we found that constitutive A1 silencing reduced OT-I accumulation and Trm frequency in the brain whereas it had no significant impact on OT-I cell frequency in the spleen. In addition, we assessed the T cell intrinsic consequence of A1-deficiency on Trm maintenance at steady state across various organs using mixed bone marrow (BM) chimeras reconstituted with a mix of wild-type (WT) and A1-deficient BM cells. No significant difference of Trm proportions across organs was observed between A1-deficient and WT T cell compartment.
Finally, our scRNAseq of brain CD8 T cells from *T. gondii* infected mice also revealed that two other pro-survival proteins, namely Mcl1 and Bcl2 were expressed in Trm albeit at lower level than A1. Since Bcl2 and Mcl1 are also keys survival proteins playing a role in the survival of various effector and memory T cell subsets during the course of an immune response, we developed a CreERT2-inducible shRNA system enabling us to silence them specifically during the chronic phase of the infection and compared their relative contribution to Trm survival. Our results revealed that silencing either molecule significantly reduced OT-I Trm accumulation in the brain, whereas only Mcl1 and Bcl2 silencing but not A1 depletion significantly reduced OT-I frequency in the spleen. Taken together, our results indicate that among the prosurvival proteins A1 specifically promoted T cell survival in non lymphoid tissues during an infection while Bcl2 and Mcl1 played a role in sustaining both circulating and resident T cell subsets.

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PS13-P03

Gain-of-function mutation in CXCR4 chemokine receptor controls the pool size of memory CD8 T-cells

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The trafficking and positioning of CD8 T-cells across anatomical compartments are essential to ensure efficient immune responses, control cell homeostasis and provide long-term protection. Immune cell positioning is tightly orchestrated by a set of chemokines and their receptors, which direct CD8 T-cells to the right place, at the right time. This is especially important during the memory stage, to favour interaction of CD8 T-cells with factors required for their maintenance, within dedicated micro-environments. CD8 T-cells notably express the CXCR4 chemokine receptor, that participates in the recruitment of naïve cells within lymph nodes, effector cells to inflamed tissues and memory cells to the Bone Marrow (BM). In line with this, several studies have pointed out a role for the BM as a site of maintenance for CD8 memory T-cells, although discrepancies remain on whether the BM provides a privileged site for proliferation and/or survival of memory CD8 T-cells.
Using a mouse model carrying a gain-of-function mutation in CXCR4 ($CXCR4^{Whim}$), we studied the role of this chemokine receptor on the dynamics of CD8 T-cells responses in mice, following lung infection with Vaccinia Virus. Our main observation shows that $CXCR4^{Whim}$ mutation considerably improves the magnitude of CD8 memory responses over long periods of time (beyond one year post-infection), by increasing the pool size of Antigen specific CD8 T-cells in the BM.
Altogether, our results uncovered an essential role for CXCR4 in controlling the long-term maintenance of a functional pool of memory cells, with putative benefits for vaccination and immunotherapy protocols.

Keywords: CD8-T cells - Memory - Maintenance.

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S2-P01

Immunovirological Discordance and AssociatedFactors among People Living with HIV underAntiretroviral Treatment at Hôpital de Jour de Donka, Guinea

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The antiretroviral treatment (ART) has significantly reduced the number of new HIV/AIDS infections and related deaths. However, cases of immunovirological discordance (IVD) are found in various locations. The objective of this study was to determine the profile of People living with HIV (PLHIV) with IVD and to identify associated factors. We conducted a cross-sectional study based on the records of PLHIV under ART for at least 6 months, followed at Hôpital de Jour Donka from 2015 to 2017, and having both viral load (CV) and CD4+ T-cell count. Prevalence of IVD was 34.57%, with 23.87% for immunological discordance (ID) and 10.7% for virological discordance (VD). Females were predominant (66.26%), and male gender influenced IVD with a statistically significant difference (p = 0.006) and was associated with VD (p = 0.007). The average age was 38.77 ± 11.30 years. PLHIV were classified at WHO stages 3 and 4 (86.01%). The median initial haemoglobin
level was 11.5 g/L [3.2 - 12]. The mean initial CD4+ T-cell count was 272.84 cells/mm3 ± 201.6. The median initial viral load (VL) was 147,337 copies/mL [1092 - 31,675,000]. The initial CD4+ T-cell count < 200 cells/mm3 was associated with IVD with a statistically significant difference (p = 0.0009) and correlated with ID (p = 0.000). Prurigo was associated with IVD with a statistically significant difference (p = 0.003). Cerebral toxoplasmosis was not associated with IVD but was associated with ID (p = 0.04). This study allowed us to describe the profile of PLHIV with IVD. The main associated factors were male gender, initial CD4+ T-cell count < 200 cells/mm3, toxoplasmosis, prurigo, and herpes zoster.

Keywords: HIV - Antiretroviral Treatment (ART) - Immunovirological Discordance.

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1. Author, Year, Journal, Page.

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S2-P02

Cardiometabolic disorders exacerbate bacterial pneumonia and reshape lung neutrophil states in a murine model

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Objective
Cardiovascular diseases are the leading cause of death worldwide. Pneumonia is among the most common infectious diseases, and its acute-phase mortalityremains a major clinical challenge. Inflammation contributes to the development and progression of both cardiovascular and respiratory diseases; however, the mechanisms by which cardiometabolic disease alters host responses to pneumonia remain poorly understood. The European HOMILUNG project aims to elucidate the link between cardiovascular and respiratory diseases (CVRD). Here, we used preclinical animal models to investigate the causal mechanisms by which CVRD affects the immune response to bacterial pneumonia.
Methods
We used LDLR$^{-/-}$ mice, a model of susceptibility to hypercholesterolemia and atherosclerosis, and wild-type (WT) controls to investigate how cardiometabolic disorders affect inflammatory and immune responses to pneumonia. Mice were fed either a high-fat diet (HFD) or a normal chow diet (NCD) for 16 weeks. Body weight and plasma cholesterol levels were monitored throughout the dietary intervention. Atherosclerotic lesion development was evaluated at the end of the diet period. At the end of the 16-week diet period, mice were either infected with *Escherichia coli* to induce pneumonia or left uninfected. Flow cytometry and single-cell transcriptomic analysis were used to characterise the immune populations.
Results
Mice on an HFD gained significant weight. Plasma cholesterol levels increased only in LDLR$^{-/-}$ mice. We found that LDLR$^{-/-}$ HFD mice exhibited significant atherosclerotic lesions, particularly compared to WT mice, which only showed signs of obesity, and LDLR$^{-/-}$ NCD mice. These results confirm the induction of hypercholesterolemia and support the validation of our atherosclerosis model. HFD-fed male mice showed high mortality within 24 h after *E. coli* infection, with the highest mortality observed in LDLR$^{-/-}$mice. These findings indicate that the combination of a high-fat diet and atherosclerosis susceptibility is associated with severe pneumonia. We therefore analysed single-cell transcriptomic data of lung cells to investigate infection-induced changes in cellular composition and immune-cell heterogeneity.
Conclusion
Following *E. coli*-induced pneumonia, lung neutrophils revealed marked heterogeneity in the lung. Diet-associated transcriptomic changes were most pronounced in neutrophils, suggesting a potential contribution of altered neutrophil states to pneumonia severity.

Keywords: Pneumonia - Cardiovascular disease - Mouse model.

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S2-P03

Integrative transcriptomic analysis reveals early host response programs associated with divergent tuberculosis outcomes

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Objective
Tuberculosis (TB) is a highly heterogeneous disease. This diversity reflects the complex interaction between host genetics and the natural genetic variability of the *Mycobacterium tuberculosis* (*Mtb*). There are currently ten well-defined phylogenetic lineages of human-adapted TB-causing bacteria with distinct biological properties and geographical distributions, and which can differentially influence clinical outcome. Among these lineages, lineage 6 (L6) is geographically restricted to West Africa and has been associated with slower progression to active TB, whereas lineage 4 (L4) is globally disseminated and an important cause of TB in the world. Comparing host responses to *Mtb* strains belonging to L6 with those induced by L4 *Mtb* isolates may provide an opportunity to identify transcriptional programs associated with protection, resistance, susceptibility and disease progression.
Methods
We performed an integrative RNA-seq analysis across human blood, murine and macrophage infection models. Human blood samples infected with *Mtb* L4 or L6 were analysed to identify lineage-specific transcriptional signatures. To dissect host pathways underlying these responses, we integrated in vivo data from relatively resistant C57BL/6 and highly susceptible C3HeB/FeJ mice infected with clinical *Mtb* isolates associated with distinct disease severities. Finally, bone marrow-derived macrophages (BMDMs) infected with *Mtb* L4 or L6 were analysed to assess whether lineage-specific responses are detectable at the innate immune cell level.
Results
Our murine and BMDMs data suggest that *Mtb* L4 and L6 isolates induce divergent transcriptional responses at very early stages of infection, both in the lung and at the macrophage-intrinsic level. In contrast, human data revealed that the overall blood transcriptomic profile was similar between patients infected with *Mtb* L4 and L6. These findings suggest that early host–pathogen interactions may imprint downstream immune trajectories and contribute to differences in bacterial control, inflammatory pathology and disease progression.
Conclusion
Our data support early transcriptional events to *Mtb* infection as orchestrators of progression towards controlled immunity, inflammatory pathology or susceptibility to disease. By integrating human, murine and macrophage RNA-seq datasets, this work provides a framework to identify specific host pathways that may inform future host-directed strategies aimed to limiting TB progression.

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Flagellin enhances innate immune responses in human airway epithelium during bacterial infection

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Enhancing innate immunity represents a promising adjunctive strategy to conventional antibiotic therapy. Bacterial flagellin, a Toll-like receptor 5 (TLR5) agonist, has been shown to stimulate innate immune defenses when delivered via the respiratory route, demonstrating efficacy in both preventing and treating bacterial pneumonia in murine models. This protective effect is primarily mediated through TLR5-driven activation of airway epithelial cells.

Objective

This study aimed to characterize the immunomodulatory effects of flagellin and to assess its tolerance on human primary respiratory epithelium.

Methods

FLAMOD, a recombinant flagellin, was administered apically as liquid droplets or by nebulization on human nasal and bronchial (MucilAir™) primary epithelial cells, cultured at the air-liquid interface. The innate immune response was followed by RNA sequencing.

Results

We demonstrated that apical administration of FLAMOD induced robust immune responses in airway epithelium derived from healthy individuals, as well as patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). TLR5-mediated epithelial signaling triggered key immune-related pathways, including cytokine production, leukocyte chemotaxis, neutrophil recruitment, and antimicrobial defense, with strong commonalities across healthy and diseased airway epithelia. Repeated FLAMOD treatment is well tolerated across a broad range of doses, with minimal effects on epithelial integrity and function. Furthermore, we demonstrated that FLAMOD effectively activated immune responses during infection of airway epithelium with the bacteria *Pseudomonas aeruginosa* or *Streptococcus pneumoniae*. However, epithelial activation alone was insufficient to directly limit bacterial colonization or replication, highlighting the potential role of epithelial-immune cell interactions in achieving effective bacterial clearance.

Conclusion

These findings support TLR5 activation as a promising therapeutic strategy to enhance host defense mechanisms and improve treatment outcomes for bacterial pneumonia in both healthy individuals and patients with COPD or CF

Keywords: Flagellin / TLR5 - Human airway epithelium - Bacterial infections.

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HIF-1α licenses BCG-induced trained immunity to promote pulmonary and systemic protection against *Brucella abortus* infection

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Bacillus Calmette-Guérin (BCG) vaccination can induce trained immunity and heterologous protection, but the contribution of hypoxia-inducible factor-1α (HIF-1α) remains incompletely defined. We investigated whether myeloid HIF-1α coordinates central and peripheral adaptations to systemic BCG immunization and determines protection against respiratory *Brucella abortus* infection. Wild-type and myeloid HIF-1α-deficient mice were immunized intravenously with BCG. Bacterial persistence and myeloid-cell phenotypes were examined in bone marrow (BM), spleen and lung, while bone marrow-derived macrophages (BMDMs) were analyzed for inflammatory, transcriptional, signaling and bioenergetic recall responses. Protection was evaluated after antibiotic treatment, washout and intranasal *B. abortus* challenge. HIF-1α deficiency increased persistent BCG burden in the lung, spleen and BM. Despite increased splenic accumulation of macrophage-enriched populations, deficient cells displayed attenuated iNOS- and CCR7-associated activation and reduced nitrite production. Macrophages generated from BCG-immunized wild-type BM retained enhanced inflammatory and metabolic responsiveness after *ex vivo* differentiation and elimination of detectable viable BCG. Upon *B. abortus* challenge, prior BCG exposure enhanced *Nos2, Ccr7, Hk2* and *Glut1* expression, IL-6 and IL-1β production, nitrite generation and compensatory glycolysis in wild-type macrophages, whereas these responses were diminished or absent in HIF-1α-deficient macrophages. Preserved mTOR-S6K phosphorylation in deficient macrophages was insufficient to restore the complete recall response, and their mitochondrial phenotype showed increased oxygen consumption without a proportional increase in ATP-linked respiration. An independent reanalysis of public ChIP-seq data linked systemic BCG exposure to H3K27ac remodeling at immunometabolic loci in BMDMs. *In vivo*, BCG immunization reduced *B. abortus* burden in the lungs, liver and spleen and limited hepatic granulomatous pathology in wild-type, but not myeloid HIF-1α-deficient, mice. BCG reduced pulmonary inflammatory involvement in both genotypes, dissociating antimicrobial control from tissue inflammation. These findings identify myeloid HIF-1α as a determinant of the immunometabolic quality of BCG-induced trained immunity, linking BM programming, tissue-specific responses and durable heterologous protection against intracellular bacterial infection.

Keywords: BCG - trained immunity - Brucella abortus.

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Development of a Simoa-Based Assay for virokine cmvIL-10 quantification.

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Background
Cytomegalovirus (CMV) is a highly prevalent virus that establishes lifelong persistence following primary infection. To sustain persistent infection, CMV has evolved numerous immune evasion strategies, including molecular mimicry of host immunomodulatory proteins. A prominent example is cmvIL-10, a viral homologue of human interleukin-10 (hIL-10) encoded by the viral UL111a gene [1], which recapitulates several of the immunomodulatory functions of its human counterpart. Although numerous *in vitro* studies have demonstrated the potent immunomodulatory properties of cmvIL-10 [2-3], clinical data on its production and biological relevance in patients remain limited. We developed a single-molecule array (Simoa) assay for the quantitative detection of cmvIL-10 in human plasma.
Methods
The assay used recombinant human IL-10 receptor alpha IL-10Rα (ACROBiosystems®) immobilized on beads as the capture reagent and the AF117 antibody (R&D Systems®) as the detection antibody. This in-house assay was compared with a commercially available Simoa-adapted assay using AF117 antibody as the capture and detection reagent. Following optimisation and verification that there is no cross-reaction with hIL-10, both assays were evaluated in healthy CMV-seronegative individuals, healthy CMV-seropositive individuals, and immunocompromised patients with CMV viremia.
Results
In plasma samples, the commercial assay showed a lack of specificity, with a positive signal detected in 100% of CMV-seronegative healthy individuals. In contrast, our assay demonstrated high analytical specificity, with no detectable signal in either CMV-seronegative or CMV-seropositive healthy individuals. cmvIL-10 was detected in 5 of 15 patients with CMV viremia, with concentrations ranging from 158 to 1941 pg/mL. Among viremic patients, cmvIL-10 concentrations were not correlated with CMV viral load, suggesting that virion and cmvIL-10 production may not be directly related.
Conclusion
We developed, for the first time, a Simoa-based assay allowing specific detection and quantification of circulating cmvIL-10 in human plasma by using the IL-10Rα as a capture reagent. The virokine cmvIL-10 was detectable at substantial concentrations in a subset of patients experiencing CMV reactivation. These findings provide the first step toward investigating the clinical relevance of circulating cmvIL-10 and raise the question of whether its immunomodulatory activity may contribute to impaired immune responses.

Keywords: Virokine - Interleukin-10 - Cytomegalovirus.

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S2-P07

Elucidating the endothelial transcriptional landscape during *Neisseria meningitidis* infection by using single-cell and spatial profiling

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Invasive infections by *Neisseria meningitidis* lead to sepsis and meningitis in humans. Bacteria proliferate attached to the endothelium inside the vessel lumen leading to inflammation, coagulation and vascular damage. Endothelial cell function is clearly perturbed during infection, but we have also shown that an effective innate immune response is dependent on endothelial cells through the expression of E-Selectin and the recruitment of neutrophils.
Using a skin xenograft humanized mouse model of *N. meningitidis* infection, we propose to investigate the impact of infection on the endothelium and its role in orchestrating the immune response in the dermal vasculature.
To dissect how endothelial cells are both impacted in their key barrier function and contribute to the innate immune response, we will employ a multi-modal approach combining single-cell and spatial transcriptomics. First, single-cell RNA-sequencing (scRNA-seq), on infected tissues, will allow us to isolate endothelial cells and define their complete transcriptional signature upon *N. meningitidis* infection. Next, spatial transcriptomics will allow us to visualize where these transcriptional changes occur within the native tissue environment.
Together, these approaches will build a high-resolution map of the vascular response, delineating the localized signaling niches that orchestrate an effective immune defense and the response leading to vascular damage at the sites of infection.

Keywords: Neisseria meningitidis - Endothelial cells - Innate immune response.

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S2-P08

Development of a Rapid Automated Functional Assay to Assess Innate Immune Function in Septic Shock Patients

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Septic shock, the most severe form of sepsis, is characterized by profound immune dysregulation associated with an increased risk of secondary infections and poor outcomes. Hallmarks of this immunosuppressed state include lymphopenia, reduced monocyte HLA-DR (mHLA-DR) expression, impaired T-cell fitness, and defective cytokine production. Interferon-γ release assays (IGRAs) have emerged as promising tools for assessing adaptive immune competence in sepsis. However, adaptive immunity represents only one component of the host response. Monitoring innate immune function, particularly monocyte responsiveness, may provide complementary information and contribute to a more comprehensive assessment of immune status. We therefore aimed to develop a rapid whole-blood immune functional assay capable of evaluating innate immune responsiveness within 4 hours.

Monocyte function was assessed using two complementary readouts: intracellular TNF-α production by flow cytometry and TNF-α secretion quantification in culture supernatants. Whole blood from healthy volunteers was stimulated for 4 hours with five Toll-like receptor (TLR) agonists: lipopolysaccharide (LPS), zymosan, lipoteichoic acid (LTA), flagellin, and poly(I:C). The two most potent stimuli were subsequently evaluated in whole blood collected from septic shock patients three days after ICU admission. Brefeldin A was added during stimulation to enable intracellular TNF-α detection. Functional results were compared with routine mHLA-DR measurements.

Screening experiments in healthy volunteers identified LPS and zymosan as the most effective stimuli for inducing monocyte TNF-α production. Under optimized conditions, septic shock patients displayed a markedly impaired response to LPS stimulation compared with healthy volunteers, characterized by both a lower frequency of TNF-α-producing monocytes and reduced intracellular TNF-α expression. In contrast, zymosan-induced responses did not differ significantly between patients and controls.

This study demonstrates the feasibility of a rapid whole-blood assay for assessing innate immune function in septic shock. Among the TLR agonists tested, only LPS consistently discriminated septic shock patients from healthy volunteers. Combined with IGRAs, this assay could provide a more comprehensive functional assessment of immune status in sepsis and support patient stratification.

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S2-P09

Bacterial Genotoxins Trigger Schlafen11-Dependent Ribotoxic Stress Response

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Many endogenous or pathogenic stimuli can cause DNA damage, leading to the accumulation of single- or double-stranded DNA (ssDNA or dsDNA) within cells. These nucleic acids act as critical molecular patterns recognized by the innate immune system. While numerous sensors of cytosolic double-stranded DNA have been identified, the mechanisms underlying the detection and immunostimulatory properties of intracellular single-stranded DNA remain poorly characterized.

Recent studies have identified CGT-rich ssDNA as a potent immune activator and Schlafen-11 (SLFN11), a member of the Schlafen protein family, as a novel pattern recognition receptor (PRR) for ssDNA. Previously known for its role in inhibiting cell proliferation and sensitizing cells to DNA-damaging agents, SLFN11 is now emerging as a key player in immune surveillance.

To explore the immunological role of SLFN11 in response to genotoxic stress, we employed molecular biology, cellular, and biochemical approaches to investigate its activation by Cytolethal Distending Toxins (CDTs)—genotoxic bacterial DNases secreted by pathogens such as *Salmonella typhi*, *Campylobacter jejuni* and *Haemophilus ducreyi*. Our results demonstrate that SLFN11 is activated by CDT-induced DNA damage, leading to its involvement in innate immune signaling.

Upon activation, SLFN11 cleaves specific tRNAs, triggering ribotoxic stress—a process known to activate the NLRP1 inflammasome. We observed robust activation of the NLRP1 inflammasome and downstream inflammatory signaling in a SLFN11-dependent manner in response to genotoxic stress. These findings provide a mechanistic explanation for the pro-inflammatory effects of CDT toxins and offer novel insight into the immune system's ability to detect and respond to intracellular ssDNA.

Keywords: Genotoxins - Inflammation - ssDNA sensing.

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Deciphering the microbiota-lactate-macrophage axis in pneumonia: the protective role of *Streptococcus mitis* and signalling via the host GPR81 Receptor

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Objective

Hospital-acquired pneumonia (HAP) remains a major global burden, with conventional therapies failing in up to 40% of patients[1]. Low abundance of commensal lactate-producing *Streptococci* in lungs positively correlates with HAP risk[2]. Given rising antimicrobial resistance and high failure rates of these therapies, we hypothesized that lactate produced by *Streptococcus mitis*(*S. mitis*) acts via the host receptor GPR81 to reprogram alveolar macrophages (AMs) toward non inflammatory pathogen clearance and maintain tissue homeostasis. This study evaluated whether *S. mitis* derived lactate regulates AM phagocytosis and cytokine responses during bacterial pneumonia.

Methodes

C57BL/6J (WT) and lactate receptor knockout (GPR81KO) mice were instilled intratracheally (D0/D3) with *S.mitis* (ATCC 49456, 10^9CFU/mL,7McF) or PBS. Then challenged (D7) with a sublethal mixture (1 :1) *of Escherichia coli K-12* (10^8 CFU/mL) and *S.mitis*, or PBS. To assess the requirement for bacterial metabolic activity, mice were exposed to heat-killed (HK) or paraformaldehyde (PFA) fixed *S.mitis*. Bacterial loads, weight loss, and clinical signs were monitored. Flow cytometry was used to analyse the lung immune compartment, specifically targeting resident (res-AM; F4/80$^+$CD11c$^+$Sigle-F$^+$) and monocyte derived (mo-AM; F4/80$^+$CD11b$^+$Siglec-F$^-$) alveolar macrophages, their production of pro-inflammatory cytokines (TNF-α, IL-1β), and their phagocytic capability.

Results

S. mitis colonized WT and GPR81-KO lungs equally, triggering a similar expansion of mo-AMs and maintenance of res-AMs without inducing clinical disease. In WT mice, prior colonization by live *S. mitis*significantly reduced *E. coli* burden, accelerated weight recovery and res-AM TNF-α and IL-1β. In GPR81-KO mice, these protective benefits and cytokine suppressions were abolished. Furthermore, metabolically inactivated *S. mitis* failed to confer protection in WT mice, confirming that active bacterial metabolism is required. Finally, while *S. mitis* colonization reduced overall inflammatory phagocytosis in both strains, cytokine suppression specifically depended on GPR81 signalling.

Conclusion

S. mitis may protect against bacterial pneumonia through active metabolic production of lactate and program alveolar macrophages toward non-inflammatory phagocytosis via TNF-α modulation

Keywords: Lung microbiota - Alveolar macrophages - Lactate.

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Characterizing CMV-Specific Immune Signatures to Predict Post-Transplant Infection Risk

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Cytomegalovirus (CMV) remains a major cause of opportunistic infection in solid organ transplant recipients even with preventive strategies, which mainly rely on donor(D)/recipient(R) serostatus. However, clinical studies have shown that combining serology with assays evaluating CMV-specific conventional cellular immunity (CMV-CMI, using either ELISA or ELISPOT measuring IFNγ after CMV-peptide stimulation of Peripheral Blood Mononuclear Cells (PBMCs)) can reduce unnecessary antiviral use in patients with positive ELISPOT results1. Yet, this approach remains imperfect. Approximately 20% of CMV-seropositive recipients (R^+) with positive CMV-CMI still develop infection2, suggesting cellular immune dysfunction. Conversely, 80% of R+ patients with negative CMV-CMI do not3 develop CMV disease, suggesting the involvement of others CMV-specific cellular actors, such as nonVd2Vg9 T cells and CD57NKG2C+ NK cells. This study aims to comprehensively characterize CMV-specific immune components by combining spectral flow cytometry, together with ELISPOT.

PBMCs from 40 R^+ kidney transplant recipients were analyzed at three time points: pre-transplant baseline, an intermediate follow-up, and either at CMV infection onset (for infected patients) or a matched time point (for non-infected patients). Four dedicated spectral flow cytometry panels were used to profile immune cell populations including αβ T cells, NK cells, and γδ T cells, and to assess dysfunction, activation markers together with transcription factors, cytokines and cytotoxicity. In parallel, ELISPOT assays were performed on the same samples to evaluate CMV-CMI.

Supervised and unsupervised profiling of non-Vδ2Vγ9 T and CD57NKG2C+ NK cells prior to infection revealed that infection-free patients had higher non-Vδ2Vγ9 T cell frequencies. In contrast, infected patients exhibited upregulated LAG-3 on these cells. Furthermore, while CD57+NKG2C+ NK cells were less abundant in infection-free patients, they demonstrated enhanced activation via elevated CX3CR1 and TIGIT expression. These findings suggest that non-Vδ2Vγ9 T cells protect via quantitative abundance, whereas CD57+NKG2C+ NK cells act through qualitative features. Ultimately, this predictive immunological signature could guide targeted CMV prophylaxis, minimizing unnecessary antiviral costs and toxicity.

Keywords: Cytomegalovirus - Prediction - Infection-risk.

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SSC5D as an Immunological Mediator in Pregnancy-Associated and Neonatal Infections

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Objective
This study aims to investigate the role of SSC5D in pregnancy and pregnancy-associated infections. SSC5D is a pattern-recognition receptor belonging to the scavenger receptor cysteine-rich family, whose expression is increased during infection and inflammation, and is particularly high in the human placenta and the mouse urogenital tract. We seek to determine whether SSC5D contributes to normal pregnancy development and modulates immune responses during gestational infections.
Methods
SSC5Dknockout (SSC5D-KO) and wild-type (WT) mice were subjected to an ascending Group B *Streptococcus* (GBS) infection model that mimics the natural route of infection in pregnant woman and transmission to the offspring. Two experimental variations of this model were established: (I) to assess SSC5D role in maternal immune responses after infection, and (II) to determine the impact of SSC5D deficiency on bacterial dissemination and neonatal outcomes.
Results
GBS infection induced upregulation of *Ssc5d* in WT placentas, accompanied by distinct systemic inflammatory profiles between infected WT and SSC5D-KO females. Our findings indicate that neonates born to GBSinfected SSC5DKO mothers did not show significant differences in mortality compared with WT newborns. However, SSC5Ddeficiency results in a marked increase in bacterial loads within the brain, lungs, and liver of exposed newborns, whereas WT neonates showed limited tissue colonization.
Conclusion
These data reveal a previously unrecognized role for SSC5D in regulating inflammation during pregnancyassociated infections while promoting bacterial clearance from newborns, suggesting that this protein may represent a promising therapeutic target in these contexts.

Keywords: SSC5D - Immune response - Pregnancy-associated infections.

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Ex vivo HIV latency reversal combined with shingrix leads to enhanced HIV reservoir reactivation and immune restoration

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Introduction
Despite effective antiretroviral therapy, latent HIV reservoirs persist, preventing viral eradication and contributing to chronic inflammation and comorbidities in people living with HIV (PLWH). Immunological non-responders (InR) exhibit incomplete CD4+ T-cell recovery, larger viral reservoirs, and persistent inflammation and immune exhaustion compared with immunological responders (IR). Latency-reversing agents (LRAs) such as AZD5582 may support "shock-and-kill" strategies by inducing HIV transcription and exposing latent reservoirs to immune clearance. However, efficient reservoir elimination requires immune recovery, highlighting the need for immunomodulatory adjuvants, particularly in InR.
Objective
To test whether Varicella zoster vaccine Shingrix, known to efficiently activate durable innate immune responses that lead to enhanced antiviral functions, may favor latency reversal and elimination of reservoirs upon LRA treatment, counteracting effects of immune dysfunctions such as platelet-PBMC conjugation, exacerbated immune activation and exhaustion.
Methods
Ex vivo latency reversal was induced in PBMCs from PLWH by AZD5582 alone or combined with Shingrix. IR and InR were included. HIV reactivation was assessed by multiparametric flow cytometry coupled with HIV RNA *in situ* hybridization (FISH-flow), alongside activation markers CD69, PD-L1, HLA-ABC, CD86. Replication-competent viral production (RCVP) was evaluated using GHOST reporter cells in supernatants from treated PBMCs.
Results
AZD5582-induced HIV reactivation is enhanced by Shingrix coadministration, in both lymphocyte and monocyte reservoirs. Furthermore, AZD5582+Shingrix enhances RCVP in HIV-reactivated PBMC. AZD5582+Shingrix treatments also induced decreased expression of CD86, HLA-DR, and PD-L1 in monocytes of both IRs and InR. Upon AZD5582+Shingrix treatment CD69 expression decreased in InR to responder levels. Platelets conjugate with transcriptionally competent HIV reservoirs and CD86+, HLA-DR+, and PD-L1+ activated PBMC in both IRs and InR. AZD5582+Shingrix treatment reduced expression of PD-L1 in IR platelet-conjugated lymphocytes and reduced the expression of CD86, HLA-DR, and PD-L1 in InR platelet-conjugated monocytes.
Conclusion
AZD5582 combined with Shingrix can be a promising shock-and-kill strategy due to its dual capacity of both reactivate the latent HIV reservoir and restore immune function, especially for the vulnerable population of InR.

Keywords: HIV latency - Latency reversal agents - Immune function.

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S2-P14

Dissecting MHC-II-restricted endogenous antigen presentation using viral proteins: the influence of HTLV-1 Tax

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CD4⁺T cells, key determinants of cellular and humoral immunity, recognize peptides presented by MHC-class-II (MHC-II) molecules. These peptides derive from exogenous and endogenous antigen degradation pathways involving autophagy-dependent and independent mechanisms. In particular, selective autophagy receptors (SLRs) such as p62, TAX1BP1, OPTN, NDP52, and NBR1 regulate autophagy and vesicular trafficking, modulating MHC-II-restricted antigen presentation. Remarkably, the HTLV-1 oncoprotein Tax induces a signalosome at peri-Golgi structures of infected T cells through interaction with IKKγ (NEMO), leading to constitutive NF-κB activation. This process depends on Tax specific domains' ubiquitination and on its interaction with SLRs. Thereafter using Tax, we investigated whether Tax might interfere with endogenous MHC-II-restricted antigen presentation, focusing on the role of SLRs.

We confirm that, in antigen-presenting cells (APCs), Tax expression induces relocalization of SLRs and IKKγ into Tax-derived cytoplasmic condensates forming the signalosome. We next asked whether Tax affects antigen presentation. APCs expressing Tax and a model antigen (HIV-Gag) were co-cultured with Gag-specific CD4+ T cells. Tax expression reduces the capacity of APCs to activate CD4+ T cells, although this effect is not significantly altered by SLRs knockout. Immunopeptidome analysis revealed that Tax modifies the repertoire of MHC-II-presented peptides without significantly affecting their binding affinity. Mutational analysis identified lysines 4–6 as critical ubiquitinylation sites required for Tax-mediated inhibition of CD4+ T cells activation. Additionally, Tax increased cathepsin B/L and S activity, suggesting altered vesicular pH in the MHC-II loading compartment.

Future work will assess signalosome formation in SLR knock-out cells and validate these findings in dendritic cells using CMV-specific CD4⁺ T cell responses.

Keywords: Antigen presentation - MHC-II - Selective autophagy receptors (SLRs) - HTLV-1 Tax.

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Sensitive detection of pathogen-specific T cells after antigen stimulation comes with phenotypic trade-offs

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Objective
Detection and characterization of pathogen-specific T cells are essential for assessing immunity to infection and vaccination. Stimulation-based assays identify responding T cells through cytokine production or activation markers, yet differences in response kinetics and their impact on subsequent phenotyping remain poorly defined.
Methods
Here, we systematically compared intracellular cytokine staining (ICS) and activation-induced marker (AIM) assays across multiple viral specificities and stimulation times. A 34-color spectral flow cytometry panel combined with high-dimensional analysis enabled comprehensive assessment of virus-specific T-cell detection, phenotype, and function across assay conditions.
Results
ICS and AIM responses displayed distinct kinetics, with optimal detection at 6 and 18 hours, respectively. At their assay-specific optimal timepoints, AIM consistently identified higher frequencies of virus-specific T cells than ICS. Importantly, prolonged antigen stimulation affected not only the activation markers used to identify responding cells, but also inhibitory, proliferative, and memory-associated phenotypes in both CD4+ and CD8+ T cells, thereby influencing the apparent phenotype of the antigen-specific responses.
Conclusion
Thus, stimulation conditions selected for sensitive detection of pathogen-specific T cells can influence their subsequent phenotypic characterization. Our findings highlight a critical trade-off between detection and preservation of biologically informative phenotypes, emphasizing the importance of tailoring assay conditions to the biological question.

Keywords: Antigen-specific T cells - Activation-induced markers (AIM) - Intracellular cytokine staining (ICS).

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Cellular and spatial features of the liver microenvironment associated with chronic hepatitis B disease progression

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Objective
Chronic hepatitis B (CHB) can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), but the mechanisms underlying disease progression remain incompletely understood. We aimed to characterize spatially distinct cellular and molecular features of the CHB liver microenvironment.
Methods
We analyzed public single-cell RNA-sequencing data from 30 CHB patients at early (F0–F1, *n* = 23) or advanced fibrosis (F2–F4, *n*= 7), complemented by in-house Visium spatial transcriptomics data from control livers (*n* = 4), HBV-associated F4 fibrosis (*n*= 7), and HBV–HDV coinfected F4 livers (*n* = 5). The Viral-Track pipeline was used to quantify HBV transcripts at single-cell resolution. Cell–cell communication was inferred using CellChat and ICELLNET.
Results
HBV transcripts were detected exclusively in treatment-naïve CHB donors. HBV-positive hepatocytes exhibited a zonated distribution, with periportal hepatocytes displaying the highest abundance and proportion of HBV-positive cells. Cell–cell communication analysis revealed spatially distinct predicted interactions with T cells. Periportal HBV-positive hepatocytes showed stronger predicted interactions with exhausted CD8+ T cells through immune checkpoint and chemokine pathways, whereas pericentral HBV-positive hepatocytes showed enhanced fibrosis-associated adhesion, extracellular matrix, and semaphorin–plexin signaling.
Conclusions
HBV-positive hepatocytes exhibit spatially distinct molecular programs, characterized by immune-regulatory interactions in periportal regions and fibrosis-associated signaling in pericentral regions. These findings provide insight into the spatial organization of the CHB liver microenvironment and suggest mechanisms that may contribute to disease progression.

Keywords: Chronic hepatitis B - Liver microenvironment - Multi-omics.

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Distinct interactions of *Tropheryma whipplei* with intestinal epithelial cells

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Objective
Tropheryma whipplei is the causative agent of Whipple's disease, a rare chronic systemic infection. Although macrophages are considered a major cellular niche for bacterial persistence and replication, the early interaction of *T. whipplei* with intestinal epithelial cells remains poorly understood. We investigated whether intestinal epithelial cells constitute a permissive niche for *T. whipplei* and characterized the cellular interaction and host response following infection.
Methods
Two human intestinal epithelial cell lines, Caco-2 and HT29, were infected with two *T. whipplei* strains, Twist and Dig54. Bacterial loads were quantified by qPCR at different time points. Bacterial localization was investigated by immunofluorescence, confocal microscopy with Z-stack acquisition, scanning electron microscopy and transmission electron microscopy. Cell viability was assessed by MTT assays, and epithelial and inflammatory responses were investigated by RT-qPCR. Differentiated Caco-2 cells and a Transwell-based epithelial barrier model were also investigated.
Results
T. whipplei was detected in epithelial cell cultures shortly after infection, but bacterial loads remained low and did not increase over time. Across Caco-2 and HT29 cells and the strains tested, imaging analyses showed bacteria predominantly associated with the epithelial surface and intercellular spaces, with limited evidence of intracellular accumulation. Infected epithelial cells remained viable and displayed limited inflammatory responses compared with *Salmonella enterica*-infected controls.
Conclusion
These findings indicate that intestinal epithelial cells do not constitute a permissive niche for *T. whipplei* replication in vitro. The predominant localization of bacteria at the epithelial surface and within intercellular spaces suggests that interaction with and crossing of the intestinal epithelial barrier may occur without extensive intracellular invasion. These results provide new insights into the cellular determinants of *T. whipplei* host–pathogen interactions.

Keywords: Tropheryma whipplei - Bacterial persistence - Epithelial barrier.

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S2-P18

Investigating the Interaction Between Tropheryma whipplei and Epithelial Cells

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Objective
Tropheryma whipplei is the causative agent of Whipple's disease, a rare chronic systemic infection. Although macrophages are considered a major cellular niche for bacterial persistence and replication, the early interaction of *T. whipplei* with intestinal epithelial cells remains poorly understood. We investigated whether intestinal epithelial cells constitute a permissive niche for *T. whipplei* and characterized the cellular interaction and host response following infection.
Methods
Two human intestinal epithelial cell lines, Caco-2 and HT29, were infected with two *T. whipplei* strains, Twist and Dig54. Bacterial loads were quantified by qPCR at different time points. Bacterial localization was investigated by immunofluorescence, confocal microscopy with Z-stack acquisition, scanning electron microscopy and transmission electron microscopy. Cell viability was assessed by MTT assays, and epithelial and inflammatory responses were investigated by RT-qPCR. Differentiated Caco-2 cells and a Transwell-based epithelial barrier model were also investigated.
Results
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Conclusion
These findings indicate that intestinal epithelial cells do not constitute a permissive niche for *T. whipplei* replication in vitro. The predominant localization of bacteria at the epithelial surface and within intercellular spaces suggests that interaction with and crossing of the intestinal epithelial barrier may occur without extensive intracellular invasion. These results provide new insights into the cellular determinants of *T. whipplei* host–pathogen interactions.

Keywords: Tropheryma whipplei - Whipple's disease - Epithelial barrier.

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PS15-P01

Optimizing Immunotherapies in rhabdoid tumors (RTs) by targeting tumor-associated neutrophils

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Objective
Rhabdoid tumors (RTs) are aggressive pediatric cancers driven by bi-allelic loss of *SMARCB1* (Lee et al., 2012). Despite their low mutational burden, RTs can respond to anti-PD-1 therapy (Leruste et al., 2019). We previously demonstrated that anti-PD-1 and poly(I) (PIC), a TLR3 ligand, synergistically improve tumor control (Manriquez et al., 2025). However, approximately 17% of mice remain resistant to this combination. As PIC increases tumor-associated neutrophil (TAN) infiltration, we investigated whether TANs, through neutrophil extracellular trap (NET) formation, contribute to treatment resistance and limit durable antitumor responses.
Methods
Multiplex immunohistochemistry (MICSSS) was used to evaluate neutrophil infiltration and NET formation following PIC treatment. In RT-bearing mice, tumor growth was monitored during PIC and NET inhibition (NETi; PAD inhibitor) treatment and after NETi withdrawal, **which resulted in tumor relapse**. Bulk RNA-seq was performed on sorted tumor cells during tumor control and at relapse following NETi withdrawal to identify associated molecular alterations. Finally, RT, B16-OVA, and MC38 murine tumor models were used to assess tumor growth and survival following combined PIC, anti-PD-1, and NETi.
Results
PIC treatment increased neutrophil infiltration and NET formation within RTs. Neutrophil depletion alone improved tumor growth control, while its combination with PIC induced complete tumor responses in 85.7% of mice, demonstrating that neutrophils hamper PIC-mediated antitumor activity. We next investigated NETs as a potential mechanism underlying this effect. Combining NETi with PIC markedly improved tumor control while NETi was maintained, whereas NETi withdrawal resulted in tumor relapse, identifying NETs as a mechanism of resistance to PIC. RNA-seq comparing tumor cells under sustained NET inhibition versus relapse following NETi withdrawal revealed enrichment of TNFα/NF-κB, interferon, EMT, and ECM pathways at relapse. Finally, combining anti-PD-1, PIC, and NETi improved tumor growth control and survival across RT, MC38, and B16 models.
Conclusion
Our findings identify neutrophils and NETs as key mediators of resistance to PIC in RTs and show that sustained NET inhibition prevents tumor relapse. Moreover, NET targeting enhances the efficacy of anti-PD-1 plus PIC across multiple tumor models, supporting this combination as a strategy to improve durable antitumor responses.

Keywords: Rhabdoid tumor - Neutrophil extracellular trap - Cancer immunotherapy.

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PS15-P02

Circulating neutrophil state mapping reveals phenotypic and functional heterogeneity in rheumatoid arthritis

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Objective
Neutrophils are increasingly recognized as a heterogeneous population, but whether this diversity is reflected in the circulation of patients with rheumatoid arthritis (RA) remains unclear. We asked whether circulating neutrophil states could reveal disease-associated patterns and capture biologically meaningful differences between patients.
Methods
Circulating neutrophils from healthy donors (HD, n=13) and patients with RA (n=18) were profiled using a 17-marker spectral flow cytometry panel. Unsupervised high-dimensional analysis was used to identify neutrophil states and compare their distribution between groups. RA patients were then grouped according to their overall neutrophil-state composition. Basal secretion of CCL2, CCL20, CCL3, CCL4, CXCL1 and CXCL8 was assessed to determine whether these phenotypic patterns were associated with distinct functional profiles.
Results
Six phenotypically distinct circulating neutrophil states (C1-C6) were identified. C1 and C3 were selectively enriched in RA compared with HD (Benjamini–Hochberg-adjusted p =0.029 and Benjamini–Hochberg-adjusted p =0.0037). Both states displayed relatively high CD64 expression while retaining distinct marker profiles. At the patient level, the relative abundance of the six states separated RA patients into two exploratory composition-based phenogroups (n=10 and n=8, respectively). Importantly, these groups were defined using phenotypic data only, yet they differed in basal chemokine secretion (p=0.023). The C3-enriched phenogroup showed higher basal secretory activity, with CXCL1 remaining significantly higher after correction for multiple testing (Benjamini–Hochberg-adjusted p =0.031).
Conclusion
Circulating neutrophils in RA form a structured phenotypic landscape in which specific states are selectively enriched. Patient-specific combinations of these states are associated with distinct basal chemokine secretion profiles, suggesting that circulating neutrophil heterogeneity may provide a biologically meaningful readout of RA diversity and a promising basis for future patient stratification.

Keywords: Rheumatoid arthritis - Heterogeneity - Patient stratification.

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PS15-P03

MYELOTRACKER®: a peptide-based tool for specific detection and functional analysis of neutrophils

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Neutrophils are central effectors of innate immunity and key drivers of inflammation, yet their study remains limited by the lack of robust and universal detection tools. Antibody-based approaches are widely used but often suffer from species specificity, variable epitope accessibility, and limited compatibility with dynamic or in vivo studies.
Lactoferrin, a transferrin protein stored at high concentrations in neutrophil secondary and tertiary granules, is one of the most abundant and specific neutrophil-derived proteins. It is rapidly released upon activation and degranulation, making it a highly relevant indicator of both neutrophil presence and functional state (1). Beyond its biomarker role, lactoferrin participates in antimicrobial responses and immune regulation, reflecting the broader functional importance of neutrophil granule secretion during inflammation (2).
MyeloTracker® (RI-MUB40) is a 40-amino-acid synthetic peptide that specifically binds glycosylated lactoferrin, enabling selective labeling of neutrophils across multiple mammalian species (3). Conjugated to fluorophores, it allows rapid, single-step staining without species-specific reagents. MyeloTracker® is protease-resistant and suitable for in vivo applications, including systemic detection of inflammatory sites (1).
Notably, MyeloTracker® enables functional analysis by detecting lactoferrin release during degranulation, providing real-time insights into neutrophil activation in infectious and inflammatory contexts, such as bacterial infections where neutrophil recruitment and activity are critical. Combined with advanced imaging approaches, this tool opens new opportunities to study host–pathogen interactions and tissue inflammation dynamics.
MyeloTracker® represents a versatile alternative to antibodies, combining specificity, cross-species applicability, and functional readouts for translational and research applications.

Keywords: Neutrophils - Lactoferrin - Inflammation.

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PS15-P04

Neutrophils dynamically orchestrate the myeloid inflammatory network in arthritis

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Neutrophils are among the earliest immune cells recruited to inflamed tissues, yet their functional diversity and contribution to the organization of the inflammatory myeloid environment remain incompletely understood.

Objective
Here, we investigated the temporal dynamics, functional heterogeneity and intercellular communication of neutrophils throughout experimental arthritis.
Methods and Results
Longitudinal profiling of the inflammatory secretome and single-cell RNA sequencing revealed extensive remodeling of the myeloid compartment, with neutrophils expanding during peak inflammation and displaying progressively diversified transcriptional states. Neutrophil subclustering identified distinct activation, metabolic and tissue-adapted states that changed in abundance throughout disease progression. Integration with an external neutrophil reference atlas demonstrated that arthritis-associated neutrophils occupy context-dependent transcriptional states that are not fully captured by canonical neutrophil categories, while specialized states persisted during the later phase of disease. Quantitative cell–cell communication analysis identified neutrophils as major signaling senders within the myeloid network, being particularly prominent during the early stages of inflammation, preceding peak disease. Specific neutrophil states emerged as communication hubs, suggesting that neutrophils contribute substantially to the early organization of the inflammatory myeloid network. Qualitative interactome analysis further highlighted chemokine signaling as one of the major communication axes, with CCL2, CCL3 and CCL4 predominantly associated with neutrophils, whereas CXCL1 was produced by both neutrophils and other myeloid cells (including monocytes and macrophages). Protein-level validation confirmed differential chemokine production across neutrophils and other myeloid populations, further supporting a bidirectional communication network between neutrophils and the broader inflammatory myeloid compartment.
Conclusion
Together, these findings establish neutrophils as dynamically instructed and functionally diverse cells that actively shape the myeloid inflammatory ecosystem in arthritis.

Keywords: Neutrophils - Intercellular communication/interactome - Experimental arthritis.

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PS16-P01

Engineering Regulatory T Cells For Rheumatoid Arthritis: Development and Evaluation of CAR Constructs

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Introduction
Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes progressive joint destruction. While treatments aim to control inflammation, they act through broad immune suppression causing significant side effects.
Objective
Regulatory T (Treg) cell-based therapies are an attractive strategy but limitations remain. Antigen (Ag) specific Tregs targeting citrullinated proteins could allow suppression at the site of inflammation while avoiding systemic immunosuppression. Engineering Tregs with Chimeric Antigen Receptor (CAR) is one strategy to produce Ag-specific Tregs. Although CAR designs have been extensively studied in conventional T cells (Tconv), there is no consensus on the optimal CAR construct that would ensure Treg functionality without destabilisation. We aimed to study the effect of second- and third-generation CARs in Tregs.
Methods
Our second (CD28) and third-generation (CD28_4-1BB) CAR constructs contain an scFv derived from a monoclonal ACPA identified from an RA patient. We purified naïve Tregs (nTregs) from healthy PBMC and determined the best MOI to transduce them using a lentiviral vector expressing ZsGreen. Engineered J.RT3-T3.5 JURKAT cells were used to assess CAR-induced activation, using CD69 expression as an activation marker. A third generation anti-CD19 CAR was used as a positive control. In Tregs, we compared the effect of our second- and third-generation CAR, in the absence of CAR-dependent activation. We assessed phenotypic stability by multiparametric flow cytometry and function using an in vitro suppression assay.
Results
Under Ag-independent conditions, nTregs transduced with either the second- (CD28), or third-generation (CD28_4-1BB) CAR construct, displayed a stable phenotype with similar expression of FoxP3, Helios and suppressive molecules like CTLA-4, LAG3 and PD-1. CAR-Treg expansion was comparable to untransduced (UT) nTregs after 23 days of cell culture. Finally, the suppressive function of both CAR-Tregs were similar to UT nTregs on day 10 and day 20.
Conclusion
Our results provide the basis for future studies to use these second and third-generation CAR constructs, as they do not seem to intrinsically destabilize Tregs. This contributes to ongoing efforts to define optimal CARs for Treg-based therapies and provide insight into how CAR signaling can influence Treg stability.

Keywords: CAR-Tregs - Second-generation CD28 CAR - Third-generation CD28_4-1BB CAR.

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PS16-P02

Identification of TCRs targeting neogene-derived neoantigens for immunotherapy of Ewing sarcoma

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Objective
Ewing sarcoma (EwS) is driven by the EWSR1::FLI1 fusion oncogene, which induces the expression of tumor-specific neogenes (NGs) encoding immunogenic neoproteins. We recently identified several NG-derived epitopes presented by HLA class I molecules, providing a unique source of tumor-specific targets. The objective of this work is to identify immunogenic neogene-derived ORFs that can serve as target for therapeutic vaccination and to isolate their cognate TCRs. The most promising TCR will then be selected for further optimization and development as TCR-T cell therapies.
Methods
EwS cell lines and Patient-Derived Xenograft (PDX) models were screened to identify HLA class-I-presented EwS-specific neoepitopes. Selected neoepitopes were subsequently used to screen antigen-specific T cells isolated from healthy donors and EwS patients. Cognate TCRs recognizing the identified neoepitopes were then cloned and further characterized. TCRs candidates were evaluated for peptide specificity, tumor-cell recognition and cytotoxic activity against EwS cell lines. Lead TCRs will subsequently being optimized through catch-bond engineering to enhance functional avidity while preserving antigen specificity, with the long-term objective of generating clinically translatable TCR-T cell products.
Results
Screening of several NG-derived ORFs identified multiple immunogenic neoepitopes capable of eliciting antigen-specific T cell responses. We isolated a panel of TCRs recognizing distinct EwS-specific neoantigens and identified candidates displaying potent and selective recognition of HLA-matched EwS cell lines. One lead TCR targeting an *Ew_NG8*-derived neoepitope demonstrated robust antigen-specific cytotoxicity in vitro with no detectable cross-reactivity by alanine scanning, although its in vivo efficacy remains limited, motivating further optimization.
Conclusion
These results establish neogene-derived neoantigens as a rich source of therapeutic targets in Ewing sarcoma and demonstrate the feasibility of isolating highly specific TCRs against these antigens. The identified neoepitopes and their cognate TCRs provide a foundation for the development of next-generation therapeutic vaccines and TCR-T cell therapies. Catch-bond engineering of selected TCRs may further enhance antitumor efficacy while preserving specificity and safety.

Keywords: TRC-T cell therapy - Neoepitopes - Cancer Vaccine.

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Exploring human T follicular cell subsets in allergic disease

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Objective
T follicular helper (TFH) cell dysregulation has been linked to several immunological disorders, whose subset-specific pathways hold a yet unexplored therapeutic potential. One clinically relevant case is IgE-mediated allergy, a type 2-driven condition whose incidence and prevalence have been rising over the past decades, currently affecting up to 30% of the global population. Although TFH2 and TFH13 subsets have been described in mice and human blood, their equivalents remain unresolved in human lymphoid tissue. This study aims to define the signature of the human type 2 T follicular subset(s), directly within their native germinal centre niche.
Methods
Paediatric tonsils and paired blood were collected from donors screened for allergy prior to tonsillectomy and assigned to allergic (IgE^+) or non-allergic (IgE^-) groups. A multi-tiered strategy was applied: spectral flow cytometry to map the follicular helper and regulatory landscape at the protein level, both at baseline and upon stimulation (intracellular cytokine staining, ICS); and single-cell multi-omic sequencing to resolve, in an unbiased manner, the transcriptional and surface protein signature of sorted T follicular cells ($CD4^+CXCR5^+$), alongside B cells and the remaining tonsillar populations to capture their cellular context.
Results
Immunophenotyping revealed a shift within the follicular and regulatory compartments of allergic donors. Notably, the regulatory deficit was apparent at two levels: fewer regulatory cells, with a reduction in both the $CD25^+$ pool and the T regulatory compartment; and a diminished responsiveness, with an overall decline in cytokine competence upon stimulation. Single-cell sequencing resolved a multimodal subset landscape spanning the follicular helper and regulatory continuum, providing candidate signatures for functional validation.
Conclusion
Together, these data support a model in which an imbalance between effector and regulatory follicular help underlies IgE-mediated allergy, with a loss of regulation and responsiveness. By combining phenotyping and single-cell characterisation directly in human lymphoid tissue, this integrated approach opens new avenues for the targeted modulation of these subsets in allergy.

Keywords: T follicular cells - Germinal centre - IgE-mediated allergy.

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PS17-P02

Leveraging a human lymphoid organ-on-chip reveals help-dependency in B cell responses to mRNA vaccines

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Objectives
Vaccine recall responses remain challenging to study directly in human lymphoid tissue. Here, we relied on a lymphoid organ-on-chip (LO chip) model with continuous antigen perfusion to compare recall responses to the SARS-CoV-2 Spike protein and a Spike-encoding mRNA vaccine.
Methods
PBMC from post-pandemic donors (n=11) were seeded at high density in a collagen-based matrix within the lower compartment of microfluidic chips (S1, Emulate). Immune responses to the mRNA-1273 vaccine (Moderna) were compared to those elicited by a recombinant Spike protein (BEI Resources). Cytokines secreted in chip effluents were quantified using a 13-plex immunoassay (BioLegend). T and B cell differentiation were analyzed in depth at D7 using a 27-parameter spectral flow cytometry panel.
Results
Deep phenotyping of B cell subsets provided evidence for a rapid differentiation of Spike-specific memory B cells into plasmablasts (PB) upon antigenic stimulation, with the mRNA vaccine favoring the induction of highly differentiated CXCR5-negative PB with follicular egress potential. Within the T cell compartment, the Spike protein induced a prominent upregulation of activation and costimulation markers in CD4+ T cells, while the mRNA vaccine induced a more balanced response between CD4+ and CD8+ T cells, suggesting differential engagement of antigen presentation pathways. Both stimuli led to a Th1-biased response, as indicated by CXCR3/CCR6 chemokine receptor expression patterns and a cytokine secretion profile dominated by IFN-gamma and IL-2. As OX40+ ICOS+ CD4+ T cell frequency correlated positively with PB induction across conditions (R=0.81), we set to explore T/B cell interactions at the functional level. The combined inhibition of OX40, ICOS and CD40L by blocking antibodies impaired T cell activation, as expected, but also markedly decreased plasmablast differentiation and Spike-specific B-cell amplification for both stimulations.
Conclusion
The model revealed a dependency of B cell recall responses on T cell help, highlighting the value of the LO chip as a platform to explore the functional dynamics of human adaptive responses to vaccines.

Keywords: Organ-on-chip - mRNA vaccine - T cell help.

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PS17-P03

Peripheral induction of regulatory T cells seeds the follicular regulatory T cell compartment

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Following infection, the immune system generates specific antibodies to neutralize pathogens. The quality and polarization of this humoral response are shaped in germinal centers (GCs) of secondary lymphoid organs via random somatic hypermutation and class-switch recombination of B cell receptors, orchestrated by two $CD4^+Bcl6^+$ T cell subsets: follicular helper T cells (Tfh), which enhance them, and follicular regulatory T cells (Tfr), which restrain them[1]. Thought as a homogeneous compartment, Tfr actually emerge from distinct developmental origins, suggesting distinct functions for these specific pathways. Indeed, Tfr were described to arise either from thymic regulatory T cells (tTregs) or naïve T cells through Tfh reservoirs, seeding the GCs with thymic Tfr (tTfr) or induced Tfr (iTfr) respectively[2,3]. However, it is yet to determine if naïve T cells can induce Tfr through peripheral Tregs (pTregs).
To dissect this heterogeneity, we developed a mouse model that enables us to track Tfr derived either from tTregs or from naïve T cells. TCR repertoire analysis and clonotype sharing between Tfr and pTregs revealed the existence of a third Tfr subset, which we termed peripheral Tfr (pTfr). Notably, pTfr displayed a distinct TCR repertoire, suggesting that they recognize a different set of antigens compared with iTfr and tTfr. In addition, scRNAsequencing projections showed that pTfr clustered more closely with tTfr than with iTfr and shared a more regulatory signature. Transcriptomic and flow cytometry analyses identified distinct expression levels of specific surface proteins across the three Tfr populations, enabling their discrimination. To further validate these results, we observed a similar expression pattern of the discriminative markers in conventional B6 mice under an inflammatory context that favors pTreg generation, enabling the identification of pTfr.
Overall, our results unravel the existence of a third way of ontogeny for the Tfr compartment, derived from pTreg populations, and characterized by distinct antigen specificity and phenotypic profiles. Beyond their discovery, we are now investigating the functions of pTfr and how their phenotype and activity evolve in space and time. Finally, given their distinct TCR repertoire, we aim to determine how pTfr influence GC reactions in physiological and auto-immune contexts. This work could provide new insights into GC regulation and potentially pave the way for new therapeutic approaches.

Keywords: Follicular regulatory T cell - Ontogeny - TCR.

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PS17-P04

Ins and outs of HIV antigen presentation by HIV-specific B cells

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The precise mechanisms by which broadly neutralizing antibodies (bNAbs) are generated in the context of HIV-1 infection remain ill-defined. bNAbs are produced by B cells whose germline (GL)-encoded B cell receptor (BCR) went through multiple cycles of affinity maturation. This process is under the control of CD4⁺ follicular helper T cells, via an interaction between B cells MHC-II molecules and the T cell receptor. Our aim is to characterize the pathways leading to MHC-II-restricted HIV-derived antigen presentation by HIV-specific B cells.
To this purpose, we developed and characterized using flow cytometry a panel of B cell lines stably expressing HIV-1-specific BCRs recognizing various sites on HIV Envelope (HIV-Env).
We showed that the co-culture of HIV-exposed Env-specific B cells with a Gag-specific T CD4⁺ clone leads to a potent T cell activation, through a process called “Intrastructural Help” where T cells specific for a core protein provide help to B cells recognizing a surface antigen. To have a broader view of the viral peptides presented by HIV-exposed Env-specific B cells, we defined their MHC-II-restricted immunopeptidome and identified around 25 HIV-derived peptides. Strikingly, all peptides were derived from HIV-Gag or -Pol and none from HIV-Env, questioning whether Env-derived peptides are processed and presented by B cells. Thereafter, using *in vitro* priming and expansion, we generated T CD4⁺ clones specific to different HIV-Env-derived peptides. We then dissected their capacity to be activated upon co-culture with HIV-Env-specific B cells exposed to (1) soluble HIV-Env, (2) whole HIV particles or (3) HIV-Env-expressing cells. The Env antigen can only be captured and processed by B cells when expressed on the surface of cells. Our preliminary results thus suggest that, in contrast to Gag-derived peptides, the formation of an immune synapse might be necessary for B cells to acquire, process and present Env-derived peptides, leading to the activation of Env-specific T cells.
Using our panel of HIV-specific B cells and our novel Env- and Gag-specific CD4⁺ T cell clones, we are currently dissecting the pathways leading to HIV-antigen routing and processing, focusing on one hand on the involvement of autophagy and on the other hand on the importance of the immune synapse formation and the release of extracellular cathepsins in the extraction, internalization, and presentation of HIV-Env by HIV-specific B cells.

Keywords: B-T cells interaction - MHC-II restricted antigen presentation - Broadly Neutralizing Antibodies.

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PS19-P01

Ontogeny Matters: How Primitive Mast Cells Drive Eczema After Birth

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Objective
Mast cells arise from distinct developmental waves and exhibit tissue-specific renewal dynamics that shape their long-term functions. Although early-life immune programming can have lasting consequences, how mast cell ontogeny contributes to disease susceptibility remains poorly understood. We investigated how prenatal environmental cues influence mast cell ontogeny, persistence, and functional programming, and how these dynamics contribute to postnatal eczema susceptibility.
Methods
Using murine models, we combined lineage tracing, molecular profiling, and functional assays to characterize fetal-derived skin mast cells and their postnatal maintenance. Prenatal stress was used to perturb the in utero environment, and its effects on mast cell development, persistence, and neuroimmune interactions were assessed. Genetic and pharmacological approaches were used to interrogate the role of glucocorticoid signaling and mast cell persistence.
Results
We identify a critical developmental window during which mast cells are highly sensitive to maternal stress signals. Prenatal stress alters the developmental trajectory of primitive, yolk sac-derived, mast cells, leading to long-lasting changes in their activation state. These fetal-derived mast cells persist postnatally with limited replacement, retaining a phenotype that promotes heightened responsiveness to mechanical stimuli and drives eczema-like skin manifestations. Interventions that normalize the prenatal environment or disrupt mast cell establishment prevent these long-term effects.
Conclusions
Our findings demonstrate that mast cell ontogeny is a key determinant of postnatal immune function and disease susceptibility. Early-life programming of long-lived, fetal-derived mast cells establishes a durable neuroimmune axis that can drive eczema after birth, highlighting developmental timing as a critical factor in prevention strategies and therapeutic intervention.

Keywords: Mast cells - Ontogeny - Prenatal stress.

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PS19-P02

Single cell transcriptomics reveal mast cell heterogeneity in the human gut in health and Irritable Bowel Syndrome

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Background
Mast cells are a major actor in abdominal pain, a hallmark symptom of Irritable Bowel Syndrome (IBS). We recently showed that local IgE production triggers mast cell activation leading to food-induced abdominal pain in mice1. However, little is known about the phenotype of gut mast cells in human health and IBS.
Objective
In this study, we characterized mast cells across the different colon layers in health and in patients with IBS using single cell transcriptomics.
Methods
FACS-sorted CD45+cells from dissected sigmoid colon layers (mucosa, submucosa, muscularis externa) and rectal biopsies from healthy individuals were included in a first single cell RNASeq dataset. Layer distribution of mast cell subsets were validated by spatial transcriptomics. We generated a second single cell RNASeq dataset from FACS-sorted CD45+ cells from healthy and IBS rectal biopsies.
Results
We identified mast cells using *KIT* and *CPA3* expression. After subclustering, we identified five mast cell clusters in the healthy colon, MC1-MC5, with distinct transcriptional signatures. MC1 were primed for immune communication. MC3/MC4 had a connective tissue mast cell phenotype and expressed neural adhesion markers, but showed phenotypic differences in prostaglandin and chemokine expression. We also showed that mast cell subsets were layer-specific and were regulated by different transcription factors.
In the IBS group, mast cells clustered similarly to healthy. However, when considering IBS subtypes, we found that IBS-M only featured MC2 and MC5. Interestingly, mast cell numbers were decreased in IBS-M compared to controls using immunostaining and expression of degranulation-related genes were increased.
In IBS, mast cells showed altered expression of several genes involved in immune regulation and targets potentially involved in pain development, in a mast cell subset- and IBS subtype-specific manner.
Moreover, we found evidence of a type 2 immune response in patients with IBS. *IL4* and *IL13* expression was upregulated in helper T cells and follicular T cells, which was associated with an increased expression of *IGHE+* B cells and plasma cells in IBS, supporting IgE-mediated activation of rectal mast cells in IBS.
Conclusion
In this study, we identified 5 mast cell subsets in the healthy human colon and showed differences in mast cell subset distribution and phenotype in patients with IBS using single cell transcriptomic analyses.

Keywords: Mast cells - Gut - Irritable Bowel Syndrome.

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PS20-P01

Humanized animals for IgA1 and FcαRI (CD89) exhibit increased susceptibility to intestinal inflammation and microalbuminuria following DSS-induced colitis

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Objective
IgA nephropathy (IgAN) is a major cause of renal failure worldwide (Monteiro et al., 2022). A gut-kidney axis is involved in disease pathophysiology (Luvizotto et al., 2022). Here, we evaluated the response to intestinal inflammation and renal impairment after induction of colitis in a IgAN model.
Methods
α1KICD89Tg mice expressing human IgA1 (hIgA1) and the FcαRI receptor (CD89) on a C57BL/6 genetic background, as well as wild-type C57BL/6 mice, were used. To induce mild intestinal inflammation, as observed in IgAN patients, animals received 0.5% DSS over 3 cycles; each cycle consisted of 5 days of DSS in the drinking water followed by a 4-day recovery period. Colitis was assessed using the Disease Activity Index (DAI), taking into account weight loss, bleeding, and stool consistency. Urinary albuminuria/creatinine ratio (uACR) was analyzed. ELISA assays were performed to quantify Cystatin C, NGAL, hIgA1, and galactose-deficient hIgA1 (Gd-IgA1). Immunofluorescence analysis was conducted to evaluate mesangial hIgA1 deposition.
Results
The α1KICD89Tg animals exhibited progressive weight loss after the second DSS cycle, accompanied by a higher DAI and significative increase in fecal NGAL levels ($P<0.01$). In contrast, C57BL/6 animals showed no evident clinical manifestations and displayed no differences in fecal NGAL. DSS treatment did not alter serum or fecal levels of hIgA1 or Gd-IgA1 in α1KICD89Tg animals compared to those receiving only water. Although mesangial hIgA1 deposition remained unchanged following DSS exposure, uACR levels were significantly higher in DSS-treated α1KICD89Tg animals compared to control groups ($P <0.01$).
Conclusion
The data suggest that expression of human IgA1 and CD89 in mice induce susceptibility to intestinal inflammation, accompanied by an increase in urinary NGAL and in uACR. These findings indicate that mild intestinal inflammation may lead to renal alterations contributing to IgAN progression. The later suggest that this inflammatory gut-kidney axis is independent of IgA1 production or renal deposition.

Keywords: IgA nephropathy - IgA1 - FcαRI receptor.

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PS20-P02

Function of novel inflammasome sensor in keratinocytes in the frame of contact dermatitis

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In recent years, the skin has emerged as an immune barrier system on its own right, rather than just a physical barrier. As a direct interface with the environment, it is continuously exposed to a large range of exogenous compounds, including toxins and allergens capable of triggering inflammatory skin disorders.
Among these toxins, Gingkolic Acids and Urushiols are well-known inducers of contact dermatitis. This skin pathology leads to a complex immune response involving both Th2-associated allergic mechanisms and an inflammatory pathway that remains to be characterised
In this context, keratinocytes, the predominant cell type in the skin, play a central role in cutaneous immune surveillance through the activation of innate immune pathways. These include inflammasomes, which are intracellular multiprotein complexes that act as key signalling platforms orchestrating the initiation of cutaneous inflammatory responses. Some inflammasomes are highly expressed in the skin, including NLRP10 inflammasome. However, while several have been well characterised, the biological function and mechanisms of action of NLRP10 inflammasome remain poorly described.
To investigate its potential role in environmentally induced skin inflammation, we mainly used molecular, cellular and ex vivo approaches. Using keratinocytes exposed to environmental toxins Ginkgolic Acids and Urushiols, we characterised its activation. Here we show that both toxins activate NLRP10 inflammasome and trigger downstream inflammatory signalling in keratinocytes.
These findings establish NLRP10 as a novel innate immune sensor in keratinocytes, detecting environmental allergens associated with contact dermatitis. Our results thus provide new insights into its function in the context of environmental exposure, suggesting a role for NLRP10 in sensing environmental toxins and triggering cutaneous inflammatory responses.

Keywords: Environmental toxins - Inflammasome - Keratinocytes.

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LIGHT⁺ memory CD4⁺ T cells have an inflammatory phenotype and their infiltration in the intestine relates to histological disease severity in CD patients

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Objective
Inflammatory bowel disease (IBD), clinically divided in Crohn's disease (CD) and ulcerative colitis (UC), is characterized by long-lasting inflammation of the gastrointestinal tract. Regulation of inflammatory memory CD4⁺ T cells is impaired in IBD leading to chronic relapsing disease. Concentrations of LIGHT (**l**ymphotoxin-like exhibits **i**nducible expression and competes with herpes simplex virus **g**lycoprotein D for binding to **h**erpesvirus entry mediator, a receptor expressed by **T** lymphocytes), a cytokine from the tumor necrosis factor superfamily, are elevated in the circulation of therapy-naive pediatric CD patients at diagnosis[1,2]. High LIGHT serum concentrations are predictive of failure to reach sustained clinical remission at one year[2]. LIGHT is expressed by neutrophils and lymphocytes, is membrane-bound and soluble. Upon binding to its receptors, LIGHT induces lymphocyte activation and proliferation. We therefore hypothesized that LIGHT has a role in the T-cell mediated inflammation in IBD.
Methods
In a cohort of pediatric IBD patients and healthy controls, we collected plasma, intestinal biopsies, resection materials and blood. We assessed the relation of plasma LIGHT concentrations with intestinal immune responses detected by RNA sequencing and histological scoring, and the phenotype and function of circulating gut-homing memory CD4⁺ T cells of pediatric IBD patients and healthy controls by flow cytometry.
Results
We report that elevated plasma LIGHT concentrations and high *TNFSF14* (encoding LIGHT) mRNA expression in intestinal biopsies relate to histological damage in the intestine of therapy-naive CD, but not UC patients. *TNFSF14* mRNA expression correlated more to intestinal T cell-, than neutrophil-, infiltration. Healthy donor-derived circulating memory CD4⁺ T cells that express LIGHT had an activated phenotype, had higher frequencies of IFN-gamma- and TNF-alpha-producing cells and were enriched in circulating gut-homing cells. LIGHT⁺ cell frequencies were increased in gut-homing memory CD4⁺ T cells of a subgroup of IBD patients, and contributed to the inflammatory cytokine production in the intestine.
Conclusion
LIGHT is of interest to study in the context of T-cell mediated inflammation in IBD patients.

Keywords: Inflammatory bowel disease - Memory CD4 T cells - TNFSF14/LIGHT.

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PS20-P04

STING Regulates Pulmonary Remodeling and Immune Responses in Experimental Hypersensitivity Pneumonitis

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Objective
Hypersensitivity pneumonitis (HP) is an interstitial lung disease caused by repeated exposure to inhaled antigens and may progress from chronic inflammation to pulmonary fibrosis. Tissue injury may promote the release of host-derived nucleic acids and engage innate immune sensors. We aimed to investigate the role of nucleic acid sensing pathways, particularly STING, in the immunopathogenesis of HP.
Methods
Mice received 100 µg of *Saccharopolyspora rectivirgula* extract by oropharyngeal administration for 3 consecutive days, repeated weekly for 3 or 10 weeks, and were euthanized 3 days after the final administration. WT and STING-deficient mice underwent pulmonary function testing and bronchoalveolar lavage (BAL), and lungs were analyzed by histology, flow cytometry, qPCR, and Western blotting. The study was approved by CEUA (1429/2025).
Results
At 3 weeks, HP mice showed peribronchoalveolar lymphoid aggregates and increased pulmonary $CD45^+$ cell infiltration, without significant collagen deposition or major pulmonary function changes. At 10 weeks, HP mice exhibited increased collagen deposition, higher dsDNA concentrations in BAL fluid, and increased STING expression in lung tissue. In STING-deficient mice, pulmonary function was impaired, with increased respiratory resistance and reduced dynamic compliance, FEV50, and peak inspiratory flow. STING deficiency was also associated with increased collagen deposition, reduced IL-17 expression, increased alveolar macrophage numbers, and reduced $F4/80^+Siglec\text{-}F^-$ macrophages.
Conclusion
These findings indicate that chronic HP is associated with accumulation of extracellular dsDNA and increased STING expression. The impaired pulmonary function, increased collagen deposition, and altered macrophage compartment observed in STING-deficient mice suggest that STING contributes to the regulation of pulmonary remodeling and immune responses during HP.

Keywords: Nucleic acid sensors - STING - Hypersensitivity pneumonitis.

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PS21-P01

Identification of a Unique TUBB3⁺ Pericyte-like Cell Population Associated with Tuberculosis Granulomas

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Objective
Tuberculosis (TB) granulomas are complex cellular structures whose non-immune components remain incompletely defined. We aimed to characterize a previously unrecognized β-III tubulin (TUBB3)-positive cell population associated with TB granulomas and determine its cellular identity and infection-associated phenotype.
Methods
TUBB3+ cells were examined in TB lesions from mice, guinea pigs, non-human primates, and humans. Their morphology, tissue distribution, proliferative status, and dependence on adaptive immunity were assessed, together with their presence in other inflammatory lung conditions. Single-cell transcriptomics and spatial proteomics were used to define their molecular identities and to compare TUBB3+ and TUBB3− pericytes.
Results
TUBB3+ cells accumulated in TB granulomas across species and displayed an elongated, highly branched morphology. They were distinct from neurons, leukocytes, and known pulmonary resident cell types, emerged independently of adaptive immunity, and were non-proliferative. Similar cells were detected in viral and fungal lung infections, but not in allergic inflammation. Transcriptomic and spatial proteomic analyses aligned TUBB3+ cells with mural cell programs and showed strong enrichment for pericyte-associated signatures. Compared with TUBB3− pericytes, TUBB3+ pericytes displayed a distinct infection-induced state associated with vascular interaction, extracellular matrix remodeling, stress adaptation, and immune-regulatory pathways.
Conclusion
TB granulomas contain a previously unrecognized TUBB3+ pericyte-like population representing a distinct infection-induced pericyte state. These findings reveal a novel perivascular–immune axis that may contribute to the organization and function of the TB granuloma microenvironment.

Keywords: Pericytes - TUBB3 - Tuberculosis.

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PS21-P02

Injury-triggered HA degradation modulates immune responses to promote cardiac valve regeneration

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Cardiac valves (CVs) maintain unidirectional blood flow through an extracellular matrix (ECM)-rich structure composed mainly of elastin, collagens, and hyaluronic acid (HA). In zebrafish, CVs fully regenerate after genetic cell ablation through coordinated recruitment and differentiation of new cells, accompanied by progressive degradation of the old decellularized ECM. While immune-cell dysregulation has been implicated in cardiac valve disease, tightly regulated immune responses are known to support tissue regeneration. However, their role in cardiac valve regeneration remains unknown.

Objective

We aimed to investigate the contribution of immune cells to ECM remodeling and regenerative progression during cardiac valve regeneration, hypothesizing that immune–ECM interactions coordinate these processes.

Methods

We combined single-cell RNA sequencing (scRNA-seq), live imaging, immunostaining, and functional perturbation approaches to characterize the immune response and investigate its contribution to CV regeneration.

Results

Neutrophils were rapidly recruited to injured valves, followed by macrophage accumulation, alongside progressive degradation of HA from the old ECM. Given that HA degradation can be mediated by reactive oxygen species (ROS), present during early regeneration, and that low molecular weight HA (o-HA) exerts pro-inflammatory effects, we investigated whether HA degradation promotes immune-cell recruitment. Consistently, endogenous HA degradation through hyaluronidase injections, or o-HA delivery to uninjured or regenerating hearts, increased immune-cell recruitment. Depletion of phagocytic immune cells using clodronate liposomes impaired regeneration, reducing cell cycle re-entry, recruitment of new valve cells, and degradation of the old ECM. Further scRNA-seq analysis revealed matrix metalloproteinase (MMP) expression in immune-cell populations. Pharmacological MMP inhibition blocked old ECM degradation, supporting a role for MMP activity in ECM remodeling during regeneration.

Conclusions

Our findings identify a functional feedback loop between ECM degradation and the immune response during cardiac valve regeneration, highlighting immune–ECM interactions as key regulators of regeneration in ECM-rich tissues.

Keywords: Hyaluronic Acid - Zebrafish - Immune cells.

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S4-P01

Role of the transcription factor ChREBP in modulating the immune function of tumor-associated macrophages during HCC development

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Objective

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality and remains poorly responsive to immune checkpoint inhibitors. Tumor-associated macrophages (TAMs), a major component of the HCC microenvironment, promote immune escape, yet the metabolic mechanisms controlling their polarization remain poorly understood. ChREBP, a glucose-responsive transcription factor with oncogenic activity in hepatocytes[1], is also highly expressed in TAMs from HCC patients. Our objective was to investigate whether and how ChREBP drives macrophage immunosuppression and HCC progression.

Methods

ChREBP-dependent macrophage reprogramming was investigated by reanalysis a single-cell RNA-sequencing data from 14 human HCCs patients[2] and by performing functional studies in THP-1-derived macrophages in which ChREBP was overexpressed or deleted. Primary BMDMs from mice with macrophage-specific ChREBP deletion were also used for mechanistic validation. The impact of macrophage ChREBP deficiency on HCC was finally assessed in a DEN/CCl4 model of chronic liver injury-driven hepatocarcinogenesis.

Results

Single-cell analysis identified two immunomodulatory (MT1G and FLM) and two immunosuppressives (FOLR2 and SPP1) HCC TAM populations. Strikingly, ChREBP was selectively enriched only in immunosuppressive FOLR2 and SPP1 TAMs. Mechanistically, ChREBP suppressed macrophage immunomodulatory activity by inhibiting NLRP3 inflammasome signaling. We identified the immune checkpoint Galectin-9 (GAL-9) as a novel ChREBP target gene promoting NLRP3 degradation, uncovering a ChREBP-GAL-9-NLRP3 immunoregulatory axis. Conversely, ChREBP inhibition strongly reduced immunosuppressive markers, including CD206, PD-L1 and IRF4. Most importantly, in the DEN/CCl4 HCC model, macrophage-specific ChREBP deletion markedly reduced tumor development and was associated with increased intratumoral infiltration of cytotoxic $CD8^+$ T lymphocytes, demonstrating that macrophage ChREBP actively promotes an immunosuppressive tumor microenvironment in vivo.

Conclusions

Our findings identify ChREBP as a metabolic checkpoint controlling TAM identity and function in HCC. ChREBP activation simultaneously restrains NLRP3-dependent immunomodulatory activity and promotes an immunosuppressive TAM phenotype that limits $CD8^+$ T-cell antitumor immunity. Targeting macrophage ChREBP may therefore reprogram the HCC microenvironment, restore effective antitumor immunity and improve response to immune checkpoint blockade.

Keywords: Macrophage - ChREBP - Galectin 9.

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S4-P02

Paraneoplastic Ovarian Tumors Reveal Cellular and Spatial Features of Naturally Effective Antitumor Immunity

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Objective
Yo-associated paraneoplastic cerebellar degeneration (PCD) is a rare autoimmune syndrome occurring in cancer patients and resulting from an immune response directed against antigens shared by tumor cells and neurons. We previously showed that PCD tumors are heavily infiltrated by T cells and antibody-secreting cells (ASCs) with signs of tumor immune attack. We investigated the cellular, molecular and spatial features associated with this naturally occurring antitumor response.
Methods
A systematic comparison of PCD vs non-PCD ovarian tumors was performed by generating bulk RNA sequencing of laser-microdissected tumor and stromal compartments and paired single-cell RNA-, TCR- and BCR-sequencing of CD45+ and CD45- cells purified from tumor cell suspensions. Key findings were further investigated by flow cytometry and multiplex immunofluorescence (mIF), including spatial analyses of tertiary lymphoid structures (TLS).
Results
PCD tumors displayed increased interferon-related signatures and higher immune scores, whereas non-PCD tumors were enriched in angiogenesis, hypoxia, epithelial-to-mesenchymal transition, glycolysis and fibroblast activity, consistent with a more immunosuppressive microenvironment. Single-cell analyses confirmed increased immune infiltration in PCD tumors and revealed enrichment in effector CD8 T cells together with higher frequencies of clonally expanded cytotoxic CD4 T cells expressing GNLY, GZMB or GZMK. Flow cytometry and mIF confirmed the presence of CD4 T cells expressing either GZMB or GNLY, with rare co-expression. Extensive plasma-cell expansions were observed in both groups. mIF analyses showed that proliferating plasmablasts were predominantly located outside organized TLS, within ASC-rich extrafollicular niches often hosting atypical memory B cells, including in tumors lacking detectable GC. Consistently, the strongest plasma-cell clonal expansions were observed in GC-negative tumors.
Conclusion
PCD-associated ovarian tumors combine enhanced tumor immunogenicity, reduced immunosuppressive stromal programs, expanded cytotoxic T-cell populations and robust local humoral responses. Highly expanded plasma-cell responses in GC-negative tumors and their association with extrafollicular plasmablast niches suggests that effective antitumor immunity can develop independently of GC. These findings provide new insights into naturally effective antitumor immunity and may identify pathways that could be therapeutically exploited.

Keywords: Paraneoplastic neurological syndrome - Ovarian Cancer - Antitumor immunity.

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S4-P03

Treg stability in cancers

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Objective
To investigate the mechanisms underlying Treg instability in the tumor microenvironment and to characterize the molecular identity and phenotype of exTreg cells.
Methods
We use an inducible genetic fate-mapping mouse model (Foxp3$^{-GFP-CreERT2}$ Rosa26$^{-LoxP-STOP-LoxP-tdTomato}$) to permanently label cells that have expressed Foxp3 and track their fate following Foxp3 loss. ExTreg were characterized by flow cytometry, single-cell RNA sequencing (scRNA-seq) and T-cell receptor sequencing (TCR-seq).
Results
We revealed that the tumor microenvironment favor the generation of abundant exTreg. These cells form a population transcriptionally distinct from conventional T cells and Tregs. ExTreg are constituted of two subsets, characterized by differential expression of an interferon-response and metabolic signatures. Both populations expressed exhaustion-associated markers, while differing in their activation state and cytokine production. TCR-seq revealed strong clonal expansion within the exTreg compartment, with shared clonotypes between Tregs and exTreg supporting a common origin. Moreover, blocking MHC class II/TCR interaction reduced exTreg generation, indicating that TCR-dependent signals contribute to Treg instability.
Conclusion
These results show high Treg instability in tumors where high amount of exTreg are continuously generated, partly through TCR signaling. These cells have their unique identity and are characterized by an exhaustion-associated phenotype. Ongoing studies will further define the transcriptomic and epigenetic identity of tumor-infiltrating exTreg, the mechanism of their generation and their function in tumor immunity.

Keywords: Treg stability - exTreg - Tumor microenvironment.

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S4-P04

High-dimensional spatial profiling of the immune microenvironment in human uveal melanoma according to BAP1 status

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Uveal melanoma (UM) is the most common primary intraocular malignancy in adults and remains highly resistant to immunotherapies despite immune infiltration. Although loss of BAP1 is strongly associated with metastatic progression and poor prognosis, its impact on the composition, functional state and spatial organization of the tumor immune microenvironment remains poorly understood. To address this question, we performed high-dimensional spatial proteomic profiling of primary human UM to characterize its immune ecosystem and relationship with BAP1 status. Primary choroidal UM specimens were analyzed using the MACSima™ Imaging Platform with a multiplex antibody panel targeting tumor, immune, endothelial and stromal cell populations, as well as immune regulatory molecules. Single-cell segmentation and phenotypic annotation enabled identification of major cellular populations, followed by analyses of immune composition and immune checkpoint expression. Spatial analyses were performed to investigate tumor microenvironment organization according to BAP1 status. High-dimensional spatial proteomics enabled characterization of the cellular landscape of primary UM at single-cell resolution. The tumor microenvironment comprised diverse immune, stromal and tumor cell populations consistently identified across patient samples. Comparative analyses revealed no major differences in the overall abundance of the principal immune cell populations between BAP1-positive and BAP1-negative tumors. In contrast, differential expression of immune checkpoint molecules was observed within specific immune cell subsets, suggesting that BAP1 status may be associated with functional remodeling of the immune microenvironment rather than substantial changes in immune cell composition. Spatial analyses are being extended to determine whether these phenotypic differences are accompanied by distinct patterns of cellular organization and local cell-cell interactions. Overall, our study provides a high-dimensional spatial characterization of the immune microenvironment in primary human uveal melanoma and offers new insights into the relationship between BAP1 status and immune regulation. These findings suggest that immune dysfunction in UM may primarily reflect alterations in immune cell functional states rather than differences in immune cell abundance, highlighting the value of spatial proteomics for deciphering mechanisms of immune escape and identifying novel therapeutic opportunities.

Keywords: Uveal melanoma - Spatial proteomic - BAP1.

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S4-P05

Intravenous BCG vaccination promotes early onset of mature tertiary lymphoid structures forming a local protective barrier against lung tumors

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Tertiary Lymphoid Structures (TLS) are transient ectopic lymphoid aggregates (LA), composed of adjacent T-cell and B-cell zones, that develop in non-lymphoid tissues during chronic inflammation. TLS progressively evolve through four maturation stages: non-organized LA, immature primary follicle-like TLS, fully mature secondary follicle-like TLS (including a germinal center (GC)), and involuted TLS. Recently, the presence of TLS, more specifically of mature TLS, has been associated with favorable prognosis and improved response to immune checkpoint blockade (ICB) in most solid cancers [1]. Identifying strategies to promote TLS formation and maturation may significantly enhance antitumor immunity and improve the efficacy of existing therapies.
Intravenous (i.v.) administration of Bacillus Calmette Guerin (BCG), the live attenuated strain of *Mycobacterium bovis* used to vaccinate against tuberculosis, establishes a chronic controlled infection in mice with BCG still present in the lungs 2 months after injection [2]. The inflammation induced by BCG could represent a promising strategy for TLS induction.
scRNA-seq data [3] of mice lungs 21 days post i.v. injection of BCG showed increase of TLS-associated T-follicular helper, GC-B cells and TLS-associated stromal and innate cells chemokines scores, compared to control group. Mice lungs showed remodeling of the lung microenvironment with high T-cell infiltration visible at D21 post i.v. BCG injection. An increase in TLS/LA area was observed starting at D33 and maintained till D43 with comparable quantified TLS/LA area. Their structure indicated the presence of GC, characterized by B cells and a network of CD21+ follicular dendritic cells (FDC). Interestingly, in a BCG-vaccination model prior to lung tumor inoculation, we observed the presence of TLS/LA exclusively in BCG-vaccinated mice at D14 post TC-1-Luc injection, whereas TLS/LA was not observed in the control group until D18. Importantly, BCG vaccination significantly protected most mice from tumor development, slowed down tumor growth in mice that developed tumors, and improved survival of mice compared to unvaccinated group.
Early presence of TLS/LA rather than a later presence could be responsible for the protection conferred by BCG-vaccination, with BCG-induced mature TLS forming a local protective barrier preventing the onset or fighting lung tumors. BCG vaccination represents a relevant pre-clinical model for the study of TLS induction and maturation.

Keywords: Tertiary Lymphoid Structures - Vaccination - Antitumor Immunity.

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S4-P06

Unraveling mechanisms of immunotherapy resistance through biomarker profiling in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype for which neoadjuvant chemoimmunotherapy with pembrolizumab has improved outcomes. However, a substantial fraction of patients fail to achieve pathological complete response, and biomarkers predicting treatment response remain limited. We hypothesized that the dynamics of circulating CD4+ T-cell populations, particularly regulatory T cells (Tregs), could reveal mechanisms of resistance and identify predictive biomarkers. We analyzed samples from 12 TNBC patients enrolled in the ALCINA4-3 cohort and treated with neoadjuvant pembrolizumab-based chemoimmunotherapy. Six patients achieved pathological complete response (responders) and six presented residual disease (non-responders). Peripheral blood samples collected at baseline and six weeks after treatment initiation were subjected to FACS sorting of CD4+ conventional T cells and Tregs followed by single-cell RNA sequencing, single-cell TCR sequencing, and CITE-seq. Tumor biopsies and matched surgical specimens were analyzed by bulk RNA sequencing and bulk TCR sequencing. Integrated analyses were performed to characterize immune cell states and clonal dynamics associated with treatment outcome. Single-cell analyses identified distinct Treg subpopulations with differential distribution between responders and non-responders both at baseline and during treatment. Combined transcriptomic and proteomic profiling by CITE-seq revealed heterogeneous expression of activation, regulatory, and exhaustion markers across T-cell subsets. Tumor TCR sequencing demonstrated substantial variability in clonal diversity among patients and enabled the identification of tumor-associated clonotypes for comparison with circulating T-cell repertoires. Preliminary integrated analyses suggest treatment-associated changes in Treg composition and TCR dynamics that correlate with clinical response. Our multiomic approach provides an unprecedented characterization of circulating and tumor-associated T-cell responses in TNBC patients receiving anti-PD-1 therapy. These results support the potential of circulating Treg signatures and TCR repertoire dynamics as biomarkers of immunotherapy response and provide a framework for the development of more personalized therapeutic strategies.

Keywords: Therapy resistance - Regulatory T cells - Biomarkers.

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S4-P07

Understanding the molecular antitumor mechanisms downstream of testosterone in the treatment of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC), also known as adrenal cortex cancer, is a rare cancer with a very poor prognosis that affects women more frequently than men. The absence of clear symptoms in nearly half of ACC cases often results in delayed diagnosis, with 35% of patients already presenting metastases at initial diagnosis. Currently, the only treatment to cure ACC is a complete surgical removal of the primary tumour, but the risk of recurrence is high (30-70% of cases) and is the main cause of death. Heavy therapeutic approaches exist for patients with aggressive tumours, but they don't increase the median overall survival, which is around 15 months. There is therefore an urgent need to identify new therapeutic targets.
To identify such targets, our team has developed a mouse model deficient for *Znrf3* (*Znrf3* KO), one of the major genetic alterations found in ACC patients. We have recently showed that the *Znrf3* KO mouse model exhibits sexual dimorphism: females develop adrenal hyperplasia that progresses to metastasis, whereas males show spontaneous regression of hyperplasia driven by the recruitment of tumour-killing macrophages. Interestingly, this sexual dimorphism emerges at puberty in mice, suggesting that testosterone may protect against ACC by promoting the recruitment of these macrophages [1].
Indeed, our results show that testosterone treatment of *Znrf3* KO females induces tumour regression by inhibiting cell proliferation and increasing apoptosis, which leads to the recruitment of tumour-killing macrophages. However, testosterone is known for its potential side effects, especially in women, which may render it unsuitable for clinical use. Our goal is now to decipher the downstream mechanisms of testosterone in the context of ACC to identify new alternative therapeutic targets. Our data show that testosterone acts by repressing the oncogene MYC. MYC controls various cellular mechanisms such as proliferation, mitochondrial function and apoptosis. Our recent results indicate that, following testosterone treatment, mitochondrial capacity is altered.
Altogether, these data suggest that MYC inhibition by testosterone leads to the modulation of key processes in tumour cells, resulting in cell death, which in turn leads to, or occurs concomitantly with, modulation of the immune microenvironment.

Keywords: Adrenocortical carcinoma - Testosterone - Macrophages.

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S4-P08

Imaging of tumor recruitment of CD8-T cells induced by tumor irradiation: is there any abscopal effect?

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Introduction

Ionizing radiation affects the immune system variably based on cell compartments, doses, volumes, and fractionation. Radiation can influence non-irradiated cells via the bystander effect, enhancing the distant untreated tumor cell elimination through the abscopal effect. Focal tumor irradiation has been shown to induce CD8-T cell tumor infiltration after single irradiation doses in preclinical models. Some patient cases are rare but documented. We aim to evaluate ionizing radiation impact on the immune system by analyzing pre- and post-CD8 infiltration.

Methods

Four patients with polymetastatic tumors were included. Before treatment, each received a single dose of 89Zr-Crefmirlimab Berdoxam from ImaginAb® and underwent PET/MRI imaging 6 hours post-injection, combining PET and T2-weighted MRI. Two weeks later, radiotherapy was delivered to one tumor lesion. A second imaging session was performed 1–3 days after the final radiotherapy, repeating the same tracer dose. Tumor and organs of interest volumes (VOI) were delineated using MRI and prior CT images for patient monitoring.

Results

The SUVpeak and tumor-to-blood pool ratio were used to evaluate CD8 uptake across different organs. Expected uptake was observed in the spleen and lymph nodes, with typical liver and kidney elimination pathways. Before treatment, CD8 uptake in tumors showed varied profiles depending on metastasis location. Post-therapy, CD8 infiltration varied among individuals and and metastasis localization, with a slight increase in both irradiated and non-irradiated lesions. A strong correlation was observed between baseline CD8 levels and post-radiotherapy increases, with higher initial uptake predicting greater changes. However, given the small sample size, the correlation between CD8 infiltration and tumour outcomes is not clear.

Conclusion

These preliminary data suggest that pre-treatment CD8 imaging 6 hours post injection may help better understand the interaction between radiotherapy and the disease's spatial heterogeneity in terms of CD8 infiltration, potentially guiding the choice of the irradiated tumor site.

This study is the first to investigate the abscopal effect in patients using PET/MRI imaging in the context of polymetastatic disease. CD8 imaging is crucial for optimizing radiotherapy planning and could guide decisions regarding combination therapies, based on CD8 activation following treatment.

Keywords: ImmunoTEP - Tumor infiltration - 89Zr-CD8.

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S4-P09

Loss of IL4I1 restrains pancreatic cancer growth and reshapes the tumor microenvironment

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Interleukin-4-Induced-Gene 1 (IL4I1) is an immunosuppressive enzyme that degrades phenylalanin. Il4I1 expression has been described in many cancer types and is often associated with poor patient outcome. We have already shown in mouse melanoma that IL4I1 absence is associated with increased cytotoxic CD8$^+$ T-cell infiltration, favouring tumor control.

Our objective was to elucidate the role of IL4I1 in pancreatic ductal adenocarcinoma (PDAC), a very aggressive type of cancer.

We orthotopically injected PDAC cells from the KPC cell line (*KRAS*^{G12D}, *Trp53*^{R172H}) in IL4I1 WT and KO mice. Four to five weeks later we measured the tumor size and analyzed the tumor microenvironment by flow cytometry and single cell RNA-sequencing (scRNA-seq).

PDAC tumor size was decreased in IL4I1 KO mice compared to WT mice. Moreover, we observed by flow cytometry increased T-cell infiltration in tumors from KO mice, which was predominantly driven by an increase in CD8$^+$ T cells. These infiltrating CD8 T cells displayed high levels of exhaustion markers, including PD-1, TIM-3, and CTLA-4.

By scRNA-seq we identified the IL4I1-expressing cell population in mouse PDAC as mature regulatory dendritic cells. However, this population was not altered in KO mice compared to WT.

scRNA-seq analysis also confirmed CD8$^+$ T cell changes observed by flow cytometry and revealed a profound reduction in Th17 cells and neutrophils, a marked increase in B cells, and the emergence of a follicular helper T-cell population in KO mice compared to WT controls.

Overall, our data revealed profound alterations in the tumor microenvironment of IL4I1 KO mice compared with WT mice. We are currently investigating the hypothesis that tertiary lymphoid structures form in IL4I1 KO tumors. These structures could serve as local antigen-presenting niches, potentially supporting the proliferation and maintenance of anti-tumor CD8$^+$ T-cell responses.

Keywords: IL4I1 - T cell exhaustion - Tumor microenvironment.

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Role of THEMIS on CD8⁺ T cell mediated anti-tumoral response

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Objective
The T-lineage protein Thymocyte-Expressed Molecule Involved in Selection (THEMIS) sustains TCR signaling by repressing the activity of the inhibitory phosphatase SHP-1. Although THEMIS has a well-established function in T-cell development and maintenance, its role in immune responses particularly in the context of cancer remains poorly explored. This work aims to determine whether THEMIS regulates the activation threshold of CD8+T cells upon tumor antigen recognition and to elucidate its impact on tumor clearance and CD8+ T-cell fate, including effector differentiation, memory formation, and exhaustion.
Methods
C57BL/6J mice were intradermally injected with B16 F10 cell line tumors expressing high and low affinity OVA antigens. CD8+T cells expressing the OT-1 TCR, either wild type (WT) or deficient for THEMIS (TKO) were transferred to tumor-bearing mice one week after tumor injection and tumor size was measured the following days. The cytotoxic potentials of OT-1 WT and TKO cells were assessed in parallel. Tumors and draining lymph-nodes (dLNs) were harvested in early and late timepoints and OT-1 populations were characterized by flow cytometry.
Results
We showed that THEMIS is critical to promote efficient tumor control by CD8+ T cells. Interestingly, despite the enhanced cytotoxic capacity conferred by THEMIS in vitro, the loss of THEMIS did not affect the early CD8+ T-cell response against tumors but rather resulted in impaired tumor control at later stages of tumor development. THEMIS deficiency did not affect numbers of tumors infiltrating T cells and the phenotypic profile of these cells. In contrast, THEMIS was required to sustain tumor-antigen specific CD8+ T cells in the dLNs and to promote the generation of memory T cells directed against the tumor. In agreement with this, THEMIS was more abundant in the central memory CD8+ T cells in the dLNs. In accordance with the clinic effect, the impact of THEMIS absence on cells populations at the dLN was observed only in advanced stages of tumor development, not in earlier time points.
Conclusion
THEMIS is essential to sustain anti-tumoral response mediated by CD8+ T cells. Although THEMIS enhances T cell cytotoxicity upon TCR engagement, its predominant *in vivo* contribution is to promote the formation of tumor-antigen specific memory T cells which enable sustained tumor control. Further studies are being carried out to explore the molecular mechanisms involved in THEMIS-dependent tumor control.

Keywords: Cancer - Themis - Memory.

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S4-P11

Differential assembly of mouse and human tumor microenvironments

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Mouse models are essential for studying tumor immunity and developing cancer immunotherapies, yet their ability to represent the diversity of human tumor microenvironments (TMEs) remains poorly defined. To address this gap, we systematically compared murine and human TMEs to identify which features of human antitumor immunity are faithfully modeled in mice.

We generated high-dimensional immune profiles across 15 widely used murine tumor models using CyTOF and single-cell RNA sequencing and benchmarked them against hundreds of human tumors profiled by the ImmunoProfiler consortium. Despite substantial variation among murine models, most of them displayed lower T cell infiltration and greater macrophage abundance than human tumors, mapping predominantly to a restricted subset of immune-desert, macrophage-rich human TME archetypes. Analysis of 2,543 additional murine tumors from public RNA-sequencing datasets confirmed that this bias toward lymphocyte-poor TMEs extends broadly across mouse models.

Beyond cellular composition, we compared chemokine networks, relationships between immune populations and transcriptional states across species. Several organizational features were conserved, whereas others diverged substantially, including the cellular sources of key chemokines such as CXCL13. Using consensus non-negative matrix factorization, we identified conserved gene expression programs (GEPs) in T cells and myeloid cells, including a coordinated cytotoxic T cell–interferon-responsive myeloid axis associated with favorable patient outcomes.

Together, these findings define both the boundaries and opportunities of mouse models for studying human tumor immunity.

Ongoing studies now test whether these cross-species similarities extend to mechanisms of therapeutic responses. At single-cell resolution, we are comparing responses to immunotherapy and other perturbations between mouse tumors and human immune-desert TMEs, while experimentally dissecting the regulation and interdependence of conserved T cell and myeloid GEP states.

Keywords: Tumor microenvironment - Mouse models.

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S4-P12

Pro-inflammatory role of granzyme K producing bystander CD8+ T cells in acute myeloid leukemia

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Objective
Acute myeloid leukemia (AML) is a heterogeneous group of blood malignancies with a 5-year survival rate below 30%, highlighting the urgent need for more effective therapeutic strategies. T cell-based immunotherapies have demonstrated remarkable success in solid tumors, yet the role of CD8+ T cells in AML remains unclear. In this study, we analyzed the composition, antigenic specificity, and function of CD8+ T cells in paired blood and bone marrow samples from AML patients.

Methods
To investigate the contribution of CD8+ T cells in AML pathology, we used high-throughput approaches, such as mass-cytometry (CyTOF), Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) and functional assays.

Results
While we did not identify exhausted CD8+ T cells as seen in solid tumors, we observed a distinct population of functional CD69+ CD8+ T cells specifically enriched in the bone marrow. These cells primarily recognized non-tumor antigens, including epitopes derived from Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Notably, this bystander CD8+ T cell population showed high expression of Granzyme K, a cytokine found in the bone marrow of AML patients. Granzyme K did not induce leukemic cell death but instead promoted the secretion of IL-8, a pro-inflammatory cytokine known to play a detrimental role in AML pathology. Rather than mounting an anti-tumor response, these CD8+ T cells contribute to a pro-inflammatory environment that may exacerbate AML progression and severity.

Conclusion
These findings provide a rationale for exploring therapeutic strategies aimed at inhibiting pro-inflammatory CD8+ T cells and targeting Granzyme K activity in association with actual therapies. Preprint can be found at https://doi.org/10.1101/2025.08.12.669682

Keywords: Granzyme K - CD8 T cells - Leukemia.

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S4-P13

Characterization of T cells phenotype and specificity in pediatric acute myeloid leukemia

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Objective
Acute leukemia is the most common form of pediatric cancer, with over 500 new cases diagnosed each year in France. Acute myeloid leukemia (AML) is the second most common type of leukemia, accounting for 15 to 20% of acute leukemias in children. AML is a cancer of the blood and bone marrow characterised by the rapid, uncontrolled production of immature cells known as myeloid blasts. These cells invade the bone marrow, preventing the normal production of red blood cells, platelets and mature white blood cells. Treatments are often based on chemotherapy or haematopoietic stem cell transplantation. The 5-year overall survival rate for children with AML is around 70%, but 30 to 40% of children relapse after responding well to treatment. This study aims to determine whether vaccination targeting tumour neoantigens could enhance the anti-tumor T-cell response and there by reduce the risk of relapse in pediatric AML patients with standard or intermediate risk. Our hypotheses are as follows:
- Specific anti-tumor T lymphocytes can be found in the bone marrow and/or blood of pediatric AML patients.
- These lymphocytes are able to respond to a stimulation by tumor neoantigens derived from fusion proteins or specific mutations found in the blasts of the patients.

Methods
Affinity of tumor neoantigens with HLA alleles were assessed in silico with NetMHC4.0 algorithm. We performed multiplex MHC class I tetramer assays by mass cytometry on pediatric aml patient blood and bone marrow samples before and after chemotherapy to analyze T cells specificity and phenotype.

Results
We successfully identified 39 peptides likely to interact with common HLA class I alleles. Our mass cytometry revealed bystander CD8 T cells in the bone marrow of pediatric AML patients and an activation of T cells after 4 cycles of chemotherapy.

Conclusions
Our results suggest that chemotherapy induces and activation of T cells, which could represent a target window for immunotherapy.

Keywords: Cancer - T cells - Pediatric.

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S4-P14

Perforin pore formation autonomously triggers pyroptotic cell death in target cells following attack by cytotoxic T lymphocytes

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Objective

CD8+ Cytotoxic T lymphocytes (CTLs) are critical effectors of anti-tumor immunity. Perforin and granzyme B (GrzB) are key weapons in the CTL arsenal that are delivered to target cells across the lytic synapse and trigger regulated cell death (RCD). By convention, GrzB directly activates RCD effectors and is considered the primary cytotoxic payload. While required for efficient CTL killing, perforin is best recognized as a conduit for GrzB entry following pore-formation on target cells (1). However, several prokaryotic pore-forming proteins (PFP) can directly activate an inflammatory RCD pathway termed pyroptosis. The canonical pyroptotic pathway is orchestrated by a potassium (K^+) efflux-sensitive NLRP3-caspase-1-Gasdermin D (GSDMD) axis that culminates in lytic death (2). Given that perforin shares structural homology with these PFPs (3), we aimed to evaluate whether perforin can autonomously initiate RCD signalling upon delivery by CTLs.

Methods

Antigen pulsed target cells (JY lymphoblasts, patient-derived and immortalized melanoma cells) were co-cultured with clonal antigen-specific human CTLs or exposed to soluble perforin. We used a multi-platform approach to monitor pyroptotic signalling, including flow cytometry, confocal and live cell microscopy.

Results

Rapid K^+ efflux from JY target cells was detected in an antigen-dependent manner within minutes of conjugation with CTLs. Using a caspase-1 activity-dependent probe, caspase-1 activation was significantly increased in target cells within 15 minutes of conjugation with CTLs and was proportional to the ratio of CTLs to targets. Caspase-1 activation was diminished upon NLRP3 silencing in targets. Using confocal microscopy, we observed an accumulation of active GSDMD in target cells upon CTL attack that was enriched near the lytic synapse. Live cell imaging and multi-paramatric cell death assays revealed morphological and molecular features consistent with pyroptotic death in target cells following CTL attack. Exposure to soluble perforin was sufficient to trigger rapid K^+ efflux, caspase-1 activation, and pyroptosis in target cells. Our findings were recapitulated in human melanoma cells, which displayed caspase-1, GSDMD activation and pyroptosis following CTL attack.

Conclusion

We reveal a novel mechanism by which perforin itself can autonomously engage pyroptotic machinery upon CTL attack, serving to complement GrzB activity and perhaps act as a compensatory pathway if GrzB is impaired.

Keywords: Perforin - Pyroptosis - Cytotoxic T lymphocyte.

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Impact of tumor microenvironment on the response to radio- and immunotherapy of pediatric glioma cells.

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Objective
Diffuse midline gliomas (DMG) are pediatric tumors with a very poor prognosis since radiotherapy, and more recently immunotherapy, remain only partially effective. To investigate whether resistance originates from the tumor microenvironment, we developed a DMG-on-chip (DoC) model recapitulating gradients of oxygen, pH, and nutrients in a 3D extracellular matrix, and providing a tool to monitor dynamic responses in real time (Terrassoux*, Hazard* et al., Small, 2025).
Methods
We used DMG spheres to investigate NK-cell activity against tumor cells. We co-cultured primary NK cells from five healthy donors with three DMG cell lines (DIPG-007, BT245, and DIPG-012), and assessed cytotoxicity by flow cytometry. We next used our DoC model to decipher how the microenvironment shapes the response to ionizing radiations (2/4 Gy) and/or NK cells, using confocal microscopy and cell segmentation.
Results
NK cells induced a dose-dependent specific lysis of DMG cells, reaching 50% for DIPG-007, 42% for BT245, and 35% for DIPG-012, highlighting the intrinsic cytotoxic activity of NK cells against DMG cells. We then investigated this activity in a more physiologically relevant model, namely the DMG-on-Chip. NK cells infiltrated this DoC and induced DMG cell death, yet NK cells mostly accumulated in the chip normoxic periphery, indicating that their infiltration remained limited in the tumor microenvironment after 48 h of co-culture. The response of DMG cells to irradiation was similarly spatially restricted. DIPG-007 cells were more resistant to irradiation in the hypoxic core but remained sensitive at the normoxic periphery. In contrast, DIPG-012 cells (*TP53* mutant*)* exhibited radioresistance regardless of their location within the DoC. Interestingly, preliminary results suggest that combining radiotherapy with NK cells may enhance treatment efficacy and potentially sensitize resistant DMG cells within the chip.
Conclusion
Together, these results highlight the role of the tumor microenvironment in shaping radioresistance and immune responses in DMG. They further establish the DoC as a relevant preclinical model for investigating tumor–immune interactions and evaluating NK-based and radio-immunotherapy combination strategies. Current work is aimed at investigating whether radiotherapy may increase the expression of NKG2D ligands and reshape the tumor secretome, potentially enhancing NK cells recognition and cytotoxicity towards DMG cells.

Keywords: Pediatric gliomas - Resistance - Tumor-on-a-chip.

References:
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S4-P16

Impact of the Glioblastoma microenvironment on the differentiation of immunosuppressive myeloid cells

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor, with a median survival of 21 months despite multimodal treatment combining surgery, radiochemotherapy, and Tumor Treating Fields (TTFields)[1]. TTFields exert antimitotic, anti-migratory, and immunomodulatory effects. GBM progression is also driven by the tumor microenvironment (TME), particularly myeloid-derived suppressor cells (MDSCs), which promote immunosuppression and tumor progression[2]. Our team recently identified a novel frailty-associated MDSC subset with immunosuppressive and pro-inflammatory properties. Current preclinical models only partially recapitulate tumor–TME interactions. Patient-derived organoids therefore represent a promising approach to preserve tumor heterogeneity and key features of the TME[3].

Objective

We aimed to longitudinally characterize circulating myeloid populations in GBM patients during the EXOFIELDS clinical trial and establish a patient-derived glioblastoma organoid (GBO) model preserving key TME compartments to investigate tumor-derived effects on myeloid differentiation and provide a relevant platform for preclinical validation of therapeutic strategies.

Methods

Circulating MDSCs were characterized by flow cytometry in blood samples collected at different time points during EXOFIELDS trial. GBOs were generated from patient tumor samples and cultured for one month. Immunofluorescence and light-sheet microscopy were used to characterize tumor, endothelial, and immune compartments. GBO-conditioned medium (CM) was applied to human bone marrow-derived cells to assess its effect on MDSC differentiation.

Results

Longitudinal analysis revealed an increased proportion of monocytic MDSC (M-MDSC) in EXOFIELDS patients, with treatment-associated changes. The frailty-associated MDSC subset was also detected in the blood. GBOs preserved tumor, endothelial, and immune populations, better reproducing GBM TME complexity than previous organoid models with limited endothelial and immune representation. GBO-CM promoted the differentiation of human myeloid cells toward an MDSC phenotype, suggesting that GBO-secreted factors contribute to an immunosuppressive TME.

Conclusion

Our GBO model preserves key cellular components of the GBM TME and provides a relevant platform to study tumor–immune interactions and evaluate therapeutic strategies. Longitudinal analysis of circulating myeloid populations further highlights treatment-associated myeloid changes in GBM patients.

Keywords: Glioblastoma - MDSC - Organoid.

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S4-P17

Uncovering the molecular determinants of APC-CD8+TRM interactions in cancer

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Tissue-resident memory CD8+ T cells (CD8+TRM; CD103+CD69+CD49a+) represent a non-circulating subset of immune cells that permanently reside within peripheral tissues. High CD8+TRM density in the tumor microenvironment (TME) has been associated with improved patient survival in breast and lung cancers. However, the mechanisms underlying their activation and regulation within the TME remain unclear. Notably, positive correlations between CD8+TRM and several antigen-presenting cell (APC) subsets including, cDC1, DC3, FOLR2+ macrophages and Langerhans cells, as well as their spatial proximity within tumors suggest that distinct APC populations may play a key role in CD8+TRM regulation.

We aim to decipher how APCs regulate CD8+TRM antitumor functions within the TME of breast and lung cancer patients. Using spectral flow cytometry, we identified heterogeneous CD8+TRM populations, including a proliferative (Ki67+) subset expressing multiple chemokine receptors. In parallel, we characterized tumor-infiltrating APC subsets with a particular focus on those expressing E-cadherin (CD103 ligand) and chemokines potentially involved in CD8+TRM localization and maintenance.

In addition, spatial analyses using high-plex tissue imaging revealed direct physical contacts between CD8+TRM and APCs, suggestive of immunological synapse formation and local reactivation. Complementary, ex-vivo live imaging analysis further confirmed that CD8+TRM establish dynamic synapses with monocyte-derived dendritic cells and Langerhans cells (MoDC/MoLC), leading to their activation.

Together, these findings highlight the phenotypic diversity of CD8+TRM and identify APCs as key orchestrators of their local activation. They provide new insights into the mechanisms driving local CD8+TRM reactivation within tumors and identify potential clues for therapeutic modulation of their antitumor activity.

Keywords: Tissue-resident memory - Cell interactions - Cancers.

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S4-P18

MAP3K8 controls CD8 T cells fate

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Persistent TCR stimulation in tumors drives CD8 T cells differentiation towards exhaustion rather than cytotoxic effector function, which represents a major hurdle to effective cancer immunity. T cell exhaustion has been primarily attributed to transcriptional and epigenetic regulation. Recently, mRNA translation appeared as another layer of regulation of exhaustion but it remains largely under investigated. We identified MAP3K8 (also known as TPL-2 or COT), a nutrient-sensitive MEK kinase and downstream effector of TCR and CD28 signaling, as a potential regulator of T cell differentiation in tumors. Previously we found that MAP3K8 activates the MEK/ERK pathway to promote tumor growth and reshapes the translational landscape of cancer cells by controlling the assembly and activity of the translation machinery. Similarly, our recent data indicate that MAP3K8 also regulates the translation machinery in CD8 T cells, possibly to confer a specific translation program in these cells. Thus, we hypothesized that MAP3K8 integrates nutrient, TCR and co-stimulatory signals to regulate a specific translational program controlling CD8 T cell fate. Our results, using antigen-specific CD8 T cells (OT-I), show that MAP3K8 is dispensable for naïve T cell activation, proliferation and survival but is required for efficient differentiation towards functional effector cells. Following OVA immunization, *Map3k8*-deficient CD8 T cells displayed reduced CX3CR1 and granzyme B expression, together with increased expression of TCF1 and PD-1, indicating impaired effector differentiation and an early dysfunction. Consistently in tumors, *Map3k8*deficiency did not affect CD8 T cell abundance, activation or proliferation but promoted the accumulation of TCF1-positive cells and altered their differentiation state. Notably, compared to control cells, *Map3k8*-deficient CD8 T cells preferentially accumulated in the progenitor-exhausted (Tpex) subset, while fewer cells progressed towards a terminally differentiated exhausted (Tex) cell state. These findings suggest that MAP3K8 promotes the early transition of antigen-specific CD8 T cells towards cytotoxic effector differentiation while limiting alternative Tpex trajectory. Here, we propose mRNA translation as a new layer of regulation of T cell exhaustion, opening avenues for future exploration of drugs targeting the translation machinery as cancer immunotherapies.

Keywords: Exhaustion - Tumor - CD8 T cells.

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S4-P19

Bright side of the dark genome: lncRNA expression is dysregulated in colorectal precancer lesions

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Objective

Long non-coding RNAs (lncRNAs) have emerged as pivotal regulators of tumorigenesis, orchestrating oncogenic and tumor-suppressive networks through diverse molecular mechanisms. Their dysregulated expression is increasingly recognized as a hallmark of malignant transformation, with specific lncRNAs acting as tumor suppressors or oncogenes, driving both tumor initiation and progression. Recent studies have revealed that a subset of these transcripts harbor small open reading frames (sORFs) encoding short antigenic micropeptides. These lncRNA-derived peptides can be processed and presented on MHC class I molecules, rendering them recognizable by cytotoxic T lymphocytes. This finding fundamentally expands the immunological landscape of the non-coding genome in cancer biology. The aim of our study is to understand lncRNAs dysregulation in early colorectal precancerous lesions and their impact on the immune system.

Methods

We performed a comprehensive multimodal characterization of the immune microenvironment in collected longitudinal premalignant colorectal lesions. Non-coding RNA expression was analyzed in parallel with the predicted MHC class I binding affinity of candidate noncanonical antigens derived from lncRNA-associated sORFs. Selected candidate peptides are currently being evaluated for immunogenicity *in vitro*.

Results

Lesions from patients with low polyp development rates showed enhanced adaptive immune infiltration and increased expression of noncoding RNAs. These transcripts were predicted to encode noncanonical antigens with high MHC-I binding affinity. The immunogenicity of these candidate antigens is currently being investigated *in vitro.*

Conclusion

We predicted lncRNAs-based peptides binding MHC-I using bioinformatic predicting tools. Validation of these predictions will be performed *in vitro*.

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S4-P20

CCL18-expressing macrophages may drive an immunosuppressive and pro-invasion colorectal tumor microenvironment

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Introduction

The colon cancer immunosuppressive tumor microenvironment (TME) is shaped by interactions between cancer, immune, stromal cells, and the extracellular matrix (ECM). We have previously demonstrated that decellularized tumor matrices, derived from colon cancer patients, modulate macrophages to secrete high levels of CCL18. We showed that this pro-fibrotic and immunosuppressive chemokine promotes colon cancer cell invasion and is expressed by macrophages at the invasive front of advanced colon tumors. Next, we aim at transcriptionally and spatially characterize CCL18-expressing macrophages and their interactions.

Materials and Methods

We performed mass spectrometry on decellularized tumor and normal matrices. Multiplex Tissue Microarray was performed on cores derived from 12 colorectal cancer patients and analyzed using the AIVIA software. We analyzed publicly available single-cell RNA-sequencing (scRNAseq) data from colorectal cancer together with single-cell spatial transcriptomics (ST) data (AC-ICAM cohort).

Results

By intersecting the increased proteins in tumor dECM with genes positively correlated with CCL18 we uncovered a 19-protein panel. scRNASeq data evidenced that these genes are mainly expressed by fibroblasts, including FAP, a well-known marker of cancer-associated fibroblasts. TMA's analysis reveals a close proximity between FAP, CD68 and CCL18 at the tumor invasive front.

scRNASeq data analysis unveiled that CCL18$^+$ macrophages comprise subpopulations of bigger macrophage populations characterized by the expression of *SPP1*, *MARCO* and *APOE*, described as markers of immunosuppressive phenotype. CCL18$^+$ macrophages express significantly more *MMP12* and several cathepsins than its counterpart. Enrichment analysis of this population reveals upregulation of extracellular matrix remodulation pathways. Additionally, spatial transcriptomics data confirms these observations and adds close spatial proximity between CCL18$^+$ macrophages and inflammatory fibroblasts characterized by *MMP1* and *MMP3* expression.

Conclusion

CCL18$^+$ macrophages may mediate increased invasive capacity of tumor cells in colorectal tumors by inducing ECM remodeling together with MMP1$^+$ and MMP3$^+$ inflammatory fibroblasts.

Keywords: Colorectal - Macrophages - CCL18.

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S4-P21

Tumor heterogeneity shapes distinct immune landscapes and therapeutic responses in triple-negative breast cancer

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Aim

Triple-negative breast cancer (TNBC) is highly aggressive and heterogeneous, complicating therapeutic management. Our goal was to capture the intrinsic and extrinsic diversity of TNBC, assess its relevance to human TNBC, and determine how distinct tumor contexts influence therapeutic responses.

Methods

We developed and extensively characterized the immunocompetent *MMTV-R26Met* mouse model, which spontaneously develops TNBC. Using an integrative approach combining histological, genomic, transcriptomic, proteomic, and immune profiling, we characterized tumor heterogeneity and the associated tumor immune microenvironment (TIME). Bioinformatic analyses were performed to compare murine tumor profiles with human TNBC datasets. Distinct tumor contexts were further evaluated following serial transplantation into syngeneic hosts and treatment with chemotherapy or anti-PD-1 immunotherapy.

Results

We identified four distinct TNBC immune landscapes characterized by the predominance of macrophages, neutrophils, lymphocytes or dendritic cells (DCs). These immune landscapes were associated with distinct tumor molecular programs and remained reproducible following serial transplantation, supporting a strong contribution of tumor-intrinsic features to the establishment of specific immune contexts. Bioinformatic analyses further revealed similarities between these murine immune landscapes and distinct human TNBC profiles. Importantly, tumors displaying distinct immune landscapes showed differential responses to therapeutic interventions. Ongoing work aims to identify tumor-derived signals governing immune cell recruitment and functional states, with a particular focus on macrophages and DCs.

Conclusion

Our findings establish distinct and reproducible immune landscapes within TNBC and support a role for tumor-intrinsic programs in shaping the TIME and therapeutic response. This model provides a framework to investigate the mechanisms driving tumor-immune heterogeneity and identify potential strategies to modulate the TIME in TNBC.

[FM1]I think you should put affiliations.

Keywords: Tumor immune microenvironment - Tumor-associated myeloid cells - Combined Immunotherapy.

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S4-P22

Focused Antibody Responses Against Tumour-Associated Antigens Emerge from Dominant Extrafollicular B-Cell Differentiation in Ovarian Cancer

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Objective
B cells and antibody (Ab)-secreting cells (ASCs) are increasingly recognised as important contributors to antitumour immunity. However, it remains unclear to what extent the extrafollicular (EF) B-cell differentiation pathway, recently described in human cancers, contributes to ASC generation and allows for Ab responses against tumour-associated antigens (Ags). High-grade serous ovarian cancer (HGSOC) associated with Yo paraneoplastic cerebellar degeneration (PCD) provides a unique natural situation to address this question, as patients develop humoral responses against CDR2L, an onconeural antigen expressed by both tumour cells and neurons. We sought to characterise the specificity of Abs produced by intratumoural ASCs in PCD and non-PCD ovarian cancers.
Methods
Tumour-infiltrating B cells and ASCs from Yo-PCD and equally infiltrated non-PCD HGSOC were analysed by paired single-cell RNA-seq and BCR-seq, generating datasets comprising >34,000 cells in each compartment. Recombinant antibodies (rAbs; n=61) were generated from highly expanded intratumoural clonotypes. Ab reactivity against CDR2L was assessed using cell-based assays and ELISA. Broader Ag specificities were investigated using HuProt protein arrays (>20,000 human proteins), followed by custom microarrays and ELISA validation.
Results
Trajectory and clonal analyses identified a dominant EF differentiation pathway involving atypical memory B cells. BCR analyses revealed extensive local ASC clonal expansion in both PCD and non-PCD tumours, with expanded clonotypes accounting for approximately 60% of the ASC compartment. Among PCD rAbs tested, 29/40 (72.5%) recognised CDR2L, with these CDR2L-reactive clonotypes representing up to 38.6% of the total ASC repertoire in individual PCD patients. Moreover, 2 of the 4 evaluated non-PCD patients showed a focused response to other tumour-associated Ag. Several antibodies displayed broader reactivity profiles, with polyreactivity more frequent among antibodies isolated from PCD tumours.
Conclusions
These findings provide direct evidence that highly expanded intratumoural B-cell clones generate focused Ab responses against tumour-associated Ags. Together with the predominance of an EF differentiation pathway, our results indicate that EF humoral immunity can produce Ag-selected Abs in human cancer. This work links non-canonical B-cell differentiation pathways to tumour-specific Ab responses and provides new insights into antitumour humoral immunity.

Keywords: Ovarian Cancer - B lymphocytes - Antibodies.

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S4-P23

The costimulatory molecule ICOSLG promotes Treg-mediated immunosuppression in human models of triple-negative breast cancer

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Introduction
Regulatory T cells (Treg) are immunosuppressive CD4 T cells that inhibit effector T cell (Teff) responses and contribute to immune evasion in cancer. The Inducible CoStimulatory molecule ICOS is preferentially expressed by Treg 1. Its ligand, ICOSLG, normally expressed on antigen-presenting cells, is upregulated in triple-negative breast cancer (TNBC) and associated with poor prognosis 2. However, in human TNBC the impact of tumor-expressed ICOSLG on Treg and on the immune response is unknown. We hypothesize that ICOSLG may promote Treg expansion and function by a direct interaction with ICOS, contributing to immune suppression in TNBC.
Methods
ICOSLG was knocked out in MDA-MB-231 cells using CRISPR-Cas9. ICOSLG+ and KO cells were implanted in humanized mice (HuNXG). The effect of ICOSLG KO on the immune system was assessed by flow cytometry and tumor growth was compared with ICOSLG+ cells. 3D co-culture with cancer cells expressing or not ICOSLG with T cells from healthy donor peripheral blood mononuclear cells, were performed to assess the direct impact of tumor-derived ICOSLG on Treg and Teff. Finally, the effect of ICOSLG blockade with an anti-ICOSLG alone or in combination with anti-PD-1 on T cell activation in HuNXG was assessed by flow cytometry and targeted single-cell RNA sequencing.
Results
ICOSLG KO is associated with a decrease in Treg frequency, number and immunosuppressive markers in the tumor. This decrease in Treg-mediated immunosuppression is associated with increased CD8 cytotoxicity and conventional T cell activation leading to reduced tumor growth in HuNXG. *In vitro*, tumor-expressed ICOSLG promotes Treg expansion. While we observed less immune activation *in vivo* in ICOSLG+ tumors, *in vitro* ICOSLG promotes CD8 cytotoxicity and tumor killing. This suggests that the CD8 inhibition observed *in vivo* with ICOSLG+ tumors is mainly due to Treg expansion rather than direct inhibition by tumor cells. In HuNXG, targeting ICOSLG decreases Treg frequency without increasing CD8 activation. However, the addition of anti-ICOSLG to anti-PD1 treatment induces increased T cells activation and cytotoxic signature in RNA sequencing and resulted in a therapeutic response to anti-PD-1, whereas anti-PD-1 alone did not reduce tumor growth.
Conclusion
In humans, tumor-derived ICOSLG drives Treg-mediated immunosuppression in TNBC, associated with reduced CD8-T cell activation and cytotoxicity and its blockade may enhance the response to anti-PD-1 therapy.

Keywords: Treg - ICOSLG - TNBC.

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S4-P24

KLRG1 Identify Tumor-Associated T-Cell Populations in Colorectal Cancer

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Colorectal cancer (CRC) is the third most common cancer worldwide and remains a leading cause of cancer-related mortality. In metastatic stages, current treatments, including surgery and chemotherapy, are often insufficient. Although immune checkpoint inhibitors have shown success in several cancer types, their effectiveness in CRC is mostly limited to microsatellite instability (MSI) tumors, which represent a small subset of patients. This highlights the need to better understand the immune landscape of CRC, particularly tumor-specific T cell responses and the pathways that regulate their function. To address this, we performed high-dimensional spectral flow cytometry on matched healthy mucosa lymphocytes (ML) and tumor-infiltrating lymphocytes (TIL) from CRC patients, using unsupervised clustering to define CD4+ and CD8+ T-cell metaclusters, with supervised flow cytometry validating key populations in 10 patients. Bulk RNA-seq of 103 paired tumor and adjacent gut samples from the IMCO cohort assessed transcriptional correlates, and functional assays using allogeneic HT29 spheroids with patients' PBMCs and autologous patient-derived tumoroids with TIL co-cultures tested the effect of KLRG1 blockade on tumor-cell killing. Unsupervised analysis of 411,606 CD45+ cells revealed marked remodeling of the CRC immune landscape. Within the CD8+ compartment, 15 metaclusters were identified, including tumor-reactive CD161+CD39+ tissue-resident memory (TRM)-like cells with an immune checkpoint profile (TIM-3+PD-1+), activated effector-memory KLRG1+CD38+ cells, and exhausted-like PD-1+TIM-3+CD39+ cells. Supervised analysis confirmed significant enrichment of KLRG1+, CD39+, PD-1+, and TIM-3+ CD8+ T cells in TIL compared with ML, and CD161+CD39+ cells were increased in TIL in both CD8+ and CD4+ compartments. KLRG1 blockade showed a trend toward enhanced tumor-cell apoptosis in co-culture models. Together, these results provide a framework for investigating KLRG1 and other T-cell regulatory pathways as potential targets to enhance antitumor immunity in colorectal cancer.

Keywords: Colorectal cancer - Spectral flow cytometry - Spheroid/tumoroid co-culture.

References:

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S4-P25

Characterization of the Immune Landscape in the Novel Prss56 Rhabdoid Tumor Model

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Objective
Rhabdoid tumors (RTs) are rare and aggressive pediatric cancers characterized by biallelic loss of *SMARCB1*. Currently available immunocompetent models used to investigate the RT immune microenvironment are predominantly extracranial, limiting the study of RTs within their native anatomical context. Here, we generated a genetically engineered mouse model in which *Smarcb1* deletion in neural crest-derived boundary cap cells spontaneously gives rise to orthotopic RTs at two clinically relevant sites: intracranially (IC) and in the spinal cord (SC). Here, we investigated how tumor location shapes the immune microenvironment and influences therapeutic responses. **Methods**
Smarcb1 deletion resulted in two distinct clinical phenotypes: early-onset ataxia associated with intracranial (IC) tumors and later-onset paralysis associated with spinal cord (SC) tumors. Single-cell RNA sequencing was used to characterize the immune infiltrate of IC and SC tumors and identify location-specific therapeutic opportunities. As a therapeutic benchmark, we evaluated whether anti-PD-1 plus poly(I:C) (PIC), previously effective in syngeneic RT models, could delay or prevent the onset of tumor-associated ataxia.
Results
Single-cell RNA sequencing revealed that both IC and SC tumors were predominantly infiltrated by myeloid cells, with monocytes and macrophages (MoMa) representing the major immune compartment. Despite a broadly similar MoMa composition, differential expression analysis revealed location-specific transcriptional programs, with IC-associated MoMa enriched in proliferative pathways and SC-associated MoMa enriched in inflammatory and signaling pathways. More pronounced differences were observed within the T-cell compartment. SC tumors were enriched in regulatory T cells (Tregs), whereas IC tumors showed a higher proportion of mucosal-associated invariant T (MAIT) cells, which was independently validated by flow cytometry and TCR sequencing. Finally, as a therapeutic benchmark, anti-PD-1 plus PIC delayed ataxia onset and prolonged the ataxia-free period in vivo.
Conclusion
Our findings reveal that anatomical location profoundly shapes the immune landscape of RTs, highlighting distinct myeloid and T-cell states and establishing this spontaneous orthotopic model as a relevant platform to explore tailored therapeutic strategies

Keywords: Rhabdoid tumor - a-PD1 - PIC.

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S4-P26

Exploring the interplay between PD-1 and BTLA in regulating T-cell antitumor responses

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Tumor-specific T cells accumulate multiple inhibitory receptors, so-called « immune checkpoints » (IC), which represent central targets of current immunotherapy approaches. Notably, combined blockade of the ICs PD-1 and CTLA-4 has demonstrated substantial clinical efficacy in melanoma, but expression of other ICs could constitute a tumor escape mechanism, underscoring the need to identify alternative combinatorial strategies. Because the ICs PD-1 and BTLA operate very similarly at the molecular level, we hypothesized that they could cooperatively dampen antitumoral T cell responses. Here, we aim to evaluate the impact of single and combined T-cell intrinsic deficiency of BTLA and PD-1 on anti-melanoma response in a pre-clinical mouse model. We also studied whether BTLA deficiency in T cells improves antitumor response upon anti-PD-1 immunotherapy.
Mice deficient for either PD-1 (PD-1TKO), or BTLA (BTLATKO), or both (DKO) in peripheral T cells were injected with B16K1 or YUMM-OVA-HVEM melanoma cell line intradermally. Impact of TCR affinity for tumoral antigen on antitumor response was assessed thanks to B16F10 cell lines expressing OVA altered-peptide ligands. Tumor growth was measured until endpoint. Tumors, draining and non-draining lymph nodes were used to perform flow cytometry.
As expected, PD-1TKO individuals control tumor growth better than their WT counterparts. In contrast, tumors in BTLATKOindividuals do not grow differently than their WT counterparts. In agreement with this hypothesis, DKO individuals do not significantly control tumors differently than their PD-1TKO counterparts, suggesting that tumor control is mostly a PD-1 deficiency-driven effect. This result has been confirmed in both high and low affinity settings. In the context of anti-PD-1 immunotherapy, BTLATKO individuals did not significantly control tumors better than their WT counterparts. The absence of impact of BTLA deficiency in T cells could be explained by a lack of upregulation of the protein at the cell surface, in tumor-infiltrating lymphocytes. BTLA seems inversely correlated with terminal exhaustion, contrary to PD-1, which renders their cooperation inside the tumor less likely.
The results of our study indicate that PD-1 and BTLA are not acting in a cooperating manner to regulate T-cell anti-tumor responses. Moreover, BTLA expression on T cells does not limit the efficacy of anti-PD-1 immunotherapy.

Keywords: Immune checkpoint - T-cell - Tumor.

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S4-P27

BCL6 acts as a regulator of T cell exhaustion in cancer

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Objective
T cell exhaustion can be defined as an adaptation to chronic antigen stimulation that allows T cell to persist in difficult environments. Nevertheless, exhausted T cells are defined by lower effector capacities and their accumulation within tumours have been associated with deleterious outcomes for patients. Thus, limiting or reversing T cell exhaustion has been one of the major focuses in immuno-oncology, leading to the introduction of immune checkpoints blockade therapies. These immunotherapies have demonstrated impressive results but the responses are limited to certain patients and types of tumours, underlining the need for a better understanding of T cell exhaustion. Among potentials new regulators of T cells exhaustion BCL6 seems to be a promising target.
Methods
To better understand the role of BCL6 in T cell exhaustion we are using mice in which BCL6 expression is specifically lost in T cells (Cd4Cre Bcl6fl/fl model) injected with models of solid (B16K1 and B16-OVA melanoma models) and haematological malignancies (Vk*Myc 12653 and 12598 multiple myeloma models) and analysed by spectral flow cytometry and single-cell RNA sequencing.
Results
We demonstrated that the loss of BCL6 is associated with a decrease of a CD4+ and CD8+ T cells exhausted population, defined by the expression of inhibitory receptors and the loss of the CD226 activatory receptor. This decreased T cell exhaustion was associated with an increase of the GrzA+ CD25+ effector/cytotoxic population. In addition, the specific loss of BCL6 expression in T cells is associated with lower tumour burden and increased survival in mice injected with the Vk*Myc multiple myeloma model suggesting a deleterious role for BCL6 in this context. Finally, BCL6 is necessary to mediate the anti-tumour response induced by the anti-CD137 treatment.
Conclusion
Thus, BCL6 seems to act as a regulator of T cell exhaustion in cancer by controlling the differentiation of T cells into the exhausted PD1+ CD226- populations and by limiting the acquisition of an effector/cytotoxic phenotype, in the context of stimulation.

Keywords: Exhaustion - BCL6 - Cancer.

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S4-P28

Prenatal maternal stress durably impairs CD8 T cell antitumour immunity through a microbiota-derived bile acid

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Objective
Prenatal maternal stress durably shapes offspring immunity and has been linked to weaker antitumour responses, yet the cells and molecular programmes involved remain undefined. We asked how prenatal stress (PS) impairs tumour control in adult offspring, and through which mediator.
Methods
PS was induced by restraint and bright light (3x30 min/day, E13-E18); analyses were performed on adult offspring (8-12 weeks). Tumour growth was followed after intradermal B16F10-OVA or MC38 engraftment. The responsible compartment was mapped by adoptive transfer of total, CD8 and OT-I CD8 T cells into Rag-deficient recipients. The microbiota was profiled and transferred into antibiotic-treated wild-type mice; faecal metabolomics was performed and the identified metabolite tested in vivo and on activated CD8 T cells *in vitro*.
Results
PS offspring developed larger tumours in both models. Total T cells from PS donors reproduced this phenotype in naive Rag-deficient recipients, showing that T cells are sufficient. Recipients of PS CD8 T cells developed larger tumours with reduced survival, and OT-I PS CD8 T cells were equally impaired, excluding a shift in TCR repertoire and identifying a cell-intrinsic defect of the CD8 lineage. In parallel, PS offspring harboured a distinct microbiota, itself sufficient to impair tumour control after faecal transfer. Metabolomics identified a single secondary bile acid selectively increased in PS mice and restored in recipients of PS microbiota. Administered to naive mice, this metabolite enlarged tumours; in vitro, it reduced the proportion of CD8 T cells expressing perforin, granzyme B, T-bet, TNF and IFN-γ.
Conclusion
Prenatal stress imprints a cell-intrinsic defect in the CD8 compartment, and a single microbiota-derived bile acid is sufficient to reproduce both the loss of effector function and of tumour control. The concomitant fall in T-bet points to impaired effector differentiation rather than loss of one effector molecule. Since PS T cells remain defective in recipients carrying a normal microbiota, this programme must be stably encoded within the CD8 lineage. Ongoing work profiles tumour-infiltrating CD8 T cells and pairs single-cell RNA-seq with ATAC-seq to link chromatin accessibility to this programme, while metyrapone blockade of maternal corticosterone synthesis tests whether glucocorticoids initiate the cascade.

Keywords: Prenatal stress - CD8 T cells - Antitumour immunity.

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S4-P29

T-cell exhaustion and immune landscapes differ between peritoneal and ovarian lesions in ovarian cancer patients

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Ovarian cancer (OC) is the most lethal gynecologic malignancy. Results from several immune checkpoint blockade (ICB) clinical trials show dismal overall response rates in recurrent OC. Resistance to ICB is in sharp contrast with the immunogenic nature of the disease, in which the T-cell infiltrate correlates with survival and adaptive responses to tumor antigens are frequently detected. In ICB sensitive malignancies, CD8 infiltrate, T-cell effector signatures or tumor mutational burden were shown to be correlated with clinical response. Our previous work investigated CD8 and CD4 T-cell exhaustion in epithelial malignancies, exploring its association with tumor antigen specificity and its impact on the response to ICB. Terminally exhausted intratumoral CD8 T cells were identified as biomarkers of response to ICB, with this exhausted state occurring only after chronic in situ stimulation of anti-tumor T cells. In a recent study in OC patients, we showed that terminal T-cell exhaustion is associated to beter prognosis upon standard surgery and chemotherapy.
Given the central role of peritoneal extension in OC therapeutic resistance and escape, we analyzed the immune infiltrate according to tumor localization. We hypothesized that upstream inhibitory mechanisms hinder activation of tumor antigen-specific T cells in peritoneal lesions.
Through flow cytometry and unbiased scRNA-Seq of tumor infiltrating leukocytes, we analyzed the immune infiltrate in ovarian and peritoneal lesions.
Firstly, we found that terminally exhausted CD8 T cells and CD4 T conventional cells were underrepresented in peritoneal lesions in comparison to primary ovarian lesions. Transcriptomic analysis of paired lesions collected prior to treatment confirmed ovarian enrichment of terminally exhausted clusters of CD8 and CD4 T cells. Analysis of clonal distribution thanks to TCR sequencing showed a high proportion of clones shared between the two sites. Nonetheless, the T-cell repertoire in ovarian lesions exhibited higher oligoclonality in comparison to the peritoneal repertoire. T regulatory cells, which heavily infiltrate ovarian tumors, and myeloid cells were characterized, showing different populations within the lesions.
Our results reveal a distinct immune landscape between ovarian and peritoneal lesions, potentially identifying immune populations and mechanisms exerting upstream control over tumor-specific T cells in this highly unresponsive, yet immunogenic, gynecological disease.

Keywords: Ovarian Cancer - T-cell exhaustion.

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S4-P30

Translation reprogramming of melanoma persister cells drives MIF secretion and an immunosuppressive tumor microenvironment

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Objective
Following BRAF/MEK-targeted therapy, a subpopulation of drug-tolerant persister cells (DTPs) emerges in BRAFV600E-mutant melanoma and constitutes a major determinant of tumor relapse. We previously showed that DTP are characterized by a profound RNA translation reprograming and now aim at exploring how they evade the immune system.

Methods
Spatial multiplex imaging (COMET) was performed on patient melanoma biopsies to map immune cell distribution around persister niches. To test a secretome-driven hypothesis, patient tumor fragments were exposed *ex vivo* to persister-conditioned supernatant and profiled by single-cell RNA sequencing, while tumor slices were analyzed by COMET under the same conditions. Supernatant composition was characterized by cytokine array to identify candidate mediators. *In vitro*, macrophages and lymphocytes were exposed to parental or persister supernatant and assessed for cytotoxicity, migration, and phagocytic function. Secretion of the candidate mediator was further validated by ELISA *in vivo* in mouse models and patient samples.

Results
Spatial analysis revealed reorganization of immune populations around persister niches, marked by exclusion of several pro-immune populations alongside increased infiltration and remodeling of macrophages toward a pro-tumoral phenotype. Persister-conditioned supernatant recapitulated this immunosuppressive shift *ex vivo*, increasing pro-tumoral macrophage polarization and T cell exhaustion in both single-cell and spatial datasets. Persister supernatant was found to be enriched in MIF (Macrophage migration inhibitory factor). MIF addition to parental cell supernatant was sufficient to mimic persister-induced effects, reducing lymphocyte-mediated killing and macrophage phagocytic capacity while increasing pro-tumoral macrophage migration. MIF secretion by persister cells was confirmed *in vivo* in both murine models and patient tumors, and was dependent on the translational remodeling characteristic of the persister state. Pharmacological inhibition of this remodeling reduced MIF secretion both *in vitro*and *in vivo*.

Conclusions
Drug-tolerant persister melanoma cells actively promote an immunosuppressive niche through translation-dependent secretion of MIF, driving macrophage reprogramming, and impaired anti-tumor immunity. Targeting persister-associated translational control may represent a strategy to disrupt immune evasion and delay relapse.

Keywords: Melanoma - Persister cells - Immune remodelling.

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S4-P31

A Dual CSF-1/IL-34 Trap Suppresses CSF-1R Signaling and Targets the Myeloid Compartment

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Aims

IL-34 is a cytokine involved in monocyte differentiation and survival. In addition to the shared receptor CSF-1R, IL-34 can also bind alternative receptors including SDC-1, PTPζ and TREM-2. In several cancers, elevated expression of CSF-1 and IL-34 correlates with poor prognosis and contributes to the establishment of an immunosuppressive tumor microenvironment. Yet, targeting CSF-1/CSF-1R axis in clinic have yielded limited benefit, possibly due to incomplete receptor inhibition of the pathway. To address this limitation, we developed a soluble CSF-1R-Fc fusion protein designed to simultaneously capture both CSF-1 and IL-34.

Methods

The sCSF-1R-Fc construct consists of the extracellular domain of CSF-1R fused to a silent Fc fragment to increase biological half-life. Using *in silico* modeling, we generated optimized mutant variants predicted to enhance ligand binding and cytokine capture. *In vitro* experiments were conducted to evaluate 3 variants of the sCSF-1R-Fc construct, including the previously described mutant [(1)] and 2 newly engineered variants. To assess their efficacy in presence of IL-34 or CSF-1, we stained elements of the resulting downstream signalization (Akt and Erk phosphorylation) and also measured CD14+ monocytes isolated from healthy donor PBMCs viability after 3 days of co-culture. Then, *in vivo* experiments were conducted on a preclinical melanoma model using the YUMMER1.7 cell line in C57Bl6 mice, which were treated with or without a checkpoint inhibitor: anti-PD-1 antibodies.

Results

2 of the 3 constructs efficiently bound IL-34 and CSF-1 and reduced downstream CSF-1R signaling. In $CD14^+$ monocytes, treatment with the sCSF-1R-Fc constructs induced increased cell death after 3 days, particularly at higher concentrations. In addition, *in vivo*, the combination of sCSF-1R-Fc and anti-PD-1 therapy increased $CD4^+$ and $CD8^+$ T-cell numbers in the spleen compared with untreated mice. Importantly, this group also displayed a lower proportion of tumor-bearing mice, suggesting improved tumor control compared with anti-PD-1 alone or combined with an anti-CSF-1R therapy groups.

Conclusion

Taken together, these results demonstrate that WT and optimized sCSF-1R-Fc mutants efficiently capture IL-34 and CSF-1, suppress downstream signaling, and affect monocyte viability, thereby targeting macrophage-driven immunosuppression and supporting the therapeutic potential of dual ligand blockade of the CSF-1/IL-34 axis as an anticancer strategy.

Keywords: Cytokine - Tumor Micro-Environment - Macrophages.

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S4-P32

Stenocytosis a mechanism for supramolecular attack particle transfer at the CTL lytic synapse

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Supramolecular attack particles (SMAPs) are recently discovered components of the cytotoxic T lymphocyte (CTL) lytic arsenal which exhibit autonomous cytotoxic behavior. Yet, the mechanisms by which these particles transfer from CTLs into target cells across the dynamic lytic synapse and mediate cytotoxicity remains to be elucidated.
In CTLs interacting with immobilized stimuli, total internal reflection fluorescence microscopy (TIRFM) and rapid 3D live cell imaging showed that granules containing SMAPs navigate through narrow areas of depleted actin within the cortical cytoskeletal network of CTLs followed by secretion across plasma membrane hot-spots.
In CTLs interacting with cognate target cells, correlative light-electron microscopy (CLEM) and structured illumination 3D imaging showed SMAP release into the synaptic cleft followed by penetration into target cells. Remarkably, our imaging analysis revealed that SMAP entry into target cells occurs through a narrow gap within the target cell cortical actin network which mirrors an equally narrow gap formed in the CTL, allowing SMAP internalization into early endosomes.
Our results reveal a previously undescribed process, *stenocytosis* (from the ancient Greek *στενός*, «narrow»), which allows hundred-nanometer-scale particles to exit CTLs and enter target cells via narrow actin cytoskeleton gaps. These findings define SMAPs as a secondary cytotoxic wave that re-enforces the first wave of CTL attack mediated by the release of soluble perforin and granzyme. This second line of attack exploits, like a Trojan horse, the intense vesicular trafficking taking place at the two sides of the lytic synapse.

Keywords: Lytic synapse - Cytotoxic T lymphocytes - Supramolecular attack particles.

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S4-P33

Microneedle-Mediated Intratumoral Delivery of Immune Checkpoint Inhibitors in Melanoma: Antitumor Activity and Biodistribution in Murine Models

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Local delivery strategies for melanoma are increasingly explored to reduce systemic exposure to immune checkpoint inhibitors while preserving antitumor efficacy and the tumor immune microenvironment (TIME). Microneedles (MNs) may enhance local immune activation and immunogenicity while providing a minimally invasive administration route.
To evaluate the antitumor efficacy and biodistribution of intratumoral (IT) delivery using MNs compared with the intraperitoneal (IP) route in murine tumor models.
Anti-PD-1 (25 µg IT; 250 µg IP) and anti-CTLA-4 (50 µg IT; 500 µg IP) were administered repeatedly at regular intervals. Tumor volume and body weight were monitored before each injection. Tumor growth was expressed as Relative Tumor Volume (RTV). Tumors were collected at study completion for analysis. Biodistribution was assessed using indocyanine green and IVIS imaging.
No significant RTV differences were observed between control and IT immunotherapy groups during the first 8 days. Significant antitumor effects emerged from day 10 onward. In the YUMM 3.3 model, RTV at day 12 was significantly lower in immunotherapy-treated mice than in controls (3.45 vs. 4.84; $p = 0.002$). Similarly, in the MC38 model, treatment markedly reduced RTV compared with controls (5.68 vs. 10.39; $p < 0.0001$). These findings indicate a delayed but progressive therapeutic effect of local immune checkpoint blockade. In the MC38 model, comparison of administration routes showed no significant differences on days 0, 3, and 6. Differences emerged from day 10 and became more pronounced by day 12, mainly driven by a stronger response in the IP immunotherapy group compared with the other groups ($p < 0.0001$). Biodistribution studies demonstrated prolonged intratumoral retention of indocyanine green following IT administration, persisting beyond 48 h in a pilot imaging study ($n = 2$), supporting sustained local delivery by the MN device.
These preliminary data demonstrate the feasibility of MN-mediated local delivery and confirm the antitumor activity of IT immunotherapy. However, dose and/or formulation optimization may be required to achieve the efficacy observed with IP administration. Future studies will investigate IT dose escalation, characterize the TIME by flow cytometry and histopathology, and assess biodistribution using labeled antibodies to enable more specific tracking of local retention and systemic dissemination.

Keywords: Microneedles - Melanoma - Intratumoral.

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PS23-P01

Dimethyl fumarate sensitizes solid tumor cells to expanded NK-cell cytotoxicity and enhances antibody-guided targeting

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Objective
Dimethyl fumarate (DMF) is an electrophilic fumarate ester with established clinical use and emerging anticancer potential. We investigated whether subcytotoxic DMF treatment can remodel solid-tumor immunogenicity and increase susceptibility to expanded natural killer (eNK)-cell cytotoxicity, alone or combined with antibody-guided NK-cell targeting.
Methods
HCT116 colorectal and BT-20 triple-negative breast cancer cells were treated with DMF, typically 100 µM for 24 h, before coculture with umbilical cord blood-derived eNK cells. Surface ligands were analyzed by flow cytometry and gene expression by qRT-PCR. Redox dependence was assessed using N-acetylcysteine (NAC), while receptor-blocking experiments evaluated the contribution of NKG2D. Tumor-cell viability/death was measured after eNK coculture. In BT-20 cells, DMF was also combined with eNK cells armed with Fc-modified cetuximab, including in 3D spheroid cultures.
Results
DMF selectively increased MICA/B and ULBP-family NKG2D ligands in HCT116 cells without altering HLA-ABC or ICAM-1 and, at 100 µM, without significant direct tumor-cell toxicity. DMF pretreatment markedly increased susceptibility to eNK-mediated killing. NAC prevented DMF-induced NKG2D-ligand upregulation and strongly attenuated the associated increase in eNK-mediated cytotoxicity, supporting a redox-sensitive mechanism. NKG2D blockade partially reduced DMF-mediated tumor sensitization, indicating an important but non-exclusive role for this pathway. The sensitizing effect was reproduced in BT-20 cells. Moreover, DMF pretreatment complemented Fc-modified cetuximab-guided eNK-cell activity, producing the lowest residual tumor-cell viability in monolayer cultures and spheroid regression in 3D assays.
Conclusion
Subcytotoxic DMF conditioning increases the susceptibility of colorectal and breast cancer cells to eNK-cell cytotoxicity through redox-dependent remodeling of the NKG2D-ligand axis. DMF also reinforces and complements antibody-guided eNK-cell activity, supporting pharmacological tumor sensitization as a complementary strategy to enhance NK-cell-based immunotherapy.

Keywords: Dimethyl fumarate - Natural killer cells - NKG2D ligands.

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PS23-P02

Metal Exposure and Immune Activation in Sarcoidosis: Combining LIBS Elemental Imaging and Functional Immunological Assays

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Background
Sarcoidosis is a systemic granulomatous disease of unknown etiology in which environmental exposures may contribute to disease onset. Laser-Induced Breakdown Spectroscopy (LIBS) is an elemental imaging technology able to detect and localize chemical elements directly in tissue. Within the ANR-funded Medi-LIBS project, LIBS has identified exogenous metals in human tissues and experimental models. We investigated whether metallic exposures may contribute to sarcoidosis and assessed their immunological effects.
Methods
LIBS was performed on mediastinal lymph nodes from patients with sarcoidosis, other granulomatous diseases, and non-granulomatous controls. In selected cases, occupational assessments documented environmental and professional exposures. Functional studies used metals identified by LIBS or suspected from exposure histories. Cryopreserved lymph node cells and peripheral blood mononuclear cells were stimulated with aluminum, zinc, or nickel and analyzed by flow cytometry at days 0, 4, and 7 to assess T-cell activation, proliferation (CFSE), and macrophage polarization.
Results
Fourteen samples were analyzed: sarcoidosis (n=6), other granulomatous diseases (n=4), and controls (n=4). Exogenous metals were detected in all groups, mainly zinc and aluminum. Four samples with the strongest signals underwent functional studies, including two sarcoidosis samples with high zinc concentrations.
Peripheral blood was available from two sarcoidosis patients and one healthy control. Zinc induced CD4+ T-cell activation in both patients, who had occupational zinc exposure, but not in the control. In lymph node cells, one sarcoidosis sample showed marked T-cell proliferation after zinc stimulation, with increased M2 macrophage polarization at day 7. Conversely, one non-sarcoid granulomatous sample showed predominant T-cell proliferation after aluminum stimulation. A progressive M1-to-M2 shift was observed between days 4 and 7.
Conclusions
Metallic exposures may contribute to immune activation in a subset of patients with sarcoidosis. Concordance between LIBS findings, occupational exposure, and metal-specific immune responses supports a potential role for environmental metals as disease triggers. Combining elemental imaging and functional assays may help identify relevant exposures and clarify granulomatous disease pathogenesis.

Keywords: sarcoidosis - metal.

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PS23-P03

IL-2-variant-based immunocytokines improve Diffuse large B-cell lymphoma outcomes in mice by promoting long-term immune surveillance

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Objective
Diffuse large B-cell lymphoma (DLBCL) is an aggressive malignancy characterized by a complex and frequently immunologically exhausted tumor microenvironment (TME)[1]. Multiple strategies are being developed to restore antitumor immunity, including engineered IL-2 variants (IL2v), which signal through IL-2Rβγ and have emerged as promising immunotherapeutic approaches[2]. IL2v has been fused to different targeting moieties, generating immunocytokines such as PD1-IL2v and FAP-IL2v. While PD1-IL2v delivers IL2v signaling in cis directly to PD1-positive T cells, particularly stem-like CD8+ T cells, FAP-IL2v acts in trans, providing localized IL2v signaling to immune cells adjacent to fibroblast activation protein (FAP)-positive fibroblasts[2]. We aimed to characterize how these IL2v-based immunocytokines reshape the TME and to assess their therapeutic benefit in DLBCL.
Methods
An immunocompetent murine DLBCL model[3] was treated with either IL2v-based immunocytokines (PD1-IL2v or FAP-IL2v), alone or in combination with anti-CD20. Long-term survival and short-term mechanistic studies were conducted. NK cell depletion before FAP-IL2v treatment was used to assess the contribution of NK cells to therapeutic efficacy. The TME was characterized by immunohistochemistry, multiparametric flow cytometry, and scRNA-seq.
Results
IL2v administration, either in cis or in trans, increased intratumoral CD8+ T cells and promoted an antitumor memory phenotype associated with durable T-cell responses. Early systemic immune changes also suggested a trend toward an increase in central memory CD8+ T cells. Furthermore, trans-targeted FAP-IL2v induced intratumoral NK-cell expansion and a significant increase in total NK frequency in the blood. NK-cell depletion abrogated the therapeutic benefit of FAP-IL2v, supporting a contribution of NK cells to its efficacy. Importantly, NK-cell depletion did not impair CD8+ T-cell activation, as the central memory population remained intact. Finally, combining IL2v-based immunocytokines with anti-CD20 therapy further enhanced long-term control of lymphoma progression, associated with sustained memory T-cell responses.
Conclusion
IL2v-based immunocytokines promote durable antitumor immune responses in DLBCL by enhancing T-cell memory and, for FAP-IL2v, engaging NK-cell activity. These findings support their combination with anti-CD20 as promising therapeutic strategies.

Keywords: Diffuse large B-cell lymphoma - Immunocytokines - IL-2 variant (IL2v).

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PS23-P04

Combined CAR- and innate receptor-mediated cytotoxicity of GCC-CAR γδ T cells limits antigen escape and curbs advanced colorectal cancer

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Colorectal cancer (CRC) remains largely unresponsive to current αβ T cell-based immunotherapies, partly due to limited neoantigen presentation and antigen escape mechanisms. To tackle these caveats, we engineered a γδ T-cell product expressing a CAR targeting the CRC-associated antigen, Guanylyl Cyclase C (GCC-CAR). Whereas CAR-mediated recognition enhanced tumor cell targeting, engagement of innate receptors highly expressed on γδ T cells, namely NKG2D and DNAM-1, maintained antitumor activity under GCC downregulation. Consequently, GCC-CAR γδ T cells displayed potent cytotoxicity against CRC cell lines and patient-derived organoids. In orthotopic CRC xenografts, a single infusion resulted in robust intratumoral GCC-CAR γδ T-cell accumulation and tumor control, even at advanced stages, without detectable toxicity. Beyond controlling primary tumor, GCC-CAR γδ T cells also prevented hematogenous tumor spread and metastasis burden. These pre-clinical results establish GCC-CAR γδ T cells as a powerful allogeneic immunotherapy platform for CRC.

Keywords: Colorectal cancer - Gamma delta T cells - Cell therapy.

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PS23-P05

Engineering CAR-T Cells to enhance tumor infiltration and antitumor function in renal Cell Carcinoma

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Objective
While CAR T cells demonstrate clinical efficacy against hematological malignancies, their effectiveness in solid tumors is limited by physical barriers like the dense tumor stroma. Clear cell renal cell carcinoma (ccRCC) and other hypoxic tumors overexpress carbonic anhydrase IX (CAIX), a strategic target due to its restricted physiological expression. This project aims to develop and validate anti-CAIX CAR T cells co-expressing cell migration modulators (CMMs) via a polycistronic lentiviral vector to optimize tumor infiltration.
Methods
Lentiviruses were produced by transient transfection. They were concentrated, titrated, and used to transduce CD4:CD8 T cells in a 2:1 ratio. The T cells were purified from the mononuclear fraction of peripheral blood from healthy donors. The resulting CAR-T cells were assessed for proliferative potential and transduction efficiency. Anti-CAIX CAR-T cells co-expressing CMMs were evaluated for migration and cytotoxicity against ccRCC cells. They were also tested in orthotopic models of immunocompromised mice implanted with human ccRCC cells. We determined the quantity, activation, and exhaustion status of tumor-infiltrated T cells.
Results
The produced CAR-T cells showed satisfactory proliferation and transduction rates. CMMs co-expression was validated both in vitro and in vivo. One specific variant, protected by patent secrecy (CMM A), significantly increased CAR-T cell infiltration into the tumor microenvironment (TME) and boosted antitumor efficacy in orthotopic models, with 60% decrease in bioluminescence and 85% in tumor weight 21 days after treatment. The data suggest attenuation of terminal exhaustion in tumor-infiltrated T cells, with a relevant fraction maintaining a central memory phenotype. This indicates the preservation of a population with greater persistence potential. For variant CMM B, effects are less relevant and do not persist for prolonged periods. Safety profiles were confirmed by appropriate levels of serum markers of hepatic and renal function.
Conclusions
Co-expression of T cell migration modulators has been demonstrated to be a promising strategy to overcome physical and biological challenges posed by solid tumors. This establishes a relevant basis for developing efficient next-generation therapies against aggressive solid tumors. CEP/UNIFESP CAAE: 84533524.0.0000.5505/ CEUA/ UFABC: 4272191124. Supported by FAPESP: 2023/03631-3.

Keywords: Chimeric antigen receptor T cells - T cell migration - Solid tumors.

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PS23-P06

Role of CD47/SIRPαcheckpoint in resistance to immune checkpoint inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC)

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Objective
Immunotherapy with immune checkpoint inhibitor (ICI) has revolutionized management of non-small cell lung cancer (NSCLC). However, many patients develop resistance.CD47, overexpressed in many NSCLC tumors could interact with SIRPα receptor on macrophages to inhibit phagocytosis. The aim of the project is therefore to evaluate the role of the CD47/SIRPα axis in NSCLC, particularly in immune resistance and to explore the predictive value of CD47/SIRPα.

Methods
39 patients with a previously untreated NSCLC were included. CD47 expression was analyzed in lung biopsies from NSCLC patient by immunohistochemistry. SIRPα was quantified on suppressive myeloid cells (MDSC) in whole blood from patients and healthy donors (HD) using flow cytometry (FCM).
Co-culture of PBMC from HD was achieved with NSCLC lines. The lymphocytes and macrophages differentiation/activation were assessed by FCM. To investigate a non-invasive analysis of CD47 expression, an orthotopic NSCLC murine model was established. Murine anti-CD47 antibody was radiolabeled with zirconium-89 (89Zr) and CD47-targeted was assessed by immunoPET.

Results
CD47 overexpression was confirmed in tumors biopsies compared with adjacent healthy lung tissue. Interestingly, high tumor CD47 expression was associated with a trend toward an improved overall survival and progression-free survival. SIRPα was highly expressed in circulating MDSC from patients compared to HD. In vitro experiments showed that loss of CD47 function promotes CD8 T cell proliferation and T cell exhaustion particularly during pembrolizumab treatment. Preliminary data showed that ALX148 (CD47 inhibitor) restores $CD8^+$T-cell proliferation, supporting our CD47-silencing findings.
The immunoPET performed in the CMT-167 orthotopic model revealed specific CD47 in vivo labelling, particularly in the tumor. The antibody dose was determined at 210 µg to obtain an optimum tumor/blood ratio at 168 h hours post injection. Ex vivo, CD47 was predominantly expressed in tumor cells, while SIRPα was enriched in macrophages, particularly of M2 orientation (immunosuppressive phenotype).

Conclusion
This work highlights the CD47/SIRPαaxis as a key player in NSCLC resistance to immunotherapy and supports its potential as a predictive and specific biomarker. CD47-targeted immunoPET emerges as a promising non-invasive tool for patient stratification and monitoring. These results will allow us to optimize therapeutic combinations in immuno-oncology.

Keywords: NSCLC - Immunotherapy - CD47, SIRPα,.

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PS23-P07

The allogeneic plasmacytoid dendritic cell line PDC*line: an off-the-shelf therapeutic cancer vaccine platform

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Background
Therapeutic dendritic cell (DC) vaccines remain limited by the cost, variability and modest potency of autologous DC. We present here PDC*line, an allogeneic human plasmacytoid DC line displaying potent antigen-presentation capacities, as an off-the-shelf platform for cancer vaccine immunotherapy.
Methods
Evidence was compiled from preclinical studies using peptide loading or retroviral engineering of the cell line and from clinical trials: phase Ib trial in stage IV melanoma (n=9; weekly sc injections of irradiated, peptide-loaded cells loaded with 4 melanoma Ag) and phase I/II trial in lung cancer (six NSCLC Ag) alone or combined with pembrolizumab (n=73). Preclinical efficacy and migration were studied in humanized mice. In clinical trials, Ag-specific CD8+ T-cell responses were assessed by multimer staining; and anti-HLA responses were monitored.
Results
Peptide-loaded PDC*cells efficiently primed and expanded multispecific tumor- and virus-specific cytotoxic CD8+ T cells across HLA-I contexts. Ex-vivo experiments in the context of NSCLC showed that tumor-Ag-specific CD8+ T cells were activated in 69% of cases, and markedly amplified by anti-PD-1. In humanized mice, the vaccine migrated from blood to lymph nodes and primed naive T cells; its irradiation triggered rapid CD62L shedding via a p38 MAPK–ADAM17-dependent pathway, potentially regulating homing to lumph nodes. In the first-in-human clinical trial in melanoma patients, the vaccine was well tolerated, antitumor T-cell priming (naïve-to-memory switch) was documented, and clinical signs of activity were observed (stable disease and vitiligoid lesions). In the NSCLC study, PDC*lung01 induced Ag-specific T-cell expansions in 50–67% of patients and, combined with pembrolizumab, met predefined objectives (ORR 51%; 9-month PFS 47%), PFS correlating with T-cell response intensity. Anti-HLA antibodies, dose-dependent and transient, were unaffected by PD-1 blockade and clinically inconsequential.
Conclusion
The PDC*line platform combines industrial manufacturability, potent priming of antitumor CD8+ T cells and synergy with PD-1 blockade. Beyond its translational value as a useful platform for Ag identification and biomarker discovery, its manageable safety in clinical trials and the absence of clinically relevant humoral alloimmunization support the progression to randomized phase II development in lung cancer and extension to hepatocellular carcinoma and infectious-disease immunotherapy

Keywords: Plasmacytoid dendritic cell vaccine - T cell priming - Cancer vaccine.

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PS23-P08

Retinoic Acid Signaling Biphasically Regulates PIB-mediated cDC1 Reprogramming

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In vivo direct reprogramming of cancer cells toward conventional type 1 dendritic cells (cDC1s) has emerged as an attractive strategy to boost anti-tumor immunity directly within the tumor microenvironment[1]. However, immunosuppressive cues may shape this niche. Retinoic acid (RA) is a well-established driver of immune tolerance in other contexts, promoting tolerogenic DCs and regulatory T cell, yet whether RA restrains cDC1 identity and immunogenicity within a tumor context, or supports cDC1 reprogramming, remains unknown.
A microscopy-based high-content chemical screen combined with flow cytometry validation was performed to identify small molecules potentiating PU.1/IRF8/BATF3 (PIB)-mediated cDC1 reprogramming, using a Clec9a reporter in mouse embryonic fibroblasts (MEFs), based on the restricted expression of CLEC9A in cDC1s. To validate retinoic acid receptor (RAR)-related hits, PIB-eGFP-transduced MEFs and human dermal fibroblasts (HDFs) were treated with the panRAR agonist TTNPB or the panRAR inverse agonist BMS493 for 9 days, followed by flow cytometry assessment of cDC1 reprogramming markers. The YUMM1.7 melanoma model was used for *in vivo* validation. Bulk RNA-seq was performed in HDFs to assess transcriptional maturation during reprogramming.
RAR agonists emerged as top hits from the screen to drive early Clec9a-tdT reporter activation. However, TTNPB failed to drive the acquisition of conventional APC markers (CD45, MHC-II, XCR1). Strikingly, it was the panRAR inverse agonist that governed reprogramming maturation and the acquisition of the aforementioned markers at later timepoints, revealing a biphasic requirement for RA signaling. These findings were extended to HDFs, where BMS493-treated PIB-transduced cells also presented increased expression of CD45 and HLA-DR. Bulk RNA-seq data from the same treatment suggests functional maturation toward an APC-like state, alongside enhanced checkpoint and cell-cycle control at later stages. Furthermore, in YUMM1.7 (melanoma) cells, RAR inverse agonism was associated with delayed tumor growth, *in vivo*. Notably, Clec9a reporter activation combined with APC markers expression in MEFs required 1 day of panRAR agonism followed by 8 days of panRAR inverse agonism.
Together, these findings show that RA signaling must be precisely tuned over time to potentiate cDC1 reprogramming. Early receptor activation drives cDC1-associated identity, while later pathway inhibition promotes maturation toward an APC phenotype.

Keywords: Cell Reprogramming - Conventional DC type-1 - Retinoic Acid.

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PS23-P09

Integration of clinical and T-cell immune profiling to predict early response to CD3xBCMA bispecific antibody immunotherapy in Multiple Myeloma

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Objective
The emergence of bispecific antibodies (BsAbs) targeting T cells (CD3+) and tumor plasma B cells (BCMA+) has provided a new therapeutic option for patients with relapsed/refractory multiple myeloma cancer. However, responses to CD3×BCMA BsAb therapy remain heterogeneous, and treatment is associated with frequent immune-related adverse events. Although baseline immune characteristics have been associated with clinical outcomes (1,2) little is known about the early immune dynamics induced by this therapy. Here, we investigated whether longitudinal clinical monitoring and high-dimensional profiling of blood circulating T cells could identify early biomarkers of response or toxicity during treatment.
Methods
Blood from multiple myeloma patients was collected at baseline and during the first four weeks of therapy. T-cell lineage, differentiation state and plasma cytokines implicated in T-cell activation were measured by mass cytometry and ELISAs. Factorial Analysis of Mixed Data (FAMD) enabled comprehensive integration of 14 clinical variables and 193 immunological features.
Results
Our results indicate that all treated patients exhibit an early depletion of circulating T cells associated with T-cell activation within the first two weeks. Integration of clinical and immunological parameters using Factorial Analysis of Mixed Data (FAMD) identified immune features associated with treatment outcome. Responders had lower plasma soluble BCMA concentrations, fewer bone lesions and higher circulating lymphocyte counts at baseline. During the first days of treatment, responders exhibited a more pronounced increase in plasma CXCL10 levels, associated with a greater decrease in T lymphocyte counts.
Conclusion
Overall, our findings suggest that integrating clinical and immune parameters measured during the first days of treatment may enable early patient stratification and support the development of a predictive score to identify patients with multiple myeloma who are most likely to benefit from CD3×BCMA BsAb therapy. Preprint can be found at https://doi.org/10.64898/2026.08.17.743749 (3)

Keywords: Immunotherapy - Bispecific antibodies - Cancer.

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PS23-P10

From Reinvigoration to Exhaustion: Tumor-Infiltrating Lymphocyte Responses to PD-1 Blockade in Melanoma

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Objective
Immune checkpoint inhibitors have substantially improved survival in melanoma, yet resistance limits durable benefit in a subset of patients. We investigated remodeling tumor-infiltrating lymphocytes (TILs) following PD-1 blockade, focusing on the balance between T-cell reinvigoration and exhaustion and its potential role in therapeutic resistance.
Methods
Bulk RNA sequencing was performed on tumor samples from 35 patients before and after 3 weeks of immunotherapy. T-cell exhaustion signatures were assessed. TCF1 expression was evaluated by immunohistochemistry before and after 3 weeks of immunotherapy in five responders and five non-responders' patients, also multiplex immunofluorescence assessed CD8, TCF1 and TOX in tumors before and after 6 to 89 weeks of immunotherapy from six non-responders. Expanded TILs from seven patients were exposed ex vivo to a PD-1 inhibitor and analyzed by spectral cytometry. CRISPR/Cas12a-mediated editing of the TOX 5'UTR was performed in TILs from three patients to evaluate the relationship between TOX and TCF1 translation. The YUMM3.3 syngeneic melanoma model was used to assess tumor growth and immune profiling following PD-1 blockade using spectral cytometry.
Results
Post-treatment tumors showed increased expression of exhaustion-associated genes, including PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, CD244, BTLA, TOX and KLRG1, with a significantly higher exhaustion signature score after treatment. TCF1 protein levels were reduced in non-responders. Immunofluorescence confirmed a decrease in progenitor-exhausted and an increase in terminally differentiated exhausted T cells after therapy in non-responders' patients. *E*x vivo PD-1 inhibition increased TOX and LAG-3 levels in tumor reactive TILs. Targeted TOX 5'UTR editing reduced TOX translation and was associated with increased TCF1 translation, indicating an inverse relationship between these factors. In YUMM3.3 tumors, PD-1 blockade increased TOX in intermediate and terminally exhausted T cells, particularly in non-responding mice, together with increased TIM-3, Nur77 and NFATc1 protein levels.
Conclusion
PD-1 blockade may transiently reinvigorate TILs but is also associated with progressive T-cell exhaustion, marked by increased TOX expression and related molecular signatures. Persistent TIL dysfunction may represent a key mechanism of resistance to PD-1 therapy. Targeting pathways driving this exhaustion phenotype may offer new strategies to immunotherapy in melanoma.

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From Target to Therapy – A Validated Workflow for Selecting the Right TCR

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TCR-based therapies require identification of TCRs with high specificity for target MHC:peptide complexes (MHCp). However, T cells bearing relevant TCRs are often rare, complicating identification. We present a workflow for proliferating and identifying rare MART-1-specific T cells from healthy donor material with undetectable baseline levels of relevant T cells.

Artificial antigen-presenting cell scaffolds (Xynapse™-T) were engineered by conjugating HLA-A*02:01/MART-1 complexes (A2/MART-1) and CD28 co-engagers to a synthetic scaffold. T cell populations were enriched via stimulation with A2/MART-1 Xynapse-T reagents, and MART-1-specific T cell (MART-1 T) expansion was monitored by staining with fluorescently labelled A2/MART-1 Dextramer® reagents and FACS analysis. From enriched cultures, MART-1 TCR clonotypes were identified using DNA-barcoded A2/MART-1 dCODE Dextramer reagents on a 10x single-cell multiomics platform. Corresponding TCR molecules were refolded from material produced recombinantly in *E. coli*, and resulting TCR Dextramer reagents were evaluated for specific binding to A2/MART-1-coated microbeads.

A2/MART-1 Xynapse™-T reagents, by simultaneously engaging TCR and CD28 on T cells, enabled selective expansion of A2/MART-1-specific T cells within polyspecific populations, as measured by flow cytometry with A2/MART-1 Dextramer detection. Across five donor samples with undetectable baseline MART-1 T cells, three of five showed detectable MART-1 T cells (0.3–2.7% of CD8+ T cells) after 14 days of culture. A further stimulation round and 19 days of culture increased MART-1 T cell frequency to 86.2%. Single-cell multiomic analysis of expanded T cells identified individual MART-1 TCR clonotypes. Selected TCRs were produced, and their specificity for A2/MART-1 confirmed via specific staining of A2/MART-1 microbeads with corresponding TCR Dextramer reagents.

We demonstrate proliferation of rare, antigen-specific T cells from healthy donor PBMC samples using antigen-specific stimulation reagents (Xynapse™-T). Expanded TCR clonotypes were identified via single-cell multiomics, and TCR specificity was validated through binding to the stimulating target MHCp.

Keywords: TCR - T cells.

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PS23-P12

Patient-Derived Lymphoma Spheroids (PDLS) Reveal Predictive Markers of Glofitamab Resistance in Relapsed/Refractory B-cell non-Hodgkin lymphomas (R/R B-NHL)

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Background
CD20×CD3 bispecific antibodies (bsAbs) such as glofitamab show substantial efficacy in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL), yet primary and acquired resistance remain frequent. To decipher mechanisms underlying heterogeneous responses, we used patient-derived lymphoma spheroids (PDLS)[1,2], a 3D *ex vivo* model recapitulating the tumor immune microenvironment, to identify predictive biomarkers of glofitamab response and actionable resistance mechanisms[3].

Methods
PDLS from 39 R/R B-NHL patients were generated from PBMC or lymph node biopsies. *Ex vivo* glofitamab sensitivity was integrated with high-dimensional immune profiling: flow cytometry, single-cell RNA sequencing and CODEX multiplex immunofluorescence imaging. Spatial transcriptomics (Xenium) were analyzed on a public 10x Genomics dataset. Functional validation comprised TIGIT blockade and $CD4^+$ T follicular helper (Tfh) cell depletion in 3D cultures.

Results
PDLS responses segregated patients into two groups and recapitulated clinical outcomes in 8/9 evaluable cases. *Ex vivo* high responders displayed significantly higher baseline $CD8^+$ T-cell frequencies, correlating with glofitamab-induced B-cell depletion, and enrichment of activated cytotoxic $CD8^+$ T cells with elevated activation signatures. Conversely, *ex vivo* low responders exhibited increased exhausted $CD8^+$ T cells, and TIGIT blockade in PDLS selectively restored glofitamab-induced depletion. *Ex vivo* low responders were enriched in functionally active Tfh cells, with higher Tfh signature scores, increased $IL21^+$ Tfh activity and stronger inferred signaling toward tumor B cells. CODEX confirmed B/Tfh niches with reduced B-cell-Tfh distances while Xenium showed that FL-like B cells drive upregulation of key Tfh-lineage transcription factor in proximal Tfh cells. Tfh depletion in *ex vivo* 3D models significantly improved glofitamab-mediated B-cell killing, and independent clinical transcriptomic data (BICAR) revealed higher Tfh abundance in patients progressing under glofitamab.

Conclusion
We identify two predictive biomarkers of glofitamab resistance in R/R B-NHL: exhausted $CD8^+$ T cells and functionally active Tfh cells sustaining tumor-supportive niches. These findings provide a rationale for combining bsAbs with immune checkpoint blockade or disruption of Tfh-B-cell crosstalk and support PDLS as a promising preclinical platform to further investigate immune escape mechanisms and candidate predictive biomarkers.

Keywords: B-NHL - Bispecific antibodies - Resistance mechanisms.

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PS23-P13

SpyTag/Catcher based Universal Platform for Evaluating the Responsiveness of CAR-NK cells

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Objective

Although the use of Natural Killer (NK) cells as vectors for CAR constructs has gained increasing attention, major challenges remain. These include tumour heterogeneity, antigen downregulation, poor infiltration and impaired CAR-NK functionality within the immunosuppressive tumor microenvironment[1]. In addition, chronic stimulation can drive NK cell "exhaustion"[2], thereby limiting therapeutic efficacy. To improve CAR-NK-based therapies, it is critical to understand antigen-CAR interactions, optimize CAR designs and prevent NK dysfunction driven by chronic stimulation. Currently available analytical platforms fail to comprehensively assess CAR-NK responsiveness. To tackle those limitations, we propose to generate a universal *in vitro*platform to rapidly and thoroughly evaluate CAR-NK responses and test genetic modifications improving their functions.

Method

By using the SpyTag/Catcher protein ligation technology[3], we have generated versatile tumour target cell lines (SpyTarget) that can be post-translationally decorated with antigens and used to test monoclonal antibodies and CAR-cells for immunotherapy. We engineered two cell-lines expressing SpyCatcher on the cell membrane. As a proof-of-concept, we chose HER2, an antigen overexpressed in various solid tumors, as a target antigen and produced SpyTag-HER2 to be displayed on SpyTarget cells. This platform allows precise control over antigen selection and density.

Results

We showed that our SpyTarget cells can display different levels of HER2 antigen. Antibody-dependent cell cytotoxicity (ADCC) assay was conducted using a reporter cell line. Effector cell activation increased significantly with increasing amounts of SpyTag-HER2 in the presence of trastuzumab (anti-HER2 antibody). Moreover, our data revealed that SpyTarget cells can trigger NK cell ADCC functions in a SpyTag-HER2 dose dependent manner and be specifically killed by anti-HER2 CAR-T cells.

Conclusion

We will now adapt this platform to chronically stimulate anti-HER2 CAR NK cells and induce CAR-NK cell "exhaustion". We will derive CAR-NK from human induced pluripotent stem cells equipped with a genetic cassette enabling flexible insertion and removal of transgenes, to test different candidates for their ability to prevent NK cell "exhaustion". Here, we aim to develop a robust *in vitro* model that can be used to accelerate the development of CAR-NK based-therapies with enhanced efficacy.

Keywords: NK cell - CAR - Immunotherapies.

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PS23-P14

Circulating effector regulatory T cells define a systemic immunosuppressive state associated with resistance to immune checkpoint blockade

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Background
Predictive biomarkers that capture the systemic immune state of patients remain a major unmet need in cancer immunotherapy. Effector regulatory T cells (EffTregs), defined as CD45RA$^-$CD25high cells within the CD4$^+$CD127$^-$CD25$^+$ Treg compartment, represent a circulating highly activated and suppressive subset. We investigated whether circulating EffTregs reflect systemic immunosuppression and are associated with clinical benefit from immune checkpoint inhibitors (ICI).
Methods
Peripheral blood mononuclear cells collected before and during treatment were analyzed by multiparameter flow cytometry in 312 patients from four prospective cohorts: metastatic non-small-cell lung cancer treated with anti–PD-1 therapy (ALCINA9, n=45), poorly differentiated lung/digestive neuroendocrine carcinoma treated with anti-PD-1 ± anti-CTLA-4 (NIPINEC, n=127), early triple-negative breast cancer treated with neoadjuvant chemo-immunotherapy (ALCINA4-3, n=52) or chemotherapy-only cohort (SCANDARE, n=88). Circulating T-cell subpopulations-including EffTreg-phenotype, abundance, and associations with clinical outcomes were evaluated.
Results
Phenotypic analyses demonstrated that EffTregs constitute the activated suppressive Treg compartment, characterized by elevated expression of CTLA-4, ICOS, CD39, HLA-DR, and Ki67. Baseline circulating EffTreg frequencies were significantly lower in responders than in non-responders in both ICI-treated cohorts and were associated with improved progression-free and overall survival. Neither total Treg frequencies nor PD-1 expression within EffTregs were associated with outcome. EffTregs outperformed PD-L1 status and all other covariates analyzed in predicting clinical benefit. Longitudinal analyses revealed a selective increase in EffTregs during treatment among responding patients, suggesting dynamic remodeling of the regulatory compartment following ICI-based treatment. The predictive association was maintained, although attenuated, in patients receiving chemo-immunotherapy but was absent for chemotherapy alone, supporting a specific association with immune-mediated therapeutic activity.
Conclusions
Circulating EffTregs identify a systemic immunosuppressive state associated with reduced clinical benefit from immune checkpoint blockade across distinct cancer types. Their biological specificity and accessibility in peripheral blood support their development as biomarkers for patient stratification and immunmonitoring during cancer immunotherapy.

Keywords: Biomarker - Effector Tregs - ICI.

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PS23-P15

Multimodal Analysis of Immunotherapy Responses in Patient-Derived Tumor Slices

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Objectives
Immunotherapy (IT) has revolutionized cancer treatment, particularly in melanoma and other solid tumors. However, only a minority of patients derive durable clinical benefit, underscoring the need for predictive models that faithfully recapitulate the tumor microenvironment (TME) and enable rapid evaluation of novel therapeutic strategies. To address this challenge, the TIFEX (Tumor Immune Function Ex Vivo) platform, developed within the Lyon Immunotherapy for Cancer Laboratory (LICL), provides an innovative framework to assess immune responses induced by emerging ITs and their combinations directly in patient-derived tumor tissues.
Methodology
We developed an ex vivo platform based on precision-cut tumor slices (PCTS, 250 µm) that preserves the spatial organization and cellular complexity of the native TME. Tumor slices are exposed to ITs targeting adaptive and/or innate immune pathways, either alone or in combination. To date, the platform has been successfully implemented using oral squamous cell carcinoma (OSCC) and skin tumor specimens.
Results
PCTS remained viable and compatible with downstream immune analyses after 48 hours of culture, yielding on average >147,000 viable cells per slice from OSCC samples and >186,000 cells per slice from skin tumors. Spectral flow cytometry identified a broad spectrum of immune populations, including T cells, B cells, NK cells, macrophages, conventional dendritic cells (DC), and plasmacytoid DC. Functional analyses detected key cytokines of innate and adaptive immunity. Multiplex immunofluorescence coupled with digital image analysis enabled quantitative spatial characterization of immune infiltrates, revealing immune cell density, distribution patterns, and cell-cell interactions within the TME. In parallel, scRNA-seq generated high-dimensional datasets allowing transcriptional profiling of both tumor and immune cells at single-cell resolution. Collectively, these data demonstrate the feasibility of integrating spatial, phenotypic, functional, and transcriptomic readouts from the same patient-derived tumor specimen, providing a comprehensive assessment of antitumor immune responses ex vivo.
Conclusion
TIFEX is an innovative ex vivo immunomonitoring platform that captures the complexity of antitumor immune responses directly in patient tissues. By integrating spatial, phenotypic and transcriptional analyses, it provides a robust framework for IT testing, biomarker discovery and precision medicine.

Keywords: Immunotherapy - Tumor slices - ex vivo testings.

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PS23-P16

Early Immunotherapy-driven peripheral immune modulation in melanoma: preliminary findings from multiparametric flow cytometry analysis

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Immunotherapy have reshaped the treatment of malignant melanoma, but substantial inter-individual variability in clinical response persists. As immune checkpoint blockade (ICB) exerts systemic effects beyond the tumor environment, peripheral blood (PB) immunophenotyping provides a minimally invasive approach to characterize therapy-associated immune remodeling and potentially identify early indicators of treatment response. We therefore aimed to characterize early changes in the peripheral immune landscape of melanoma patients receiving adjuvant Pembrolizumab.

PB samples from 20 early-stage melanoma patients were collected before treatment and after 21 days of Pembrolizumab. A multiparametric flow cytometry-based "peripheral immunogram" comprising more than 50 lymphoid and myeloid immune subpopulations was used to assess T-cell differentiation, CD57 and PD-1 expression, regulatory T cells (Tregs), IFN-γ production, dendritic cell (DC) subsets, monocytes, B cells, NK cells, and additional myeloid populations. Data were analysed using FlowJo® and GraphPad Prism®. This preliminary analysis focuses on the immune populations evaluated to date, while characterization of the remaining subsets is ongoing. Parallel analysis of the same immune populations in 20 healthy donors is also being performed.

Preliminary analysis revealed early Pembrolizumab-induced changes across lymphoid and myeloid compartments. The CD4/CD8 ratio decreased significantly ($p<0.05$), as did naïve CD8+ T cells ($p=0.02$), while CD57+ CD8+ T cells showed a trend toward expansion. IFN-γ production increased in both CD4+ and CD8+ T cells, consistent with enhanced effector function. Circulating Tregs also markedly increased ($p<0.001$). An increase of DCs was observed ($p=0.03$), driven by conventional DC expansion ($p<0.001$). It was also observed that there was an overall increase in the total monocyte population ($p=0.03$), associated with a reduction in the classical monocytes (p=0.01), and a concomitant expansion of non-classical monocytes ($p=0.009$).

Adjuvant Pembrolizumab induces measurable peripheral immune remodeling as early as 21 days after ICB initiation. These preliminary findings support peripheral immunophenotyping as a minimally invasive strategy to monitor early immune modulation. Ongoing completion of the full immunogram, together with comparisons with healthy donors and clinical outcomes, will further define the biological and predictive relevance of ICB-driven immune signatures in melanoma.

Keywords: Cancer Immunotherapy - Liquid biopsy - Biomarkers.

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PS23-P17

Contribution of the dark genome to immunotherapy response in melanoma

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Objective
Immune checkpoint blockade (ICB) has markedly improved survival in advanced melanoma, yet half of patients do not show durable benefit[1]. It remains challenging, prior to treatment, to identify patients who will respond or those in whom high toxicity could be avoided. RNA-sequencing markers are promising for potential use in routine practice. However, standard approaches rely on the quantification of protein-coding transcripts that only represent a small fraction of the true diversity of RNA sequences. Current predictive markers of response to ICB capture overlapping mechanisms of effective antitumor immunity, while no consensual marker reliably identifies non-responders. Our objective is to explore markers derived from the whole transcriptome, in particular sequences originating from poorly annotated and little-studied regions, referred to as the dark genome.
Methods
Fresh-frozen tumors from 163 patients with advanced melanoma, collected before PD-1 blockade alone or in combination with CTLA-4, were sequenced using high-depth total RNA-seq. Response status was assessed according to best overall response (RECIST 1.1). Analysis was based on the quantification of short RNA sequences recurrent across samples, independently of their genomic origin. These sequences were assembled, annotated, and statistically analyzed for association with response status.
Results
We identified markers associated with response status that are inaccessible using standard Methods
(1) enrichment of centromeric tandem repeats in non-responders, (2) enrichment of transposable elements in responders, and (3) enrichment of aberrantly expressed intergenic regions, distinct between responders and non-responders. These signatures were validated in an independent cohort, and their integration with conventional gene expression markers improved predictive performance.
Conclusion
Predictive markers of response to ICB are a critical clinical need. High-depth total RNA sequencing from pretreatment tumors enables the identification of diverse markers, with the aim of their translation into signatures that can be measured in routine practice. Our results suggest the existence of markers derived from genomic regions that are normally transcriptionally silenced. These may reflect epigenetic dysregulation owing to cell plasticity or providing a source of neoantigens. Further validation is needed, in particular through integration with chromatin accessibility and antigen repertoire data.

Keywords: Immunotherapy - Melanoma - Predictive Biomarkers.

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PS23-P18

Evaluation *in vivo* of the antitumoral effect of several cytokines and immunocytokines expressed in the tumor microenvironment using recombinant AAV vectors

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In the last decade, immunotherapies have considerably improved cancer treatment. However, immunologically cold tumors are resistant to such therapies and remain a major challenge. In cold tumors, characterized by low immune infiltration and local immunosuppression, one promising strategy is to promote the recruitment and activation of antitumor immune effector cells.
In this study, the first objective was to evaluate the antitumor efficacy of selected cytokine-based immunotherapies expressed *in vivo* using recombinant adeno-associated-vectors (rAAV). Administered intratumorally in murine models, these vectors efficiently transduce tumor cells and ensure local and transient cytokine production, thereby stimulating antitumor immune responses. Among the several candidate molecules tested, IFN-a4 and IL-12sc significantly induced tumor rejection, abscopal effects, and improved long-term survival, with limited, if any, systemic side effects. Their combination resulted in an even greater therapeutic benefit. To further limit the potential systemic toxicity associated with the pleiotropic nature of cytokines, we developed immunocytokines (ICK) by fusing them to nanobodies targeting surface proteins expressed in the tumor microenvironment, thereby promoting their local retention rather than their systemic dissemination. Our results confirmed their therapeutic efficacy and their safety profile, both as monotherapy and in combination.
Overall, these findings demonstrate that localized rather than systemic administration of selected cytokines represents an effective strategy to promote antitumor immune responses. Moreover, our results highlight the efficacy and safety profile of immunocytokines, a strategy used here to restrict the potent activity of cytokines to the local tumor microenvironment. Such treatment, used alone or in combination with other clinically approved immunotherapies, is expected to enhance tumor control and rejection, thereby expanding the number of patients who may benefit from these therapeutic strategies.

Keywords: rAAV - Immunocytokines - Tumor Microenvironment.

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PS24-P01

Glycoengineering branched *N*-glycans limits T cell exhaustion and enhances CAR-T cell cytotoxicity against solid tumors

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Introduction & Objective

T cell therapies have revolutionized cancer treatment. However, it shows limited efficacy in solid cancer patients, highlighting the need to identify mechanisms of cancer immunoediting within the tumor microenvironment (TME). A key cause of immunotherapy resistance in solid tumors is the complexity of TME that creates immunosuppressive signals that suppress tumor-fighting T cells. While surface glycans have been shown to regulate T cell development and function in homeostasis and inflammation (1,2), their role in T cell-mediated anti-tumor immunity remains largely unexplored. Thus, this study aims to investigate whether and how the T cell glycome influences T cell-mediated tumor immunity in TME.

Methods

In this study, we analyzed intratumor T cells from premalignant lesions of different colorectal cancer (CRC) subtypes. CRISPR/Cas9-mediated deletion of *Mgat5*-mediated branched *N*-glycosylation was performed in mouse therapeutic CD8$^+$ T cells and human anti-CD19-CAR-T cells. Functional activity was evaluated in culture-based assays and in vivo tumor studies.

Results

In this study, we demonstrated that intratumor T cells exhibit altered branched *N*-glycan expression in premalignant lesions of different CRC subtypes, imposing suppressive T cell functions. CD8$^+$ T cells expressing branched *N*-glycans exhibit an exhausted phenotype with increased PD1 and Tim3 expression, suggesting that the expression of branched *N*-glycans defines T cell properties in the TME associated with effector-memory versus exhausted programs. CRISPR/Cas9-mediated deletion of this suppressive branched *N*-glycosylation layer on therapeutic CD8$^+$ T cells limits exhaustion, imprinting an activated phenotype. *Mgat5* deletion enhances cytotoxicity and tumor killing, suppressing tumor growth and improving overall survival in mice. Translating this approach to CAR-T therapy, we showed that *MGAT5* KO in human anti-CD19-CAR-T cells exhibited increased cytotoxicity associated with reduced tumor growth of CD19-transduced solid tumors.

Conclusion

Together, these results identify T cell branched *N*-glycans as a checkpoint that regulates T cell cytotoxicity in cancer, proposing the modulation of the T cell glycocalyx as a strategy to enhance T cell function and immunotherapy efficacy, including CAR-T cells, in solid tumors.

Keywords: T-cell immune response - N-glycosylation - CAR-T cell therapy.

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PS24-P02

Glycoengineering Tumor Neoantigens: a novel strategy to enhance CD8⁺ T cell anti-tumor immune response in Colorectal Cancer

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Introduction and objectives

Colorectal Cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide. This global burden, together with the rising incidence of early-onset cases and the limited efficacy of immunotherapy, underscores the need for more effective immunotherapies (1). Anti-tumor immune response relies in the recognition of tumor neoantigens, presented by Human Leucocyte Antigen (HLA), by CD8⁺ T cells triggering their activation/cytotoxic activity. However, in CRC, this process is often inefficient, contributing to immune evasion and tumor progression. Glycosylation, consisting in the post-translational addition of glycans to proteins, has been proven to have a key role in tumor biology, as CRC cells display an overexpression of complex *N*-glycans, associated with invasion, metastasis and immune evasion, fostering cancer progression (2,3). Nevertheless, how the glycoprofile of CRC HLA-I neoantigen modulates CD8⁺ T cell activity remains unclear, leading us to hypothesize that glycoengineering of neoantigens may be used as a new therapeutic strategy to enhance CD8⁺ T cell anti-tumor cytotoxic activity.

Methods

Firstly, in order to correlate CD8⁺ T cell infiltration with tumor cell glycome, we analyzed formalin-fixed paraffin-embedded tissue, through PCR, and fresh biopsies of HLA-I CRC human samples, by flow cytometry. Furthermore, to validate these findings, we analyzed bulk and scRNA sequencing data. Lastly, to assess how tumor cell glycome influences susceptibility to CD8⁺ T cell-mediated cytotoxicity, we performed the glycoengineering of a murine colon adenocarcinoma neoantigens toward a less complex *N*-glycome, in a co-culture setup with CD8⁺ T cells.

Results

Preliminary results show that an increased *CD8* expression and cytotoxic activity is associated with an elevated expression of glycogenes linked to the synthesis of less complex *N*-glycans in CRC samples, whereas a decreased cytotoxic activity correlates with an increased expression of complex *N*-glycans-related glycogenes in CRC samples. Finally, we showed that tumor cells expressing a differential/simpler glyco-neopeptidome were more susceptible to T-cell mediated cytotoxicity.

Conclusion

Altogether, these results led us to propose these specific glyco-neopeptidome as strategy to enhance T cell recognition and anti-tumor immune response, paving the way for a new therapeutic avenue in CRC.

Keywords: Glycosylation - Neoantigens - Colorectal cancer.

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PS24-P03

A sialylation–SIGLEC axis defines immune suppression and tumor cell quiescence in metastatic niches

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Metastasis depends on the dynamic interactions between cancer cells and the immune microenvironment. Glycosylation can regulate these interactions through tumor-associated glycans and immune glycan-binding proteins, but its contribution to metastatic progression and latency remains poorly understood. We hypothesised that coordinated changes in tumor glycosylation and immune glycan-sensing programs could contribute to the establishment of metastatic niches.

To tackle this, we integrated publicly available single-cell RNA-sequencing datasets from breast, colorectal and pancreatic cancer metastases, including matched primary tumors. Glycosylation-related gene expression was assessed in cancer cells, while glycan-binding protein expression was evaluated across immune populations. Differential expression, enrichment and gene-signature analyses were used to identify conserved changes associated with metastatic progression and to define their relationship with cancer cell and immune functional states. Our observations were then further investigated in an experimental model of liver metastatic dormancy.

Across independent datasets, metastatic progression was associated with coordinated remodelling of glycosylation-related programs in cancer and immune cells. Cancer cells from metastatic lesions displayed selective changes in glycosyltransferase expression compared with primary tumors, such as *ST3GAL1* and *ST6GAL1*. In parallel, immune glycan-sensing programs, namely SIGLEC-encoding gene expression, were preferentially detected within specific immune compartments and were associated with the emergence of distinct transcriptional states in the metastatic microenvironment.

Furthermore, these immune populations displayed functional features compatible with altered immune surveillance. Glycosylation-related changes in metastatic cancer cells were also associated with non-proliferative cellular states. Experimental observations in a mouse model displaying features of cancer dormancy in the liver validated this association between altered tumor glycosylation, immune glycan recognition and metastatic dormancy.

Together, these findings reveal coordinated glyco-immune remodelling during metastatic progression and support a role for glycosylation in shaping cancer cell states and immune functionality within metastatic niches. This work provides a framework for future mechanistic studies investigating glycan-dependent tumor–immune interactions in metastatic disease.

Keywords: Metastasis - Glycosylation - Dormancy.

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PS24-P04

Dissecting the functional implications of ACPA V-domain glycans in autoreactive B cell selection in autoimmunity and in the pathogenesis of Rheumatoid arthritis

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Introduction and Objective

Rheumatoid arthritis (RA) is an autoimmune disease characterized by high titers of anti-citrullinated protein autoantibodies (ACPA), which are present before disease onset. Therefore, it is important to understand how self-reactive ACPA-expressing B cells escape central and peripheral mechanisms, leading to compromised immune tolerance and pathogenic B cell selection. Above 90% of circulating ACPA IgGs carry sialylated complex *N*-glycans in their variable domain (VDG) that increases the risk of RA in ACPA-positive healthy individuals[1]. Given this, we want to investigate whether VDG on B cell receptor (BCR) imposes a selective advantage to ACPA-B cells[2], allowing them to overcome important gatekeepers in germinal centres (GC). Since glycan-mediated immune regulation depends on glycan-binding proteins (GBPs), we aim to understand how VDG interacts with GBPs in the GC, and how this interaction modulates autoreactive B cell selection.

Methods

We analysed a publicly available dataset on human RA-derived PBMCs, focusing on glycogenes and GBPs expression profiles. This was further validated by flow cytometry comparing healthy controls, ACPA-negative and ACPA-positive RA patients. Mechanistically, we used glycoengineered mouse models with B cell-specific glycosylation deficiency in two different approaches: B cell surface[3] and VDG-restricted (developed by us). We have analysed B cell subsets regarding their frequency, glycosylation profile, GBPs expression and binding motifs, focusing on the GC compartment.

Results

Both scRNA-seq and FACS analysis on human RA-derived PBMCs show a glycosylation profile alteration in B cells that aligns with the increased expression of a specific GBP targeting these alterations. Then, by taking advantage of the two mouse models, we demonstrated the impact of B-cell surface glycosylation profile and VDG on B cell function, GC formation, selection (spleen), and autoantibody production. We also characterized the GBPs expression profiles in B cells, as well as their affinity for GBPs. Our data pinpoints for a specific GBP, whose expression/affinity is altered both in RA patients and in our mouse models, possibly indicating its role in mediating the altered B cell responses we observed.

Conclusion

Our data highlight the importance of glycan-mediated fine-tuning on B cell differentiation, ultimately contributing to the mechanisms driving pathogenic B cell selection and the loss of self-tolerance.

Keywords: Rheumatoid arthritis - Glycosylation - Pathogenic B cell selection.

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PS24-P05

Antigen-specific antibody glycosylation signatures are associated with increased risk to Crohn's disease

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Crohn's disease (CD), a prevalent form of inflammatory bowel disease, is a chronic inflammatory disorder primarily affecting the gastrointestinal tract. Emerging evidence highlights protein glycosylation, a key post-translational modification—particularly immunoglobulin G (IgG) Fc glycosylation—as a critical factor in disease development. Alterations in IgG glycosylation have been observed years before clinical onset. Anti-*Saccharomyces cerevisiae*antibodies (ASCA), hallmark anti-glycan antibodies in CD, have been associated with less complex, agalactosylated serum IgG N-glycans during preclinical stages. Building on these findings, we aim to identify disease-specific ASCA glycosylation profiles using a robust, well-established MS-based methodology and investigate their potential roles in immune modulation.

We employ a mass spectrometry–based workflow (GlYcoLISA) for site-specific Fc glycosylation analysis of serum ASCA. This approach uses antigen-specific immunocapture via enzyme-linked immunosorbent assay (ELISA), followed by enzymatic digestion of these target antibodies. Nano-liquid chromatography–electrospray ionization–mass spectrometry (nanoLC–ESI–MS) is then used for subclass-resolved and site-specific Fc glycosylation profiling. Data processing uses automated glycopeptide quantification platform LaCyTools, for spectral calibration and signal integration, followed by GlycoDash curation to ensure stringent quality control through isotopic pattern matching, mass accuracy filtering, signal-to-noise thresholds, and calculation of derived glycosylation traits. Using this established workflow, a large cohort of high-risk individuals was analyzed, enabling comprehensive and reproducible glycosylation profiling and revealing key differences in ASCA glycosylation.

ASCA levels were significantly elevated in individuals who later developed CD, with IgM, IgG1, and the dominant IgG2 subclasses. Site-specific Fc glycan analysis revealed N-glycan alterations associated with increased risk for CD. Distinct glycosylation patterns were detectable several years prior to diagnosis and remained stable over time, with additional changes emerging closer to disease onset.

This study demonstrates that antigen-specific antibody glycosylation captures early immune alterations preceding Crohn's disease onset, underscoring its potential as a predictive biomarker and providing new insights into disease pathogenesis.

Keywords: Antibody glycosylation - Immunoglobulin - Liquid chromatography-Mass spectrometry.

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PS25-P01

The Neonatal Fc Receptor is present in extracellular vesicles isolated from perfusion samples of renal transplants

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Background
The neonatal Fc receptor (FcRn) plays a central role in the recycling and biodistribution of immunoglobulin G (IgG), as well as in immune responses. FcRn expression is ubiquitous and is predominantly localized within endosomes. However its expression varies under pathophysiological conditions (1) such as those observed in cancer, autoimmune diseases, and kidney transplantation (2). We have previously demonstrated that FcRn expression is regulated by autophagy during macrophage differentiation (3). Autophagy is also known to regulate the biogenesis and release of extracellular vesicles (EVs), thereby influencing their trafficking. In the context of kidney transplantation, autophagy and EV secretion contribute to ischemia-reperfusion injury, suggesting a link between FcRn expression and the ischemia-reperfusion process. Renal grafts release substantial quantities of EVs into the extracellular space. These vesicles have immunomodulatory properties, which are particularly evident in perfusion fluid samples from kidneys preserved using hypothemic perfusion machine prior to transplantation.
Objectives
Characterize EVs and FcRn expression released in kidney perfusion fluid samples.
Methods
We isolated EVs from perfusion fluid samples by differential ultracentrifugation followed or not by size-exclusion chromatography. We analyzed FcRn expression in EVs using nanoparticle tracking analysis, transmission electron microscopy, Western blot, flow cytometry and proteomics.
Results
Using these different methods, we demonstrated the presence of FcRn on the surface of EVs in the graft perfusion fluids. FcRn was detected on the surface of EVs, in association with IgG within the EV corona. Additionnaly, we revealed that these EVs originated from various renal cell types, including hematopoietic cells, endothelial cells and podocytes.
Conclusions
The identification of FcRn in EVs provides new insight into the role of this receptor in renal pathophysiology. EV-associated FcRn may contribute to the maintenance of renal homeostasis and modulate graft tolerance or rejection. Further investigations are warranted to elucidate the functional role of FcRn within EVs in the setting of renal transplantation and, more broadly, in renal pathologies, particularly with respect to the handling of IgG immune complexes.

Keywords: FcRn - EV - Renal transplantation.

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PS25-P02

Induction of stable human Treg cells from effector CD4+ T cells in vitro

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Regulatory T cells (Tregs), characterized by high expression of FOXP3, are essential for the control of immune responses, particularly in autoimmunity and transplantation. The majority of Tregs are thymus-derived (tTregs) and display the $CD4^+$ CD25high CD127low FOXP3+++ phenotype. Another subset, peripherally induced Tregs (pTregs, also referred to as iTregs), originates from naïve $CD4^+$ T cells and contributes to the regulation of immune responses against exogenous antigens, including those derived from the microbiota.
Despite their therapeutic potential, Treg-based cellular therapies remain limited by the low frequency of tTregs and the requirement for prolonged ex vivo expansion, which may compromise their functional stability. The abundance of naïve $CD4^+$ T cells represents a potential alternative for iTreg generation. This induction primarily relies on the presence of TGF-β and IL-2 in the microenvironment. In mice, several studies have demonstrated the efficacy of generating iTregs with functional properties in vivo. In contrast, human iTregs exhibit phenotypic and functional instability, limiting their therapeutic potential. A clinical trial using in vitro-induced Tregs with TGF-β and IL-2 showed limited efficacy, highlighting the challenges of generating stable iTregs in humans and indicating that TGF-β alone is insufficient.
We aimed to further investigate the molecular signaling pathways underlying iTreg induction, with the goal of generating large numbers of these cells, optimized for potential therapeutic administration, to improve patient quality of life and reduce dependence on immunosuppressive treatments.
Molecule X attracted particular interest for its capacity to induce Tregs from naïve $CD4^+$ T cells, leading to the generation of cells displaying stable phenotypic and functional characteristics. Our results demonstrate that FOXP3 induction mediated by molecule X is associated with activation of the TGF-β signaling pathway. Blockade or CRISPR/Cas9-mediated deletion of the primary receptor of molecule X did not impair its capacity to induce FOXP3 expression in iTregs. These results suggest that molecule X operates through alternative signaling pathways, potentially involving an as-yet-unidentified receptor or mechanism, providing novel insights into the molecular regulation of iTreg generation.

Keywords: Autoimmunity - Regulatory T cells - FOXP3.

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PS25-P03

Fate control of FOXP3 expressing human Treg cells for cell therapy

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Objective
Regulatory T (Treg) cell therapies have shown favourable safety profiles but limited clinical efficacy. We investigated how human naïve Treg cells differentiate during ex vivo expansion and whether their fate can be pharmacologically redirected toward a stable, highly suppressive effector state.
Methods
Human circulating Treg subsets and naïve Treg cells expanded for 14 days were profiled by single-cell RNA sequencing combined with surface-protein analysis. Transcriptomic signatures, pathway activity and developmental trajectories were integrated with phenotypic, suppression and DNA-methylation analyses. Rapamycin, methylprednisolone and IRAK4 inhibition were tested as modulators of Treg fate.
Results
Circulating FOXP3hi effector Treg cells were defined by a 287-gene signature. Standard expansion of naïve Treg cells predominantly generated a highly proliferative P1 state with reduced expression of FOXP3 and immunoregulatory genes, whereas a minority acquired a P2 state resembling circulating effector Tregs. Trajectory inference indicated that P1 and P2 represent divergent developmental fates. Rapamycin and methylprednisolone increased the P2 fraction and suppressive potency. IRAK4, identified from P1-associated trajectories, was pharmacologically inhibited, increasing FOXP3 expression and Treg-mediated suppression while limiting proliferation. Treg-associated loci remained demethylated across conditions, indicating that the observed instability was primarily transcriptional.
Conclusion
Human naïve Treg cells adopt distinct fates during expansion that can be pharmacologically controlled. Redirecting differentiation toward an effector Treg-like state provides a strategy to improve the potency and consistency of Treg cell therapy products.

Keywords: Cell Therapy - Treg.

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Regulatory T cell stability at steady state across tissues

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Foxp3+ regulatory T cells (Tregs) play a crucial role in mice and humans by dampening immune responses, thereby preventing autoimmune diseases. Indeed, ablation of Tregs in mice leads to severe inflammation and multi-organ autoimmunity. Moreover, mutations in the coding sequence of *Foxp3* lead to Treg deficiency and severe autoimmunity in mice and humans, highlighting the crucial role of this transcription factor in Treg biology and function. Thus, the maintenance of Foxp3 expression in Tregs is a major question. Here, we have studied Treg instability through a *fate mapping* system allowing to track, identify, and characterize Tregs that have lost Foxp3 (exTregs) across tissues. At steady state, we found a significant fraction of unstable Tregs in all tissues. In the spleen for example, exTregs represent 8% of the conventional T cell pool in healthy mice. Strikingly, exTregs have an activated phenotype and express Tfh markers. By looking at the Tfh pool in a preimmune repertoire, we show that half of the Tfh cells are actually exTregs. Finally, we assessed the function of exTregs and show that they have partially lost their suppressive function and produce pro-inflammatory cytokines. Our study will help define the identity, phenotype and function of exTregs.

Keywords: Treg - Stability - Steady state.

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PS26-P01

Deciphering the Glycan–Microbiota Interface: Mucosal Glycans Shape Intestinal Microbial Communities During the Transition to Inflammation

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State of the art
The gut is inhabited by a reservoir of microorganisms that co-evolves with host immune system, maintaining gut homeostasis. Gut dysbiosis results from imbalances in the microbiota composition and function, commonly associated to Inflammatory Bowel Disease (IBD). A dense layer of glycans coat the gut epithelium (glycocalyx), serving as an interface between gut microorganisms and intestinal mucosa. Evidence from our group showed that alterations in host glycosylation play a key role in IBD. Patients with ulcerative colitis showed deficient levels of branched *N*-glycans in mucosal T cells associated with disease severity (1). We also showed that glycan supplementation of mice lacking branched *N*-glycans, either therapeutic or prophylactic, resulted in disease control (2,3). However, the impact of alterations in the mucosal glycocalyx on host microbiota composition in IBD remains poorly understood.
Objective
Our goal is to elucidate glycome-microbiome interactions during the transition from health to intestinal inflammation and investigate whether modulation of glycosylation can prevent IBD development.
Methods
Intestinal tissue samples from a well-characterized cohort of Crohn's disease patients were collected, in remission (n=30) or relapse (n=30), at surgery and six months post-surgery, in which both gut glycome and microbiome were analysed. We also explored the impact of glycosylation remodelling *in vivo*, assessing the gut microbiome of glycoengineered mouse models lacking complex *N*-glycans at the intestinal mucosa and supplementing these with glycans, in both homeostatic and inflammatory conditions.
Results
Our results suggest that shifts in gut microbiome are associated with specific glycosylation profiles in the gut mucosa in IBD relapse and remission. We further showed that glycosylation remodelling in mice impacted microbial communities in the gut, leading ultimately to different susceptibility to DSS-induced colitis.
Conclusion
Overall, exploring host-microbiota interactions from the glycosylation perspective may unlock novel precision-targeted interventions for the prevention of IBD.

Keywords: Microbiome - Mucosal glycocalyx - IBD.

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PS27-P01

AltraFlowSOM: A Semi-Supervised Framework for Scalable Phenotyping of Imaging Mass Cytometry Data

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Introduction

Imaging Mass Cytometry (IMC) enables high-dimensional spatial profiling of tissue microenvironments. However, current workflows rely heavily on unsupervised clustering followed by manual annotation, a process that is labor-intensive, difficult to scale, and sensitive to batch effects. To address these challenges, we developed **AltraFlowSOM**, a semi-supervised clustering framework that integrates prior biological knowledge directly into cluster formation while preserving the ability to discover novel cell states.

Methods

AltraFlowSOM extends the FlowSOM[1] framework by utilizing Supervised Self-Organizing Maps (SUPERSOM)[2]. It combines a primary layer of marker expression with auxiliary layers of biological knowledge, such as partial manual gating labels. This dual-layer approach guides clustering toward biologically meaningful phenotypes. The method was validated using two IMC autoimmune datasets: Lupus Nephritis (22 ROIs) and Sjögren's Disease (10 ROIs). Performance was benchmarked against unsupervised algorithms (FlowSOM and PhenoGraph) and supervised Random Forest classifiers using leave-one-ROI-out cross-validation under different scenarios (without/with Batch Effect Correction (CyCombine or Harmony methods), 2 different markers selections, different cluster resolutions).

Results

AltraFlowSOM consistently outperformed all comparators. It improved clustering performance (both datasets), achieving stronger agreement with expert-defined phenotypes (higher Adjusted Rand Index, F-measure and purity) than FlowSOM and PhenoGraph. While Random Forest classifiers showed high concordance with expert gating, they lacked the capacity to identify novel or transitional cell states and struggled with population abundance imbalance. In contrast, **AltraFlowSOM** provided a superior balance, stabilizing the identification of canonical populations while improving the recovery of rare phenotypes, such as Tregs, dendritic cells (DCs), and PMNs.

Conclusion

AltraFlowSOM combines biological knowledge guidance and automated clustering for high-dimensional tissue phenotyping. By integrating prior knowledge into clustering, it enhances interpretability, sensitivity to rare populations, and reproducibility, while preserving the ability to discover previously unrecognized cell states. Applicable to IMC, Flow, and Mass Cytometry, its multi-layer architecture allows integration of multimodal data (e.g. transcriptomics), offering a scalable tool for systems and spatial immune research.

Keywords: Imaging Mass Cytometry (IMC) - Single-cell phenotyping - Spatial immunology.

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PS27-P02

Trophoblast Extracellular Vesicles Rewire Immunity: A Symptom-Relief Avenue for Recessive Dystrophic Epidermolysis Bullosa

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Redirecting immune responses toward tissue repair represents a promising strategy for treating inflammatory and degenerative diseases. Extracellular vesicles (EVs), derived from allogeneic stem cells, have shown potential for modulating proinflammatory immunity. Among these, placental-derived EVs (PEVs) are emerging as candidates for immune-mediated inflammatory disorders due to their role in maternal immune tolerance. However, translation is hindered by limited understanding of their cellular origin, mechanisms of action, and applicability beyond pregnancy. In this study, we identify extravillous trophoblasts (EVTs), critical for early placental development, as key source of immunoregulatory PEVs. To overcome donor variability, we employed the HIPEC cell model, as an established surrogate for primary EVTs, providing reproducible platform for scalable production of EVT-derived EVs (EVT-EVs). We then assessed their effects on circulating monocytes, pivotal mediators of inflammatory responses. High-dimensional molecular profiling revealed that EVT-EVs carry a distinctive anti-inflammatory signature, including a unique miRNA repertoire enriched for immunoregulatory pathways. Integrated proteomic and lipidomic analyses demonstrated that EVT-EVs reprogram monocytes toward a tolerogenic, inflammation-resolving phenotype. Importantly, EVT-EVs reversed the inflammatory bias of monocytes from patients with recessive dystrophic epidermolysis bullosa (RDEB), a genetic disorder characterized by chronic inflammation, thereby restoring immune balance. These findings establish EVT-EVs as a scalable, off-the-shelf therapeutic platform and highlight their potential as a novel treatment for chronic inflammatory diseases.

Keywords: Monocytes - Inflammation - Recessive Dystrophic Epidermolysis Bullosa.

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PS28-P01

Improving Monoclonal Antibody PK Predictability Through Comparison of Humanized FcRn Mouse Models

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Background/Objectives
The pharmacokinetics (PK) of monoclonal antibodies (mAbs) are strongly influenced by interactions with the neonatal Fc receptor (FcRn), which regulates IgG recycling and half-life. Humanized FcRn mouse models have been developed to improve human PK prediction, but direct comparisons of these models remain limited. This study evaluated the impact of FcRn humanization, human Fcg receptor co-expression, sex, and human IgG competition on mAb PK.
Methods
Eight therapeutic mAbs with diverse targets, Fc-engineering strategies and clinical half-lives were selected: eculizumab, ravulizumab, palivizumab, nirsevimab, rituximab, obinutuzumab, durvalumab and trastuzumab. Binding to mouse, cynomolgus and human FcRn, as well as selected FcγRs, was characterized by surface plasmon resonance (SPR). Antibodies were administered intravenously (10 mg/kg) to male and female mice from four strains: C57BL/6 (wild-type), Tg32 (human FcRn), hSA/FcRn (human FcRn and human serum albumin) and hFcγR/FcRn (human FcRn and FcγRs). Human IgG competition was assessed by mice IVIg pre-treatment. Serial sampling was performed up to Day 62. Antibody concentrations were quantified by validated LC-MS/MS methods, and PK parameters were determined using non-compartmental analysis.
Results
All humanized strains expressed human FcRn in major organs while lacking murine FcRn. SPR analyses confirmed distinct FcRn and FcγR binding profiles associated with antibody-specific engineering. Marked differences in serum concentration-time profiles were observed between antibodies and mouse strains. The effect of sex varied across molecules, influencing the elimination of selected mAbs. Human IgG competition altered the PK of some antibodies but had minimal impact on others. Antibodies incorporating Fc modifications designed to enhance FcRn interactions generally exhibited prolonged exposure. Overall, PK behavior reflected both antibody-specific properties and model-specific receptor expression patterns.
Conclusions
Humanized FcRn mouse models do not perform equivalently for all therapeutic antibodies. The predictive value of each model depends on antibody characteristics, Fc engineering, and interactions
with FcRn and FcγRs. Consideration of sex and endogenous IgG competition further improves translational relevance. These findings provide guidance for preclinical model selection to better predict human mAb PK and support antibody discovery and development.

Keywords: Pharmacokinetic - FcRn - Mice models.

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PS28-P02

Roles of the human IgH locus 3' Super enhancers in BCR expression and Class Switch Recombination

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Class switch recombination (CSR) allows B cells to diversify antibody effector function while preserving antigen specificity, adapting the immune response to tissues, antigens and cytokinic environment dependent on T-cell help. In rodents, the IgH locus 3'RR super-enhancer regulates CSR. In humans, a duplication has generated two super-enhancers, 3'RR1 and 3'RR2 with unknown roles. Based on the genomic organization of the IgG subclass genes relative to each super-enhancers (1,2), we hypothesise that 3'RR1 regulates IgG3 and IgG1 CSR, whereas 3'RR2 regulates IgG2 and IgG4 CSR.

We identified a B cell line able of undergoing CSR for IgG and generated targeted knock-outs (KO) of 3'RR1 and 3'RR2 by CRISPR-Cas9. To facilitate cell sorting we tagged the IgH locus with a Venus reporter gene inserted by Crispr-Cas 9 downstream of the 3'RR1. Whereas 3'RR2 KO clones retain the Venus tag, 3'RR1 KO and double-KO clones lose it. Homogeneous clones were isolated, expanded and stimulated to induce CSR. Functional impact of each super enhancer was evaluated at several levels. BCR expression (*i.e.*density of the IgM or IgG BCR at the cell surface) and IgG CSR were evaluated by flow cytometry. Additionally, transcriptomic analysis of BCR repertoire in each stimulated clones was performed using bioinformatic tools to dissect molecular mechanisms underpinning the phenotypic observations.

BCR expression, as evaluated by cell cytometry was reduced in 3'RR1 and 3'RR2 KO clones with a more pronounced reduction in double-KO clones. Deletion of 3'RR1 impaired CSR, as evidenced by a reduction in the proportion of IgG positive cells. In contrast, deletion of 3'RR2 weakly reduced CSR and IgG levels. Interestingly, Venus control clones displayed a phenotype similar to that of 3'RR2 KO clones, suggesting that the observed reduction of CSR, may be associated with the Venus reporter gene rather than with the loss of 3'RR2. Finally, dual deletion of both 3'RR1 and 3'RR2 resulted in abolition of CSR.

Whereas loss of 3'RR2 modestly reduced CSR, 3'RR1 deletion resulted in a significant reduction and confirmed, as reported in rodent, that human 3'RR super-enhancers are key players of CSR. Combined deletion of both 3'RR resulted in complete loss of CSR together with a marked reduction of BCR density. These results suggest that 3'RR2 can partially compensate for 3'RR1 deficiency. Further experiments will evaluate the degree of functional redundancy between these major IgH regulatory elements.

Keywords: BCR - 3'Regulatory Regions - CSR.

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PS28-P03

Biological Effects of VLA-4 Blockade by Natalizumab on Human T Cells

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Introduction

Multiple sclerosis is a chronic immune-mediated inflammatory disease of the central nervous system (CNS), characterized by the infiltration of activated immune cells across the blood–brain barrier (1). Natalizumab (NTZ) is a monoclonal antibody targeting the α4 integrin subunit (CD49d), inhibiting α4 integrin-mediated interactions, particularly α4β1 (VLA-4) binding to vascular cell adhesion molecule-1 (VCAM-1) and Fibronectin, reducing leukocyte trafficking into the CNS (2). Despite its well-established clinical efficacy and more than two decades of therapeutic use, the effects of VLA-4 blockade on T-cell signaling, morphology, motility, and other processes directly related to T-cell function remain poorly understood (3).

Objectives

This work aimed to investigate the biological effects of NTZ on T-cell functions.

Methods

To this end, high-content cell imaging was used to evaluate NTZ effect on purify T CD8+ cell adhesion, transmigration, motility under confined environment and T CD8+ cytotoxicity against P815 target cells.

Results

Our data show that cell adhesion on fibronectin was not impacted by NTZ treatment, suggesting the effect of NTZ on cell adhesion is mainly VCAM-1-mediated. Interestingly, NTZ reduced cell transmigration over Fibronectin. Similarly, NTZ reduced T CD8+ interstitial migration on fibronectin, with reduced motility even in the absence of an integrin ligand. These results suggest that VLA-4 blockade may affect cellular processes that operate beyond the VCAM-1-specific interaction. We next investigated whether NTZ also affected CD8+ T-cell effector function. CD8+ T-cell adhesion was not affected by NTZ treatment, either in the presence or absence of TCR engagement. Likewise, no apparent reduction in specific killing was observed in the presence of fibronectin following NTZ treatment, suggesting that CD8+ T-cell cytotoxic activity was preserved under the tested conditions. This may reflect compensatory mechanisms, potentially involving the engagement of the LFA-1 integrin.

Conclusion

Altogether, our findings indicate that VLA-4 blockade by NTZ reducesCD8+ T-cell transmigration and motility without impairing cytotoxic activity. These effects suggest that VLA-4 influences T-cell migration beyond VCAM-1-dependent adhesion.

Keywords: Integrin α4β1 - Immune-cell trafficking - Monoclonal antibody.

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Heavy chain protein: disease or not disease?

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Objective
Heavy chain disease (HCD) is a rare B-cell neoplasm characterized by the presence in the blood and/or urine of a truncated monoclonal heavy chain (HC), lacking associated light chains (LC). HCDs remain largely underdiagnosed. The objective of this study was to identify specific biological patterns to improve HCD diagnosis.
Methods
This was a retrospective study reporting the immunological and hematological characteristics of a large cohort diagnosed over a 20-year period at immunology laboratory (January 2005 – December 2025). Immunological diagnosis was performed using serum protein electrophoresis (SPE), immunotyping or immunofixation (IFE) and immunoselection, gold standard technique for diagnosis of HC protein to confirm IFE results. HCD clinical contexts were recorded.
Results
Thirty-five patients with HC protein were included with a median age at diagnosis of 66 years. Heavy chain isotypes were 29 gamma-HCD (83%), 5 alpha-HCD (14%), and 1 mu-HCD (3%). No mu or epsilon HCD was diagnosed. Among patients, 23% presented with a normal SPE profile. As reported in the literature, HC protein were predominantly associated B cell neoplasm, including diffuse large B cell lymphoma, marginal zone and MALT lymphoma, myeloma, as well as autoimmune diseases (rheumatoid arthritis, SLE) and T-cell lymphomas. Interestingly, renal and hepatic transplant patients are also found in this series, as well as MGUS. Six (17%) patients had no pathology that was described as associated to HCD in literature. *Twelve/35* patients underwent a myelogram, 4/35 patients had lymphoid tissue (spleen and ganglion). We investigate plasma cells and lymphocytes morphologies.
Discussion
In this study, we highlight that a normal SEP does not rule out the presence of a monoclonal heavy chain and most of our HCD patient had no specific clinical signs. SPE and IFE are not sufficient techniques for the diagnosis of HCD ; immunoselection remains essential. No hematological characteristic allowing the diagnosis of HCD has been found, except in the case of mu-HCD. Some heavy chains were not associated with lymphoproliferative diseases signs and the term "disease" might not be adapted for most patient. Such as MGUS, the presence of truncated heavy chain could be considered as HCUS (Heavy Chain of Undetermined Significance).

Keywords: Heavy Chain protein - Immunoselection - B-cell neoplasm.

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PS28-P05

Development of a Fully Human Broadly Neutralizing Anti-SARS-CoV-2 mAb Using Tonsil Organoids

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Background
The COVID-19 pandemic highlights the need for therapeutic monoclonal antibodies (mAbs) to fight infections in individuals who may have insufficient responses to vaccines. Fully human mAbs can be generated using transgenic mice expressing human immunoglobulin genes or using phage display technologies. However, access to these platforms remains limited, motivating the development of new approaches. The successful identification of antiviral mAbs from antigen-specific B cells isolated from the blood of infected individuals demonstrates the potential of human-derived samples for antibody discovery. However, antigen-specific B cells are rare in peripheral blood, making the isolation of relevant B cell clones challenging. Lymphoid tissues such as tonsils represent an important reservoir for memory B cells, and human tonsil organoids have recently been shown to support antibody production, somatic hypermutation, and affinity maturation following influenza vaccination. Here, we evaluated whether human tonsil organoids could be used for the isolation of fully human anti-SARS-CoV-2 mAbs with therapeutic potential.
Methods
Human tonsil organoids were stimulated with the COVID-19 mRNA vaccine (Pfizer-BioNTech). Spike-specific B cells were single-cell isolated and expanded on feeder cells prior to paired sequencing of antibody variable heavy and light chains. The corresponding recombinant mAbs were expressed in HEK cells. Their specificity, affinity, and cross-neutralization potential against different variants of concern were assessed and compared with clinically approved anti-SARS-CoV-2 antibodies. The protective potential of tonsil organoid-derived antibodies was also evaluated in K18-hACE2 mice infected with the ancestral SARS-CoV-2 strain.
Results
mRNA vaccination promoted antigen-specific B cell maturation into antibody-secreting cells with preserved polyclonality and a high rate of somatic hypermutation. Recombinant tonsil-derived antibodies displayed high affinity for the spike receptor-binding domain (RBD), demonstrated potent *in vitro* neutralizing activity, and protected K18-hACE2 mice against lethal SARS-CoV-2 infection. Notably, one tonsil-derived antibody showed broad cross-neutralization against different SARS-CoV-2 variants of concern, comparable to the therapeutic antibodies Pemivibart and Sipavibart.
Conclusion
Tonsil organoids could be used for the rapid identification of high-affinity fully human mAbs against SARS-CoV-2 or other pathogens.

Keywords: Organoid - Antibody - Tonsil.

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PS28-P06

Engineering a Nanobody-Reporter Fusion (VHH-APEX2) for Epidemiological Surveillance of Shiga Toxin 2

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Background
The detection of Shiga toxin 2 (Stx2) is critical for the diagnosis and epidemiological surveillance of pathogenic Shiga-producing *Escherichia coli* outbreaks. Traditional diagnostics often rely on expensive and complex multi-step immunoassays. Recombinant antibody engineering offers a solution by genetically fusing recognition molecules (nanobodies/VHH) to reporter enzymes. The VHH-APEX2 platform is a promising strategy, as it creates a reagent with a defined 1:1 stoichiometry that allows for direct antigen detection without secondary antibodies, providing a rapid and cost-effective tool for resource-limited outbreak scenarios.
Objective
To develop and characterize a recombinant fusion protein comprising a Stx2-specific VHH and the APEX2 reporter enzyme, aiming to establish a direct detection reagent for epidemiological surveillance.
Methods
A synthetic gene encoding the anti-Stx2 VHH–APEX2 fusion was cloned into the pFab periplasmic expression vector. The recombinant plasmid was insert into *E. coli* WK6. Protein expression was induced with IPTG in the presence of hemin. The fusion protein was recovered via osmotic shock from the periplasmic fraction and purified using Ni-NTA affinity chromatography. Protein integrity was validated by SDS-PAGE and Western blot using an anti-VHH antibody. Stx2 interaction was investigated through molecular docking, dot blot assays, and both direct and capture ELISAs. **Results**
Sequencing confirmed the integrity of the anti-Stx2 VHH–APEX2 construct. Successful expression and purification of the recombinant protein were evidenced by SDS-PAGE and Western blot. Molecular docking predicted a stable interaction between the anti-Stx2 VHH domain and the Stx2 B-subunit. Functionally, the fusion protein generated a specific signal in dot blot assays against immobilized Stx2, matching the positive control (polyclonal anti-Stx2). Direct and capture ELISA assays are currently undergoing optimization regarding blocking and alternate developing systems to enhance signal-to-noise ratios.
Conclusion
The anti-Stx2 VHH–APEX2 fusion protein was successfully expressed and purified in a bacterial system. Preliminary functional assays and *in silico* modeling demonstrated its capacity to recognize Stx2. Once microplate assay conditions are fully optimized, this engineered nanobody presents strong potential as a rapid, accessible, and direct diagnostic tool for STEC outbreak monitoring.

Keywords: VHH-APEX2 - Nanobody - Stx2.

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Biomarkers based machine learning approach to evaluate the response to targeted antibodies and other therapy in metastatic colorectal cancer patients

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Introduction

Metastatic colorectal cancer (mCRC) has a high incidence and mortality. Despite therapeutic advances, outcomes for mCRC patients remain poor and variable due to intrinsic or acquired resistance. Therefore, is necessary to examine the ability of artificial intelligence-based platforms to build clinical-genomic models for predicting response to chemotherapy and targeted therapy in cohorts of mCRC patients.

Material and Method

Response to targeted antibodies and other therapy is studied by conducting a retrospective study where samples of formalin-fixed, paraffin-embedded metastatic lesions are collected from a cohort of 150 mCRC or recurrent patients who underwent surgery at ISMETT. Molecular analyses are performed using Oncomine Comprehensive Assay v3C and Affymetrix microarrays. Different models, including Random Forest and XGBoost will be performed in accordance with the Institutional Review Board of ISMETT (protocol code IRRB/22/24, 17 July 2024).

Result and Discussion

120 mCRC patients were enrolled from Jan 2016-Dec 2023. Average age was 68 years. 50% of mCRC patients underwent to cytotoxic chemotherapy and 50% to targeted antibodies therapy. The study of mutational profiling is underway with a panel of 161 genes for the detection of SNVs, CNVs and fusions. Chromosomal instability and transcriptome analyses are currently performed with genomic/transcriptomic microarrays.

Conclusion

Our previous EU-funded REVERT project developed an AI-based based network showing a significant improvement in PFS of mCRC patients: at 9 months, >PFS1 was observed in 77% of responder vs. 68% of comparative group. The current model should have improved accuracy to predict response to targeted antibodies and other therapy and to assist oncologists in selecting the most effective combinatorial treatments for mCRC patients.

Acknowledgement

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Keywords: Antibody targeged therapy - Biomarkers - Machine Learning.

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A CD2 blocking antibody for inflammatory and autoimmune diseases

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CD2, a T cell adhesion and co-stimulatory receptor, is highly expressed by effector and memory T cell subsets compared to naïve and regulatory T cells, making it an attractive target for inflammatory and autoimmune diseases. To date, only two CD2-targeting agents went into clinical development: SBT-11-5301, a CD58-Fc fusion protein (CD2 ligand) and Siplizumab, a non-blocking CD2 antibody (mAb) that mediates CD2 high T cells depletion. Here, we describe the identification and characterization of a differentiated novel CD2-blocking mAb.
Evotec's Function-Focused mAb platform was used to identify binders selective for effector memory T cells (Tem) using Tem cells as immunogens. Functional screening was followed by target identification and epitope characterization. Binding affinity, specificity and species cross-reactivity were evaluated using recombinant CD2 and cell-based assays. Functionality was assessed using mixed lymphocyte reaction (MLR) assays. The mechanism of action was then investigated by evaluating CD2-CD58 interaction. Siplizumab served as benchmark.
FACS screening identified several antibodies selective for memory T cells as compared to naïve T cells. Target deconvolution identified CD2 as the target of our lead mAb. Phenotypic analysis showed CD2 expression across all T cells, with the highest levels on effector and memory subsets. This lead mAb bound human and cynomolgus CD2 and showed single digit nanomolar affinity for human CD2 in SPR, comparable to Siplizumab. In functional assays, this anti-CD2 mAb completely inhibited the MLR response with potent modulation of T-cell mediated IFNg release. Mechanistically, it effectively blocked CD58 binding to primary human CD8+ T cells, whereas Siplizumab showed no detectable blocking activity. These findings indicate recognition of a distinct functional epitope involved in the CD2-CD58 interaction.
Using a function-driven antibody discovery approach based on primary human Tem cells, we identified a novel anti-CD2 mAb targeting a functional blocking epitope within the CD2-CD58 interaction. The MLR assay, a well-established model of T-cell activation mimicking pathological immune responses, demonstrated potent suppression of T-cell responses. By preferentially targeting CD2 high effector and memory T-cell populations and inhibiting CD2-mediated co-stimulation through CD58 engagement, this novel CD2-blocking mAb represents a differentiated therapeutic approach for immune cell-mediated indications.

Keywords: CD2 - Blocking antibody - T cell costimulation.

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PS28-P09

A single-domain antibody-based anti-CD20 bi-modular fusion protein redirects endogenous anti-EBV antibodies to trigger potent complement-dependent cytotoxicity

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Objective
Therapeutic monoclonal antibodies targeting CD20 have considerably improved the treatment of B-cell malignancies. We previously developed bi-modular fusion proteins (BMFPs), an immunotherapeutic platform, designed to redirect pre-existing endogenous antibodies against Epstein-Barr virus (EBV) toward defined cellular targets (1). Here, we engineered an anti-CD20 BMFP combining a single-domain antibody (VHH) with P18F3, an EBV-derived antigenic fragment recognized by circulating anti-EBV antibodies, and evaluated its capacity to recruit endogenous antibodies and induce complement-dependent cytotoxicity.
Methods
VHHCD20-P18F3 was evaluated on CD20-positive Daudi Burkitt lymphoma cells. CD20 binding and recruitment of anti-P18F3 IgG from human plasma were assessed by flow cytometry. Complement activation was evaluated by membrane attack complex (MAC) deposition and cell death. The previously developed scFvCD20-P18F3 and rituximab were used as comparators.
Results
VHHCD20-P18F3 showed enhanced binding to Daudi cells and increased recruitment of endogenous anti-P18F3 IgG compared with the scFv-based BMFP. Antibody recruitment and subsequent complement activation depended on anti-P18F3 antibody levels in human plasma. In the presence of plasma containing high anti-P18F3 antibody levels, VHHCD20-P18F3 induced robust MAC deposition and cell death. Under these conditions, VHHCD20-P18F3 induced significantly greater MAC deposition than rituximab at 5.5 µg/mL, which translated into significantly increased Daudi cell death.
Conclusion
Thus, VHHCD20-P18F3 efficiently redirects endogenous anti-EBV antibodies toward CD20-expressing cells to trigger potent complement-dependent cytotoxicity. These findings support nanobody-based BMFPs as a modular strategy for harnessing pre-existing humoral immunity against therapeutically relevant cellular targets, with potential applications in B-cell malignancies.

Keywords: Bi-modular fusion proteins (BMFPs) - Anti-EBV antibodies - B-cell maligancies.

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PS28-P10

A long-read sequencing strategy to reveal truncated immunoglobulin heavy chains in monoclonal gammopathies of renal significance

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Background
Some monoclonal gammopathies of renal significance (MGRS) involve B-cell clones secreting truncated immunoglobulin (Ig) heavy chains (HC), which are challenging to detect using conventional techniques. While RACE-RepSeq on Illumina has improved uncertain MGRS diagnosis (1), it cannot identify HC-deleted transcripts. We aimed to assess the added value of long-read sequencing (Oxford Nanopore Technologies) for detecting such truncated heavy chains in the context of global Ig repertoire analysis.
Materials and Methods
Bone marrow RNA from 26 patients was analyzed: 13 with a known monoclonal Ig (MIg) identified by Illumina RACE-RepSeq, and 13 with suspected truncated heavy chain disease (heavy chain deposition disease, AH amyloidosis, or heavy chain disease). A modified RACE-RepSeq protocol was used to amplify Ig transcripts up to the CH3 domain. Long read sequencing was performed, and dedicated bioinformatic pipelines were developed to reconstruct full-length sequences and detect truncated clones.
Results
Long read sequencing yielded complete Ig repertoires in all 13 MIg cases, with high concordance to Illumina in terms of V gene usage, somatic hypermutation, and clonotype frequency. Dominant clones identified by Illumina were consistently detected by Nanopore. Notably, 9 truncated heavy chain transcripts were identified among the 13 cases, involving deletions in the V region, part of initial constant domain, or both. These sequences matched those independently confirmed by Sanger sequencing.
Discussion and Conclusion
Long read sequencing provides repertoire fidelity equivalent to Illumina while enabling the detection of structurally truncated Ig undetectable by conventional techniques. This approach enhances diagnostic accuracy in MGRS and may also support therapeutic monitoring by tracking pathogenic clones over time.

Keywords: Oxford Nanopore - Immunoglobulin repertoire - MGRS.

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PS28-P11

Phage Display-Based Identification and Functional Screening of Recombinant Anti-TIM-3 Nanobodies

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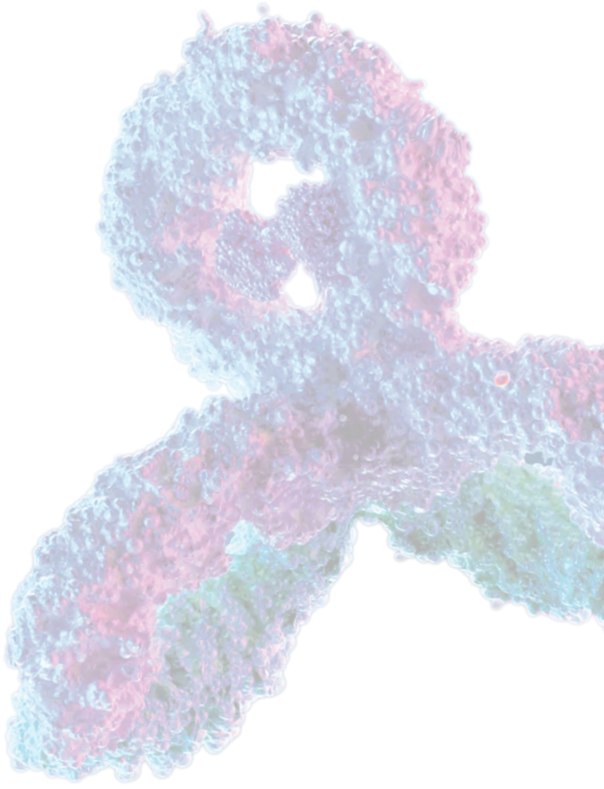
Objective
T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is an inhibitory receptor and a promising immune checkpoint target in oncology. Blocking TIM-3 represents a potential strategy to enhance T-cell activity within tumors and restore antitumoral immune responses. Nanobodies (VHHs) are attractive candidates for targeting TIM-3 due to their small size and high stability, which make them suitable for diverse molecular formats. This study aimed to select and characterize specific anti-TIM-3 VHHs and identify promising candidates based on sequence and binding reactivity.
Methods
Selection was performed by Phage Display using an immune llama library. Candidate clones were screened by sequence analysis using Chromas Lite, while Expasy Translate was used to identify complementarity-determining regions (CDRs), reading frames, and the VHH-specific KEREF signature in framework region 2. Multiple sequence alignment was performed using the Job Dispatcher platform (EMBL-EBI) to support germline lineage assignment, while MEGA11 was used to assess genetic relationships and clustering by neighbor-joining analysis with 1,000 bootstrap replicates. Reactivity was evaluated by periplasmic ELISA against recombinant and native glycosylated commercial TIM-3 following VHH expression in *E. coli* BL21 induced with IPTG and periplasmic extraction using TES buffer.
Results
From 56 initial candidates, 17 clones were successfully amplified and sequenced. Bioinformatic analysis identified 11 clones with complete sequences, representing 6 distinct germline lineages. Based on sequence analysis and exclusion of redundant clones, 5 unique nanobody candidates were selected for further characterization. Periplasmic ELISA identified clone 2F as the clone with the strongest reactivity against TIM-3. Significant reactivity was also observed for clones 4E, 1E, and 2D, in descending order, whereas clone 3E showed no differential reactivity.
Conclusion
The combined use of Phage Display selection, sequence analysis, and reactivity assessment enabled the identification of five distinct anti-TIM-3 nanobody candidates. Among these, clone 2F exhibited the strongest reactivity against TIM-3, identifying it as the leading candidate of this study, while also offering potential for further molecular engineering into formats such as bivalent constructs, enzyme conjugates, and chromobodies.

Keywords: Recombinant nanobodies - TIM-3 - Phage Display.

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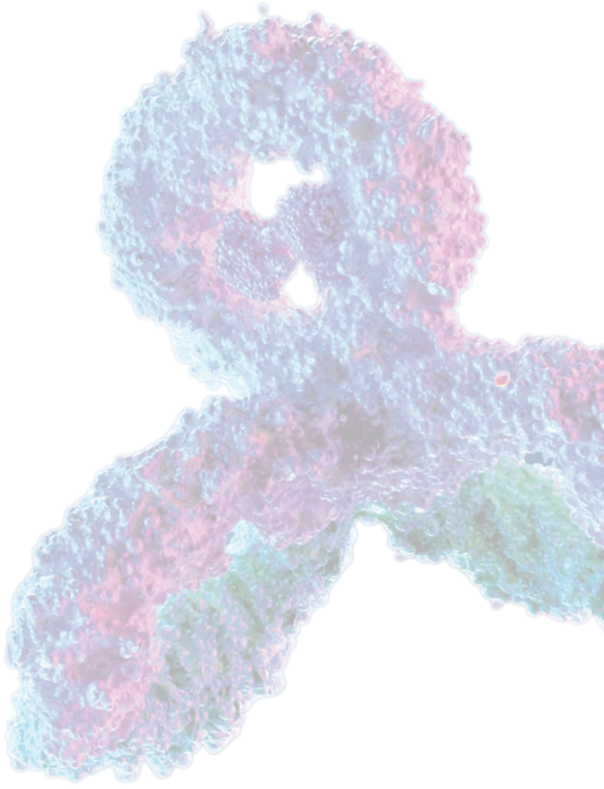
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UNITC - Consortium national de recherche sur les thérapies cellulaires et géniques en cancérologie
www.unitc.fr/

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www.utoulouse.fr/en

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+44 118 944 8000
yannick.martinez@moldev.com
www.moleculardevices.com

New England Biolabs France

Stand 3

New England Biolabs is a private company manufacturing reagents for the life science industry particularly focused on products for genomics research.

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info.fr@neb.com
www.neb-online.fr

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info@ozyme.fr
www.yris.ozyme.fr

Pixelgen Technologies

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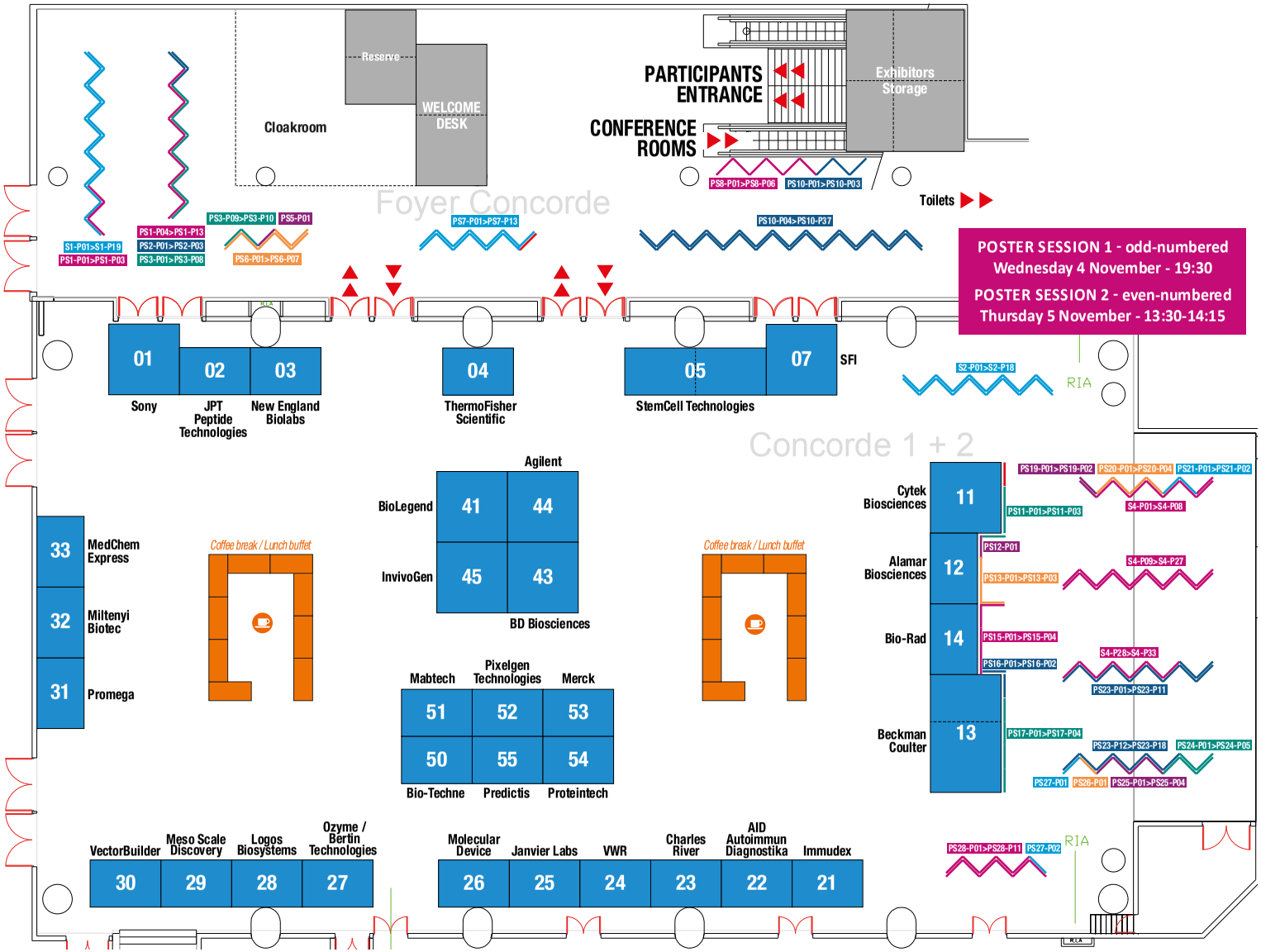
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www.sanofi.fr/fr

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EXHIBITION PLAN - CENTRE DES CONGRÈS PIERRE BAUDIS, TOULOUSE, FRANCE

FOYER & CONCORDE 1&2 - LEVEL -1



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- StemCell Technologies Stand 05
- ThermoFisher Scientific Stand 04
- VectorBuilder Stand 30
- VWR Stand 24

HOTEL LOCATION - SFI-SPI 2026 - TOULOUSE, FRANCE



1 Hôtel Mercure Toulouse Centre Compans ****

Located 2 minutes-walk (120 m) from meeting venue.
Parking: € 19 / 24h.

2 Novotel Toulouse Centre Compans Caffarelli ****

Located 5 minutes-walk (400 m) from meeting venue.
Parking: € 18 / 24h.

3 Hôtel de Brienne ****

Located 9 minutes-walk (600 m) from meeting venue.
Parking: € 19 / 24h.

4 The Social Hub Toulouse ****

Located 8 minutes-walk (550 m) from meeting venue.
Public parking 'Place de l'Europe'.

5 B&B Hôtel Toulouse Centre Canal du Midi ***

Located 13 minutes-walk (900 m) from meeting venue.
Parking: € 8 / 24h.

6 Odalys City Toulouse Centre Compans Caffarelli **

Located 12 minutes-walk (850 m) from meeting venue.
Parking (by reservation): € 12.50 / 24h.

ACCESS MAP - CONGRESS DINNER

THURSDAY 5 NOVEMBER, 20:00

Espaces Vanel - 1 Allée Jacques Chaban-Delmas, 31500 Toulouse

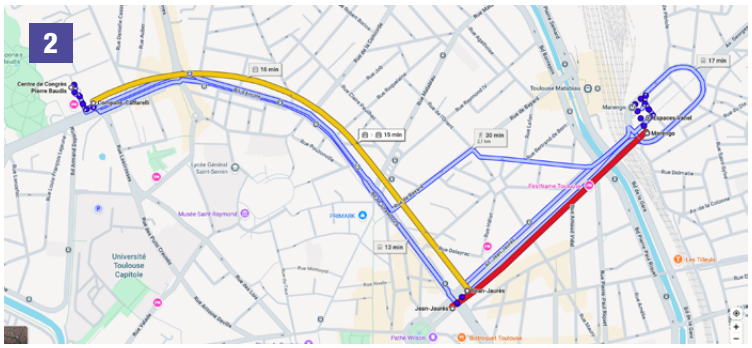
How to get to Espaces Vanel from Centre de Congres Pierre Baudis:



1 Option 1: On foot

Allow approximately 25–30 minutes (around 2 km).

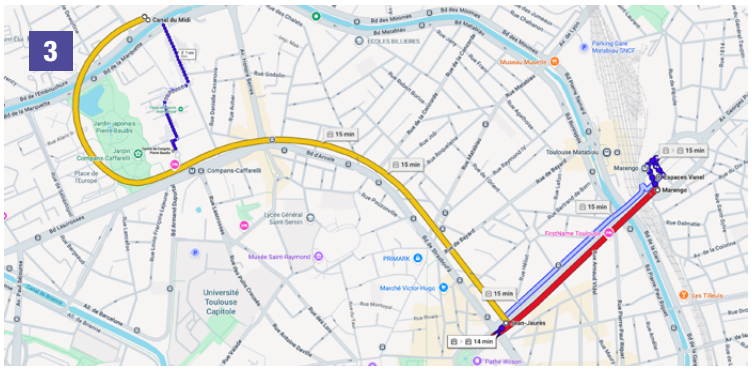
- Walk towards Toulouse city centre and continue in the direction of Toulouse-Matabiau train station.
- Espaces Vanel is located near the station.



2 Option 2: By metro

Allow approximately 15–20 minutes in total, including walking and the metro journey.

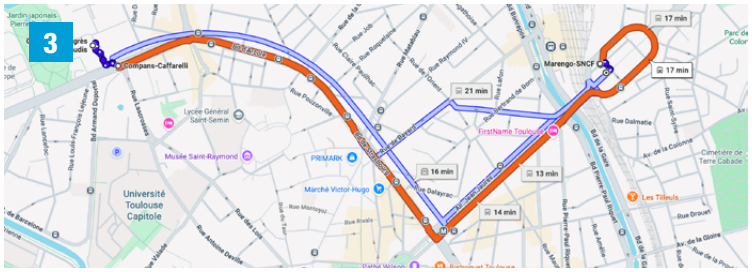
- Walk to Compans-Caffarelli metro station.
- Take Metro Line B towards Ramonville and get off at Jean-Jaurès (2 stops).
- Change to Metro Line A towards Balma-Gramont.
- Get off at Marengo-SNCF (1 stop).
- Walk to Espaces Vanel, located near Toulouse-Matabiau train station.



3 Option 3: By metro

Allow approximately 15-20 minutes in total, including walking and the metro journey.

- Walk to Canal du Midi metro station.
- Take Metro Line B towards Ramonville and get off at Jean-Jaurès (3 stops).
- Change to Metro Line A towards Balma-Gramont.
- Get off at Marengo-SNCF (1 stop).
- Walk to Espaces Vanel, located near Toulouse-Matabiau train station.



3 Option 4: By bus

Allow approximately 15-20 minutes in total, including walking and the bus journey.

- Walk to Compans-Caffarelli bus station.
- Take Bus Line L14 towards Marengo-SNCF and get off at Marengo-SNCF (7 stops).
- Walk to Espaces Vanel, located near Toulouse-Matabiau train station.

Last public transport departures near Espaces Vanel: Metro Line A at approximately 12:17 a.m. and bus L14 at approximately 1:00 a.m. Please check the latest timetables before travelling.

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