Interests
Gene therapy;Oncolytic viruses;Oncology;Immunology/Immunotherapies;In vivo models;Biocollections;Biomarkers;Clinical research

Therapeutic innovation in pancreatic cancer

Pierre CORDELIER

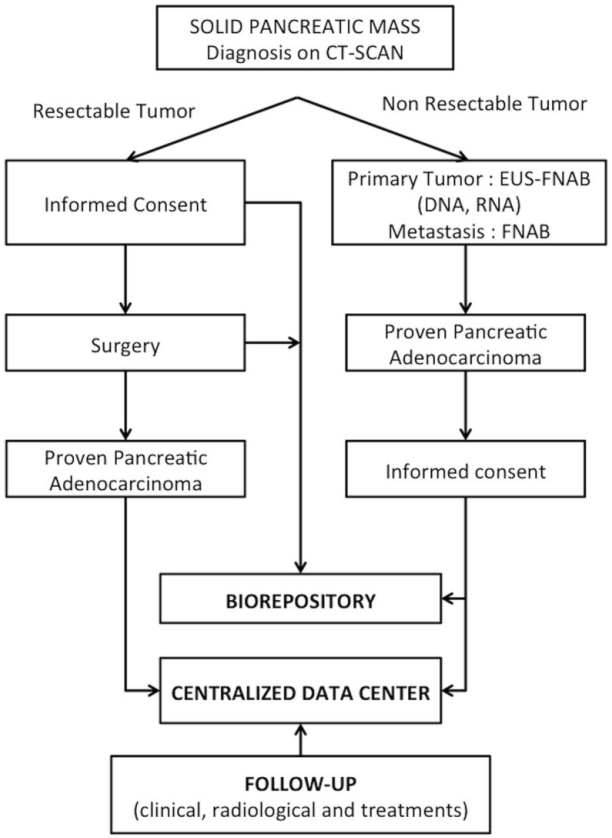
Centre de recherches en cancérologie de Toulouse, Toulouse

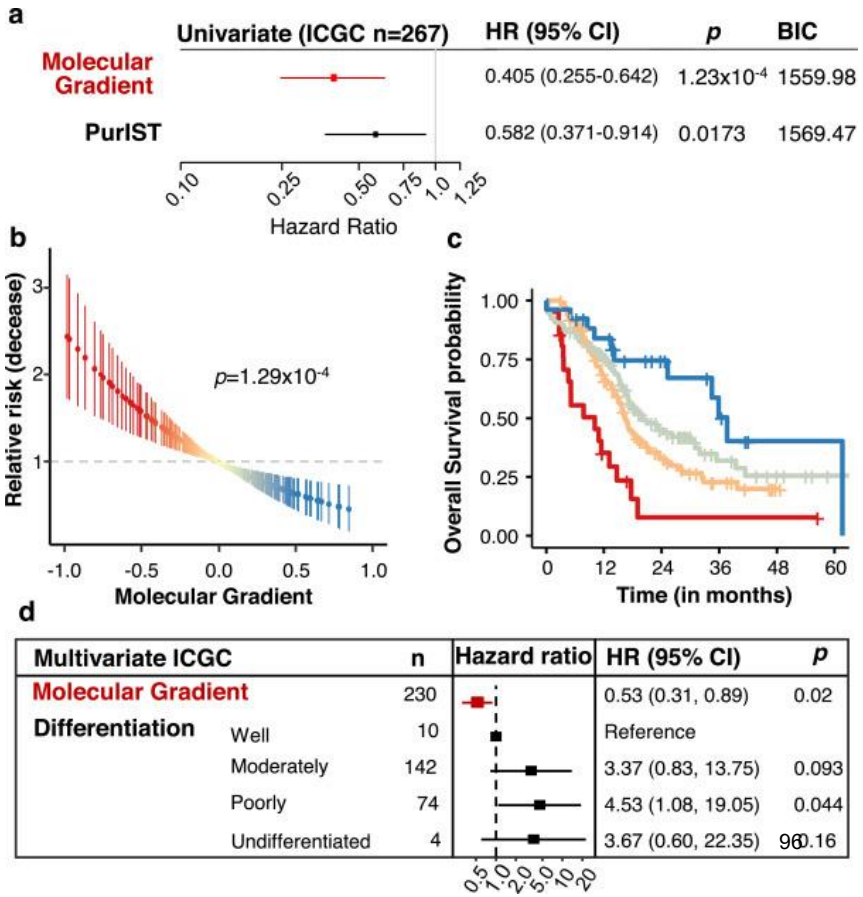
- **Objectives:**
  - To identify the molecular mechanisms involved in therapeutic resistance (chemotherapy, immunotherapy) of pancreatic cancer
  - To devise tailor-made innovative therapies to defeat therapeutic resistance in pancreatic cancer
  - To identify molecular profiles / signature / markers predictive of efficacy or for treatment efficacy follow-up (liquid biopsies)

- **Tools:**
  - Largest biobank for pancreatic cancer samples and clinical data worldwide
  - Collection of primary cell lines, PDX and syngenic experimental models of cancer
  - Single-cell, spatially resolved screening platforms (imaging, transcriptomics)
  - Production of intracellular, single-domain antibodies
  - Repertoire of oncolytic viral strains with distinct properties
  - Strong interface with physics and AI

Exploring the Bacap Cohort

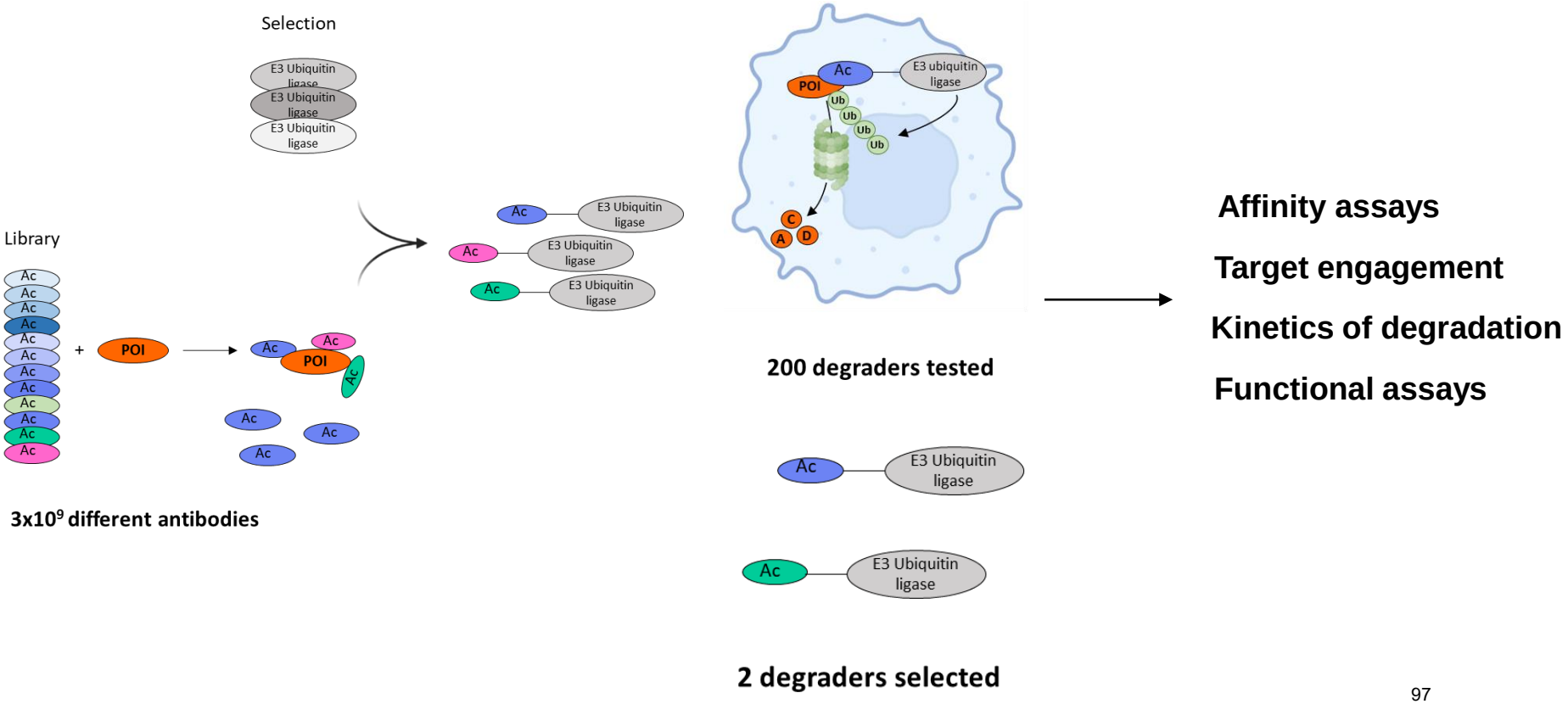
- **Results:**
  - A new Score to Predict the Resectability of Pancreatic Adenocarcinoma
  - Significant progress into the identification ofmolecular parameters characterizing tumours and allowing a personalized treatment





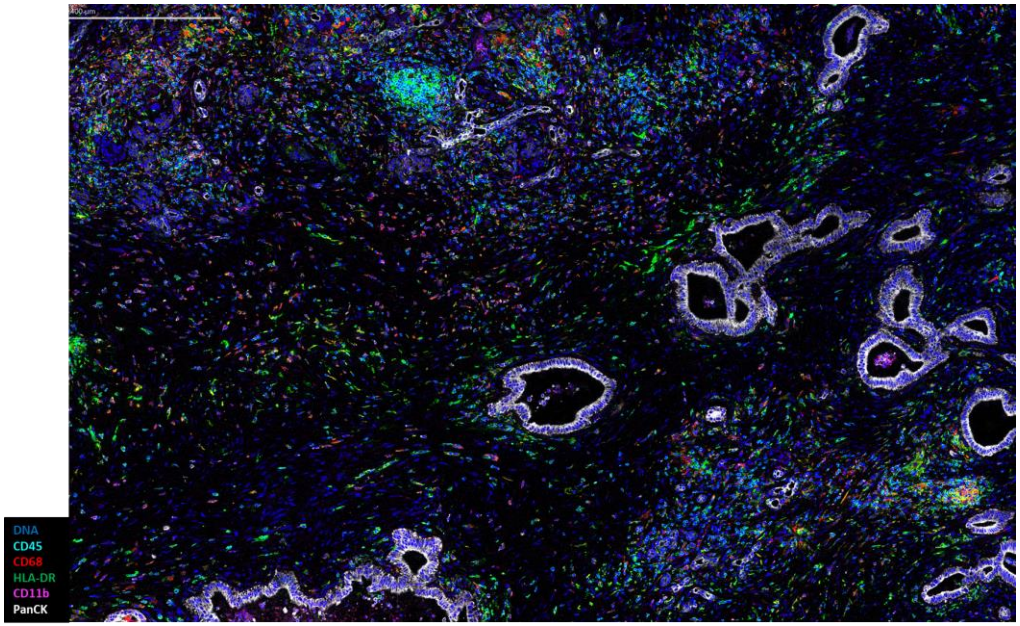
Devising single domain antibodies to target protein of interest

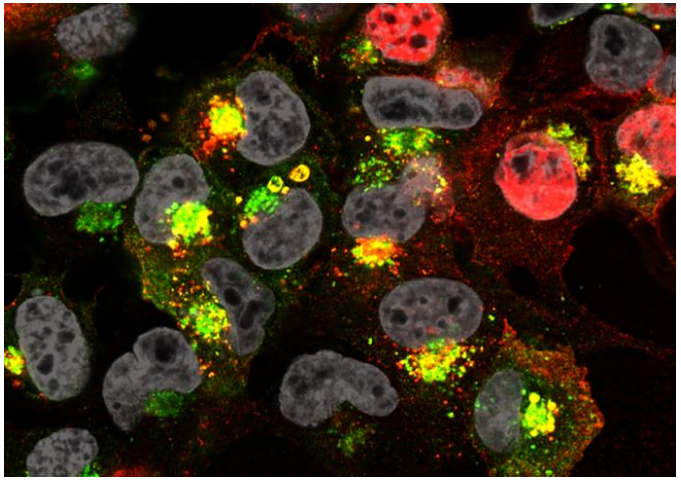
- **Results:**
  - Successful targeting of intracellular protein of interest (POI)
  - Strong sensitization to chemotherapy *in vitro* and *in vivo* (including experimental tumor regression)

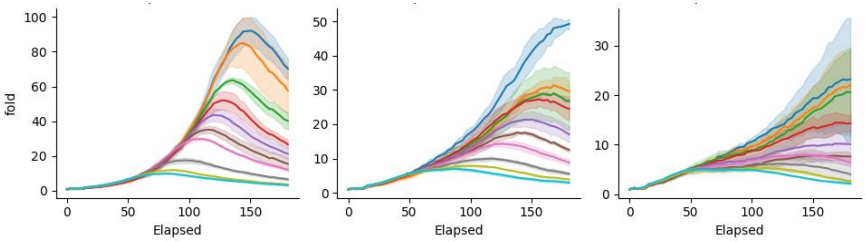


Going toward precision immuno(viro)therapy

- **Results:**
  - Extensive characterization of the immune landscape in patients and experimental models of pancreatic cancer
  - Identification of host factors and mode of action of oncolytic virus in experimental models of pancreatic cancer
  - Computing-based optimization of virotherapy







- **Perspectives:**
  - Providing and exhaustive description of the molecular and cellular mechanisms involved in resistance to treatment in pancreatic cancer
  - Devise and transfer into tumors tailor-made single-domain, intracellular antibodies to defeat tumor resistance to chemotherapy
  - Improve survival and defeat resistance to immunotherapies of patient with pancreatic cancer using precision virotherapy

- **Unique selling points**
  - Organization of a unique biobank for pancreatic cancer samples and clinical data
  - Capacity to go from discovery research to first-in-man clinical trials of antitumoral gene therapy on the site of CRCT / Oncopole
  - Integrated genomic, transcriptomic and immune characterization of patients and experimental pancreatic tumors
  - Strong interface with physics and AI

Selected bibliography

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- A Novel Imaging Approach for Single-Cell Real-Time Analysis of Oncolytic Virus Replication and Efficacy in Cancer Cells. Quillien L, Top S, Kappler-Gratias S, Redouté A, Dusetti N, Quentin-Froignant C, Lulka H, Camus-Bouclainville C, Buscail L, Gallardo F, Bertagnoli S, Cordelier P. Hum Gene Ther. 2021 Feb;32(3-4):166-177. doi: 10.1089/hum.2020.294.
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ILC3 and Tertiary Lymphoid Structure

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Keywords
B cell, dendritic cell
inducible bronchus-associated lymphoid tissue,
innate lymphoid cell
immune checkpoint molecule
immunotherapy, non-small cell lung cancer
sympathetic nerve fiber
T cell
tertiary lymphoid structure

Abstract
In 2008, we showed for the first time the presence of tertiary lymphoid structures (TLS, also termed iBALT) in non-small cell lung cancer and their association with long-term survival. Since then, many studies on TLS in cancers have been published showing the anti-tumour potency of these structures. Later, we showed that the presence of B cells in TLS is associated with a protective immunity in patients with lung cancer although B cells were barely considered as playing a key-role in anti-tumour immunity. Also, we could demonstrate that dendritic cells in TLS license the positive prognostic value of tumour infiltrating CD8+ T cells.
On the one hand, with the help of a network of clinicians, we are studying in detail the dialogue occurring between various immune cell subsets present in the tumour micro-environment, in particular between plasma cells and CD8+ T cells, regulatory T cells (Tregs) and macrophages, and their relationship with functional TLS. On the other hand, using two mouse models, we have started (1) deciphering the relationship between TLS formation upon inflammatory conditions and sympathetic nerve fivers present in lung tissues and (2) analysing the role of innate lymphoid cells type 3 (ILC3) as Lymphoid Tissue inducers (LTi) of TLS and their ability to participate to a TLS-based immunotherapy in a pre-clinical model of mouse lung tumour. These studies also enabled us to generate fusion molecules currently tested for their ability at inducing TLS and mounting anti-tumour responses.

Research area
Our laboratory is studying the cellular and molecular mechanisms underlying the formation, maintenance and disappearance of functional tertiary lymphoid structures (TLS) in solid tumours such as non-small cell lung cancer, head and neck carcinoma, and glioblastoma. For that purpose, in collaboration with clinicians from various hospitals and cancer centres, we have developed studies on TLS and their relationship with immune microenvironment using techniques ranging from multiplexed immunofluorescence analyses combined with AI to single cell RNA sequencing and spatial immuno-oncology. We have also developed mouse models

to define cells and molecules that contribute to the generation of TLS and represent putative immunotherapeutic tools

Synopsis
Our research aims at understanding and manipulating tertiary lymphoid structures in solid tumours to propose and develop third generation immunotherapeutic tools, based on our strong and unique expertise of TLS in solid tumours

Interests
Oncology;Immunology/Immunotherapies;In vivo models;Artificial Intelligence (AI)

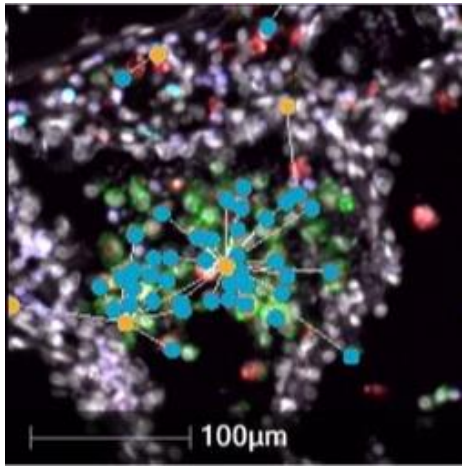
ILC3 and Tertiary Lymphoid Structure

Marie-Caroline DIEU-NOSJEAN

Center of Immunology and Microbial Infections
U1135 Inserm, UMRS1135 Sorbonne University
Paris

- **Objectives:**
  - To induce tertiary lymphoid structure (TLS) neogenesis in cancers
  - To convert cold tumor to hot tumor following TLS induction
  - To overcome resistance to ICP blockade (synergy TLS induction + ICI)

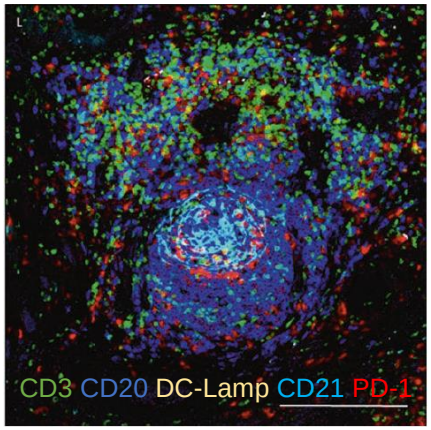
- **Tools:**
  - Functional in vitro assays
  - Multiplexed immunofluorescence analysis combined with AI
  - Flow cytometry (CyTOF, spectral FC)
  - scRNA sequencing
  - Antibody engineering
  - Pre-clinical murin models including humanized mice



TLS, as a powerful prognostic biomarker in cancers

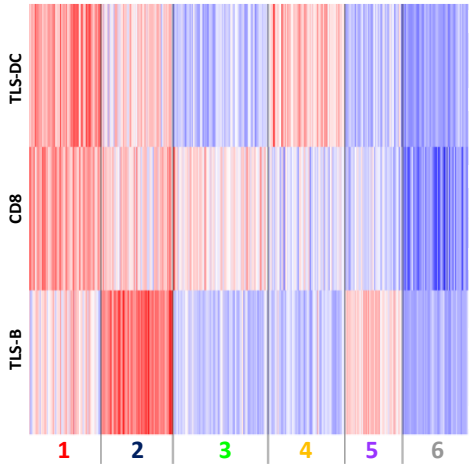
- **Results:**
  - High densities of TLS is associated with a favorable clinical outcome in most solid tumors (ex. NSCLC)
  - TLS are critical site for the differentiation of T and B cells into effectors
  - TLS presence correlates with a Th1, activation and cytotoxic gene signature
  - TLS are required to license the positive prognostic value of CD8+ T cells
  - Treg can inhibit TLS function

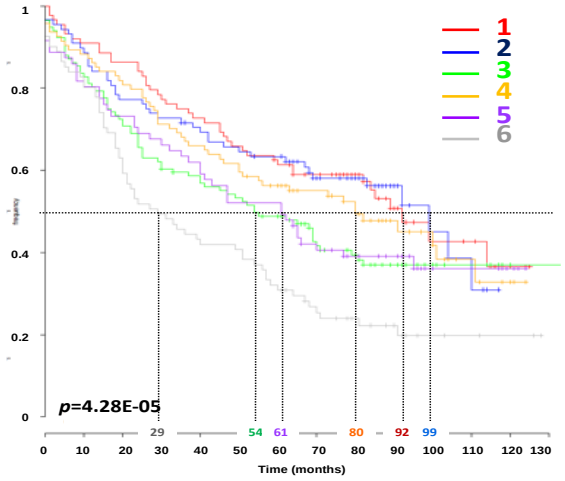
NSCLC



T-cell rich areas:
- T cells
- mature DC

B-cell rich areas:
- B cells
- FDC
- T_{FH} cells
- macrophages

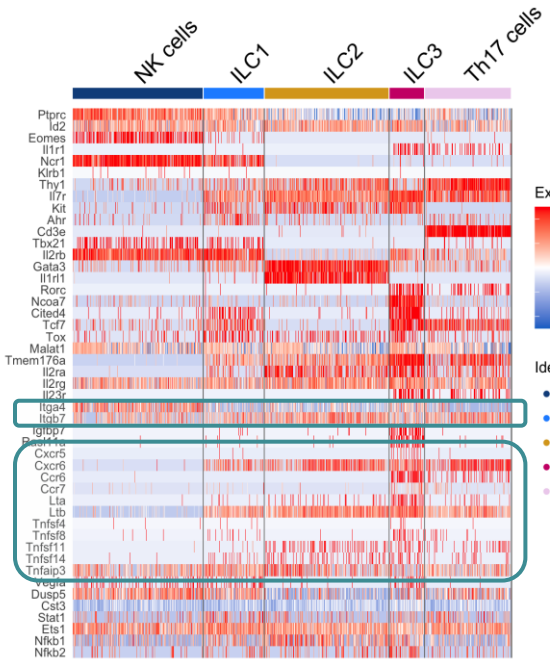




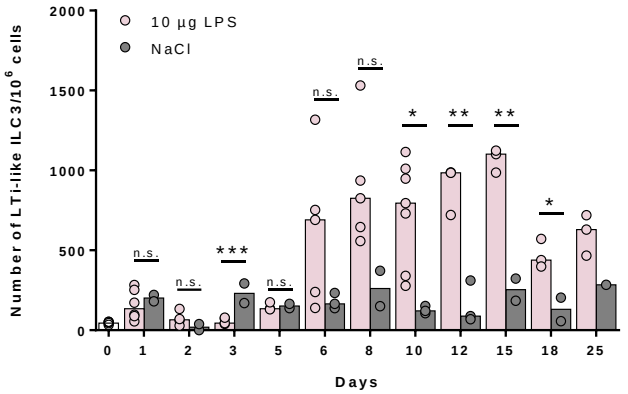
Dieu-Nosjean et al., JCO 2008; Goc et al., Cancer Res 2014, Germain et al., 2014; Klein et al., Springer 2018; Germain et al., 2021; Devi-Marulkar et al., 2022)

Correlation between ILC3 recruitment and TLS neogenesis in a pre-clinical model of lung inflammation

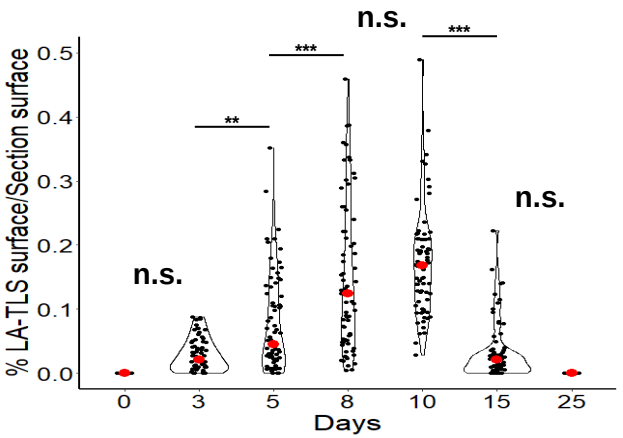
- **Results:**
  - ILC3 recruitment parallel the formation of TLS following lung inflammation
  - ILC3 home in TLS
  - ILC3 express genes related to lymph node organogenesis



LTi-like ILC3



Lymphoid aggregates/TLS



Riffard et al., in revision

- **Perspectives:**
  - To demonstrate that ILC3 cell is a powerful TLS inducer cell
  - To test the ability of ILC3 cells to participate to a TLS-based immunotherapy
  - To induce a long-lasting immune responses against the tumor following TLS induction
  - To test the combination of a TLS-based immunotherapy with other (immuno)therapies

- **Unique selling points**
  - Over 15 years of expertise in the field of TLS (publications, patents)
  - Complementary skills in the Team (from basic and translational research to immunotherapy)
  - Long-lasting interactions with clinicians
  - Large access to patient biopsies
  - Ability to set-up partnerships with pharmaceutical companies (+ Inserm Transfert)

Selected bibliography

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Monitoring and optimizing CAR T cells

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Keywords
cancer immunotherapy
CAR T cells
resistance mechanism
tumor microenvironment
preclinical tumor model
epigenetic.

Abstract
Adoptive T-cell therapies are starting to transform the treatment of several cancers. However, despite recent successes in hematological malignancies, most patients with solid tumors fail to respond to these treatments. It is therefore important to identify resistance mechanisms in order to overcome them and propose more powerful strategies. To address this issue and monitor CAR T cell activities in the complex environment of human tumors, we established an experimental system of fresh tumor slices combined with dynamic imaging microscopy. In human solid tumors, our data indicate that CAR T cells are unable to reach and kill cancer cells. We identified several factors (T cell intrinsic and extrinsic) that prevent CAR T cells to perform their antitumoral activities. Based on this knowledge, several strategies to increase the efficacy of CAR T cells in solid tumors have been developed. This includes the targeting of RINF, an epigenetic factor, which results in enhanced persistence of CAR T cells in solid tumors.

Research area
Head of 'Cancer and Immune responses' team at the Institut Cochin (INSERM, CNRS, Univ. Paris Cité)

Synopsis
Monitoring CAR T cell efficacy in a preclinical patient-derived model and developing strategies to increase CAR T cell activity

Interests
Cell Therapy;Chimeric Antigen Receptor (CAR)-T cells;Oncology;Immunology/Immunotherapies;In vitro models/ Organ-on-chip;Imaging

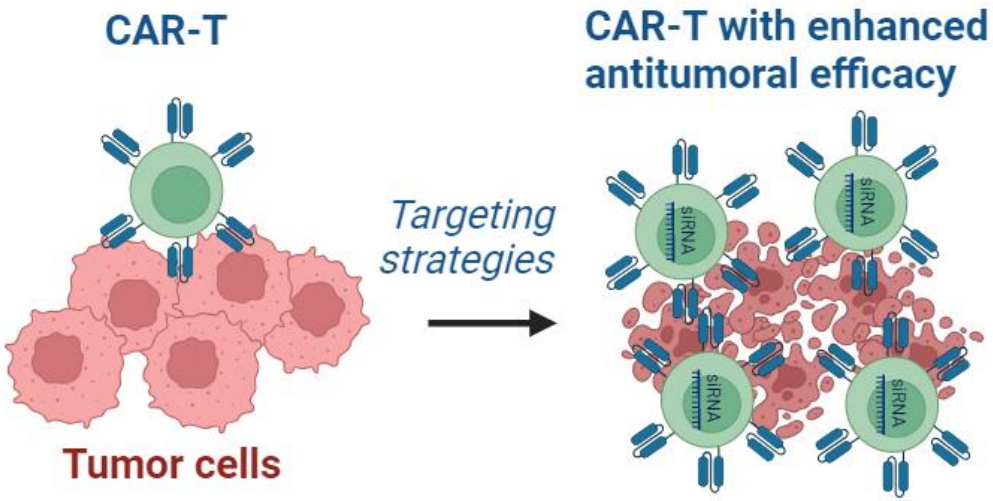
Monitoring and optimizing CAR T cells

Emmanuel Donnadieu

Institut Cochin, INSERM U1016, Paris

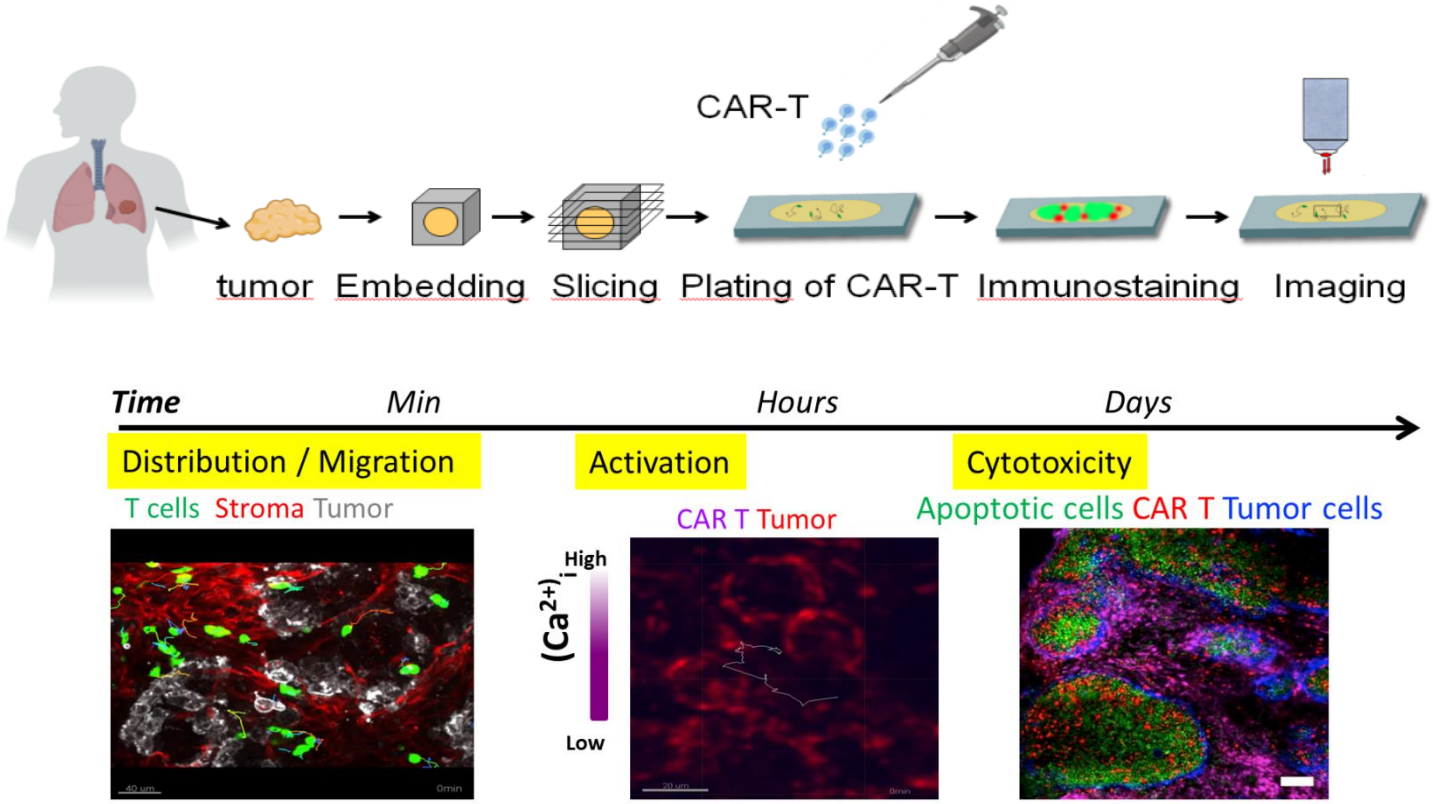
- **Objectives:**
  - To study the mode of action of CAR T cells within the tumor microenvironment
  - To identify obstacles to CAR T cell activity
  - To test novel approaches improving CAR T cell antitumor activities

- **Tools:**
  - A preclinical model of fresh human tumor slices that closely recapitulates the tumor microenvironment
  - Analytical technologies to monitor CAR T cell activities
  - Targeting strategies to increase the antitumoral activities of CAR T cells



Development of a preclinal human tumor model for monitoring CAR T cells

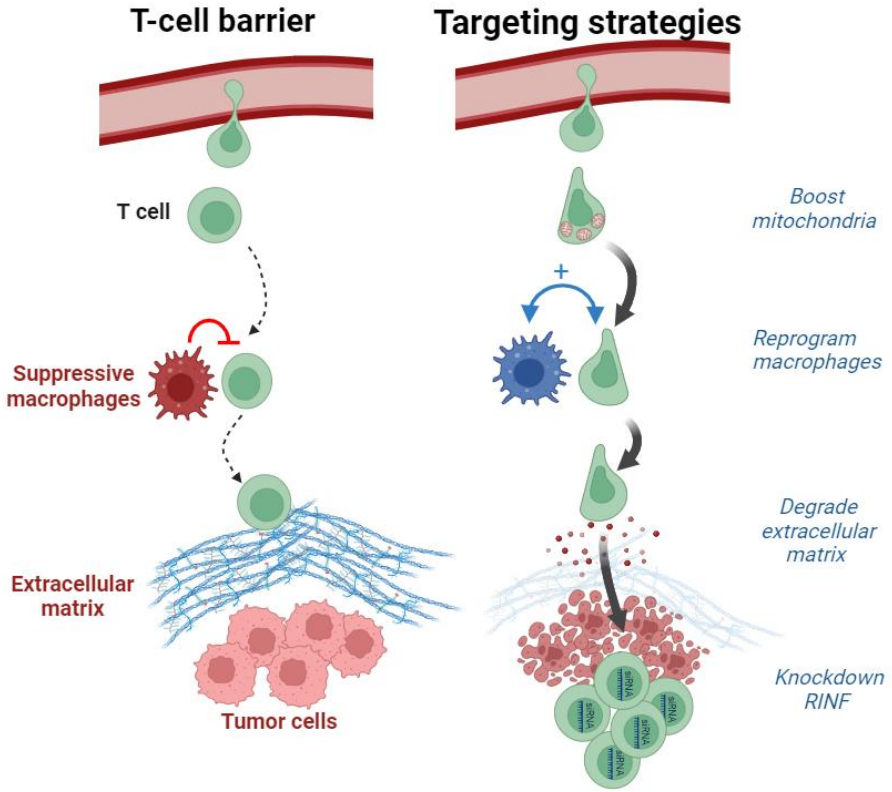
- **Results:**
  - Establishment of a human *ex vivo* tumor model to assess CAR T cell efficacy
  - This technique has been optimized to track CAR T cells in an intact human tumor microenvironment
  - In human solid tumors, CAR T cells are poorly able to contact tumor cells



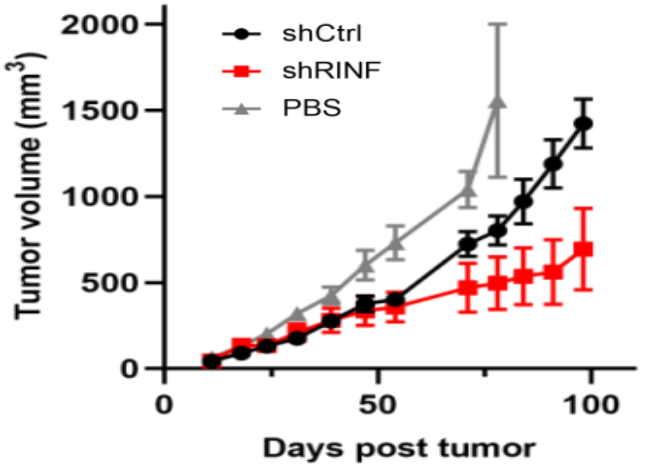
The *ex vivo* tumor slice assay for monitoring CAR T cell activities in a preserved human tumor microenvironment.

Targeting strategies to increase the antitumoral activity of CAR T cells

- **Results:**
  - In human solid tumors CAR T cells are unable to reach and kill cancer cells
  - Identification of obstacles that limit CAR T cell activity within solid tumors
  - Targeting the epigenetic factor RINF increases the efficacy of CAR T cells



Targeting strategies to increase the migration and activation of CAR T cells in tumors



Targeting the epigenetic factor RINF increases the efficacy of CAR T cells in a murine solid tumor model

- **Perspectives:**
  - Use of the tumor slice assay as a platform for evaluating the effects of novel T cell products
  - Screening for therapeutic molecules able to restore CAR T cell activity within tumors
  - Investigate how the tumor microenvironment impacts on CAR T cell efficacy
  - Investigate how CAR T cells remodel the tumor microenvironment
  - Use of the tumor slice assay for testing the toxicity of engineered T cells

Emmanuel Donnadieu Monitoring and optimizing CAR T cells

- **Unique selling points**
  - Development of a preclinical and relevant patient-derived tumor model
  - Development of innovative targeting strategies to improve CAR T cell efficacy
  - Development of state-of-the-art imaging techniques to track CAR T cells
  - Strong collaboration with clinicians for obtaining fresh tumor biopsies
  - Collaborations with renown labs in the field of CAR T cells through various networks (Cancer Grand Challenges NexTGen, T2EVOLVE…)

Selected bibliography

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- **Tumor stiffening reversion through collagen crosslinking inhibition improves T cell migration and anti-PD-1 treatment . Nicolas-Boluda, …, Donnadieu. (2021). *Elife*10:e58688**
- **CAR T cells targeting Aspergillus fumigatus are effective at treating invasive pulmonary aspergillosis in preclinical models . Seif, …, Donnadieu, …, Loffler. (2022). *SciTransl Med* 14, eabh1209.**
- **Time to evolve: predicting engineered T cell-associated toxicity with next-generation models. Donnadieu,…, Casucci. (2022). *J Immunother Cancer* 10(5):e003486.**
- **ALPL-1 is a target for chimeric antigen receptor therapy in osteosarcoma . Mensali,…, Donnadieu, …, Walchli. (2023). *Nat Commun*, 14(1), 3375.**

Cell and Particle Engineering for Therapeutics

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Keywords
- Nanomedicine
- Nucleic Acids
- inflammatory diseases
- Lung administration
- Tissue and cell targeting

Abstract
The research team (Particle and Cell Engineering for Therapeutics) carries research across disciplines with expertise in synthesis, formulation, and biological evaluation of biodegradable polymers, micro, and nanoencapsulation for drug delivery and imaging: lipid and polymer systems, and murine pharmacokinetics after pulmonary or systemic administration of drug-loaded micro or nanoparticles. Our research strategy is to develop nanomedicines with the main goal of delivering drugs for infection and immunity. The final goal is to develop precision nanomedicines to treat lung infections and fibrosis and improve the treatment of sepsis-associated inflammation and macrophage reprogramming. ii) design delivery systems for imaging and theranostics. We have designed several delivery platforms: one is based on lipid nanoparticles which demonstrated that it was possible to deliver glucocorticoids or anti-miR 155 in a rheumatoid arthritis murine model demonstrating better targetability and improved efficiency. A second approach involved lung delivery of siRNA against TNF- using polymer and lipid nanoparticles demonstrated a high efficiency in treating lung injury.

Research area
The main objective of the Institut Galien Paris-Saclay (UMR CNRS 8612) is to design novel dosage forms and new strategies for the controlled delivery and targeted administration of drugs. It also develops systems for in vitro and in vivo diagnostics.

Synopsis
Our research relies on the design of polymer and lipid-based nanotechnologies for drug delivery particularly small anti-inflammatory drugs and nucleic acids (aptamers, siRNA, and mRNA) by local (lungs) and systemic administration.

Interests
Non viral delivery systems;Oligonucleotides;Immunology/Immunotherapies;Infectious diseases;Imaging;Nanotechnology

Cell and Particle Engineering for Therapeutics

Elias FATTAL

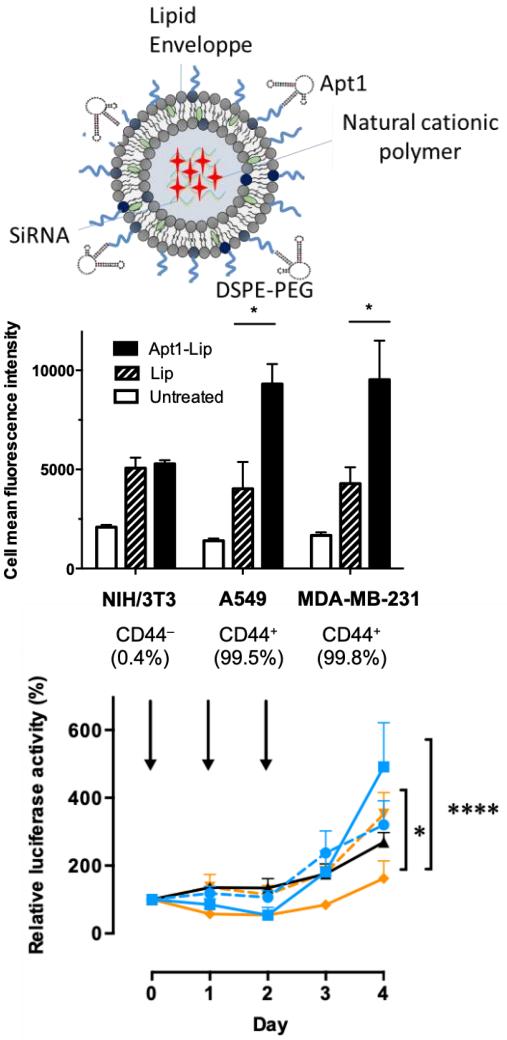
Institut Galien Paris-Saclay, UMR CNRS 8612, Orsay

- **Objectives:**
  - Develop nano/microparticles for spatio-temporal delivery in inflammatory diseases with focus in sepsis and rheumatoid arthritis
  - Improve drug/nucleic acids cellular, subcellular distribution
  - Discover new ligands from aptamer family for improved cellular delivery

- **Tools:**
  - Synthesis, formulation and biological evaluation of biodegradable polymers
  - Micro and nanoencapsulation for drug delivery and imaging: lipid and polymer systems
  - Protein and Cell SELEX for aptamer discovery
  - Cellular trafficking of drugs, nucleic acids and nanoparticles
  - Murine pharmacokinetics after pulmonary or systemic administration of drug-loaded micro or nanoparticles
  - In vitro and in vivo lung nanotoxicology

Topic 2: Anti CD44 Apatmer-guided delivery of siRNA

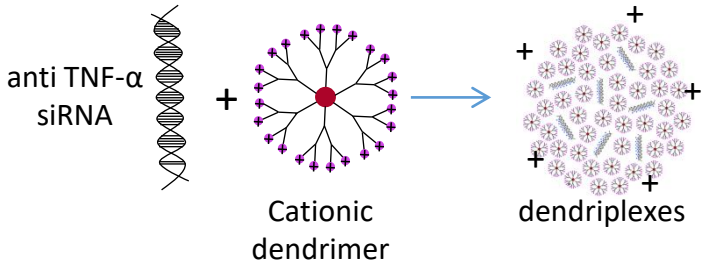
- **Results:**
  - Successful entrapment of siRNA in Anti CD44 aptamer-guided lipid nanoparticles
  - Enhanced internalization in CD44 expressing tumor cells
  - Strong inhibition of target protein in a triple negative murine breast cancer model

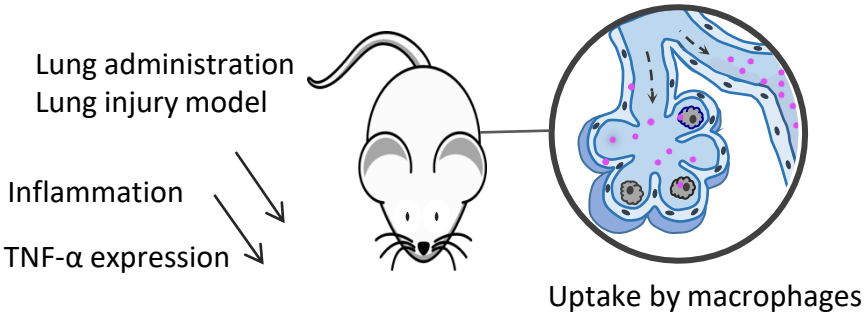


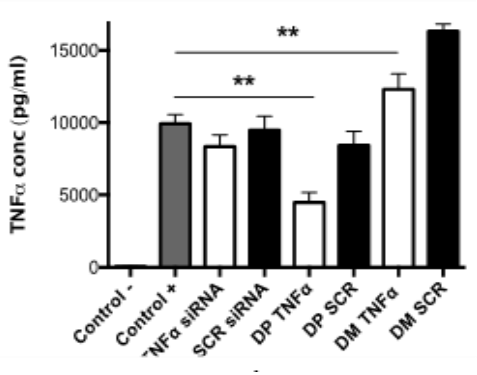
Encapsulation of siRNA in apatmer guided lipid nanoparticles and protein inhibition in a murine triple negative breast cancer model

Topic 1: Anti-Inflammatory Effect of Anti-TNF-α SiRNA Cationic Phosphorus Dendrimer Nanocomplexes

- **Results:**
  - Cationic phosphorus-containing dendrimers can bind anti-TNFα siRNA
  - Improvement of siRNA stability against degradation in biological fluids
  - Significant inhibition of TNFα in LPS-activated macrophages
  - Strong reduction of TNFα in a murine lung injury model







Formation of dendriplexes with SiRNA and demonstration of TNF-α inhibition in lung injury

- **Perspectives:**
  - Nucleic acid delivery to activated monocytes in sepsis and arthritis
  - Combination of nucleic acids and small drugs in one nanoparticle to improve the treatment of several inflammatory disease
  - Investigate the relations between composition of lipid nanoparticles and delivery of mRNA and siRNA

- **Unique selling points**
  - Expertise in designing polymer or lipid nanoparticles for nucleic acid delivery
  - Partner of the IHU Prometheus for improving lung drug delivery in hyperinflammation response to pathogens
  - Combination of different expertise in one group from chemistry to pharmacology

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Deciphering the Molecular Landscape of B-Cell Commitment to Plasma Cells

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Keywords
- B-cell differentiation,
- B-cell lymphoma,
- Multiple myeloma,
- Primary culture models,
- Epigenetic control of B-cell differentiation,
- PIM kinases, control of B-cell death,
- Antisense oligonucleotides,
- RNA,
- Drug synergy

Abstract
Having gained insights from my clinical experience with patients grappling with lymphoproliferative diseases, specifically non-Hodgkin's B lymphoma and multiple myeloma, I expanded my expertise through a fellowship at the National Cancer Institute in Bethesda (Maryland, USA) focusing on hematopathology. Upon returning to France, I initiated a research program delving into the intricacies of normal B lymphocyte terminal differentiation, aiming to unravel the molecular events underlying lymphomagenesis. Leveraging our ANR Carnot/CALYM-accredited tumor library of live lymphoma cells, we've devised innovative culture systems incorporating cells from the tumor microenvironment allowing cocultures of B and T cells. This approach has uncovered several functional variations during differentiation, with detailed investigations into cytokine/STAT signaling and epigenetic modifications at the DNA or histone level. Notably, our recent findings pinpoint PIM2 kinase as a pivotal factor in plasma cell generation, retaining its essential enzymatic role in mature plasma cells, adapting them to the challenges of extensive immunoglobulin secretion. Remarkably, PIM2 continues to exert influence in tumor plasma cells, exacerbating cancer aggressiveness. Our research demonstrates that inhibiting PIM2, particularly through its impact on the mitochondrial apoptosis pathway, synergizes with drugs used in treating these cancers, notably MCL1 inhibitors. For the precise targeting of PIM2 in tumor plasma cells in multiple myeloma, we are pioneering a strategy centred on antisense oligonucleotides encapsulated in lipid nanoparticles, with the eventual goal of coating them with monoclonal antibodies. This innovative approach holds promise for advancing therapeutic interventions in lymphoproliferative diseases.

Research area
Normal and tumor B cell differentiation

Synopsis

Engaged in the exploration of human primary B cells through sophisticated in vitro culture models replicating the intricate stages of B cell differentiation into plasma cells, our team is unraveling distinctive molecular pathways and factors potentially co-opted in the context of malignant lymphoproliferative diseases.

Interests

Non viral delivery systems;Oligonucleotides;mRNA;Oncology;Haematology;In vitro models/ Organ-on-chip;Translational research;Clinical research

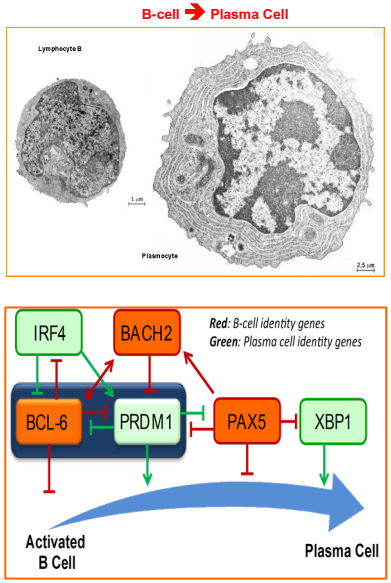
Deciphering the Molecular Landscape of B-Cell Commitment to Plasma Cells: Unraveling Signaling, Transcription Factor Networks, and Epigenetic Pathways in Normal Physiology and their Implications in B-Cell Neoplasia – Insights from the B_DEVIL Team at Inserm U1236

Normal, Tumor B cell
Differentiation and
Environmental Cues

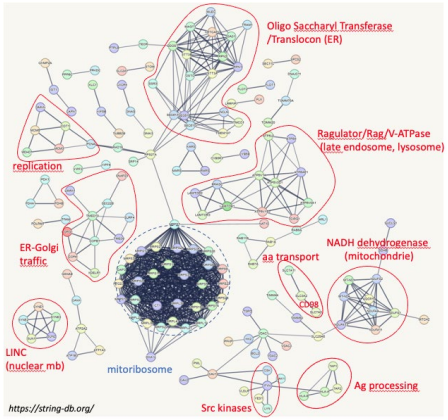
Thierry FEST M.D., Ph.D.

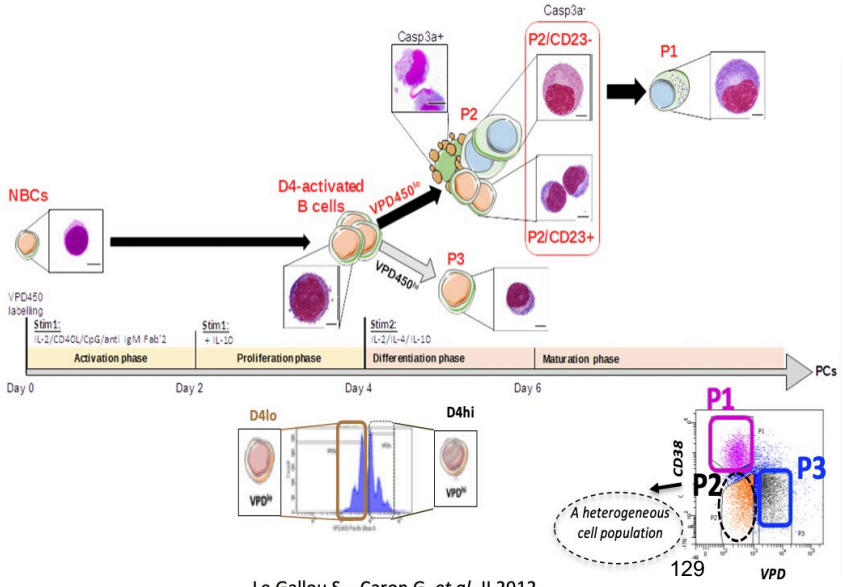
Inserm U1236 MOBIDIC,
Rennes

- **Objectives:**
  - Plasma cell commitment: signal integration
  - Cell fate heterogeneity: single-cell resolution of trajectories
  - Regulatory network: genomic integrative analysis
  - Plasma cell biology: metamorphosis & survival pathways
  - Epigenetic reprogramming: chromatin modifications & epidrugs



- **Tools:**
  - Work on primary human cells
  - Primary lymphoma & myeloma cell collections
  - Big data management
  - Original mouse models
  - Multiomic approaches
  - Patient cohorts for data validation

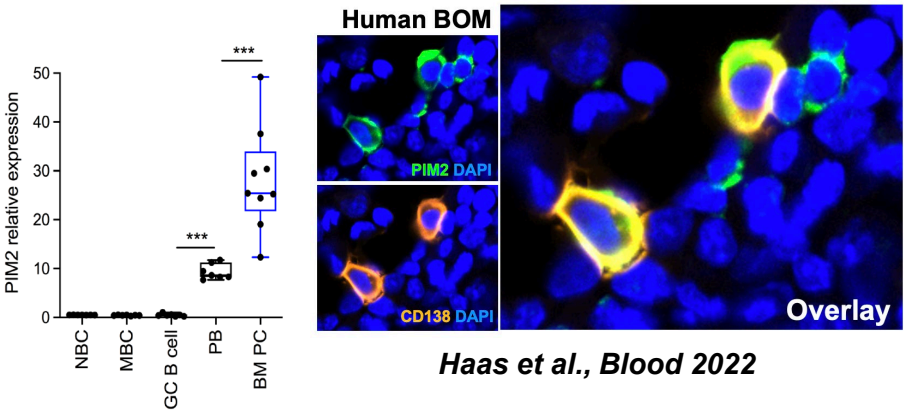




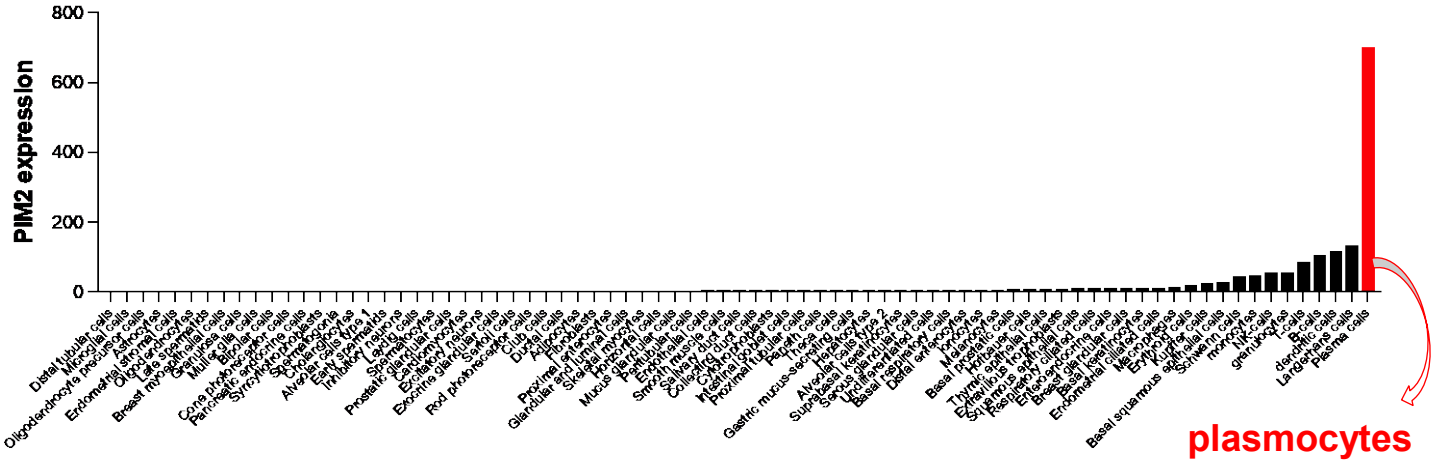
Le Gallou S. , Caron G. *et al.* JI 2012

PIM2 Kinase in Normal & Tumoral B cell differentiation

- **Results:**
  - B-cell commitment into PCs activates PIM2 via STAT3, which promotes G1/S transition and inhibits caspase 3-driven apoptosis
  - PC survival requires strong expression of PIM2

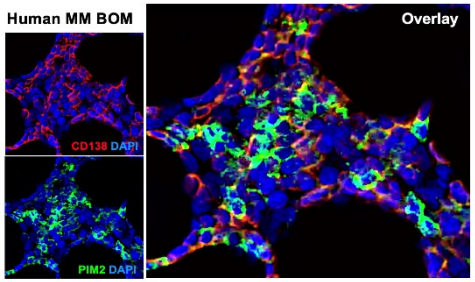


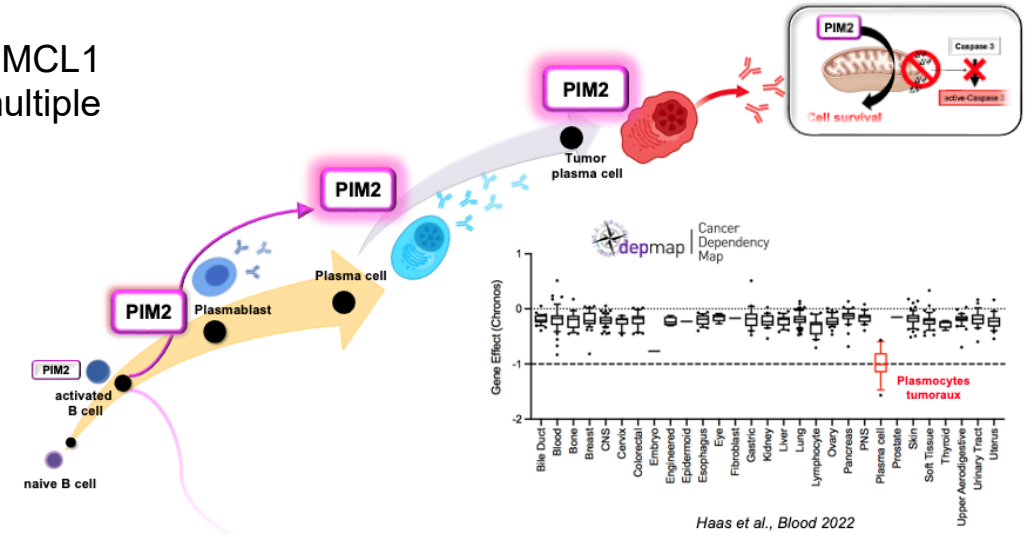
Haas et al., Blood 2022



PIM2 Kinase; a Valuable Target in PC Malignancies

- **Results:**
  - Malignant PC maintain high PIM2 expression
  - PIM2 lowers mitochondrial apoptosis priming
  - Inhibition of PIM2 synergizes with MCL1 inhibitors and standard multiple myeloma drugs



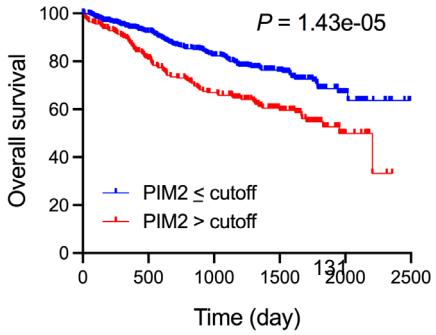


Haas et al., Blood 2022

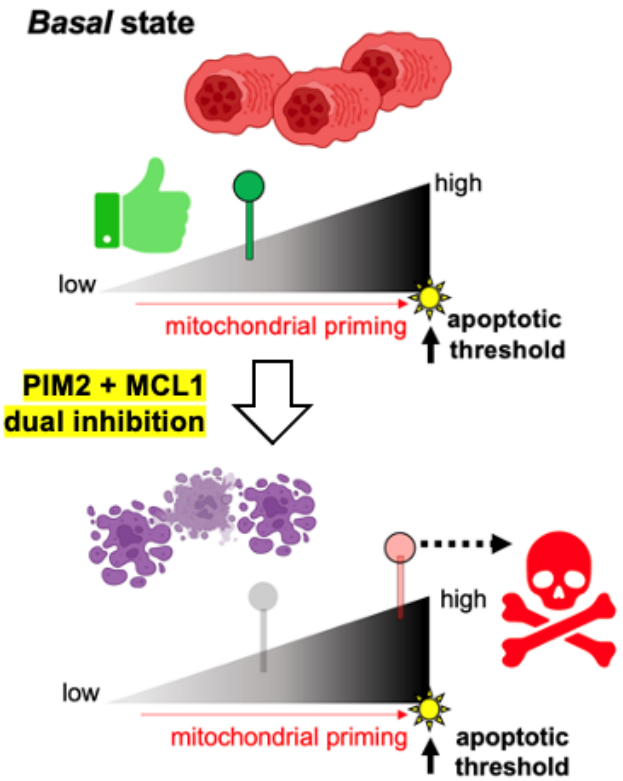
Toxicity & weak efficacy

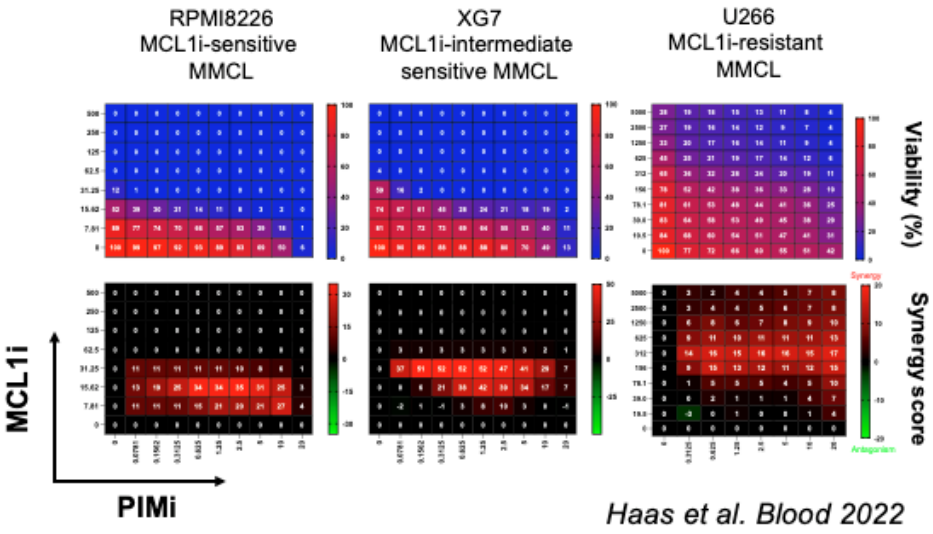
Pan-PIM inh

Good Target



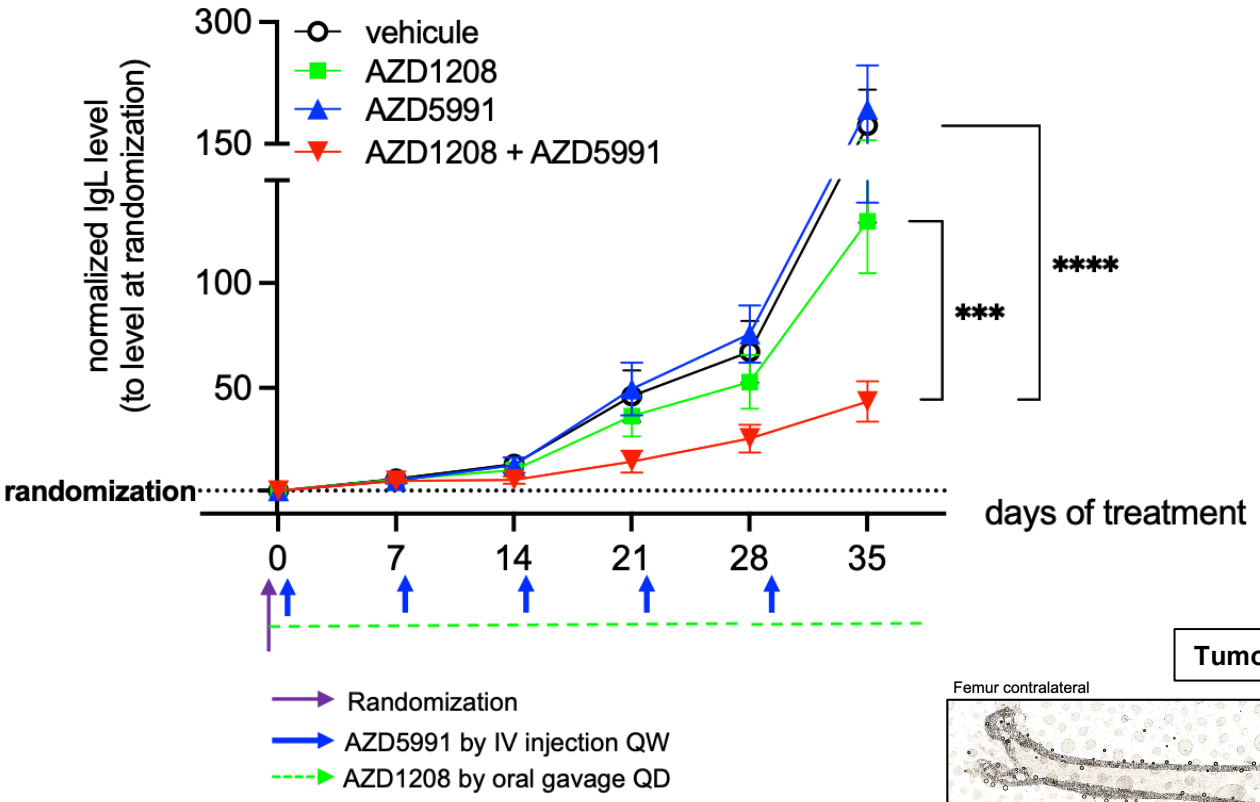
- **Perspectives:**
  - Dual inhibition PIM2 & MCL1 in myeloma





Haas et al. Blood 2022

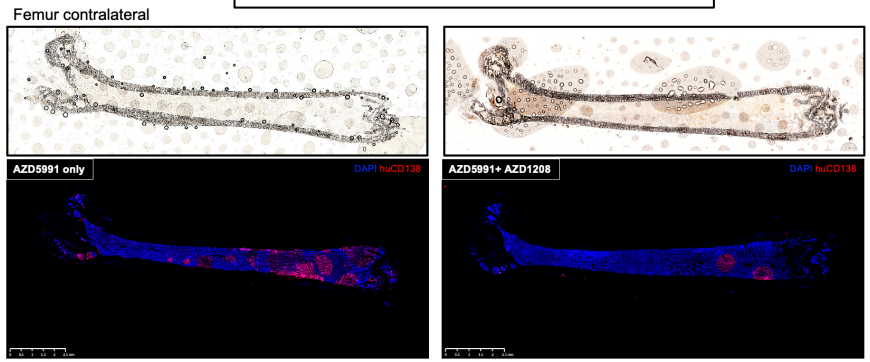
- **Perspectives:**
  - Dual inhibition PIM2 and MCL1 in myeloma
  - Dual targeting reverse primary MCL1 resistance



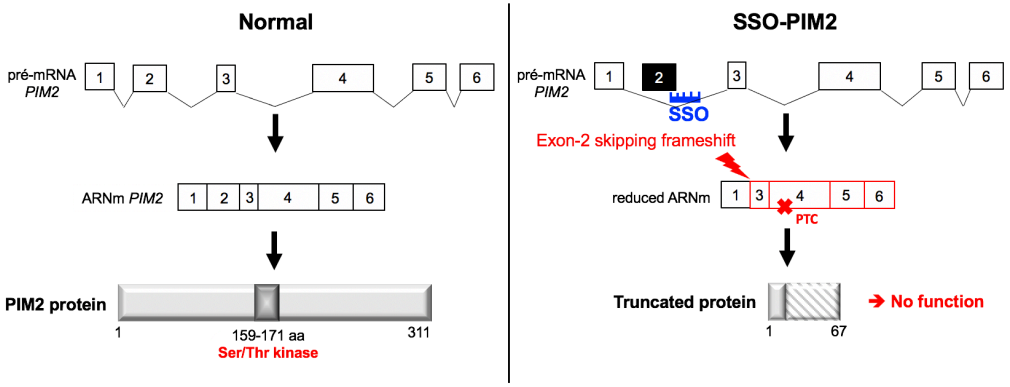
U266

MCL1i-resistant

Tumor dissemination at end-point



- **Perspectives:**
  - Dual inhibition PIM2 and MCL1 in myeloma
  - Reverse primary MCL1 resistance
  - Splice-Switching Oligonucleotides (SSO) targeting malignant PCs



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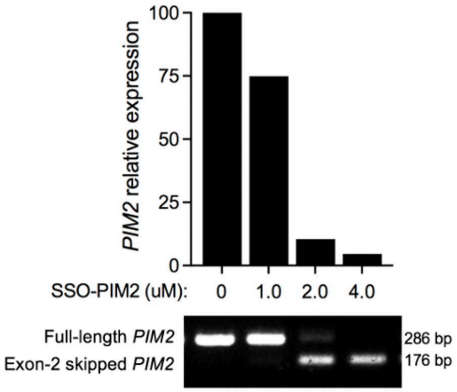
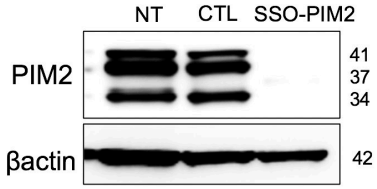
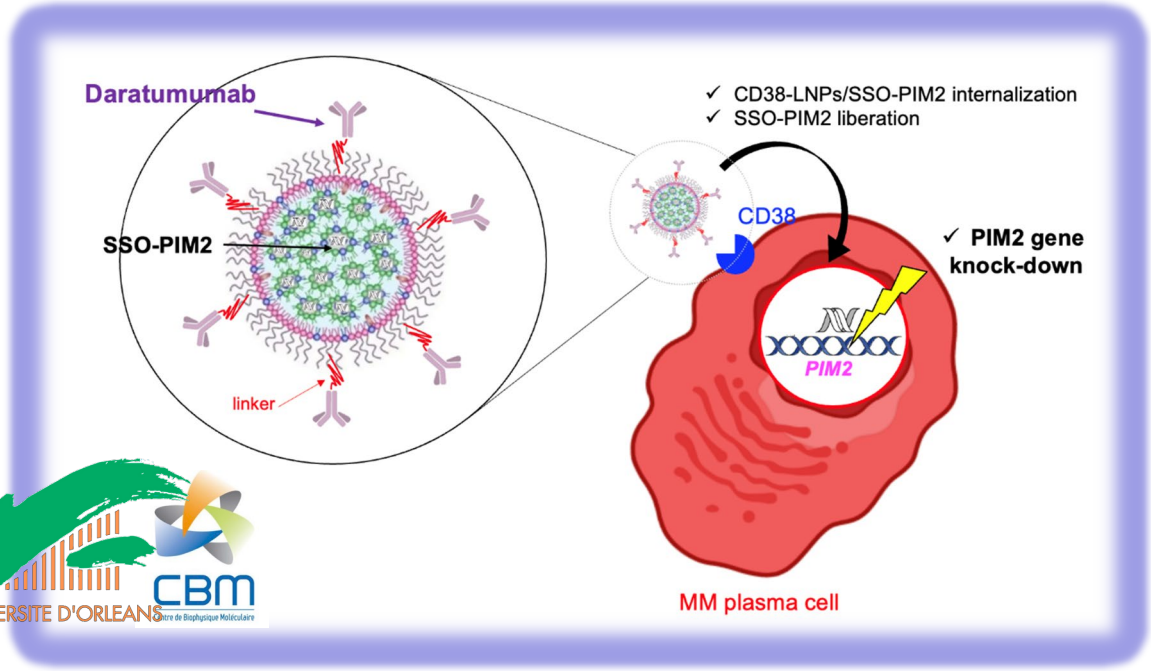




- **Unique selling points**
  - Lipid-nanoparticles decorated with antibodies



***LNP : liponanoparticules**

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Innovations in the field of skin cell therapy

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Keywords
Human skin – Stem cells – Keratinocytes – Fibroblasts – Regeneration – Skin grafting – Cell therapy – Bio-production – Radio-pathologies – Fibrosis

Abstract
A fundamental research axis developed at LGRK focuses on knowledge of the fundamental characteristics of stem cells and epithelial progenitors of the epidermis. Points of interest include the search for characteristic criteria of the 'stem cell' status, as well as the deciphering of the regulatory networks of the 'immaturity versus differentiation' balance. This research integrates the conventional genome coding proteome, as well as genes producing non-coding transcripts. The latter are involved in physiological functions and pathological processes.
A translational axis developed by the LGRK aims to generate innovations in the field of skin cell therapy. One line of work concerns the development of effectors allowing more effective preservation of epidermal stem cells ex vivo, in the context of bioengineering in culture of skin substitutes. The targeted gain concerns the quality of skin regeneration. A second line of work concerns the problem of immune rejection, which restricts the fields of use of allogeneic grafts. The approach explored consists of vectorizing factors that promote a tolerogenic signal, in order to produce skin grafts with attenuated immunogenicity.
Finally, the LGRK is interested in the cutaneous consequences of genotoxic stress induced by ionizing radiation, in particular the exposure of healthy skin inherent to medical applications (imaging, radiotherapy). A goal of this research axis is understanding the impact of this medical exposome on the integrity and functions of stem cells and progenitors of the epidermis. Another focus concerns dermal fibroblasts, studied for their primary effector cell status in the development of radiation-induced skin fibrosis.

Research area
Innovations in the field of skin cell therapy

Synopsis
Translational research: from the basic knowledge on skin stem cells to innovation in the domain of cell and tissue bioengineering for regenerative medicine purpose

Interests
Cell Therapy;Stem cells;Toxicology/Immune tolerance;Translational research;Bioproduction

No results presentation available

Accelerating innovation in cell and gene therapy

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Laboratory Inserm
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Keywords
- Gene therapy
- Immunotherapy
- Lentiviral vectors
- CRISPR gene editing
- B cell therapies
- CAR T cells
- Cancer
- HIV
- Sickle cell disease
- Fibrosis

Abstract
The Technological Research Accelerator in Genomic Therapy (ART-TG) is an R&D laboratory created by Inserm to accelerate translational research in the field of cell and gene therapies, addressing a need for frequent disorders. Operational since 2020, ART-TG is headed by Anne Galy Ph.D.

ART-TG offers a capacity for preclinical development and IND-enabling studies using lentiviral vectors or CRISPR gene editing in hematopoietic stem cells or immune cells. A quality management system is in place. A particular feature of ART-TG is its capacity to support lentiviral vector gene therapy projects (enabling novel CAR-T cell studies for instance), spanning from the development of the vector manufacturing processes to analytical studies on target cells including genomic insertion site studies.

The expertise of ART-TG is based on its research. Ongoing projects include studies on novel strategies for vectorization and novel approaches to treat HIV infection, sickle cell disease of fibrosis. ART-TG is a member of various scientific networks and coordinates the PEPR Biotherapy-Bioproduction program to develop B-cell-based immunotherapies (THERA-B).

Located within the Génopole of Evry, ART-TG benefits from the rich ecosystem of the University Paris-Saclay and of the GENOTHER biocluster and collaborates with numerous academic, industrial and private partners. It was awarded the label “Bioproduction Biotherapies Integrator ».

For further information, visit www.art-tg.com.

Research area
Cell and gene therapy, immunotherapy

Synopsis

Our mission is to accelerate the pace of development for novel cell and gene therapies by discovering innovative treatments, principally for immunotherapy, and by supporting more broadly the industrial and clinical translation of cell and gene therapies.

Interests

Gene therapy;Gene editing;Cell Therapy;Chimeric Antigen Receptor (CAR)-T cells;Viral vectors;Oncology;Immunology/Immunotherapies;Haematology;Specific targeting;Clinical research;Bioproduction

Accelerating innovation in cell and gene therapy

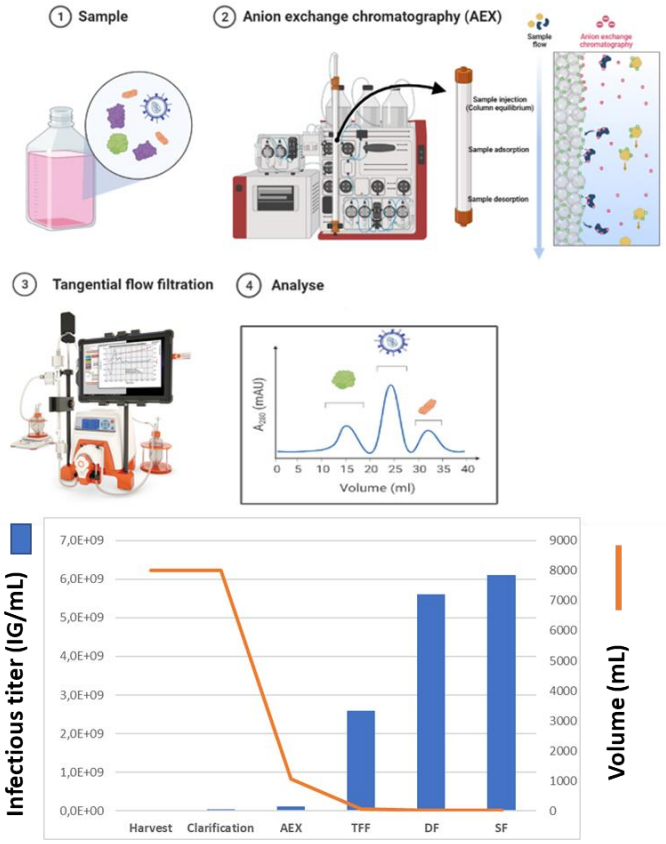
Anne GALY, PharmD, PhD

ART-TG, Corbeil-Essonnes

- **Objectives:**
  - To develop innovative cell and gene therapies for oncology and non-oncology applications
  - To improve the industrial bioproduction of cell and gene therapy products
  - To accelerate clinical transfer through specialized preclinical and CMC IND-enabling support
- **Tools:**
  - Lentiviral gene therapy vectors (tool design including new envelopes, production and purification, transduction, specialized analytics)
  - CRISPR genome editing (tool design, viral and non viral delivery)
  - Automated cell processing (hematopoietic stem cells and immune cells)
  - Bioinformatics for genome-modifying analytics

Subject 1: Lentiviral vector-dedicated R&D platform supporting innovative gene therapies in oncology and non-oncology

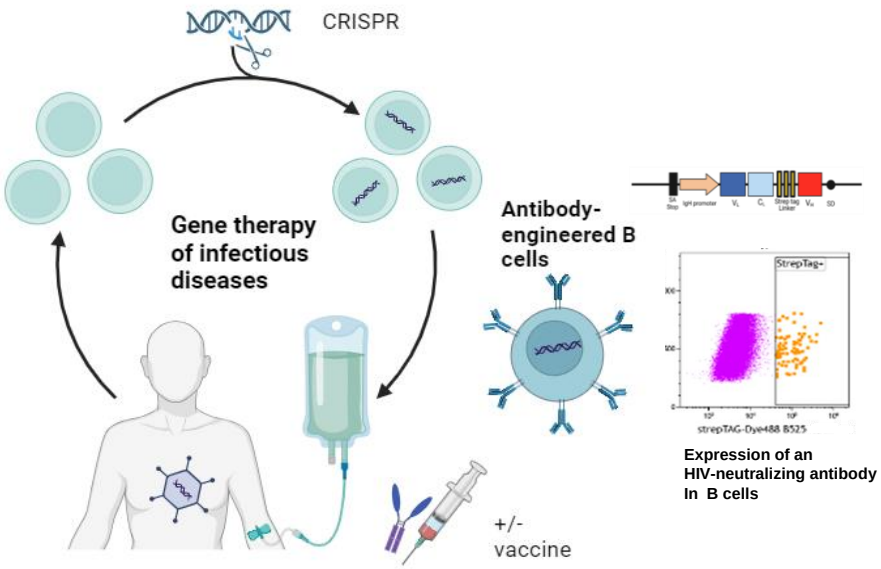
- **Results:**
  - Lentiviral vector-dedicated preclinical platform integrating:
    - pre-GMP manufacturing for preclinical studies and industrial transfer (*e.g.* CD123 CAR-T cells)
    - Specialized analytics including integration safety studies
    - *In vivo* models for biodistribution and safety studies for genetically-modified cell products
  - Innovative lentiviral vector-based strategies against cancer or against chronic conditions (e.g. CAR-T cells against fibrosis)
  - Design and manufacture of novel lentiviral vectors capable of in vivo gene transfer (e.g. vectors pseudotyped with syncytin fusogens for B cell gene delivery)



Legend: Lentiviral vector production downstream process steps showing concentration and purification of infectious particles in large scale conditions.

Subject 2: Novel B cell and stem cell gene therapies using precise genome editing

- **Results:**
  - Novel vaccine and immunotherapy strategies against cancer or infectious diseases based on re-programmed antibodies in human B cells (e.g. inducing broadly-neutralizing anti-HIV antibodies in healthy B cells)
  - Novel strategy for the gene therapy of sickle cell disease based on precisely regulating hemoglobin expression in human hematopoietic stem cells and conducting preclinical development (just started)
  - Genetically-engineering human B cells or hematopoietic stem cells using CRISPR/Cas9-based systems and non viral gene delivery



Created with BioRender

Legend: Programming anti-HIV antibody production by B cells using CRISPR/Cas9 and ssDNA genome editing in the IgH locus in autologous B cells . Orange dots in the FACS plot show the CD19+ B cells expressing a single-chain anti-HIV antibody.

- **Perspectives:**
  - Bring novel therapeutic candidates to clinical stage
    - B cell therapies including new vaccination modalities
    - Sickle cell disease therapies
    - Anti-fibrosis CAR-T cells therapies
  - Provide IND-enabling service to researchers and start-ups
    - Process and analytical development (vector and cell manufacture)
    - Bioinformatics
    - Biosafety studies
  - Valorize innovation through the creation of start-ups

- **Unique selling points**
  - Label “Integrator Bioproduction Biotherapy” since 2020
  - Quality management system
  - Capacity for R&D in gene therapy and immunotherapy
  - Capacity for bioproduction (lentiviral vectors) development
  - Supporting technology innovation

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Bioproduction, engineering, and characterization of extracellular vesicles (EVs) and nanovectors for early diagnosis and personalized therapy

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Keywords
- nanomedicine,
- biotherapies,
- extracellular vesicles,
- bioproduction,
- nanoparticle,
- drug delivery,
- regenerative medicine,
- cancer,
- AI

Abstract
Our team include biologists, chemists, physicists, data scientists, medical doctors, and pharmacists of scientific excellence dedicated to promoting research projects on extracellular vesicles (EVs) and nanovectors and accelerating their technological maturation and clinical transfer. We pioneered scalable and GMP compliant methods for high throughput high yield bioproduction and engineeering of extracellular vesicles as innovative cell-free biotherapies for regenerative medicine and precision drug delivery (cofoundation of two spin off). We are also expert in nanomedicine approaches to break physical and biological barriers for therapy delivery with spatio-temporal control using remote light or magnetic activation for precision oncology. Our IVETh innovation hub has been labeled as a the first “France 2030” Biotherapy-Bioproduction Industrial Integrator dedicated to extracellular vesicles and nanovectors for personalized diagnostic and biotherapies, representing a national and international reference with a unique park of equipements and breakthrough technologies. IVETh's integrated and multidisciplinary scientific strategy combine the development of (i) bioproduction, bio-engineering and purification bioprocesses compatible with automation, scaling-up and regulatory constraints for clinical batch production; (ii) analytical tests to assess the identity, quantity and purity of EVs or isolated subpopulations of interest of the cellular nanosecretome; (iii) high throughput and high content information potency tests for screening and optimization of therapeutic properties; (iv) artificial intelligence and machine learning for the search for markers and signatures for quality control; (v) analytical validation of quality control tests according to European regulations/ IVETh mission is to promote research, education, professional training, scientific networking, R&D and innovation support to promote the transition between academic discoveries, innovation and high-value-added products/services to the industrial sector and the emergence of new disruptive biotherapies in the fields of regenerative medicine, precision oncology, drug delivery and gene therapy.

Research area
Physics, Bioengineering, Nanomedicine

Synopsis
We provide multidisciplinary expertise and technological innovations for bioproduction, engineering, and characterization of extracellular vesicles (EVs) and nanovectors for early diagnosis and personalized biotherapy development.

Interests
Gene therapy;Cell Therapy;Non viral delivery systems;Extracellular vesicles;Oncology;Immunology/Immunotherapies;Neurology;Specific targeting;Artificial Intelligence (AI);Translational research;Bioproduction

No results presentation available

Development of genome editing tools

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Keywords
- Genome editing
- DNA repair
- Cas fusion proteins and variants
- Biochemistry
- Molecular genetics

Abstract
Our research addresses mechanisms of DNA repair, with applications to the development of improved genome editing approaches, and a focus on little characterized alternative end-joining mechanisms; finally we study DNA repair in DNA damage resistant species such as tardigrades which could unravel unexpected deployment of DNA repair pathways. Our team has contributed to the improvement of genome editing tools to obtain controlled modifications (for example: design of donor DNA, use of microhomologies, fusion of Cas9 repair proteins). We also developed an online tool for selection of guide RNAs (http://crispor.tefor.net/) and were among the first to explore the impact of the nuclease delivery method and to produce and use recombinant nucleases in order to facilitate genome editing. Importantly, based on our successful development of genome editing tools, starting with TALEN and shifting to CRISPR, we set-up in 2011 a facility that proposes genome editing strategies, called TACGENE, that is part of the national infrastructure Celphedia. The Tacgene platform has facilitated, thanks to fruitful collaborations, our access to important biological models that were not available in our laboratory: different animal models; or therapeutically relevant systems, to generate chromosomal translocations and study the corresponding cellular responses, or for gene therapy. We were thus able to validate the improvements that we proposed in numerous systems. We are now focusing on recent double strand break-free genome editing strategies that allow to reach increased safety and purity of sequence modification. We are currently involved in different networks aimed at developing these safer genome editing strategies in gene therapy for blood diseases, muscular and retinal dystrophies: EIC Pathfinder, PEPR Biotherapy, and 2 ANR grants

Research area
- DNA repair mechanisms and Development of genome editing tools.

Synopsis
- From basic research in DNA repair to improved genome editing strategies (and their application in gene therapy)

Interests

Gene editing;Genetic engineering;Ophtalmology;Neuromuscular disorders;Haematology;In vitro models/ Organ-on-chip;In vivo models

Development of genome editing tools

Carine Giovannangeli,
Jean-Paul Concordet

Genome Structure and Instability lab,
Inserm U1154, CNRS UMR 72196, Museum National d'Histoire Naturelle, Paris

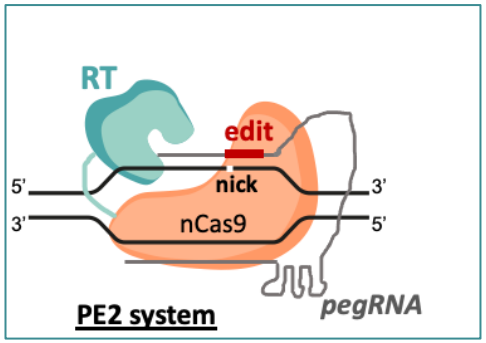
Development of genome editing tools

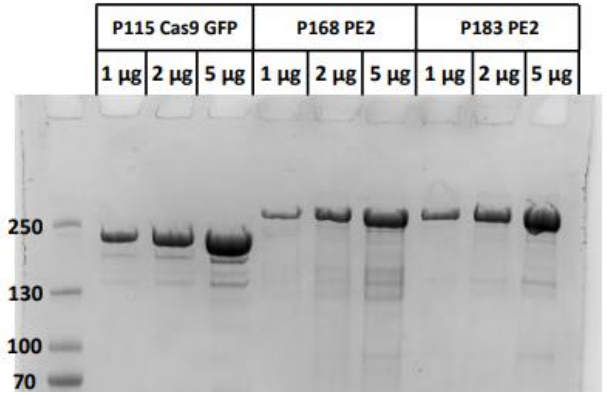
- **Objectives:**
  - To develop improved genome editing tools
  - To optimize genome editing strategies in a variety of gene therapy applications
  - To develop novel delivery solutions for genome editing reagents

- **Tools:**
  - Production of recombinant Cas proteins
  - *In vitro* evaluation of genome editing reagents
  - Cellular model systems for evaluation of genome editing strategies
  - CRISPR screens for identification of factors impacting genome editing activity
  - Tacgene platfom for genome editing services

Topic 1: Producing basic tools for genome editing

- **Results:**
  - Production of recombinant Cas proteins
  - *In vitro* evaluation of CRISPR reagents
  - crispor website for guide selection
  - software for mutation analysis from NGS data





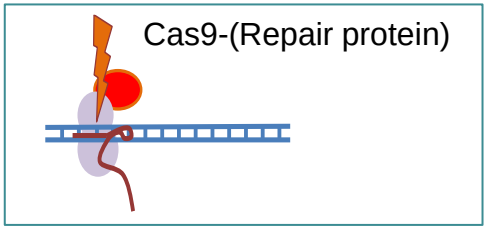
Optimized protocol for production of Prime Editing protein.

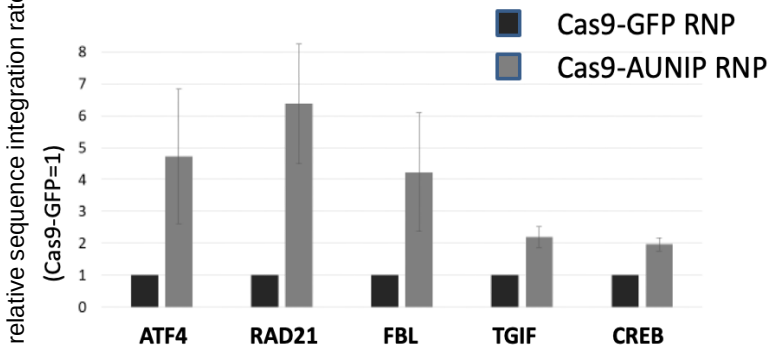
(Left) Schematic representation of the prime editing system: the prime editor protein consists in the fusion of Cas9 nickase to MMLV reverse transcriptase (RT); the prime editing guide RNA (pegRNA) architecture includes a standard guide RNA and a 3' extension that will be copied by the RT.

(Right) Purity of full-length PE protein from the optimized protocol (P183 PE2), compared to the initial protocol (P168 PE2) and to Cas9-GFP, which is routinely produced in the lab and has been used by many collaborators in a wide variety of experimental systems.

Topic 2 : Increasing efficiency of precise genome editing

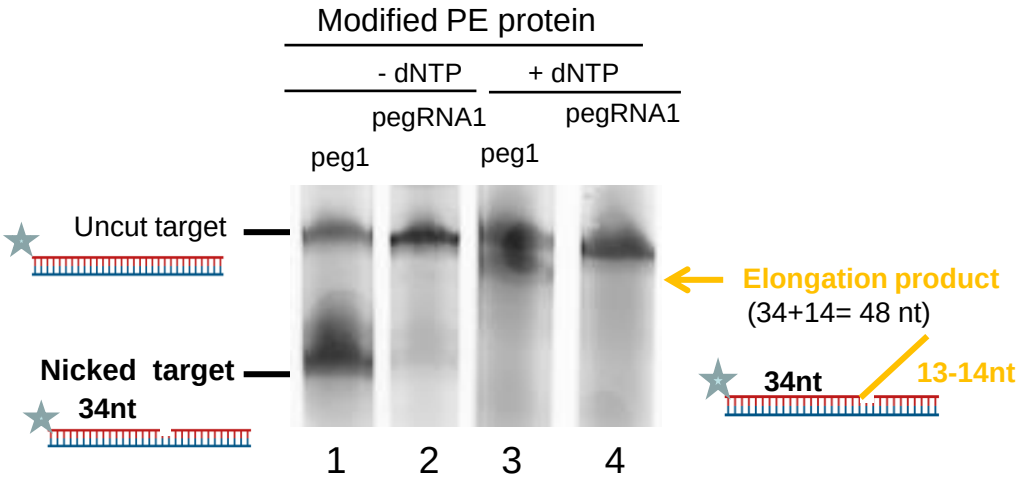
- **Results:**
  - Cas9 fusions to HDR proteins for enhanced precise genome editing
  - Development of Improved prime editing strategies





Stimulation of precise editing by Cas9-AUNIP fusion.

The guide RNA/Cas9 protein complexes (RNP) and ssODN donor were transfected in HEK293 cells (n=5) for gene tagging and efficiency of sequence integration at the target gene is represented for Cas9-GFP and Cas9-AUNIP. AUNIP is a repair protein involved in Homology-directed repair (HDR).



Improvement of the Prime Editing system.

In vitro assay of prime editing activity. Nickase activity of a modified PE protein in presence of pegRNA1 and an optimized peg1 version in the absence (1 & 2) or presence of dNTP (3 & 4). The optimized guide RNA (lane 1 & 3) is active (generating nickase and polymerase activity together with the PE protein) while the standard PE design (lanes 2 & 4) is inactive.

- **Perspectives:**
  - Developing DSB-free genome editing tools
  - Optimizing and Validating these strategies in gene therapy applications
  - Develop novel delivery strategies for genome editing tools

- **Unique selling points**
  - Strong expertise in design and development of genome editing strategies
  - Involvement in EC and French networks aimed at genome editing based gene therapy
  - Involvement in French networks aimed at developing cellular and animal models for investigation of disease mechanisms

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From retinal development to retinal repair: the use of human pluripotent stem cells

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Keywords
- Vision
- Retina
- Cell therapy
- iPS cells
- Organoids
- Disease modeling
- Neurodegeneration

Abstract
Our research interests focus on the development of strategies using human induced pluripotent stem (iPS) cells in order to better understand human retinal development, degenerative diseases of the retina and to propose new therapeutic approaches, with the main concern of developing translational research allowing visually impaired patients to benefit from therapeutic innovations.
Our team is one of the pioneering teams in iPS cell-based organoid technology in the field of vision research and has developed innovative and robust protocols allowing the differentiation of human iPS cells into different retinal cell types including cells affected by the main retinal diseases, such as retinal ganglion cells (glaucoma) or photoreceptors (age-related macular degeneration). We are now conducting stem cell-based preclinical studies necessary for the development of stem cell therapy by developing transplantation approaches (combination of cell and gene therapy) of photoreceptors derived from human iPS cells.

Research area
From retinal development to retinal repair: the use of human pluripotent stem cells

Synopsis
Development and use of induced pluripotent stem (iPS) cells for the investigation of dystrophic retinal diseases, with the aim of promoting innovative stem cell-based therapies for these blinding degenerative diseases.

Interests
Cell Therapy;Stem cells;Ophtalmology;Aging;In vitro models/ Organ-on-chip;Modelling/Digital Twin;Translational research

From retinal development to retinal repair: the use of human pluripotent stem cells

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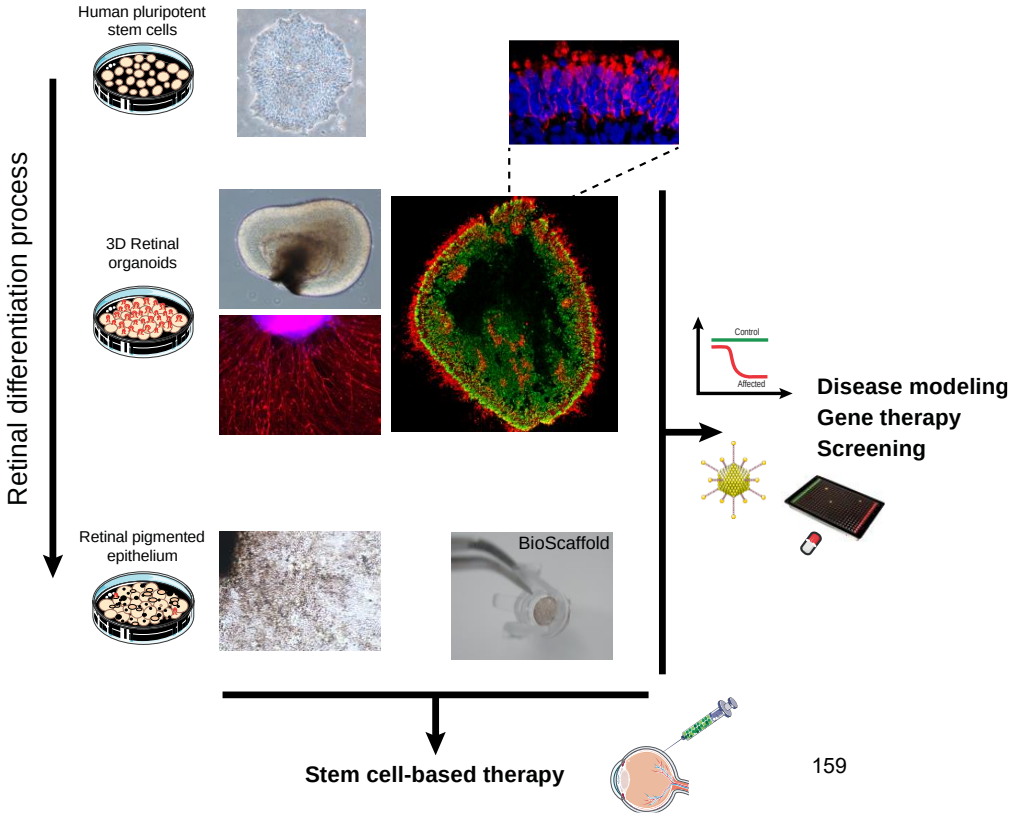
Sorbonne University, INSERM, CNRS
Paris

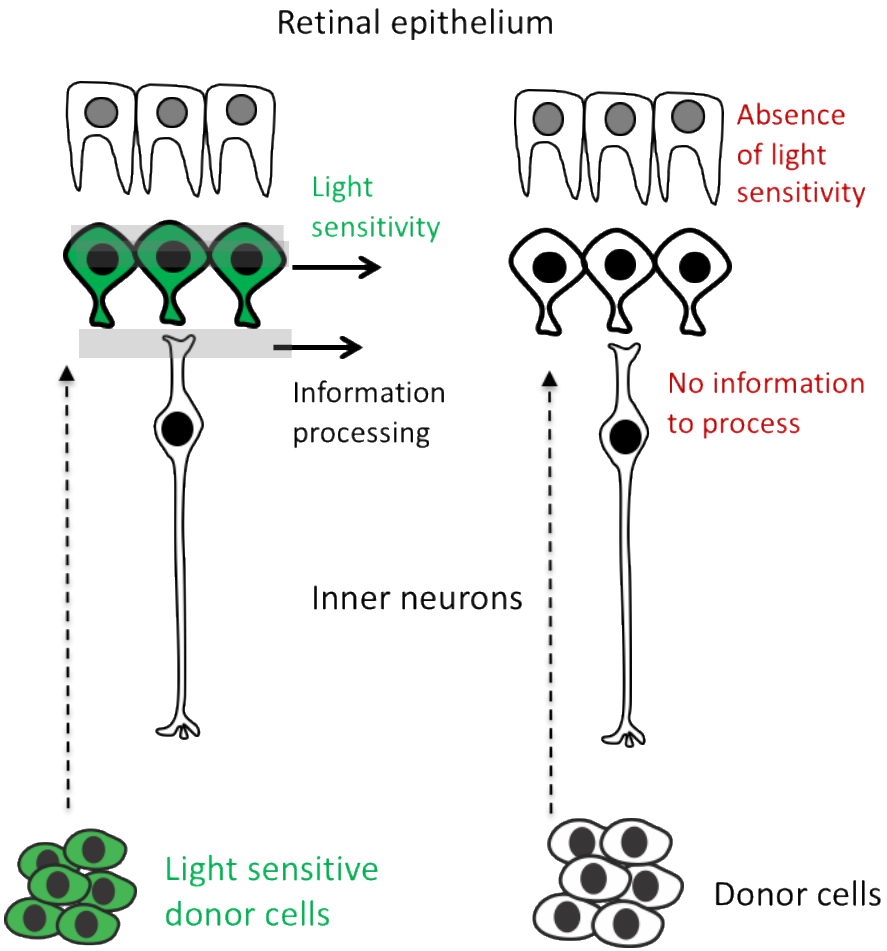
- **Objectives**
  - Developing cell transplantation approaches for outer retina reconstruction and visual restoration
  - Modeling inherited retinal dystrophies to propose new therapies for visually impaired patients

- **Tools**
  - Human pluripotent stem cells (iPS cells)
  - Bioengineering and organoids
  - Optogenetic and genome editing



Stem-cell based therapies

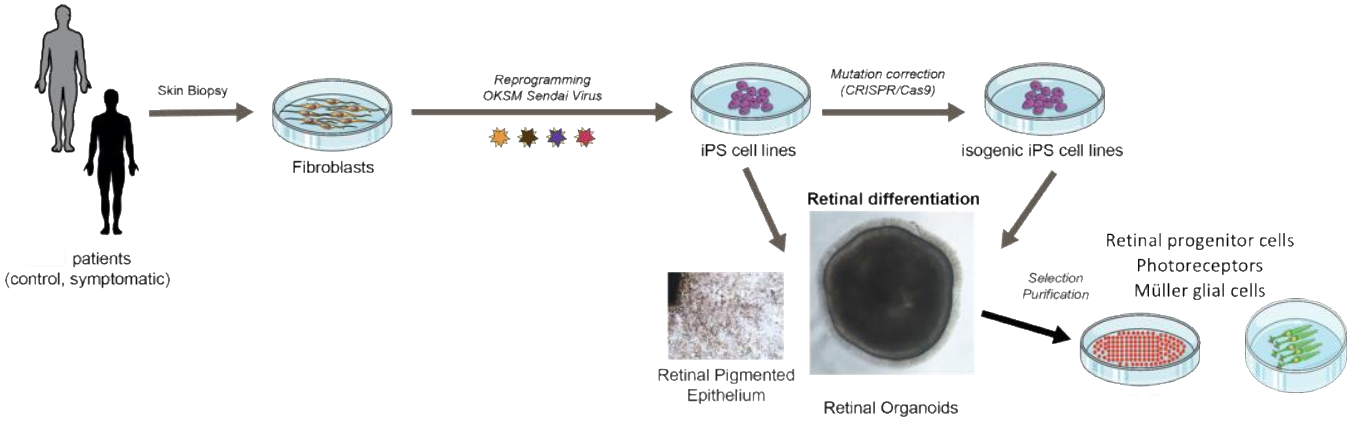
- **Results**
  - First clinical trial to treat retinitis pigmentosa patients with stem cell-derived retinal pigmented epithelium sheet (*Science Transl. Med. 2017, Biomaterials 2020*): **NCT03963154**
  - Substantial restoration of vision by combining stem cell therapy and optogenetics (*Nat Comm 2019*)

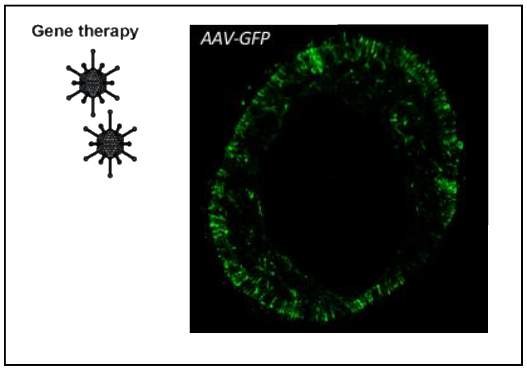


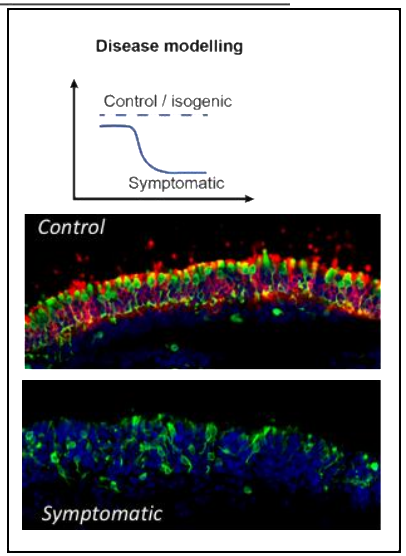
Combining optogenetic and cell therapy to confer artificial light sensitivity to donor cells (photoreceptors derived from stem cells)

Retinal disease modelling

- **Results**
  - 3D retinal organoids for understanding and validating gene therapy approach for inherited retinal dystrophy (npj Reg. Med. 2022)







- **Perspectives**

  - Genome editing for iPS cell-based therapies for photoreceptor cell replacement
  - Scaffold bioengineering for iPS cell-based therapies for photoreceptor cell replacement
  - Bio-inspired synthetic matrices for retinal organoids to improve disease modelling approaches
  - Development of new iPS cell-based retinal models for drug discovery

- **Unique selling points**

  - Combination of optogenetic and cell therapy
  - Visually impaired non human primates models
  - Adapted AAV vectors to specifically target photoreceptor
  - Large collection of iPS-derived retinal cells and tissues

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Keywords
- Antisense therapy
- Splice modulation
- Antisense Oligonucleotides
- AAV mediated splice switching
- Translational research
- Neuromuscular disorders
- Duchenne Muscular dystrophy
- Preclinical development
- Rare diseases

Abstract
Our Research interests focus on gene and antisense therapies for the treatment of neuromuscular disorders. Our laboratory pioneered an exon-skipping gene therapy strategy for Duchenne muscular dystrophy (DMD) using AAV vectors (approach currently in Phase I/IIa clinical trial: NCT04240314). More recently, we demonstrated the therapeutic potential of a novel class of antisense oligonucleotides (ASO) made of tricyclo-DNA (tcDNA), which displays unique pharmacological properties and unprecedented uptake in many tissues after systemic administration (approach also currently in Phase I/IIa clinical trial NCT05753462). Despite these recent advances, ASO based therapies still face major challenges in particular for neuromuscular disorders where systemic delivery is required. We therefore focus on developing innovative combined strategies to overcome the poor delivery limitation and allow ASO- therapies to reach their full therapeutic potential.
We are also developing tools to address the brain comorbidities of DMD and have recently shown that postnatal restoration of brain dystrophins partially alleviates emotional and cognitive deficits in dystrophic mouse models.

Research area
Development of antisense-based therapeutic approaches for the treatment of neuromuscular disorders.

Synopsis
Developing innovative antisense-based approaches for the treatment of neuromuscular disorders: combining strategies to reach full therapeutic potential

Interests
Gene therapy;Oligonucleotides;Viral vectors;Neuromuscular disorders;Rare diseases;Toxicology/Immune tolerance;In vivo models;Translational research;Clinical research

Development of antisense based approaches for the treatment of neuromuscular disorders

Aurélie GOYENVALLE

UMR1179 Inserm – UVSQ, Versailles

- **Objectives:**
  - Develop innovative therapeutic approaches based on antisense technology (modulation of splicing)
  - Improve the current state of the art on antisense approaches for neuromuscular disorders
  - Treat brain comorbidities of Duchenne Muscular Dystrophy
  - Combine therapeutics approaches for synergistic effects

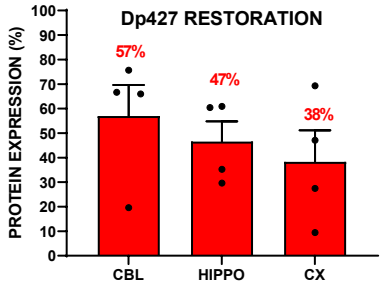
- **Tools:**
  - Antisense oligonucleotides (ASO)
  - AAV-mediated antisense therapies
  - *In vitro* and *in vivo* models of neuromuscular disorders
  - Preliminary and predictive tox assays for ASO safety

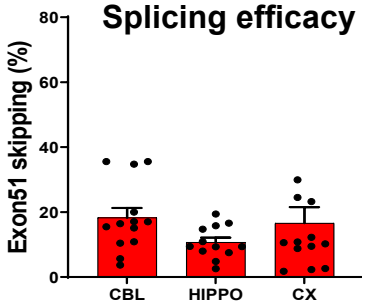
BRAIN INVOLVEMENT IN DUCHENNE MUSCULAR DYSTROPHY

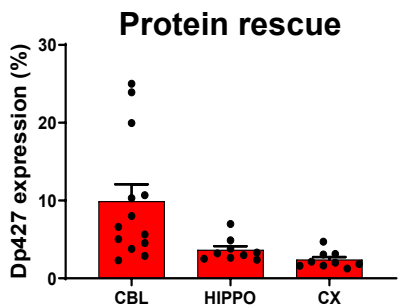
Impact of postnatal restoration of dystrophin in the brain of DMD mouse models

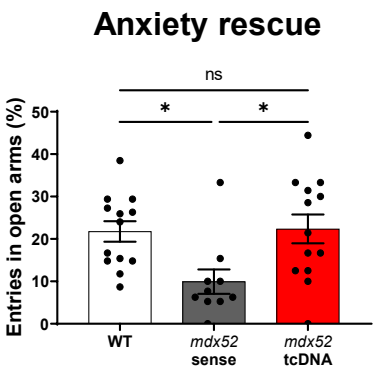
- **Results:**
  - Characterization of mouse models that recapitulate the emotional and cognitive deficits observed in DMD patients (Saoudi et al, DMM 2021)
  - Optimization of ASO delivery routes to the CNS (Saoudi et al., Cells 2023)
  - Partial restoration of dystrophin in the brain of dystrophic mice improves the behavioral outcomes (Saoudi et al., MTNA 2023)

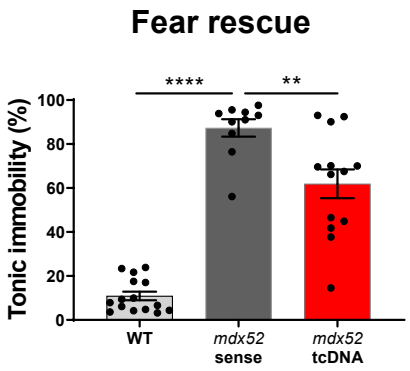
- **Perspectives:**
  - Early postnatal restoration of brain dystrophin mediated by AAV-U7snRNA vectors could rescue more deficits











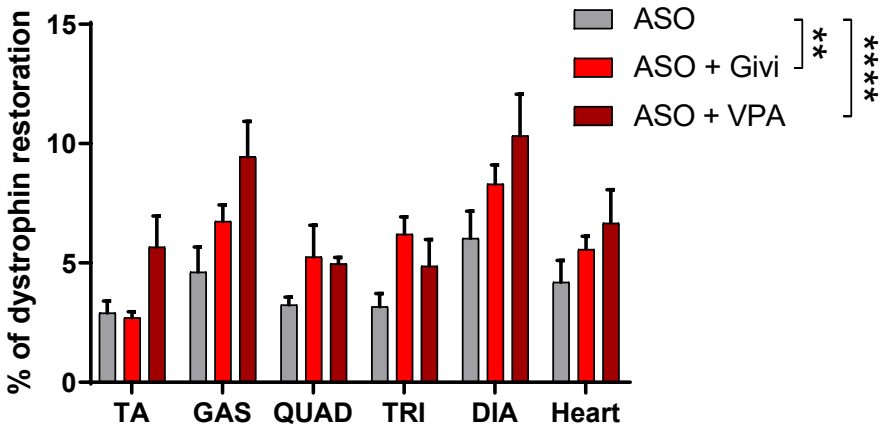
Legend: intracerebroventricular injection of ASO in *mdx52* mice induces widespread exon skipping, leading to partial rescue of dystrophin in different brain structures and improvement of anxiety and fear phenotypes (Saoudi et al., MTNA 2023).

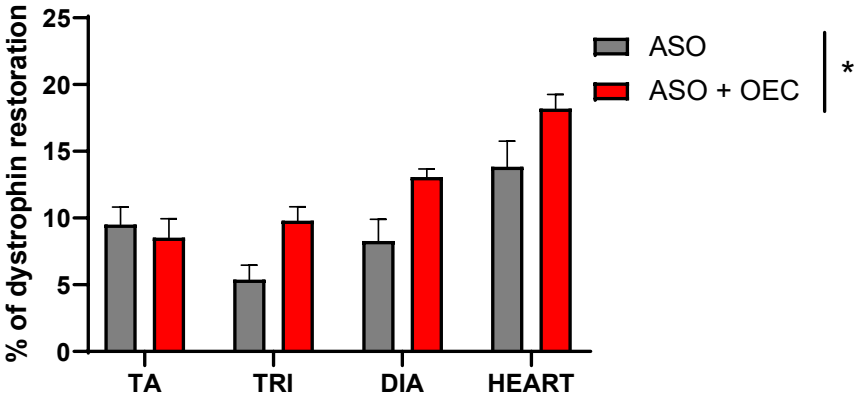
IMPROVE THE THERAPEUTIC POTENTIAL OF ANTISENSE THERAPIES

Combine therapeutic approaches for synergistic effects

- **Results:**
  - Histone deacetylase inhibitors (Givinostat or VPA) improve antisense-mediated exon-skipping efficacy in dystrophic mice
  - Oligonucleotide Enhancing Compound (OEC) increases ASO-Mediated Exon-Skipping Efficacy in dystrophic mice

- **Perspectives:**
  - Other on-going studies to improve the biodistribution and intracellular trafficking of ASO





Legend: Combining HDAC inhibitors treatment such as Givinostat or VPA (top panel)) or an Oligonucleotide Enhancing Compound (OEC) (bottom panel) with ASO treatment significantly improves the therapeutic potential of antisense strategy (1.5 to 2 fold).

- **Perspectives:**
  - AAV mediated splice switching offers higher therapeutic potential in neonates than ASO (that require re-administration)
  - Combined therapeutic strategies can act synergistically to reach ASO full therapeutic potential
  - Possibility of combining strategies with one AAV tool

- **Unique selling points**
  - Part of international consortium on Brain comorbidities on DMD (BIND)
  - Unique expertise in ASO technology in France (recognized by the Oligonucleotide Therapeutic Society)
  - Pioneered the AAV-mediated exon skipping strategy
  - Capacity to go from early preclinical development to Clinical program (ASO currently in Phase 1/2a trial for DMD)

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Development and implementation of expansion culture processes of human immune cells in bioreactor

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Keywords
- Immune cells
- GMP
- Bioreactor
- Human cell culture process in bioreactor
- Enrichment in specific cell phenotype
- Real time monitoring using spectroscopic sensors
- Cell therapy applications

Abstract
Based on a strong practice in animal and human cell (CHO, VERO, hMSC…) culture processes in bioreactor gained from numerous industrial partnerships, our researches are focused on the development of new and efficient processes dedicated to the expansion of immune cells, offering various applications in cell therapies and derived treatments. Our specificities rely on the interaction of multidisciplinary domains such as Biochemistry, Cell Biology, Process Engineering, Spectroscopy and Automatism, allowing establishing, in a single place, strong interfaces that are important to address scientific and technological bottlenecks.

Research area
Bioprocess Engineering for health

Synopsis
Development and implementation of expansion process cultures of immune cells in bioreactor for cell therapy purposes: from lab scale to integrated GMP processes

Interests
Cell Therapy;Immunology/Immunotherapies;Automation;Process monitoring;Sensors and biosensor;Bioproduction

Development and implementation of expansion culture processes of human immune cells in bioreactor

Emmanuel GUEDON

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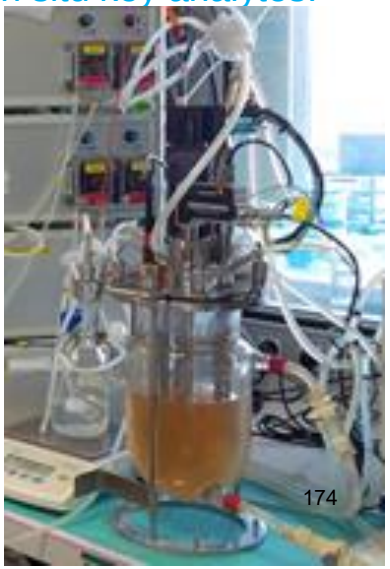
Université de Lorraine, Vandoeuvre-lès-Nancy

- **Objectives:**

  - A better understanding of immune cell biology based on their behaviors in various environments, including bioreactors
  - to develop new strategies of cell monitoring in real time to guarantee a better control of the process expansion in term of quantity (amount of viable cells) and quality (targeted cell phenotypes and functionalities).
  - to scale up immune cell expansion processes from lab (20 mL) to 5-10 liters bioreactor in GMP systems and facilities

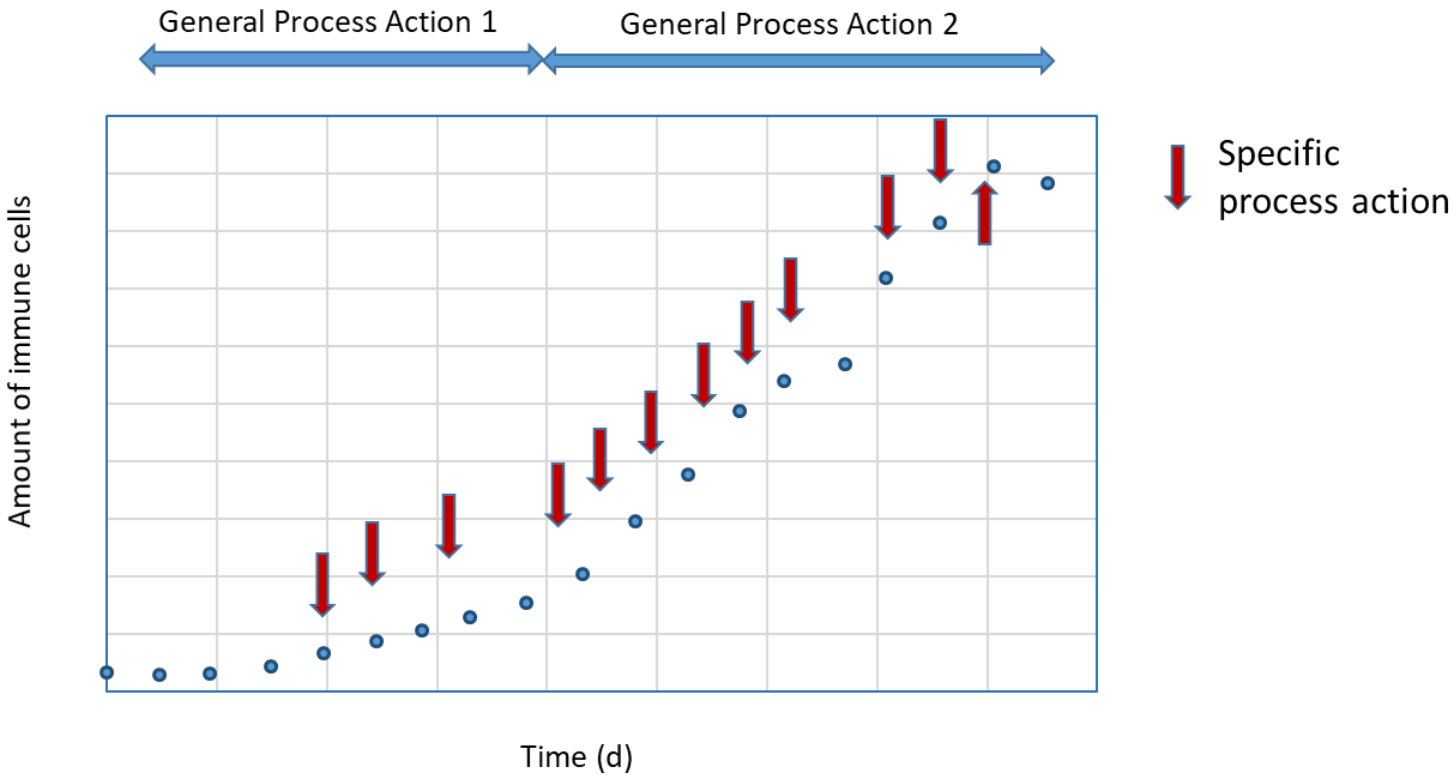
- **Tools:**

  - Bioreactors fully instrumented from 250 mL to 5 Liters
  - Cell analysers (Vi cell XR, nucleocounter, Flow cytometer) for cell viability and phenotype caracterisation
  - Automatic biochemistry analyser (Gallery)
  - Dielectric and Raman spectroscopies for the bioreactor monitoring of in situ key analytes.
  -



Subject 1

- **Results:**
  - Strong expansion of immune cells in a monitored and controlled bioreactor, suggesting a good scalability of the process (up to 5 liters)
  - Flow cytometry characterization of cells during the kinetic, indicating a good phenotype quality at the end of the process
  - A well established process with a good robustness



Legend: kinetic of immune cell expansion in agitated, monitored and controled bioreactor. Blue double arrows indicate general actions caried out during the process. Red arrows indicate specific process actions carried out during the expansion. Blue bullet point indicate amount of cells during the kinetic

Perspectives:

- Whereas largely anticipated, to adapt the whole workflow process to GMP requirements
- To improve the process in order to get better focused cell phenotypes
- Depending on the culture mode, to scale up the process at least up to 5 liters has to be established
- Implementation of spectroscopic sensors for a real time monitoring and control (general and specific process actions)
  -
  -

- **Unique selling points**

  - A strong expertise in animal and human cell cultures in bioreactor
  - A strong expertise in the developpement and implementation of spectroscopic sensors for real time monitoring of animal cell culture processes
  - integrated development of the process taking into account GMP conditions from scratch
  - Capability to go from basic and academic research studies, to (pre) industrial application for clinical trials, on Nancy site as a part MTInov platform.

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- Zavala-Ortiz, D. A., Ebel, B., Li, M. Y., Barradas-Dermitz, D. M., Hayward-Jones, P. M., Aguilar-Uscanga, M. G., MARC A. & Guedon, E. (2020). Support Vector and Locally Weighted regressions to monitor monoclonal antibody glycosylation during CHO cell culture processes, an enhanced alternative to Partial Least Squares regression. *Biochemical Engineering Journal*, *154*, 107457.

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- Sion, C., Loubière, C., Wlodarczyk-Biegun, M. K., Davoudi, N., Müller-Renno, C., Guedon, E., .Chevalot, I., & Olmos, E. (2020). Effects of microcarriers addition and mixing on WJ-MSC culture in bioreactors. *Biochemical Engineering Journal*, *157*, 107521.

- Sion, C., Ghannoum, D., Ebel, B., Gallo, F., de Isla, N., Guedon, E. Chevalot I.,& Olmos, E. (2021). A new perfusion mode of culture mode for WJ-MSCs expansion in a stirred and on-line monitored bioreactor. *Biotechnology and Bioengineering*, *118*(11), 4453-4464.

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Multidiciplinary approaches to regenerating skeletal tissue

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Last name GUICHEUX
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Laboratory INSERM UMR 1229-RMeS, Nantes University Hospital
City NANTES

Keywords
- Regenerative Medicine
- Skeleton
- 4R medicine
- Aging
- Chronic age-related diseases
- Skeletal inflammatory
- Stem cells
- Extracellular vesicles
- Biomaterials
- Bioprinting

Abstract
The promising field of regenerative medicine aims to restore the function of damaged tissues including those constituting the skeleton. It also intends to conceive biomaterial- and cell-assisted therapeutic solutions for tissues that become ineluctably degrade with aging or inflammatory diseases. Considering the large number of chronic diseases for which clinicians can only manage patients' symptoms using drugs or medical devices, regenerative medicine has for long been contemplated as a game-changer in medicine. Interestingly, recent advances in biomaterial sciences (biomimicry, hydrogels, 3D bioprinting...), skeletal physiopathology (developmental diseases, osteoarthritis, age-associated diseases, inflammation...), developmental biology (cell fate and tissue modeling), and stem cell biology (reprogramming and differentiation) are paving the way to new concepts that will undoubtedly improve skeletal regenerative strategies.
Our RMeS laboratory aims to reinforce his international positioning as a center of excellence and a leader in skeleton aging and regenerative medicine. Our research goals range from deciphering the mechanisms that govern development, growth and aging of bone and cartilaginous tissues to promote the advance of innovative 4R medicine strategies for the skeleton. Four "R" medicine relies on concepts we recently developed in our lab and refers to:
1-Replacement. It involves using synthetic biomaterials for the prosthetic replacement of damaged joints (hip, knee, intervertebral disc). The improvement of the current knowledge on cells/biomaterials interfaces receives a specific attention in our lab.
2-Repair. It means exploiting the body's natural ability to spontaneously heal. While some organs or tissues don't repair themselves as readily (ie. Cartilage), bone naturally heals by itself. The understanding of the molecular control of tissue formation and remodeling leads to the identification of biological cascades playing key roles in skeletal diseases. Boosting the tissues' ability to remodel and selfheal through the elaboration of supportive scaffolding biomaterials (i.e. hydrogel, calcium phosphate ceramics) is one of our therapeutic research objectives.

3-Regeneration. It includes delivering regenerative cells (autologous or not) and/or biofactors (i.e.cytokines, growth factors, RNA) combined or not with advanced biomaterials to treat degenerated tissues with poor self-healing ability. The human and veterinary clinical transposition of such concepts is also one of our strongest research efforts.
4-Reprogramming. It implies changing the natural fate of cells towards the exploitation of their capacity for tissue repair. Deciphering the embryonic development of skeletal tissues generates instrumental data for the elaboration of cell reprogramming approaches. The use of bioengineered cells (i.e. multipotent or induced pluripotent stem cells) or EVs for regenerative application is one of our emerging research topics.

Research area
Regenerative medicine and skeleton: Replace, Repair, Regenerate, Reprogram

Synopsis
Multidisciplinary approaches to regenerating skeletal tissue

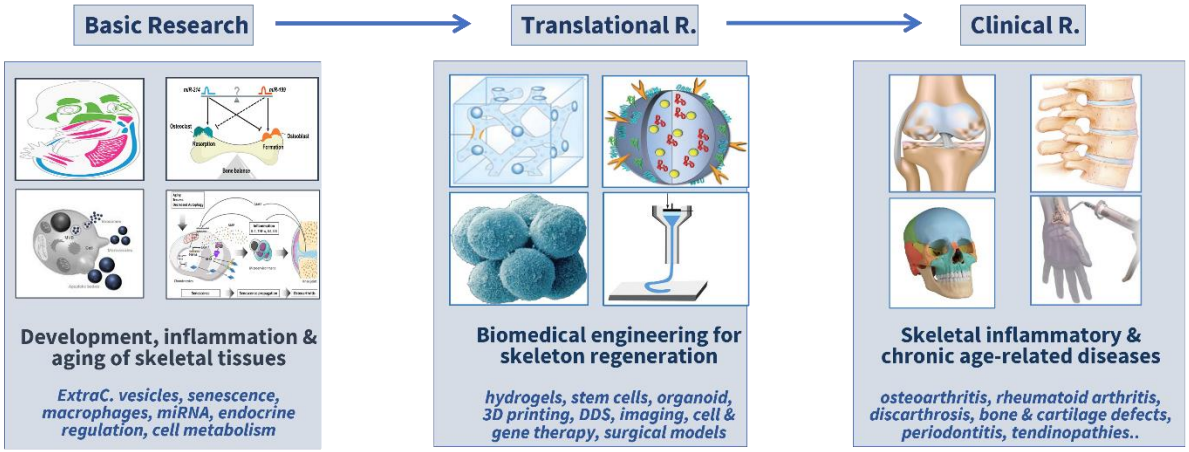
Interests
Cell Therapy;Stem cells;Extracellular vesicles;Aging;In vivo models;Translational research;Clinical research

Multidiciplinary approaches to regenerating skeletal tissue

Jérome GUICHEUX

Regenerative Medicine and Skeleton research centre
INSERM UMR 1229-RMeS
Nantes, France

- **Objectives:**
  - Support basic, translational and clinical research pertinent to the 4R medicine (Replace, Repair, Regenerate and Reprogram) related to skeleton diseases and aging.
  - Explore the pathophysiology and aging of the joints and bone tissues from their basic aspects to more applied aspects.

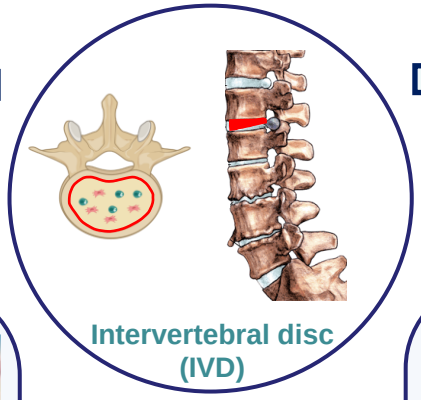


- **Tools:**
  - Electron Microscopy, Microcharacterization and functional Morphohistology and imaging
  - Biomaterial synthesis
  - Biofabrication through electrospinning and additive manufacturing
  - Mechanical tests and physical chemistry caracterisation
  - INOA facility for experiments related to the characterization of skeletal cell responses

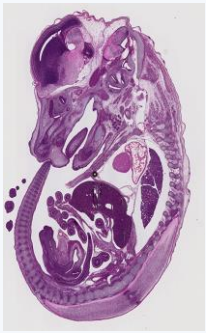
Subject 1: BIODIV : Stem Cells and Axial Skeleton Development

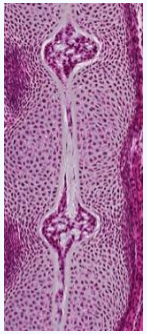
Intervertebral disc, Pluripotent Stem Cells, Embryonic development, Morphogenesis, Organoïds

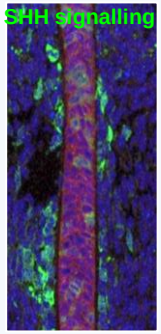
Anne Camus (CRCN CNRS-HDR)



Program 1. Axial skeleton development and morphogenesis


Mouse embryo
E14.5 HES

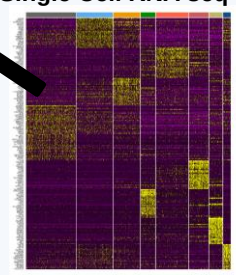

Transgenic notochord

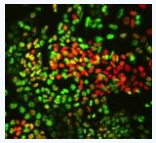


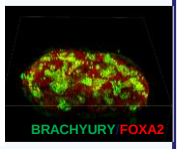

Skeletal prep.

- Identify molecular regulators of IVD development and morphogenesis

Program 2. Stem cells for IVD regeneration







- Generate disc cells from pluripotent stem cells for regenerative medicine

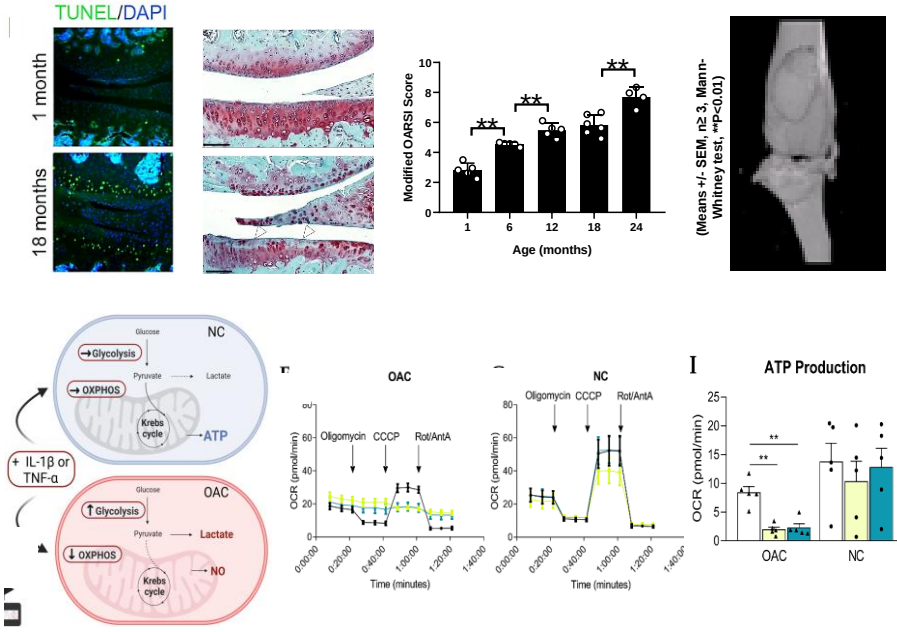
Paillat et al., Eur Cell Mater 2023
Bach et al., Front Cell Dev Biol 2022
Colombier et al., Cells 2020

Subject 2: AGE-OA: Aging and Osteoarthritis pathophysiology
Osteoarthritis, intervertebral disc , senescence, metabolism, aging

Claire Vinatier (MCU-HDR)

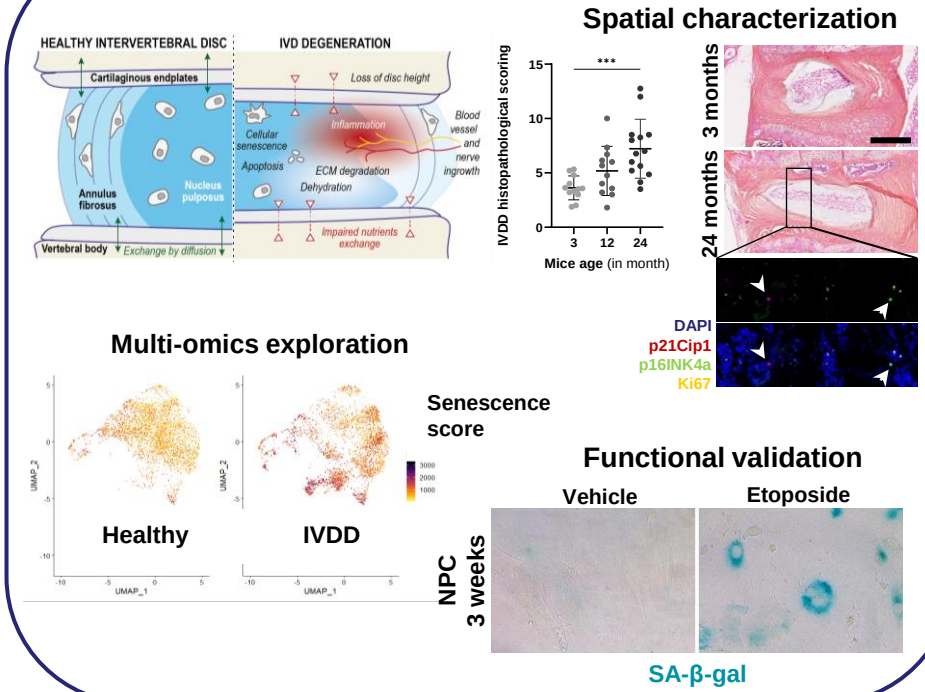
pouce coeur

Program 1. Age-related mechanisms and metabolism dysregulation in OA



➢ Dysregulated energetic metabolism in OA and Aging

Program 2. Cellular senescence in spinal OA



Defois et al., Cell Commun Signal 2023
Georget et al., Aging 2023
Bodic et al., Osteoarthritis cartilage 2022

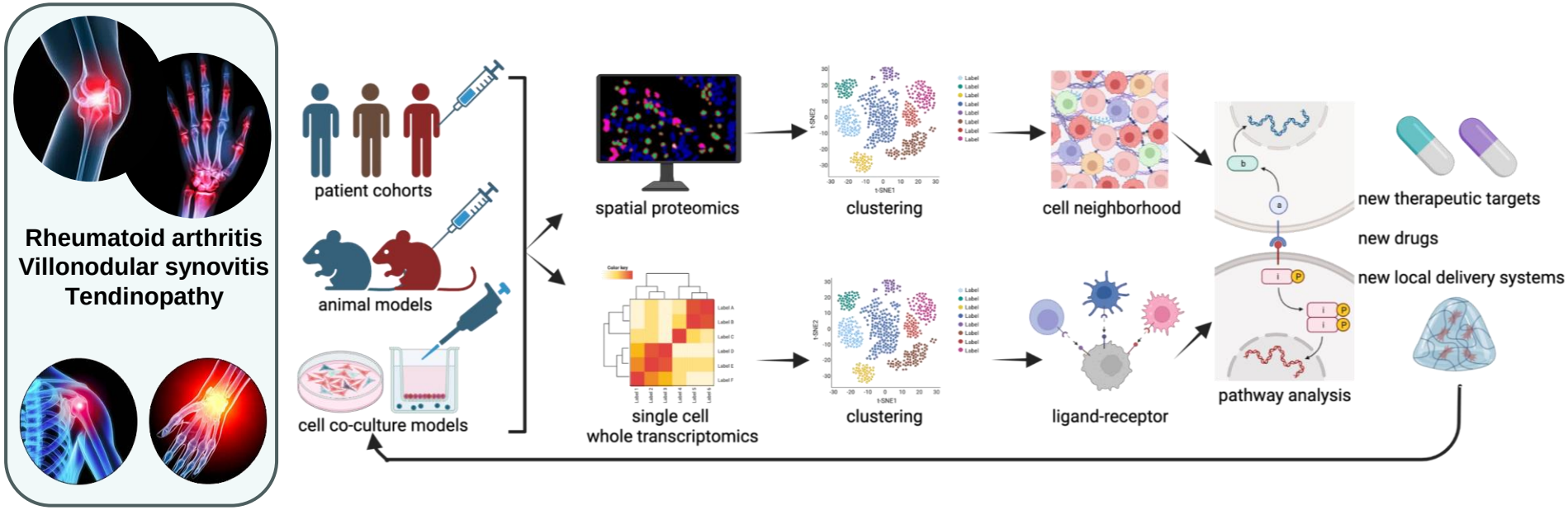
Subject 3: T-SYNO: Tendon and Synovial pathophysiology

Chronic inflammatory rheumatisms, tendinopathy, macrophages, spatial biology

Frédéric Blanchard (DR2 INSERM)

Program 1. To better characterize synovial and tendon cells in inflammatory rheumatisms and tendinopathies

Program 2. To identify novel cellular and molecular therapeutic targets within the synovium and tendon



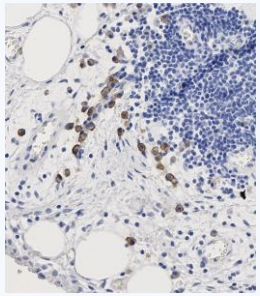
Boutet et al., Autoimmun Rev 2021
Najm et al., Arthritis Rheumatol 2020
Darrieutort-Laffite et al., Ann Rheum Dis 2019

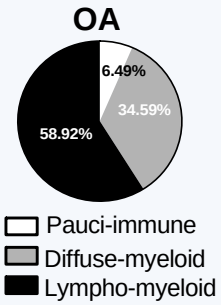
Subject 4: StratOA: Immune cells and osteoarthritis personalized therapies

Osteoarthritis, Stratification, Immune cells, Synovium, Personalized medicine, Therapeutic strategies

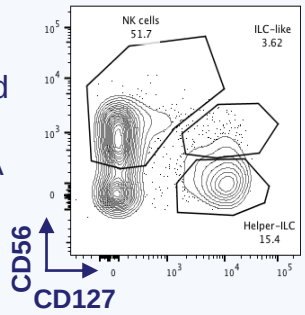
Marie-Astrid BOUTET (CRCN INSERM)

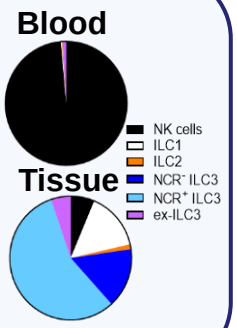
Program 1. Characterize the **synovial immune cell heterogeneity** to **better stratify OA patients**



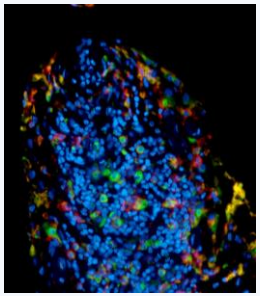


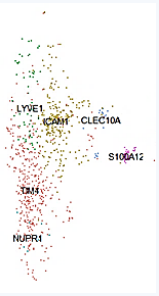
Program 2. Understand the involvement of the **immune system** in OA development



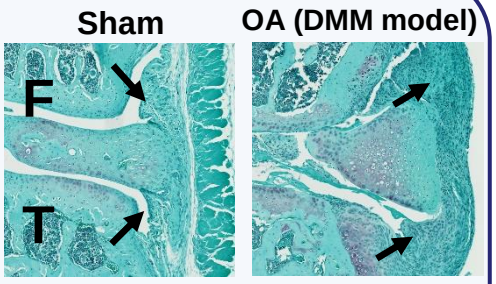


Program 3. Develop macrophages modulation strategies for the **personalized treatment of OA**





Program 4. Decipher the relationship between **intestinal microbiota and joint inflammation** in OA

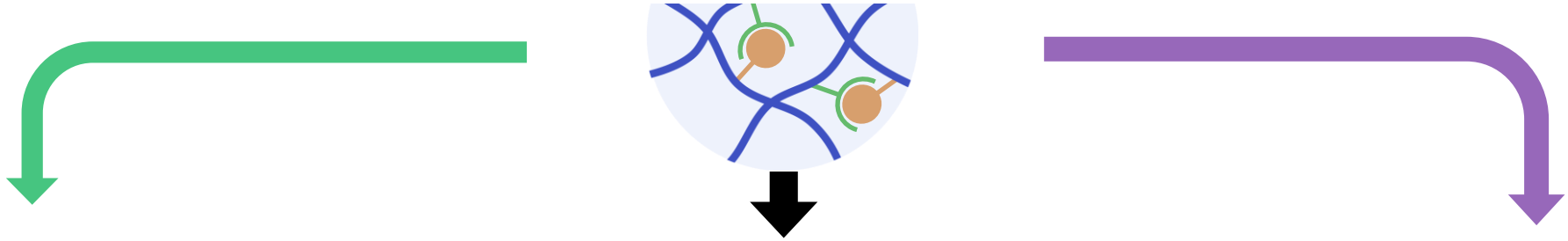


Boutet MA et al., OAC, in press
Boutet MA et al., Autoimmun Review, 2021
Nerviani A*, Boutet MA*, et al., Ann Rheum Dis. 2021

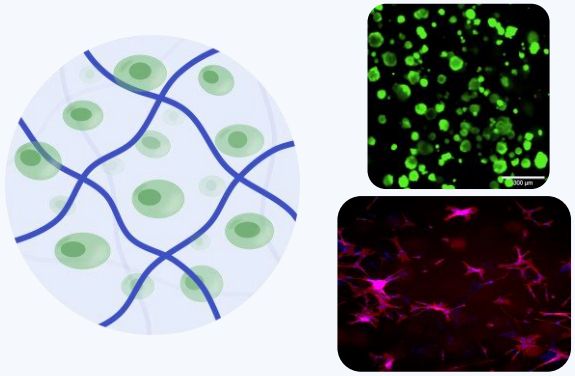
Subject 5: BIOMAX: Bio-Inspired Material concepts

Biomaterials, biofabrication, disease modeling, osteoarthritis

Vianney DELPLACE (CRCN INSERM)

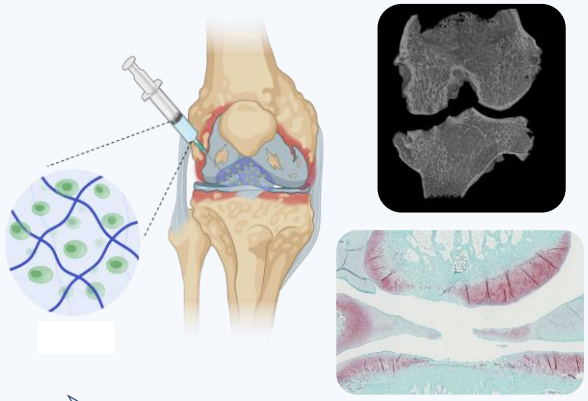


Program 1. 4D cell culture



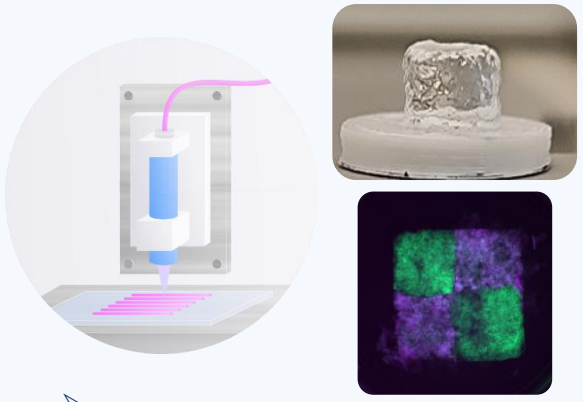
- Tunable synthetic matrices
- 4D cell culture

Program 2. Drug/cell delivery



- Injectable hydrogels
- Controlled release

Program 3. Biofabrication



- Innovative bioinks
- In vitro disease modeling

Lagneau et al., Biomaterials 2023
Lagneau et al., Bioact Mater 2023
Tournier et al., Adv Sci 2023
Patent EP 20162062.2

Subject 6: HEAL: hydrogels and joint translational research

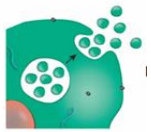
Therapeutic evaluation; Experimental models; Imaging; Osteoarthrtitis; Intervertebral disc disease

Catherine LE VISAGE (DR2 INSERM)

Program 1. Design of novel biomaterials/biologics-based therapies
Program 2. In vitro, ex vivo, and in vivo evaluation in osteoarthritis and disc disease

Design of therapies

Cells

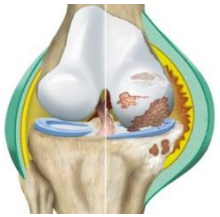


Extracellular Vesicles

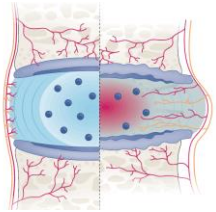
Nucleic acids

Evaluation

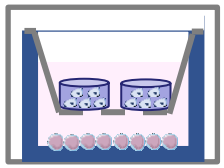
Osteoarthritis



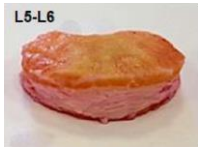
Disc disease



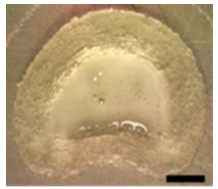
2D / 3D co-cultures



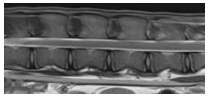
Organ culture



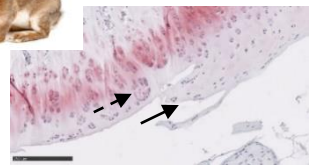
Bioprinted model



Age-related model



ACLT model



Clinical trial

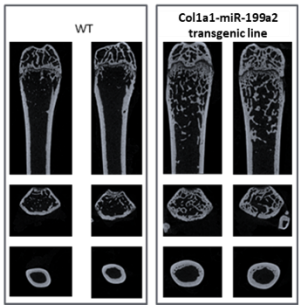
Nativel et al., Mater Today Bio 2023
Le Moal et al., Int J Pharm 2022
Bouhsina et al., Sci Rep 2022

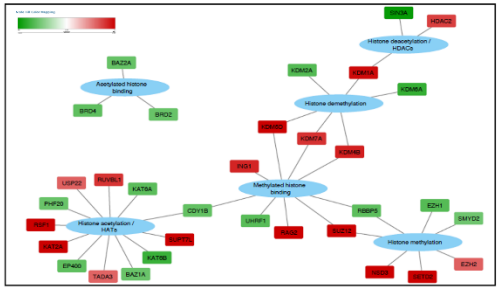
Subject 6: EPIGEN: Molecular control of bone aging and regeneration

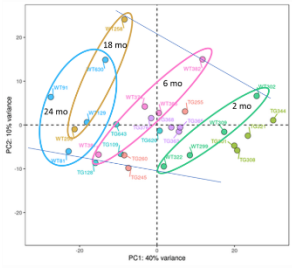
Bone, aging, extracellular vesicles, microRNAs, epigenetics, gene regulation

Valérie Geoffroy (DR2 Inserm)

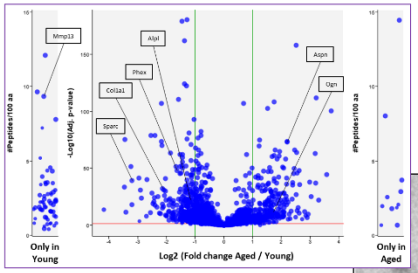
Program 1. Epigenetic and aging in osteoblasts

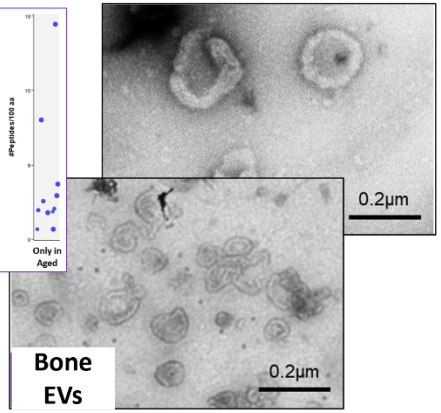




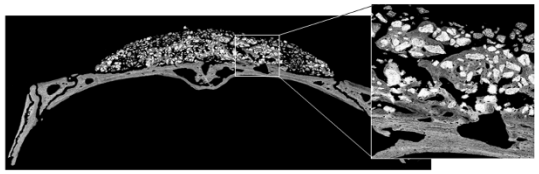


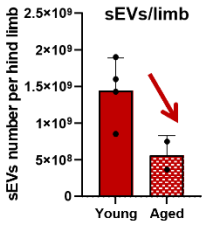
Program 2. Extracellular vesicles in bone aging





1/ Identify new actors of bone aging
2/ Develop new strategies for bone regeneration





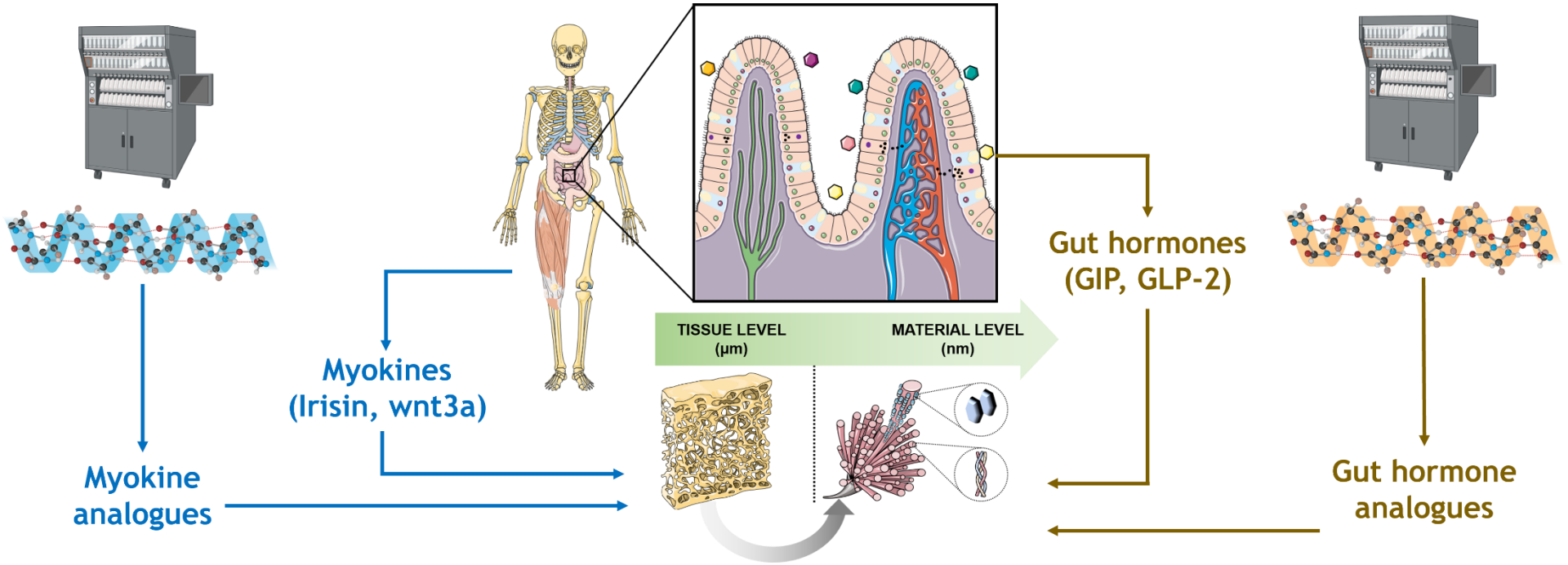
Jehan et al., Faseb bioAdv 2022
Tournier et al., Sci Rep 2021.

Subject 7: SMILE: Skeleton-Muscle-Intestine crosstaLk & innovative thErapeutics

Bone quality, bone fragility, myokines, gut hormones

Guillaume Mabilleau, (MCU-PH)

Program 1. To understand how myokines and gut hormones affect bone quality & regeneration
Program 2. To develop analogues that could be used for bone fragility & regeneration



Gobron et al., J Bone Miner Res 2023
Gobron et al., J Bone Miner Res 2020
Libouban et al., Calcif Tissue Int, 2018

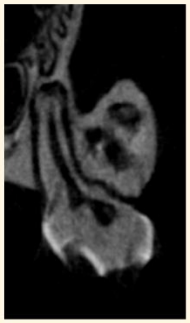
Subject 8: INFLAMED: Inflammatory mediators and microenvironment in bone and teeth

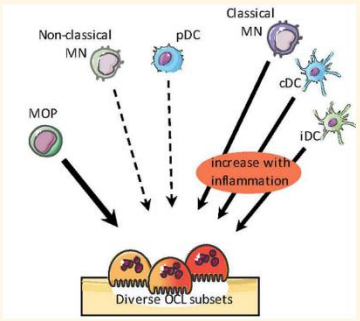
Drug delivery systems, Bone resorption, Inflammation

Alexis Gaudin (PU-PH)

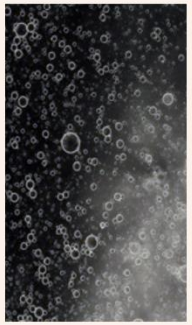
To <u>modulate inflammation</u> in order to promote basic understanding, tissue repair or regeneration in different clinical contexts

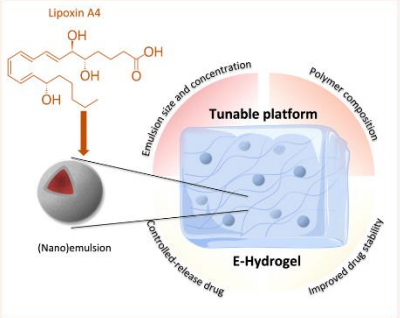
Program 1: Identification of therapeutic targets in alveolar bone resorption



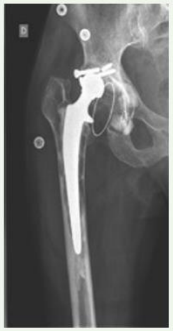


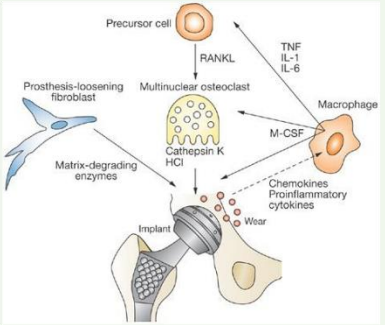
Program 2: Drug delivery systems and resolution of inflammation





Program 3: Bone resorption and implant loosening related to wear debris particles



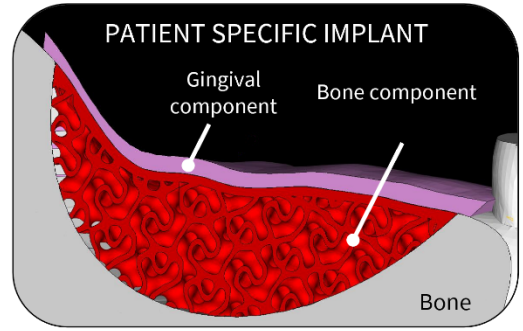


Aubeux et al., Mol Biol Rep 2023
Hascoët et al., Bone Res 2023
Nich et al., Int Orthop 2022

Subject 9: SAMBA: 4D Scaffolds for Atrophic Mandible Bone Augmentation

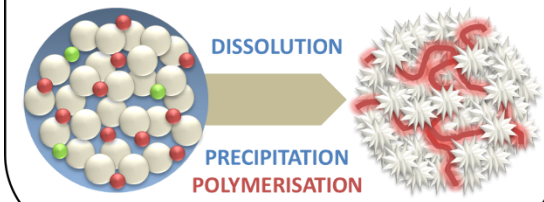
Dental implants, Osteogingival regeneration, Personalized medicine, Additive manufacturing

Baptiste Charbonnier (CRCN Inserm)



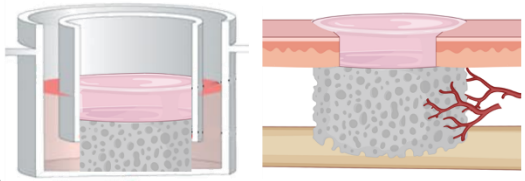
Program 1: Design and of innovative printable biomaterials

- *Inorganic bone cements*
- *Hydrogels*
- *Hybrids/composites*

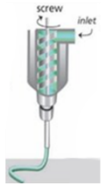


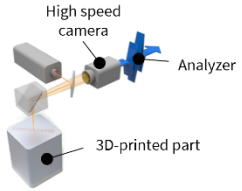
Program 2: *In vitro* & *in vivo* models of complex bone loss

- *Osteogingival*
- *Osteocutaneous*
- *…*



Program 3: Development of dedicated additive manufacturing technologies





- *Capacity/capability*
- *Live correction*
- *…*

Patent EP23305052.5 (2023)
Paré et al., Acta Biomat. 2022
Moussi et al., Material Advances 2022