HYBRID
Health Bioscience Research Industry Days

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MARCH 16-17 2021

IMMUNOLOGY & INFLAMMATORY DISORDERS

ACADEMIC BOOK

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HYBRID
Health Bioscience Research Industry Days

Edito

Eleven years after from the launch of "Rencontres Internationales de la Recherche (RIR)", 2021 gives rise to HYBRID, created from the merging of RIR and "Rencontres Internationales des Biotechnologies (RIB)". This new 2021 edition aims to strengthen global health innovation and enhance sharing and cohesion of the French research ecosystem, by bringing together academic research, the health industry, and biotechs on an integrated two-day conference dedicated to **"Immunology : inflammation and associated chronic disorders".**

This event is organised jointly by the Alliance for Research and Innovation in Health Industries (Ariis), the French National Alliance for Life Sciences and Health (Aviesan), BpIfrance, FranceBiotech and Leem. This meeting will cover all aspects of fundamental to clinical research tied to chronic inflammatory diseases such as intestinal or metabolic disorders, neuroinflammation, sclerosis, fibrosis, autoimmune diseases and allergies.

The incidence of chronic diseases continues to rise and represents a major financial and societal burden. An estimated 12 to 20 million people have chronic inflammatory diseases. In France, chronic diseases account for 65% of health spending. Diabetes affects 3.48 million people in France (4.8% of 20-79 year olds) and 59.32 million individuals in Europe (6.3% of 20-79 year olds). There is still no cure for inflammatory bowel disease (IBD) and medical practitioners constantly resort to novel immunomodulators and surgical treatments in the case of more advanced forms, incurring heavy costs to the public health system.

Although progress has been made, the treatment of both monogenic and multifactorial inflammatory pathologies remain mainly symptomatic relying on the use of immuno-suppressive drugs or corticosteroids. Recent therapies have unfortunately not been able to provide satisfactory solutions to patients and the inflammatory response, which is common to inflammatory pathologies, is often at the origin of morphological alterations, including the establishment of tissue fibrosis, one of the main causes of treatment failure.

Reducing the burden of chronic diseases requires the development of a multidisciplinary and systemic approach based on a research continuum including : understanding the molecular and cellular mechanisms between different biological systems and epigenetic regulation mechanisms underlying inflammation, as well as the regulation of homeostasis and host inflammatory reactions and tolerance; increasing knowledge in systems physiology and epidemiology; improving the management of interventional clinical trials (including therapeutics). In parallel, it is essential to promote the development and access to new cutting-edge technologies provided by artificial intelligence to model diseases and ultimately propose new personalised multimodal biomarkers. These biomarkers will help improve early diagnosis and the prediction of the evolution of disease, for the benefit of the patient and health policy.

These issues regarding chronic inflammatory diseases and their consequences will be addressed during this two-day conference either in the form of presentations or during round table discussions involving leading players from the academic, health industry and biotech spheres. These exchanges will serve to advance knowledge and highlight the commitment of French research players in this national health priority, thanks to the common engagement of public and private research, including production and business development teams.

Yazdan Yazdanpanah,
Director of the Thematic Institute of Immunology, Inflammation, Infectiology and Microbiology, AVIESAN/Inserm

Sylvie Guerder,
Deputy Director of Institute of Biological Sciences, CNRS

Evelyne Jouvin Marche,
Deputy Director of the Thematic Institute of Immunology, Inflammation, Infectiology and Microbiology, Aviesan/Inserm and Director of Research at Inserm-CNRS-University Grenoble Alpes-Institute for Advanced Biosciences.

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Pathogenesis and innovative therapies in scleroderma and chronic fibro-inflammatory diseases

Keywords:

- Fibrosis,
- Inflammation,
- Auto-immunity,
- Genetic,
- Epigenetic,
- Oxidative stress,
- Immunology,
- Immunotherapy,
- Translational research,
- Biomarkers.

We use an orphan disease for which we have established a large biobank and collection of clinical data, together with a platform of complementary animal models, to decipher how chronic inflammation and autoimmunity can drive generalized fibrosis leading to end-stage organ involvement.

Systemic sclerosis is an orphan chronic fibro-inflammatory disease, affecting the connective tissue. The **pathophysiology** relates to interaction between genetic susceptibility and environmental factors. Our team has a long history of dismantling the pathophysiology of this disorder. Our strategies are based on the study of **genetic bases,** polarizations of **innate and adaptive immune responses**, the role of oxidative stress in the interfaces between these systems, **epigenetic modifications** involved in the dysfunction of the cells involved (such as fibroblasts) and **chronic inflammation**. Our ultimate goal is to identify relevant biomarkers and new therapeutic approaches. We have built a large bank from patients (DNA, RNA, serum, plasma, tissue and cells), and have set up a platform of **preclinical mouse models** that reproduce different aspects of the disease to explore in detail any candidate therapeutic molecule. We work closely with the clinical teams from Cochin Hospital so that our research can benefit patients as much as possible. Thanks to intense networking and position in international bodies, we are leading international proof of concept studies derived from our generated hypotheses.

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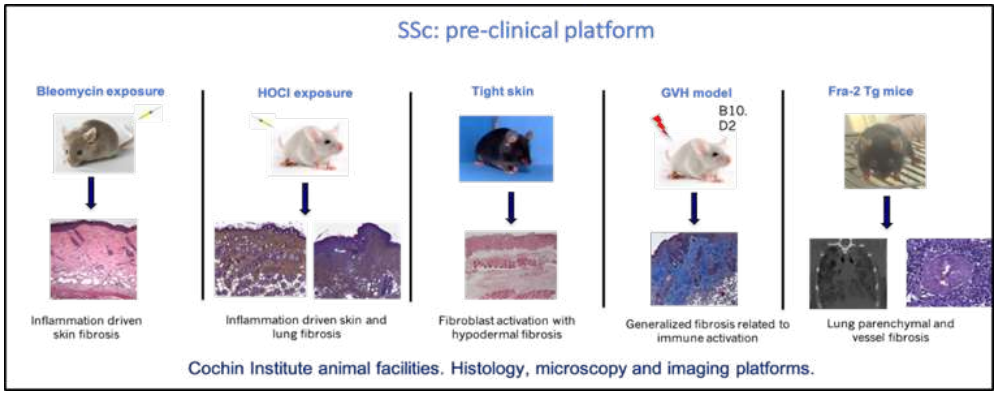
OBJECTIVES:

- To decipher scleroderma pathogenesis
- To investigate how chronic inflammation can promote fibrosis
- To identify relevant biomarkers and innovative therapies

TOOLS:

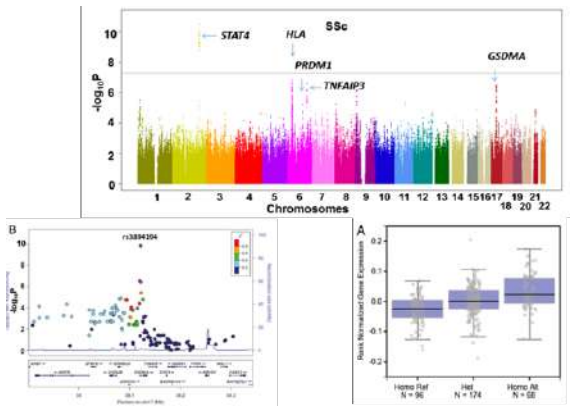
- Large biobank from patients: DNA, RNA, serum, plasma, tissue and cells
- A platform of complementary preclinical mouse models (see below)
- Close work with the clinical teams from Cochin Hospital



Genetic bases of SSc

RESULTS:

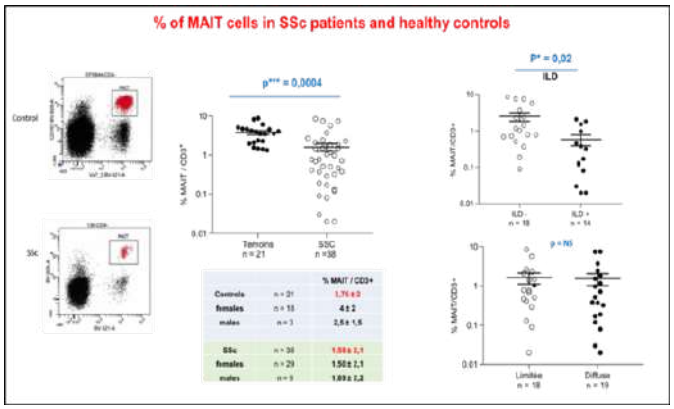
- Performance of the 2nd international GWAS study that highlighted the role of NFkB pathway (Plos Genet 2011)
- Performance of the first trans-ethnic GWAS that identified new susceptibility genes (Ann Rheum Dis 2017)



PERSPECTIVES:

- New transethnic GWAS in 2021 together with RIKEN Institute (Japan)

MAIT cells in SSc and related fibrotic damages

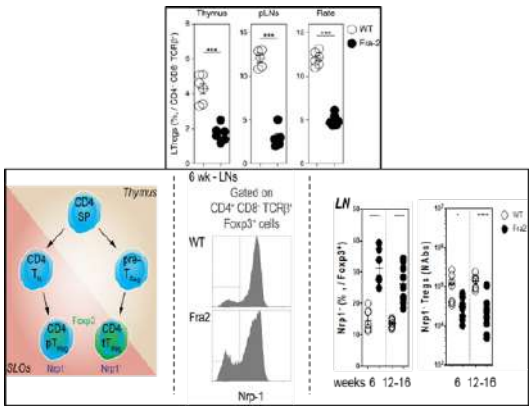


RESULTS:

- Circulating MAIT cells are decreased in SSc

May they have a role in fibrosis as seen in liver fibrosis?
Ongoing backcrossing of MR1−/− C57BL/6J and V 19 transgenic C57BL/6J mice onto C57BL/6J Fra2 transgenic mice to answer this question

Tregs in SSc



RESULTS:

- Regulatory CD4 T cell are deficient in Fra2 mice

Adoptive transfer and other strategies to increase Treg cells are ongoing to prevent fibrosis spreading

PERSPECTIVES:

- Identifying new targets by unbiased approaches
- Deciphering the role of the immune system (cells and signaling molecules) in its ability to induce and perpetuate fibrosis
- Improving the management of SSc patients by new biomarkers for risk-stratification and innovative therapies: (B-cell depletion induced by CAR-T C19 (collaboration with Dr Bousso, Pasteur))

UNIQUE SELLING POINTS:

- Clinical expertise recognized in the labeling of National and European referral center
- Intense networking with academics and pharmaceutical companies, recognized with past position of chairman of the European network
- Ability to set up a clinical trial (lanifibranor, arsenic trioxide (MEDSENIC partnership))
- Unique databank collected in the last 15 years
- Complementary preclinical mouse models that reproduce different aspects of the disease and offer to investigate in details any potential therapies
- Complementary expertise in the team from genetic and biochemistry to cell and molecular biology and various mice models

APPARAILLY Florence

Ph.D

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Pathophysiology of joint inflammation

Keywords:

- Rheumatisms,
- Synovial inflammation,
- Whole exome sequencing,
- Bone erosion,
- MicroRNAs,
- Immunophenotyping,
- Macrophages,
- Osteoclasts,
- Neutrophils,
- Immunotherapy.

Translational research in chronic joint inflammation: from basic research in genetics and immunology to the clinic.

Our team aims at studying the pathophysiology of articular disorders associated with chronic joint inflammation, from rare monogenic autoinflammatory disorders affecting kids to more frequent and polygenic forms of adult diseases, with 2 objectives : 1) to improve disease diagnosis and classification and patients' stratification because a delay in proper diagnosis delays optimal treatment and leads to irreversible organ damages, and 2) to provide insight into biological mechanisms to design new immuno-intervention strategies.
Gathering skills for genetics, functional (epi)genomics, molecular and cellular immunology, gene and cell therapy, experimental animal models of joint inflammation, biobanking and in-depth patients' immunophenotyping, mass cytometry imaging and cutting-edge fate mapping approaches, we study the molecular and cellular mechanisms that initiate, perpetuate and regulate immune response in human healthy and inflamed joints.
We identified (1) new molecular mechanisms of autoinflammatory diseases, (2) novel disease combining autoinflammatory and autoimmune features, (3) new diagnosis biomarkers that discriminate between inflammatory and septic arthritis in children, (4) markers specific for pathogenic osteoclasts in arthritis, (5) the circulating classical monocyte subset as precursors of the arthritis-associated osteoclasts and demonstrated their therapeutic potential to interfere with inflammation and joint erosion using RNAi-mediated in vivo targeting. We are currently dissecting joint tissue-specific identity of myeloid cells and their pathogenic interplay with other cells of the synovial niche in rheumatoid arthritis and osteoarthritis, both in patients' biopsies and animal models.

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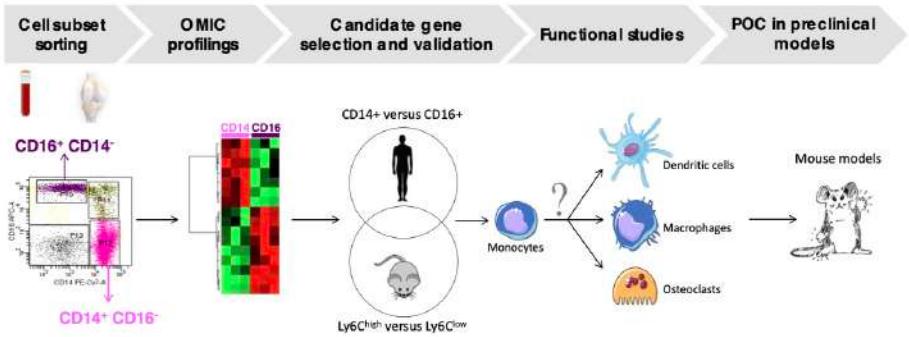
OBJECTIVES:

- Identify key regulators of joint tissue homeostasis
- Identify biomarkers for novel disease taxonomy and personalized medicine
- Characterize synovial myeloid cell diversity in human and mouse arthritis
- Bring POC for targeted therapies interfering with inflammation and/or bone erosion

TOOLS:

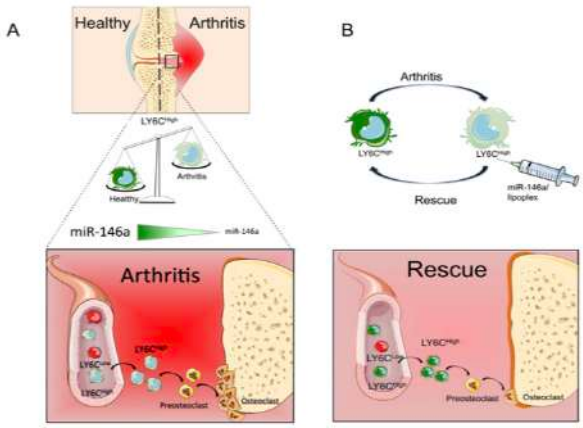
- Reference Centre for Autoinflammatory diseases
- Hight-throughput omics (WES, miRNome and (sc)RNAseq)
- In vivo imaging of mouse locomotion and bone architecture
- Hight-throughput immunophenotyping platform
- In vitro models to screen myeloid cell functions
- Preclinical models of arthritis and osteoarthriti



Subject 1: Basic and preclinical research in joint inflammation

RESULTS:

- Identification of immune cell subsets and new genes controlling inflammation or bone erosion in juvenile and adult forms of arthritis
- Identification of new diagnosis biomarkers and miRNAs predicting response to therapy in arthritis
- Identification of markers specific for pathogenic osteoclasts in arthritis
- Demonstration of the feasibility to target specific monocyte subsets to interfere with joint inflammation and erosion.



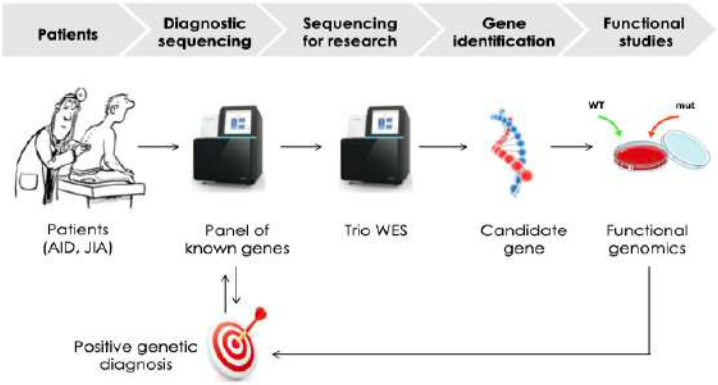
miR-146a controls Ly6Chigh monocytes commitment into osteoclasts ***(A)***
- Arthritis is associated with Ly6Chigh monocytosis displaying reduced miR-146a expression and increased osteoclastogenic potential.

- In vivo delivery of miR-146a mimics to Ly6Chigh monocytes upon intravenous injection efficiently restores normal bone erosion. ***(B)***

Subject 2: Genetic studies on well-characterized cohorts of patients to improve clinical practice

RESULTS:

- Description of a novel disease: NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)
- Identification of a novel causative gene responsible for CANDLE/PRAAS syndrome: PSMB10 is the third immunoproteasome gene for which the mutation led to IFN type I dysregulation and targeted the patient to anti-JAK 1/2 therapy.



Workflow strategy to identify new diseases and new genes in rare forms of arthritis and translate into clinical practice.
AID: autoinflammatory diseases; JIA: juvenile idiopathic arthritis; WES: whole exome sequencing; WT: wild type; Mut: mutated.

PERSPECTIVES:

- Characterize the dynamic landscape of synovial joint tissue macrophages
- Identify markers for pathogenic myeloid subsets
- Manipulate identified targets to study their role in controlling myeloid functions and to restore joint homeostasis and develop therapeutic strategies
- Improve disease diagnosis and classification and patients' stratification to give the right drug to the right person

UNIQUE SELLING POINTS:

- Translational research (4 patents including 1 already licensed)
- Capacity to translate marker discoveries into clinical diagnosis for autoinflammatory disorders
- Evaluation of therapeutic strategies mouse models of arthritis
- Capacity to perform genetic and immune monitoring of patients' cohorts

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Early-onset autoimmunity with a special interest for Type I interferonopathies and juvenile systemic lupus erythematosus

Keywords:

- Systemic lupus erythematosus,
- Autoimmunity,
- Rare diseases,
- Gene therapy,
- Drug repurposing,
- Monogenic diseases,
- Immunological signatures,
- Type I Interferonopathies.

Exploring genetic causes of Juvenile Systemic Lupus for personalized therapies

Juvenile systemic lupus erythematosus (jSLE) is a rare autoimmune disease that can affect virtually all organs. **The diagnosis is often delayed, especially in children**. The disease course in children is more severe than in adult-onset SLE, with more frequent renal and central nervous system involvement, possibly as a consequence of a **higher genetic contribution** to the disease. We have introduced the concept of **monogenic lupus**, showing that **at least 7% cases of jSLE are monogenic**. Monogenic lupus represents a new field of Mendelian diseases that often start in childhood and cannot be easily separated from non-monogenic SLE. The affected genes are critical for immune tolerance and identifying genetic causes of SLE is of major importance to consider therapy targeting the underlying molecular defect. We also demonstrated the accumulation of predicted pathogenic variants in jSLE patients with up to 3 variants per individual raising the question of the oligogenic nature of the disease.
Our project aims at:

- **Identifying** new rare and predicted pathogenic genetic variants by using whole genome sequencing and deep sequencing
- **Determining** how genetic variants impact on immune system by using fast track immunophenotyping and nucleic acid sensing analysis
- **Evaluating** personalized medicine in models and patients considering drug repurposing or gene editing strategies.

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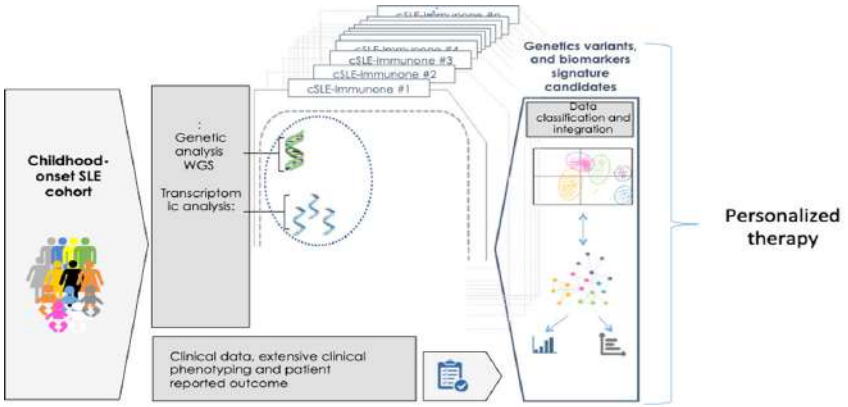
OBJECTIVES:

- Identify rare and predicted pathogenic variants in jSLE
- Characterize the immunological impact of variants in nucleic sensing, B cell activation and autoantigen production
- Test personalized therapy strategies in models and patients

TOOLS:

- Whole Genome / Exome sequencing strategies of the National Biobank (Lyon, n=450)
- Fast track immunophenotyping and functional immunology
- Drug repurposing, gene editing strategies

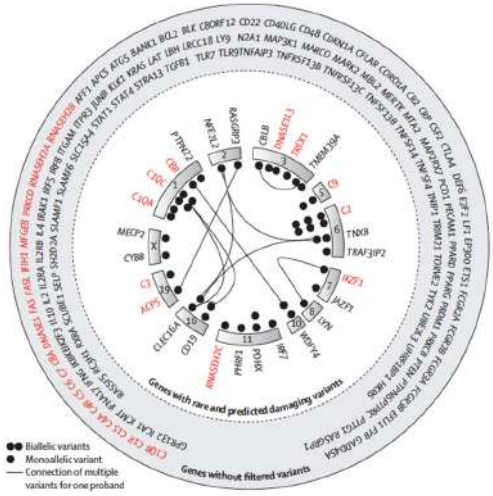
Exploring genetic causes of Juvenile Lupus for personalized therapies



Subject 1: Genetic heterogeneity of jSLE

RESULTS:

- **7%** of jSLE are **Mendelian diseases**
- **20% of jSLE carry rare and prediciting pathogenic variants**
- Evidence for an accumulation of rare variations in jSLE (Oligogenicity).

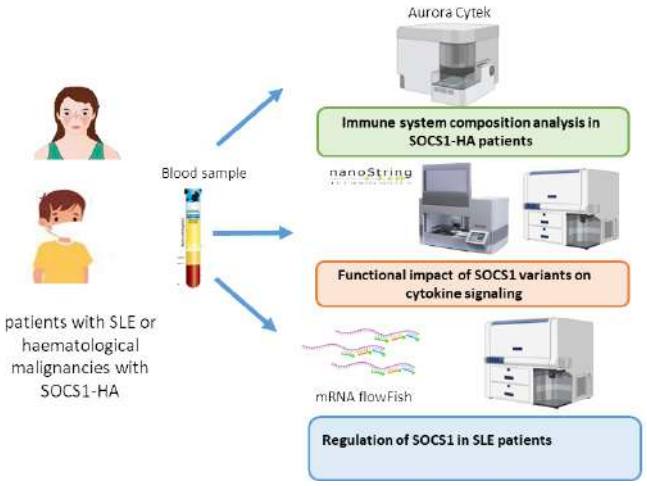


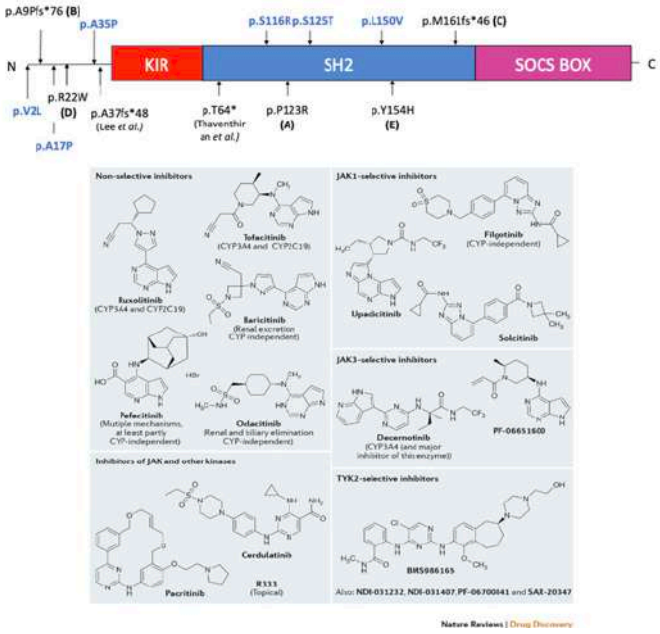
***Genetic architecture of jSLE**, Belot et al. Lancet Rheumatol 2020*

Subject 2: Personalizing drug therapy. Example of SOCS1 haploinsufficiency

RESULTS:

- Haploinsufficiency of SOCS1 and autoimmunity (Lupus, Psoriasis…)
- JAK inhibitors restore normal cytokine signaling.





Early-onset autoimmunity & SOCS1, haploinsufficiency, *Hadjadj et al. Nat Com 2020*

PERSPECTIVES:

- Identification of molecular defects responsible for autoimmunity
- Change the paradigm of therapies in jSLE
  from large population clinical trials to personalized therapy
- Drug repurposing
- Gene therapies in some monogenic SLE (CRISPR/CAS technology)

UNIQUE SELLING POINTS:

- Largest biobank for Juvenile Lupus hosted by the National Reference Center (Pr Belot)
- Integrated genomic and immune facilities in Lyon for clinical & translational use
- From basic research to first in human clinical trial

BLANCO Patrick

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UMR/CNRS 5164. ImmunoConcept.
University of Bordeaux

Towards a better understanding of inflammatory disorders pathogenesis, example of Systemic Lupus Erythematosus (SLE)

Keywords:

- T lymphocytes,
- Platelets,
- Autoimmunity,
- Systemic lupus erythematosus,
- Type I interferon,
- Antigen presenting cells,
- B lymphocytes.

Observations in the field of autoimmunity (systemic lupus erythematosus) are translated into scientific questions, addressed from in vitro to in vivo aspects, in order to fuel back innovative clinical trials.

Our research interest focus on clinical and basic research in the field of autoimmunity including systemic lupus erythematosus (SLE), and systemic sclerosis (SS) in close connection with our centre of reference for rare systemic autoimmune diseases. Our goals are not only to create new tools to help for a better diagnosis implementing artificial intelligence as an example but also to better understand their pathogenesis in order to propose innovative studies.
Our research encompass: creation of new tools to better diagnose SLE and SS, to better diagnose neuropsychiatric complications of SLE, to understand the implication of follicular helper T cells (Tfh) and peripheral helper T cells (Tph) in SLE pathogenesis, to understand new interactions of platelets with the immune system, to understand the implication of innate lymphoid cells in skin fibrosis, to implicate alternative differentiated macrophages in fibrosis, to evaluate the therapeutic value of cancer-derived peptides to treat autoimmune diseases.

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OBJECTIVES:

- A better characterization of T cell-dependent B cell response in SLE at the tissue level
- Implement new therapeutic targets in human SLE
- Better define the crosstalk between the coagulation pathway and the immune system in SLE

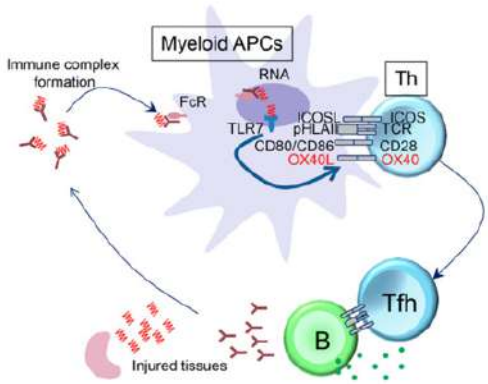
TOOLS:

- Center of reference for rare autoimmune systemic diseases (RESO)
- Ex vivo, in vitro & in vivo characterization of pathogenic pathways at work in SLE

A better characterization T cell-dependent B cell response in SLE at the tissue level

RESULTS:

- OX40L is expressed by antigen-presenting cell (APCs)
- OX40L promotes functional follicular helper T cell generation
- OX40L signaling blocks the immunosuppressive properties of regulatory T cells

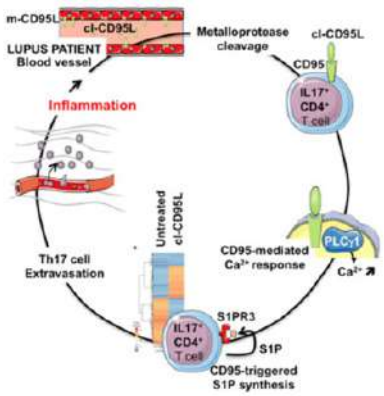


Jacquemin C., et al Immunity. 2015
Jacquemin C., et al JCI Insight. 2018

Implement new therapeutic targets in human SLE

RESULTS:

- Soluble FasL is increased in SLE patients
- Soluble FasL promotes the migration of Th17 cells in inflammatory tissues
- Soluble FasL is valuable target in SLE mouse models

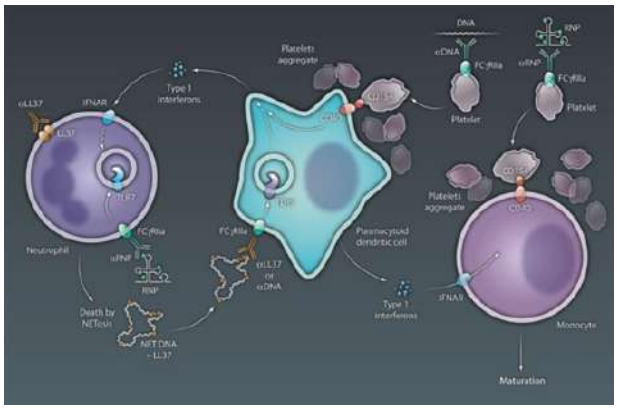


Sanséau D., et al Immunity. 2016 Poissonnier A., et al Nat Chem Biol. 2018

Better define the crosstalk between the coagulation pathway and the immune system in SLE

RESULTS:

- Platelets are activated in SLE patients by circulating immune complexes
- Activated platelets activate dendritic cells and block immunosuppressive properties of regulatory T regs
- P-selectin is a valuable target in SLE mouse models.



Scherlinger M. et al In revision

PERSPECTIVES:

- Immune profiling to better assess disease heterogeneity
- Integrate new treatments based on the discovery of new pathogenic loops
- Prevent long-term appearance of comorbidities

UNIQUE SELLING POINTS:

- International network
- Capacity to go from clinical observations, to fundamental question and back to the patients through innovative clinical trials
- Integrated immune characterization platform for routine and clinical use
- Scientists, physician scientists, and physician within the same team

BONIFACE Katia

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Crosstalk between inflammation, skin microenvironment, and pigment cells

Keywords:

- Vitiligo,
- Immunology of inflammatory skin diseases,
- Translational research,
- Multi-omics approaches ,
- New drug development,
- Biomarkers,
- Clinical research,
- Pre-clinical models,
- In vitro 3D model of depigmentation,
- Functional assays.

From basic to translational research to identify biomarkers and new therapeutic targets to treat vitiligo and depigmentation associated with skin inflammatory disorders.

Our research focuses on the understanding of the immune mechanisms underlying skin inflammatory diseases, in particular vitiligo, the most common skin depigmenting disease with high unmet needs. Based on a strong clinical research program dedicated to this disease in the department of dermatology of Bordeaux hospital, we developed basic and translational research studies aiming to better understand the immune physiopathology of vitiligo with the ultimate goal to identify biomarkers and new therapeutic targets.
Our projects highlighted the role of type I interferon during disease initiation together with the involvement of skin resident memory T cells expressing CXCR3 and NKG2D, a subset likely involved during flares of the disease. By combining translational research on patients tissues, in vitro 3D models and mouse pre-clinical models, we identified a new mechanism to explain melanocyte loss, involving inflammatory cytokines (TNF and IFN) and a so far uncovered role of matrix metalloprotease (MMP)-9 in destabilizing melanocyte adhesion. New therapeutic targets emerged as potential candidates (CXCR3, NKG2D, MMP9, JAK inhibitors). Patents have been published for the development of targeted therapies in vitiligo and close collaborations have been developed with national and international academic teams and industrial partners.
Ongoing studies aim at dissecting the role of the microenvironment in the crosstalk between immune and epidermal cells to decipher phenotypic and functional cellular changes observed in vitiligo patients skin. Interfering with pathways involved is of utmost importance for therapeutic perspectives. Lastly, our research could be generalized to pigmentation disorders affecting inflammatory skin diseases, such as psoriasis, atopic dermatitis, or scleroderma.

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- **Type-1 cytokines regulate matrix metalloprotease-9 production and E-cadherin disruption to promote melanocyte loss in vitiligo**. Boukhedouni N, Martins C, Darrigade AS, Drullion C, Rambert J, Barrault C, Garnier J, Thiolat D, Lucchese F, Morel F, Ezzedine K, Taieb A, Bernard FX, Seneschal J, Boniface K. JCI insight 2020 Jun;5(11):133772.doi: 10.1172/jci.insight.133772.
- **NKG2D defines a subset of skin effector memory CD8 T cells with pro-inflammatory functions in vitiligo.** Jacquemin C, Martins C, Lucchese F, Thiolat D, Taieb A, Seneschal J, Boniface K. J Invest Dermatol. 2020 Jun;140(6):1143-1153.e5. doi: 10.1016/j.jid.2019.11.013.
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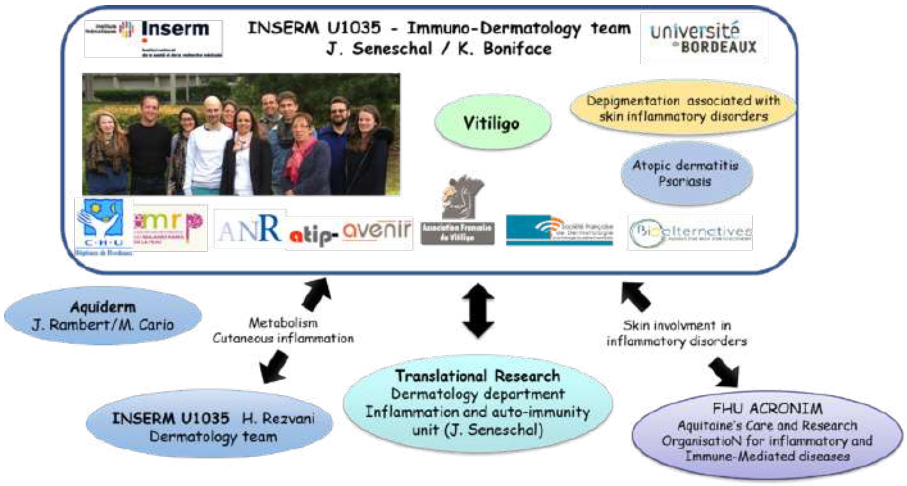
- **Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3.** Boniface K, Jacquemin C, Darrigade AS, Dessarthe B, Martins C, Boukhedouni N, Vernisse C, Grasseau A, Thiolat D, Rambert J, Lucchese F, Bertolotti A, Ezzedine K, Taieb A, Seneschal J. J Invest Dermatol. 2018;138(2):355-364. doi: 10.1016/j.jid.2017.08.038
- **Vitiligo: Focus on Clinical Aspects, Immunopathogenesis, and therapy.** Boniface K, Seneschal J, Picardo M, Taieb A. Clin Rev Allergy Immunol. 2018 Feb;54(1):52-67. doi:10.1007/s12016-017-8622-7.
- **Heat shock protein 70 potentiates interferon alpha production by plasmacytoid dendritic cells: relecance for cutaneous lupus and vitiligo.** Jacquemin C, Rambert J, Guillet S, Thiolat D, Boukhedouni N, Doutre MS, Darrigade AS, Ezzedine K, Blanco P, Taieb A, Boniface K, Seneschal J.Br J Dermatol. 2017 Nov;177(5):1367-1375. doi: 10.1111/bjd.15550.

OBJECTIVES:

- Characterization of the immune response defining vitiligo patients skin
- Deciphering the crosstalk between immune and epidermal cells
- Identification of new therapeutic targets
- Identification of biomarkers to stratify patients

TOOLS:

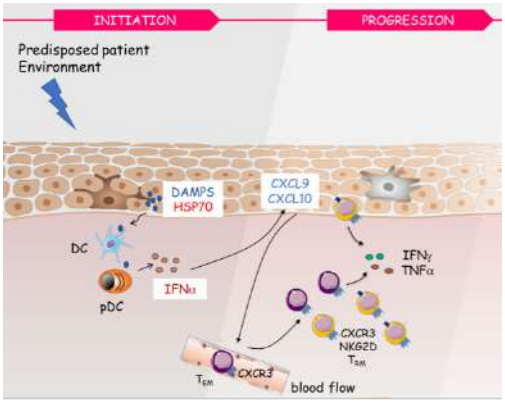
- In vitro (2D, 3D) culture models of epidermal cells and skin T cells
- In vivo pre-clinical models of depigmentation
- Healthy and patients samples (blood and skin specimens)
- Core facilities (transcriptomic, proteomics, FACS, microscopy)
- Functional assays (migration, proliferation, metabolic activities)



Characterization of the immune response defining vitiligo skin

RESULTS:

- Type 1 skewed immune response in vitiligo skin
- Infiltration of plasmacytoïd dendritic cells (pDC) important for disease initiation
- Presence of skin resident memory T cells (TRM) both in patients with stable and active disease, suggesting their involvment during disease progression and flares
- Moderate cytotoxic activity of infiltrated skin T cells
- Identification of therapeutic targets / biomarkers: CXCR3, NKG2D

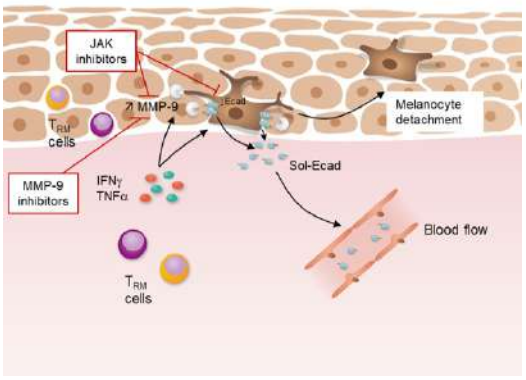


Vitiligo skin is defined by a type 1 skewed immune response. *Infiltration of plasmacytoid dendritic cells (pDC) able to mount high levels of interferon (IFN)-, inducing the recruitment of effector memory T cells (TEM) expressing CXCR3 through upregulation of chemokines expression by epidermal cells (CXCL9, CXCL10). Presence of melanocyte-specific resident memory T cells (TRM) expressing NKG2D, CXCR3, and producing high levels of type 1 cytokines (IFN, TNF).*

Characterization of the immune response defining vitiligo skin

RESULTS:

- New mechanism to explain melanocyte loss through disruption of E-cadherin expression and cleavage by type 1 cytokines produced by TRM cells
- Uncovered role of MMP-9 in melanocyte destabilization
- Identification of therapeutic targets: MMP-9, JAK signaling



Putative model of primary event leading to loss of melanocytes. *Type-1 cytokines TNF and IFN produced by activated TRM cells induce an E-cadherin defect in melanocytes. TNF and IFN induce the production of MMP-9 by epidermal cells, that cleaves E-cadherin (E-cad) to release its soluble form. E-cadherin cleavage leads to melanocyte destabilization. This effect is inhibited in the presence of MMP-9 or JAK inhibitors.*

PERSPECTIVES:

- Multi-omics approaches to characterize the phenotype and cellular changes in vitiligo skin
- Role of resident memory T cells during relapse of the disease
- Better understanding of the role of the microenvironment in vitiligo skin leading to the loss of melanocytes and the defect of melanocyte regeneration
- Interfering with key identified pathways to provide attractive therapeutic strategies

UNIQUE SELLING POINTS:

- Strong collaboration with Bordeaux's hospital: access to patients' samples
- Translational research involving in vitro and in vivo pre-clinical models
- Development of a 3D human model of vitiligo (patent)
- International and national collaborations, industrial partners
- Collaboration with vitiligo patients' organization
- Involvement in academic and industry-sponsored clinical trials

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Determination of the cellular and molecular pathophysiological mechanisms involved in autoantibody-mediated diseases: from in vitro/in vivo models to therapy of myositis and pemphigus

Keywords:

- Autoimmune diseases,
- Myositis,
- Immune-mediated necrotizing myopathy autoimmune bullous diseases,
- Pemphigus,
- Clinical research,
- Translational research,
- Animal models.

Our research aims at elucidating the cellular/molecular mechanisms involved in two groups of autoimmune diseases (myositis and skin bullous diseases) and ameliorating their treatment.

In myositis, we brought definitive evidence of the pathogenicity of anti-SRP and anti-HMGCR autoantibodies (aAbs) in immune-mediated necrotizing myopathy (IMNM). Patients' aAbs induce muscle fibre atrophy and impair myofiber regeneration in vitro. In the first in vivo humanized model of IMNM, we demonstrated that anti-SRP and anti-HMGCR aAbs are the main pathogenic effectors of disease, acting mostly through a complement-mediated mechanism. These results have led to a new understanding of the mechanisms of IMNM and preclinical therapeutic research is ongoing.
In autoimmune bullous diseases, our multicenter randomized study demonstrated that first-line use of rituximab, an anti-CD20 monoclonal antibody, is more effective than the standard high-dose of oral corticosteroid alone. We found that initial PDAI score and anti-desmoglein aAbs are predictors of relapse, leading to major changes in the management of pemphigus patients. Autoreactive B/T single cell transcriptome analysis and aAb pathogenicity are further investigated.

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- Modifications of the Transcriptomic Profile of Autoreactive B Cells From Pemphigus Patients After Treatment With Rituximab or a Standard Corticosteroid Regimen. Hebert V. et al. Front Immunol, 2019; 10:1794.
- B-cell depletion induces a shift in self antigen specific B-cell repertoire and cytokine pattern in patients with bullous pemphigoid. Berkani N. et al. Sci Rep, 2019; 9:3525.

OBJECTIVES:

- Understand pathogenesis of aAb-mediated diseases
- Ameliorate therapy

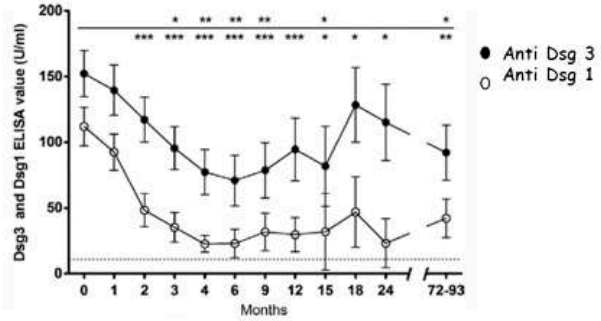
TOOLS:

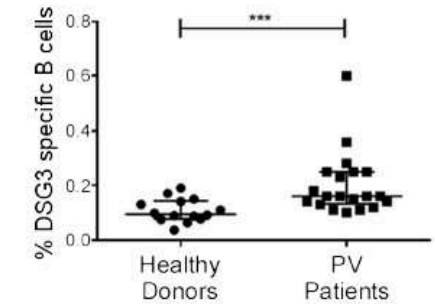
- Development of immunoassay (Albia/Luminex)
- Cell sorting –Elispot
- Autoantibody characterization
- Isolation of antigen specific B cells (single cell)
- In vitro cellular models
- In vivo animal models

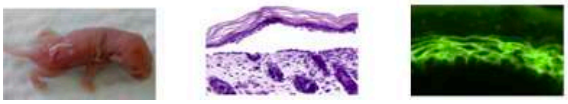
Cellular and molecular pathophysiological characterization

RESULTS: PEMPHIGUS

- Rituximab treatment reduces aAb level and induces long-term complete remission
- Antigen-specific B cells have distinct transcriptomic profile
- Autoantibodies are pathogenic

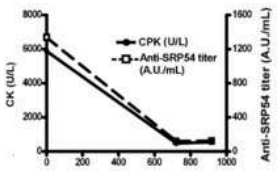


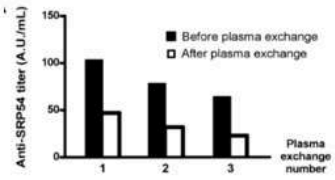


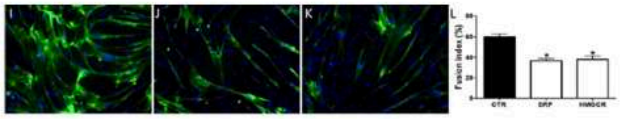


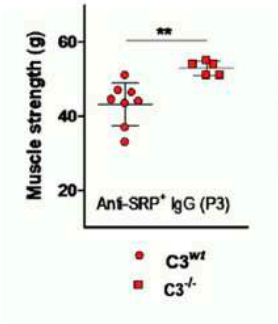
RESULTS: NECROTIZING AUTOIMMUNE MYOPATHIES

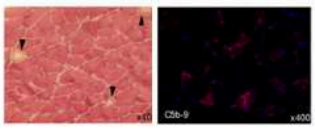
- Autoantibody titers correlate with disease severity
- Autoantibodies impair muscle regeneration
- Autoantibodies are pathogenic in vivo through a complement-mediated mechanism











PERSPECTIVES:

- delineate the pathogenic roles of autoreactive B cells and aAbs through:
  (i) experimental studies based on animal immunization or autoantibody/cell transfer, as well as spontaneous autoimmune animal models or new models under development
  (ii) translational studies with in-depth characterization of human autoreactive B cell responses at the bulk and single cell level and structural/functional features of aAbs isolated from patients
- evaluate therapies (targeted to B cells, Ig, complement) through:
  (i) in vitro cellular models
  (ii) in vivo animal models

UNIQUE SELLING POINTS:

- National and international network on myositis and pemphigus
- Center of Excellence of the Federation of Clinical Immunology Societies (FOCIS)
- Unique immunoassays for autoantibodies
- Muscle and skin cellular models
- Humanized animal models
- Capacity to go from basic research to clinical trials

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INSERM

Genetic-based disorders of the human intestinal barrier

Keywords:

- Gut barrier,
- Intestinal immunity,
- Coeliac disease,
- Autoimmunity,
- Very early onset inflammatory bowel diseases ,
- Congenital diarrhoea,
- Genetic studies,
- Host-microbiota interactions,
- Gnotobiotic mouse models.

To identify mechanisms of diseases impairing the intestinal barrier and guide diagnostic and personalized care.

Our research combines the study of human diseases and of animal models to delineate the mechanisms that promote, maintain and restore the intestinal barrier and to improve diagnostic and care of severe intestinal diseases. In celiac disease, we study how cytokines can impair local immunoregulation and select for somatic mutations that drive lymphomagenesis. Through the identification and characterisation of constitutional mutations that impair the epithelial and immune components of the gut barrier; we intend to establish the repertoire of genes and pathways that participate in the human gut barrier and to build an atlas of signatures that may allow to stratify patients with severe intestinal diseases and guide personalized therapy. In parallel, we analyse how the gut microbiota influences the post-natal maturation of the gut immune barrier through the use of gnotobiotic mouse models and intend to study how the microbiota may influence the onset and severity of genetic diseases of the gut barrier.

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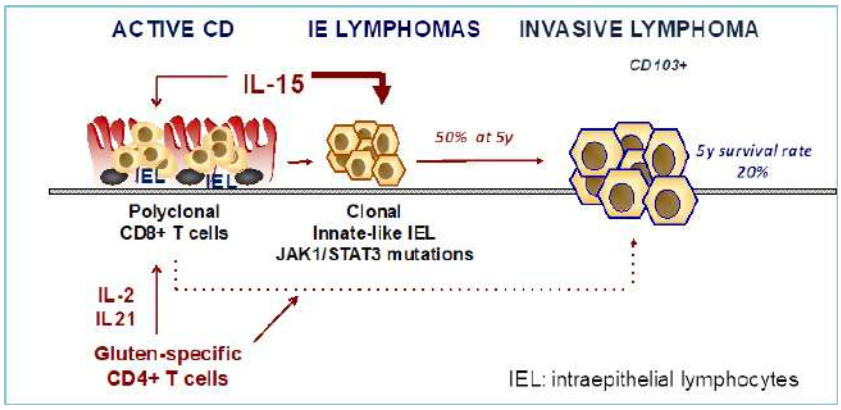
OBJECTIVE:

- To identify mechanisms of diseases impairing the intestinal barrier and provide rationale based therapy

TOOLS:

- Cohorts of well-phenotyped pediatric and adult patients with severe enteropathies
- Genotyping of constitutive and somatic mutations (targeted and non targeted NGS).
- Functional studies including single-cell transcriptomics (blood, intestinal biopsies). iPSC-derived intestinal organoids.
- Mouse models (including gnotoxenic mice), zebrafish models (in collaboration)

Dissecting the mechanisms of tissue damage and malignant transformation in coeliac disease



Pathogenesis ot coeliac disease and its malignant complications`

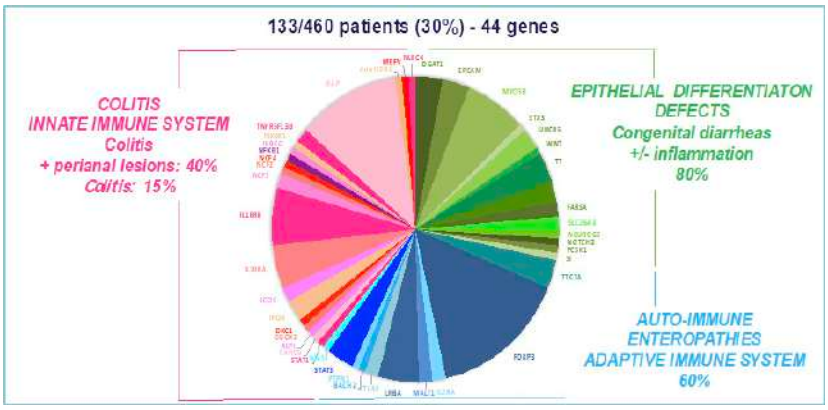
RESULTS:

- Intestine-derived IL-15 impairs immunoregulation and cooperates with antigen-specific CD4+ T cells to drive non cognate activation of CD8 T cells and autoimmune-like tissue damage
- Resistance to gluten-free diet results from malignant transformation of IL-15-dependent innate-like lymphocytes containing somatic JAK1 or and STAT3 mutations. NKP46 expression provides a diagnosis marker to detect lymphoma at the intraepithelial stage in tissue sections

Dissecting genetic defects impairing the human gut barrier

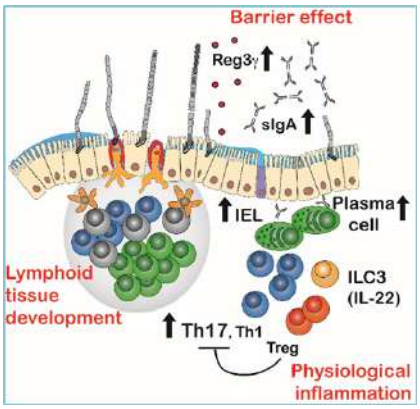
RESULTS:

- Identification of causal monogenic disorders in over 30% of children developing severe chronic diarrhea with or without inflammation before the age of 6 years (60-80% in diseases of the small intestine; 15-40% in colonic diseases)
- Identification of causal monogenic disorders in 40% of adult patients with non celiac severe enteropathies
- Identification of 6 novel gene defects
- Stratification of affected pathways depending on presentation
- Successful use of JAK inhibitor in enteropathy due to STAT3 gain of function mutation



Distribution, phenotype-genotype comparison and yield of genetic diagnoses ih the pediatric cohort of severe chronic diarrhea (adapted from Charbit-Henrion et al JCC 2018)

Defining the role of the microbiota in the development of the gut immune barrier



Role Segmented filamentous bacteriium
In the post natal development of the gut barrier

RESULTS:

- Identification of the unique role of Segmented Filamentous bacteria in driving the coordinated development of homeostatic gut innate and adaptive immune responses and setting a state of physiological inflammation indispensable to build an efficient gut barrier in mice

PERSPECTIVES:

- To analyze mechanisms controlling progression of lymphomas complicating coeliac disease and improve early diagnosis and therapeutic efficacy.
- To pursue identification of signaling pathways and therapeutic targets in severe diseases of the intestinal barrier in pediatric and adult cohorts.
- To describe the human version of segmented filamentous bacterium and more generally to define how microbiota influences onset and expression of genetic-based intestinal disorders.
- To translate results from monogenic to complex intestinal inflammatory disorders in order to improve patients' stratification and guide therapeutic choice
- To set up pharmacological approaches in order to improve care of developmental defects of intestinal epithelium.

UNIQUE SELLING POINTS:

- Pediatric and adult cohorts of patients with severe enteropathies
- Methods to identify and characterize severe diseases affecting the hematopoietic and epithelial components of the human gut barrier
- Development of therapeutic approaches for epithelial developmental disorders
- Possibility to test therapeutic approaches in pediatric IBD and rare intestinal diseases

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Host / microbiota interaction in chronic inflammatory diseases

Keywords:

- Microbiota,
- Inflammation,
- Metabolism,
- Mucus.

Environmental factors-mediated modulation of the intestinal microbiota
We are studying environmental factors that can impact the intestinal microbiota. We have previously reported that emulsifiers, highly used by the food industry, are able to detrimentally alter the intestinal microbiota, characterized by an increased ability to penetrate the normally protective mucus layer and an increase pro-inflammatory potential. We reported that the consumption of emulsifying agent is sufficient to induce intestinal inflammation that will manifest as chronic colitis in genetically susceptible host. Moreover, in unimpaired host, such food additives are inducing the development of metabolic syndrome characterized by diabetes and an increase in body weight, as well as by an increased susceptibility to colonic carcinogenesis. We are now working on the mechanism by which an altered microbiota can drive chronic inflammatory diseases

Innate immunity / microbiota relationship in health and disease
We have studied for many years how the host is controlling the intestinal microbiota in order to keep it under control and at a proper/safe distance from the intestinal mucosa. We have for example demonstrated that the flagellin receptor TLR5 is playing a central role in keeping the intestinal microbiota under control.

Modulation of the intestinal microbiota using pre- and pro-biotics approaches
While our research is mainly focusing on detrimental impacts of the microbiota, our expertise in this field of research, our data-set of identified detrimental bacteria and metabolites, as well as the numerous animal models available in the laboratory lead us to work on the development of tools aiming to beneficially alter the intestinal microbiota to promote health.

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- Intestinal Epithelial cell Toll-like Receptor 5 Regulates the Intestinal Microbiota to Prevent Low-grade Inflammation and Metabolic Syndrome in Mice. Chassaing et al. **Gastroenterology**, 2014.
- Prevention and cure of rotavirus infection via TLR5/NLRC4–mediated production of IL-22 and IL-18. Zhang, Chassaing et al. **Science**, 2014.

OBJECTIVES:

- Understand mechanisms by which the intestinal microbiota promotes chronic intestinal inflammation
- Identify modern stressors of the intestinal microbiota
- Characterize inter-individual variations in microbiota composition

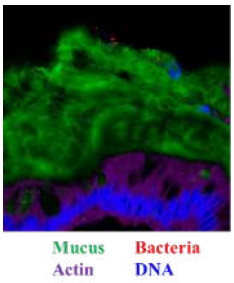
TOOLS:

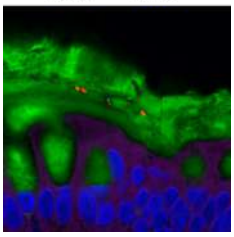
- Compositional and functional characterization of the intestinal microbiota
- Gnotobiotic facility
- Innovative *in vitro* microbiota systems

Role of the mucosal microbiota in chronic inflammatory diseases

RESULTS:

- A microbiota able to penetrate the normally sterile mucus layer is associated with detrimental effects on the host
- Only select members of the intestinal microbiota are able to penetrate the normally sterile mucus layer

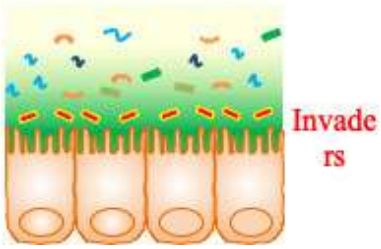




PERSPECTIVE:

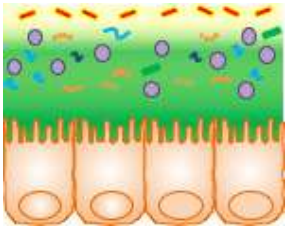
- The Identification of these bacteria is ongoing in our laboratory

Prevention of microbiota encroachment



RESULTS:

- A microbiota able to penetrate the normally sterile mucus layer is associated with detrimental effects on the host
- Only select members of the intestinal microbiota are able to penetrate the normally sterile mucus layer



PERSPECTIVE:

- We are also investigating innovative ways to prevent / revert microbiota encroachment through targeted modulation of the intestinal microbiota

Understand inter-individual variations in microbiota composition and functions

RESULTS:

- Each individual harbor a unique intestinal microbiota
- Inter-individual variations in microbiota composition and functions are playing central roles in response to perturbations

PERSPECTIVE:

- Our innovative *in vitro* microbiota system allow us to characterize inter-individual variations in microbiota composition and functions for future precision in medicine and nutrition

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Ph.D

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Harnessing inflammation through cell mobility control

Keywords:

- Chemokines,
- Receptors,
- Migration,
- Antagonists,
- Monocytes,
- Anti-inflammatory drugs,
- imaging tools.

Defining the molecular and cellular processes that normally function to enhance, limit or resolve inflammation is essential and can lead to useful therapies.

Inflammation is a hallmark of numerous human diseases and a key aspect of it is trafficking of immune cells into and out of the specific injured tissues. Thus, the challenge for the future will be to identify the trafficking molecules that will most specifically inhibit the key subsets of cells that drive disease processes without affecting the migration and function of leukocytes required for protective immunity. Chemokines (CK) are typical immune and inflammatory mediators that not only allow a rapid and appropriate leukocyte migration to emergency signals but also control cellular responses. CK and their receptors (CKR) are central to the inflammatory process and are thus attractive targets for the pharmaceutical industry.
Our research program aims to establish the evidence that the CK-based therapy could become a new way of treatment of inflammatory diseases. It includes four approaches; 1) structural and functional analysis of inflammatory CK and CKR, 2) ex vivo studies that analyze the role of CK/CKR on subsets of leukocytes in human diseases, 3) in vivo studies that characterize the role of CK/CKR in inflammatory mouse models, and 4) the development of CK/CKR-based therapeutic tools.
The project pipeline, from molecular analysis, proof-of-principle evaluation in murine models to valorization, is taking advantage of new short peptide-based antagonist candidates that have already shown strong efficacy in limiting monocyte infiltration in organs.

SELECTED BIBLIOGRAPHY:

- Chemokine receptor 2-targeted molecular imaging in pulmonary fibrosis. Brody S.L. et al. **Am. J. Respir. Crit. Care Med. 2020**
- CX3CL1 homo-oligomerization drives cell-to-cell adherence. Scientific report. Ostuni M.A. et al. **Sci Rep. 2020 Jun 3;10(1):9069.**
- PET-based imaging of Chemokine receptor-2 in experimental and disease-related lung inflammation. Liu Y. et al. **Radiology 2017 Jan 3:161409.**
- Plasmodium falciparum proteins involved in cytoadherence of infected erythrocytes to chemokine CX3CL1. Hermand P. et al. **Sci. Rep. 2016**
- ECL1i, d(LGTFLKC), a novel, small peptide that specifically inhibits CCL2-dependent migration. Auvynet C.et al. **FASEB J. 2016 Jun;30(6):2370-81.**
- CX3CR1 deficiency promotes muscle repair and regeneration by enhancing macrophage ApoE production. Arnold L. et al. **Nat. Commun. 2015 Dec 3;6:8972.**
- Ly6Chigh monocytes protect against kidney damage during sepsis via a CX3CR1-dependent adhesion mechanism. Chousterman B.G. et al. **J. Am. Soc. Nephrol. 2015**

Controlling Inflammation

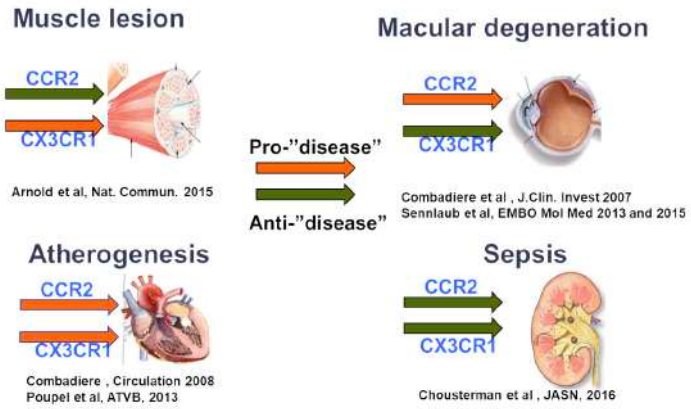
OBJECTIVES:

- Characterize the molecular codes that control immune cell trafficking,
- Characterize the spatio-temporal orchestration of the inflammatory response,
- Develop immune selective pro- and anti-migration drugs,
- Develop Immune-selective tools to visualize inflammation

TOOLS:

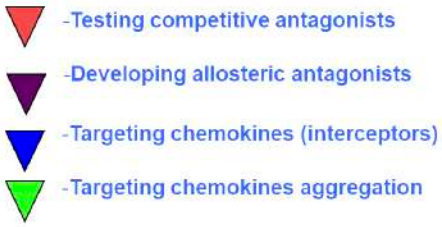
- Screen for selective agonists and antagonists of the chemokine pathways
- Receptor/ligand in silico modelization
- Murine Models of inflammation
- In vivo imaging

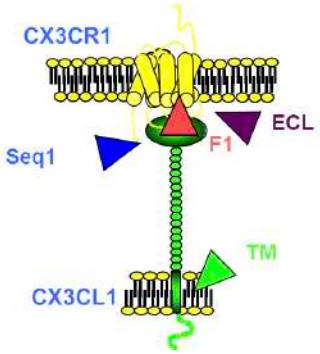
Role of CCR2 and CX3CR1 in pathologies



Developping molecular tools to control cell mobility

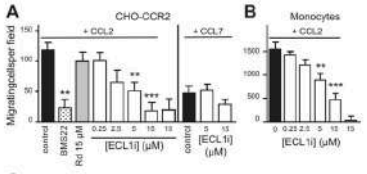
RESULTS:

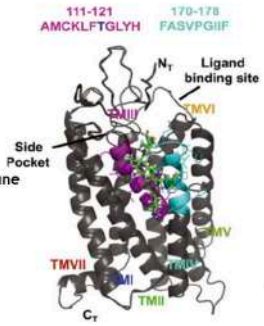




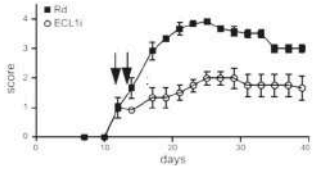
Allosteric inhibition of CCR2-expressing inflammatory cells

- ECL1i is the first small peptidic CCR2 allosteric antagonist





- ECL1i blocks the progression of experimental autoimmune encephalomyelitis (EAE)



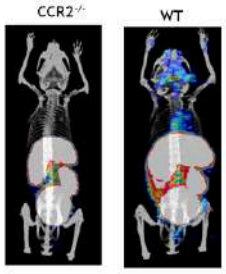
Auvynet et al, FASEB J. 2016
European Patent No. 11305816.8,

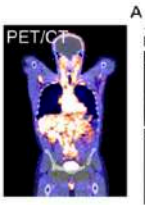
RESULTS:

- ECL1i is the first non invasive imaging peptide for CCR2 expressing cells

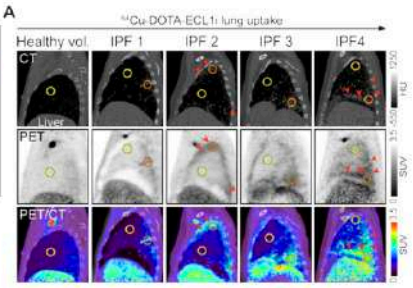
Non Invasive imaging of inflammatory cells in lung

In mice





In human



Brody et al, AJRCCM. 2020

Liu et al, Am. J. Transplant 2016

Liu et al, Radiology, 2017

Heo et al, Circ. Res. 2018

In collaboration with Washington University (St Louis, MO)
Yongjian Liu, PhD and Steven Brody, MD

PERSPECTIVES:

- Better characterizing the spatio-temporal orchestration of the inflammatory responses
- Redefining the molecular and cellular processes that control inflammatory cells dynamic and functions during inflammation.
- Modulating deployment of inflammatory cells through chemokine axis
- Improving patient's quality of life by accelerating remission, relief and regeneration

UNIQUE SELLING POINTS:

- Three decades of chemokine/chemokine receptor expertise,
- Unique combinations of reporter murine models to discriminate the different inflammatory cells,
- Original molecular tools to modulate migration and functions of inflammatory cells,
- Original molecular tools to visualize inflammatory cells in vivo,
- Integrated settings to study inflammation from murine preclinical models to clinical studies

DECHELOTTE Pierre

INSERM 1073, CHU Rouen

Nutrition, Inflammation and dysfunction of the gut-brain axis

DEJEAN Anne S.

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Inserm U1043 - CNRS UMR5282 - Université Toulouse III
INSERM

Inflammatory diseases of the Central nervous system

Keywords:

- Neuroinflammation,
- Neurodegeneration,
- Immunology,
- Transcription factor,
- Metabolism,
- Multi-Omics studies (RNA-Seq, ATAQ-Seq).

Our main interest is to determine the molecular mechanisms whereby pathogenic properties are acquired by immune cells in the CNS using experimental model of neuroinflammation and neurodegeneration as well as patient samples.

Our team is composed of physicians and scientists sharing a long-lasting interest in deciphering the pathophysiology of inflammatory diseases that target the central nervous system (CNS), with the ambition to propose new therapeutic strategies. Our projects are based on the development of novel and original animal models of neuroinflammation, neurodegeneration and on biological material collected from patients with neurological disorders.
Our current project aims to uncover the mechanisms by which T cells accumulate in tissues and contribute to tissue damage and chronicity of immune-mediated disorders. This project relies on metabolomic and fluxomic analysis, as well as transcriptomic and epigenetic studies. These Multi-Omics data will be integrated and validated to provide a more comprehensive understanding of the molecular mechanisms whereby metabolic checkpoints regulate T cell persistence and function in tissue during chronic inflammatory diseases.

SELECTED BIBLIOGRAPHY:

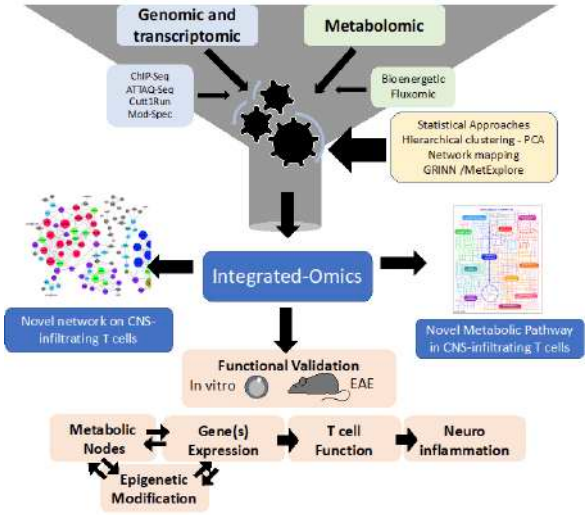
- Eomes-Dependent Loss of the Co-activating Receptor CD226 Restrains CD8+ T Cell Anti-tumor Functions and Limits the Efficacy of Cancer Immunotherapy.Weulersse M, Asrir A, Pichler AC, Lemaitre L, Braun M, Carrié N, Joubert MV, Le Moine M, Do Souto L, Gaud G, Das I, Brauns E, Scarlata CM, Morandi E, Sundarrajan A, Cuisinier M, Buisson L, Maheo S, Kassem S, Agesta A, Pérès M, Verhoeyen E, Martinez A, Mazieres J, Dupré L, Gossye T, Pancaldi V, Guillerey C, Ayyoub M, **Dejean AS**, Saoudi A, Goriely S, Avet-Loiseau H, Bald T, Smyth MJ, Martinet L. Immunity. 2020 Oct 13;53(4):824-839.e10. doi: 10.1016/j.immuni.2020.09.006.
- Foxo3 Transcription Factor Drives Pathogenic T Helper 1 Differentiation by Inducing the Expression of Eomes.Stienne C, Michieletto MF, Benamar M, Carrié N, Bernard I, Nguyen XH, Lippi Y, Duguet F, Liblau RS, Hedrick SM, Saoudi A, **Dejean AS**.Immunity. 2016 Oct 18;45(4):774-787. doi: 10.1016/j.immuni.2016.09.010. Epub 2016 Oct 11.
- A spontaneous mutation of the rat Themis gene leads to impaired function of regulatory T cells linked to inflammatory bowel disease.Chabod M, Pedros C, Lamouroux L, Colacios C, Bernard I, Lagrange D, Balz-Hara D, Mosnier JF, Laboisse C, Vergnolle N, Andreoletti O, Roth MP, Liblau R, Fournié GJ, Saoudi A, **Dejean AS**.PLoS Genet. 2012 Jan;8(1):e1002461. doi: 10.1371/journal.pgen.1002461. Epub 2012 Jan 19.PMID: 22275874
- The p.Arg63Trp polymorphism controls Vav1 functions and Foxp3 regulatory T cell development.Colacios C, Casemayou A, **Dejean AS**, Gaits-Iacovoni F, Pedros C, Bernard I, Lagrange D, Deckert M, Lamouroux L, Jagodic M, Olsson T, Liblau RS, Fournié GJ, Saoudi A.J Exp Med. 2011 Oct 24;208(11):2183-91. doi: 10.1084/jem.20102191. Epub 2011 Sep 26.PMID: 21948080 **Free PMC article.**
- Transcription factor Foxo3 controls the magnitude of T cell immune responses by modulating the function of dendritic cells.**Dejean AS**, Beisner DR, Ch'en IL, Kerdiles YM, Babour A, Arden KC, Castrillon DH, DePinho RA, Hedrick SM.Nat Immunol. 2009 May;10(5):504-13. doi: 10.1038/ni.1729. Epub 2009 Apr 12.PMID: 19363483

OBJECTIVES:

- Decipher the mechanisms whereby immune cells acquire pathogenic functions in the central nervous sytem (i.e. neuroinflammation and neurodegeneration)
- Demonstrate the relevance of our results to human pathology (MS)
- Provide rational basis for new drugs development in neuroinflammatory and neurodegenerative diseases

TOOLS:

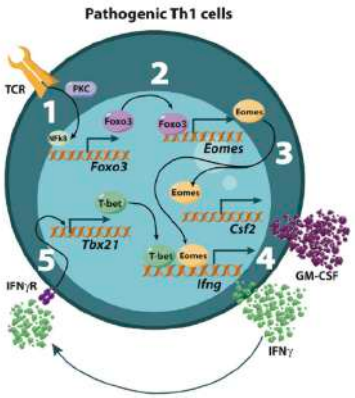
- Murine model of neuro-inflammation and neurodegeneration
- Immunophenotyping (Multicolor Flow cytometry using Symphony)
- Multiple 'Omics' analyses (RNA-Seq, ChIP-Seq, ATAQ-Seq, Cut&Run)
- Metabolomic studies (SeaHorse, MNR, Mass Spectrometry)
- Bioinformatic, pathway analysis and data integration
- Molecular biology (siRNA, lentivirus…)



Subject 1: Foxo3 Transcription Factor Drives Pathogenic T Helper 1 Differentiation by Inducing the Expression of Eomes

RESULTS:

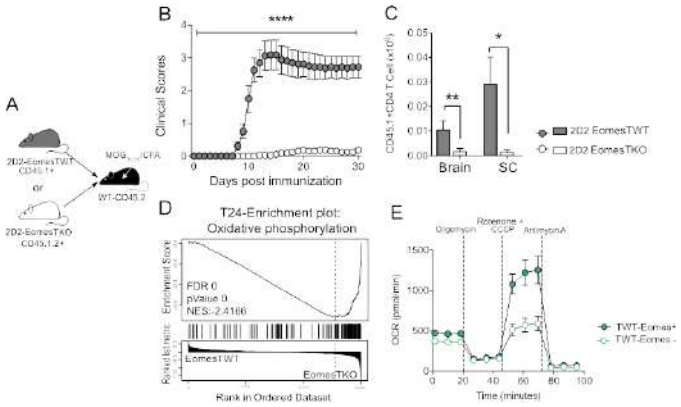
- Strength of TCR signal controls Foxo3 expression in effector CD4+ T cells
- Foxo3 drives pathogenic Th1 cell differentiation through direct regulation of Eomes
- Foxo3 and Eomes act independently of T-bet for pathogenic Th1 cell differentiation
- Foxo3 controls the susceptibility to neuroinflammation



Subject 2: Eomes controls chronic CNS inflammation by increasing survival of effector CD4 T cells through the regulation of mitochondrial metabolism

RESULTS:

- Eomes deletion in CD4 T cells protects from neuroinflammation
- Eomes controls long-term survival and persistence of CNS-infiltrating CD4 T cells
- Eomes drives mitochondrial metabolism
- Eomes links mitochondrial metabolism and cell longevity by regulating glutathione antioxidative response



(A) Naive 2D2-Eomes-TWT or 2D2-Eomes-TKO cells (CD45.1) were injected into CD45.2 C57BL/6 mice and Recipient mice were immunized. (B) clinical scores were evaluated and (C) absolute number of 2D2 cells were assessed at 15-dpi. (D) GSEA related to genes involved in oxidative phosphorylation of RNA-sequencing performed on Eomes-TKO and Eomes-TWT cells and (E) measure of mitochondrial respiration by activated CD4 T cell from EomesGFP mice purified according to GFP expression

PERSPECTIVES:

- Metabolomic characterization of CNS-infiltrating cells
- Understand how metabolic adaptation impacts immune cell functions
- Provide a comprehensive picture of the Eomes role in the connection between CD4 T cell metabolic reprogramming associated with CNS invasion and transcriptomic and epigenetic regulation.
- Demonstrate the relevance of our results to human pathology

UNIQUE SELLING POINTS:

- Expertise in animals' model of Inflammation, auto-immunity and neurodegenration
- Physiopathology (Immunophenotyping, cellular and molecular mechanisms)
- Translational Immunology (human cohort of Multiple sclerosis)
- Test of new drugs (Preclinical studies and mechanisms)
- Immunotherapies (Antibodies, cytokines)

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Inserm

From bench to bedside: use antimicrobial peptides to tackle autoimmune diseases

Keywords:

- Innate immunity,
- Autoimmune diseases,
- Antimicrobial peptides,
- Type 1 diabetes.

From bench to bedside: use antimicrobial peptides to tackle autoimmune diseases.

Our research explores original aspects of the immunopathology of autoimmune diseases. We investigate the complex interaction between the immune system and the microbiota that plays a major role in the development of autoimmunity. Our group is focused on antimicrobial peptides that are key molecules of the innate immune system. Through their immunomodulatory and microbicide capacities, they occupy a central place in the maintenance of the homeostasis between the microbiota and the immune system. During the past years, using preclinical models, we revealed whether antimicrobial peptides are crucial in the protection against autoimmune diabetes. We propose that these molecules may represent attractive therapeutic tools against autoimmune diseases and other microbiota-associated diseases.

SELECTED BIBLIOGRAPHY:

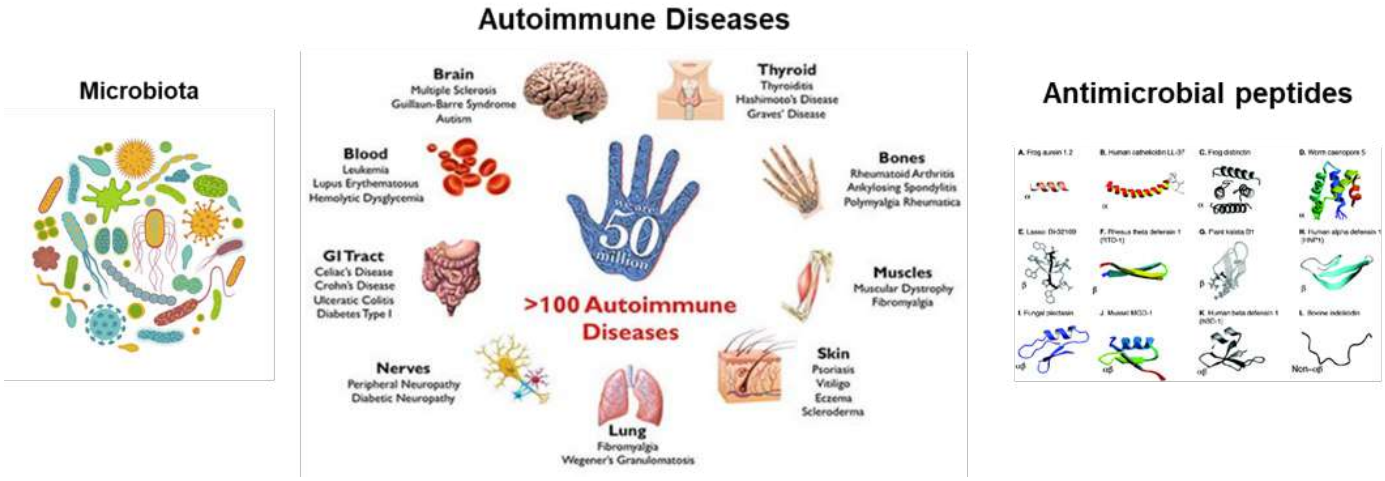
- **The Dual Role of Antimicrobial Peptides in Autoimmunity.** Liang W, **Diana J**. *Front Immunol.* 2020, PMID: 32983158
- **Gut Microbiota-Stimulated Innate Lymphoid Cells Support β-Defensin 14 Expression in Pancreatic Endocrine Cells, Preventing Autoimmune Diabetes.** Miani M, Le Naour J, Waeckel-Enée E, Verma SC, Straube M, Emond P, Ryffel B, van Endert P, Sokol H, **Diana J.** *Cell Metab.* 2018, PMID: 30017352
- **Pancreatic β-Cells Limit Autoimmune Diabetes via an Immunoregulatory Antimicrobial Peptide Expressed under the Influence of the Gut Microbiota.** Sun J, Furio L, Mecheri R, van der Does AM, Lundeberg E, Saveanu L, Chen Y, van Endert P, Agerberth B, **Diana J**. *Immunity*. 2015, PMID: 26253786
- **Crosstalk between neutrophils, B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes. Diana J,** Simoni Y, Furio L, Beaudoin L, Agerberth B, Barrat F, Lehuen A. *Nat Med.* 2013, PMID: 23242473

OBJECTIVES:

- To determine the role of antimicrobial peptides in autoimmune diseases.
- To determine the role of gut microbiota in extraintestinal diseases.
- To build antimicrobial peptide-based therapy against autoimmune diseases.

TOOLS:

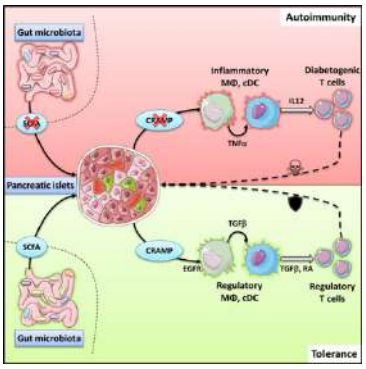
- Preclinical animal models and patient samples.
- Transcriptomic analysis of affected tissues.
- 16s RNA sequencing and metabolomic analysis for microbiota characterization.



Pancreatic b-cells limits autoimmune diabetes via an immunoregulatory antimicrobial peptide expressed under the influence of the gut microbiota.

RESULTS:

- Pancreatic b-cells express the cathelicidin-related antimicrobial peptide (CRAMP).
- CRAMP is protective in the adult NOD mice, a model for type 1 diabetes.
- CRAMP converts inflammatory into regulatory immune cells in the pancreas.
- The gut microbiota via short-chain fatty acids governs CRAMP production by b-cells.

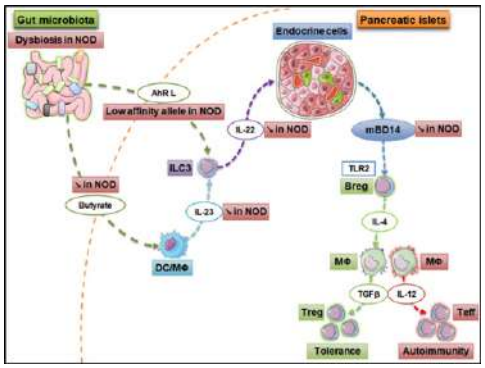


Cathelicidin expressed by the pancreatic endocrine cells is protective against autoimmune. The gut microbiota governs this expression maintaining immune homeostasis in peripheral tissues.

Gut Microbiota-Stimulated Innate Lymphoid Cells Support b-defensin 14 Expression in Pancreatic Endocrine Cells Preventing Autoimmune Diabetes.

RESULTS:

- MBD14 is expressed by pancreatic endocrine cells but poorly in NOD mice.
- MBD14 treatment of NOD mice dampens the autoimmune response and diabetes.
- Pancreatic innate lymphoid cells (ILCs) stimulates mBD14 expression via IL-22.
- Gut microbiota-derived metabolites control IL-22-secretion by pancreatic ILCs.



The b-defensin 14 expressed by pancreatic endocrine cells prevents the development of autoimmune diabetes in NOD mice. The expression of this immunoregulatory b-defensin is controlled by a complex interplay between the gut microbiota, and pancreatic-resident innate lymphoid cells.

PERSPECTIVES:

- Extend our knowledge on antimicrobial peptides to other autoimmune disease contexts.
- Explore the potential of antimicrobial peptides to adjust the pathogenic microbiota in autoimmune context.
- Use our knowledge on antimicrobial peptides to build therapeutic approaches against autoimmune diseases.

UNIQUE SELLING POINTS:

- Unique expertise on antimicrobial peptides in autoimmune context.
- Development of innovative mouse models and patient samples.
- Potential for translation of our research to clinical practice.

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Ph.D

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Immuno-metabolic cross-talk in metabolic and cardiovascular diseases and comorbidities

Keywords:

- Immunometabolism,
- Inflammation,
- Metabolic and cardiovascular diseases and comorbidities,
- Nuclear receptors,
- Patho-physiology,
- Preclinical models,
- Translational studies,
- NAFLD/NASH,
- Psoriasis,
- Allergic diseases.

We study the cellular and molecular mechanisms of the immuno-metabolic cross talk taking place in metabolic and cardiovascular diseases and their comorbidities using multidisciplinary approaches, preclinical models and human cohorts with an emphasis on patho-physiology.

The immuno-inflammatory and metabolic systems are tightly linked, as revealed by the frequent co-morbidities between (auto)inflammatory or (auto)immune diseases and metabolic pathologies and their cardiovascular complications. Nuclear receptors are transcriptional regulators that control immune and metabolic processes and are therapeutic targets of choice. Our research aims to identify and elucidate the keys to the immuno-metabolic dialogue, and in particular the contribution of nuclear receptors expressed by immune cells in various pathophysiological contexts related to metabolism (obesity, type 2 diabetes, atherosclerosis, NAFLD/NASH...) and its co-morbidities. Using multidisciplinary approaches (in vivo and in vitro models, transcriptomic and metabolomic analyses...), we discovered how fatty acids from the metabolic environment modulate the innate immune response through triggering of a specific UPR-mediated Integrated Stress Response and demonstrated their role in psoriasis exacerbation (Mogilenko et al., ***Cell***, 2019). We identified a specific transcriptomic and cellular signature of the transition from benign steatosis to NASH in humans and in a preclinical model with cDC subsets and cytotoxic CD8 T cells as hallmarks (Haas, et al., ***Nat. Metab.***, 2019). We discovered that Innate Lymphoid Cells as essential for aggravation of allergic asthma by obesity (Everaere et al., ***JACI***, 2016). We unraveled the key role of CX3CL1-CX3CR1 axis for CD4 T cell function in allergic asthma and atopic dermatitis (Mionnet et al., ***Nat. Med.***, 2010, Staumont-Salle et al., ***J. Exp. Med***, 2014). We established a Metabolic ImmunoPhenotyping Platform equipped with state of the art flow and mass cytometrs. We are implementing single cell "omics" approaches to further elucidate the contribution of immunity to NAFLD/NASH.

SELECTED BIBLIOGRAPHY:

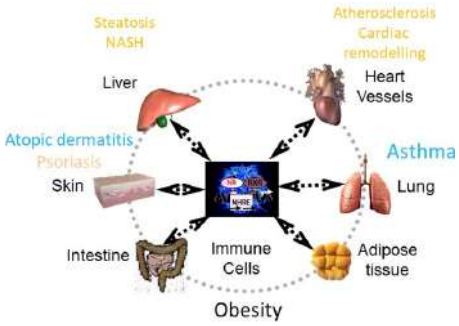
- Metabolic and innate immune cues merge into a specific inflammatory response via UPR. Mogilenko, D.A, et al. 2019. **Cell.** 177:1201-1216 (with editorial material). Avancée de l'Inserm 2019
- Transcriptional network analysis implicates altered hepatic immune function in NASH development and resolution. Haas, J. T., et al. 2019. **Nat Met.** 1:610-614
- Keratinocyte expression of A20/TNFAIP3 controls skin inflammation associated with atopic dermatitis and psoriasis. Devos, M et al. 2019. **J Invest Dematol** 139:135-45.
- Innate lymphoid cells contribute to allergic airway disease exacerbation by obesity. Everaere, L. 2016. J **Allergy Clin Immunol.** 138:1309-1318 e1311(with editorial material).

OBJECTIVES:

- Decipher the underlying mechanisms of immune contribution to metabolic and cardiovascular diseases
- Assess how metabolism and its alterations impact on immune function and chronic inflammatory diseases
- Evaluate the contribution of immune-expressed nuclear receptors in metabolic and chronic inflammatory diseases
- Unravel potential therapeutic targets

TOOLS:

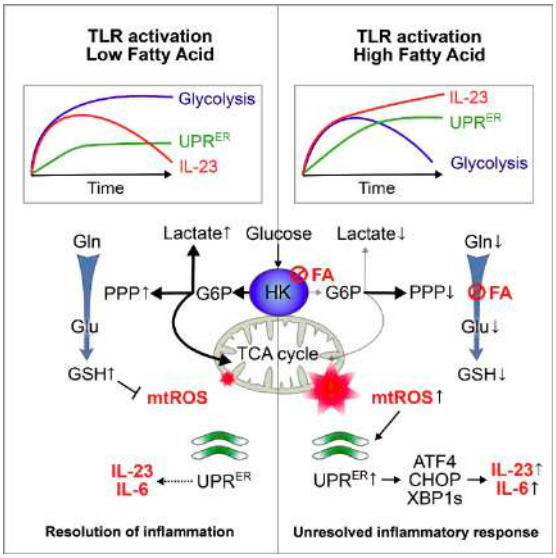
- Preclinical models of metabolic and inflammatory diseases
- (Immune) Cell-specific gene targeting in mice and vitro
- Translational studies in metabolic cohorts
- Immune profiling (cytometry, extracellular fluxes)
- Transcriptomics
- Metabolomics
- Bioinformatics



Exacerbation of innate immune response and psoriasis by fatty acids

RESULTS:

- Extracellular fatty acids inhibit hexokinase activity and rewire metabolism in late TLR activation
- Fatty acid-mediated adaptation of glycolysis leads to perturbed mitochondrial fitness
- Metabolic adaptation and mitochondrial ROS exacerbate TLR-induced Unfolded Protein Response activation
- The UPR links metabolic alterations to a distinct inflammatory signature
- TLR-induced psoriasis is exacerbated in an UPR-dependent manner by high fat diet feeding in mice.

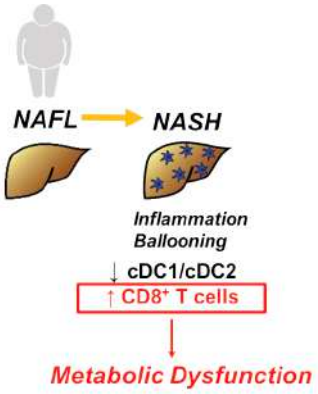


High fatty acid (FA) concentrations increase a TLR-induced inflammatory response characterized by IL-23 production through direct hexokinase (HK) and glycolysis inhibition and increased unfolded protein response (UPR) triggered by increased mtROS production and decreased antioxidant glutathione (GSH) synthesis (Mogilenko et al. Cell. 2019)

Contribution of immunity to NASH

RESULTS:

- Transcriptional network analysis identifies immune cell alterations with NASH and its resolution independently of body weight changes
- Plasma and hepatic classical dendritic Cells (cDC) and CD8+ T-Cell populations associate with NASH severity
- Proportion of Plasma Activated Cytotoxic CD8+ T cells Increase in Patients with NASH and T2D
- Hepatic cDC and CD8+ T-Cells Are Altered in a Diet-Induced Murine NASH Model

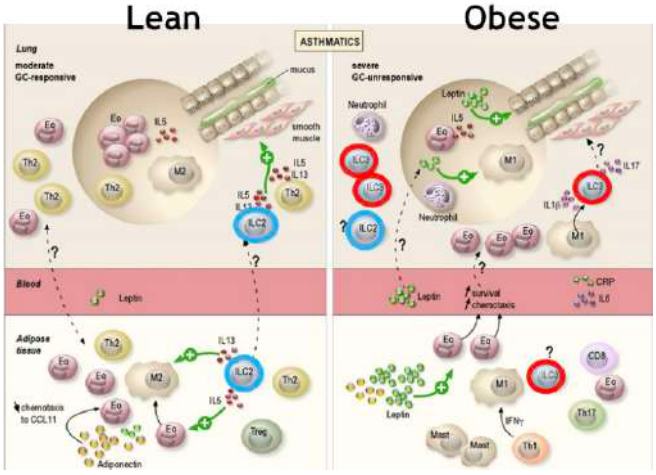


Reversible transition from benign steatosis (NAFL) to NASH is associated to decreased blood and liver cDC1/cDC2 ratio and to increased cytoxic CD8+ T lymphocytes.
(Haas et al. Nat Metab. 2019)

Exacerbation of asthma by obesity

RESULTS:

- High fat diet feeding exacerbates asthma features
- Obese non asthmatic mice have increased lung innate lymphoid cells and eosinophilia
- Asthma induction further increases lung ILC2 and ILC3 with high IL-33 and IL-1 and decreases adipose tissue ILC
- Depletion of ILC strongly decreases asthma in obese mice



Innate lymphoid cells (ILC) type 2 and 3 contribute to exacerbation of allergic airway inflammation by obesity.
(Everare et al. JACI 2016, Julia et al. Nat. Rev. Immunol. 2015)

PERSPECTIVES:

- Decipher the impact of (combined) dietary compounds (cholesterol, glucose, fatty acids) on DC and T cell function
- Analyze cDC - (CD8) T cell interactions in and contribution to NAFLD/NASH
- Evaluate the contribution of IgE and its high affinity receptor in exacerbation of asthma by obesity

UNIQUE SELLING POINTS:

- Dual expertise in immunology and metabolism
- Very wide range of preclinical models of metabolic and inflammatory diseases
- Unique mouse lines with immune cell-specific inactivation of nuclear receptors
- Access to cohorts of patients with metabolic condition (obesity, T2D, NAFLD/NASH…)
- In house metabolic immuno-phenotyping platform (flow and mass cytometry, Seahorse)

DOROTHEE Guillaume

Ph.D

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Inserm

Deciphering neuroimmune interactions in neurodegeneration and neurovascular conditions: development of innovative immunotherapies and immune biomarkers

Keywords:

- Neuroimmunology,
- Neuroinflammation,
- Alzheimer's disease,
- Tauopathies,
- Neurovascular conditions (Stroke, CAA, Epilepsy),
- Innate & adaptive immunity,
- Immune biomarkers,
- Immunotherapy / Immunomodulation,
- Pre-clinical models,
- Translational research.

Translational research for deciphering neuroimmune interactions in neurodegeneration and neurovascular conditions: development of innovative immunotherapies and immune biomarkers.

Our studies aim at better understanding the role of recently emerging aspects of innate and adaptive neuroimmune interactions in the pathophysiology of neurodegeneration (Alzheimer's disease (AD), Tauopathies) and other neuroinflammatory and/or neurovascular conditions (cerebral amyloid angiopathy (CAA), stroke, epilepsy) for developing and evaluating i) innovative disease-modifying immunotherapy approaches, and ii) diagnostic and/or prognostic blood-based immune biomarkers. Our research strategy is based on a translational approach combining pre-clinical studies in transgenic mouse models, together with transversal and longitudinal clinical studies.
Our pre-clinical studies evidenced a beneficial role of Tregs in the pathophysiology of AD-like pathology, showing for the first time the therapeutic potential in AD of a Treg-targeting peripheral immunomodulatory approach (low-dose IL-2 treatment). Findings are now translated into a Phase 2 therapeutic clinical trial. Our works on neutrophils (PMNs) evidenced that altered homeostasis of circulating PMNs correlate with disease progression and/or severity in AD patients and ischemic stroke, supporting their potential interest as innovative prognostic blood biomarkers and therapeutic targets in immunomodulatory approaches. Finally, we developed a multiparametric serological test defining anti-A antibodies as serological biomarkers of potential diagnostic interest for inflammatory and hemorrhagic forms of CAA.

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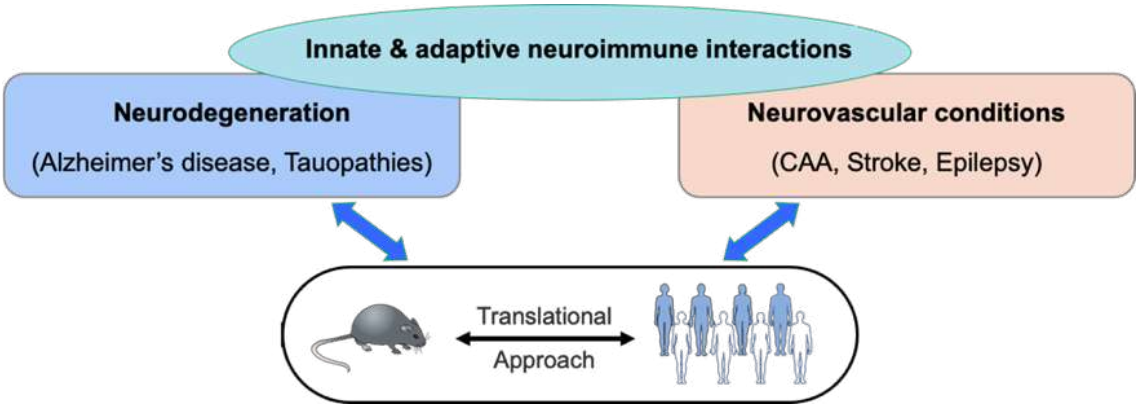
- **Harmful neutrophil subsets in patients with ischemic stroke: Association with disease severity.** Weisenburger-Lile D, et al. *Neurol Neuroimmunol Neuroinflamm.* (2019) 6:e571.
- **Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease.** Hamelin L, et al. *Brain*. (2018) 141: 1855-1870.
- **Neutrophil hyperactivation correlates with Alzheimer's disease progression**. Dong Y, et al. *Ann Neurol.* (2018) 83: 387-405.
- **Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of Tauopathy.** Laurent C, et al. *Brain*. (2017) 140: 184-200.
- **Regulatory T cells delay disease progression in Alzheimer-like pathology.** Dansokho D, et al. *Brain*. (2016) 139: 1237-51.

OBJECTIVES:

- Role of T-cell immunity in neurodegeneration (Alzheimer, Tauopathies)
- Role of neutrophils in neuroinflammatory conditions (Alzheimer, Stroke, Epilepsy)
- Role of anti-Ab antibodies in cerebral amyloid angiopathy (CAA)
- Development of innovative immunotherapy / immunomodulatory approaches
- Development of prognostic / diagnostic immune biomarkers

TOOLS:

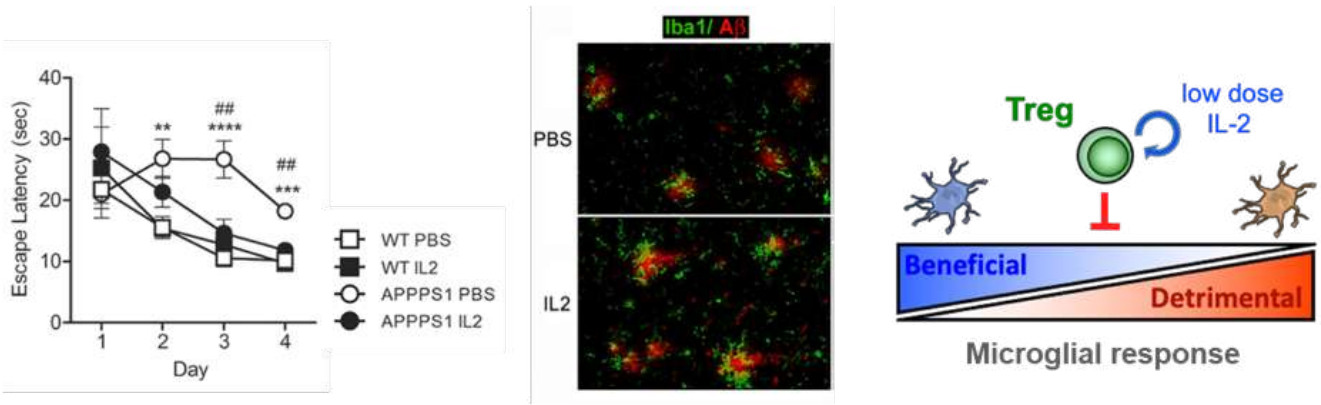
- Transgenic mice (Amyloid, Tau, CAA) and in vitro models (human / mouse BBB)
- Neuropathology, behavior, electrophysiology
- Phenotypic, functional and molecular immune phenotyping
- Transversal / longitudinal clinical studies with neuroimaging (PET, MRI)



Subject 1: Role and therapeutic potential of T-cell immunity in neurodegeneration

RESULTS:

- Beneficial role of regulatory T cells (Tregs) in Alzheimer-like pathology
- Peripheral modulation of Tregs impacts microglial response to amyloid
- Amplification of peripheral Tregs (low dose IL-2) restores cognitive functions
- Phase 2 therapeutic clinical trial initiated

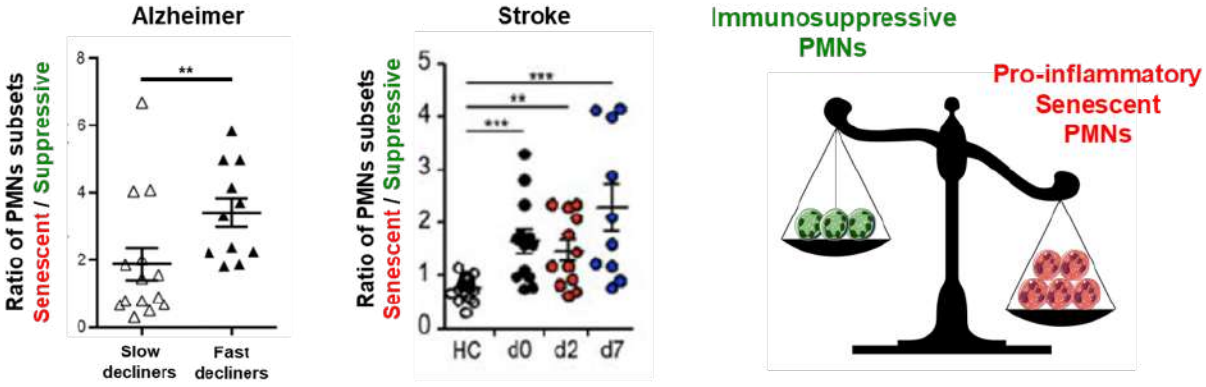


Amplification of peripheral Tregs via low-dose IL-2 treatment restores cognitive functions (left panel) in Alzheimer-like amyloid pathology (APPPS1 mice) including by promoting beneficial microglial response (middle panel) (Dansokho et al, Brain, 2016).

Subject 2: Role of neutrophils (PMNs) in neuroinflammatory conditions

RESULTS:

- Enhanced peripheral pro-inflammatory PMNs in Alzheimer's disease (AD) and stroke
- Altered homeostasis of PMNs correlates with rate of cognitive decline in AD patients
- Altered homeostasis of PMNs correlates with disease severity in acute stroke

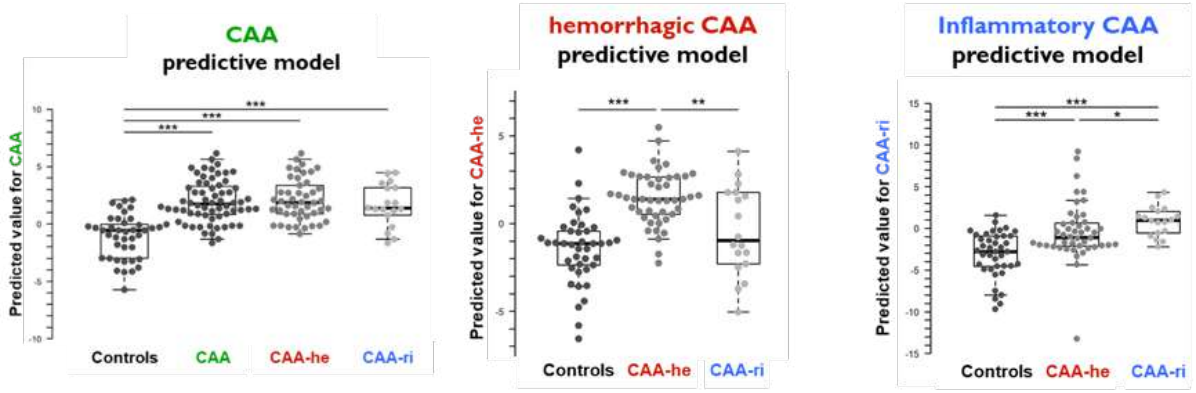


Altered homeostasis of circulating PMNs correlates with disease progression and/or severity in AD patients (Dong et al, Ann Neurol, 2018) and ischemic stroke (Weisenburger-Lile et al, Neurol Neuroimmunol Neuroinflamm, 2019).

Subject 3: Role of anti-Ab antibodies in cerebral amyloid angiopathy (CAA)

RESULTS:

- Development of a multiparametric serological test for characterizing anti-Ab antibodies
- Multivariate models are predictive of CAA and its inflammatory or hemorrhagic forms



Multiparametric serological characterization of anti-Ab antibodies allowed defining multivariate models as potential predictive diagnostic biomarkers for inflammatory and hemorrhagic forms of CAA (Chantran et al, in revision)

PERSPECTIVES:

- Refine patients' stratification by using broad spectrum immune phenotyping
- Identify novel immune biomarkers and effectors / targets of therapeutic interest
- Develop and evaluate innovative immunomodulatory approaches
- Translation from basic and translational research to routine clinical practice

UNIQUE SELLING POINTS:

- Key expertise in recently emerging aspects of neuroimmune interactions
- Tight collaborations with renowned clinical departments at Sainte-Anne Hospital (Pr. M. *Sarazin; Alzheimer & Tauopathies*), Saint-Antoine Hospital (Pr. *S. Alamowitch*; CAA & Stroke) and Pitié-Salpétrière (Pr. *V. Navarro; Epilepsy*).
- Translational approach with the capacity to go from basic / pre-clinical research to human clinical trials (e.g. low dose IL-2 trial in Alzheimer)

DUMORTIER Hélène

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Inserm / CNRS unit, University, Pasteur Institute,...)
CNRS – Université de Strasbourg
CNRS

Pathophysiological mechanisms and therapeutic regulation of autoimmune responses: from basic to translational research

Keywords:

- Autoimmune diseases
- Lupus
- Rheumatoid arthritis
- B and T cells
- Checkpoint inhibitor
- Stroma / microenvironment
- Tertiary lymphoid structures (TLS)
- Targeted delivery
- Carbon-based nanoparticles
- Nanomedicine

Our research interests are at the interface between basic and translational research, they focus on the dysregulated molecular and cellular mechanisms in autoimmune diseases and on the development of innovative therapeutic strategies.

The research program developed by my team (PhD, MD, students) consists in studying the pathophysiological mechanisms of autoimmune responses at the molecular and cellular level, in the circulating cell compartment and in secondary lymphoid organs, but also in tertiary lymphoid structures located in inflamed target organs of the disease. These aspects are addressed both in mouse models and using patient-derived samples. Our main interest lies in systemic lupus erythematosus (SLE), but also in two other related systemic autoimmune diseases, i.e. rheumatoid arthritis and Sjögren's syndrome. We aim i) at gaining a better understanding of the processes that are altered at the immune and microenvironment levels, in order to ii) identify new targets and iii) develop innovative therapeutic strategies, among others using carbon-based nanoparticles as carriers (in collaboration with the chemists of the Unit).

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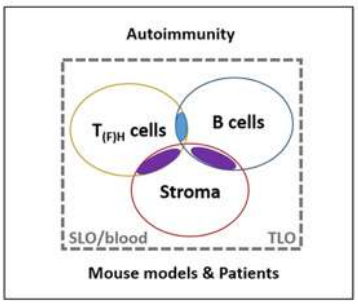
OBJECTIVES:

- To dissect the mechanisms leading to the development of autoimmunity (focus on B & T lymphocytes and on the stromal microenvironment in secondary and tertiary lymphoid organs)
- To identify new molecular and cellular targets (e.g. BTLA, checkpoint inhibitor)
- To develop innovative targeted therapeutic strategies for autoimmune diseases (e.g. multifunctionalized carbon-based nanoparticles)

TOOLS:

- Mouse models of autoimmune diseases
- Samples from patients
- Flow cytometry
- Microscopy
- Transcriptomics
- Functionalization and characterization of carbon-based nanoparticles

FROM MECHANISMS...

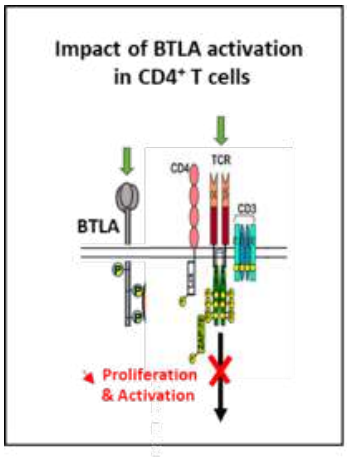


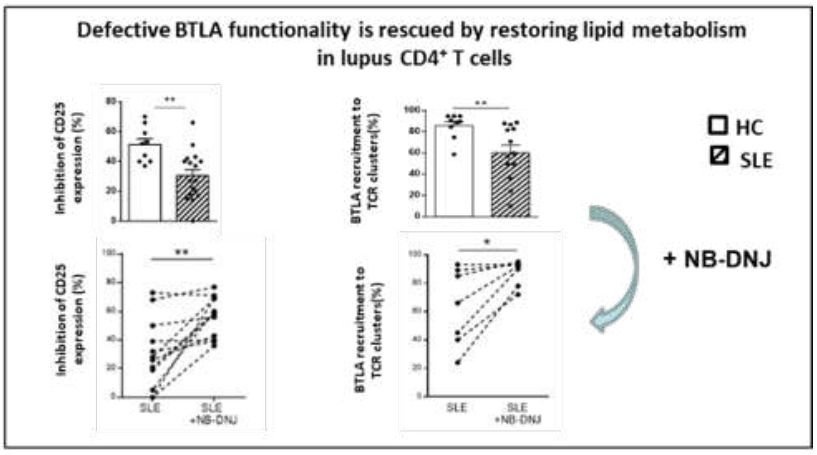
... TO NEW THERAPEUTIC STRATEGIES

Subject 1: Role of the co-inhibitory receptor BTLA in Systemic Lupus Erythematosus

RESULTS:

- Demonstration of an altered capacity of BTLA to inhibit CD4+ T cell activation in active SLE patients due to a poor BTLA recruitment to the immunological synapse following activation
- Restoring intracellular trafficking is sufficient to restore the capacity of BTLA to associate with TCR clusters, and to inhibit lupus CD4+ T cell activation





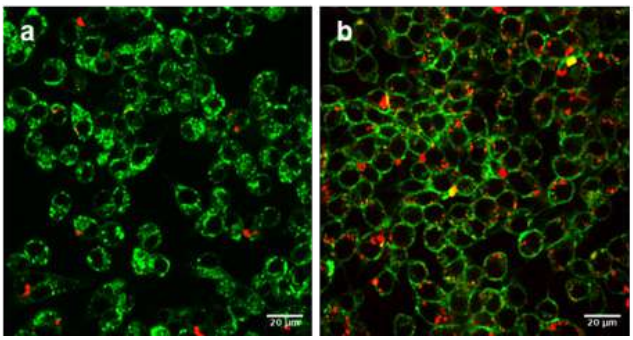
The activation of the BTLA pathway attenuates T-cell activation, leading to decreased cell proliferation, cytokine production and cell cycle progression

- *BTLA engagement (thanks to an agonistic antibody) fails to efficiently inhibit activation of CD4+ T cells from SLE patients compared to Healthy Controls, due to a poor BTLA recruitment to TCR clusters*
- *N-Butyldeoxynojirimycin (NB-DNJ), a glucosylceramide synthase inhibitor, by normalizing lipid metabolism in lupus CD4+ T cells restores BTLA recruitment to TCR clusters and BTLA functionality*

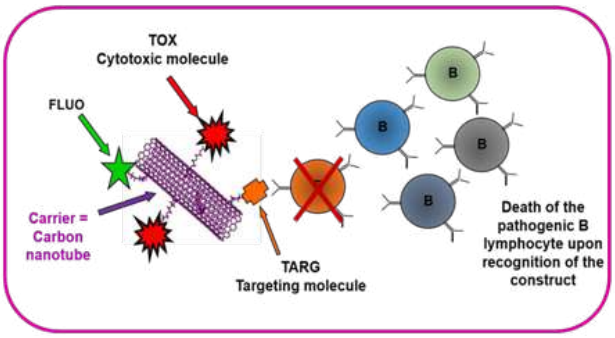
Subject 2: Carbon-based nanoparticles as therapeutic tools for inflammatory autoimmune diseases

RESULTS:

- Development of powerful methods allowing multi-functionalization
- Development of biocompatible and biodegradable carbon-based nanoparticles
- Demonstration of the possibility to selectively and efficiently target cells of interest
- Ongoing experiments regarding targeting of cells involved in inflammatory autoimmune diseases.



Fluorescence images of HeLa cells incubated with 100 µg/mL of RCND–FA (Red emissive Carbon NanoDots functionalized with Folic Acid) (b). When cells are pretreated with free FA, the red staining is clearly inhibited (a) indicating specific targeting to the cells through their surface FA receptor. In green, cell membranes stained with CellMask; in red, RCND–TEG–FA. (Ji DK. et al. 2020, Nanoscale Horizons)



Development of multi-functionalized carbon-based nanoparticles (here carbon nanotubes as an example) to target, visualize and eliminate pathogenic cells (e.g. autoreactive B lymphocytes) thanks to a unique triple functionalization method.

PERSPECTIVES:

- To investigate further the role of the BTLA pathway in lupus and assess its therapeutic efficiency
- To identify other pathways that can be targeted for therapeutic intervention in inflammatory autoimmune diseases (e.g. to modulate the stromal microenvironment or the neogenesis of tertiary lymphoid structures in target organs)
- To use multifunctional nanoparticles for targeted delivery to pathogenic cells in order to increase efficiency and reduce side effects
- Translate our findings to the clinics, from bench to bed

UNIQUE SELLING POINTS:

- Long-term expertise in autoimmune diseases
- Long term expertise in nanoparticles (toxicity and use for therapeutic applications)
- MD / rheumatologists in the team (clinical samples and data)
- Close collaboration with the chemists of the Unit (design of nanoparticles for therapeutic approaches)
- Mouse models available with a SPF or SOPF health status

EBERL Gérard

Professor

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Institut Pasteur

Combining immunology with microbiology and neurosciences to understand immunity

Keywords:

- Mucosal immunology,
- Symbiotic microbiota,
- Neuro-immunology,
- Inflammatory pathologies.

Combining immunology with microbiology and neurosciences to understand immunity.

Since 15 years, we explore the mechanisms by which the symbiotic microbiota cross-talks with the immune system for mutual benefits. We have shown that the bacteria colonizing the intestine after birth are necessary for the development of immune organs, and key for setting the long-term reactivity of the immune system. Later in life, the microbiota maintains a homeostatic equilibrium in the immune system, the failure of which leads to inflammatory pathologies. We are now extending our scope to include the nervous system, a key regulator of immunity through its broad sensing of the environment. In order to achieve such transversal research, we rely on a close partnership with immunologists, geneticists microbiologists and neuroscientists, and believe that such team work is necessary to develop holistic preventive and therapeutic approaches against inflammatory pathologies and their multiple consequences.

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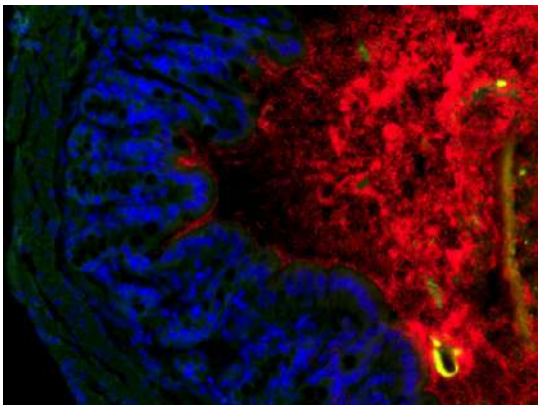
OBJECTIVES:

- Decipher the functional cross-talk between symbiotic microbiota and immune system
- Identify perturbations of this crosstalk leading to inflammatory pathologies
- Identify key modulators in the diet, microbiota and nervous system

TOOLS:

- Unique and genetically diverse mouse models
- Cutting-edge molecular and cellular immunology
- Partnership with geneticists, microbiologists and neuroscientists

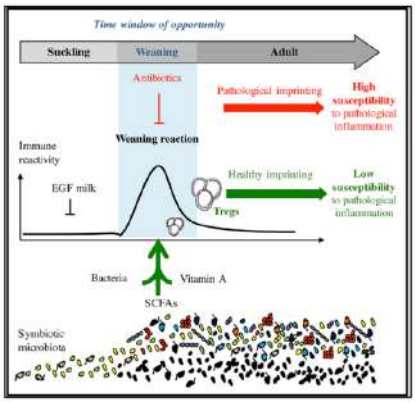


Bacteria (red) in the mouse colon (blue)

Topic 1: The weaning reaction and neonatal immune imprinting

RESULTS:

- A vigorous immune response is programmed in response to microbial expansion at weaning – the weaning reaction
- A specific time window of opportunity restricts the necessary exposure to microbiota at weaning
- Perturbation or absence of the weaning reaction leads to pathological imprinting – increased susceptibility to inflammatory pathologies later in life.

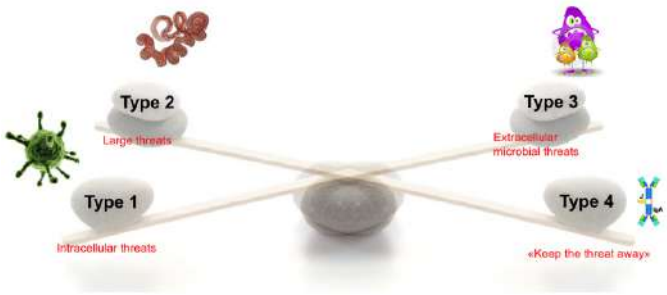


Al Nabhani et al, Immunity 2019, Nature Metabol 2019, Mucosal Immunol 2020

Topic 2: Innate lymphoid cells (ILCs) and mucosal homeostasis

RESULTS:

- Bacterial symbionts are required to maintain immune equilibrium and prevent inflammatory patholgy
- ILCs, regulatory T cells and Th17 cells are key in maintaining immune equilibrium
- Failure in this equilibrium leads to inflammatory pathologies (allergy, IBD, autoimmunity, diabetes)

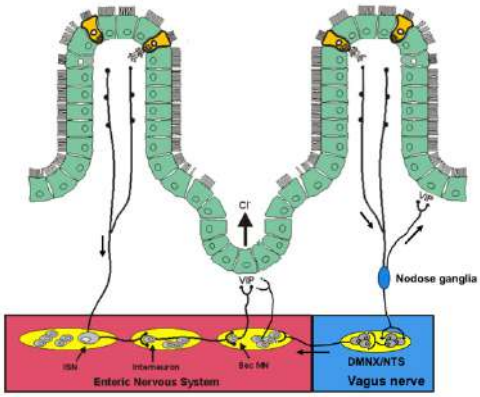


G. Eberl, Nat Rev Immunol 2016; Ohnmacht et al., Science 2015.

Topic 3: Microbiota, immune system and nervous system crosstalk

RESULTS:

- Activity of the intestinal immune system is regulated by the enteric nervous system and neuropeptides
- The microbiota activates the immune system, which modifies brain activity and host physiology
- Stress modifies the microbiota, perturbs the metabolism of the host and promotes depression



Siopi et al., Cell Rep 2020; Chevalier et al., Nat Comm 2020

PERSPECTIVES:

- Identify early life dietary and microbial factors that promote or prevent inflammatory pathology (allergy, IBD, autoimmunity) and their consequences (diabetes, neurodegenerative diseases, cancer)
- Identify of genetic, dietary and microbial factors that determine immune reactivity to infection and immunotherapy
- Decipher the microbiota-immune-nervous cross-talk that maintains health or drives immunopathology
- Identify biomarkers of immune reactivity and develop corrective or preventive measures to counter inflammatory pathologies

UNIQUE SELLING POINTS:

- Transversal research based on Immunology, Microbiology and Neurosciences
- Identification of intrinsic and extrinsic promoters of inflammatory pathologies
- Use mouse models reflecting human diversity in pathology
- Biomarkers of broken homeostasis, and development of corrective measures

GAUDENZIO Nicolas

PhD

INFINITY (Toulouse Institute for Infectious and Inflammatory Diseases) – UMR Inserm unit U1291 / CNRS, University of Toulouse
Immception Lab (www.immception.com) - Neural regulation of immune response
Inserm

Neuro-immunology and skin diseases

Keywords:

- Neuro-immunology,
- skin,
- allergy,
- inflammation,
- mast cell,
- type 2 immunity,
- Atopic dermatitis.

The Immception lab combine trans-disciplinary expertizes including basic and clinical immunology, basic neurobiology, clinical dermatology and computational analyzes to better understand how immune cells and peripheral neurons communicate to regulate the development of inflammatory processes.

The "IMMCEPTION" Lab (contraction between IMMunity and nociCEPTION) aims to better understand the etiology of chronic allergic disorders, with a primary focus on the skin and atopic dermatitis (AD) pathology. The body is innervated by an intricate network of nociceptive sensory neurons (i.e. nociceptors) that have their peripheral axons located in the skin, joints and muscles, and their cell bodies in dorsal root or trigeminal ganglia. The primary function of nociception is the transmission of sensations to the spinal cord and brain to elicit behavioral responses. Despite their role in the transmission of sensation, recent evidences have suggested that nociceptors could be powerful regulators of ongoing immune response. We recently showed that interactions between nociceptors and mast cells play a critical role in the development of pathogenic type 2 skin inflammation. Using our mouse model of AD-like pathology we showed that mice that lack the neuropeptide substance P, or nociceptors, or functional mast cell receptor Mrgprb2 were almost protected from the development of pathogenic allergen-specific type 2 immune response and associated AD-like pathological features (Serhan, Basso. Nature Immunology 2019; Gaudenzio, Galli Annual Review of Immunology 2020, Meixiong. Trends in Neurosciences 2020).
Based on the novelty of our results, we proposed a revisited versions of the etiology of AD pathology by focusing on skin neuroimmune interactions prior to the development of pathogenic type 2 immunity. This hypothesis is also backed up by the fact that AD restarts within weeks in most patients after stopping treatment with dupilumab, suggesting that additional underlying mechanisms are controlling the production of type 2 cytokines. Our current focus now is to analyze the translational relevance and extension of these findings to additional pathologies and develop relevant therapeutic molecules specifically targeting neuro-immune interactions.

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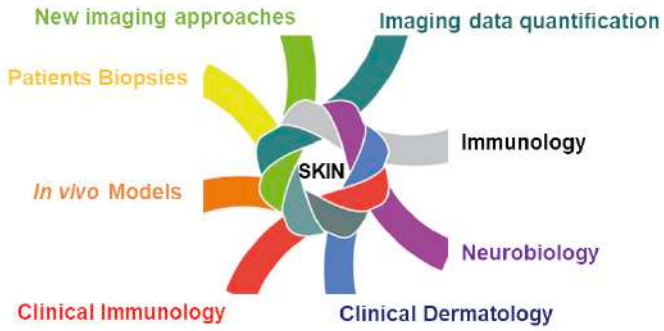
OBJECTIVES:

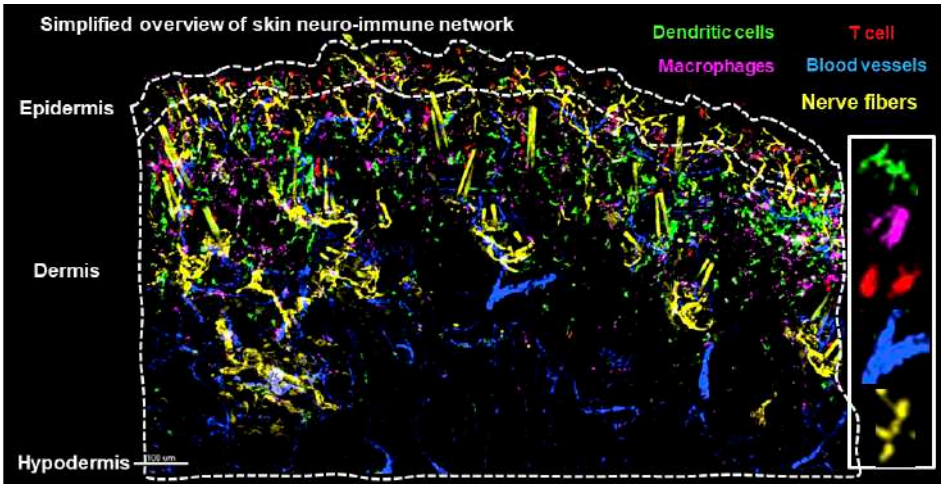
- Combine transdisciplinary approaches to better apprehend human skin conditions
- Understand how neuroimmune interactions regulate skin inflammatory diseases
- Identify new neuroimmune-oriented therapeutic targets

TOOLS:

- In vivo transgenic models and translational relevance in human biopsies
- Transcriptomic, proteomic and integrated multiparametric analyzes
- Intravital imaging of living animals
- Highly multiplexed imaging coupled to machine learning



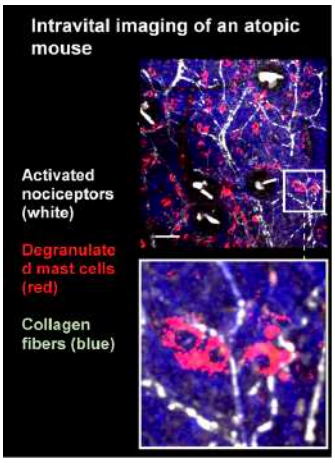
Development of new image- and proteomic-based approaches to study neuroimmune interactions in mouse and human biopsies

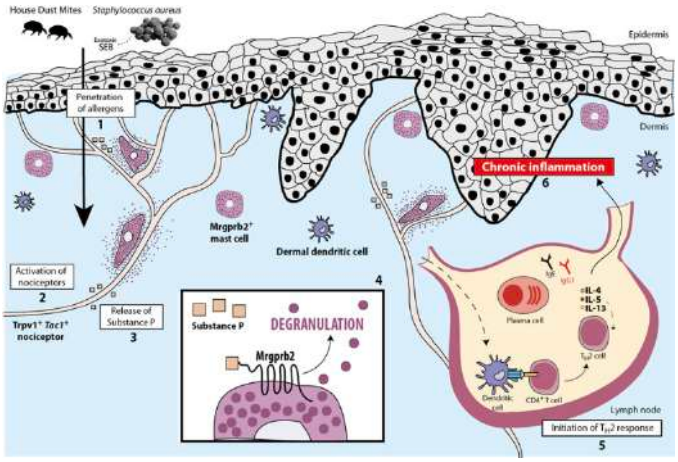


A revisited version of the etiology of atopic dermatitis based on neuro-immune interactions

RESULTS:

- Using our new mouse model of atopic dermatitis-like pathology we showed that mice that lack the neuropeptide substance P, or nociceptors, or functional mast cell receptor Mrgprb2 were almost protected from the development of pathogenic allergen-specific type 2 immune response and associated pathological feature (Serhan, Basso et al. Nat Imm. 2019).





Extracted from Serhan, Basso et al. Nature Immunology 2019

PERSPECTIVES:

- Prospective clinical protocol in which we biopsy patients with moderate to severe atopic dermatitis to analyze the translational relevance of our findings in the mouse (initiated)
- Investigate the role of such neuron-mast cell functional units in different organs and in the regulation of additional pathological conditions

UNIQUE SELLING POINTS:

- The neural regulation of immune response is an emerging and fast growing field with promising therapeutic perspectives
- In mouse models, neuro-immune interactions are controlling the development of pathological type 2 immune response in the skin
- Targetting neuro-immune interactions in skin diseases could have significant impact on both inflammation and pruritus as neurons are involved in those two clinical manifestations
- We need to revisit what is currently known of atopic dermatitis to target biological processes that are prior to type 2 cytokines

GEORGEL Philippe

Ph.D

INSERM UMR_S1109 / Strasbourg University

Genetic analysis of inflammation: from human diseases to mouse models and back

Keywords:

- Inflammation,
- Immune-mediated diseases,
- Genetics
- Animal models,
- Inflammasomes.

My lab is interested in inflammatory diseases, starting from patient's description and samples analysis to the development of animal models: In essence, we perform a translational research.

Philippe Georgel's interest in innate immunity started during his post-doctoral and assistant professor position in Pr Hoffmann's lab, where he identified the gene Imd, the mutation of which is responsible for the first immunodeficiency phenotype in Drosophila. This discovery, together with the elucidation of the role of the Toll gene in antimicrobial defence, paved the way for the concept of "Pattern recognition Receptors". Next, during a sabbatical in Pr Beutler's lab (Scripps Research Institute, La Jolla), P.Georgel performed screens in mice to identify antiviral defence genes. His main achievements are (i) the identification of a connection between TLR4 and type I IFN expression and (ii) the identification of TLR9 as a major sensor of viral infections. Back in France in 2005, he joined Pr Bahram's lab and built together an Inserm unit devoted to analysis of the genetic basis of Immune-mediated diseases, where he leads the "ImmunoRheumatology" group. In the past 10 years, he described several miRNAs involved in the control of inflammation in Rheumatoid Arthritis patients, and showed that the Dicer gene is an important player in RA. Next, he demonstrated that plasmacytoid dendritic cells (pDCs) negatively regulate inflammatory responses. More recently, he was also interested in crystal-induced arthritis and developed an innovative pre-clinical mouse model to test the efficacy of molecules (e.g. imiquimod) targeting innate immune receptors. In collaboration with internists, he also investigated to role of IFN in sepsis patients and how the modulation of these molecules in endothelial cells might become an attractive therapeutic option. He plans to pursue this work in mice to better understand the connection between danger signals, inflammation and IFN signalling. In humans, he is now involved in the identification of genes important for the development of gout in patients, using high throughput technologies (exome sequencing).

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- **JAK-STAT Targeting Offers Novel Therapeutic Opportunities in Sepsis**. Clere-Jehl R, Mariotte A, Meziani F, Bahram S, Georgel P*, Helms J*. ***Trends Mol Med.*** (2020) Jul 3:S1471-4914(20)30158-1. * corresponding authors.
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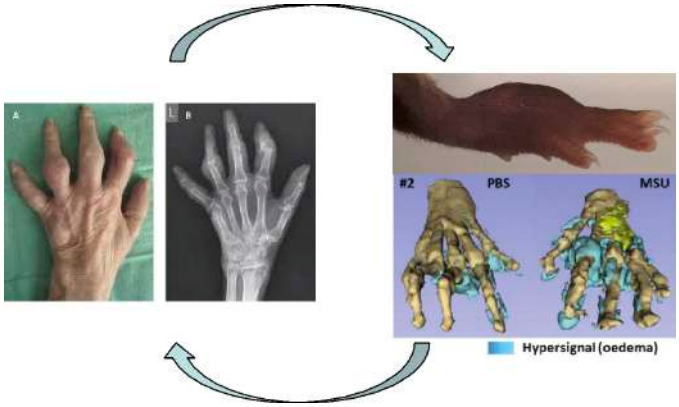
OBJECTIVES:

- Identify mutated genes in patients suffering auto-inflammatory / Immune-mediated diseases
- Develop cellular and animal models to investigate pathogenic mechanisms
- Perform pre clinical studies

TOOLS:

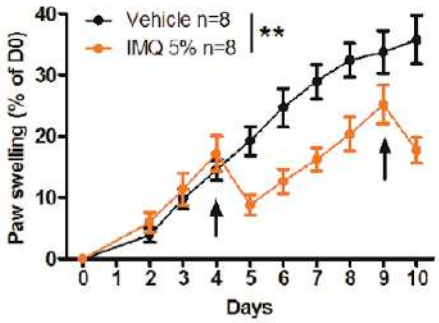
- High throughput sequencing platform (Illumina, Nanopore technologies)
- Mouse and Zebrafish animal facilities



Subject 1: pDC activation reduces joint inflammation

RESULTS:

- Plasmacytoid dendritic cells (pDCs) are major regulators of acute joint inflammation
- Activating / recruiting pDC with imiquimod (IMQ) on the inflamed site decreases neutrophil infiltration and subsequent articular and bone damage

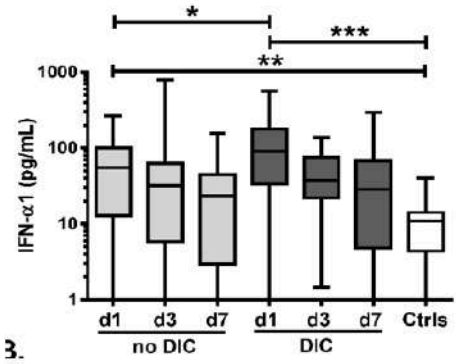


Topical application of IMQ (to recruit/activate pDCs) on an inflamed joint triggered by arthritogenic serum injection reduces paw swelling.

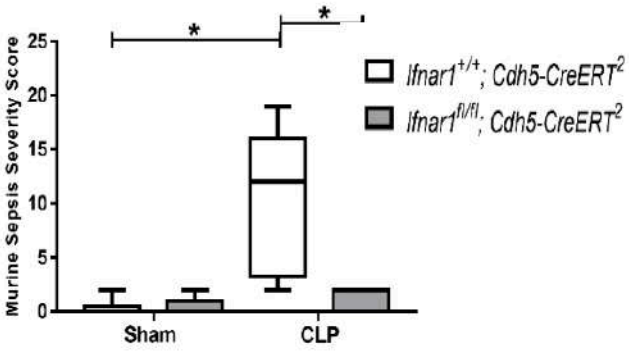
Subject 2 : Role of type I Interferons (IFNs) in sepsis

RESULTS:

- Interferon a1 expression is increased in sepsis patients which, evolving towards disseminated intravascular coagulation (DIC), have reduced chances of survival.
- Impairing type I IFN in the endothelium of sepsis mice (following cecal ligation and puncture – CLP) lowers the severity score and increases survival



Increased type I IFNs in sepsis patients with DIC. *Time-course of IFN- 1 in DIC and non-DIC septic shock patients. Results are shown in white (healthy controls), light grey (no DIC) or dark grey (early DIC).*



Endothelium-targeted Ifnar1 deletion provides protection against septic shock. *Assessment of severity 20 hours after surgery in CLP- vs. sham-operated mice, by measuring murine sepsis severity score.*

PERSPECTIVES:

- Identify novel families with inherited auto-inflammatory / Immune-mediated diseases
- Identify the mutated genes by exome sequencing
- Describe the pathological mechanisms / affected pathways by high throughput analysis (multi OMICs approach) and investigations in animal models
- Develop innovative therapeutic of sepsis by targeting IFN signaling (using Jakinhibs for instance) in endotheliam cells; this could be done with an industrial partner

UNIQUE SELLING POINTS:

- Research Unit fully integrated inside a major french University hospital
- The clinician of the Rheumatology are members of the INSERM research Unit
- An in-site, fully equipped, sate-of-the-art genosequencing facility is located within the research unit
- An animal facility where both mouse and zebrafish models can be developed
- The situation of our research lab (affiliated to both Strasbourg University and Strasbourg Medical Center), equipped with high throughput technologies and animal facilities for pré-clinical studies, offers unique opportunities for medical research

GRESSENS Pierre

M.D. (neurologist and child neurologist), Ph.D. (neurosciences)

Inserm – Université de Paris
Inserm

Neuroinflammation: mechanisms and targets for neuroprotection

Keywords:

- Neurodevelopmental disorders,
- Neuroinflammation and microglia,
- Neuroprotection and nanoparticles,
- Blood-brain barrier,
- hIPS cells and brain organoids,
- Translational research,
- Clinical research,
- Integrative genomics.

Understanding the role of neuroinflammation and microglia in neurodevelopmental disorders and identifying novel targets and strategies for neuroprotection.

Over the last 20 years, we have acquired a recognized scientific expertise in the field of neurodevelopmental disorders (NDDs) with a special emphasis on the role of neuroinflammation and microglia. We have developped a unique technical platform to study several complementary aspects of neuroinflammation: cell sorting and phenotyping (MACS and FACS), ROS production, exosome production, phagocytic activity, and microglia phenotyping (J. Van Steenwinckel & V. Faivre); BBB evaluation (P. Dournaud); bank of human brain tissues (T. Vitalis); human brain organoids containing microglia (V. El Ghouzzi); integrative genomics and drug repurposing pipelines (A. Delahaye); and computational structural pharmacology (B. Villoutreix). We have developped and characterize several models of NDDs (systemic inflammation – Poly:IC, LPS, IL-1beta-, protein malnutrition, excitotoxicity, hypoxia-ischemia, traumatic brain injury). We have accumulated datasets of bulk and single cell RNAseq of microglia and astrocytes in different brain areas and at different developmental stages. We have demonstrated a key role of microglia and several models and showed links between molecular pathways identified in rodents and risk factors (corresponding SNPs) in human infants with white matter damage. Our projects combine four sets of approaches: i) rodent models to further decipher cellular and molecular pathways and to identify new protective strategies; ii) human post-mortem tissues and brain organoids to validate key pathways; iii) drug repurposing and candidate drug screening; iv) clinical trials in humans.

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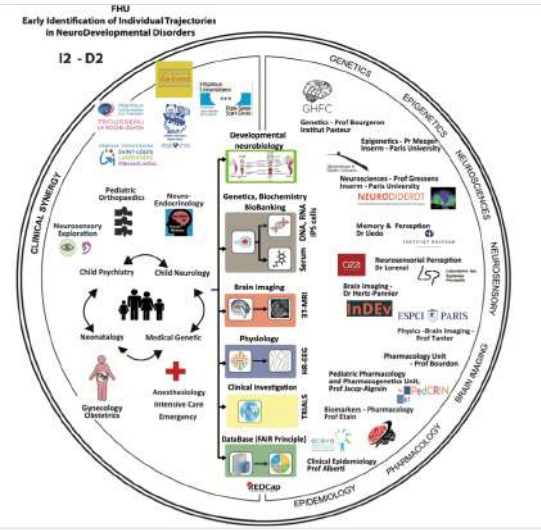
OBJECTIVES:

- To decipher the mechanisms of microglial activation in disorders affecting the developing brain
- To describe the microglial phenotypes through comprehensive transcriptomic profiling
- To determine the consequences on other brain cells
- To design original neuroprotective strategies targeting microglia and neuroinflammation
- To translate experimental data to humans

TOOLS:

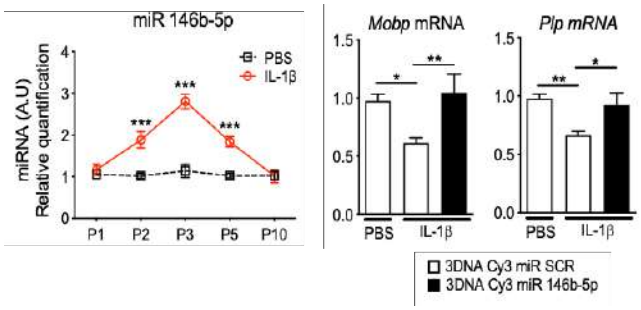
- Neuroinflammation platform (http://www.neuroinflammation.fr/index.html#microglie)
- Multiple in vitro & in vivo rodent models
- Human brain organoids, human brain tissues
- Integrative genomics & computational structural pharmacology
- 3-DNA nanoparticles specifically targeting microglia
- Leading the clinical-research network (FHU) I2-D2



Topic 1 : Mechanisms of microglial activation

RESULTS:

- Transcriptomic profiling of activated microglia with identification of Wnt inhibition and overexpression PSD95 as key pathways
- Identification of related SNPs as risk factors for white matter damage in human neonates
- Role of miR146b-5p and other epigenetic changes in microglia modulation

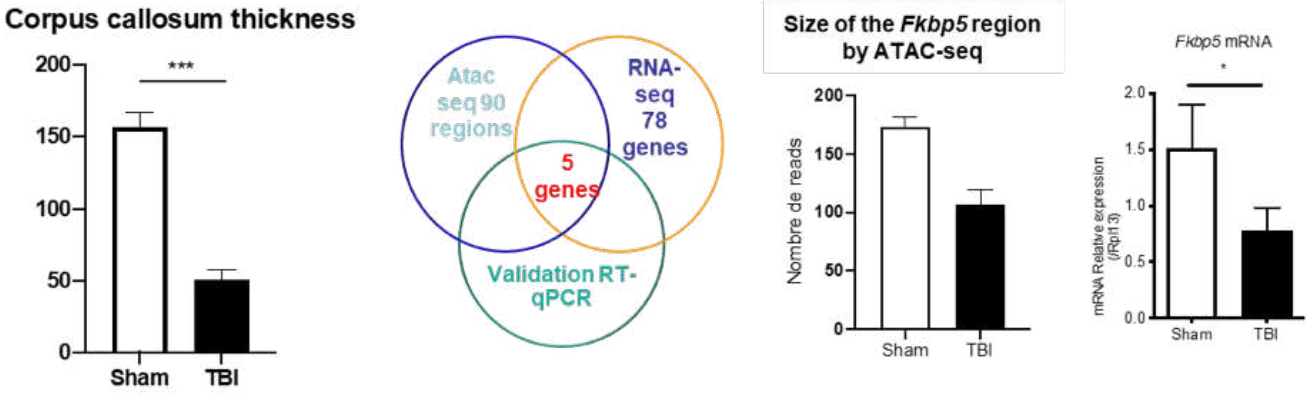


Left panel: Brain expression of miR146b-5p following neonatal systemic inflammation (IL-1b). Right panels: Manipulating microglial expression of miR146b-5p through 3-DNA nanoparticles prevents inflammation induced myelination deficit.

Topic 2: Role of microglia in progressive white matter atrophy induced by traumatic brain injury (TBI)

RESULTS:

- Mild TBI performed in newborn mice leads to a progressive white matter atrophy
- Microglia play an important role in this process
- Combined ATAC-seq and RNA-seq of microglia during the progression of the disease has allowed to identify novel pathways and potential target for neuroprotection



Left panel: Mild TBI at P7 induces a progressive corpus callosum atrophy (thickness measured at P45). Right panels: Combined ATAC-seq and RNA-seq analysis of microglia at P45 identified chromatin access changes in the Fkbp5 region accompanied by a reduced expression of Fkbp5 mRNA.

PERSPECTIVES:

- To provide an exhaustive phenotype profiling of activated microglia in the developing brain
- To identify and validate novel targets for neuroprotection
- To repurpose drugs through integrative genomics
- To improve neurological outcome of infants exposed to neuroinflammation

UNIQUE SELLING POINTS:

- Unique combination in France of rodent and human models, phenotyping platforms, and bio-informatic pipelines (at RNA and protein level) to study neuroinflammation
- Member of NeurATRIS, a unique translational research infrastructure dedicated to innovative therapies in neurociences (http://www.neuratris.com/index.php/fr/neuratris-en-bref-fr)
- Coordinator of the FHU I2-D2 for translation to human

GUERMONPREZ Pierre

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Keywords:

- Immunotherapy,
- Vaccines,
- Dendritic cells.

Dendritic cells, T cell responses

Dissecting and harnessing the immunogenic function of dendritic cells to induce T cell-dependent immunity.

Dendritic cells (DCs) are sentinel of the immune systems. Our group investigate:

- DC heterogeneity,
- how DC develop from hematopoietic stem cells and seed peripheral tissues,
- how DCs present antigens to T cells by MHC molecules,
- how DC instruct the differentiation of tissue memory T cells.

Based on these approaches, we develop interventions aiming at stimulating T cell dependent immunity by:

- increasing DC infiltration in tumors,
- targeting vaccine antigens to defined DC subsets,
- developing DC-based cellular vaccines from iPSCs.

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OBJECTIVES:

We investigate:
- DC heterogeneity,
- How DC develop from hematopoietic stem cells and seed peripheral tissues,
- How DCs present antigens to T cells by MHC molecules,
- How DC instruct the differentiation of tissue memory T cells.

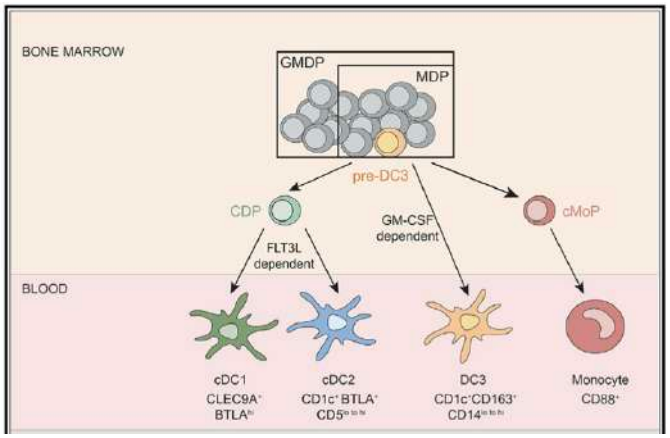
TOOLS:

- Mice models of cancer (lung, NSCLC, melanoma)
- Genetically modified mice deficient in DCs subsets
- In vitro systems for huDC differentiation from CD34+ cord blood HSPCs
- In vitro systems for huDC differentiation from human iPSCs (CRISPR/Cas9 KO)
- In vivo models of huDC differentiation from CD34+ cord blood HSPCs (organoids)
- High dimensional analysis at the single cell level (scRNAseq)

Subject 1: The heterogeneity and development of dendritic cells

RESULTS:

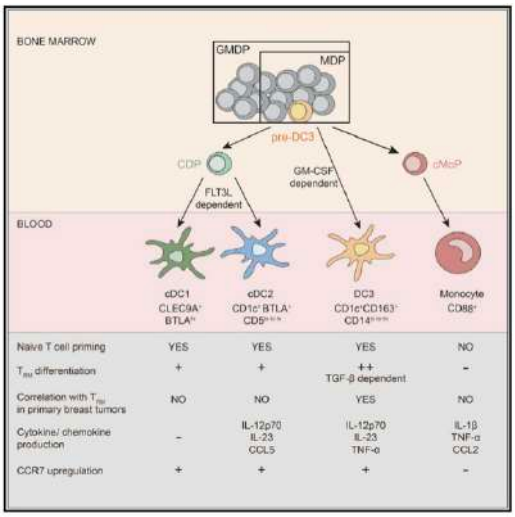
The heterogeneitity of human CD1c+ dendritic cells.
- DC3s are phenotypic and functional intermediates between cDC2s and monocytes
- GM-CSF alone, but not FLT3L, supports efficient differentiation of DC3s
- DC3s do not differentiate via cDC (CDP)- or monocyte- restricted (cMoP) progenitors



Subject 2: the priming of Tissue Resident Memory CD8+ T cells by dendritic cell subsets

RESULTS:

- Human DC3s prime TRM cells in vitro
- Human DC3s infiltration correlate with TRM expansion in primary luminal breast cancer
- IRF4-dependent DCs control the activation of lung CD8+CD103+ TRMs in a pre-clinical KrasG12D p53ko murine lung adenocarcinoma model
- GM-CSF promotes the activation of lung CD8+CD103+ TRMs in a pre-clinical KrasG12D p53ko murine lung adenocarcinoma model



PERSPECTIVES:

- Identifying equivalents of mouse DC3s: Mgl2/Clec10A+ CD11b+ DCs?
- Regulation by IRF4 transcription factor?
- Regulation of TRMs in breast and lung cancer?
- Mobilizing TRM-inducing DCs by hematopoietic growth factors (GM-CSF)?
- Mechanisms underlying the activation of lung and upper respiratory tract tissue resident CD8+ TRMs in cancer and infectious diseases.
- Application to intranasal vaccination: Targeting the delivery of vaccine antigens to Clec10A murine/human DCs using VHH nanobodies to induce lung/upper respiratory tract tissue resident memory CD8+ T cells (TRMs) upon airway immunization (synergy with im vaccination).

UNIQUE SELLING POINTS:

- Expertise in murine and human dendritic cell subsets
- In vitro human DCs models, in vivo humanized models, in vivo preclinical murine models
- Integrating developmental biology of DCs subsets with function in T cell priming

HENRI Sandrine

Ph.D

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Heterogeneity of the myeloid compartment: from phenotype to functions

Keywords:

- cDC subsets,
- macrophage subsets,
- monocyte subset,
- skin immunity,
- prostate immunity,
- tumor immunity,
- DC-targeting for vaccine,
- mouse models.

Deciphering the myeloid complexity in healthy tissues and in tumor environment (phenotype and functions) and DC-targeting for vaccine development.

Our research is focusing on the study of the myeloid complexity within tissues such as the skin and determine the specific immunological functions of each given myeloid subset at steady state but also in pathologies such as psoriasis and melanoma and use this knowledge to design innovative DC targeting vaccine as well as myeloid based immunotherapies.

We contributed to the identification of several monocyte, macrophage subsets and melanophages as well as DC subsets (cDC1 and cDC2) with functional specialization in the skin using flow-cytometry, transcriptomic signature and developed innovative mouse-models to study their functions in vivo. We contributed significantly to the identification and characterisation of the XCR1+ cDC1 subset, showed its potent cross-presentation function and with the development of the new Xcr1-cre-mTFP1 mouse model showed the cDC1 cross-tolerance regulation and used cDC1-targeting strategies to target dermal cDC1 and induce protective anti-tumor immunity. We also contributed to the identification of dermal melanophage and showed the role of macrophages in tattoo persistence.
Her group is currently capitalizing on this knowledge to disentangle mononuclear phagocytes associated to melanoma with a specific focus on XCR1+ cDC1 and melanophages and also to better understand the prostate immunity and its regulation during prostate cancer development using a mouse model recapitulating prostate cancer development in human.

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- Macrophages and fibroblasts differentially contribute to tattoo stability. Strandt, H, et al, Dermatology. 2020
- Unveiling skin macrophage dynamics explains both tattoo persistence and strenuous removal. Baranska, A, et al, J Exp Med. 2018
- Laser-assisted intradermal delivery of adjuvant-free vaccines targeting XCR1+ dendritic cells induce potent antitumoral responses. Terhorst, D, et al, J Immunol. 2015
- Dynamics and transcriptomics of skin dendritic cells and macrophages in an imiquimod-induced, biphasic mouse model of psoriasis. Terhorst, D, et al, J Immunol. 2015

OBJECTIVES:

- To decipher the myeloid complexity in melanoma mouse models
- To describe the immunological landscape of murine healthy prostate and during the development of prostate cancer using a mouse model recapitulating the human prostate cancer development
- To compare cDC1 and LC vaccine targeting and the route of immunization to propose innovative vaccines against tumor and pathogens

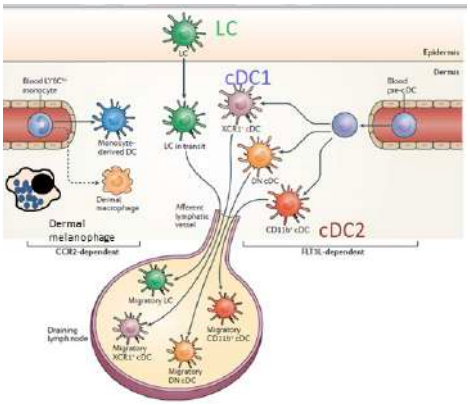
TOOLS:

- Multi-parametric advanced flow cytometry
- Knock-in, knockout, transgenic mouse models
- Transcriptomic analysis

Deciphering the myeloid complexity in murine skin

RESULTS:

- Identification of dermal macrophage subsets and dermal melanophages
- Role of macrophage in tattoo persistence
- Identification of XCR1+ cDC1 in dermis
- Cross-presentation functions of cDC1 and role in CD8-mediated immunity and tolerance
- ALDH production by dermal cDC2 and role in Treg induction and peripheral tolerance
- Suppressive functions of epidermal Langerhans cells (LC) in a psoriasis mouse model

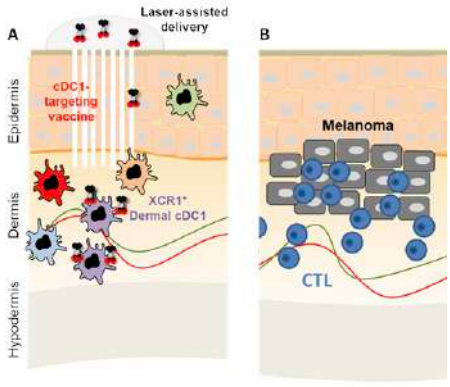


The skin is populated with various myeloid cells such as conventional dendritic cells subsets (cDC1, cDC2, DN cDC and LC) which can migrate to the draining lymph node and prime naive Tcells, monocyte and monocyte-derived DC, macrophages and melanophages.

Dermal cDC1-targeting vaccine

RESULTS:

- Skin laserporation allowing a needle free vaccine
- Specific targeting of the vaccine antigen to dermal cDC1
- Needle and adjuvant free vaccine against melanoma



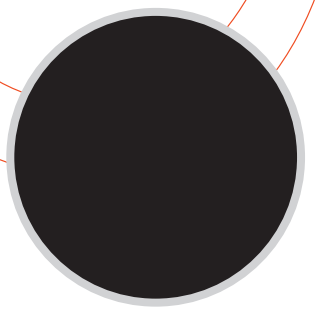
Skin laserporation followed by topical application of cDC1-targeting vaccine allowed to induce CD8+ cytotoxic T cells (Tcells) and to reject melanoma tumor growth.

PERSPECTIVES:

- Providing an immunological landscape of melanoma and prostate tumors to design innovative therapeutic approaches targeting the myeloid compartment
- Design innovative DC-targeting vaccine against tumor and pathogens

UNIQUE SELLING POINTS:

- Expert in myeloid cells
- Expert in skin immunity
- Using various mouse models to decipher myeloid cell functions in vivo
- Capitalizing our knowledge on cancer immunity to design innovative therapeutic approaches



HENRY Thomas

Ph.D

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Inflammasomes and autoinflammation

Keywords:

- Inflammasome,
- systemic inflammation,
- Familial Mediterranean Fever,
- functional diagnosis,
- Inflammatory cell death,
- monocytes/ macrophages,
- IL-1 /IL-18,
- inflammasome activator/inhibitor.

The team has 15 years of expertise on inflammasomes, from molecular mechanisms to translational research, in cohorts of patients suffering from hereditary autoinflammatory diseases.

Our research interests are centered on innate immune complexes termed inflammasomes and involved in numerous autoinflammatory syndromes. We have been focusing on the pyrin and the NLRP3 inflammasomes and their implication in different autoinflammatory diseases, including the most frequent hereditary autoinflammatory disease, Familial Mediterranean Fever. Familial Mediterranean fever (FMF) is due to a deregulation of the pyrin inflammasome leading to high inflammatory cell death (IL-1 and IL-18 production). Starting from mechanistic studies on the pyrin inflammasome, we uncovered the defect causing FMF and have validated our results on primary monocytes from a large cohort of patients.
Based on these results, we have developed a fast functional diagnostic test for FMF patients.
In addition, we have developed an original screen that has led us to identify novel activators of the pyrin inflammasome, that may act as immunostimulants.
We are currently adapting the screen to identify pyrin inhibitors, that could be more specific or better tolerated than colchicine, the current pyrin inhibitor used in clinic.
In addition to our current work on primary cells from patients suffering from inflammasomopathies, we are developing novel mouse models of Familial Mediterranean Fever.

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- Pyrin dephosphorylation is sufficient to trigger inflammasome activation in Familial Mediterranean Fever patients. Magnotti F, (…) Jamilloux Y@, Henry T@@Co-corresponding author. **EMBO Molecular Medecine** 2019 Oct 7
- A genome-wide screen identifies IRF2 as a key regulator of caspase-4 in human cells. Benaoudia S, Martin A, Puig Gamez M, Gay G, Lagrange B, Cornut M, Krasnykov K, Claude JB, Bourgeois CF, Hughes S, Gillet B, Allatif O, Corbin A, Ricci R, Henry T. **EMBO Reports** 2019 Jul 29
- Human caspase-4 detects tetra-acylated LPS and cytosolic Francisella highlighting functional differences with murine caspase-11. Lagrange B, Benaoudia S, Wallet P, Magnotti F, Provost A, Michal F, Martin A, Di Lorenzo F, Py FB, Molinaro A, Henry T. **Nature Communications**, 2018 Jan; 9 (1), 242
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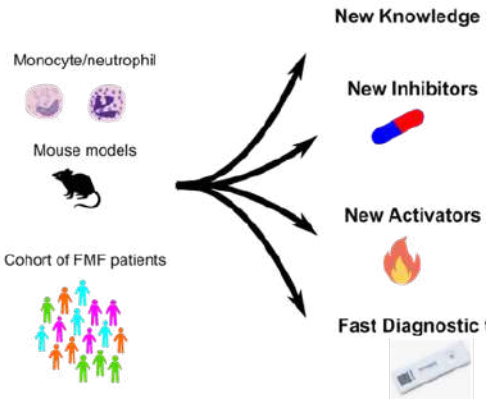
OBJECTIVES:

- Understand inflammasome-related autoinflammatory syndromes (Familial Mediterranean fever (FMF) and others)
- Develop a fast diagnostic test for FMF
- Identify novel inhibitors and activators (immunostimulants) of the pyrin inflammasome

TOOLS:

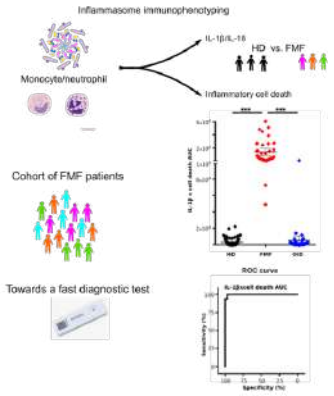
- Engineered cell lines
- Comprehensive inflammasome monitoring platform in primary human monocytes
- Cohorts of patients (Familial Mediterranean fever, Cryopyrin-associated periodic syndromes, Still's disease)
- Chemical screening platform (pyrin inflammasome)
- Novel mouse models being developed



Understanding autoinflammation in Familial Mediterranean fever patients
From innate immune complex to a fast diagnostic test

RESULTS:

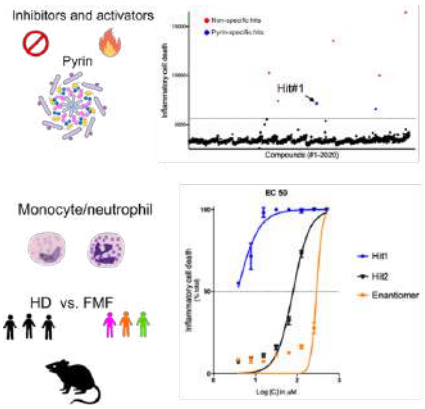
- By studying the molecular mechanisms of pyrin inflammasome activation, we identified the cause of autoinflammation in FMF patients
- This result was validated in a large cohort of FMF patients
- This knowledge leads to a fast diagnosis of FMF



Identification of novel activators and inhibitors of the pyrin inflammasome

RESULTS:

- The only inhibitor of pyrin described so far is colchicine
- High need for new inhibitors
- Potential use of pyrin activators as immunostimulants
- We have developed a pipeline to screen for activators and inhibitors of the pyrin inflammasome
- Novel activators have been identified and validated.



PERSPECTIVES:

- Identify novel pyrin inflammasome inhibitors to be tested in monogenic autoinflammatory diseases and complex inflammatory diseases
- Whole blood diagnostic test for FMF (inflammasomopathy biomarker)
- Investigate vasculitis and serositis in mouse models of FMF
- Use monogenic diseases (FMF) to learn about complex autoinflammatory diseases

UNIQUE SELLING POINTS:

- 15 years of expertise on inflammasomes in mice and humans
- Comprehensive Inflammasome monitoring in primary cells from patients
- From fundamental mechanisms to cohort of patients
- Novel activators identified
- Screening platform ready for inhibitor identification
- Novel mouse models of Familial Mediterranean Fever
- Team including clinicians & Inserm researchers
- Large clinical network (in Lyon-Lyon University Hospital, in France-CeRémAIA-national reference center for rare autoinflammatory diseases and amyloidosis, in Europe-ImmunAID)

HUGOT Jean-Pierre

Professor (MD, PhD)

UMR 1149, INSERM, Université de Paris
Research Center for Inflammation team "gut inflammation"
Université de Paris, Assistance Publique Hôpitaux de Paris

Gut inflammation

Keywords:

- Gut inflammation,
- Crohn Disease,
- Ulcerative Colitis,
- Chronic Juvenile Arthritis,
- Patient cohorts,
- Translational research,
- Mucosal immunity,
- Gut microbiota,
- Genetics and epigenetics,
- Micro RNA.

Defining the mechanisms and testing new therapeutic approaches to progress in the diagnosis, prognosis, prevention and treatment of gut inflammation.

Based on original animal models, patient cohorts and biobanks, our research is focused on gut inflammation. The laboratory is part of the Research Centre for Inflammation which consists in 12 different teams with complementary expertise in immunology, molecular biology, animal models and imaging, especially in the field of digestive diseases (https://cri1149.fr/). It is backed to large adult and children hospitals in the North of Paris (Hospitals Beaujon, Bichat, Robert Debré and others); the research clinical networks GETAID, Pediatric GETAID and REMIND and the network for rare digestive disease centres. It is in strong interaction with patient "association François Aupetit" and the epidemiological "EPIMAD" registry. These well-established collaborations allow to develop combined approaches at population, patient, cellular and molecular levels and to transfer easily the results to clinical practice.
We develop research programs in order to understand the interactions between susceptibility genes, exposure to food and microbial agents, gut microbiota composition, gut permeability and mucosal immune system.
A selection of recently published works is shown below (laboratory members are first, last or corresponding authors of the listed original articles).

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- Al Nabhani Z et al. Nod2 Protects the Gut From Experimental Colitis Spreading to Small Intestine. J Crohns Colitis. 2020 Jun 19;14(5):669-679.
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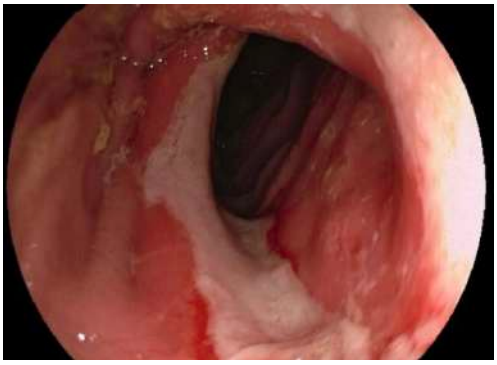
- Maurel M et al. Control of anterior GRadient 2 (AGR2) dimerization links endoplasmic reticulum proteostasis to inflammation. EMBO Mol Med. 2019 Jun;11(6):e10120.
- Morilla I et al. Colonic MicroRNA Profiles, Identified by a Deep Learning Algorithm, That Predict Responses to Therapy of Patients With Acute Severe Ulcerative Colitis. Clin Gastroenterol Hepatol. 2019 Apr;17(5):905-913.

OBJECTIVES:

- To understand the role genetic and epigenetic markers in inflammatory bowel disease (IBD).
- To identify food and microbial determinants of inflammatory bowel disease
- To propose new prognostic tests
- To dissect the crosstalk between the microbiota, the epithelium and the immune system.
- To explore and validate new therapeutic approaches in relevant animal models.
- To describe the impact of gut inflammation on other organs (joints, liver, etc).

TOOLS:

- Access to French and European academic research networks
- Large cohorts of pediatric and adult patients
- Biobanks of mucosal biopsies (5000 samples)
- A microbiota analysis platform within the lab
- Original animal models
- An imaging platform for small animals.
- A platform of cellular and molecular biology

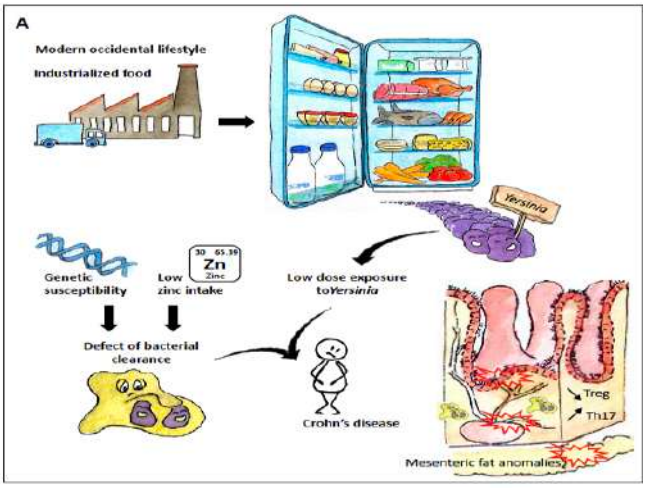


Crohn Disease-like phenotype after neonatal Ileocaecal surgery (Frémond ML JCC 2014)

Subject 1: understanding the genetic and environmental causes of IBD.

RESULTS:

- Identification of IBD susceptibility genes.
- Dissection of the genetic architecture of the disease.
- Low Zinc intake is a risk factor for Crohn Disease.
- Yersinia species are good candidates to trigger the inflammation in Crohn Disease.
- Dietary emulsifiers impact Adherent-Invasive E. coli gene expression to drive chronic intestinal inflammation.
- New mathematical models for complex genetic disorders.

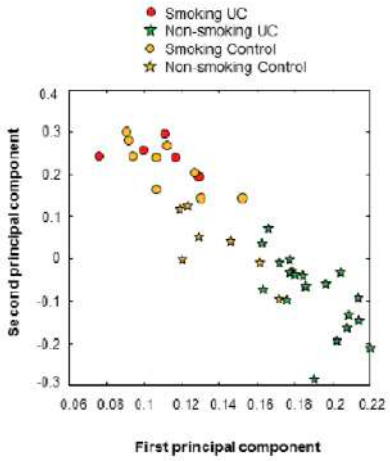


According to the « cold chain hypothesis », refrigerated food leads to exposure to Yersinia species which promote gut inflammation in genetically at risk Crohn Disease patients. (Hugot JP. JCC 2020)

Subject 2: identification of pronostic markers for IBD

RESULTS:

- Identification of several mRNA signatures in the mucosa of ulcerative colitis patients associated with cancer risk, disease extension, risk of pouchitis or responses to treatments.
- Mucosal signatures of detoxification gene network in ulcerative colitis and its relation with tobacco.
- Identification of mi-RNA present in stools and able to modulate the inflammation in mice.
- Quantitative MRI characteristics as markers of histological inflammation in mice.
- Early arthritis is a prognostic marker of failure of immunosuppressive drugs in Pediatric Crohn Disease.
- Children with an ileocaecal resection may develop a Crohn Disease-like phenotype.

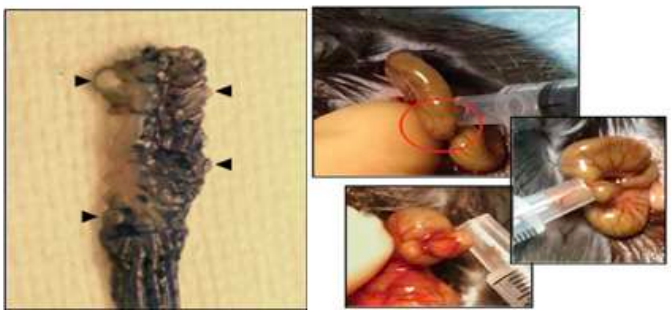


PCoA based on the expression of detoxifying genes in the mucosa of ulcerative colitis (UC)
And healthy controld according to smoking habits
(Ding YP et al. JCC 2016)

Subject 3 : dissecting the mechanisms of gut inflammation

RESULTS:

- Validation of original animal models for ulcerative colitis, perianal fistulas, and post-irradiation enterocolitis.
- Appendectomy is associated with a lower risk of colitis but a higher risk of colon cancer.
- Dissection of the crosstalk between the microbiota, the epithelial layer and the mucosal immune system.
- Nod2 regulates the intestinal permeability and limits the extension of gut inflammation in the digestive tract.
- AGR2 is a key regulator of the intestinal inflammation.
- Mechanisms of action of Yersinia species on intestinal permeability and gut inflammation.
- Epithelial reticulum stress and autophagy are key players in gut inflammation.



A. The NOX1/IL10 double KO mouse has been validated in the lab as a model of spontaneous colitis and colitis-related colonic cancer. B. A surgical procedure of neo-appendicitis improved the colitis.
(Harnoy Y et al. Br J Surg 2016)

PERSPECTIVES:

- To identify food habits associated with IBD relapses.
- To define the role of the gut barrier on joint inflammation.
- To explore the role of stool mi-RNA in mice and IBD patients.
- To validate a prognostic algorithm using the very early biopsies in pediatric Crohn Disease.
- To dissect the mechanisms carrying the impact of appendectomy and appendicitis on colonic cancer.
- To explore the impact of food habits and microbiota settlement on the epigenetics of healthy infants.

UNIQUE SELLING POINTS:

- A team of pediatric and adult gastroenterologists personally involved in the research lab.
- A large network of medical and scientific collaborators.
- The access to both rare diseases and large cohorts of patients
- Multiscale integrated research programs from the molecule to the population
- Original animal models

JOSIEN Régis

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Nantes Université, CHU Nantes

Translational immunology of immune-mediated inflammatory diseases, transplantation and infectious diseases

Keywords:

- Immunoregulation,
- Immune tolerance,
- Inflammatory bowel disease,
- Multiple sclerosis,
- Autoimmune hepatitis,
- Lung inflammation,
- Preclinical models,
- Biocollections,
- Immunointervention,
- Clinical research.

An integrated research centre devoted to translational immunology of immune-mediated inflammatory diseases, transplantation and infectious diseases.

We develop disease-oriented basic and translational research programs aiming at: 1. Understanding the molecular and cellular mechanisms by which the immune system promotes or control diseases or lesions in autoimmune/inflammatory diseases, transplantation and infectious diseases; 2. Translating these advances from the laboratory to the clinic by bringing new diagnostic and therapeutic developments; 3. Opening new avenues for alternative tissue repair strategies through better understanding the biology of cell and organism development. These programs are developed by multidisciplinary scientists and clinicians and rely on close collaboration with clinical departments at Nantes University Hospital as well as dedicated biocollections.

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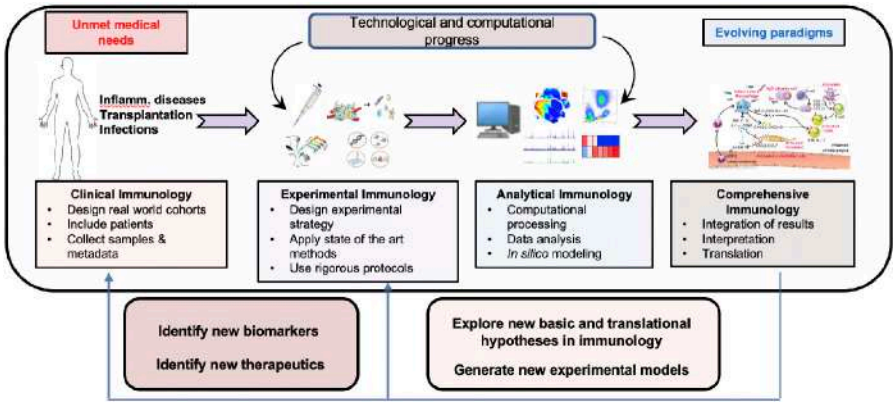
OBJECTIVES:

- To decipher the basic cellular and molecular mechanisms of tolerance and immunoregulation (central tolerance, Treg, Breg, TolDC)
- To decipher the role and mechanisms of action of T cell subsets in autoimmunity (multiple sclerosis, autoimmune hepatitis)
- To characterize mononuclear phagocytes heterogeneity and functions in inflammatory bowel diseases and lung inflammation for better understanding their role and discovering new relevant therapeutic targets
- Development of new cellular and molecular immunointervention strategies

TOOLS:

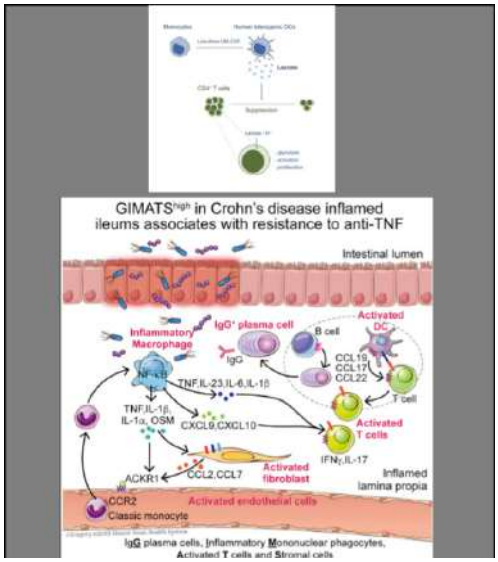
- Patients cohorts, samples and biorepositories
- High dimensional analyses of immune responses (spectral flow cytometry, multiplex imaging, functional genomics)
- Single cell genomics facility
- Clinical immunomonitoring platform (CIMNA) in compliance with ISO 15189
- Preclinical models including in house generated genetically modified rodents, humanized rodents, Large animal models



Mononuclear phagocytes in mucosal inflammation and immunoregulation

RESULTS:

- Immunoregulatory role of lactate produced by human tolerogenic dendritic cells
- Identification using single cell RNAseq of a gene and cellular module enriched in Crohn diseases patients' resistant to anti-TNF, likely driven by inflammatory mononuclear phagocytes
- Long term Immunoparalysis of alveolar macrophages after lung inflammation due to epigenetic remodelling

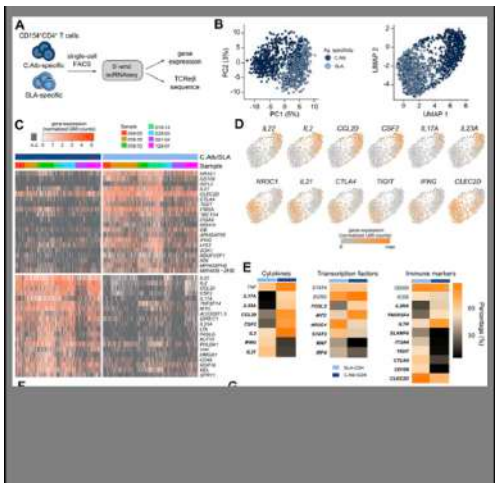


Legend: a. The potential role of lactate produced by tolerogenic dendritic cell in immunoregulation (Cell Metab 2019); b. The role of inflammatory macrophages in driving immunopathology and TNF blocker resitance in Crohn's disease (Cell 2019)

T cells subsets in human autoimmune diseases

RESULTS:

- Identification of a rare circulating autoreactive T helper subsets in human autoimmune hepatitis
- Characterization of pathogenic CD8+ T cells in multiple sclerosis
- Mechanisms of action of AIRE in central tolerance



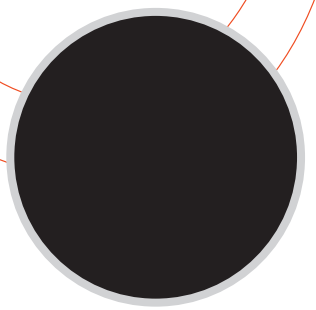
Legend: high dimensional characterization of a circulating auto reactive T helper subsets in human auto immune hepatitis (J Hepatol 2020)

PERSPECTIVES:

- In depth characterization of effector and immunoreguylatory cells in autoimmune/inflammatory diseases using single cell and high dimensional approaches
- Discovering new therapeutic target
- Proof of concept for innovative immunointervention in pre-clinical models
- Development of first-in-human clinical trials
- Applying single cell genomics to stratify patients, understand resistance to treatment and help designing therapeutic clinical trials

UNIQUE SELLING POINTS:

- Expertise in translational immunology at the epigenomic, genomic, molecular and cellular levels
- Expertise in high dimensional functional genomics and single cell omics approaches (integrating bioinformatics analysis)
- Expertise in immunomonitoring through the CIMNA platform dedicated to translational and clinical research
- Long standing commitment to translational research and long term expertise in early clinical development
- Numerous active external international collaborations and collaborative networks
- Solid experience in data valorization and industry partnerships



KLATZMANN David

Professor of Immunology, M.D., Ph.D.

U959, Sorbonne University, INSERM
APHP and Sorbonne University

Leveraging multi-omics reductionist and systems immunology approaches for understanding and treating autoimmune/inflammatory diseases

Keywords:

- Systems immunology,
- Autoimmunity,
- Inflammation,
- Biotherapies,
- Immunotherapies,
- Lymphocytes,
- Regulatory T cells,
- Interleukine-2,
- TCR repertoire;
- Microbiome.

We assembled an interdisciplinary group of biologists, data scientists and clinicians that together leverage reductionist and systems immunology approaches based on multi-omics investigations for understanding and treating autoimmune/inflammatory diseases..

We have developed, optimized and standardized a deep immunomonitoring pipeline based on multi-omics investigations: cell proteomics, serum proteomics and cell transcriptomics including T cell receptor (TCR) deep sequencing, all these being performed on (i) purified effector and regulatory T cell bulk populations or (ii) single cells; microbiome.
We have implemented data integration processes based on Open Clinica and TranSmart.
We have benchmarked data analyses tools and developed our own ones for supervised and unsupervised analyses of these multi-omics, both at single scale and multi-scale levels.
We are applying these unique expertise and tools to 3 main themes:

- *Understanding the pathophysiology of autoimmune/inflammatory diseases*, under the LabEx Transimmunom and ERC TRiPoD. We have collected and are analysing the clincial data and samples from over 500 patients with various AIDs. We aim to discover underlaying causal pathways and biomarkers *of diseases.*
- *Understanding the biology and therapeutic efficacy of low-dose IL-2*, under the RHU iMAP. We are studying samples from 6 clinical trials of low-dose IL-2 in SLE, T1D, MS, RSA, healthy volunteers and a basket trial of 11 different AIDs. We aim to understand the biology of IL-2 in humans and to discover biomarkers of efficacy.
- *Developing improved Treg-based biological and cell therapies of AIDs*. We have developed and patented such novel therapeutics that cannot be disclosed here.

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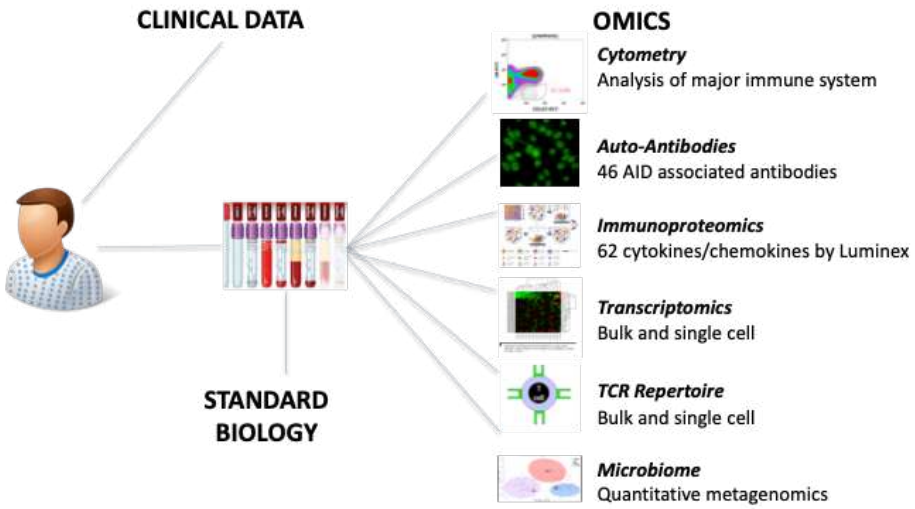
OBJECTIVES:

As an interdisciplinary group of biologists, data scientists and clinicians, we leverage multi-omics for implementing a translational systems immunology approach aimed at:

- Understanding the pathophysiology of autoimmune/inflammatory diseases (AIDs)
- Understanding the biology and therapeutic efficacy of low-dose IL-2
- Developing improved Treg-based biological and cell therapies

TOOLS:

- A comprehensive database with clinical and biological multi-omics data covering 19 AIDs
- A unique precision phenotyping panel comprising high throughput data acquisition
- A unique systems biology approach including supervised and unsupervised single- and multi-scale analyses



Precision Immunophenotyping: Data integration and analysis

RESULTS:

Clinical and biological data are integrated in:
- *OpenClinica* that we used to assemble an unprecedented database composed of 28 eCRFs. The coding is harmonized following CDASH rules and represents over 835 parameters and more than 6000 different values (Lorenzon et al. BMJ Open)
- tranSMART that stores and manage multi-parametric and heterogenous data for high-dimensional analyses

Deep immunophenotyping by flow cytometry :
- generates 700 parameters per patient that are analysed with multiparametric unsupervised automated workflow using R packages (flowCore, tSNE, flowMeans…)

TCR repertoire:
- a robust, reproducible and automated methodology has been developed after an international benchmarking study (Barennes et al. Nature Biotechnology)
- an integrated workflow has been developed and allows the identification of disease specific signatures in AIDs

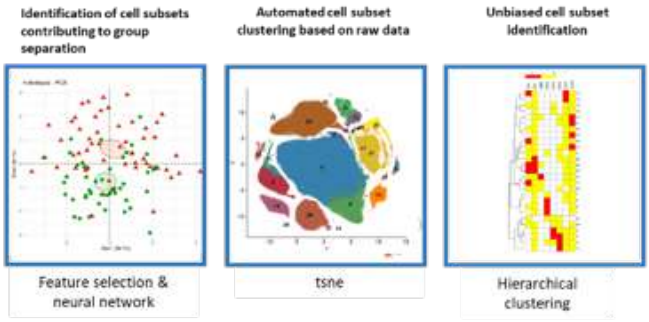
Transcriptome:
- RNAseq has been optimized using low input RNA from sorted Treg and Teff cells
- Transcript analysis and gene co-expression network analysis are performed

Microbiome:
- quantitative metagenomic sequencing is performed on stool collected according to international quality procedures for human microbiome standards

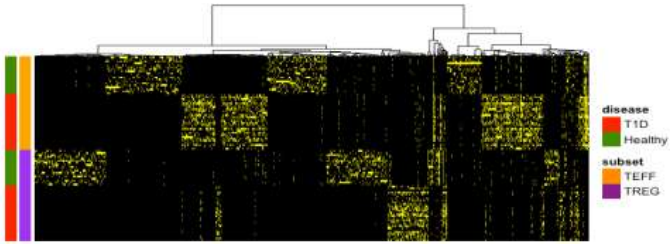
Multi-scale analysis:
- integration of using MixOmics approaches allows to establish correlation and predictive models from heterogeneous datasets

Single cell studies:
- 10X Genomics single-cell transcriptomic and TCR data collection and analyses

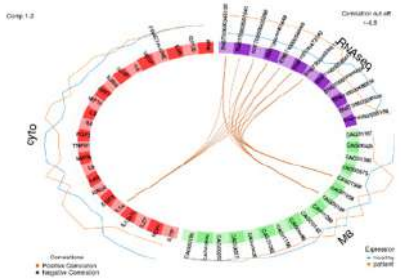
Unsupervised flow cytometry data analysis



Ingetrated workflow for TCR data analysis



Multi-scale analysis



Precision immunophenotyping: a unique data collection

RESULTS:

The entire precision immunophenotyping panel has been acquired from:

- An observational cohort : Transimmunom (NCT02466217) that is currently composed of 500 patients with 19 autoimmune/inflammatory diseases and healthy volunteers

6 clinical trials of low dose IL2 that currently gather more than 400 patients with:

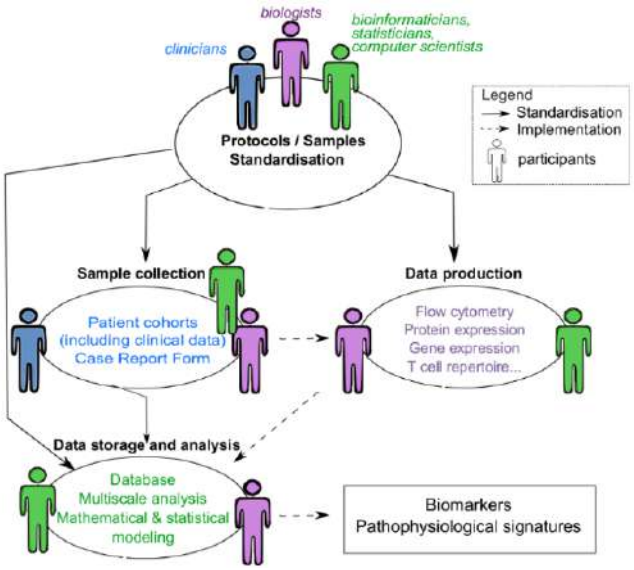
- Systemic lupus erythematosus: LUPIL2 (NCT02955615),
- Type 1 diabetes: DIABIL-2 (NCT02411253),
- Remitting relapsing multiple sclerosis: MS-IL2 (NCT02424396),
- Recurrent spontaneous abortion: FACIL-2 (NCT03970954)
- One of 13 selected autoimmune diseases: Transreg (NCT01988506)
- Or in healthy volunteers: HEALTHIL-2 (NCT03837093)

PERSPECTIVES:

- Providing an **exhaustive clinical and biological database** including more than 500 patients with AIDs and healthy donors, that will allow to decipher **underlaying causal pathways and biomarkers of diseases**
- Providing an integrated platform for **high-throughput data production, integration and analysis for the in-depth study of AIDs**
- Providing **unprecedented insights on the biology of low-dose IL2 therapy**
- Providing **unprecedented insights on sorted Treg and Teffs in the context of diseases and of immunotherapies**
- Providing a **unique expertise in TCR repertoire analysis**
- Developing **improved Treg-based biological and cell therapies of AIDs**

UNIQUE SELLING POINTS:

- The CIC-BTi and i3 structures provide a unique setting and **expertise for translational systems immunology**
- The CIC-BTi has structured a truly **multidisciplinary group** composed of clinicians, data scientists and biologists to tackle the challenges of big data in immunology and medicine
- The CIC-BTi possesses a **unique set of multiOMICs data** generated in more than 19 autoimmune and inflammatory disorders



LAPLAUD David-Axel

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Multiple Sclerosis: from translational immunology to epidemiology

Keywords:

- Multiple sclerosis,
- Neuromyelitis Optica,
- CD8 T cells,
- Multidimensional single-cell approach,
- Treatment effectiveness,
- OFSEP database.

I work on the immunological mechanisms involved in multiple sclerosis as well as on the use of observational databases to answer clinical questions related to the disease.

My scientific activity is built around two axes:

- A research activity in translational immunology in order to discover or deepen the pathophysiological mechanisms leading to multiple sclerosis (MS). Currently, my work is more specifically focused on the role of CD8 T lymphocytes but we have also opened up research axes on B lymphocytes, on the analysis of the Kir4.1 antigen and on the interaction of the intestinal microbiota with the immune system in MS. CD8 T lymphocytes are the predominant cells within MS lesions with a memory phenotype and granzyme B secretion, suggesting an active role of these cells in lesion formation. However, in the periphery, there is no identification of the CD8 T cells specifically involved in central nervous system enrichment yet, which would eventually allow the development of new therapeutic targets and/or specific biomarkers. Using a multidimensional single cell approach, we are able to define CD8 T cell phenotype(s) specifically associated i) with MS in comparison to healthy controls and other inflammatory disorders of the CNS and ii) with clinical activity of the disease in comparison with remission.
- An epidemiological research activity in collaboration with OFSEP, on the comparative effectiveness of treatments, on the prognostic determinants of MS, on the long-term effectiveness of treatments or on the effectiveness of stratification of the risk of PML under Natalizumab. I developed a group within OFSEP (Methodology Group made up of Prof. Sandra VUKUSIC, Neurologist, Dr Emmanuelle LERAY, Epidemiologist, Dr Yohann FOUCHER, Biostatistician, Fabien ROLLOT, Biostatistician, Romain CASEY, Epidemiologist) in order to set up new projects based on OFSEP database.

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OBJECTIVES:

- To define a specific immunophenotype of circulating CD8 T cells associated to MS
- Predictive medicine: to stratify MS patients according to their potential treatment respons

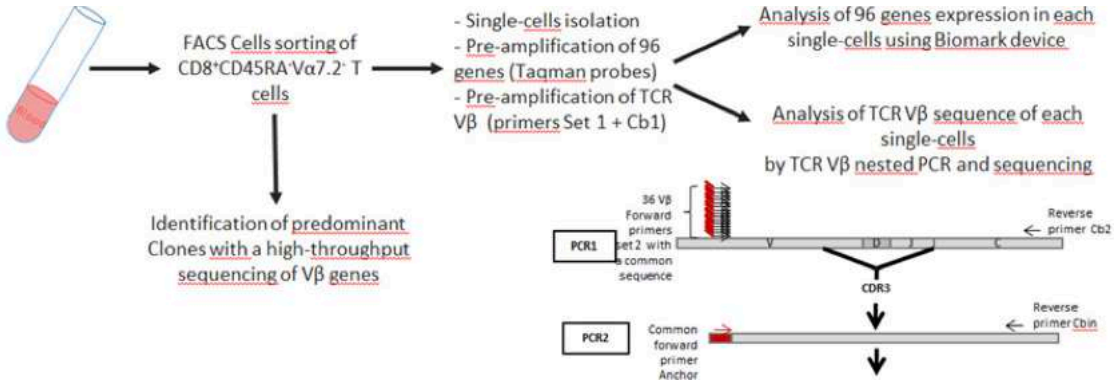
TOOLS:

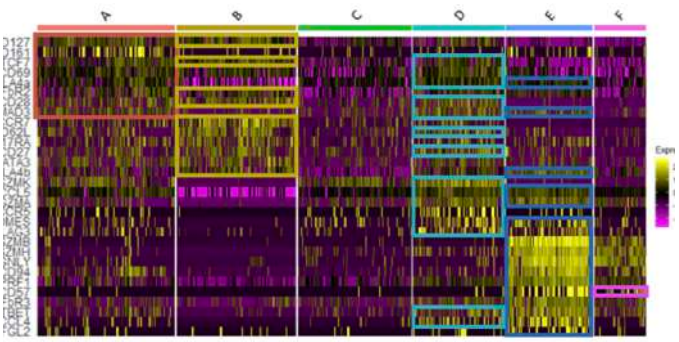
- Single cell analyses (RNAseq, qPCR single cell, flow cytometry)
- Laser microdissection/in situ high-scale immunophenotype
- OFSEP Database

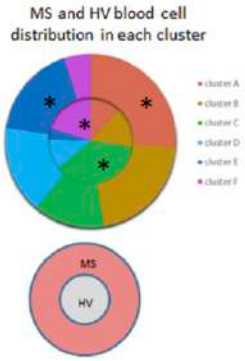
To define a specific immunophenotype of circulating CD8 T cells associated to MS

RESULTS:

- Two different subsets of circulating memory CD8 T cells are associated to MS, one of them being associated with clinical/radiological activity
- Validation with a specific cohort using a different technological approach
- Subset of cells enriched in MS lesions



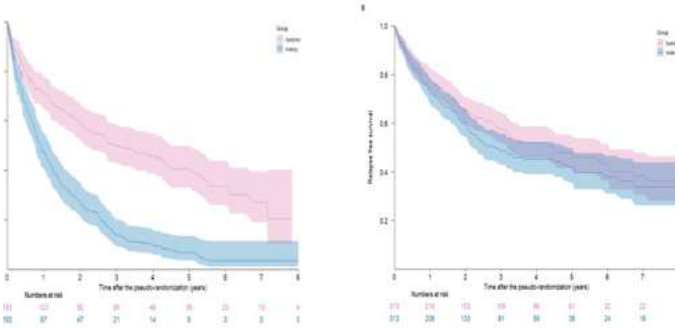


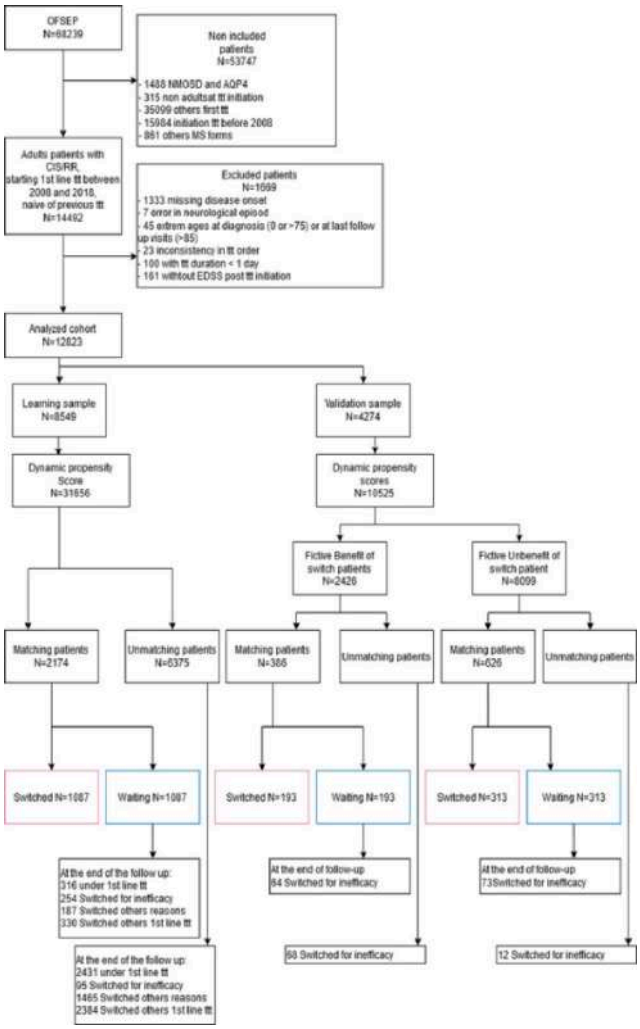


Predictive medicine: to stratify MS patients according to their potential treatment response

RESULTS:

- Construction and validation of a dynamic scoring system able to discriminate MS patients treated with first line drugs having advantage to switch to a second-line treatment
- Validation with pseudo-randomized clinical trials using dynamic propensity scores



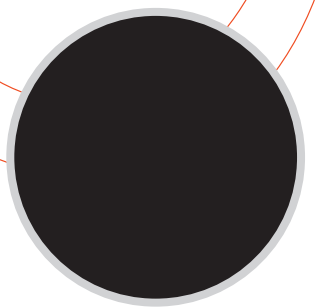


PERSPECTIVES:

- Genomic analyses in NMO-SD and comparison with MS
- Gut and saliva microbiota in MS: role of IgA
- Determining cell subsets associated with remyelination abilities using single-cell RNAseq
- Determining cell subsets associated with a poor outcome in patients seen at the time of the first demyelinating event

UNIQUE SELLING POINTS:

- Patient cohorts of neuroinflammatory disorders including PBMCs, CSF and autopsy
- Strong collaborations with OFSEP and NOMADMUS databases
- Up-to date technologies (single-cell RNAseq, high-dimensional single-cell qPCR, high-dimensional in situ immunophenotyping, spectral flow cytometry)



LE BOURHIS Lionel

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Lympho-epithelial interactions in human intestinal immunity: Impact on inflammation and cancer

Keywords:

- Intestinal immunity,
- Inflammatory Bowel Diseases,
- Colorectal Cancers,
- T cells,
- Epithelial cells,
- Organoids,
- Immunotherapies,
- TCR repertoire.

We study the role of human T lymphocytes in intestinal immune responses in the context of Inflammatory Bowel Diseases or Colorectal Cancers.

Intestinal tissue resident T lymphocytes acquire particular features that have major impact on tissue homeostasis, the physiopathology of inflammatory bowel diseases (IBD) and the response to colorectal cancers (CRC). We characterize, exclusively from human samples, the specific functions of intestinal T cells and dissect the underlying mechanisms that govern their regulation in health and diseases.

First, in IBD patients, we established that activation of cytokine-related pathways (such as JAK/STAT) in the surgical specimen was associated with disease relapse. We also determined that the T cell repertoire was altered as persistent oligoclonal expansions, along the mucosal tissue and over time, are present in IBD patients and are associated with disease activity. We analysed the phenotype and function of T cells in human intestinal mucosa and show that integrins implicated in the recruitment and retention of T cells in the tissue, which might be implicated in the physiopathology of CD.

Second in CRC, we perform phenotypic analyses of effector T cells isolated from tumours and paired healthy tissues; and show modulation of activatory and inhibitory molecules at their surface. Using an in vitro spheroid model, we show that T cells and NK cells can be modulated to enhance the anti-tumour response in a three-dimensional context.

In both pathological context, we constitute bio-banks of tissue samples to perform histological, microscopic and transcriptional analyses. In parallel, we isolate primary intestinal epithelial cells or cancerous cells in order to co-culture the obtained organoids with autologous tissue resident T cells. These technics allow the study of lympho-epithelial interactions in health, inflammation or cancer; as well as their modulation by clinically relevant molecules.

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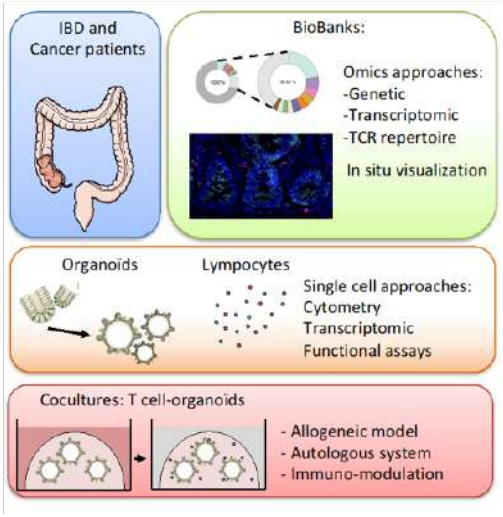
OBJECTIVES:

- To study the role of T cells in the physiopathology of Inflammatory Bowel Diseases
- To study the impact of mucosal T cells on ColoRectal Cancer
- To study lympho-epithelial interactions in clinically relevant organoid culture models
- To test new immuno-modulatory pathways for the treatment of IBD and CRC

TOOLS:

- Extensive IBD and CRC patient biobank
- Molecular analyses
  - Transcriptomic
  - TCR repertoire
  - ...
- Cytometry and microscopy analyses
- Human intestinal organoid culture
  - Lympho-epithelial co-cultures
  - Epithelial differentiation
  - Cell proliferation and death



T cells impact on the physiopahtology of Inflammatory bowel diseases

RESULTS:

- T cells are implicated in IBD physiopathology
- TCR repertoire is altered in IBD patients
- Resident T cell populations interacting with epithelial cells could be key druggable targets in IBD

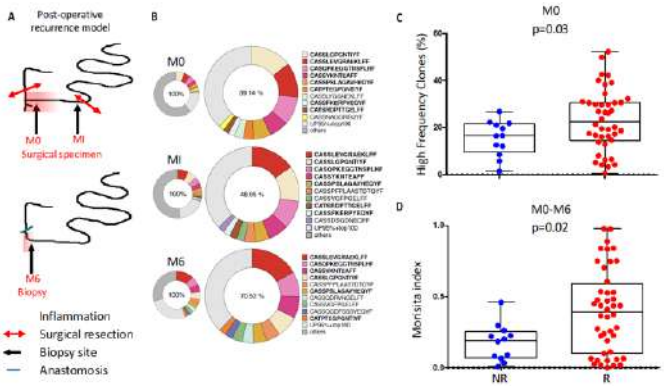
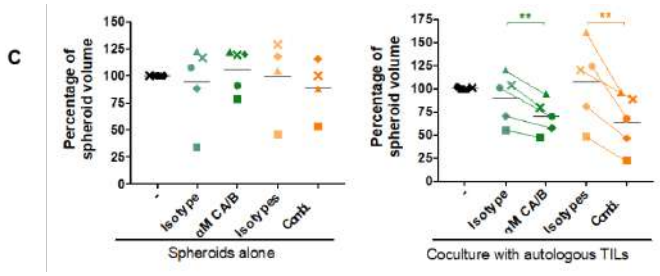


Figure 1: T cell clonal expansions are associated with post-operative recurrence of the disease. A. Ileo-cecal post-operative recurrence model. B. Sequencing results of three biopsies from one patient of the REMIND cohort at M0, MI and M6. C. Percentage of high frequency clones at M0 in patients without (NR) or with (R) recurrence of the disease six months post-surgery. D. Morisita similarity index of the TCR repertoire between M0 and M6 in patients without (NR) or with (R) recurrence of the disease six months post-surgery.

Intestinal specific immune check-points control immune responses to colorectal cancers

RESULTS:

- The NKG2D-MICA/B pathway is involed and can be targeted against CRC
- NKG2A is an inhibitory molecule impacting immune responses to CRC
- Modulation of these pathways in organoid model in CRC



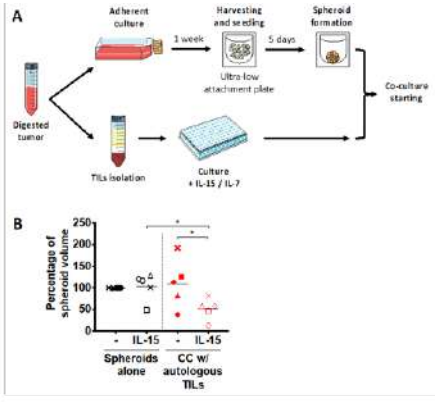


Figure 2: Tumor-derived spheroids are destroyed by autologous tumor infiltrating lymphocytes (TILs): A. Co-culture model. B. Spheroids derived from CRC patients (n=5) were culutreud in presence or absence of autologous TILs with or without human IL-15. Volume of spheroids were measured by microscopy. C. Spheroids were cultured as in B. in presence of agonist anti-MICA/B and antagonist anti-NKG2A antibodies.

PERSPECTIVES:

- Large TCR repertoire analyses in IBD and CRC patient cohorts
- Detection and characterization of T cell clones in IBD and CRC in situ
- Characterization of intestine specific immuno-modulatory pathways involved in IBD and in response to CRC
- Study and modulation of lympho-epithelial interactions in IBD and CRC using organoid T cell autologous co-culture models

UNIQUE SELLING POINTS:

- Large extensive biobank of IBD and CRC patients
- Access to primary intestinal tissue samples for cells isolation and culture
- Organoid culture technology from healthy, inflamed and cancerous tissues
- T cells analyses expertise: phenotypic, functional, in situ, TCR repertoire

LE PANSE Rozen

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Myasthenia Gravis: etiology, physiopathology and therapeutic approaches

Keywords:

- Autoimmunity,
- Myasthenia Gravis,
- Thymus,
- Inflammation,
- Muscle,
- Experimental mouse models,
- Mesenchymal stem cells,
- Biomarkers.

Understand the etiological and pathophysiological mechanisms involved in myasthenia gravis to propose new therapeutic approaches.

Acquired Myasthenia Gravis (MG) is a rare neuromuscular disorder, characterized by a defective transmission of nerve impulses to muscles, leading to muscle weakness and disabling fatigability. **MG is due to autoantibodies directed against components of the neuromuscular junction**, mainly the acetylcholine receptor (AChR). **The thymus is most likely the site of initiation of MG with anti-AChR antibodies**. Histological abnormalities of the thymus are very common: 50-60% of the patients present follicular hyperplasia with ectopic germinal centers, and 10-15% of the patient present a tumor of the thymus (Thymoma). Thymectomy is one of the treatments proposed to these patients.

The research projects developed by my team aim to understand the **etiological and pathophysiological mechanisms involved in myasthenia gravis and to propose new therapeutic approaches.** More specifically, our objectives are to:

- Elucidate the etiological mechanisms involved in autoimmunity by analyzing the impact of sex hormones and endocrine disruptors in central tolerance processes.
- Understand the cellular and molecular mechanisms at the origin of thymus inflammation and remodeling observed in patients.
- Study the immunoregulatory defects in myasthenia gravis patients by studying the functional phenotype of peripheral and thymic cells by mass cytometry (CyTOF).
- Develop new therapeutic approaches. In this context, we are studying the immunomodulatory and therapeutic potential of mesenchymal stem cells, and the potential of molecules interfering with inflammatory pathways.
- Search for circulating biomarkers to follow the evolution of the disease and the response to treatments.

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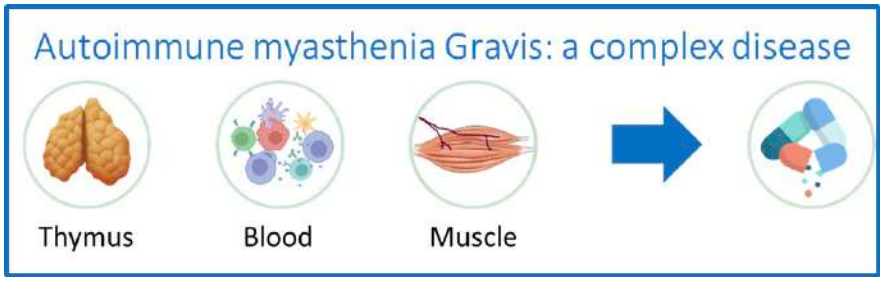
OBJECTIVES:

- Elucidate the etiological mechanisms involved in autoimmunity by analyzing the impact of sex hormones and endocrine disruptors in central tolerance processes.
- Understand the cellular and molecular mechanisms at the origin of thymus inflammation and remodeling observed in patients.
- Study the immunoregulatory defects in myasthenia gravis patients by studying the functional phenotype of peripheral and thymic cells by mass cytometry (CyTOF).
- Develop new therapeutic approaches: we are studying the immunomodulatory and therapeutic potential of mesenchymal stem cells and of molecules interfering with inflammatory pathways.
- Search for biomarkers to follow the evolution of the disease and the response to treatments.



TOOLS:

- Database and Biobank with MG samples: serum, PBMC, thymus and muscles biopsies
- Experimental mouse models for MG
- Expertise in thymic epithelial cell cultures
- Expertise in Cytometry and CyTOF analyses

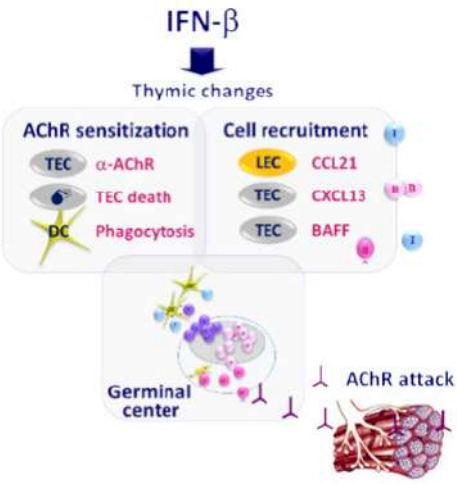
Subject 1: Study of thymic and peripheral signatures in MG

IFN-β is the orchestrator of thymic changes in MG inducing:

- The overexpression of the autoantigen (α-AChR) by thymic epithelial cells (TECs)
- The overexpression of chemokines and the recruitment of B cells
- An increased sensitization of DCs
- The production of huge amount of BAFF by TECs
- The production of Il-23 by TECs favoring Th17 cell differentiation

Multi-OMICs approaches for peripheral cells to discover convergent networks

- MG-associated genes discovered by the analysis of transcriptome and methylome of the main peripheral blood cell subsets in discordant monozygotic twins
- Mass Cytometry (CyTOF) of peripheral cells in progress
- Dysregulation of specific miRNAs in the sera of MG patients

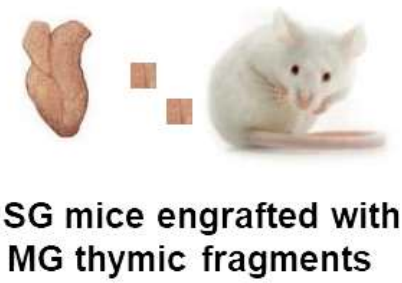


Subject 2: Development of new experimental MG models

Improve of the classical AChR experimental MG model

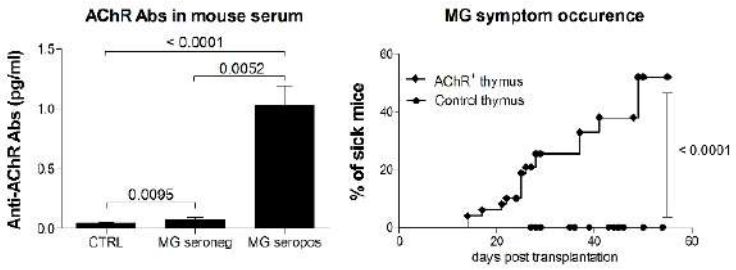
Robinet - Front. Immunol. 2017

Development of a CXCL13 transgenic model with thymic hyperplasia



Weiss - Oncotarget 2016

Development of a humanized MG-NSG mouse model



Sudres - J. Clin. Invest. Insight 2017

PERSPECTIVES:

- Single cell RNA sequencing of stromal thymic cells from MG patients combined to Imaging Mass Cytometry (Hyperion-Fluidigm)
- Analyses of the impact of endocrinal disruptors on the thymus
- Development of experimental models more relevant for the human pathology
- Preclinical studies on mouse models

UNIQUE SELLING POINTS:

- Database and Biobank with MG samples: serum, PBMC, thymus and muscles biopsies
- Unique research team in France working on myasthenia gravis
- Clause collaboration with Clinicians and patient's associations
- Experimental preclinical mouse models
- International network

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MAIT cells and riboflavin metabolites in host-microbiota interactions

Keywords:

- Microbiota,
- MAIT cells,
- Inflammatory bowel disease.

We use unique tools to reveal how the immune system monitors and responds to bacterial stress during intestinal inflammation.

Alterations in the composition and metabolic activity of the microbiota (eg dysbiosis) drives a number of pathological processes, but how the host monitors such changes remains poorly understood. Mucosal Associated Invariant T (MAIT) cells are conserved T cells with an emerging role in the recognition of microbiota-derived antigens. MAIT cell antigens are riboflavin metabolites produced by most bacteria and yeasts, but not by mammalian cells (reviewed in1). MAIT cells are abundant in human blood (1-8% of T cells), liver (20-40%) and mucosal tissues (1-10%) and are modified in many infectious and non-infectious pathologies including inflammatory bowel disease2,3, diabetes4, obesity5 and asthma6, and thus represent an important health issue.
We reported that the development of MAIT cells relies on the transfer of microbiota-derived metabolites from the gut to the thymus7. The study provided a first example of a foreign antigen controlling thymic development of specific T cells, and suggested a strong link between MAIT cells and the microbiota.
Building on these results we are now interested in the function of MAIT cells in the gut. We developed a sensitive bioassay to quantify MAIT antigens produced in the gut, and found over-production upon intestinal dysbiosis. MAIT antigen production was associated with oxidative stress in anaerobic bacteria such as Clostridia. A newly developed mouse strain revealed that MAIT cells produce tissue-repair mediators upon TCR stimulation in the gut, and protect against intestinal inflammation. Thus, we propose that MAIT cells sense oxidative stress in anaerobic bacteria and strengthen the gut barrier in response. The results help understand why the mammalian immune system has evolved the recognition of riboflavin metabolites, and will pave the way for controlled MAIT cell activation or inhibition to promote intestinal health.

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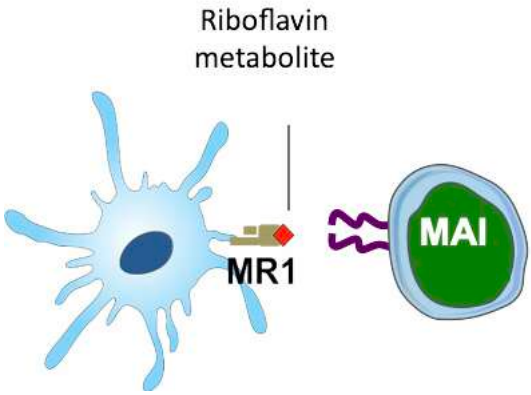
- **Microbial metabolites control thymic development of Mucosal Associated Invariant T cells**. Legoux#, Bellet, Daviaud, El Morr, Darbois, Niort, Procopio, Salou, Gilet, Ryffel, Balvay, Foussier, Sarkis, El Marjou, Schmidt, Rabot and Lantz#. Science (IF 37.2) 2019 366: 494-499. #Co-corresponding authors.
- **Molecular mechanisms of lineage decisions in metabolite-specific T cells.** Legoux*#, Gilet*, Procopio, Echasserieau, Bernardeau, Lantz#. ***Nature immunology*** (IF 21.8) 2019 20: 1244-1255. *Equal contribution. #Co-corresponding authors.
- **A common transcriptomic program acquired in the thymus defines tissue-residency of MAIT and NKT subsets**. Salou*, Legoux*, Gilet*, Darbois, du Halgouet, Alonso, Richer, Goubet, Daviaud, Menger, Procopio, Premel, Lantz. ***Journal of Experimental Medicine (***IF 10.9) 2019 216:133-151. *Equal contribution.

OBJECTIVES:

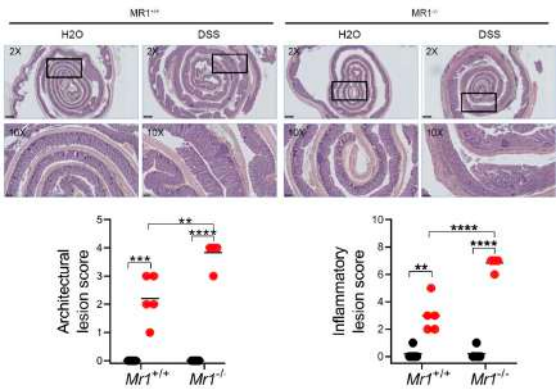
- Mechanistic understanding of a host-microbiota interaction associated with gut inflammation
- Develop tools for controlled manipulation of this interaction

TOOLS:

- Mice with controlled expression of the MHC molecule MR1
- In vitro and in vivo assays to quantify MAIT antigens produced by microbiota
- Synthetic agonist and antagonists for MAIT cells
- Gnotobiotic mice
- Genetically modified bacteria
- Metagenomics

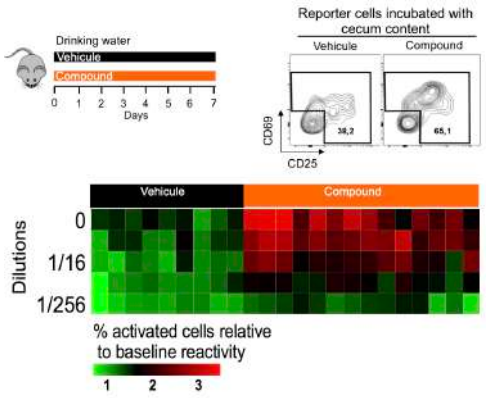


MAIT cells are protective in a mouse model of colitis



Legend: WT and MR1-/- mice, which lack MAIT cells, were treated with Dextran Salt Sulfate (DSS) to induce intestinal inflammation. Histological analysis of the colon reveals MR1-/- mice are more affected, indicating that MAIT cells are protective in this model.

Microbiota production of MAIT antigens can be manipulated



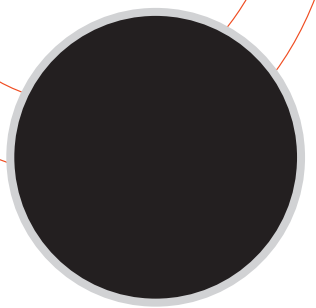
B6 mice were administered a compound for 7d in the drinking water. The concentration of MAIT antigens in intestinal contents was then measured using an in vitro assay, in which MAIT antigens are detected via CD69/ CD25 expression on reporter cells. The administered compound drives over-production of MAIT antigens.

PERSPECTIVES:

- Understand the rules governing MAIT cell activation by the microbiota
- Identify antigen presenting cells for MAIT cells in the gut
- Manipulate the microbiota or the host to improve MAIT cell function against intestinal inflammation
- Manipulate MAIT cells in other intestinal pathologies: infections and colorectal cancer

UNIQUE SELLING POINTS:

- Unique tools to study MAIT cells (mouse models, tetramers)
- Unique tools to study the microbiota (in vitro assays, modified bacteria, gnoto facility)
- Unique tools to manipulate MAIT cells (dedicated mouse model, synthetic compounds)



LEHUEN Agnes

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Inserm / CNRS unit, University, Pasteur Institute,...
For your lab: Cochin Institute, Université de Paris, Inserm 1016, CNRS UMR 8104
For yourself (your employer): CNRS

Immunology of Diabetes

Keywords:

- Type 1 diabetes, obesity,
- Innate immune cells,
- MAIT cells, inflammation,
- Cytotoxicity,
- Clinical studies,
- New mouse models

Immune cell dysfunction in type 1 diabetes and metabolic diseases: from biomarkers to therapeutic strategies

Our research interests focus on immune cell alterations leading to type 1 diabetes and metabolic diseases, as well as their complications in particular liver diseases. Our translational research benefits from international and national pediatric and adult cohort studies, from our unique mouse models and in vitro bioassays.

MAIT cells represent a unique innate T cell subset abundant in the blood, mucosal and metabolic tissues. Our recent studies highlight the role of MAIT cells in diabetes, obesity and liver diseases. Deciphering the mechanisms leading to specific MAIT cell activation in metabolic tissues and the gut mucosa could open new avenues for innovative treatments. Since MAIT cells recognized bacterial ligands the link between microbiota alterations and MAIT function in these pathologies is presently under investigation in our laboratory.

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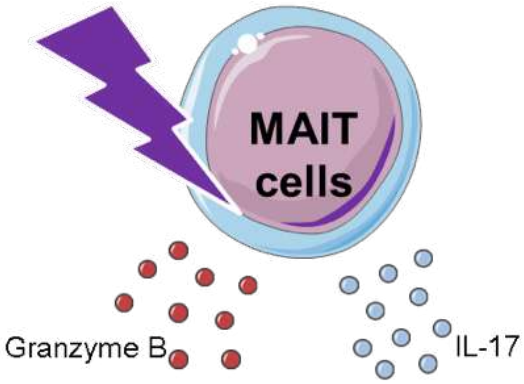
OBJECTIVES:

- Determine immune dysfunctions in type 1 diabetes and obesity/type 2 diabetes
- Determine the mechanisms controlling Mucosal-Associated Invariant (MAIT) cell function
- Develop innovative therapeutic strategies to prevent diabetes and its complications

TOOLS:

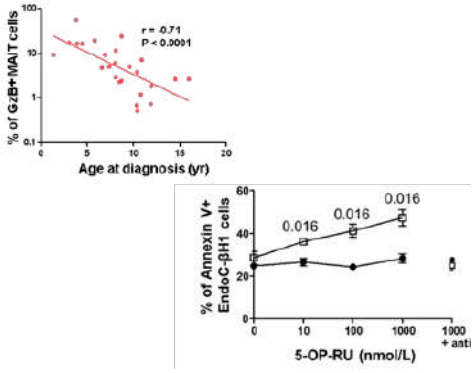
- Cohorts :
  - Type 1 diabetic patients and children at risk for this disease (DIABIMMUNE, EDIA, FFRD-T1D-MAIT-GUT)
  - Type 2 diabetic patients with/without liver disease complications (RHU QUID-NASH)
- New mouse models to decipher the role of MAIT cells in these metabolic pathologies (MR1KO and Va19 transgenic)
- New bioassays to study MAIT cell function



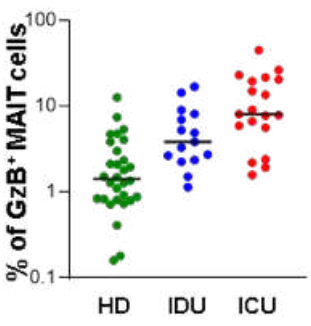
Impact of MAIT cell cytotoxicity in human pathologies

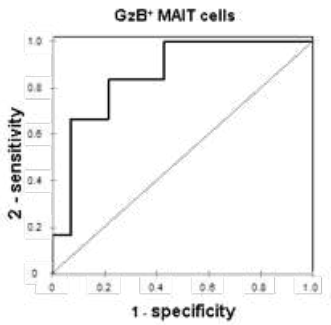
RESULTS:

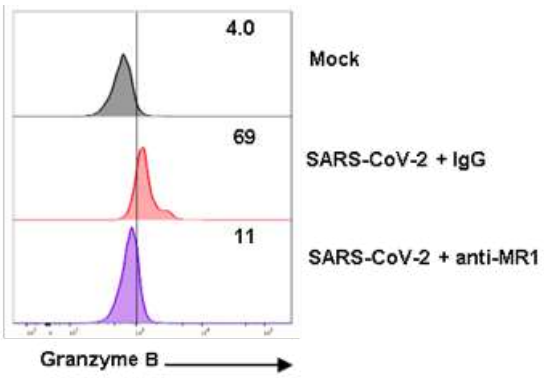
- Increased cytotoxicity of MAIT cells in children with Type 1 diabetes (T1D) that scales with disease severity
- MAIT cells can kill beta pancreatic cells
- MAIT cell cytotoxicity in severe SARS-CoV-2 patients is linked to severity and disease outcome



Rouxel et al. Nat Immunol 2017 and PCT/EP2017/056859

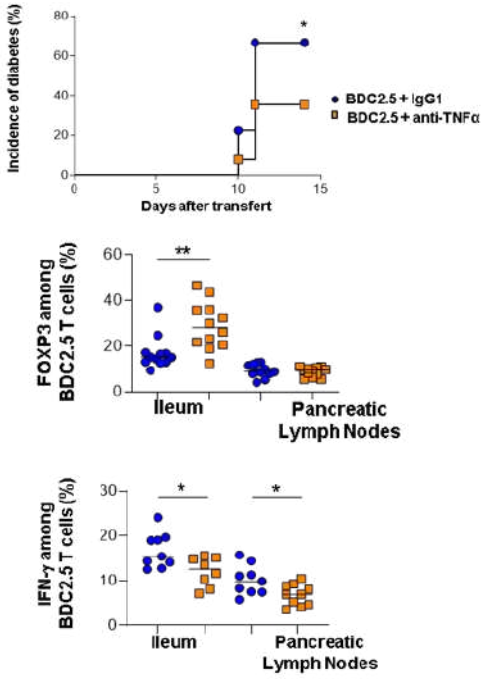






Flament et al. Nat Immunol 2021 and EP20305983.7

Role of gut inflammation in Type 1 Diabetes

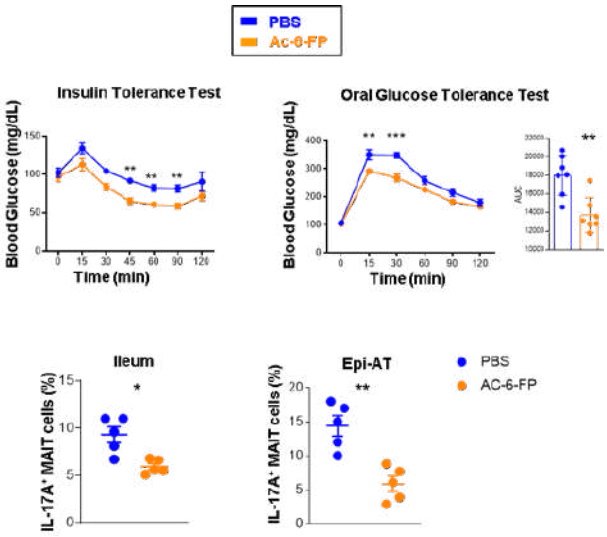


RESULTS:

- Gut mucosa is inflamed in type 1 diabetes
- Anti-TNFα treatment reduces diabetes onset
- Anti-TNFα treatment increases Treg cell frequency in gut mucosa
- Anti-TNFα treatment decreased the frequency of pathogenic autoreactive T cells

Rouland et al. Gut 2021

Role of gut inflammation in Type 1 Diabetes



RESULTS:

- Inhibition of MAIT cell activation by Ac-6-FP improves glucose metabolism during obesity
- Inhibition of MAIT cell activation decreases inflammation in adipose tissue and gut mucosa during obesity

PERSPECTIVES:

- Decipher the local regulation of MAIT cell function in metabolic tissues
- Identify the link between the gut microbiota and MAIT cells
- Manipulate MAIT cell functions for innovative treatments
- Study of MAIT cells in diabetes and obesity complications

UNIQUE SELLING POINTS:

- International leader in innate and adaptive immunity in diabetes: international and national networks, Laboratory of Excellence Inflamex
- Continuum from the clinics to the laboratory and vice versa:
  - Head of the department on Metabolism and Diabetes at Cochin Institute,
  - Board of the Paris Diabetes Institute and RHU QUID-NASH,
  - Head of French-Finish T1D consortium, FFRD T1D-MAIT-GUT French Network
  - Partners of the Microbiota Cross-cutting Inserm Network
- At the crossroad of immunology and metabolism

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Inflammatory diseases of the central nervous system: mechanisms and therapies

Keywords:

- Multiple sclerosis,
- Susac syndrome,
- Narcolepsy,
- Paraneoplastic neurological diseases,
- T cells,
- Regulatory T cells,
- Blood-brain barrier,
- Immune cell migration.

The overarching objective of our team is to decipher the pathophysiology of inflammatory diseases that target the central nervous system (CNS), with a particular focus on Multiple Sclerosis as well as other CNS autoimmune or infectious diseases using both mouse models and patient samples.

The team "inflammatory diseases of the central nervous system: mechanisms and therapies" is composed of physician-scientists and basic scientists sharing a long-lasting interest in deciphering the pathogenesis of inflammatory diseases of the central nervous system (CNS) with a focus on multiple sclerosis (MS). MS is the leading cause of neurological disability amongst young adults, mostly women. Due to its increasing prevalence and its chronic course, MS has major socio-economical consequences. A comprehensive understanding of MS etiology and of pathways leading to disease could provide rational bases for developing new treatments. The aim of our team is to decipher the pathophysiology of MS and other inflammatory neurological disorders by developing novel experimental animal models and collecting unique bio-resources from patients. Our objective is to identify immune cell types, pathways and molecular mechanisms responsible for experimental and human CNS inflammatory disorders. Another key objective is to identify biomarkers that could improve the care of people with MS under disease-modifying therapies. Finally, we aim at identifying potential therapeutic targets in CNS inflammatory diseases such as narcolepsy, Susac syndrome, and paraneoplastic neurological syndromes. To this goal we have developed original mouse models mimicking the key features of these diseases and have collected biological samples from large cohorts of patients. The cross-fertilization between information drawn from animal experiments and clinical research should ensure the relevance of the new knowledge.

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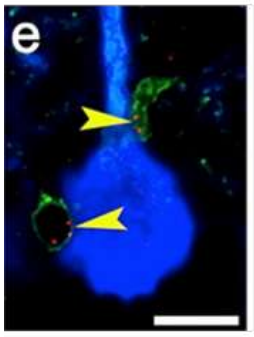
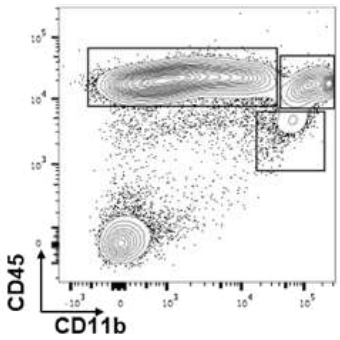
OBJECTIVES:

- Study the migration of T cells into the CNS during steady state and pathological conditions.
- Identify biomarkers to predict MS activity and response to MS therapies.
- To unravel the immunopathogenesis of rare CNS inflammatory diseases, such as Narcolepsy type 1, paraneoplastic neurological diseases and Susac syndrome, to identify new therapeutic targets.

TOOLS:

- Original models of CD4 and/or CD8-mediated CNS inflammatory or autoimmune diseases
- Biological samples (serum, PBMCs, CSF, RNA, brain tissue) from patients with CNS inflammatory diseases
- Cutting-edge technological approaches:
    - *In vivo* animal studies
    - Cellular immunology
    - Flow cytometry
    - Transcriptomics
    - Histology

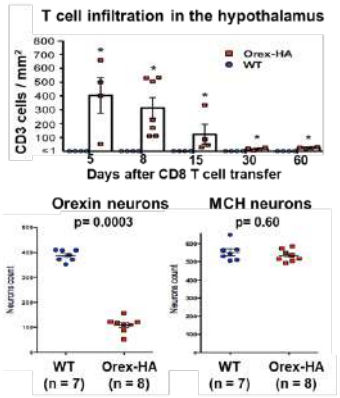




Subject 1: Study the immunopathogenesis of rare CNS inflammatory diseases The exemple of Narcolepsy type 1

RESULTS:

- Define the activation and increased cytokine production by patients' T cells using high-dimensional single cell analysis
- Identify high proportion of circulating follicular helper T cells (TFH) in the blood of persons with narcolepsy
- Reveal the presence of narcolepsy-specific clones among circulating CD4 T cells
- Demonstrate that CD8 T cells can induce narcolepsy-like manifestations in an autoimmune mouse model of narcolepsy
- Develop a mouse model of narcolepsy following 2009 H1N1 flu vaccination

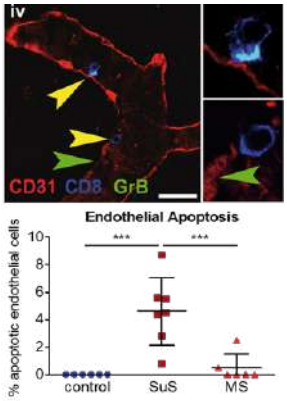


Top: Quantification of T cells in the hypothalamus of Orex-HA and WT mice at different time points after CD8 T cell transfer.
Bottom: Quantification of orexin+ and MCH+ neurons in the hypothalamus of Orex-HA mice and WT animals 60 days post-CD8 T cell transfer.

Subject 2: Study the influence of antigen presentation by blood-brain barrier (BBB)-endothelial cells on the migration of T cells into the CNS

RESULTS:

- Migration of pathogenic CD8 T cells into the CNS is dependent on the a4b1-integrin
- Activated CD8 T cells can interact in an antigen-dependent manner with BBB-endothelial cells both *in vitro* and in vivo
- We developed a model of CD8 T cell-mediated BBB disruption very reminiscent of the pathology of people with Susac syndrome, a rare inflammatory CNS disease that often mimics MS
- We showed clinical efficacy of anti-a4 integrin blockage in the mouse model and therefore, tested it in few patients with Susac syndrome



Top: Accumulation of CD8+ T cells in a brain microvessel in a patient with Susac syndrome. Yellow arrowheads point to CD8+ T cells (blue) attached to CD31+ of endothelial cell (red). The enlargement of the upper CD8+ T cell shows its GrB+ granules polarized toward the endothelial cells. Bottom: Quantification of endothelial cell apoptosis in brain specimen from controls, Susac syndrome (SuS), and MS patients

PERSPECTIVES:

- Investigate the contribution of different CD4 and CD8 T cell subsets to CNS inflammation.
- Leverage the new knowledge gained from our previous studies to perform proof-of-concept therapeutic strategies at the pre-clinical level.
- Integrate immune landscape analyses and molecular studies from animal models and human diseases.
- Identify immunological biomarkers associated with disease severity and treatment response.

UNIQUE SELLING POINTS:

- Large biobank of circulating immune cells, RNA, serum from patients with CNS inflammatory diseases.
- Unique animal models of CNS inflammatory diseases.
- Capacity to integrate in vivo studies with cell-type specific molecular analyses (single-cell proteomics, genomics).
- Capacity to go from laboratory experimental work to exploratory clinical trials and drug repurposing, such as anti-PD1 mAb for PML (N. Engl. J. Med. 2019); CCR5 inhibitor for IRIS (Nat Rev Neurol. 2016); anti-a4 integrin for Susac syndrome (Nature Commun. 2019)

LUCAS Bruno

M.D., Ph.D

Inserm / CNRS / Université de Paris
CNRS

Regulation of T-cell effector functions

Keywords:

- CD4 T cells
- Regulatory T cells
- Secondary lymphoid organs
- T-cell trafficking
- T cells
- Aging
- Inflammation
- Microbiota

Our team conducts an exploratory type of basic research that aims at a better understanding of the contribution of steady state interactions between T cells and their environment in both the maintenance of immune tolerance and the ability of the immune system to mount efficient responses in various "pathophysiologic conditions", especially cancer and aging.

Following activation in the periphery, naïve CD4 T cells (CD4 TN cells) can differentiate into a variety of well documented effector T-helper (TH) cell subsets, such as TH1, TH2, TH17 or induced regulatory (iTreg) T cells, characterized by their cytokine production profiles and specific effector functions. The immunological context in which CD4 TN cells are immersed at the time of their activation is known to guide lineage commitment and thereby to adjust the quality of T cell responses to the nature of the stimuli. In particular, cytokines orientate CD4 TN cell differentiation upon activation into the most appropriate effector cells. The objective of the main project currently developed in our team is to decipher the role of the Foxo1 transcription factor in the differentiation of CD4 TN cells into fully competent effector cells. Indeed, we have recently observed that Foxo1 restrains CD4 TN cell differentiation into TH1 and TH2 effectors and is strongly down-regulated in T cells with age. We will thus now study how the transcription factor Foxo1 adjusts the response of CD4 TN cells to their cytokine environment. In parallel, we will evaluate the impact of Foxo1 down-regulation with age on the quality of T cell responses. Finally, we will identify the factors (inflammaging, microbiota dysbiosis, ...) leading to the loss of Foxo1 expression with age. The results we will obtain could allow the design of new tools, necessary to better deal with pathologies due to a dysfunction of the immune system, such as the anergy observed in cancers and the lack of effective immune responses observed in the elderly.

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OBJECTIVES:

- To decipher the early steps of anti-tumor T-cell responses
- To understand when, where, how and which regulatory T cells are interfering with anti-tumor responses
- To assess the role of inflammation in T-cell immunosenescence

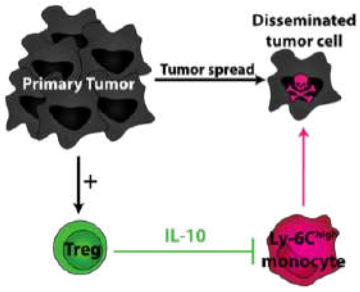
TOOLS:

- Complementary expertise in flow cytometry and in vivo mouse experimental models
- Access to the top facilities of the Institut Cochin (Cellular imaging, Immunobiology, Histology, Genomics, Proteomics, Small animal imagery etc).
- A collection of genetically modified mouse strains including knock-out mice, gene-reporter mice, Cre mice and lox mice

Inflammatory monocytes are potent antitumor effectors controlled by regulatory CD4 T cells

RESULTS:

- Inflammatory monocytes (Ly6C^{high}) exhibit anti-tumor properties
- Regulatory CD4^{+} T cells promote tumor progression by inhibiting Ly-6C^{high} monocytes
- IL-10 derived from regulatory T cells suppress anti-tumor innate effectors

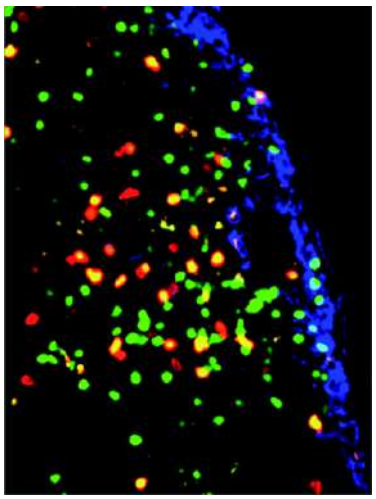


Inflammatory monocytes and dendritic cells (Ly-6Chigh) exert antitumor functions that can be counteracted by regulatory T cells.

Macrophages lock Up IL-17-producing gd T Cells in secondary lymphoid organs

RESULTS:

- IL-17-producing gd T cells (RORgt+) are trapped into secondary lymphoid organs (SLO) in the steady state as a result of close interactions with subcapsular macrophages in peripheral lymph nodes (pLNs), medullary sinus macrophages in pLNs and mesenteric LNs, and red pulp macrophages in the spleen.
- SLO-resident gd T cells secrete upon a few hours huge amounts of IL-17 following infection and represent. They may thus represent a major barrier blocking the systemic spread of pathogens within SLOs by providing rapid innate responses.



Localization of RORgt+ et RORgt- gd T lymphocytes in mouse peripheral lymph nodes. TCRgd (red), CD169 (blue) and RORgt-GFP (green). ROR t+ gd T cells (IL-17 producers) are yellow.

PERSPECTIVES:

- To assess the factors (inflammaging, microbiota dysbiosis, ...etc..) leading T-cell immunosenescence with age
- To study changes in the quality and quantity of resident T cells within tumor-draining lymph nodes

UNIQUE SELLING POINTS:

- A recognized expertise in T cells and especially in regulatory Foxp3-expressing CD4 T cells
- Complementary expertise in flow cytometry and in vivo mouse experimental models
- A collection of genetically modified mouse strains

MALLONE Roberto

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From benign to progressive islet autoimmunity: disease endotypes, biomarkers and therapeutic targets in type 1 diabetes

Keywords:

- Antigens,
- Antigen-specific immunotherapies,
- Beta cells,
- Coxsackievirus,
- Disease endotypes,
- Immune tolerance,
- T cells,
- T-cell receptors,

Our aim is to understand how the autoimmunity against pancreatic beta cells develops and progresses toward type 1 diabetes (T1D), and how to track and halt this progression. Our research spans from mechanistic and biomarker studies on human cohorts and mouse models to therapeutic trials.

Beta-cell destruction involves the recognition of peptide-HLA Class I complexes on the surface of beta cells by autoreactive CD8+ T cells. Surprisingly, we observed that CD8+ T cells recognizing known and novel β-cell peptides (identified by HLA peptidomics and transcriptomics strategies) circulate at a similar frequency in T1D and healthy donors and display a largely naïve phenotype. Thus, a universal state of 'benign' islet autoimmunity exists in all individuals, to a much larger extent than previously appreciated.
Our objective is to decipher the mechanisms by which this benign autoimmunity progresses toward T1D, at variable rates, in few individuals, and not in many others. Schematically, such progression may rely on two non-mutually exclusive mechanisms: a) loss of immune ignorance toward beta cells that are normally invisible to T cells; and b) loss of the immune regulation that controls autoreactive T cells.
Understanding these mechanisms will allow to dissect disease heterogeneity, to develop early biomarkers of autoimmune aggressiveness predictive of beta-cell loss before and after clinical onset, and to identify novel therapeutic targets to revert autoimmunity to its benign state.

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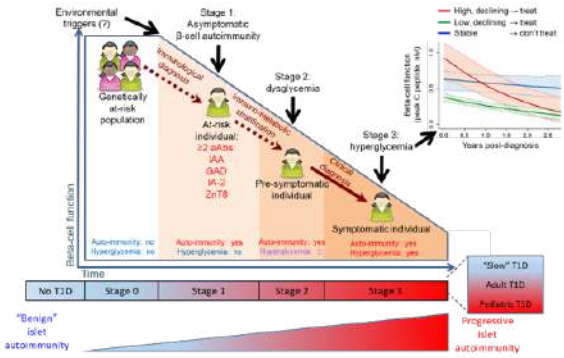
OBJECTIVES:

- Dissect T1D heterogeneity and personalize immunotherapy:
  - o T-cell biomarkers of benign vs. progressive islet autoimmunity
  - o Mechanisms of progression and identification of novel therapeutic targets

TOOLS:

- HLA peptidomics
- T-cell tetramer/functional assays
- Single-cell RNAseq/CITEseq
- TCR sequencing/re-expression
- Combinatorial peptide libraries
- In-vitro beta-cell killing assays

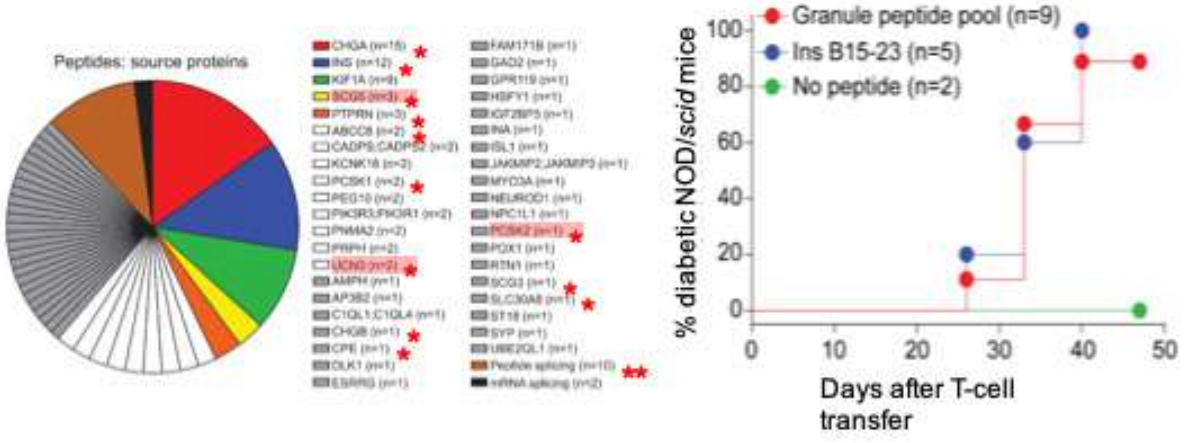


The continuum of benign and progressive islet autoimmunity: key to dissect T1D heterogeneity and personalize immunotherapy

Topic 1: identifying the antigens exposed by beta cells via HLA Class I

RESULTS:

- Over-representation of peptides derived from granule proteins*
- Novel granule antigens identified and patented:
- Secretogranin-5 (SCG-5)
- Urocortin-3 (UCN-3)
- Proconvertase-2 (PCSK2)
- These 3 granule antigens are diabetogenic in NOD mice



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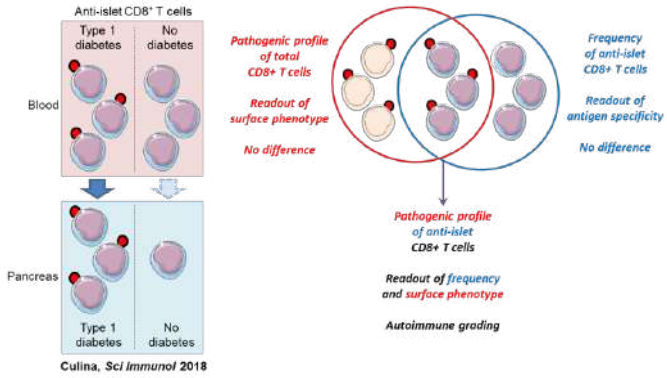
Azoury, Diabetes 2020
James, Mallone, Kent, DiLorenzo, Diabetes 2020

Topic 2 : developing circulating T-cell biomarkers



PERSPECTIVES:

- Assays to measure the global autoimmune T-cell 'burden' of a given individualthrough comprehensive antigen coverage
- Identification of T-cell biomarkers to grade the progression potential of this burden
- Development of an in-vitro beta-cell killing assay platform to screen for beta-cell-protective agents
- Development of tolerogenic oral vaccines based on Fc-coupled islet antigens

UNIQUE SELLING POINTS:

- A comprehensive approach to T-cell autoimmunity:
  Epitope identification → T-cell detection → functional/TCR characterization
- An integrated view of type 1 diabetes pathology:
  Approach covering both T-cell effectors and beta-cell targets
- A research pipeline "from bedside to bench and back again":
  Clinical phenotyping → laboratory investigations → prognostic/therapeutic translation
- Partner in international T1D consortia: INNODIA, nPOD

MANOURY Bénédicte

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Intracellular Toll-like Receptors (TLRs) activation: from basic research to clinical applications

Keywords:

- Innate immunity,
- Inflammation,
- Toll-like receptors,
- Dendritic cells,
- Proteases,
- Animal models of diseases.

Our research interests focus on the biology of TLRs signalling, trafficking, and activation in immune cells and mice models for various diseases using state of the art technology.

Toll-like receptors (TLRs), which are conserved throughout evolution, sense microbial products and play a critical role in innate and adaptive immunity. TLRs are synthetized in the endoplasmic reticulum and traffic either to the plasma membrane where they recognize the presence of proteins and lipids from a wide variety of pathogens or to endosomal-lysosomal organelles where they bind nucleic acids from bacteria or viruses. Once they interact with their specific ligands, they undergo conformational changes leading to the production of proinflammatory cytokines and cell surface expression of costimulatory molecules. TLRs genetic deficiency can lead to the development of inflammatory diseases, and their dysfunction can contribute to autoimmunity. However, despite our current knowledge, we still lack some understanding in the dynamic of TLRs activation. Our research focuses on the biology of TLRs signalling, trafficking, and activation in immune cells and mice models for various diseases using state of the art technology. In that respect, we have identified key proteases, Asparagine Endopeptidase and Insulin Responding Aminopeptidase, required for TLR7 and TLR9 activation and trafficking *in vitro* and *in vivo*.

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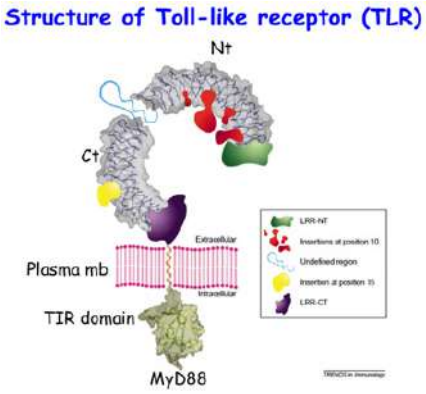
OBJECTIVES:

- To identify new proteins/pathways necessary for TLR7 and TLR9 activation
- To develop new ligands: fluorescent, photo inducible or not, pH sensitive or not, for TLR7 and TLR9 to identify sub-cellular compartments where TLRs traffic
- To describe an endosomal map where TLR7/9 are trafficking in primary immune cells
- To investigate TLR7 and TLR9 activation in animal disease models

TOOLS:

- Molecular characterization of TLRs signaling pathways using standard biochemistry and molecular biology tools
- Functional in vitro (primary cell culture) and in vivo (animal models) assays
- High throughput flow cytometry
- High-resolution confocal microscopy (STORM and FIB Technologies)

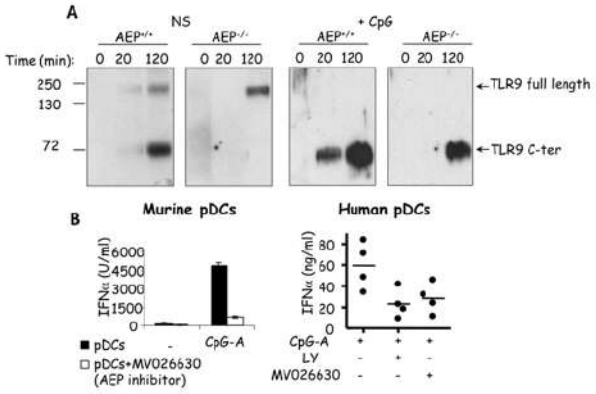


Subject 1: TLR9 activation in dendritic cells

RESULTS:

- Identification of Asparagine Endopeptidase (AEP) for TLR9 processing
- TLR9 cleavage is required in vitro and in vivo for its activation
- Use of a specific AEP inhibitor to demonstrate the role of AEP in cytokines/INFa secretion following TLR9 stimulation

Our results demonstrate a key role for AEP in TLR9 activation



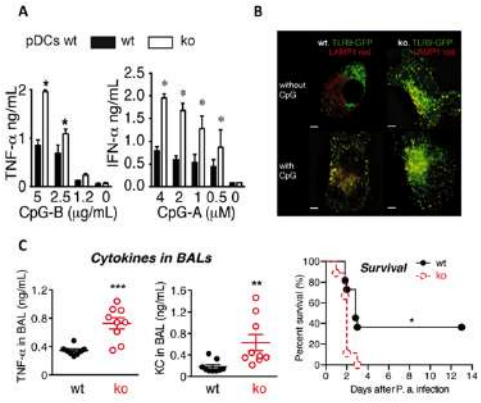
Lack or inhibition of AEP regulates TLR9 activation and signalling. (A) *Delay in TLR9 cleavage in AEP deficient cells and* ***(B)*** *inhibition of INFa secretion in murine and human cells pulsed with a specific AEP inhibitor.*

Subject 2: TLR9 trafficking in dendritic cells

RESULTS:

- Identification of IRAP positive endosomes, as major vesicles where TLR9 traffics
- In the absence of IRAP TLR9 trafficking, processing and signaling are enhanced in dendritic cells and in mice following bacterial infection
- IRAP, by interacting with the actin nucleation factor FODH4, allows the stabilization of VAMP3 endosomes where TLR9 is transported

- **Our data** demonstrate that IRAP tightly regulates TLR9 by slowing down its trafficking to VAMP3 vesicle avoiding excess proinfammatory cytokine production and survival upon bacterial infection



IRAP controls TLR9 signalling and trafficking. *Enhanced cytokines production (A) and TLR9 trafficking* ***(B)*** *in IRAP deficient cells. (C) Mice deficient for IRAP are more susceptible to bacterial infection.*

PERSPECTIVES:

- Fine-tuning of spatio temporal signalling of endosomal TLRs by developing new fluorescent, photo inducible or not, pH sensitive or not-ligands for TLR9 and TLR7 to identify sub-cellular compartments where TLRs traffic. These reagents will allow us to (photo-) chemically control ligation of the TLR in a specific type of endosomal compartment
- Studying the anti-viral properties of these ligands in mice models infected with influenza viruses whose RNA is sensed by TLR7 as an example
- Applying our in vitro results to animal models developing autoimmune and neurodegenerative diseases
- Identifying new proteins/pathways required for TLR7 and TLR9 trafficking and activation

UNIQUE SELLING POINTS:

- Intracellular map of spatio-temporal signalling of endosomal TLRs in primary cells
- Generation of mice inactivated for TLR9 in peripheral dendritic or myeloid cells and in microglia useful to the research community to investigate autoimmunity and neurodegenerative diseases

MARIE Julien C.

Ph.D

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Inserm

TGF-b and immune regulation

Keywords:

- T lymphocytes,
- Colorectal cancer,
- Inflammation,
- Autoimmunity microbiota.

By keeping physiological context the Marie lab assesses how the cytokine TGF-beta affects the immune responses.

The immune system has to be ignorant against the self-cells and the microbiota to avoid autoimmunity and chronic inflammation. However, it should also be able to eliminate the self-cells that are noxious for the organism such as tumor cells. Transforming Growth Factor beta (TGF-β) is a highly conserved cytokine present in all mammals. TGF-β has been described as a key regulatory cytokine of the immune system. Interestingly, this cytokine is highly produced by the tumor micro-environment and it is known to contribute also to tumor growth. Our previous works revealed that within the immune system the target-cells of the regulatory effects of TGF-β are T lymphocytes (Immunity 2006) and that TGF-β signaling represses their activation against self-cells. We reported that TGF- influences the differentiation of memory T cells (Nature Com 2014, Immunity 2012), NKT (J. Exp Med 2009, Blood 2012) and thymic development (Nature Com 2019). We also revealed that TGF-β prevents from autoantibody development by regulating T follicular helper cell differentiation (J. Clin invest 2014). Our works also revealed a key role for TGF-β in Foxp3 regulatory T cell biology (J. Exp. Med 2009, Immunity 2015, Nature Immun 2020) and in anti-tumor response (Cancer Res 2020). Our lab developed several innovative tools to study the molecular and cellular mechanisms responsible for the control of peripheral T cell tolerance to self-cells by TGF-β and analyses their effects on autoimmune diseases and tumor development.

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OBJECTIVES:

- To decipher the effects of TGF-b on the immune system,
- To analyze these effects on pathologies ie: auto-immune diseases, chronic inflammation and cancers,
- To thwart TGF-b noxious effects,

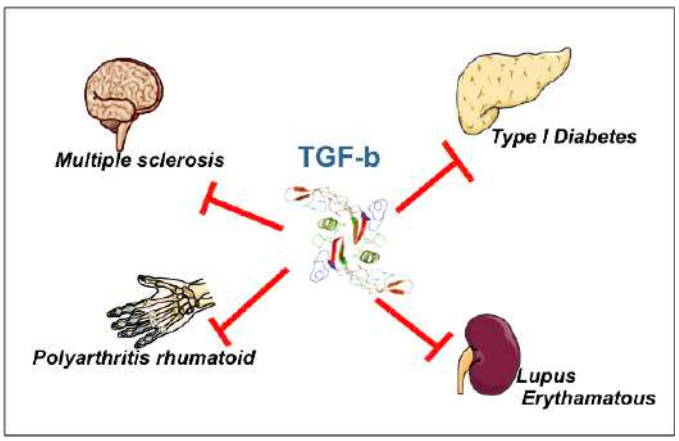
TOOLS:

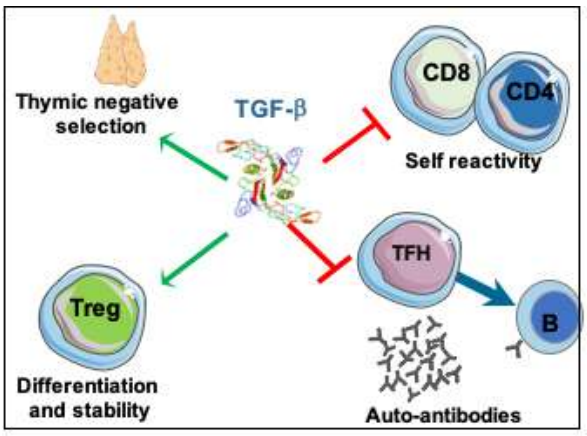
- Unique mouse models with specific cellular targeting of TGF-b signaling (gain and loss of functions in T cells
- Unique access to patient biopsies and unique ex-vivo tissue analysis
- Unique compounds and therapeutic approaches

Auto-immunity/ chronic inflammation

RESULTS:

- T lymphocytes are the target cells of TGF-b anti autoimmunity effects (Marie et al Immunity 2006, Havenar-Daugthon Blood 2012, Soudja et am Immunity 2012, Mc carron et al Nature Com 2019)
- TGF-b controls regulatory T cell biology (Marie et al J.exp Med 2005, Worthington et al Immunity 2015, Ferreira et al Nature Immunology 2020)
- TGF-b prevents auto-antibodies production, (Mc Carron et al J. Clin Invest 2014)

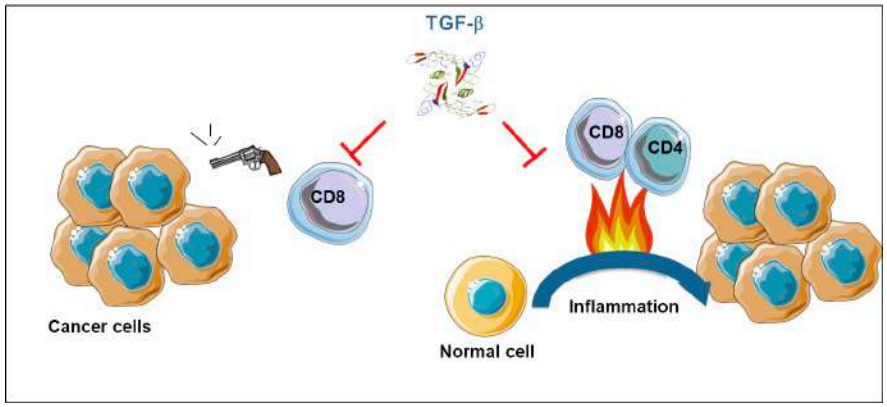




Cancers

RESULTS:

- TGF-b prevents CD8 T cell cytotoxic functions in tumors (Marie et al Immunity 2006, Bonnet et al Cancer research 2020)
- TGF-b prevents inflammatory colorectal cancer (Bauché et al Science Trans Med 2017)



PERSPECTIVES:

- Propose ex-vivo technologies on human fresh tissues to test compounds and antibodies
- Finalization of TGF-b targets we are developing for clinics

UNIQUE SELLING POINTS:

- 25 years of expertise in TGF-b and Immunology
- World class expert recognized in TGF-b and immunopathology/ immunotherapy
- Pioneer in the identification of TGF-b cellular targets
- Unique ex-vivo approaches maintaining alive tissue and its micro-environment
- Unique mouse models to selectively targets TGF-b effects on a given cell subset
- Unique mouse models of spontaneous colorectal and gastro intestinal development with 100% of efficiency and in a small region 500µm

MARIETTE Xavier

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Rheumatoid arthritis and Sjögren's syndrome: From pathophysiology to treatment

Keywords:

- Autoimmunity,
- Translational research,
- Clinical trials,
- Sjögren's syndrome,
- Rheumatoid arthritis,
- Lymphoma,
- Cancer,
- Immune related adverse event,
- Immunotherapy,
- COVID-19.

Pathophysiology of Sjögren's syndrome and of rheumatoid arthritis
Pathophysiology of lymphomas complicating autoimmune diseases
Relationships between autoimmunity and cancer
New targeted therapies in autoimmune diseases
Long-term safety of immunomodulators
New potential indications of immunomodulators (COVID-19, IrAEs in cancer)

We focus our research on pathophysiology and treatment of two prototypic autoimmune diseases and to the link between autoimmunity and cancer and between autoimmunity and infections.
Our strengths are a global vision of immunomodulation in the triangle of immunopathology (autoimmunity, cancer and infections) and to conduct a research from bench to bed

Our scientific expertise is pathophysiology and treatment of two prototypic autoimmune diseases: Rheumatoid arthritis (RA) and Sjögren's syndrome (SS). In both diseases, our research strategy is to start from samples of patients. Indeed, we have the chance, as clinician, to follow large cohorts of patients with autoimmune diseases. Our centre is labelled ***"French and European reference centre for rare systemic autoimmune diseases" and "EULAR centre of excellence", a recognition based on publications.***
In RA, our main result was the discovery of a **specific defect of differentiation of monocyte into anti-inflammatory macrophages**, defect possibly due to an increase in a microRNA: miR155. We also validated this defect in a mouse model of the disease (CIA) and our objective is now to correct this defect with encapsulated antagomiRs in nanoparticles. This treatment could be very specific of RA, without any side effect.
In SS, there is no available treatment yet. Our objective in the lab is ***to decipher the mechanisms of the B-cell activation***, which is a hallmark of the disease. For that, we developed co-culture between epithelial cells and B-cells or T-cells and now we are developing a culture of explants from labial salivary gland biopsies. This technique will be able to test different new drugs with, as primary endpoint, the inhibition of the activation of B- or T-cells by the salivary gland epithelial cells.
In SS we participate and coordinate different clinical trials with new immunomodulators. We are coordinating ***an IMI-2 IU project (NECESSITY)*** for developing a new clinical activity score to be used in clinical trials.
Our third domain of interest is ***the transition between autoimmunity and lymphoma.*** We have demonstrated in SS that lymphoma developed from autoimmune B-cells and we work for understanding this transition. We have explored the possible role of immunomodulators in this development.
More generally we also now address the relationships between autoimmunity and cancer (similar and converse immunological mechanisms) and the possible use of immunomodulators for treating immune related adverse events of immunotherapy of cancer. For that, we are coordinating a ***"Fédération Hospitalo-Universitaire" (FHU), called CARE (Cancer and Autoimmunity Relationships).***
Lastly, studying for a long time safety of immunomodulators in autoimmune diseases, we now explore the possibility of ***using these immunomodulators in two other immunopathological diseases: cancer and chronic infections like COVID-19.***

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OBJECTIVES:

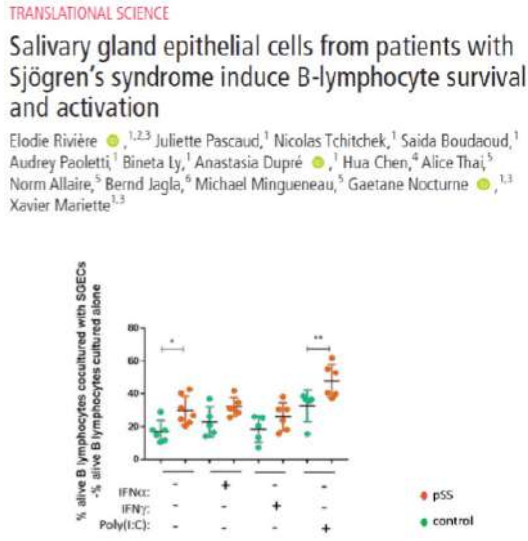
- Pathophysiology of Sjögren's syndrome and of rheumatoid arthritis
- Pathophysiology of lymphomas complicating autoimmune diseases
- Relationships between autoimmunity and cancer
- New targeted therapies in autoimmune diseases
- Long-term safety of immunomodulators
- New potential indications of immunomodulators (COVID-19, IrAEs in cancer

TOOLS:

- Large cohorts of patients with autoimmune diseases
- French and European reference centre for rare systemic autoimmune diseases
- EULAR centre of excellence, a recognition based on publications
- A translational research based on patients samples
- Coordination of an EU IMI2 on Sjögren: NECESSITY
- Coordination of a FHU CARE: Cancer and Autoimmunity
- Access to a high quality technology platform and to animal facility (IDMIT closely related to IMVA)
- Technique of co-culture of salivary gland epithelial cells and T or B cells and culture of salivary glands explants

Axis 1: Sjögren's syndrome: from pathophysiology to treatment

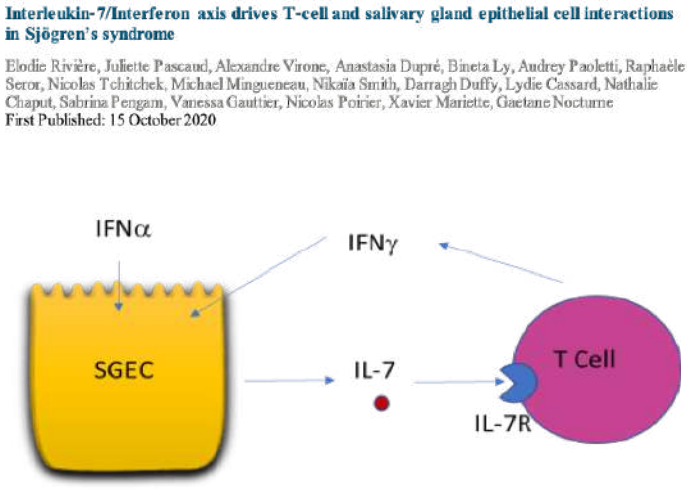
- **Cross-talk between salivary gland epithelial cells and B cells**


TRANSLATIONAL SCIENCE

Salivary gland epithelial cells from patients with Sjögren's syndrome induce B-lymphocyte survival and activation

Elodie Rivière, [1,2,3] Juliette Pascaud,[1] Nicolas Tchitchek,[1] Saida Boudaoud,[1] Audrey Paoletti,[1] Bineta Ly,[1] Anastasia Dupré,[1] Hua Chen,[4] Alice Thai,[5] Norm Allaire,[5] Bernd Jagla,[6] Michael Mingueneau,[5] Gaetane Nocturne,[1,3] Xavier Mariette[1,3]

- **Cross-talk between salivary gland epithelial celles and T cells**


Interleukin-7/Interferon axis drives T-cell and salivary gland epithelial cell interactions in Sjögren's syndrome

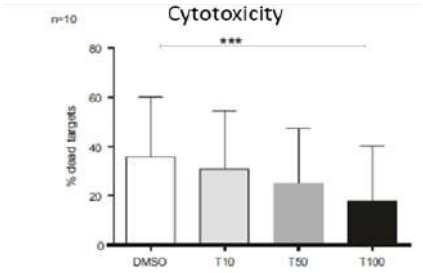
Elodie Rivière, Juliette Pascaud, Alexandre Virone, Anastasia Dupré, Bineta Ly, Audrey Paoletti, Raphaèle Seror, Nicolas Tchitchek, Michael Mingueneau, Nikaïa Smith, Darragh Duffy, Lydie Cassard, Nathalie Chaput, Sabrina Pengam, Vanessa Gauttier, Nicolas Poirier, Xavier Mariette, Gaetane Nocturne

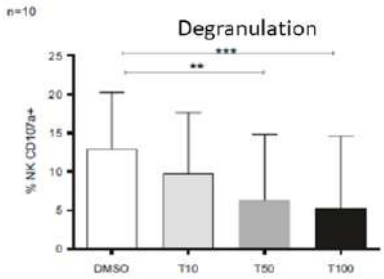
First Published: 15 October 2020

- **NEw Clinical Endpoints in primary Sjögren's Syndrome: an Interventional Trial based on stratifYing patients. EU IMI2.**
  - **Coordination X Mariette**

Axis 2: Rheumatoid arthritis (RA) : from pathophysiology to treatment

- RA: Defect of differentiation of monocytes in anti-inflammatory macrophages due to increased miR155 (A Paoletti et al J Immunol 2019)
- Effect of antagomiR155 encapsulated in PEGylated liposomes in a mouse model (CIA). A Paoletti.
- Effect of classical biological treatment on this defect (S Bitoun). EU IMI2 project ABIRISK. Cohort leader: X Mariette
- Predictive factors of anti-drug antibodies against biologics in RA (CD47 on B cells and CD206 on macrophages for predicting anti-RTX (S Bitoun) **EU IMI2 project ABIRISK**
- **Long-term safety of biologics and Jak inhibitors in RA**
- Tofacitinib decreases ability of NK cells to react to lymphoma cell lines





Nocturne et al. Cell Mol Immunol. 2020 May;17(5):552-553.

Axis 3: Mechanisms of lymphomagenesis associated with autoimmune diseases and their treatment

- **FHU CARE (Cancer and autoimmunity Relationships). Coordination: X Mariette**
  No increased risk of cancer with TNF inhibitors (R Seror. SNDS)
  Genetic mechanisms involved in immunosurveillance for avoiding lymphoma in autoimmune diseases
  (G Nocturne, Post-doc Institut Imagine)

CARE

Chronic inflammatory arthritis following checkpoint inhibitor therapy for cancer: game changing implications

Leonard Calabrese [1], Xavier Mariette [2,3]

Ann Rheum Dis. 2020 Mar;79(3):309-311 (IF: 16,4)

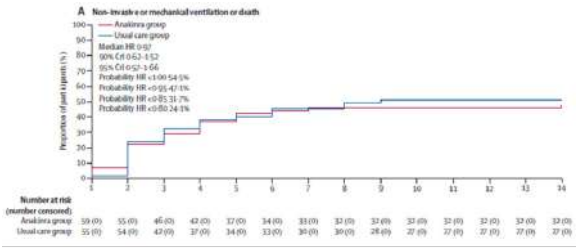
New axis in 2020: Immunomodulators for treatment of the hyperinflammatory state in COVID19

The CORIMUNO platform for running randomized clinical trials: 1,000 included patients

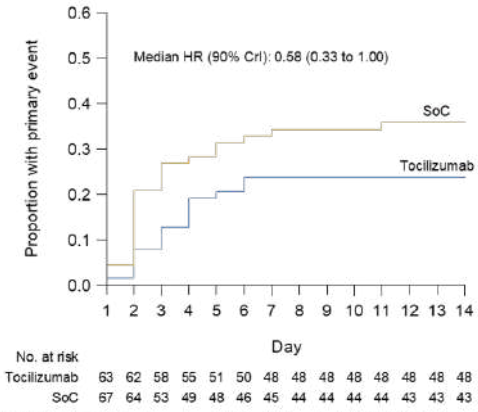
To immunosuppress: whom, when and how? That is the question with COVID-19

Kevin L Winthrop [1], Xavier Mariette [2,3]

Ann Rheum Dis. 4 Aug 2020 (IF: 16,4)

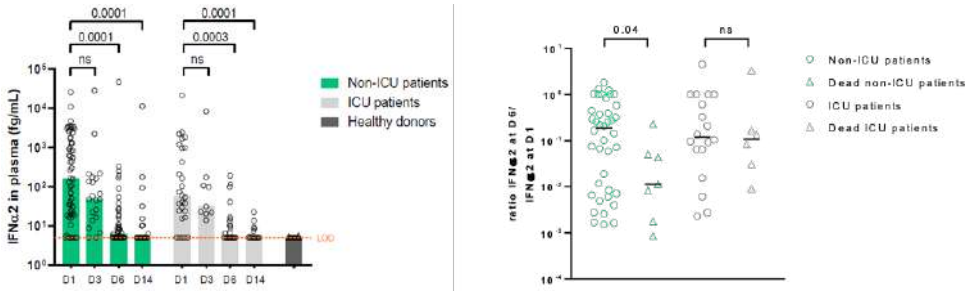


ANAKINRA: X Mariette et alLancet Repir Med 22 Jan 2021



TOCILIZUMAB: O Hermine, X Mariette et al. JAMA Int Med. 20 Oc t2020

A rapid decline in type 1 interferon is associated with mortality



C Joly, D Desjardins, … R Le Grand, X Mariette. In preparation

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Nephrology & Immunology
Chronic kidney disease, IgA nephropathy, Fc receptor

NANCEY Stéphane

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CIRI, Centre International de Recherche en Infectiology, Team Autophagy infection immunity, Université de Lyon, Inserm U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon
Hospices Civils de Lyon, Lyon-Sud University hospital, department of Gastroenterology, Lyon

Autophagy machinery: Novel relevant markers and therapeutic targets for IBD

Keywords:

- Inflammatory bowel disease,
- Crohn's disease,
- Ulcerative colitis,
- Autophagy,
- Biomarkers,
- Translational research,
- Autophagy flux profiling,
- Clinical research,
- Biobanking,

Our research interests focus on better understanding how the functional deviation of autophagy impacts Crohn's disease (CD) activity, severity and response to therapy. Thanks to the close interactions between basic researchers with high levels of expertise in the field of autophagy, and clinician specialists in inflammatory bowel disease, we aimed to better characterize the signature of the autophagy flux in CD with the goal of further clinical applications in the fields of diagnosis, prognosis and identification of future therapeutic targets.

Our labteam studies the role of macroautophagy, which is an essential lysosomal catabolic pathway for the maintenance of cellular homeostasis, in basic immunity and immunopathologies, especially in the context of infections and chronic inflammation. The team, highly recognized in basic research in the field of autophagy, identified:

- the first human pathogen receptor directly connected to the autophagy machinery (Cell Host and Microbe, 2009)
- a common molecular strategy used by several RNA viruses to manipulate autophagy (PloS Pathogens, 2011),
- described the close relationship between the measles virus and autophagy (PloS Pathogens, 2013).

Beyond basic projects on autophagy in the context of infection, several translational projects aiming to identify novel surrogate inflammatory, immune and autophagy biomarkers relevant for the monitoring of Crohn's disease have progressively emerged with the strong contributions of both researchers and clinicians. For this purpose, we have developed and validated a relevant non-invasive tool to determine the signature of the autophagic flux from primary immune cells in a large cohort of CD patients, according to various autophagy-related single nucleotide polymorphisms and to intestinal microbiota. Thanks to this platform, by linking high quality and exhaustive clinical data, with dedicated analysis of patients' samples with various approaches integrating genetic, immunity and microbiota, our objective is to provide the future novel relevant biomarkers able to predict disease course and therefore to guide clinicians making decisions for CD management. The expertise and the high quality of preclinical, clinical data integration and biobanking should give us, in the future, the unique opportunity to determine a relevant stratification of CD patients by identifying risk factors, predictors of disease severity and therapeutic response at an individual level. All these high throughput profiling of patients represent a key driver of precision medicine.

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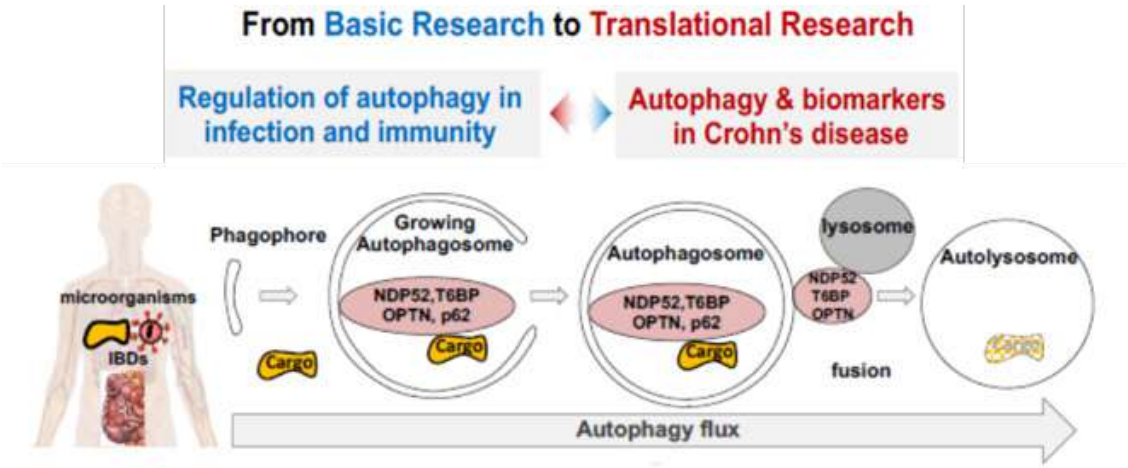
OBJECTIVES:

- Characterization of the autophagy machinery in Crohn's disease
- Identification of surrogate markers predictive of activity, severity and response to therapy in inflammatory bowel disease
- Identification of novel promising therapeutic targets in inflammatory bowel disease

TOOLS:

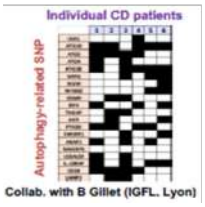
- Expertise in the fields of autophagy and IBD
- All facilities for basic, translational and clinical research (genomic, transcriptomic, proteomic, mass cytometry, imagery platforms, animal facilities, endoscopic and Gastroenterology units)
- Open access to various human biological samples (including intestinal specimens)

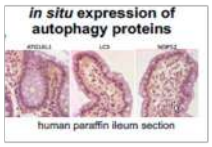


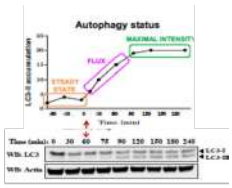
Topic 1: Autophagy flux signature in Crohn's disease: Towards a better understanding of the autophagy machinery for identification of novel relevant markers and therapeutic targets

RESULTS:

- Genotyping NOD2 and various set of **autophagy** related SNPs in CD patients
- Immunohistochemistry labelling of autophagy proteins is **altered in CD patients**
- Validation of an innovative screen to test functional autophagy flux of primary cells







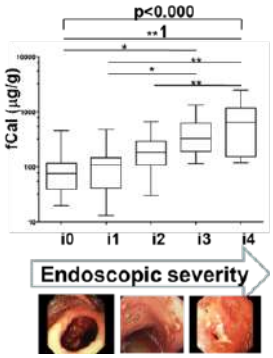
Quantitative analysis of autophagy flux in human primary dendritic cells

Towards a new diagnostic and pronostic test and hopefluly new targets

TOPIC 2 : Predictors in Crohn's disease : Surrogate biomarkers predictive of postoperative disease course

RESULTS:

- Are gradually associated with postoperative endoscopic severity in CD
- Correlate with negative predictive value
- Could allow to avoid ≈ 30 % of colonoscopies



Fecal calprotectin levels

PERSPECTIVES:

- Providing an exhaustive characterization of the autophagy machinery in CD
- Identifying specific immunologic/autophagy flux signature associated with the course, severity and response to therapy in IBD
- Validating accurate novel biomarkers capable to guide the physician's making decisions in the management of IBD patients

UNIQUE SELLING POINTS:

- A unique ecosystem of the team at the crossing between academic basic research, clinical and translational researches, and a tertiary department of Gastroenterology referent in IBD at a University hospital giving an open access to various human biological samples and allowing fruitful collaborations with the best national/international research groups
- High levels of expertise in the fields of autophagy and its regulation mechanisms
- A successful comprehensive research and health care network fully dedicated to IBD
- Full integration into various collaborative networks in the field of IBD (GETAID, REMIND groups) and biobanking networks
- Generation of a large prospective cohort of Crohn's disease patients
- Biobanking (serum, fecal, intestinal specimens)

NEUNLIST Michel

Ph.D

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Inserm

The Enteric Nervous System in Gut and Brain Disorders -TENS

Keywords:

- Gastrointestinal tract,
- Enteric nervous system,
- Gut-brain axis,
- Microbiota,
- Organoids,
- Autism,
- Neurodegenerative Diseases,
- Inflammatory Bowel Diseases,
- Spinal cord injury,
- Colorectal cancer.

Microbiota gut brain axis in health and inflammatory diseases.

The Inserm U1235 'The Enteric Nervous System in Gut and Brain Disorders (TENS)' is a Translational Research Unit in Neurogastroenterology accredited by the National Institute of Health and Medical Research (Inserm) and the University of Nantes. The research projects developed in the lab foster 3 main objectives: 1/ to understand the regulation of digestive functions (intestinal barrier, immune cells and motility) by the enteric nervous system in health, in particular during the perinatal period, and in diseases of interests (inflammatory bowel diseases; colorectal cancers; neurodevelopmental and neurodegenerative diseases; spinal cord injury) 2/ to develop innovative tools (organoid, organ-on-chip, imaging, multi-omic integrative and analysis methods) and models to characterize pathogenic mechanisms and identify factors leading to digestive, and contributing to, brain diseases, 3/ to identify therapeutics (nutrition, microbiota, neuromodulation) to restore gut functions in diseases of interests. TENS takes advantage of the rich research infrastructure that includes state of the art equipment to study intestinal epithelial cells and the enteric nervous system and perform functional studies on in vitro, ex vivo and in vivo models.

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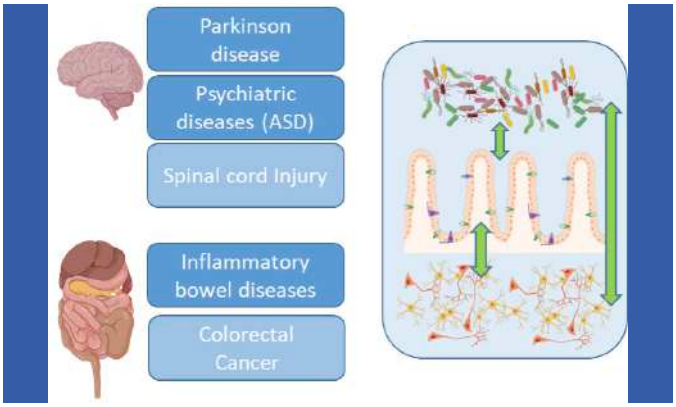
OBJECTIVES:

- **Physiology**: understand the interactions between the Enteric Nervous System and its cellular micro-environment (intestinal epithelial cells, microbiota, immune cells)
- **Physiopathology**: identify and characterise alterations in these cellular interactions and their functional consequences in digestive and CNS diseases
- **Therapeutics**: restoring these interactions by targeted (pharmacological) and/or systemic approaches: neuromodulation- microbiota (metabolites – pre/probiotics)

TOOLS:

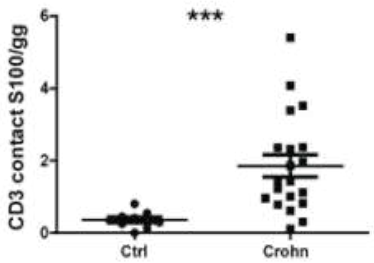
- Organoid core facility
- Innovative imaging core facility
- Bio-collection human tissue / animal models
- Digestive and behavioral core facility
- Electrophysiology
- Neuromodulation

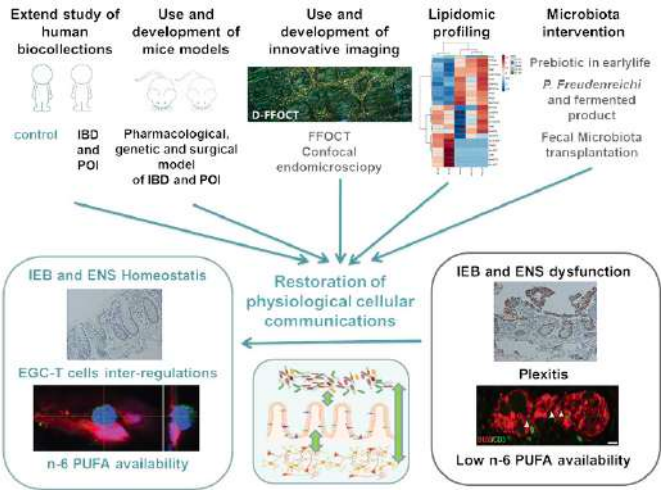


Inflammatory Bowel Diseases - IBD

RESULTS:

- ENS produces novel lipid-derived mediator factors involved in intestinal barrier functions and inflammation resolution
- Altered ENS phenotype and functions in IBD
- Identification of image biomarkers of CD and UC
- Altered ENS/T-cell interactions in IBD
- Neuromodulation restores intestinal barrier repair and inflammation resolution (clinical trials in RCH and in post-operative ileus)



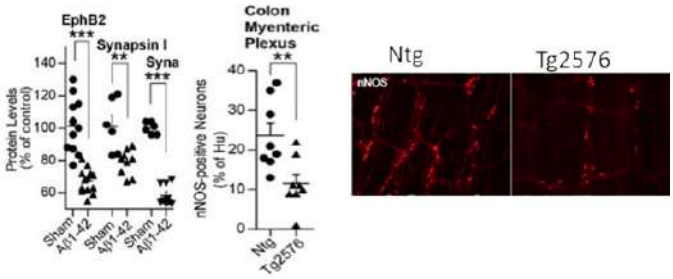


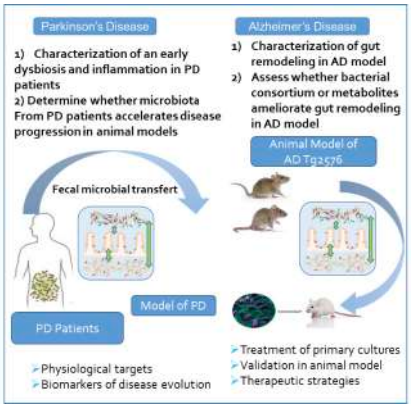
Through the generation of human biocollections, mouse models and their association with innovative imaging technologies and molecular profiles (lipidomic, transcriptomic and bacteriological), TENS carries out a detailed characterization of physiological and pathological mechanisms in order to define new therapeutic strategies such as modifications of the intestinal microbiota or neuromodulation in intestinal inflammation

Gut dysfunctions in neurodegenerative diseases (Alzheimer and Parkinson's diseases)

RESULTS:

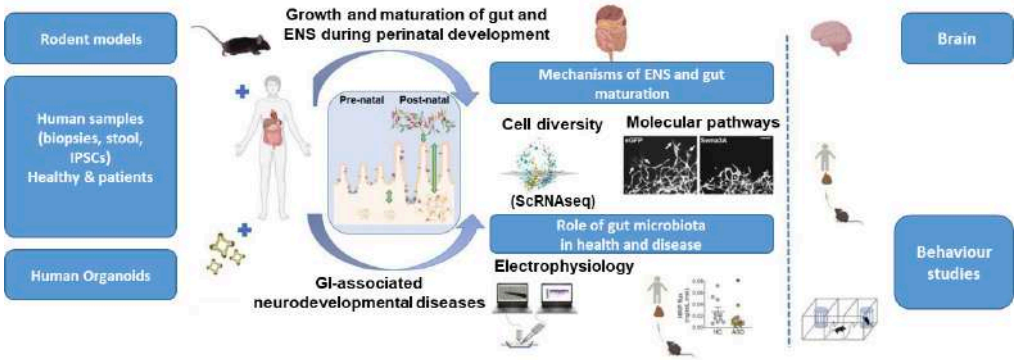
- Characterization of an early dysbiosis and inflammation in Parkinson's Disease
- The role of gut microbiota on the progression of Parkinson Disease
- Identification of mechanisms involved in gut remodeling in Alzheimer's disease





TENS will characterize gut remodeling in AD and PD pathologies by using animal models and cutting edge imaging, biochemistry, electrophysiology and multi-omic technologies. Furthermore, new therapeutic strategies and biological markers will be identified through FMT and treatment with bacterial consortium metabolites in A537T and Tg2576 mouse models of PD and AD, respectively.

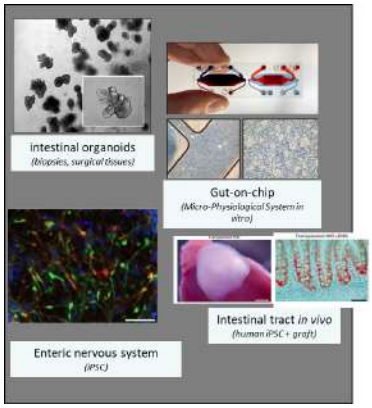
Neurodevelopmental disorders of the gut and brain



RESULTS:

- Characterization of the postnatal maturation of ENS/gut functions and its modulation by bacterial metabolites
- Role of HPA axis activation in perinatal stress induced gut dysfunctions in the adult.
- Impact of bacterial strains upon psychological stress induced gut and brain dysfunctions.
- Identification of barrier functions and ENS as predictive biomarkers of HD post-operative complications.
- Clinical trials for determining beneficial effects of butyrate upon HD post-operative complications
- Identification of pathogenic role of gut microbiota in gut dysfunctions (inflammation, barrier, ENS) in patients with autistic spectrum disorders

GALOP an organoid core facility - Development of tools applied to the understanding of physiopathological mechanisms in digestive and central nervous system pathologies



RESULTS:

- Development and utilization of human and murine intestinal organoids
- Biobank of murine and human-derived organoids
- Technical tools (Transwell, Gut-on-chip) and analyses (permeability, 3D imaging)
- European Networks
- Industrial partnerships

PERSPECTIVES:

- Understanding microbiota /environmental factors/ gut-brain interactions
- Developing innovative imaging and organoid based models to study host/environment interactions.
- Transfer preventive or therapeutic innovation to patients /society
- Further strengthen industrial partnerships
- Prepare relocation in the new University Hospital Campus and integration of iSiteNExt

UNIQUE SELLING POINTS:

- Translational research approaches combining animal models of diseases, human relevant complex models and human tissue bio-collections.
- Ability to transfer findings from bed to bedside (clinical trials)
- Ability to collaborate with industrial partners leading to co-owned intellectual property

PAUL Stéphane

Ph.D

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Ecole Normale Supérieure de Lyon - Université Claude Bernard Lyon-1
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From understanding the mucosal immunopathology of inflammatory disorders and infections to the development of new mucosal biotherapies and vaccines

Keywords:

- Mucosa
- Infections
- IBD
- Vaccines
- Adjuvants
- Secretory Immunoglobulins
- Reservoir
- Gut
- Nasal
- Ageing

From understanding the mucosal immunopathology of inflammatory disorders and infections to the development of new mucosal biotherapies and vaccines

The team federates a coherent and original research at cross-roads between mucosal immunology, inflammation and infection. The research activity is currently organized around three main themes: 1) study of viral reservoirs and mucosal infection transmission; 2) mucosal immunology of secretory antibodies and their development as vaccines and/or immunotherapy treatments against mucosal infections and inflammatory diseases; 3) epithelial and endothelial inflammation. This research program includes both fundamental and translational research activities focused on the understanding of the physiopathology of infectious and inflammatory mucosal pathologies and the development of biotherapies.

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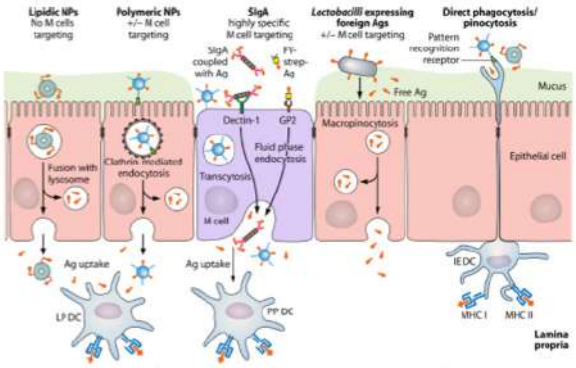
OBJECTIVES:

- Study of viral reservoirs and mucosal infection transmission
- Mucosal immunology of secretory antibodies and their development as vaccines and/or immunotherapy treatments against mucosal infections and inflammatory diseases
- Epithelial and endothelial inflammation

TOOLS:

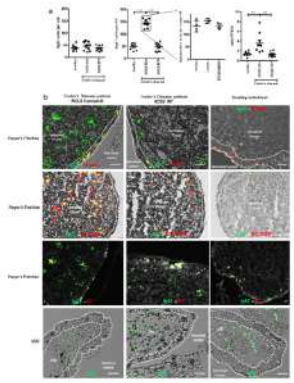
- Gut and nasal mucosal models in vitro and ex vivo
- Delivery systems for mucosal targeting
- Mucosal adjuvants
- Clinical Investigation Center for vaccine developmentand IBD therapies



Subject 1: Role of secretory immunoglobulins in the regulation of dysbiosis in IBD

RESULTS:

- Secretory IgA2 bind to M cells in GALT via Dectin-1 and Siglec-5
- Secretory IgAs bind differentially to mucosal DCs and regulate their activation
- Reverse transcytosis of IgA is dramatically increase in IBD as Crohn disease and increase the inflammation
- Modification of IgA glycosalyation is observed in IBD which promote the neutralization of anti-inflammatory commensals and also the transcytosis of pathogens into the gut

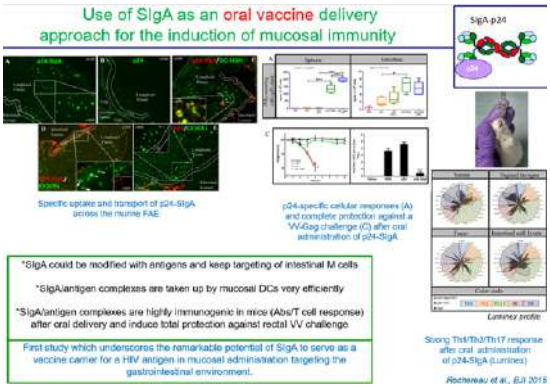


Legend: *NOD2 mutation increases SIgA reverse transcytosis in CD patients.*

Subject 2: Use of secretory IgA as a mucosal vaccine delivery systems

RESULTS:

- IgA backbone could be use to deliver antigens very efficiently to the GALT
- IgA backbone could be use to deliver antigens very efficiently to the NALT
- Mucosal delivery of IgA-based vaccine is very efficient to promote B and T cell activation
- STING ligands and chimeric TLR/TLR or TLR/NOD ligands are very efficient to promote mucosal immune responses



Legend: *Delivery of p24 antigen by a mucosal IgA-based vaccine strategy is very efficient to promote mucosal immunity and protect from a lethal challenge in mice.*

PERSPECTIVES:

- Role of secretory immunoglobulins in the shaping of inflammatory microbiota
- Modification of IgA and IgM functions during ageing
- Development of very efficient mucosal delivery systems and adjuvants
- Development of new strategies to increase vaccine efficacy in Elderly

UNIQUE SELLING POINTS:

- Highly translational research between clinicians and researchers
- Modeling of mucosa both in vitro and ex vivo
- Knowledge's on secretory immunoglobulin biology
- Important contribution to mucosal vaccine and adjuvant field

PEDUTO Lucie

Ph.D

Institut Pasteur, INSERM U1224
For yourself (your employer) : Institut Pasteur, Paris

Targeting stromal cells in inflammation and immunotherapies

Keywords:

- Inflammatory diseases (skin, kidney, intestine)
- Stromal targets in inflammation
- Fibrosis
- Obesity and metabolic disorders
- Inflammation and cancer
- Immunotherapies
- Carcinoma-associated fibroblasts (CAFs)
- Single-cell RNAseq

Using unique mice models developed in the lab and transcriptomics approaches, we are investigating the role of stromal mesenchymal cells in inflammation and repair, and how dysregulation of this essential process contributes to chronic inflammatory/fibrotic diseases and resistance to immunotherapies.

We are interested and have large expertise in the role of stromal cells in inflammation and cancer.
We have developed unique transgenic mice models to establish proof of concept in vivo. This work led to the award of several grants including an ERC Consolidator Grant in 2014 (to L. Peduto) to pursue our investigations on stromal cells in inflammatory diseases and cancer. We have two major thematics:

- **Stromal cells in inflammatory and metabolic diseases.** We are investigating the crosstalk of stromal cells and immune cells in several murine models for inflammatory diseases (scleroderma, kidney fibrosis, IBD) as well as in obesity/metabolism. The aim is to identify novel stromal targets/therapeutic approaches in inflammatory/fibrotic diseases and related metabolic diseases
- **Improving tumor immunotherapies.** Using immuno-competent preclinical models and transgenic mice, we are investigating the role of specific subsets of CAFs in tumor immunity and designing strategies to improve efficiency in immunotherapies in desmoplastic tumors.

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Our lab is investigating the role of stromal mesenchymal cells in inflammation and repair, and how dysregulation of this essential process contributes to chronic inflammatory/fibrotic diseases and resistance to cancer immunotherapies.

OBJECTIVES:

- Decipher the role of stromal cells in inflammatory diseases and autoimmunity
- Identify novel inflammation-associated stromal signatures and targets
- Improve efficiency of immunotherapies by targeting the stromal tumor microenvironment

TOOLS:

- Unique mice models generated in the lab for in vivo manipulation of specific stromal subsets
- Mice model for inflammatory / fibrotic diseases (ischemia induced kidney injury, colitis, ileitis, skin autoimmunity/fibrosis)
- Pre-clinical mice models for melanoma, pancreatic cancer and breast cancer
- Expertise in single cell /bulk RNAseq

Stromal cells in inflammation and fibrosis

RESULTS:

- We identified proinflammatory myofibroblasts progenitors expressing ADAM12 (Nat Med 2012)
- ADAM12 is not expressed in normal adult organs, it is induced after injury and in several fibrotic diseases
- Genetic depletion of ADAM12+ cells is sufficient to decrease inflammation and fibrosis after skeletal muscle injury (Fig 1)
- ADAM12 regulates TGFb signaling

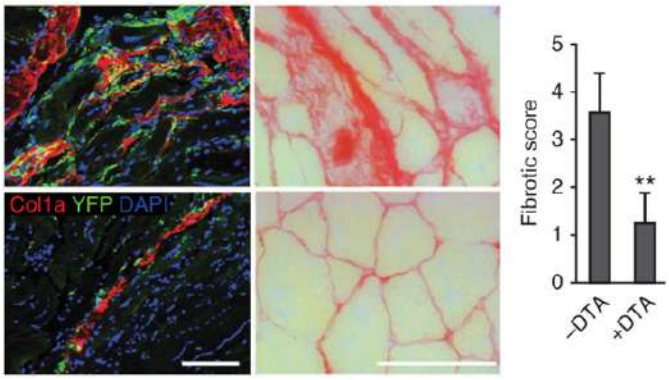
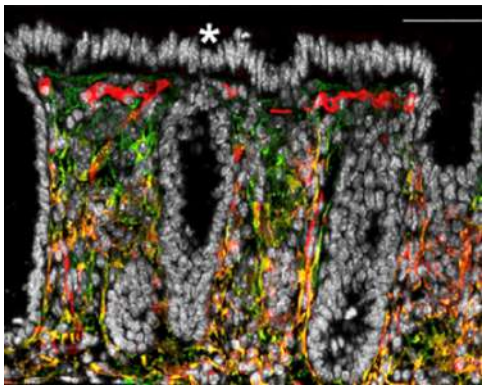


Fig1: Diphteria-mediated depletion of ADAM12+ cells (green) in ADAM12-DTR mice decreases collagen (red) accumulation after tissue injury in the skeletal muscle (Dulauroy et al., Nat Med 2012)

Stromal cells regulation of intestinal immunity

RESULTS:

- Intestinal stromal cells are major producers of proinflammatory cytokines and drivers of colitis (Stzepourginski, PNAS 2017)
- Oxysterol production by intestinal stromal cell controls ILC3 activity and colitis (Emgard, Immunity 2018)
- Intestinal stromal cells production of IL11 protects from enteropathogens infection but promotes colitis in a mechanism dependent of myeloid cells and IL23 (Disson, JEM 2018)

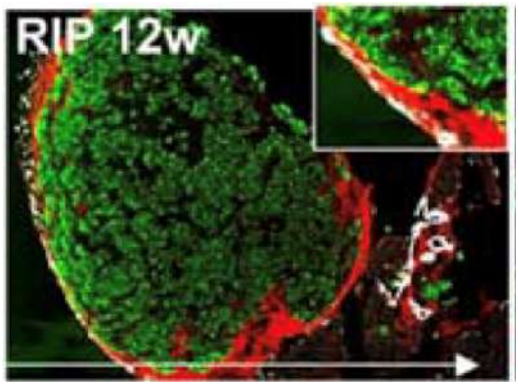


Intestinal stromal cells expressing Pdpn (green) and CD34 (red) are major producer of pro-inflammatory cytokines in chronic DSS-induced colitis (Stzepourginski, PNAS 2017)

Targeting the tumor stromal microenvironment

RESULTS:

- Pdpn+ lymphoid stromal cells secreting chemokines and cytokines accumulates at the margins of solid tumors (Peduto, JI 2009)
- Using immuno-competent preclinical models and transgenic mice, we are investigating the role of specific subsets of stromal cells (CAFs: Carcinoma-Associated-Fibroblasts) in tumor immunity
- We are designing strategies to improve the efficiency of immunotherapies in desmoplastic tumors (pancreas, breast, prostate) by co-targeting the stromal microenvironment



Pdpn+ lymphoid stromal cells (red) accumulates around pancreatic tumors (green)to form a collagenous capsule (Peduto JI 2009).

PERSPECTIVES:

- Identify novel stromal targets and therapeutic approaches in chronic inflammatory diseases, autoimmune diseases and fibrosis (skin, lung, kidney, heart)
- Determine the added effect of targeting the stroma combined with current available drugs in inflammatory diseases and cancer therapies
- Investigate the pathogenic crosstalk of stromal cells and immune cells in obesity and related metabolic diseases
- Role of stromal cells in complex multifactorial pathologies (obesity and autoimmunity /skin disease, etc..)
- Generate specific inhibitors or therapeutic antibodies against stromal cells

UNIQUE SELLING POINTS:

- Unique transgenic mice models generated in the lab to establish proof of concepts *in vivo. These models are not available elsewhere at this point.*
- Strong expertise in isolation and analysis of stromal cells in inflamed organs (FACS/ IF/ RNAseq)
- Combined expertise in immunology and stroma in a variety of experimental mice models for inflammation, fibrosis and cancer

RIEUX-LAUCAT Frédéric

Ph.D

Inserm / CNRS unit, University, Pasteur Institute...
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For yourself (your employer): INSERM

Autoimmune Mechanisms deciphering through integrated bulk and single-cell multi-Omics

Keywords:

- Autoimmunity,
- Apoptosis,
- JAK-STAT,
- RAS,
- Single Cell RNAseq,
- CyTOF,
- Inference network,
- Artificial Intelligence.

Define the molecular identity card of autoimmune patients at the single cell levels to identify specific therapeutics

Research director at INSERM since 2006 my team focuses on the immunogenetic bases of autoimmunity (ALPS, Evans Syndrome, Juvenile Myelomonocytic Leukemia, pediatric Lupus and I discovered the first genetic cause of autoimmunity in humans through the description of dominant negative mutations of the FAS gene in patients presenting with autoimmune lymphoproliferative syndrome. Later on, my team described the first FAS somatic mutations in sporadic cases of ALPS, and combined germline and somatic FAS mutations in families with non-Mendelian expression of ALPS.
Recently, we discovered the first inherited mutations of STING1 in patients presenting with skin vasculopathy, lung fibrosis and lupus-like features4, leading to the repurposing of JAK inhibitors as specific therapeutics5. We also described SOCS1 deficiencies in patients presenting autoimmune cytopenia, Lupus or psoriaris, opening again an avenue for JAK-inhibitor-based therapy. This is illustrating the Bedside to Bench back to bedside spirit developed at the Imagine Institute, a research center dedicated to explore and treat patients with rare genetic diseases.
Coordinator of a consortium project granted by the 4th RHU call (9.9M€), dedicated to develop AI-based tools to reduce the diagnosis wandering and to guide the clinician decision in Primary Immune deficiencies associated with auto-immunity and auto-inflammation.

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Project & Expertise

OBJECTIVES:

- Delineate the genetic spectrum of autoimmune diseases (Autoimmune lymphoproliferative syndromes, cytopenia, hepatitis, pediatric Lupus, Juvenile arthritis)
- Identify autoreactive cellular clusters
- Provide a molecular identity card of autoimmune patients
- In vitro prediction of therapeutic drugs response

TOOLS:

- In-depth immune phenotyping by flow and mass cytometry
- Cytokine dosage by digital ELISA (SIMOA)
- WES/WGS analysis
- Bulk and Single-cell Transcriptomic
- Assessment of immune checkpoints regulation
- Cellular and molecular functional assays (apoptosis, Tregs suppressive function, pathways activation)

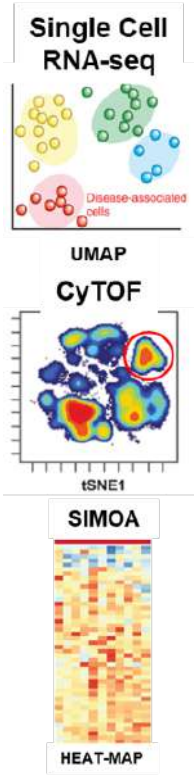


Fig 1: *Multi-Omics analyses of early-onset autoimmunity*

Autoimmune Lymphoproliferative syndromes and organ specific autoimmunity From genomic and transcriptomic data to new therapeutic approaches

RESULTS:

- Monogenic predispositions to autoimmunity are frequently associated with haploinsufficiency and variable clinical expression, from no expression (healthy carriers) to various autoimmune manifestations (i.e FAS, CTLA-4, SOCS1 deficiencies).
- By combining genomic and transcriptomic approaches we are unraveling the genetic modifiers (somatic mutations or digenic inheritance) and the pathological molecular pathways, opening new therapeutic avenues.

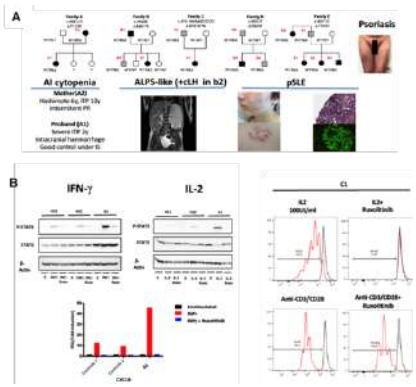


Fig.2 : *A- Identification of SOCS1 deficiencies in 10 patients (black symbols) of 5 healthy carriers (grey symbols) in 5 pedigrees. Patients presented with variable autoimmune diseases including cytopenia, lupus and psoriasis. B- The SOCS1 mutations are associated with hyperactivation of the JAK-STAT pathway and hyperproliferation upon cytokine stimulation. Ruxolitinib (ruxo) corrected this immune dysregulation in vitro.*

From autoimmunity to leukemia
Identification of a molecular signature of leukomogenesis

RESULTS:

- We have described a patient with a somatic activating KRAS mutation in lymphoid and myeloid cells who developed a benign autoimmune leukoproliferative syndrome (Lanzarotti et al Blood 2014). Twenty years later he developed leukemia suggesting a clinical continuum from the benign proliferation and fatal acute leukemia.
- Additional KRAS or NRAS patients presenting autoimmune lymphoproliferative syndrome and later developing leukemia, have been characterized and longitudinal samples obtained. This provided a unique opportunity to identify molecular signatures associated with leukemogenesis.

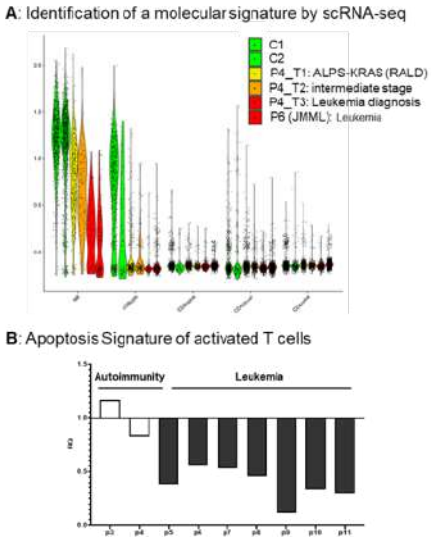
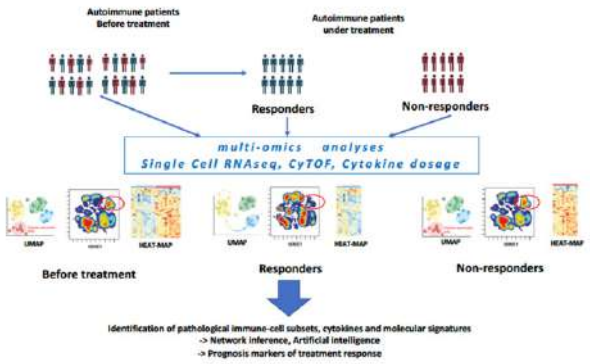


Fig.3: *A- Using scRNA-seq we identified a molecular signature associated with leukemia development. B- Using qRT-PCR we confirmed the asssociaiton of this molecular signature in 7 patients diagnosed with Juvenile Myelomonocytic Leukemia (JMML).*

PERSPECTIVES:

- Identification of key pathways involved in autoimmune development in a given genetic context (Patients versus Healthy carriers)
- Validation of a "leukemia signature" beyond the JMML context
- Application to responders and non-responder's patients to a given therapeutic
- In vitro validation of new therapeutics on the identified pathological pathways



UNIQUE SELLING POINTS:

- Recognized expertise in clinical and molecular characterization of pediatric autoimmune diseases
- Access to unique cohorts of >2,000 patients with early-onset autoimmunity
- Availability of biobanked PBMCs and plasma from patients
- Single-cell and spatial transcriptomic approaches
- Integrated multi-Omics analyses

RUA Rejane

Ph.D

CNRS UMR7280, INSERM U1104, AMU UM2
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Control of neuroinflammation by meningeal immunity

Keywords:

- Virus
- CNS
- Infection
- Immunology
- Macrophages
- Development

We aim to understand the contribution of meningeal immunity in brain functions in health and disease states.

Due to the vital importance of the Central Nervous System (CNS), its infection and inflammation have to be tightly controlled. The surface of the CNS is connected to the periphery by a rich and complex tissue, the meninges. They contain a vast network of macrophages subdivided in two populations endowed with elusive functions. Using innovative depletion strategies in experimental mouse models, we discovered that meningeal macrophage populations represent the first line of protection against neuroinvasive pathogens. In their absence, specific areas in the meninges become highly infected, leading to fatal brain disease. The goal of our team is to understand 1/the mechanisms controlling the spatiotemporal distribution of macrophage populations at the brain surface and 2/the relative contribution of the two macrophage populations in protecting the CNS against neuroinvasive pathogens. To this aim, we developed innovative strategies to visualize and manipulate meningeal macrophages in vivo that we will combine with cutting-edge gene editing techniques, in mice infected with lymphocytic choriomeningitis virus (LCMV). This pioneer work will help understand the spatial organization of the brain defence system and the molecular mechanisms involved in CNS protection, and will provide new avenues to design therapeutic strategies.
In addition, we found that other meningeal immune sentinels (such as innate lymphocytes) were crucial for the development of autoimmune diseases. We are investigating the role of the meninges in brain functions in this setting (auto-immunity).
Finally, with the help of our clinical partners, we are interested in the role of meningeal immunity in neurodegenerative diseases as well as brain development.

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- T-bet-dependent NKp46+ innate lymphoid cells regulate the onset of TH17-induced neuroinflammation. Kwong B*, Rua R*, Gao Y, Flickinger J Jr, Wang Y, Kruhlak MJ, Zhu J, Vivier E, McGavern DB, Lazarevic V. Nat Immunol. 2017 Oct;18(10):1117-1127.
- In vivo cellular tropism of gorilla simian foamy virus in blood of infected humans. Rua R, Betsem E, Montange T, Buseyne F, Gessain A. J Virol. 2014 Nov;88(22):13429-35. doi: 10.1128
-
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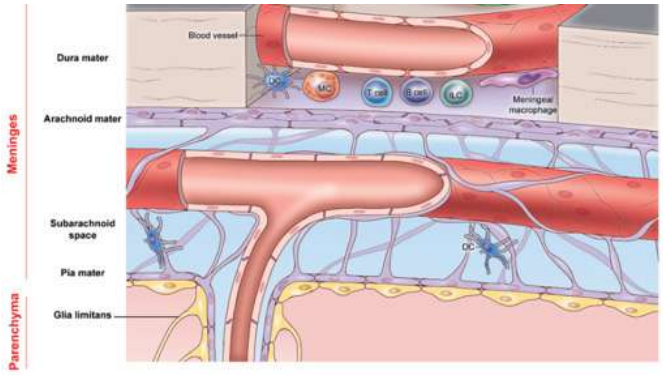
- Rua R, Pujol N. IL-17: good fear no tears. Nat Immunol. 2020 Nov;21(11):1315-1316. doi: 10.1038/s41590-020-0792-4.
- Rua R, McGavern DB. Advances in Meningeal Immunity. Trends Mol Med. (Cell Press) 2018 Jun;24(6):542-559. doi: 10.1016.

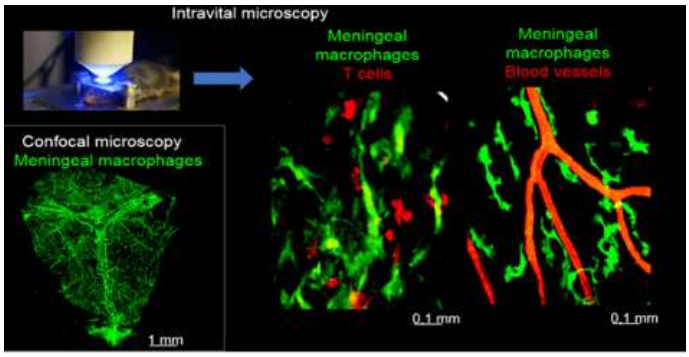
OBJECTIVES:

- Understanding the development of the meningeal immune system
- Manipulating immune sentinels in the meninges to :
  - Prevent autoimmunity
  - Prevent neuroinfection
  - Prevent neuroaging
  - Boost brain development



TOOLS:

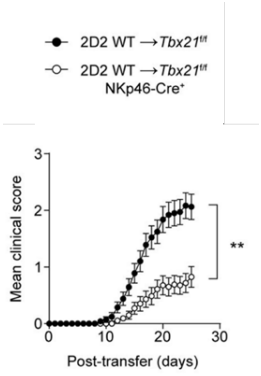
- Transcranial drug delivery to deplete meningeal macrophages
- Transgenic mouse models to deplete and manipulate meningeal immune subpopulations
- In vivo CrisprCas9 gene editing
- Spectral cytometry, intravital imaging

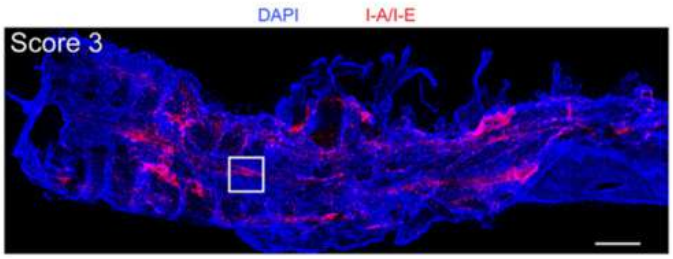


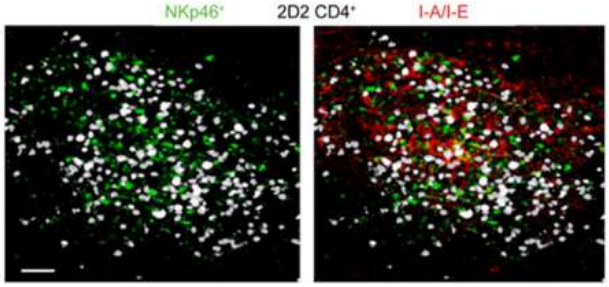
Role of meninges in autoimmunity

RESULTS:

- ILCs in the meninges cluster with pathogenic T cells
- Depletion of ILCs prevents the disease





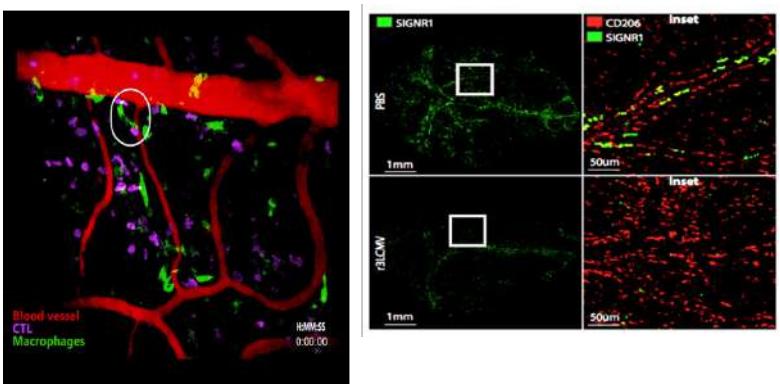


Kwong B, Rua R*, et al. Nature Immunology, 2017*

Role of meninges in neuroinfection

RESULTS:

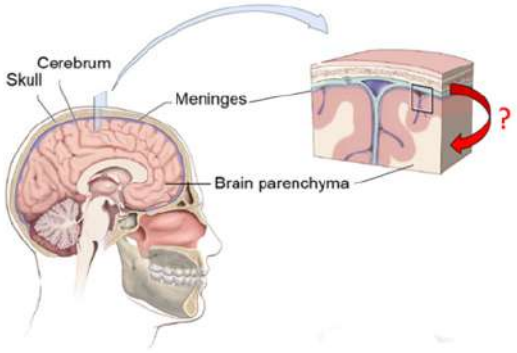
- Meningeal macrophages respond to CNS infection
- Meningeal macrophages are replaced by impaired blood-derived cells after inflammatory events



Rua R et al. Nature Immunology, 2019

PERSPECTIVES:

- Multiparametric analysis of the meningeal immune cell network and the brain (intravital imaging, single-cell RNA seq, 30 colors-cytometry, in situ histocytometry) in different conditions:
  - o steady state (development)
  - o neuropathologies (autoimmunity, infection, neurodegeneration, psychiatric disorders)
- Harnessing meningeal immune responses: molecular targets to treat neuropathologies



UNIQUE SELLING POINTS:

- Topic:
  - Meninges: understudied, mostly unknown
  - General properties of the development of the immune system and enveloping tissues in an accessible tissue (imaging+drug)
  - Better drug penetrance than in the brain parenchyma
- Team:
  - Expertise in immunologoy, infection, neuroscience
  - Rich collaborative network to study the role of meningeal responses with multiple angles (clinicians, immunology and neuroscience institutes, biophysics teams)

SALOMON Benoit

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Role of Treg in auto-immune diseases and therapeutic implications

Keywords:

- Foxp3 Treg,
- Auto-immune diseases,
- Mouse models,
- In vivo suppressive mechanisms of Treg,
- Physiopathology of inflammatory diseases,
- Biotherapy of inflammatory diseases,
- New generation of anti-TNF drugs.

Biology and function of Treg and new therapies in inflammatory diseases using unique genetically modified mouse models.

We have developed genetically modified mice that have a Treg-specific deficit of selected genes (encoding TNFR2, 4-1BB, ICOS, NF-kB or regulating cell metabolism) to better understand their role in autoimmune and inflammatory diseases and in cancer. This work allows us to decipher the mechanisms of Treg suppression in the target tissue of an autoimmune attack and within tumors. It also allows the identification of therapeutic targets for these diseases, which can then be tested in humanized mice before their development in the clinic.

We showed that Treg are strongly co-stimulated by agonists of TNFR2 and 4-1BB, which depend on cell intrinsic NF-kB activation. Using a mouse model of multiple sclerosis, we showed that TNFR2 expression by Treg is critical to control the disease within the inflamed central nervous system. This finding explains why anti-TNF drugs induced disease exacerbation, which led us to propose a second generation of drugs targeting TNF. We are also analyzing the role of mTOR and AMPK in Treg biology and function and found that mTOR is critical for Treg migration and stability. Using our unique genetically modified mice, we are studying the mechanism of drugs, such as anti-TNF, metformin or rapamycin, in the control of autoimmune diseases and obesity.

Our perspectives are to better understand the in vivo suppressive mechanisms of Tregs in inflammatory diseases, to determine when, where and how do Tregs suppress inflammatory diseases and to propose new treatments of auto-immune and inflammatory diseases.

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Patents of the last 5 years:

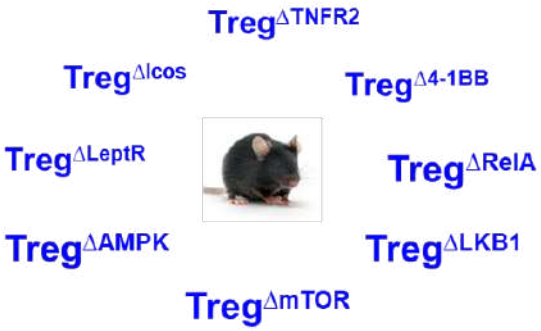
- Use of adjuvants for the prevention and/or treatment of autoimmune diseases. Wo2017102939a1
- Prevention or treatment of hematologic malignancy relapse using a tnfr2 antagonist. Wo2017220711a1
- A method for obtaining hematopoetic cell population containing regulatory t cells (tregs) specific for an irrelevant antigen. Wo2017098014a1

OBJECTIVES:

- To decipher the mechanism of Treg suppression in inflammatory diseases,
- To study the role of TNFR2 and 4-1BB in Treg biology and function.
- To assess the metabolic specificity of Treg and study the involvement of Treg in the therapeutic effect of metformin and rapamycine
- To test drugs targeting Tregs for new biotherapy of inflammatory diseases

TOOLS:

- Portfolio of mice with conditional knock-out genes in Tregs (see figure)
- Mouse models of EAE, colitis, diabetes, obesity and spontaneous autoimmunity
- Multidimensional studies of immune cells in various inflamed tissues in mice

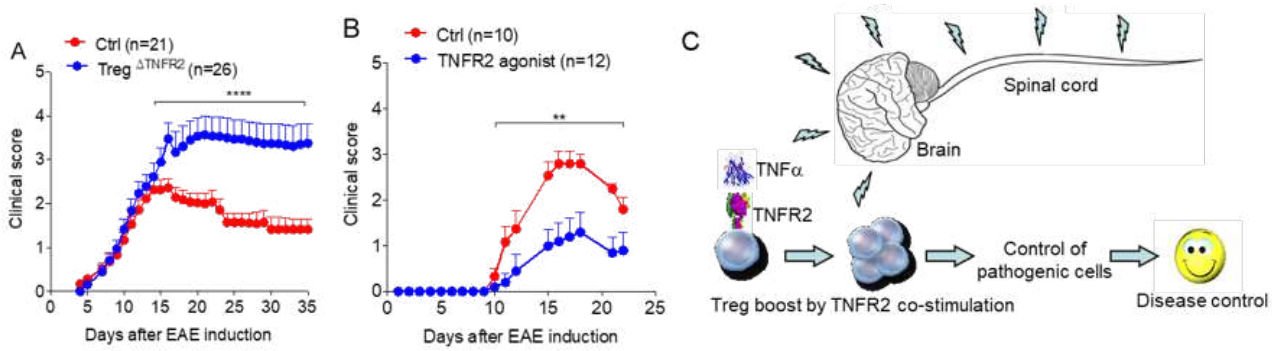


Portfolio of mice with conditional knock-out genes in Treg

Subject 1. Role of TNFR2 and 4-1BB expressed by Treg in the control of inflammatory diseases

RESULTS:

- TNF strongly co-stimulates Treg via TNF receptor type 2 (TNFR2) in mice and human,
- Anti-TNF treatments may lead to paradoxical exacerbation of auto-immune and inflammatory diseases due to Treg activation via TNFR2,
- During EAE (model of MS), colitis and sepsis, TNF stimulates Treg via TNFR2 to suppress the disease (figure and not shown).

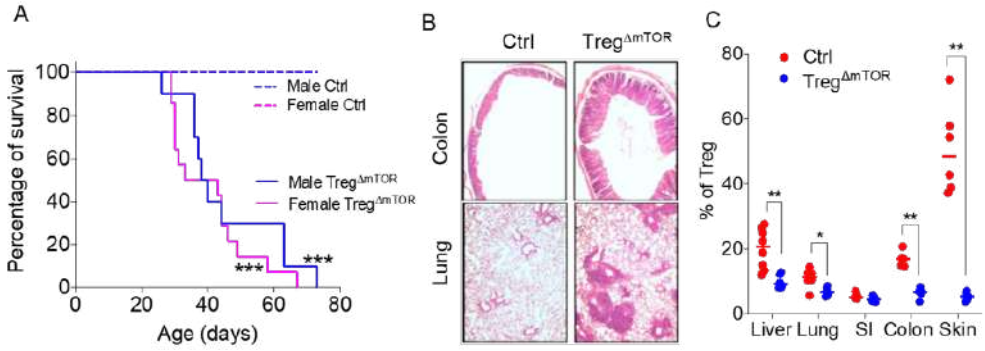


TNFR2 expressing Treg control the inflamed central nervous system during EAE, a mouse model of multiple sclerosis. (A) *Score of EAE in control mice (Ctrl) and mice that have a conditional deletion of TNFR2 only in Treg (TregΔTNFR2).* ***(B)*** *Score of EAE in Ctrl mice and mice treated with an agonist of TNFR2.* ***(C)*** *During EAE, TNF produced in the inflamed central nervous system stimulates Treg locally via TNFR2 to increase their expansion and suppressive activity, which leads to increased Treg-mediated suppression of pathogenic cells, limiting disease severity.*

Subject 2. Cellular metabolism in Treg

RESULTS:

- mTOR play a critical role in Treg biology and function (figure),
- mTOR controls Treg stability and tissue migration (figure),
- LKB1 expressed by Treg, but not AMPK, is critical in Treg biology at steady state.



Mice that have a conditional deletion of mTOR in Treg (Treg$^{\Delta mTOR}$) develop a lethal autoimmune syndrome with reduced Treg migration in non-lymphoid tissues. *(A) Mouse survival. (B) Severe inflammation in the colon and lung of 5-week old Treg$^{\Delta mTOR}$ mice. (C) Treg proportion among CD4+ cells of 2-week old Treg$^{\Delta mTOR}$ and control mice in various non-lymphoid tissues. SI: small intestine.*

PERSPECTIVES:

- Better understand the in vivo suppressive mechanisms of Tregs in inflammatory diseases
- Determine when, where and how do Tregs suppress inflammatory diseases
- Identify new targets to boost Tregs during inflammation
- Propose new treatments of auto-immune and inflammatory diseases.

UNIQUE SELLING POINTS:

- Portfolio of unique genetically modified mouse models to study Treg biology and function in vivo
- Integrated transcriptomic and cellular platform to study the role of Tregs in inflammatory diseases (EAE, obesity, colitis, sepsis).
- Unique mouse models to study the in vivo mechanism of drugs targeting TNF family members (Treg$^{\Delta TNFR2}$ and Treg$^{\Delta 4\text{-}1BB}$ mice), ICOS (Treg$^{\Delta mTOR}$ mice) and cellular metabolism (Treg$^{\Delta LKB1}$, Treg$^{\Delta AMPK}$ and Treg$^{\Delta mTOR}$ mice).

SARRAZIN Sandrine (Michael Sieweke's lab, CIML)

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Stem cell and macrophage biology

Keywords:

- Hematopoietic stem cells,
- Tissue macrophages,
- Transcription factors and gene expression,
- Cell fate decision,
- Self-renewal/ cell cycle in hematopoietic stem cells and macrophages,
- Therapeutic applications of hematopoietic stem cells and macrophages,
- Murine models for normal and pathological haematopoiesis, inflammation and tissue regeneration,
- Genome wide epigenetics and transcriptomic,
- Single cell NGS and multiparametric flow cytometry,
- Genome editing.

From bench to bedside: translation into clinical applications of basic research discoveries in hematopoietic stem cells and tissue macrophages for transplantation, resolution of inflammation and tissue regeneration.

Michael Sieweke's lab is located at the interface of immunology and stem cell research. We study the molecular and cellular mechanisms of self-renewal and cell fate choice that guide the differentiation from hematopoietic stem cells to macrophages, cells with important roles in immunity and tissue regeneration. We are interested in the regulation of these processes by transcription factors, particularly of the Maf family. Currently we develop research projects investigating the lineage commitment of hematopoietic stem cells, self-renewal and reprogramming in mature macrophages and the role of monocyte/macrophage subtypes in inflammation and tissue regeneration.

Our recent findings lay the groundwork for new cellular therapy approaches in regenerative medicine.
One important line of our work has revealed mechanisms how hematopoietic stem cells can generate more myeloid cells, including macrophages, to protect transplant recipients from lethal infections.
Furthermore, we discovered that macrophages, mature cells of the immune system, could activate a network of self-renewal genes shared with embryonic stem cells that enables them to proliferate indefinitely. This makes it possible to amplify macrophages in culture as mature differentiated cells, without stem cell intermediates or tumorigenic transformation. Our results show that not only stem cells but also mature cells like macrophages can activate self-renewal mechanisms. This opens the door for new macrophage-based therapies.

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- #:co-last authors

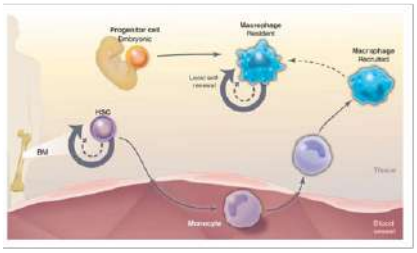
OBJECTIVES:

- Understand and control early commitment of hematopoietic stem cells for therapeutic applications
- Understand and control immune function of hematopoietic stem cells
- Understand and control self-renewal, anti-inflammatory activity and regenerative capacities of tissue macrophages

TOOLS:

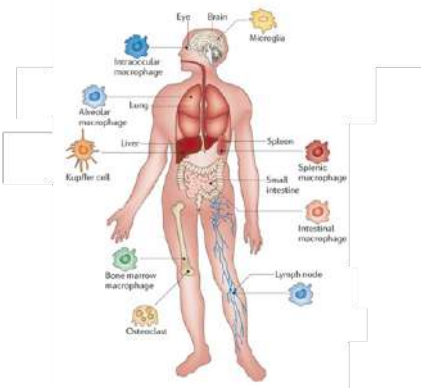
- Murine models for normal and pathological haematopoiesis, inflammation and tissue regeneration
- Genome wide epigenetics and transcriptomic
- Single cell NGS and multiparametric flow cytometry
- Genome editing

Macrophages originate from embryo or adult hematopoietic stem cells



Sieweke MH and Allen JE , Science (2013)

Macrophages are present in all tissues where they display immune an regenerative functions

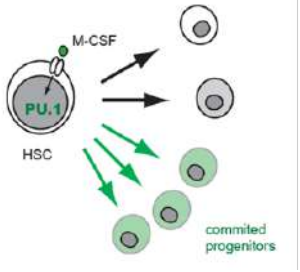


Murray PJ and Wynn TA, Nat Rev Immunol. (2011)

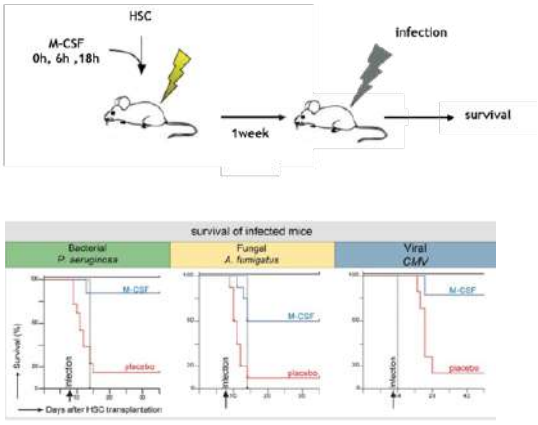
Using cytokine-based therapy to treat infections occurring after chemotherapy, bone-marrow transplantation and sepsis

RESULTS:

- The cytokine M-CSF induces early commitment of the hematopoietic stem cell (HSC) and increase production of innate immune cells (macrophages, granulocytes) involved in first line defense against microbes
- This property can be used to protect immunocompromised recipients against fatal infections occurring after chemotherapy, bone-marrow transplantation and sepsis.



Sarrazin et al, Cell (2009)
Mossadegh-Keller, Sarrazin* et al. Nature (2013)*

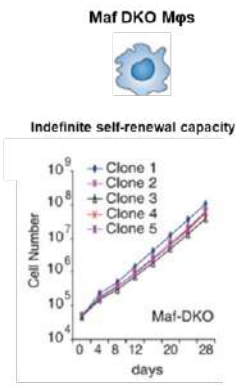


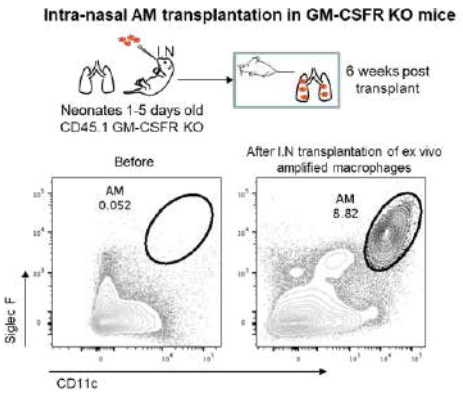
Kandalla et al. JEM 2016 Kandalla et al., in preparation

Using ex-vivo amplified tissue macrophages for cellular therapies

RESULTS:

- Inactivation of MafB and c-maf transcription factor genes both in mouse and human leads to sustain self-renewal of anti-inflammatory macrophages
- Ex-vivo amplified macrophages can be transplanted to alveolar macrophages-deficient humanized mice, self-maintain long term and provide normal functions of alveolar macrophages.





PERSPECTIVES:

- Applying M-CSF-based therapy to human for treatment of infections occurring after chemotherapy, bone-marrow transplantation and sepsis
- Evaluate anti-tumorale activity of self-renewing MafB and c-maf double KO macrophages
- Set-up pre-clinical diseases models in mice for cellular therapies with ex-vivo amplified tissue macrophages

UNIQUE SELLING POINTS:

- European leader in hematopoietic stem cell and macrophage biology
- Modern lab set-up on 2 sites with complementary and synergic expertise in immunology, hematopoietic development and regenerative medicine
- Strong expertise in pre-clinical models of human diseases
- Unique collection of genetically modified murine models for normal and pathological haematopoiesis, inflammation and tissue regeneration
- Integrated genomic, cell biology and immune characterization platform

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INSERM

New players involved in the regulation of immune receptor trafficking and signaling

Keywords:

- Endocytic signaling,
- Insulin Responsive Aminopeptidase,
- TCR signaling,
- FcgR signaling,
- Chimeric antigen receptors,
- Chronic inflammation,
- Fibrosis.

Harnessing the mechanisms of intracellular endocytic trafficking to better understand and optimize immunotherapy tools.

Endocytosis of cell surface receptors was believed for decades to terminate receptor signaling. Our recent results demonstrate that endocytosis of key immune receptors leads to amplification of receptor signaling, instead of signal extinction. We discovered that the antigen T cell receptor (TCR) and the activating receptors for the Fc fragment of immunoglobulins (Fc Rs) build signaling platforms in a particular population of endosomes whose formation and stability is dependent on a type II transmembrane protein, the Insulin Responsive Aminopeptidase (IRAP).
Based on these recent findings, we propose to investigate if the chimeric antigen receptors (CAR) are also using endocytic signaling platforms. To fully characterize these platforms and to find new players involved in endocytic signaling, we have set up a dynamic proximity labeling assay based on the peroxidase APEX2. APEX2 was fused to different receptors (TCR, Fc R, CAR) and the proteins labeled in situ will be purified and identified by quantitative mass-spectrometry. The role of identified proteins in receptor trafficking and signaling will be validated both in vitro and in vivo, using murine models. The obtained results might lead to novel strategies to manipulate signaling through endogenous antigen receptors. In addition they can help to optimize CAR receptors, especially for their use against fibrosis, which is often a severe life-threatening consequence of chronic inflammation.

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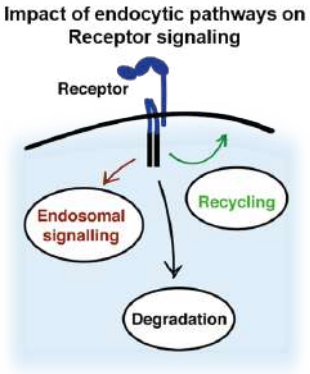
OBJECTIVES:

- To identify molecular mechanisms that regulate the trafficking and signaling of several ITAM-coupled immune receptors:
  - Antigen T cell receptor (TCR)
  - Receptors for Fc fragment of Immunoglobulin G (FcgR)
  - Chimeric Antigen Receptors (CAR)
- To describe the localization and composition of their signaling platforms
- To develop CAR receptors adapted for the therapy of inflammation and fibrosis

TOOLS:

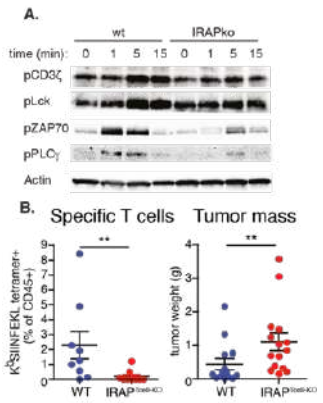
- Study receptor trafficking and signaling using cell imaging (FRET-FLIM, TIRF)
- Find new players involved in receptor signaling by in situ biotinylation and mass-spectrometry using the peroxidase APEX2
- Validate the role of newly identified proteins by protein deletion (CRISPR/Cas9, shRNA) or overexpression (lentiviral systems) and functional assays
- Functional assay in vitro (cytotoxicity against fibrogenic cells) and in vivo (animal models of inflammation and fibrosis).



Subject 1: Insulin responsive aminopeptidase (IRAP) controls TCR trafficking and endocytic signaling

RESULTS:

- Identification of IRAP interaction with the main signaling unit of the TCR, the CD3z chain
- Demonstration that IRAP is required for the ability of TCR to build endocytic signaling platforms
- IRAP acts as a TCR "chaperone" and IRAP enzymatic activity is not required for TCR signaling and trafficking
- Generation of mouse models with T cell specific IRAP deletion
- Finding that TCR endocytic signaling is essential for an efficient T cell response against solid tumors and for T cell survival in periphery.

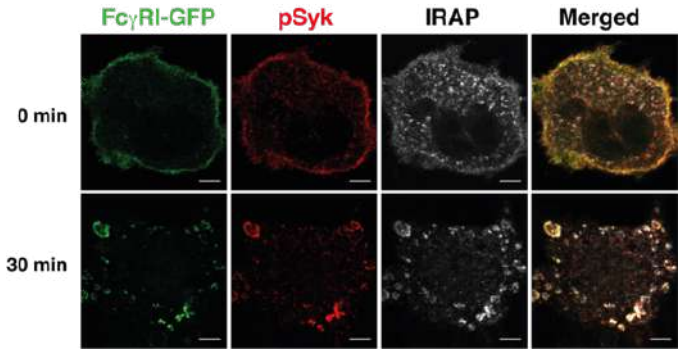


IRAP deficiency affects TCR function. *A. Phosphoblots of control and IRAPko T cells after activation with soluble anti-CD3/anti-CD28 antibodies for the indicated time points.*
B. Wild type (WT) or mice deficient for IRAP exclusively in T cells (IRAPTcell-KO) were injected s.c with 0.5 million EL4-Ovalbumin tumor cells. After 16 days, IRAPTcell-KO mice showed a reduced number of Ovalbumin-specific CD8+ T cells in the tumors and increased tumor weight.

Subject 2: Activating Fc R are recruiting the signaling machinery in IRAP endosomes

RESULTS:

- The common γ chain of FcγR is highly similar to the CD3z chain of the TCR
- Similar to the TCR, activating FcγR are able to use endocytic signaling platforms that depend on IRAP
- IRAP deletion compromises endosomal signaling of FcγRs
- IRAP deficient macrophages showed compromised antibody dependent cellular cytotoxicity (ADCC) against tumor cells in vitro
- The impact of FcγR endosomal signaling on ADCC in murine models in vivo is currently under investigation.



Activating FcRs are recruiting the signaling machinery in IRAP+ endosomes. *The DC-like cell line DC2.4 was engineered to express FcRs-GFP. Cells were incubated with human IgG followed by cross-linking with secondary antibodies at 4°C. The receptor internalization was followed at 37°C at several time points. After cell fixation, the cells were stained with anti-IRAP (mouse) and anti-pSyk (rabbit) antibodies. Similar results were obtained for activating Fc RIIA and Fc RI.*

PERSPECTIVES:

- Identify the composition of plasma membrane signaling versus endocytic signaling platforms of the TCR, FcγR and engineered CARs.
- Identify unexpected new players involved in these receptors signaling that can provide new ideas for optimization of existing CAR receptors.
- Generation of new CAR receptors for the treatment of fibrosis that accompanies chronic inflammation and often leads to organ failure.

UNIQUE SELLING POINTS:

- Simultaneous skills in immunology and in cellular and molecular biology (advanced cell imaging, in situ protein biotinylation, expression of engineered receptors in primary cells), as well as expertise in complex transgenic murine models
- Excellent environment for development and evaluation of new murine models of chronic inflammation and fibrosis
- Possibility to collaborate with the clinical departments of Bichat Hospital for translational research.

SEGURA Elodie

Ph.D

INSERM

Biology of antigen-presenting cells in health and pathology

Keywords:

- human,
- dendritic cells,
- macrophages,
- monocytes,
- inflammation,
- aryl hydrocarbon receptor,
- inflammatory disorders.

By combining the analysis of clinical samples, human primary cells and pre-clinical mouse models, my research program provides a unique insight into the biology of myeloid cells in health and pathology, with great potential for clinical applications in inflammatory diseases.

Our goal is to better understand the biology of human antigen-presenting cells (dendritic cells, macrophages and monocytes) in health and pathology, in order to manipulate the properties of these cells for disease treatment, in particular for cancer and inflammatory diseases. To achieve this, we combine studies of human cells directly isolated from tissues, in vitro models using human cells, and in vivo models in mice.
Current research

1. Properties of human macrophages. We found that human lymphoid organ macrophages, but not macrophages from other tissues, participate in T follicular helper cells activation, which is essential for inducing efficient humoral responses. We will better characterize the properties of human macrophages in relation to their anatomical niche, with a focus on tonsil macrophages.
2. Molecular circuits governing monocyte differentiation. Using a novel culture model for human monocyte differentiation, we showed that they are not pre-committed to become dendritic cells or macrophages, but react to cues from their micro-environment. Using high throughput transcriptomics, we will identify novel molecular regulators that drive monocyte differentiation towards dendritic cells versus macrophages. By better understanding the molecular regulation of monocyte differentiation, we aim to identify strategies to manipulate this process for improving the efficacy of therapies against cancer and inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis.
3. Role of Aryl Hydrocarbon Receptor in antigen-presenting cells. Using a combination of in vitro assays with human cells and a series of conditional knock-out mice that we have generated, we will decipher the role of Aryl Hydrocarbon Receptor in macrophages for tissue repair and in dendritic cells for T cell activation. We will also explore how diet and microbiota impact antigen-presenting cells via activation of the Aryl Hydrocarbon Receptor.

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- Human in vivo-generated monocyte-derived dendritic cells and macrophages cross-present antigens through a vacuolar pathway. Tang-Huau TL, Gueguen P, Goudot C, Durand M, Bohec M, Baulande S, Pasquier B, Amigorena S, Segura E. (2018). *Nature Communications* 9, 2570. 10.1038/s41467-018-04985-0
- Aryl hydrocarbon receptor controls monocyte differentiation into dendritic cells versus macrophages. Goudot C, Coillard A, Villani AC, Gueguen P, Cros A, Sarkizova S, Tang-Huau TL, Bohec M, Baulande S, Hacohen N, Amigorena S, Segura E. (2017). *Immunity*. 47(3):582-596.

OBJECTIVES:

- Better understand the properties of human macrophages in relation to their anatomical niche
- Unravel the molecular circuits governing monocyte differentiation
- Decipher the role of Aryl Hydrocarbon Receptor in antigen-presenting cells

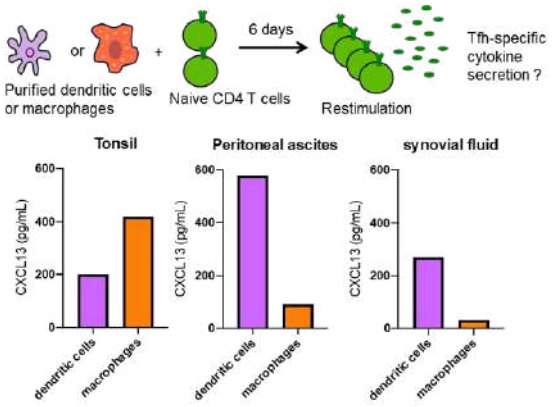
TOOLS:

- Ex vivo assay on human antigen-presenting cells directly purified from tissues
- In vitro model for human monocyte differentiation (generated in-house)
- Conditional KO mice deficient for AhR in specific immune cells

Properties of human macrophages

RESULTS:

- cDC2 dendritic cells are specialized for inducing T follicular helper cells
- Macrophages from tonsils can also induce T follicular helper cells, but not macrophages from other tissues

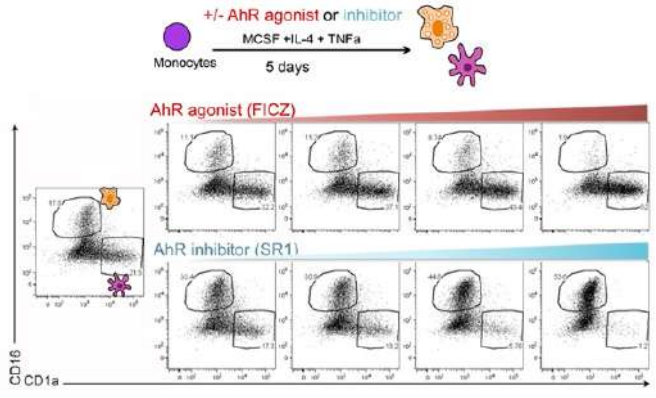


Macrophages from tonsils, but not from other tissues, can induce Tfh cells

Molecular regulators of monocyte differentiation

RESULTS:

- Monocytes are not pre-committed to differentiate into dendritic cells or macrophages, but respond to micro-environmental signals
- Aryl Hydrocarbon Receptor (AhR) activation is essential for monocyte differentiation into dendritic cells
- AhR agonists derived from food or microbiota impact monocyte differentiation in vivo



Aryl Hydrocarbon Receptor is a molecular switch for monocyte differentiation

PERSPECTIVES:

- To characterize the tissue-derived signals that imprint macrophage functional properties in humans
- To identify novel molecular targets to manipulate monocyte differentiation for therapies against cancer and inflammatory diseases
- To provide new insight on the impact of diet and microbiota on antigen-presenting cells via the activation of the Aryl Hydrocarbon Receptor

UNIQUE SELLING POINTS:

- Strong expertise in the analysis of human antigen presenting cells directly purified from tissues
- Generation of the most relevant model for analyzing monocyte differentiation into dendritic cells versus macrophages
- Unique collection of AhR deficient mice for performing integrated analysis from molecular to whole organism level

SOKOL Harry

M.D, Ph.D

Sorbonne University / INSERM UMRS 938, team "Microbiota, Gut & Inflammation"
Sorbonne University / APHP

Host-microbiota interactions in health and diseases

Keywords:

- Gut Microbiome,
- Intestinal inflammation,
- Tryptophan Metabolism.

The work of this team focuses on deciphering the gut microbiota-host interactions in health and diseases (particularly IBD), in order to better understand their role in pathogenesis and develop innovative treatments.

- Multidisciplinary expertise
- Access to human samples biobanks we built
- Access to human samples from Clinical trial on fecal microbiota transplantation we are coordinating
- Coordination of the Paris Center for Microbiome Medicine (PaCeMM) FHU including over 50 medical departments and research labs in the Paris area (http://www.fhu-pacemm.fr/)

Our main goal is to decipher the mechanisms underlying host-microbiota interactions in health and disease, particularly inflammatory bowel diseases. Our projects are based on multidisciplinary expertise, including gastroenterology, intestinal microbiota ecology, intestinal epithelial cells physiology, immunology, metabolomics and host-microbe interactions. These skills, at the frontier of cell biology, immunology, microbiology and medicine, allow us to conduct extensive studies from bedside to bench and back again.
A large part of our projects focuses on deciphering the impact of gut microbiota-derived metabolites on the host in health and pathological contexts, with a particular interest for tryptophan metabolites and bile acids for which we have strong expertise.

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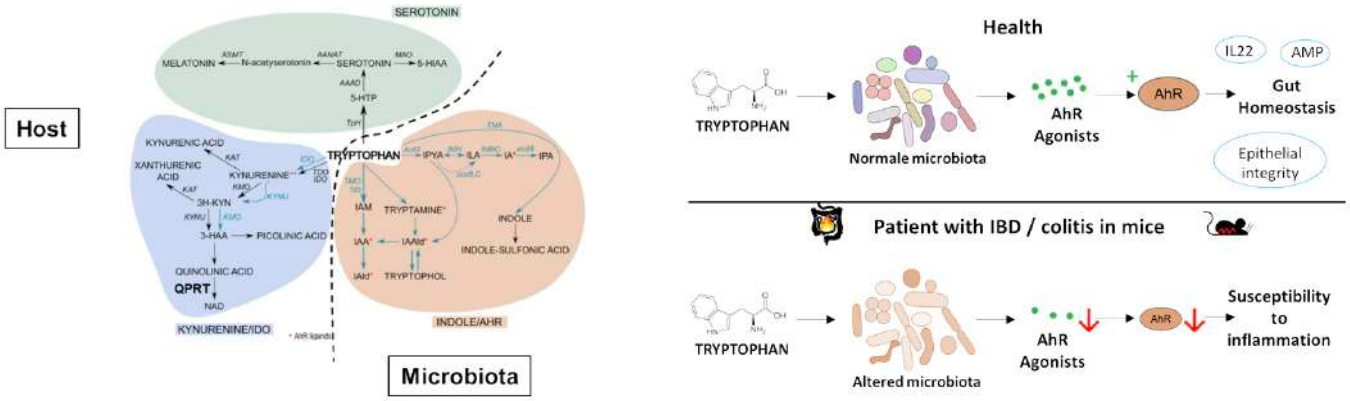
Tryptophan metabolims by the gut microbiota: impact in health and diseases



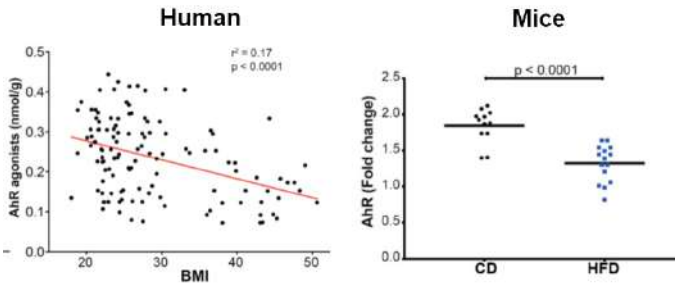
Agus A et al. Cell Host & Microbe 2018

RESULTS:

- Correcting the AhR defect with next generation probiotics or metabolite exhibits therapeutic effect in colitis model

Tryptophan metabolims by the gut microbiota: impact in health and diseases

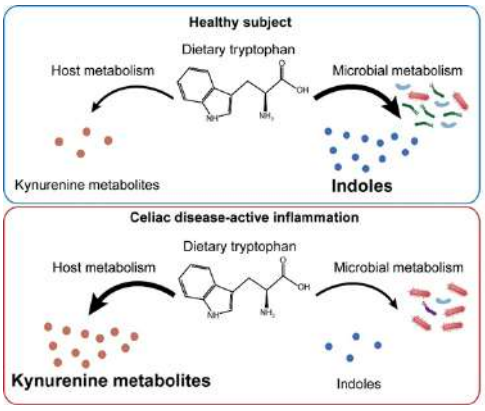
Metabolic syndrome



RESULTS:

- Correcting the AhR defect with next generation probiotics or metabolite exhibits therapeutic effect in mouse models of metabolic syndrome (high fat diet, ob/ob mice).

Celiac disease



Lamas et al. Science Translational Medicine 2020

RESULTS:

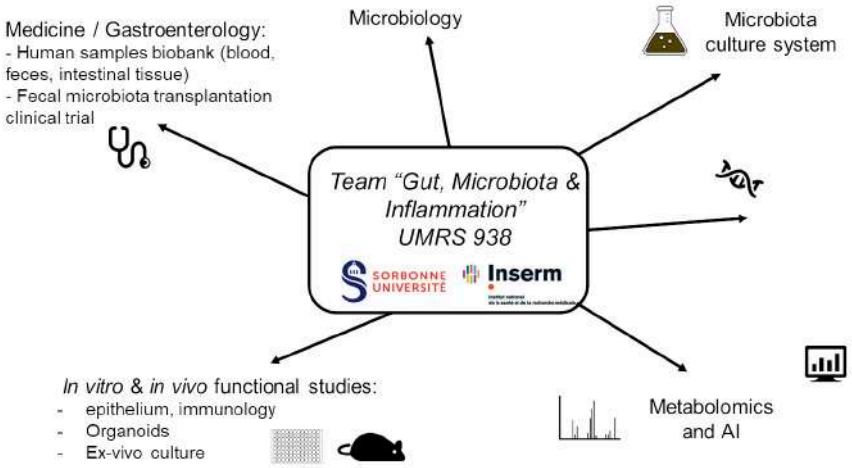
- Correcting the AhR defect with next generation probiotics or metabolite exhibits therapeutic effect in mouse model of coeliac disease (high fat diet, ob/ob mice).

PERSPECTIVES:

- Deciphering the role of the other tryptophan metabolism pathways (IDO, Serotonin) and the interactions between the 3 tryptophan metabolism pathways
- Exploring the functional role of the bile acids and other microbiota-derived metabolites in the host-microbiota interactions
- Explore the inter-microorganisms interactions in the gut microbiota
- Explore the host genetics-microbiota interactions
- Develop innovative preventive and therapeutic solution using or targeting the gut microbiota

UNIQUE SELLING POINTS:

- Multidisciplinary expertise to explore the host-gut microbiota interactions from cellular system to mice to human



UGOLINI Sophie

Ph.D

Inserm / CNRS unit, University, Pasteur Institute…
Inserm / CNRS unit, Aix Marseille University
Inserm

Neuroimmune interactions in the skin, from molecular mechanisms to therapeutic perspectives

Keywords:

- Sensory neurons,
- Innate immunity,
- Infection, Inflammation,
- Skin, Tissue repair,
- Macrophages,
- Innate lymphoid cells,
- Neuropeptides,
- Stress hormones.

The nervous and immune systems play major roles in maintaining tissue homeostasis. Both systems are activated during inflammatory processes suggesting that they could interact to control tissue repair and resistance to infectious diseases. A new paradigm in which the nervous system regulates immune functions is emerging but the mechanisms involved remain unclear. The goal of our lab is to identify new regulatory mechanisms affecting the immune response by investigating the functional role of the sensory nervous system in immunity. We have already identified a major role for subsets of cutaneous sensory neurons in regulating the immune response in a model of HSV-1 infection and upon skin exposure to ultra-violet (UV) radiation.

Inflammation is a defense response to tissue damage that requires tight regulation to prevent impaired healing. Macrophages play a key role in tissue repair and undergo major functional changes during the healing process. However, the precise molecular mechanisms underlying this functional reprogramming remain poorly understood. We demonstrated recently a major role for a subset of sensory neurons in promoting macrophage tissue repair functions in a sunburn-like model of skin damage. We also dissected the underlying molecular mechanisms and identified a new neuropeptide, produced in the skin after overexposure to UV light, which was able to modulate the inflammatory profile of macrophages, reducing their production of inflammatory cytokines and increasing their production of interleukin (IL)-10. Furthermore, this pathway was required to promote the survival of pro-repair IL-10-producing dermal macrophages, leading to the resolution of skin inflammation and tissue repair (Hoeffel et al. In revision). These results identify a new neuroimmune regulatory pathway driven by a novel neuropeptide that promotes macrophage anti-inflammatory functions and prevents fibrosis upon tissue damage, opening up new therapeutic perspectives for inflammatory diseases.

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OBJECTIVES:

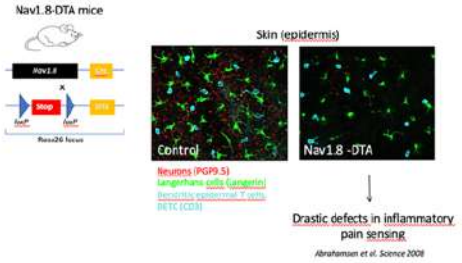
- To identify new regulatory mechanisms affecting the immune response by investigating the functional role of the sensory nervous system in immunity
- To test the effect of a newly identified neuropeptides in treating inflammatory diseases.
- To identify new pathways to treat inflammatory diseases

TOOLS:

- Genetic mouse models
- Models of skin inflammation and infection
- Single cell RNA Seq
- New tools to measure neuropeptide production in tissues (Antibodies, ELISA, Immunofluorescence)
- Collaboration with MDs from the La Timone hospital (Marseille Immunopole)

Nociceptive sensory neurons promote antiviral T cell response by regulating skin inflammation

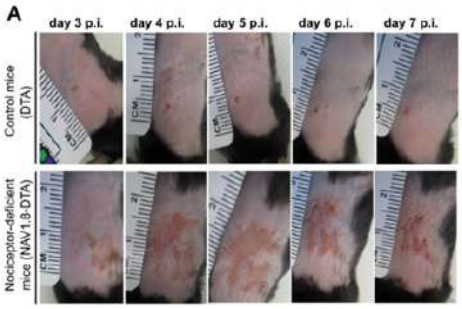
A genetic mouse model with impaired skin innervation by Nav1.8 sensory neurons



Cutaneous HSV-1 infection

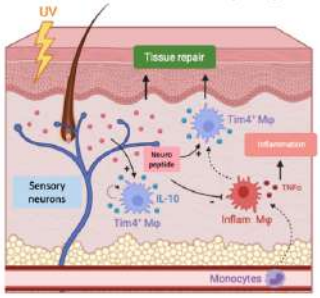
Nav1.8+ sensory neurons:

Infection with the HSV-1-OVA-TK⁻ strain



- Down-regulate inflammatory cytokine production by monocytes
- Are required to limit neutrophil influx in the infected skin
- Promote the resolution of inflammation
- Promote tissue repair
- Promote a robust T cell response

A novel neuroimmune pathway which promotes macrophage tissue repair functions



- Skin overexposure to UV-light induces the release of a new neuropeptide by a subset of sensory neurons
- This neuropeptide induces IL-10 production by Tim4+ dermal macrophages and promote their survival
- This pathway controls inflammatory macrophage response and limit inflammatory cytokine production in the skin
- This neuropeptide promotes the polarization of monocyte-derived macrophages in IL-10-producing macrophages
- The regulation of the myeloid response by TAFA4 protects the skin from excessive inflammation, promotes tissue repair and prevents skin fibrosis

Hoeffel et al., in revision (confidential)

PERSPECTIVES:
Therapeutic potential of a new neuropeptide in inflammatory diseases

Aim

- Evaluation of the protective effect of the newly identified neuropeptide using animal models of inflammatory diseases (COVID-19, Rheumatoid arthritis, HSV-1 infection, EAE, others…)

Expected effects

- Inhibition of inflammatory cytokine production
- Reduction of myeloid cell influx in inflamed tissues
- Reduction of cytokine and chemokine production by monocytes/macrophages (IL-6, IL-1b, TNFa, CCL2, CXCL1…)
- Up-regulation of IL-10 production
- Tissue repair
- Reduction of tissue fibrosis

VERGNOLLE Nathalie

Ph.D

DIGESTIVE HEALTH RESEARCH INSTITUTE, INSERM UMR 1220, INRA UMR 1416, ENVT, UNIVERSITÉ TOULOUSE PAUL SABATIER
Inserm (Research Director)

Chronic Inflammation and Pain of the Intestine

Keywords:

- Inflammation,
- Pain,
- Intestine,
- Proteases,
- Microbiota,
- Inflammatory Bowel Diseases,
- Irritable Bowel Syndrome.

From our comprehension of pathophysiological mechanisms, we identify new therapeutic targets in chronic inflammation and pain of the intestine, using a full range of human and animal pre-clinical models. We focus on fostering the return to homeostasis of chronically inflamed tissues..

Our expertise is on mechanisms of chronic inflammation and pain of the intestine: inflammatory bowel disease (IBD), celiac disease, irritable bowel syndrome (IBS).
We have constant and regular access to intestinal biopsies and microbiota samples from such patients. We use such samples for "omic" approaches, but also for primary cultures of organoids or mucosa-associated biofilm cultures. We also have a full range of animal models of intestinal inflammation and visceral pain.
We postulate that in chronic intestinal diseases, the return to tissue homeostasis is hampered by uncontrolled molecular mechanisms that maintain tissue dysfunctions, leading to relapses. Targeting such mechanisms could constitute new therapeutic options for the treatment of chronic non-transmissible diseases. We investigate the molecular mechanisms that are affected in chronic intestinal diseases and we are studying their impact on intestinal functions (barrier, epithelial renewal, immune tolerance, motility, sensory functions, microbiota diversity, etc.).
We have identified that IBD, IBS and Celiac Disease are associated with a severe disruption of tissue proteolytic balance, that plays a major role in maintaining tissue dysfunctions. We have identified the molecular actors of this proteolytic unbalance and some of their mechanisms of action. This has led us to propose several, but disease-specific therapeutic targets for chronic intestinal inflammation and pain disorders (2 targets for Crohn's, 2 targets for ulcerative colitis, 1 target for IBS), as well as companion assays for patient's selection.

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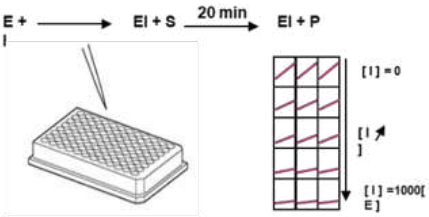
OBJECTIVES:

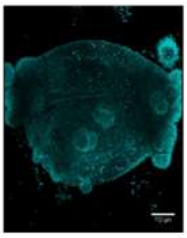
- Identify the molecular mechanisms associated with tissue dysfunctions in chronic intestinal inflammation and pain
- Study the pharmacology of identified targets
- Establish the POC of identified targets

TOOLS:

- Human intestinal biopsy collection (Healthy, IBD, IBS, Celiac)
- Human microbiota collection (Healthy, IBD, IBS, Celiac)
- Hight throughput human organoid cultures (Healthy, IBD)
- Animal models of intestinal inflammation and pain
- Molecular constructions for drug screening (proteolytic assays, cell lines, transgenic mice)



Drug screening assays

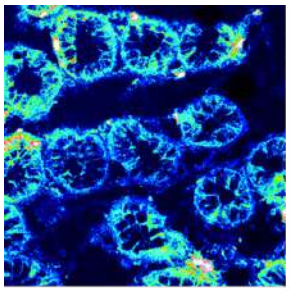


Human colon organoid

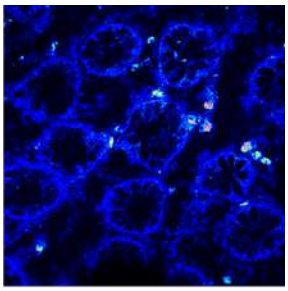
Subject 1: Active protease profiling in Inflammatory Bowel Diseases (IBD)

RESULTS:

- A complete profile of active proteases present in tissues of IBD patients has been performed, compared to healthy tissues.
- Several of the identified proteases have been studied for their effects on barrier function, on activation of the immune system, on microbial biofilms, on visceral pain and on motility.
- Several proteases originate from the epithelium and control epithelial renewal, barrier, and secretion.



Proteolytic activity in tissues from IBS patients

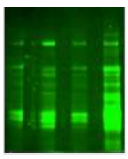


IBS tissues + inhibitor identified from screening

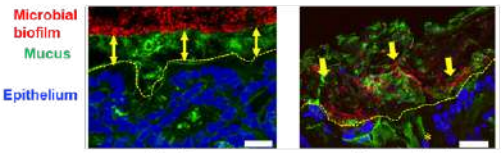
Subject 2: Screening and development of protease inhibitors for the treatment of visceral pain

RESULTS:

- Prestwick library screening for inhibitors of a protease identified in IBS patients: 2 hits.
- Development of specific nanobodies blocking the activity of a protease identified in IBS patients.
- Tests of identified targets on tissues from IBS patients



Activity-based protein profiling:
Several bands of active proteases have been identified and sequenced.



Healthy

Dysregulated proteolytic activity

PERSPECTIVES:

- Study the role of dysregulated proteases on epithelial functions: barrier function, Ig transcytosis, chemokine processing, epithelium renewal.
- Investigate the effects of epithelial actors (proteases and protease inhibitors) on mucosa-associated microbial biofilms.
- Screen for protease inhibitors
- Identify protease inhibitors present in human commensal microbiota

UNIQUE SELLING POINTS:

- A range of tools and models to screen for protease inhibitors as therapies for chronic intestinal disorders.
- Access to an organoid culture biobank from healthy individuals and IBD patients.
- Access to tissue samples and human microbiota biofilms from healthy individuals, IBD, IBS and Celiac patients.

VILLANI Axel

M.D, Ph.D

CIRI, Inserm U1111/CNRS UMR5308, ENS de Lyon, Université Claude Bernard Lyon 1
Claude Bernard Lyon I University

Epithelial immunity and skin allergy

Keywords:

- Inflammatory skin disorders,
- Translational research,
- Pathophysiology,
- T resident memory cells (Trm),
- Atopic dermatitis,
- Contact dermatitis,
- Hidradenitis suppurativa,
- Psoriasis,
- Microbiota.

Comprehensive molecular profiling of immune-mediated skin diseases to develop new diagnostic strategies and treatments.

Our research focuses on the pathophysiology of inflammatory and allergic skin diseases, namely the eczemas (allergic contact dermatitis (ACD) and atopic dermatitis (AD)), delayed-type drug allergies (Maculo-Papular Exanthema, Toxic Epidermal Necrolysis), hidradenitis suppurativa and psoriasis, which are frequent and often severe dermatoses in industrialized countries.
Our projects involve both pre-clinical studies using mouse models and translational and clinical studies in patients.
Our project aims to:

- decipher the mechanisms by which environmental allergens (chemicals, drugs, proteins) and skin pathobionts promote or circumvent immune tolerance and induce inflammatory reactions,
- analyze the phenotype and functions of specific T cell subsets that are responsible for the development or the regulation of these diseases, in order to stratify the patients upon their phenotype and the severity of the disease,
- understand the chronicity and relapses of the diseases by a comprehensive analysis of the tissue resident memory (Trm) and regulatory T cells (Tregs),
- make the proof of concept of strategies that can target Trm, and prevent recurrence and severity of skin pathologies.

Our fundamental work has applications for the development of in vitro /in vivo immunoassays, for the diagnosis of drug allergy and eczemas and for predicting the sensitizing properties of skin allergens. Finally, we are developing/assessing innovative therapeutic strategies for future personalized medicine.

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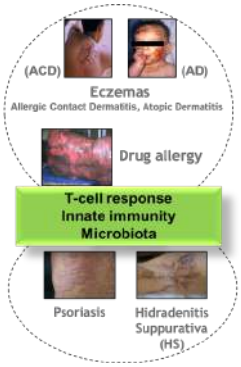
Research activities: Immune-mediated skin diseases

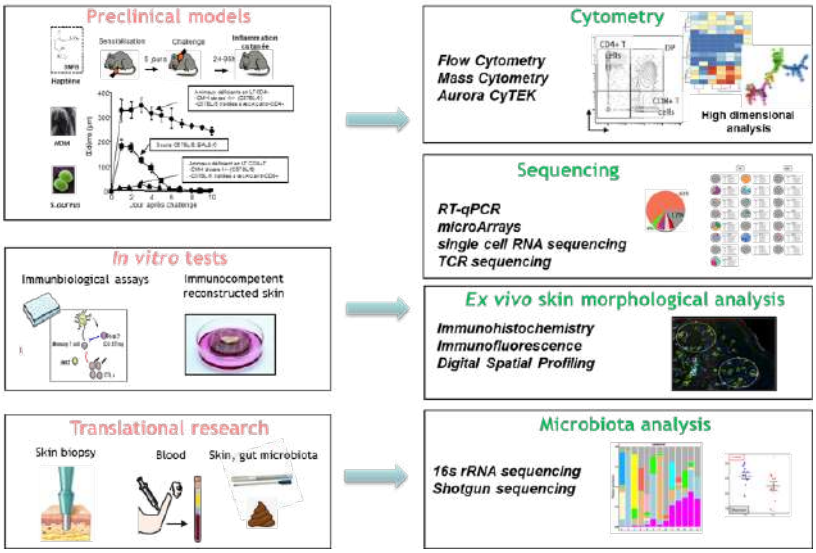
OBJECTIVES:

- Decipher the pathophysiology of immune-mediated skin diseases
- Develop new diagnostic/predictive assays
- Develop new therapeutic strategies to restore skin tolerance

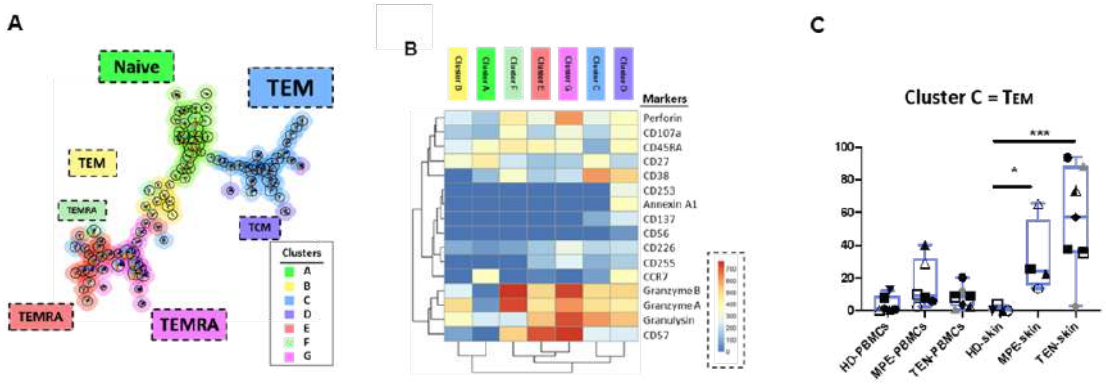


Key words: Immunology, skin allergy, T cells

Research activities: Tools



Result 1: Massive expansion of clonotypic and polycytotoxic CD8+ T cells in Toxic Epidermal Necrolysis



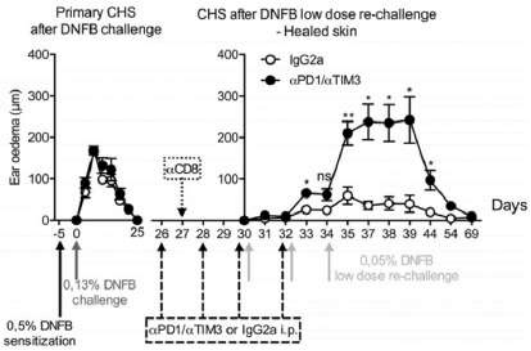
OBJECTIVE :

- To understand the immune mechanisms driving severe cutaneous drug allergy, we compared the skin infiltrate of mild (Maculo-popular exanthema/MPE) and severe (Toxic Epidermal Necrolysis/TEN) drug allergy

RESULT :

- Flowsom (A) and Heatmap analysis (B) revealed the presence of CD38+ polycytotoxic CD8+ T cells (cluster C) that were over-represented and clonotypic in TEN/severe drug allergy (C)

Result 2: Inhibitory checkpoint receptors control CD8+ resident memory T cells to prevent the recurrence of ACD



OBJECTIVE :

- To understand the chronicity of skin allergic reactions, we examined the phenotype and functions of CD8+ resident memory T cells (Trm) that persist in the sites of previous eczema

RESULT :

- CD8+ Trm express high levels of inhibitory checkpoint receptors (such as PD-1, Tim-3). Blocking their signaling increases their reactivity and exacerbates flare-up reactions in vivo

PERSPECTIVES:

- To target CD38+ polycytotoxic CD8+ T cells using anti-CD38 mAbs to improve the course of TEN/severe drug allergy patients
- To target CD8+ Trm in ACD (persistence/reactivation) using new mAbs, to improve the course of ACD patients

UNIQUE SELLING POINTS:

1 - Quality of Scientific outputs and training:
- A - Scientific outputs
  - a - Publications
    66 Publications (13 scientific, 22 reviews, 31 clinical) with first/last authorship + 8 books/book chapters
  - b – Grants
    4 National grants as coordinator/partner (3 ANR+1 INCA+1PHRC)
  - c – Conferences / Meeting (co)organization
    International/national conferences: ERGECD2021, WAC2019, AllergoLyon2015/18, COBIP2018-20, CFA2013-20, JDP2016-20…
- B - Interactions with non-academic world
  -1 filled patent (Inserm transfer EB19417)
  -13 industry contracts: Shiseido, Bioversys, Pfizer, DBV, Pierre Fabre Dermo-Cosmétiques, Pierre Fabre Pharmaceuticals, Galderma, Cosmetics Europe, Consortium (Chanel, Unilever, Givaudan)
  -6 translational clinical trials + 15 clinical studies
  -Regular participations to general public events: patient associations, lay press, radio
- C - Training through research:
  -9 PhDs trained
  -European expert center (EUMS diploma)
  -Organisation of two Master degrees

2 - Team organisation and Life:
- Mixed core of scientists & clinicians
- International students
- Measures to manage scientific integrity and conflicts
- Monthly steering committee to organize Allergol. & Clin. Immunol. department

3 - 5-year Project and Strategy:
- Scientific strategy from « bed to bench to bed »
- Funding balance between academic and industry grants
- Each work package is led by experienced PI

WALZER Thierry

Ph.D

"Innate immunity in infectious and autoimmune diseases" Team, Centre International de recherche en infectiologie (CIRI), Inserm U1111, CNRS, Université de Lyon, ENS de Lyon
Inserm DR2

Understanding NK cell biology for the rational design of cancer immunotherapies. Identifying genetic causes of early-onset autoimmunity for the design of personalized therapies

Keywords:

- NK cells,
- Functional exhaustion,
- Anti-tumor responses,
- Immunotherapies,
- Genetics of autoimmune diseases,
- Exome sequencing,
- Mouse models.

Understanding NK cell biology for the rational design of cancer immunotherapies / Identifying genetic causes of early-onset autoimmunity for the design of personalized therapies.

Two main themes: NK cell biology and early-onset autoimmunity.

NK cells: we aim to understand what molecular pathways are required for the generation of efficient NK cell antiviral or anti-tumor responses. We previously discovered that Eomes is a major lineage-defining factor for NK cells, required for their cytotoxic function; that mTOR acts as a molecular rheostat in NK cells controlling signal transduction downstream activating receptors and bioenergetics metabolism; that NK cell exhaustion occurs during tumor progression as a result of impaired protein expression of signaling molecules. Our current goal is to decipher in detail how mTOR is activated in NK cells, what metabolic reactions it controls, and how we can design novel NK cell-based cancer immunotherapies.

Auto-immunity: our goal is to identify genetic causes of early-onset autoimmunity, especially lupus. A. Belot, who leads this theme, is coordinating the national reference center for early-onset autoimmunity (RAISE) and the associated cohort. In the past years, we identified new mendelian disorders that cause autoimmunity, including mutations in PRKCD and in SOCS1 that control BCR and cytokine signaling respectively. We also found that many patients are affected with "oligogenic" forms of autoimmunity, i.e. genetic diseases caused by heterozygous mutations in several genes. Our current projects aim to identify more genetic causes of lupus, and to develop new and personalized therapies in patients (drug repurposing, gene therapy).

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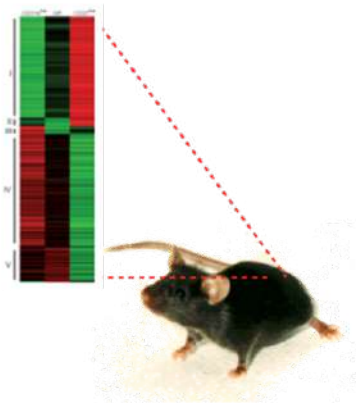
OBJECTIVES 1: Understanding NK cell biology for the rational design of cancer immunotherapies

- Transcriptional networks underlying NK cell development and maturation
- Metabolic pathways sustaining NK cell activation
- Mechanisms of NK cell activation and exhaustion during anti-tumor responses

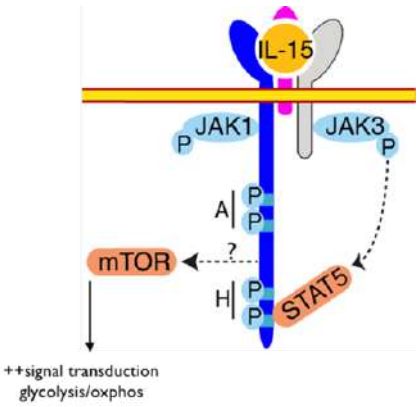


TOOLS:

- Crispr/Cas9 for genetic screens or for the generation of new mouse models
- Functional and metabolic screens using compound libraries
- Mouse genetic models of NK cell biology
- Mouse tumor models

RESULTS:

- Eomes is a major lineage-defining factor for NK cells, required for their cytotoxic function
- mTOR acts as a molecular rheostat in NK cells controlling the amplitude of signal transduction downstream activating receptors and bioenergetics metabolism to modulate NK cell effector potential

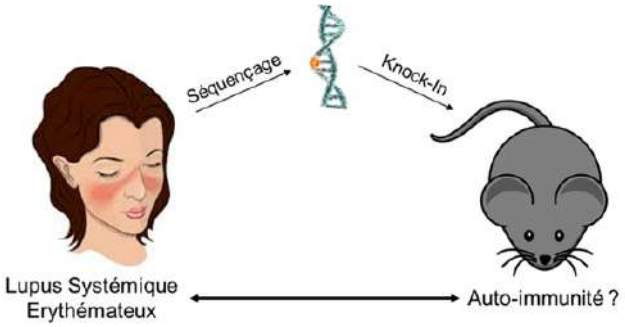


OBJECTIVES 2: Identifying genetic causes of early-onset autoimmunity for the design of personalized therapies

- Identify new genetic causes of early-onset autoimmunity, especially lupus
- Find new and personalized treatments

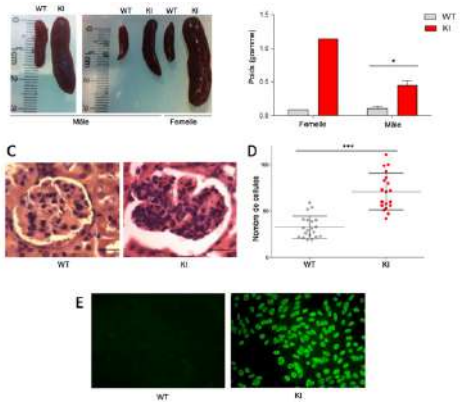
TOOLS:

- Exome sequencing in patients and all "omics" techniques
- Immunological assays (phospho-flow, interferon score, autoantibodies, etc
- Mouse models of human disease



RESULTS:

- Mutations in PRKDC or in SOCS1 define novel forms of autoimmunity associated with exacerbated BCR signaling and cytokine signaling respectively.
- The identification of gene mutations in patients can lead to the selection of personalized treatments e.g. JAK inhibitors in patients with interferonopathies.



PERSPECTIVES (NK CELLS):

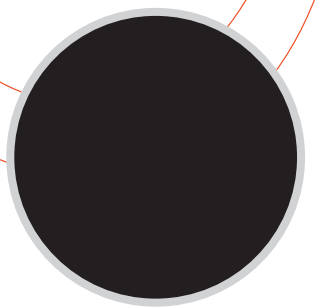
- NK cell immunometabolism : can we exploit it to boost NK cells?
- mTOR pathway: regulators and regulated pathways
- NK cell-based cancer therapies

PERSPECTIVES (AUTOIMMUNITY):

- Understand what causes the wide clinical spectrum observed in mendelian forms of autoimmunity
- Personalize treatments in patients with genetic forms of autoimmunity

UNIQUE SELLING POINTS:

- One of the leaders amongst teams working on NK cell immunometabolism
- Links with hospital and industry in the oncology field
- Reference center for early-onset autoimmune disorders
- Strong expertise in genetics, Crispr/Cas9 gene/genome editing



ZIMMERMANN Valérie

Ph.D

CNRS – University of Montpellier
CNRS

Hematopoiesis and Immunotherapy

Keywords:

- Hematopoiesis,
- Metabolism,
- Gene and cell therapies,
- T cells,
- Hematopoietic stem cells,
- Erythropoiesis, Thymopoiesis,
- Cancer,
- immunodeficencies, HIV.

Our laboratory has developed an expertise on the metabolic regulation of hematopoietic stem cells differentiation and T cell effector functions together with thymus-based stem cell and gene therapies.

The research of our group focused on various aspects of human and murine T cell development and function, in the context of genetic and acquired immunodeficiencies as well as cancers. In particular, we have developed an innovative and efficient strategy to improve T cell development based on the direct targeting of hematopoietic stem cells (HSC) or viral vectors into the thymus. Notably, we have achieved long-term T cell differentiation and effector function following in vivo intrathymic AAV gene therapy in a murine model of genetic immunodeficiency. One of our next objectives is to translate this approach for cancer treatments (HSC transplantation or CAR (Chimeric Antigen Receptor)- T cell therapies).
In parallel, we have also studied the role of metabolism and more specifically of nutrient utilization in hematopoietic stem cell differentiation in general, and T cell effector function, in particular. We have identified the glutamine-dependent de novo nucleotide biosynthesis as a critical regulator of erythroid differentiation from HSCs. These results reveal extracellular nutrients as previously unsuspected regulators of HSC lineage commitment and suggest their potential to condition erythroid differentiation. Moreover, we demonstrated the role of extracellular nutrients in T cell differentiation. We identified glutaminolysis and in particular, -ketoglutarate, a glutamine-derived metabolite, as a key factor in the regulation of the balance Th1/ Treg differentiation. Furthermore, our studies allowed us to identify carbon entry into the TriCarboxylic Acid (TCA) cycle as a critical regulator of HIV-1 infection. We are now interested in the potential relevance of these discoveries to the clinic and notably for the development of anti-tumor CAR-T cell therapies.

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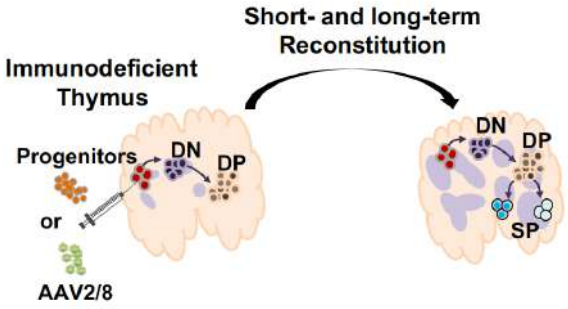
OBJECTIVES:

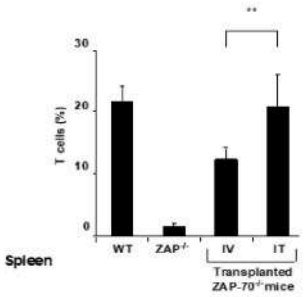
- Improving thymus function
- Immunodeficiencies
- Cell and gene therapies
- Deciphering metabolic regulation of hematopoiesis
- HSC differentiation
- T cell differentiation and function
- Enhancing anti-tumor T cell therapy
- Cytokine regulation
- Metabolic regulation

TOOLS:

- Hematopoietic stem cell transplantation
- Ex vivo and in vivo gene therapy
- Murine and human ex vivo T cell development and differentiation
- Ex vivo human erythropoiesis
- Immunometabolism (seahorse, mitochondria function, …)
- Anti cancer immunotherapy (CAR-T cell)

INTRATHYMIC TRANSPLANTATION RESULTS IN AN ENHANCED AND SUSTAINED T CELL RECONSTITUTION





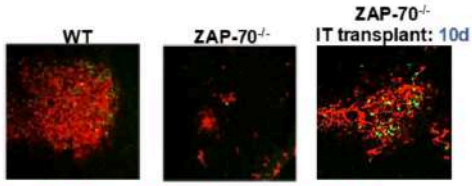
Adjali et al, *PNAS* 2005
Vicente et al, *Blood* 2009
De Barros et al., *Blood* 2013

IT ADMINISTRATION OF HEMATOPOIETIC PROGENITORS RESULTS IN:

- Faster/enhanced T cell reconstitution
- Long term thymopoiesis

IT ADMINISTRATION OF AAV VECTORS RESULTS IN:

- Rapid thymic architecture restoration
- Stable and long term maintenance of functional peripheral T cells



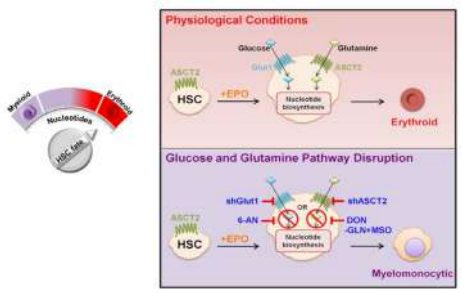
Keratin 14 = medullary thymic epithelial cells
Aire = Autoimmune Regulator (required for self tolerance)

Moreau et al., *Mol Ther* 2009 Pouzolles et al., *JACI* 2019

"Metabolite Shift Model": Fuel source and utilization regulate lineage fate (I)

HSC commitment and differentiation:

- Glutamine-dependent de novo nucleotide biosynthesis is a crucial factor for erythroid differentiation
- Glutamine availability and utilization define a new checkpoint between myeloid and erythroid lineage

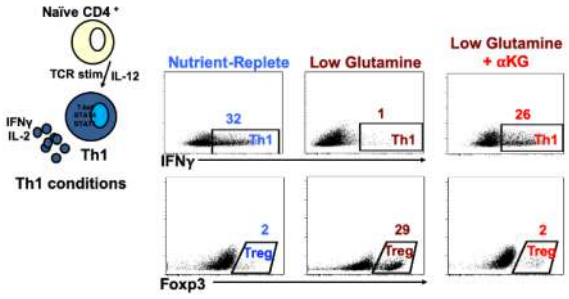


Lineage specification of HSCs to an erythroid lineage fate is regulated by nucleotide biosynthesis. Under physiological conditions, erythropoietin promotes erythroid differentiation of HSCs, a process requiring glucose and glutamine metabolism. Under conditions where glutaminolysis is blocked by downregulation of the ASCT2 glutamine transporter or by pharmacological inhibition (DON, MSO), erythroid differentiation is abrogated and cells progress to a myelomonocytic cell fate. Erythroid specification requires de novo nucleotide biosynthesis which is also provided by the glucose-fed pentose phosphate shunt and can be blocked by downregulating the glucose transporter Glut1 or pharmacological inhibition of G6PD (6-AN).

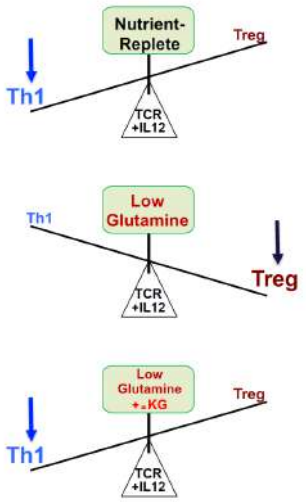
"Metabolite Shift Model": Fuel source and utilization regulate lineage fate (II)

Th1 versus Treg cell differentiation:

- Glutamine deprivation shifts Th1 differentiation into Treg differentiation
- Ectopic a-Ketoglutarate rescues the Th1 differentiation in glutamine deprived condition



Naive CD4 T under TH1-polarizing conditions in nutrient-replete or glutamine-depleted conditions in the absence or presence of soluble form of a-Ketoglutarate. After 6 days of stimulation, the cells were analyzed by flow cytometry to determine the percentages of IFN- + and Foxp3+ cells, indicative of Th1 or Treg polarization respectively.



Klysz et al., Science Signaling, 2015

PERSPECTIVES:

- Improving thymus function in pathological conditions as immunodeficiency or after chemiotherapeutic treatments
  - Identification of the progenitor subset(s) promoting short and long term thymocyte differentiation
  - Determination of the molecular mechanisms supporting the rapid thymic architecture restoration
- Deciphering metabolic regulation of hematopoiesis in physio-pathological conditions
  - Role of metabolic reprogramming in Myelo-Dysplasic Syndrom
- Enhancing anti-tumor T cell therapy
  - Cytokine regulation
  - Metabolic regulation

UNIQUE SELLING POINTS:

- Expertise in gene and cell therapy targeting the thymus
- Expertise in immunometabolism
- Research at the interface from bench to bed and bed to bench: tight collaboration with the
- Hematology service of the Montpellier CHU and the Pediatric Oncology Branch at the NIH

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