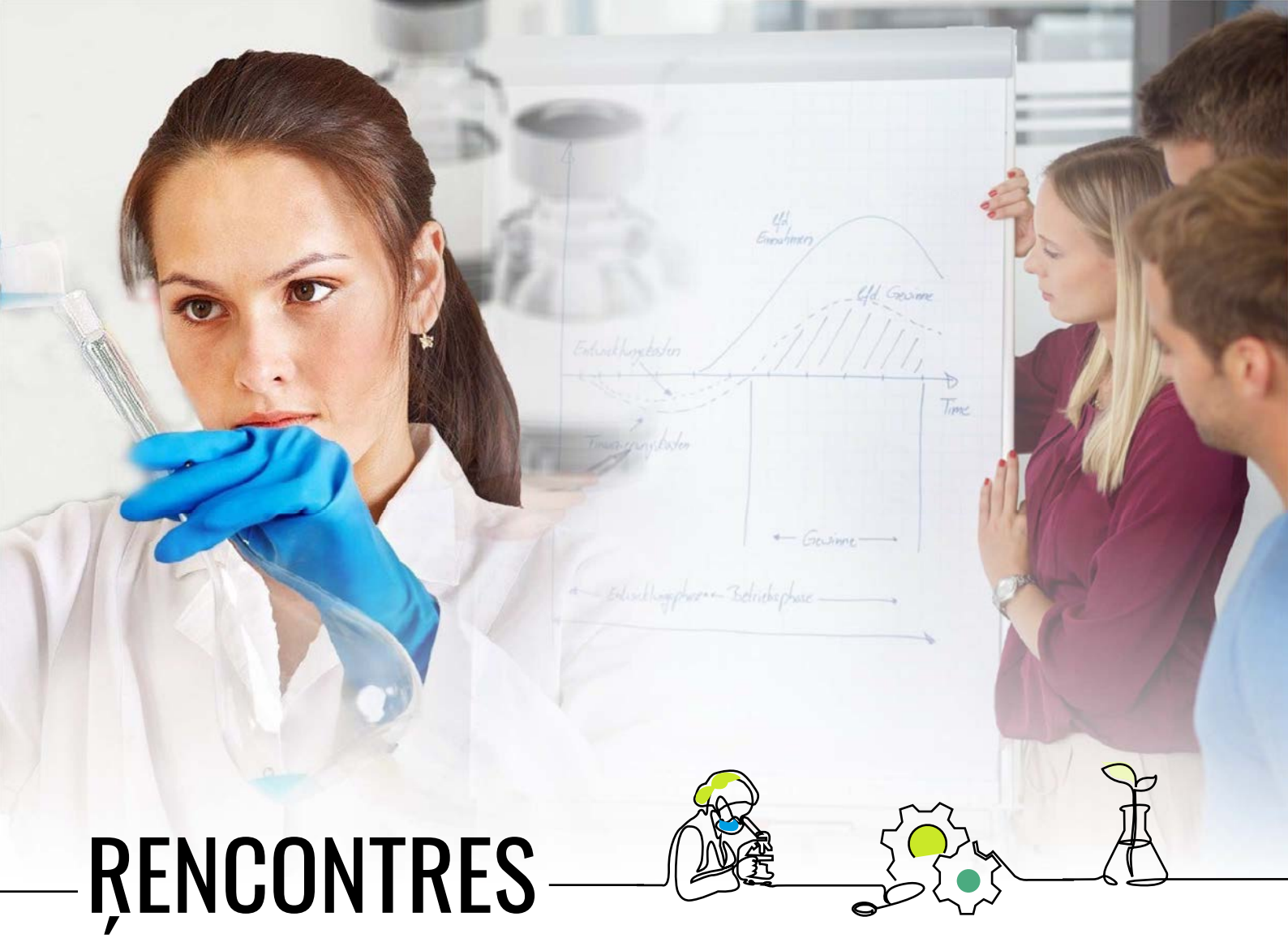


RENCONTRES ÉTUDIANTS - CHERCHEURS

Stages Master 2 pour des projets interdisciplinaires :

BIOMARKERS & THERAPY - DATA & LIFE SCIENCES - FOOD & HEALTH

LIVRET DES ABSTRACTS

30 SEPTEMBRE 2021 | 9H00-12H30

9h00 à 11h00 : présentations en direct sur le site de la faculté de médecine
11h00 : speed-dating (fac de médecine de Montpellier : hall UPM & salle du 4ème étage)

MUSE
MONTPELLIER UNIVERSITÉ D'EXCELLENCE

AVEC LE SOUTIEN DE :
KIM « Biomarkers & Therapy » | KIM «Data & Life Sciences» | KIM «Food & Health»
LabMUSE EpiGenMed | LabMUSE Chimie | LabEx Agro | LabEx NUMEV | CoEN
Pôle de recherche Biologie-Santé | SIRIC Montpellier Cancer | SATT AxLR

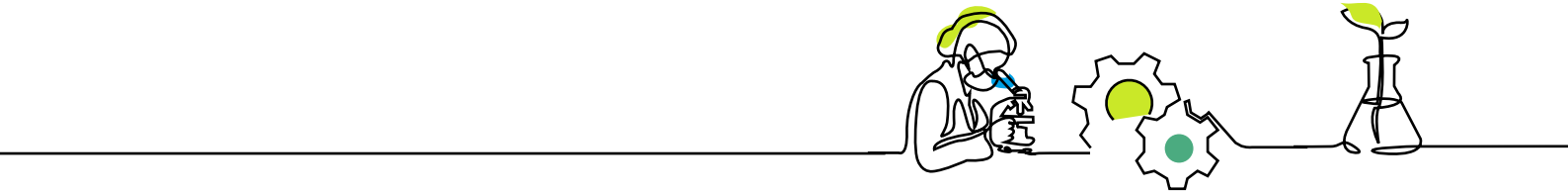
PROGRAMME DE LA MATINÉE

8h45	**Accueil des participants**
9h00-9h10	**Ouverture de la matinée** Michel Mondain, Doyen de la Faculté de Médecine de Montpellier François Pierrot, Directeur exécutif de l'I-SITE Montpellier Université d'Excellence
9h10-9h40	**Présentation des Pôles de recherche** par leurs Directeurs • MIPS (Mathématiques, Informatique, Physique, Systèmes) : Lionel Torres • Biologie-Santé : Pierre-Emmanuel Milhiet • Sciences Sociales : Marie-Christine Sordino • Chimie : Philippe Miele • A.E.B (Agriculture, Environnement, Biodiversité) : Daniel Barthélemy
9h40-9h55	**Présentation des Key Initiative MUSE** par leurs Directeurs • Biomarkers & Therapy : John De Vos • Data & Life Sciences : Jean-Michel Marin • Food & Health : Marie-Josephe Amiot-Carlin
9h55-10h00	**Présentation du Collège Doctoral,** par son Directeur Gilles Subra
10h00-11h00	**Présentation des Écoles Doctorales** par leurs Directeurs • CBS2 (Sciences Chimiques et Biologiques pour la Santé) : Sofia Kossida • SCB (Sciences Chimiques Balard) : Jean-Jacques Vasseur • I2S (Information, Structures et Systèmes) : Pascale Nouet • SMH (Sciences du Mouvement Humain) : Stéphane Perrey • GAIA : Valérie Micard **Témoignage de 5 étudiants ayant suivi un cursus interdisciplinaire**, en alternance avec les présentations des Écoles Doctorales
11h00 - 12h30	**SPEED-DATING ÉTUDIANTS - CHERCHEURS AUTOUR DE POSTERS**

* AAP «Bourses de Master» clôturé le 2 juillet 2021

ABSTRACTS DES PROJETS LAURÉATS

KIM BIOMARKERS & THERAPY



1 ROLE OF MACROPHAGES AND MICROGLIA IN ACQUIRED HEARING LOSS – MAC COCHLEA

Sensorineural hearing loss occurs when a significant number of sensorineural cells (hair cells and auditory neurons) of the cochlea (part of the inner ear dedicated to hearing) is damaged Tissue resident macrophages and microglial cells CX3CR1+ (TRM) are directly targeted after cochlear damage. Indeed, the damaged cochlea might contain several macrophage subpopulations with different origins and functions since TRM might be lost and progressively replaced by infiltrating monocyte-derived macrophages (MDM). In the present project, we hypothesize that CX3CR1+ TRM play a pivotal role in cochlea homeostasis and that they might be progressively replaced by infiltrating pro-inflammatory MDM causing the progressive loss of hair cells and cochlear neurons. The main objective of MAC-COHLEA is to define the MDM recruitment kinetic impairing the maintenance of TRM number and to identify the mechanisms responsible for MDM recruitment to the injured cochlea.

ÉQUIPES

ÉQUIPE

Encadrant : Frederic VENAIL (CHU de Montpellier & Institute for Neurosciences of Montpellier INSERM U1298)

Encadrant : Farida DJOUAD (IRMB Institute for Regenerative Medicine and Biotherapy INSERM U1183)

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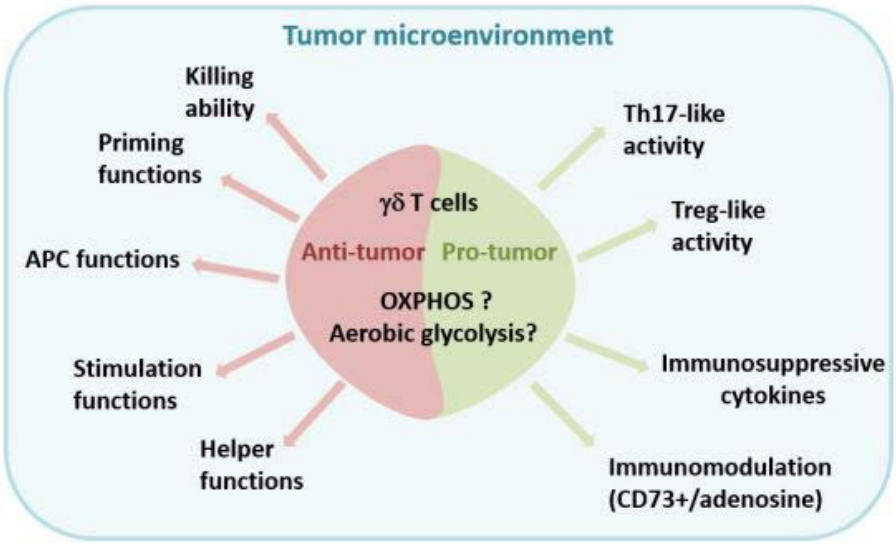
ÉQUIPE

Encadrant : Virginie Lafont (IRCM : Institut de Recherche en Cancérologie de Montpellier)

Encadrant : Michel Fabbro (ICM : Institut du Cancer de Montpellier)

2 METABOLIC ANALYSIS OF EFFECTOR AND REGULATORY γδ T CELL POPULATIONS AND IMPACT ON ANTI-TUMOR IMMUNE RESPONSE

γδ T cells participate to the immune response against many tumors through their direct cytotoxic activity against cancer cells and their capacity to regulate the biological functions of other immune cells. Nevertheless, their presence in the tumor microenvironment has also been associated with poor prognosis suggesting that γδ T cells may also display pro-tumoral activities. Accordingly, we recently described that γδ T cell subsets expressing CD73 display regulatory functions through the production of immunosuppressive molecules, such as IL-10, adenosine and the chemotactic factor IL-8. In parallel, we showed that in human breast and ovarian tumors that ~20% of tumor-infiltrating γδ T cells expressed CD73 and displayed suppressive functions. The project will aim at providing the characterization and comparison of metabolic programs used by CD73- (effector) and CD73+ (regulatory) γδ T cell subsets with the final goal to identify mechanisms able to boost the anti-tumor immune response.



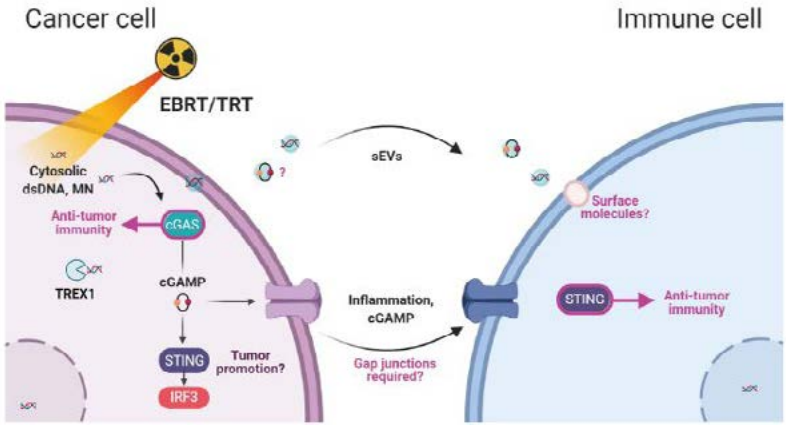
3 ANTITUMOR IMMUNE RESPONSE AND CYTOTOXICITY CHARACTERIZATION OF SMALL EXTRACELLULAR VESICLES RELEASED BY IRRADIATED TUMORS IN PATIENTS

Context. To date, 50% of cancers are treated with radiotherapy worldwide. While it has been for long considered that only irradiated cells would die, it is now clear that cell-to-cell communication play a central role in radiation response and lead to death of cells located at distance from the irradiated cells. Short distance communications (called *bystander* effects) involve the release of soluble factors, such as small extracellular vesicles (sEVs) by irradiated cells or transfer of signals molecules via gap junctions[1]. Long distance communications (called *abscopal* or systemic effects) involve activation of an immune response[2].

sEVs have an endocytic origin and are formed by invagination of the multivesicular body membrane before being released by the fusion of the latter with the plasma membrane[3,4]. Structurally, sEVs have a phospholipid bilayer containing surface and transmembrane proteins, and they can enclose proteins and nucleic acids mostly RNA species such as small RNAs, as well as DNA from genomic or mitochondrial origin. In addition, one of the major pathways that mediate the immune response to DNA is governed by the enzyme cGAS. cGAS is activated upon binding to double-stranded DNA (dsDNA), which will lead to the activation of the stimulator of interferon genes (STING) pathway, inducing an immune response and tumor clearance in preclinical models[5]. Therefore, dsDNA-containing sEVs may prime antitumor immunity.

We therefore focused on sEVs as a second messenger released by cancer cells that may activate an antitumor immune response through the STING pathway. One our recent study[6] showed that sEVs were released by tumor cells exposed to targeted radionuclide therapy (TRT). Then, we demonstrated that these sEVs released by cells exposed to TRT were cytotoxic for recipient cells *in vitro* and were delaying tumor growth *in vivo* after their intra-tumoral injection (6). In addition, this project will benefit from the ICM Biobank BCBRIV set up by Dr. E. Deshayes, which collects patients' blood samples before, during and after TRT within a prospective registrated clinical trial (NCT04104529).

Objectives. These 6 months of training will offer the candidate to characterize the therapeutic potential of sEVs released into patients' blood following TRT, mainly in inducing an antitumor immunity. Cytotoxic, genotoxic and immunostimulatory properties of patients' sEVs will be determined *in vitro*.



Summary of cancer-immune cell interactions after irradiation (EBRT: external beam radiation therapy; TRT: Targeted Radiotherapy) and the involvement of double-stranded DNA (dsDNA), micronuclei (MN), small extracellular vesicles (sEVs) and cyclic GMP–AMP (cGAMP) in bystander immunity. From Constanzo et al., Front Immunol, 2021.

1 Pouget & Constanzo, Front. Med (2021). doi: 10.3389/fmed.2021.692436.
2 Pouget et al., Nat Rev Clin Oncol (2011). doi:10.1038/nrclinonc.2011.160
3 Malloci et al., Antiox& Redox Signaling (2019). doi:10.1089/ars.2017.7265
4 Théry et al., Journal of Extracellular Vesicles (2018). doi:10.1080/20013078.2018.1535750
5 Constanzo et al., Front Immunol. (2021). doi:10.3389/fimmu.2021.680503
6 Karam, Constanzo et al., Int. J. Rad. Biol. (2021), doi: 10.1080/09553002.2021.1955999

ÉQUIPES

ÉQUIPE

Encadrant : Julie Costanzo (IRCM : Institut de Recherche en Cancérologie de Montpellier)

Encadrant : Emmanuel Deshayes (ICM : Institut du Cancer de Montpellier)

4 MICROBIOTA-DERIVED BIOMARKERS FOR ALZHEIMER'S DISEASE

Changes in the composition of the gut microbiota (GM) have recently emerged as being involved in neurodegenerative diseases, such as Alzheimer's disease (AD), suggesting new therapeutic avenues based on GM-modulation. In partnership between the technology transfer office of the Pasteur Institute, the Institute of Functional Genomics (IGF) and the Memory Research and Resource Center (CMRR) of the University Hospital of Montpellier, this internship will aim to achieve human GM transfer to mice to understand the therapeutic potential of the GM against age-associated memory decline and AD. The project will mobilize manipulations of human samples, behavioral experiments in rodents and the evaluation of neuropathology (amyloid quantification, neuroinflammation).

ÉQUIPES

ÉQUIPE

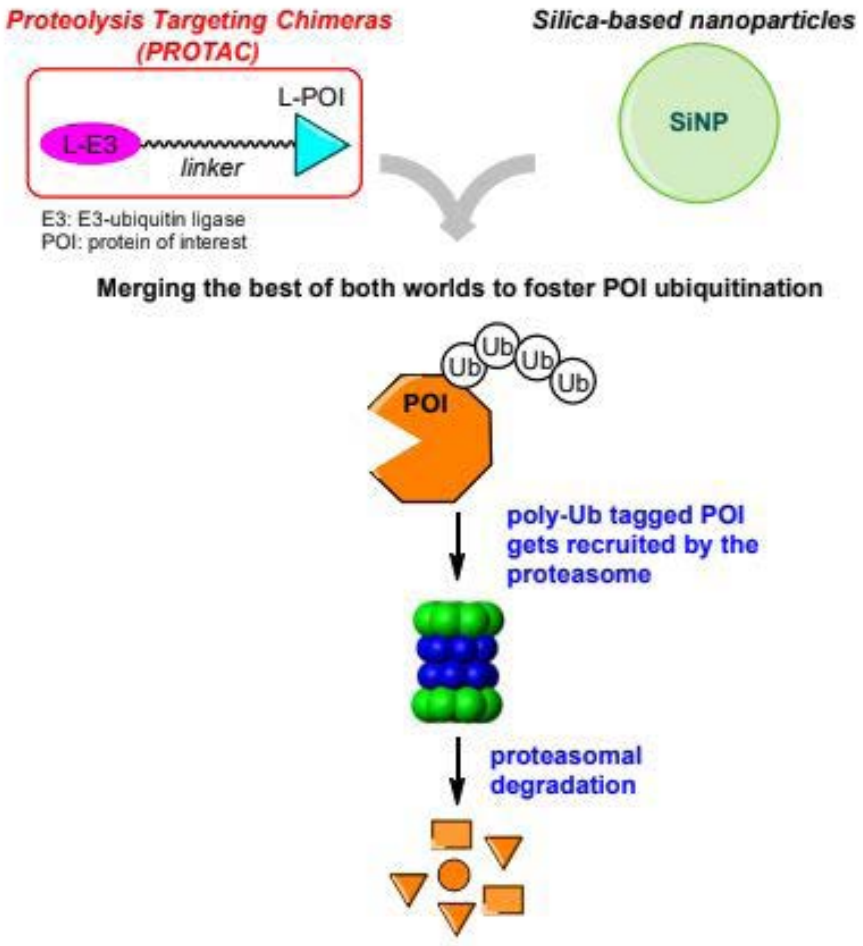
Encadrant : Sylvie Claeysen (IGF : Institut de Génomique Fonctionnelle)

Encadrant : Damien Rei (Institut Pasteur)

Encadrant : Audrey Gabelle (CHU de Montpellier)

5 HARNESSING THE UBIQUITIN/PROTEASOME MACHINERY TO DEGRADE ONCOPROTEINS USING NANOSCOPIC PROTACS

PROTACs are heterodimeric compounds displaying two ligands connected through a linker. One is a ligand for a protein of interest (POI) that is to be degraded, and the other one for an ubiquitin-E3 ligase (Ub-E3). PROTACs enable the hijacking of the ubiquitin-proteasome system to degrade a protein involved in a pathological process. To be fully functional, it must allow the recruitment of POIs and Ub-E3 in a finely controlled spatial arrangement. Therefore, the design and development of PROTACs can be tedious. Our project aims at solving this bottleneck by merging the PROTAC technology with the advantages of nanoscopic objects.



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Encadrant : Jean-Marc Pascussi (IGF : Institut de Génomique Fonctionnelle)

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ÉQUIPE

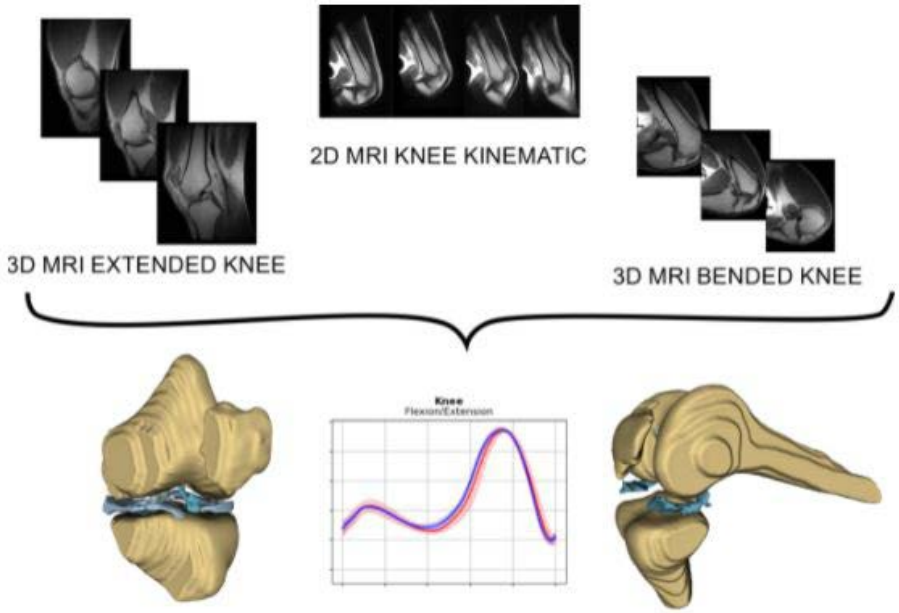
Encadrant : Gilles Dusfour (CARTIGEN)

Encadrant : Simon Le Floc'h (LMGC : Laboratoire de Mécanique et Génie Civil)

Encadrant : Christian Jorgensen (IRMB : Institute for Regenerative Medicine and Biotherapy)

6 IDENTIFICATION OF THE RELATIVE *IN VIVO* KNEE KINEMATICS *VIA* AN OPEN MRI

The main objective of the study proposed in the framework of the master's degree is to develop an experimental and numerical method to describe the *in vivo* kinematic parameters of the knee in healthy subjects. The G-Scan MRI device from ESAOTE, integrated into the CARTIGEN platform and operated by the engineer Dr. G. Dusfour, enables dynamic 2D and 3D MRI images to be taken under patient load. The image analysis method should allow the evaluation of the relative *in vivo* kinematics (rotation and translation) of the tibia, femur and patella during a simple flexion movement. Further development of the method will also be considered and should allow the relative mobility of the menisci and the anterior and posterior cruciate ligaments to be assessed. All the different bodies of the joint (tibia, femur, patella, menisci and ligaments) will be modelled initially as non-deformable bodies. In the long term, the methodology developed should make it possible to evaluate the impact of knee orthoses on the kinematics and mechanical loading of the knee.



7 TISSUE ENGINEERING BY 3D PRINTING FOR SUSTAINABLE TREATMENT OF OSTEOCLASTOMA

This transdisciplinary and translational project aims at the development and characterization of new biodegradable biomimetic multifunctional implants for the treatment of osteoclastoma, allowing both bone regeneration and inhibition of cancer cell proliferation in order to prevent local recurrences through the controlled release of active ingredients/medications adapted to the targeted pathology. In this project, we are particularly interested in scaffolds based on polylactic acid biopolymers. The scaffold will be 3D printed in order to adapt to the bone defect and location. The biomaterials will be loaded with bisphosphonates (Alendronate) and with 2D materials (Graphene oxide (GO) and Boron Nitride), which altogether will improve the mechanical properties of the biodegradable implants, stimulate bone formation and inhibit the proliferation of cancer cells. This project will include validation from in vitro studies in regards to the local toxicity of drugs, antitumor and bone healing efficacies. The development of a 3D bioresorbable scaffold, with optimized biological properties, would provide a «best in class» therapeutic solution for orthopedic and oncologist surgeons (Figure 1).

Figure 1. Schematic representation of scaffold implantation as a therapeutic solution for osteoclastoma

ÉQUIPES

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Encadrant : Mikhael Bechelany (IEM : Institut Européen des Membranes)

Encadrant : Louis Dagneaux (CHU de Montpellier)

Encadrant : Vincent Cavailles (IRCM : Institut de Recherche en Cancérologie de Montpellier)

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Encadrant : Pierre-Antoine Bonnet (IBMM : Institut des Biomolécules Max Mousseron)

Encadrant : Christel Larbouret (IRCM : Institut de Recherche en Cancérologie)

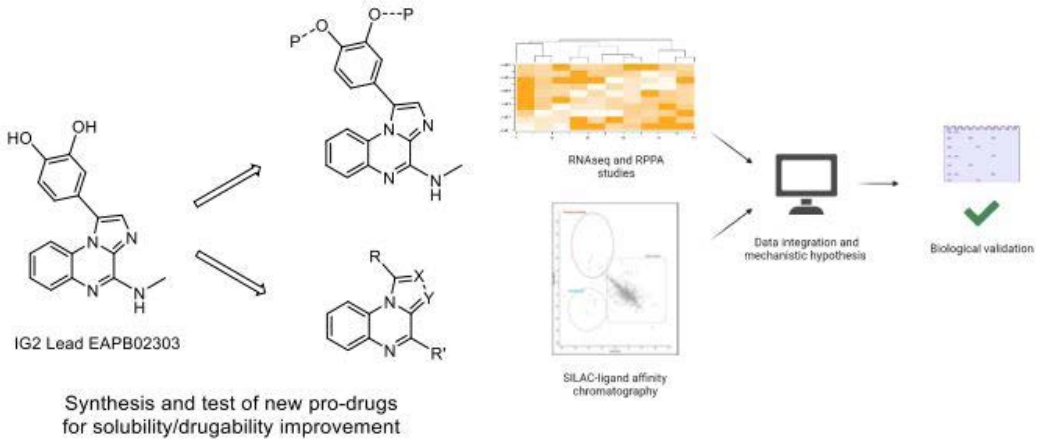
Encadrant : Cindy Patinote

Encadrant : Carine Masquefa

Encadrant : Kevin Bigot

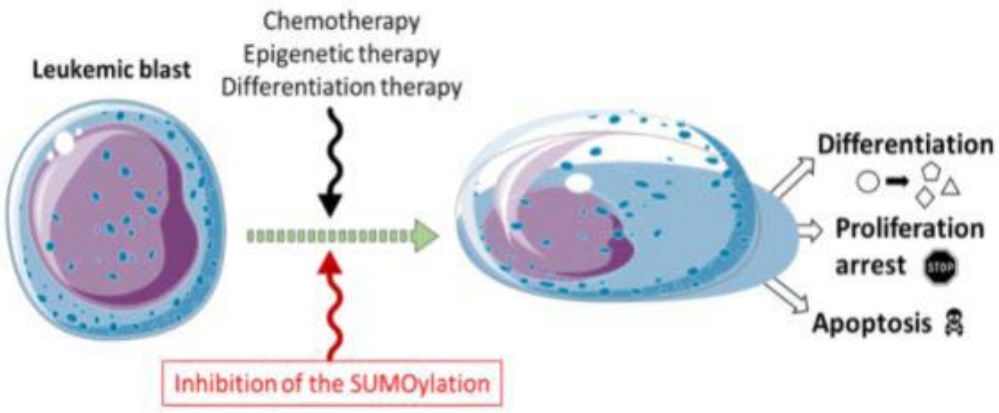
8 INNOVATION IN CHEMISTRY FOR PANCREAS CANCER PRECISION THERAPY: ONCOMEDCHEM & CHEMICAL BIOLOGY

The master program is based on two complementary approaches of Medicinal Chemistry and Chemical Biology, specifically designed for the development of innovative highly potent small heterocyclic IG2/3 molecules for Pancreas Cancer biotherapy:
1. A lead-based MedChem approach starting from our IBMM lead EAPB02303 for the development of new pro-drugs and drugs.
2. Western Blot validation experiments to confirm results from the mechanism of action (MoA) study based on data from SILAC-ligand affinity chromatography studies, RNA-seq and reverse phase protein analysis (RPPA) set of data already obtained from pancreas cell lines. The validation study will define and precise the specific signaling pathways involved in the unique nanomolar activity of our lead. Work will be performed in both IBMM recent facilities on MUSE UM CNRS campus and IRCM.



9 SUMOYLATION INHIBITORS AS INNOVATIVE TREATMENT AGAINST ACUTE MYELOID LEUKEMIA

SUMOylation, a post-translational modification of intracellular and particularly nuclear proteins, plays a critical role in the response of Acute Myeloid Leukemia (AML) to chemotherapies and differentiation therapies. AMLs are the only hematologic malignancies that have not benefited from a major therapeutic advance during the past 40 years. They are still treated via intensive treatments based on genotoxic agents, with very high fall rates and a poor 5-year survival rate of around 20%. To fill the urgent need for alternative therapies against AML, we are developing new classes of SUMOylation inhibitors using cutting-edge technologies. The Master 2 student that will be recruited on this multidisciplinary project will be in charge of the design and synthesis of peptide inhibitors at the Institut des Biomolécules Max Mousseron (IBMM) and will then evaluate their toxicity, ability to inhibit the SUMOylation and anti-leukemic efficiency at the "Institut de Génétique Moléculaire de Montpellier" (IGMM).



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Encadrant : Olivier Coux (IGMM : Institut de Génétique Moléculaire de Montpellier)

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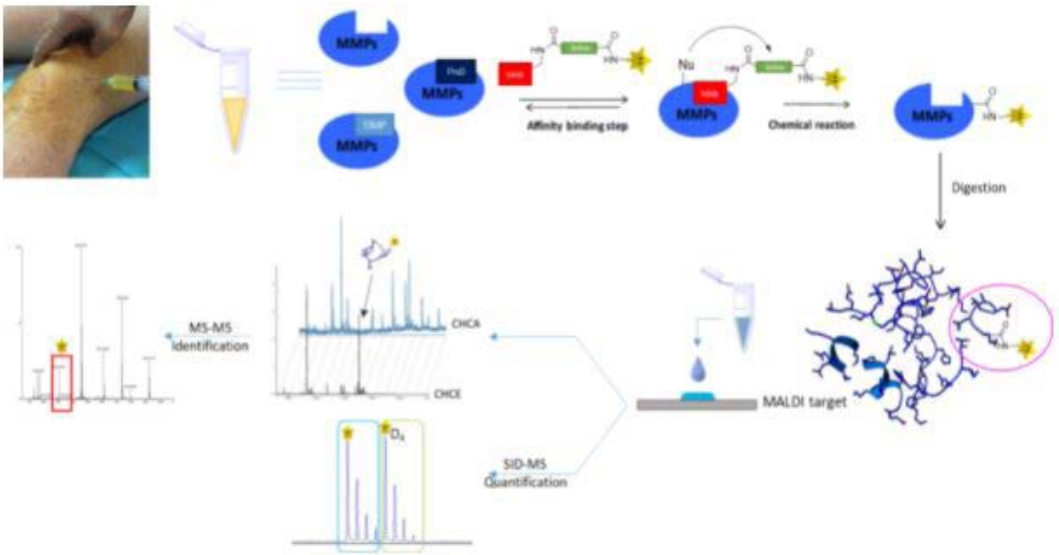
Encadrant : Sonia Cantel (IBMM : Institut des Biomolécules Max Mousseron)

Encadrant : Gilles Subra (IBMM : Institut des Biomélucles Max Mousseron)

Encadrant : Danièle Noël (IRMB : Institut de Médecine Régénératrice et Biothérapies)

10 DEVELOPMENT OF NOVEL MOLECULAR TARGETED PROBES FOR PROFILING METALLOPROTEASES ACTIVITIES BY MALDI-MASS SPECTROMETRY IN SYNOVIAL FLUID

Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people worldwide. Detection of MMP activity in biological samples provides important information for diagnosis, prognosis, and therapeutic monitoring of these diseases.
Thanks to dedicated engineered biomolecular constructions based on[1] very affine ligands of MMPs,[2] a reactive spacer and[3] MS probes, we are able to transfer these activity based probes (ABP) on active MMPs, in the idea of identifying them by mass spectrometry (MS). The objective is here to show the presence of specific active MMPs and quantify them in healthy synovial fluid or issued from osteoarthritis/ arthritis suffering patients. By varying designed probes and assisted by MALDI Mass spectrometry detection, we could hope to operate a multiplexing detection on several MMPs and define signature for each active MMP present in the synovial fluid via the generation of a specific fragment, thus allowing easier identification/activity/involvement of MMPs in such pathologies.



1 Simin L, Qiping S, Junyuan C, Huajun W, Wenrui W, Zhengang Z, Expression and Significance of MMPs in Synovial Fluid, Serum and PBMC Culture Supernatant Stimulated by LPS in Osteoarthritis Patients With or Without Diabetes, Exp Clin Endocrinol Diabetes 2019 ; 127: 195–202

2 a) D. Paramelle, G. Subra, L. L. Vezenkov, M. Maynadier, C. Andre, C. Enjalbal, M. Calmes, M. Garcia, J. Martinez, M. Amblard, Angew. Chem. Int. Ed., 2010, 49, 8240–8243. b) M. Rossato, G. Miralles, C. M'Kadmi, D. Gagne, M. Maingot, M. Amblard, B. Mouillac, J. Martinez, G. Subra*, C. Enjalbal and S. Cantel*, "Quantitative MALDI-MS Binding Assays: an Alternative to Radiolabeling", ChemMedChem, 2016, 11 (23), 2582-2587.

3 L.Devel, M. Kaminska, P. Bruyat et al., "Ligand-directed modification of active Matrix Metalloproteases: New activity-based probes with no photolabile group" Angew. Chem. Int. Ed., 2021, doi.org/10.1002/anie.202106117.

11 MECHANISMS OF LIVER REGENERATION IN A RAT MODEL OF LIVER VEINOUS DEPRIVATION TECHNIQUE AND ROLE OF HYPOXIA

Surgery is the curative therapy for liver cancer but liver failure can occur and lead to death when the remnant liver is insufficient. To avoid this phenomenon, a pre-operative portal vein embolization is realized to make the liver grow before surgery. It takes up to 6 weeks. A novel technique of Liver deprivation (LP) is a portal and sus-hepatic vein embolization in one procedure. It permits a double time liver growth in only 3 weeks. It's a new model of liver regeneration whose mechanisms are not yet solved. The aim of the study is to investigate, in a rat model, the role of hypoxia in the liver regeneration on the both techniques. Hypoxia will be assessed by combining: Fluoromisonidazole - PET TDM (imagery), immunofluorescence (histology), and analysis of Hypoxia inductible factors (HIF1α, HIF2 α) and target genes (VEGF, NOS, Glut.) expression (Q-PCR, Western blot, IHC) at different time after procedure. The impact on the immune cell populations in the liver, spleen and blood will be analyzed.

ÉQUIPES

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Encadrant : Martine Daujat. U1183/Institute for regenerative medicine and biotherapy IRMB, Montpellier

Encadrants : A.Herrero & L. Sommier (CHU de Montpellier)

Encadrant : E. Deshayes (IRCM : Institut de Recherche en Cancérologie de Montpellier)

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ÉQUIPE

Encadrant : Guillaume Bossis
(IGMM : Institut de Génétique Moléculaire de Montpellier)

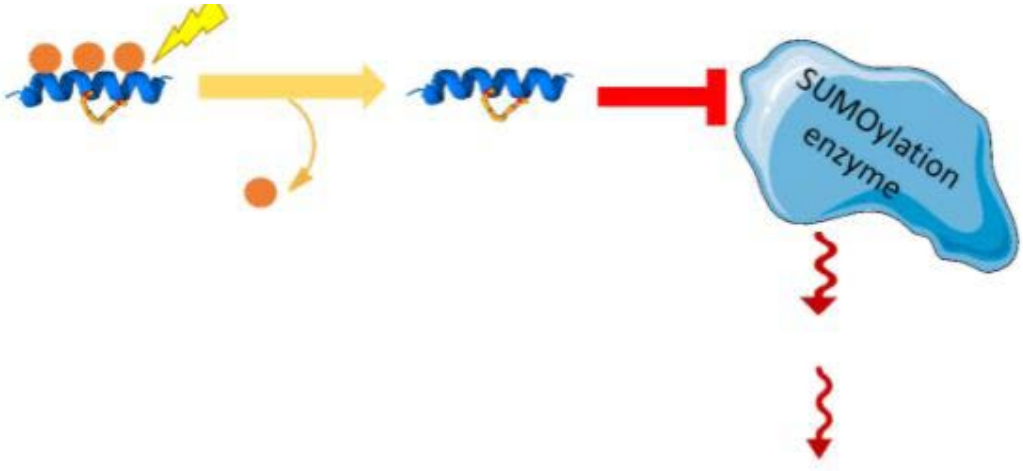
Encadrant : Muriel Amblard
(IBMM : Institut des Biomolécules Max Mousseron)

12 PHOTOACTIVABLE PEPTIDES FOR A TARGETED INHIBITION OF SUMOYLATION IN CANCER CELLS

SUMOylation is a post-translational modification, which consists in the covalent conjugation of the small protein SUMO to lysine-side chains of proteins. SUMOylation has been involved in the regulation of most cellular processes. Because of its pleiotropic roles, SUMOylation is emerging as a promising target for the treatment of cancers. In particular, G. Bossis's team (IGMM) has shown that SUMOylation plays a critical role in Acute Myeloid Leukemias (AML) response to therapies (chemotherapies, differentiation therapies and epigenetic therapies). However, the study of SUMOylation is hampered by the lack of tools to modulate its conjugation to target proteins. To fill this gap, we are, together with M. Amblard's team (IBMM), developing a new kind of SUMOylation inhibitors.

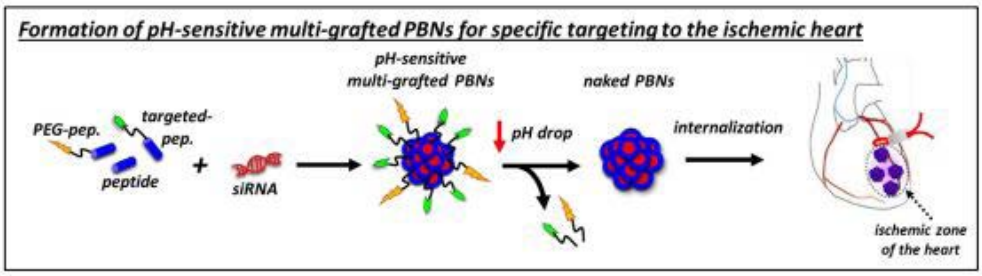
As SUMOylation is highly dynamic and plays critical roles in numerous cellular processes, a general inhibition of SUMOylation can have pleiotropic effects and have deleterious consequences on normal cells. Finding ways to inhibit SUMOylation in a controlled manner would thus be highly valuable both to study the function of SUMOylation and for therapeutic intervention to limit potential side effects. On the basis of peptide-based SUMOylation inhibitors we already identified, we therefore propose to develop photoinducible inhibitors of SUMOylation.

The student recruited on this interdisciplinary project will be trained for peptide synthesis and incorporation of the photo-caged amino-acids at the IBMM and will test the activity of the photo-inducible peptides in cancer cells, in particular AMLs, at the IGMM.



13 SYNTHESIS OF MULTI-GRAFTED NANOPARTICLES FOR SIRNA TRANSFECTION AS A NOVEL TREATMENT FOR MYOCARDIAL INFARCTION

The objective of the M2 project is to develop peptide-based nanoparticles (WRAP5)[1] encapsulating a small interfering RNA (siRNA-FADD) to specifically reduce the expression of FADD in the infarcted myocardium. In an innovative way, PEG entities and targeting peptides will be grafted onto the nanoparticles to prolong their half-life in the bloodstream and allow myocardial addressing, all forming multi-grafted nanoparticles. In order to release the siRNA at the site of infarct injury (acidic extracellular pH during ischemia), a pH-sensitive acylhydrazone binding[2] will be introduced between the grafts and the nanoparticles. The recruited M2 student will participate in the following tasks:
Task 1: synthesize the different modified peptides
Task 2: characterize multi-grafted siRNA-loaded nanoparticles by biophysical methods (e.g. DLS)
Task 3: evaluate the internalization and release of the cargo in cellulo
The project will be conducted in collaboration between chemical (IBMM) and biological (PhyMedExp) teams.



1 a) Peptide-Based Nanoparticles to Rapidly and Efficiently «Wrap 'n Roll» siRNA into Cells, K. Konate, M. Dussot, G. Aldrian, A. Vaissiere, V. Viguier, I. F. Neira, F. Couillaud, E. Vives, P. Boisguerin, S. Deshayes, Bioconj. Chem., 2019, 30, 592; b) Deciphering the internalization mechanism of WRAP:siRNA nanoparticles, S. Deshayes, K. Konate, M. Dussot, B. Chavey, A. Vaissiere, T. N. N. Van, G. Aldrian, K. Padari, M. Pooga, E. Vives, P. Boisguerin, Biochim. Biophys. Acta Biomembr., 2020, 1862, 183252; c) In Vivo Follow-Up of Gene Inhibition in Solid Tumors Using Peptide-Based Nanoparticles for siRNA Delivery, I. Ferreiro, C. Genevois, K. Konate, E. Vives, P. Boisguerin, S. Deshayes, F. Couillaud, Pharmaceutics, 2021, 13;

2 a) Dynamic covalent polymers for biomedical applications, Y. Zhang, Y. Qi, S. Ulrich, M. Barboiu, O. Ramström, Mater. Chem. Front., 2020, 4, 489; b) Cationic Dynamic Covalent Polymers for Gene Transfection, D. Su, M. Coste, A. Diaconu, M. Barboiu, S. Ulrich, J. Mater. Chem. B, 2020, 8, 9385; c) Growing Prospects of Dynamic Covalent Chemistry in Delivery Applications, S. Ulrich, Acc. Chem. Res., 2019, 52, 510; d) Biomolecular dynamic covalent polymers for DNA complexation and siRNA delivery, C. Bouillon, Y. Bessin, F. Poncet, M. Gary-Bobo, P. Dumy, M. Barboiu, N. Bettache, S. Ulrich, J. Mater. Chem. B, 2018, 6, 7239; e) Degradable hybrid materials based on cationic acylhydrazone dynamic covalent polymers promote DNA complexation through multivalent interactions, C. Bouillon, D. Paolantoni, J. C. Rote, Y. Bessin, L. W. Peterson, P. Dumy, S. Ulrich, Chem. Eur. J., 2014, 20, 14705;

ÉQUIPES

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Encadrant : Prisca BOISGUERIN (PhyMedExp)

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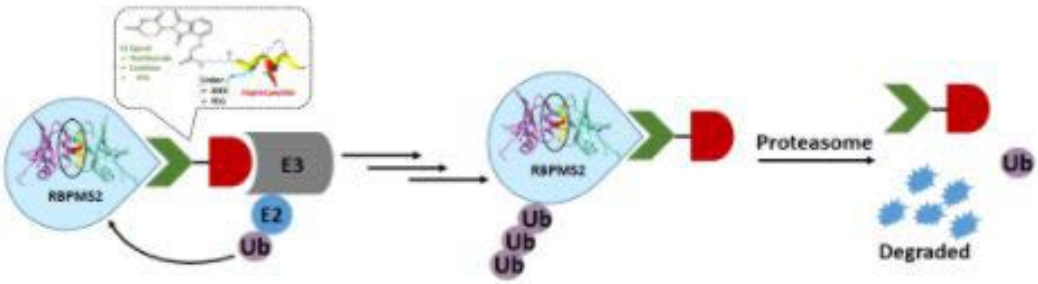
Encadrant : Stéphane Marchal (PhyMedExp)

Encadrant : Muriel Amblard (IBMM : Institut des Biomolécules Max Mousseron)

14

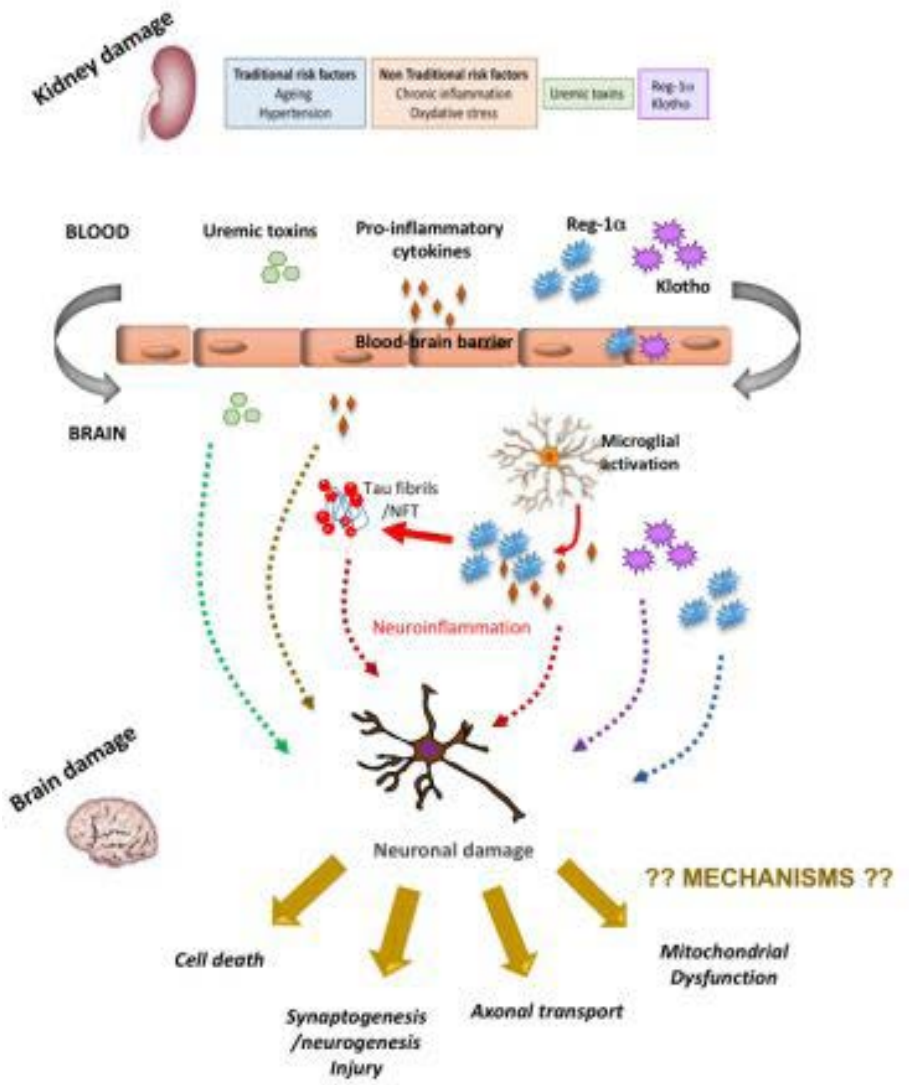
Digestive motility disorders are frequently encountered in pediatric and aging population. Studying the development and the physiological dedifferentiation (plasticity) of the gastrointestinal smooth muscle, our team demonstrated that the smooth muscle cell (SMC) plasticity process was unbalanced in Chronic Intestinal PseudoObstruction (CIPO) patients. We identified the function of the RNA-binding protein RBPMS2 in the plasticity of SMCs and a positive correlation between high level of RBPMS2 in CIPOs.



The objectives of the Master proposal aim to develop different Proteolysis-Targeting Chimeras (PROTACs) peptides from the RBPMS2 stapled peptides that have been identified by the consortium (PhyMedExp and IBMM) and to test the effectiveness of these molecules on the degradation of RBPMS2. This work paves to the development of specific inhibitory approach in the context of smooth muscle alterations and promising treatments for pediatric and adult CIPO patients.

15 CONSEQUENCES OF CHRONIC KIDNEY DISEASES (CKD) ON BRAIN DYSFUNCTION: IDENTIFICATION OF NEW BIOMARKERS LINKING CKD, NEURONAL INJURY AND NEURODEGENERATIVE DISEASES

Exploring modifiable risk factors and identifying new biomarkers are promising approaches for Alzheimer disease (AD) prevention and therapy. Among risk factors, chronic kidney disease (CKD) is a serious but still little studied candidate. The reported prevalence of moderate to severe CKD varies between 6 and 12 % and individuals at all stages of CKD have a higher risk of developing neur degenerative diseases (NDD). Moreover, kidney failure has been shown to increase the severity of cognitive impairment in AD. So, in this collaborative project between neurobiologists and nephrologists, we want to analyze the link between neurodegenerative processes and peripheral internal risk factors as renal impairment. We will use a multi-model strategy ranging from cellular and animal models to Human. The student will be responsible for determining the impact of peripheral factors induced by renal disease on neuronal function and analyzing the intracellular signaling pathways involved in neurodegenerative mechanisms on cell culture models.



ÉQUIPES

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Encadrant : Françoise Trousse (MMDN : Mécanismes Moléculaires dans les Démences)

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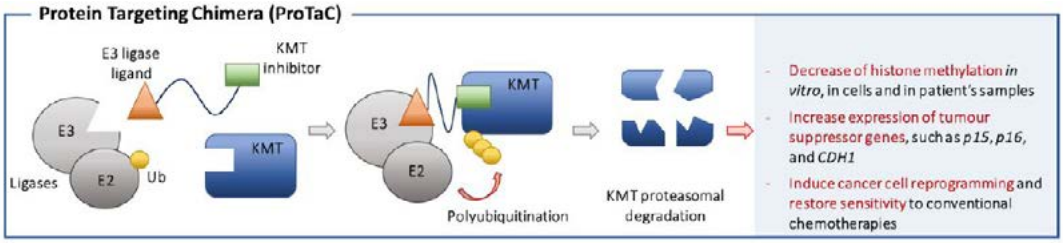
Encadrant : Eric Julien (IRCM : Institut de Recherche en Cancérogie de Montpellier)

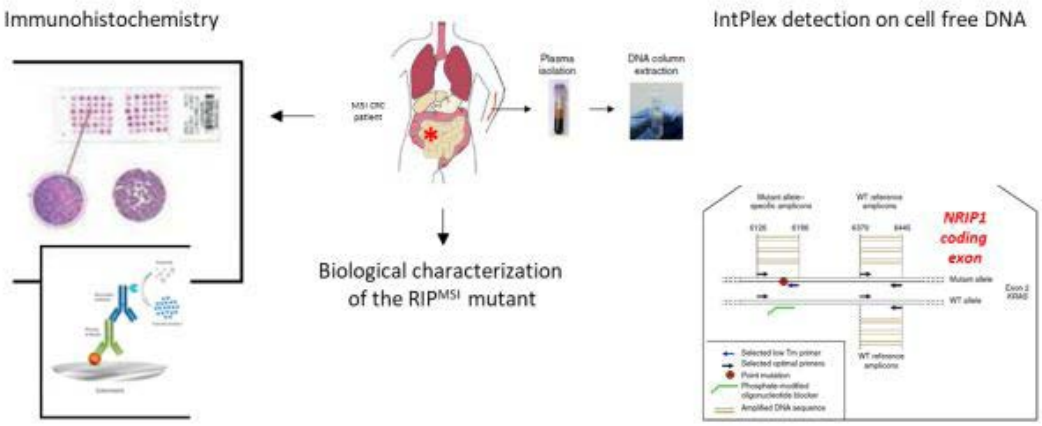
16 PROTAC STRATEGY APPLIED TO EPIGENETIC MECHANISMS IN CANCERS

Epigenetic modifications, including histone methylation, catalysed by lysine methyltransferases (KMTs), are involved in tumour formation and progression. However, despite the unquestionable role of KMT in cancers, only one KMT inhibitor (KMTi), targeting EZH2 (Tazemetostat), has to date been approved for anticancer treatments in 2020. This shows the urgent need to identify new strategies to target this epigenetic mechanism in cancer. The aim of this Master internship project is to apply the protein targeting chimers (PROTAC) strategy to target KMTs. This strategy consists in connecting a E3 ligase ligand and a KMTi to induce selective proteasomal degradation of KMT. We expect to restore a non-pathological histone methylation profile, rescue tumour suppressor gene expression in cancer cells and ultimately restore sensitivity of resistant cancer cell lines to conventional chemotherapies. This multi-disciplinary project involves organic synthesis as well as biochemical evaluation of the $PROTAC_{KMT}$.



17 DETECTION AND CHARACTERIZATION OF THE RIP140 MUTATION IN PATIENTS WITH MICROSATELLITE INSTABLE COLORECTAL CANCER

The RIP140 gene plays a key role in the transcriptional regulation of intestinal tumorigenesis. In colorectal cancer (CRC) with microsatellite instability (MSI), RIP140 increases the expression of the MMR genes and regulates the MSI and hypermutator phenotypes (Palassin et al., Cancers 2021). In MSI CRC, a truncative mutation of RIP140 (RIP^{MSI}) exerts a dominant negative effect and is associated with a significant decrease in the survival of patients. The RIP^{MSI} mutation thus represents a new potential prognosis/predictive marker for MSI CRC patients. The goal is now to further characterize the RIP^{MSI} mutant and develop new techniques to detect this mutant. We will use the Intplex technique on circulating cell-free DNA (cfDNA) from blood samples and immunohistochemistry on tissue sections with a specific anti-RIP^{MSI} antibody. We will compare the sensibility and specificity of these techniques and identify new RIP^{MSI} positive CRC patients to validate the correlation with survival.



ÉQUIPES

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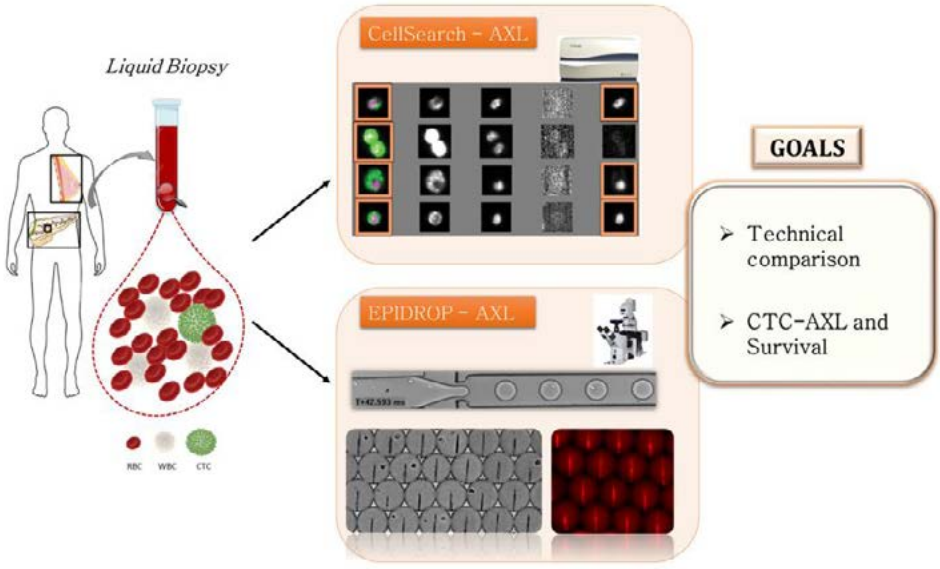
Encadrant : Jean-Michel Fabre (CHU de Montpellier)

18 DETECTION OF FUNCTIONAL AXL(+) CIRCULATING TUMOR CELLS USING THE INNOVATIVE EPIDROP IN BREAST AND PANCREATIC CANCERS

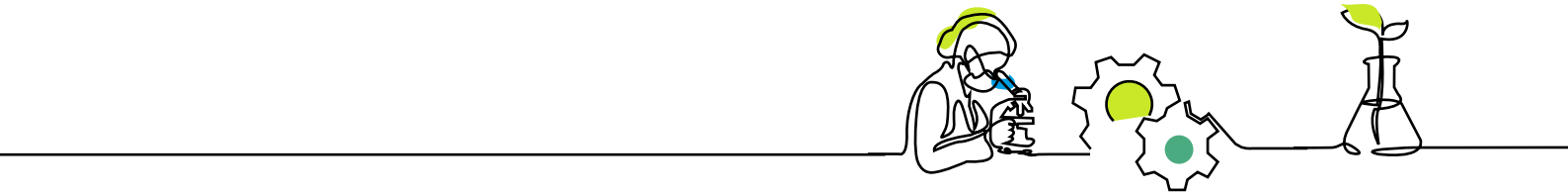
In solid cancers, more aggressive tumor cells, called CTCs, can detach from the primary tumor and migrate through the bloodstream to reach distant organs and form metastases. Detecting CTCs in the blood is relevant for evaluating tumor progression and also a promising biomarker for prognosis and therapeutic monitoring. These last years, the AXL protein became a target of growing interest, as its overexpression has frequently been identified in patients with pancreatic adenocarcinoma or breast cancer.

The LCCRH lab has developed two completely new 'CTC-AXL' tests: (i) a CTC-AXL test using the CellSearch® system and (ii) a functional CTC-AXL test using the innovative EPIDROP technique. The project we are proposing today corresponds to the clinical validation of the CTC-AXL tests with the recruitment of patients diagnosed with pancreatic cancer (n = 30) and metastatic breast cancer (n = 30) : we want to validate our promising results obtained on pancreatic and mammary cancer cell lines. Main objectives are to (1) compare the 2 techniques for CTC-AXL(+) detection, (2) evaluate the correlation between CTC-AXL levels and overall survival and (3) establish a liquid biopsy biobank (e.g., plasma for further analyses).



ABSTRACTS DES PROJETS LAURÉATS

KIM DATA & LIFE SCIENCES



1 DATA ENRICHMENT AND KNOWLEDGE EXTRACTION FROM GENE INFORMATION

A better understanding of gene-phenotype relationships requires an integration of biological information of various kinds. However, this information is often dispersed in several databases on the Internet, each with different means of access. The current challenges faced are related to the development of methods for the functional analysis of genes and in particular with methods for prioritizing candidate genes. Indeed, observations made on data integrated from databases show that they are insufficient to infer with certainty the function of genes. Moreover, we found that numerous database fields are in the form of unstructured text that may contain interesting functional information. Hence, in order to enrich the data, one of the first objectives will be the development of text mining methods to extract functional information about genes from these unstructured fields. Finally, we will exploit the information available in scientific publications in order to find gene information along with some functional evidence.

ÉQUIPES

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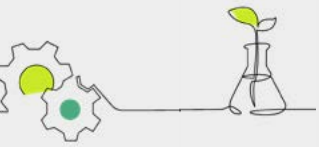

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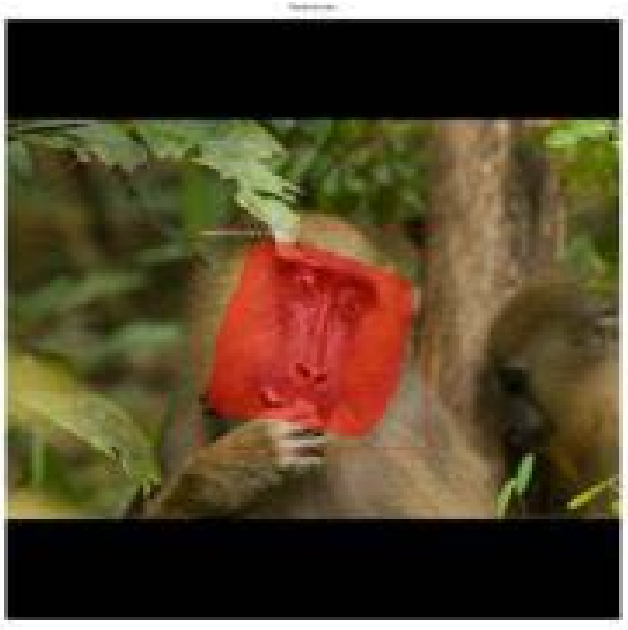
2 OPENING THE ACCESS TO THE MANDRILLUS FACE DATABASE

The Mandrillus Project (www.projetmandrillus.com) in south-eastern Gabon is a long-term research program studying the unique wild population of habituated mandrills (Mandrillus sphinx) worldwide. In 2019, as part of this project, we created the Mandrillus Face Database (MFD), which includes 30,000 portrait images representing 276 individuals. MFD is central to several ongoing research projects studying the importance of face perception in animal communication. Approximately 20,000 pictures of MFD have been manually cropped, centred, aligned and annotated, and approx. 2,000 new images are taken in the field every month. The goal of this internship is to participate to the development of a pipeline using AI algorithms to pre-process the incoming images automatically. The student will use the already pre-processed and labelled data to train deep convolutional neural networks (CNNs), and apply these models to new pictures. Moreover, we wish to open and give full access to MFD to the scientific community. The student will thus also create a webpage (Gitlab) allowing the public to download both the images and the metadata of MFD. The student will be hosted in team E3CO at the CEFE, which includes several students and researchers working on AI applied to ecology and evolution.



3 IMPROVEMENT OF BIOINFORMATICS TOOLS FOR DETECTION OF AGGREGATION-PRONE PROTEINS, ITS APPLICATION TO PROTEOME-WIDE ANALYSIS AND SUBSEQUENT EXPERIMENTAL TESTS

Formation of protein aggregates and amyloids are linked to a wide range of age-related human diseases and important biological functions. Numerous studies have demonstrated that the propensity to form amyloids is coded by the amino acid sequence. This opens up opportunities for the development of bioinformatics tools for prediction of aggregation-prone proteins. The main objective of this project is to develop a computer program whose performance will be superior over the existing programs. The improvement will be based on newly determined 3D structures of amyloids, molecular modeling, known results of the mutational analysis. The program will be used to perform a proteome-wide analysis of amyloidogenicity. Newly predicted amyloid-forming proteins will be chemically synthesized and tested experimentally using our approach, Taylor Dispersion Analysis, which allows to observe not only the final aggregation states of proteins but also their intermediate structural states (oligomers and protofilaments).

ÉQUIPES

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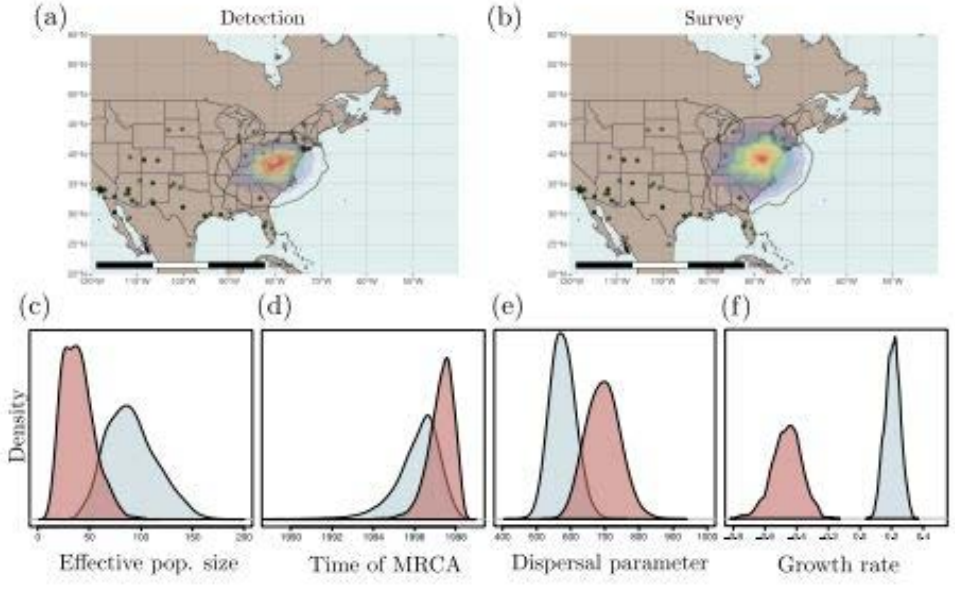
Encadrant : Denis Fargette (Plant Health Institute of Montpellier)

Encadrant : Paul Bastide (IMAG : Institut Montpelliérain Alexander Grothendieck)

4 ASSESSMENT OF BAYESIAN PHYLOGEOGRAPHIC INFERENCE TECHNIQUES WITH AN APPLICATION TO THE ANALYSIS OF THE RICE YELLOW MOTTLE VIRUS IN AFRICA

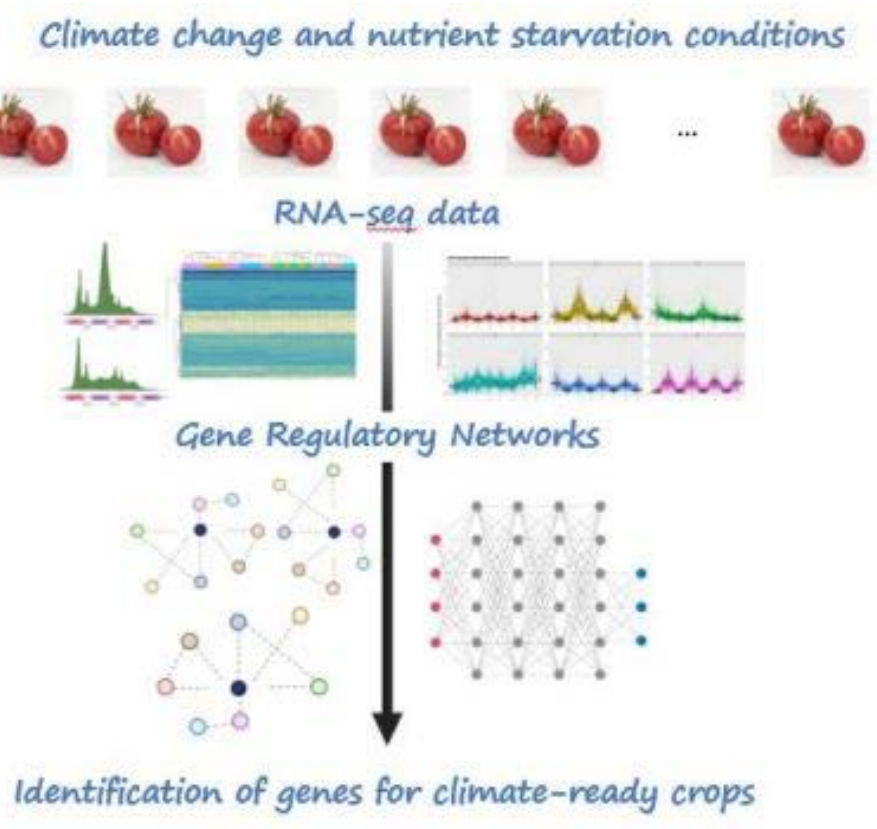
The analysis of georeferenced genetic sequences using methods from the field of phylogeography makes it possible to characterize the spatial dynamics of an evolving species or population. During the course of an epidemic, Bayesian inference methods can, in principle, reconstruct both the mutation history of the sequences, represented by a phylogenetic tree, and the geographical spread of the pathogen. Using simulated data for which we can control both the true phylogeographic scenarios and the level of difficulty, along with real data from a virus with strong societal impact (the Rice yellow mottle virus in Africa) for which we have a good knowledge of the biological processes involve, our objective in this project is to verify that the available tools are able to correctly recover the general dynamic of the process, as well as the values of the parameters of the phylogeographic models.



Phylogeography analysis of the West Nile virus in North America

5 STATISTICAL INFERENCE OF PLANT GENE REGULATORY NETWORKS UNDER CLIMATE CHANGE

Elevated atmospheric CO_2 level (eCO_2) associated with climate change will lead to a degradation of plant nutritional quality, representing a major threat for human health in the coming decades. We recently generated several transcriptomic datasets from plants in the context of eCO_2, in order to understand the effect of eCO_2 on plant physiology, and to identify candidate genes or pathways able to improve plant nutritional content under eCO_2. The main objective of the project is to re-construct gene regulatory networks using Machine-Learning approaches. Combinatorial dataset from plants growing with contrasting CO_2 and nutrient levels, as well as pseudo-temporal data-set generated from plants under gradient of CO_2 will be used to infer, explore and characterize gene regulatory networks of plants growing under eCO_2, with the objective of generating valuable knowledge for the development of climate-ready plants.



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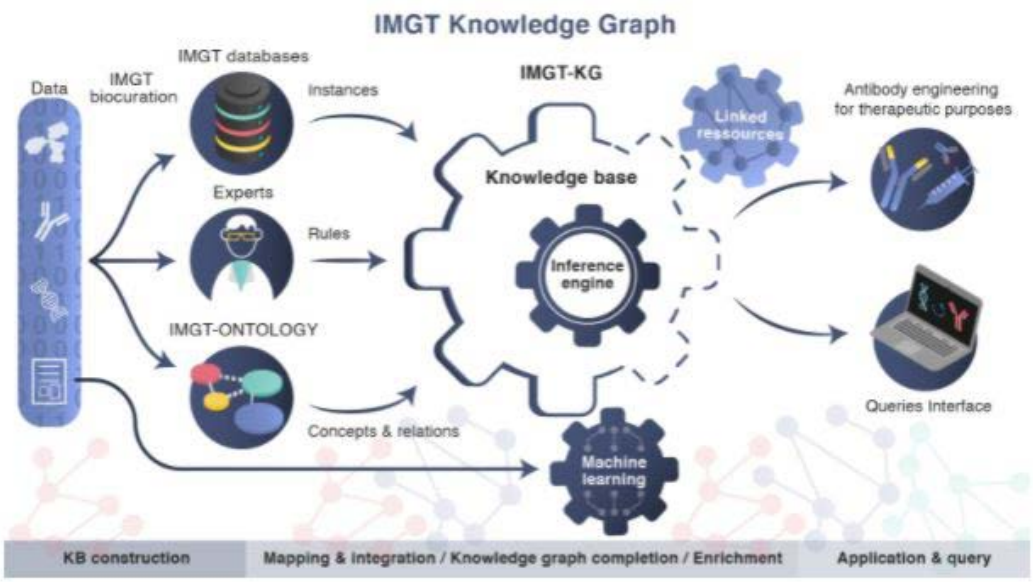
Encadrant : Konstantin Todorov (LIRMM : Laboratoire d'Informatique, de Robotique et de Microélectronique de Montpellier)

6 A KNOWLEDGE BASE IN IMMUNOGENETICS FOR THE DISCOVERY OF NEW SCIENTIFIC KNOWLEDGE, IMMUNO-GNOSIS

Ontologies are today major technological components in the context of Open and Big Data. They allow the federation, integration and structuring of data into knowledge graphs (KG). KG improve data access and information retrieval. The field of life sciences abounds in complex and sometimes subjective terms, making their computer formalization challenging.

IMGT® is the international reference in the field of immunogenetics and contains seven relational databases, seventeen analysis tools and a large number of web pages. Its strength lies in particular in the construction over time of an ontology.

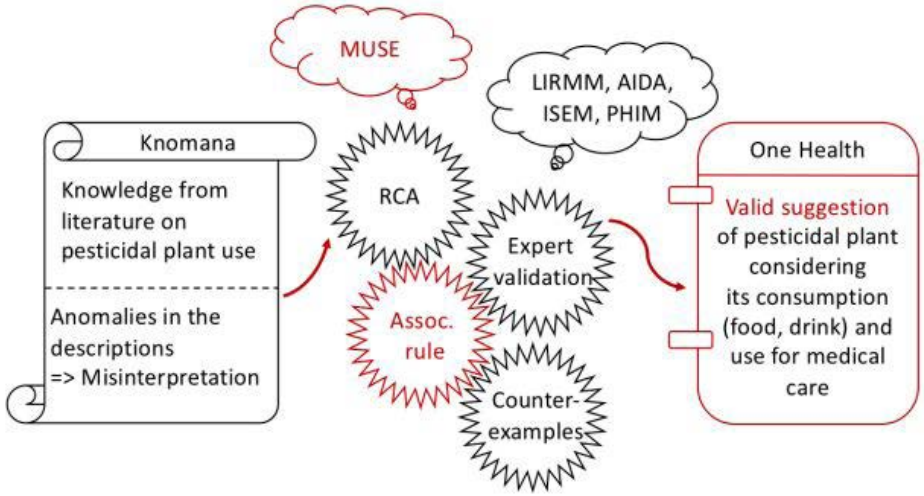
Antibody engineering for therapeutic purposes is a booming branch that requires the structuring of knowledge in the form of knowledge graphs. The main objective of the project is to offer tools to help the expert to extract information and knowledge from structured (KG) and unstructured data (other data within IMGT) and thus provide support to generate and validate scientific hypotheses in the field of antibodies for therapeutic purposes.



7 DETECTION AND CORRECTION OF ANOMALIES IN A KNOWLEDGE BASE ON PLANTS WITH PESTICIDAL AND ANTIBIOTIC EFFECT

Reducing the use of pesticides and antibiotics is a major challenge for the natural environment. One of the alternatives to these synthetic products is the use of plants. To this end, the Knomana knowledge base gathers 42,000 descriptions of the use of plants, mainly from the Global South, with pesticidal, antifungal, antibacterial and antiparasitic effects, for animal, plant, human, and public health (Silvie et al. 2021). The ambition of the core team made up of researchers from UPR AIDA, UMR ISEM, UMR PHIM and UMR LIRMM is to provide farmers with an exploration software (thus including an inference mechanism) of Knomana that offers solutions adapted to users' needs and enhances the value of local biodiversity while subscribing to the One-Health approach. For instance, in (Mahrach et al. 2020), we developed an algorithm that identifies pesticidal plants in Knomana that are not harmful to humans, meaning the pesticidal plant has to be not toxic if the crop is consumed (drink or food) or should have a limited and conscious use if the pesticidal plant is already used for medical care. The plant use descriptions included in Knomana are taken from the scientific literature. Some algorithms already allow to correct typographical errors (territory, etc.) and some others to manage the synonyms of species names from reference websites (e.g. PlantsOfTheWorld, CatalogueOfLife, and FishBase). However, there are still anomalies in these descriptions, i.e. information with incorrect or missing values. The problem caused by these anomalies is that they alter the results obtained by the exploration algorithm, which is based on the Relational Concept Analysis (RCA; Hacene et al. 2013). RCA is an unsupervised classification method based on lattice theory. It is one the intelligence artificial symbolic methods which supports explainable results. With respect to Knomana, RCA makes it possible to consider the ternary relationship that structures the description of a plant used to protect a system (cultivated plot, stored grains, fish tank, human being, etc.) against a pest (insects, bacteria, fungus, etc.). Correcting anomalies is therefore mandatory before providing such exploration tool, composed of the exploration algorithm and the knowledge set, to end users.

The objective of the internship is therefore to develop a methodology and algorithms for the semi-automatic detection and correction of these anomalies. The approach will be based on the extraction of a synthetic association rule set summarizing main information provided by RCA on Knomana. The rules will be organized using semantic patterns and quantitative interestingness measures (e.g. support, 2 / 2 confidence, and lift) conducive to highlight anomalies and incompleteness, to be presented to experts. In return, the experts will validate some of the rules (that will be considered acquired), invalidate others, propose counter-examples, complements or corrections that will improve the dataset quality. This method provides experts continuous improvement of Knomana and increase of the acquired knowledge. The originality of the work lies in the use of rules as the revealer of anomalies, where they are usually used to reveal frequent knowledge patterns.



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Encadrant : Christian Jorgensen (IRMB : Institute for Regenerative Medicine and Biotherapy)

Encadrant : Denis Mottet (EuroMov Digital Health in Motion)

8 CLUSTERING IMPERFECT DATA FOR PERSONALIZED MEDICINE: MULTIMODAL (KINETIC, CLINICAL AND BIOLOGICAL) DATA IN SPONDYLARTHRITIS

Spondylarthritis affects 1/1000 individuals, mainly young men, with a delay in diagnosis resulting in high medical costs. Spondylarthritis is characterized by disabling back pain and 2/3 of patients show biological signs of chronic inflammation. In 90% of these people, there is a particular gene in the histocompatibility system (HLA B27), which makes it very likely that they have an inappropriate immune response that causes inflammation. Logically, most patients respond well to biotherapy (anti-TNFα, anti-IL-17), but this is not the case for 30% of them. Especially for these non-responders, we need novel discriminating features to tailor therapy.

To do so, we record clinical, biological and movement data over time and we analyze this data within an interdisciplinary team at the interface of Health, Movement and Data sciences. We recruit 3 master students (medical sciences + movement sciences + data sciences) working together under the co-supervision of 3 senior scientists: C. Jorgensen (medicine), D. Mottet (movement) and A. Imoussaten (data sciences). The present grant application is for the internship of the student in data sciences, the other two students being already funded.

In the data science project, the goal is to build cautious algorithms to classify patients by analyzing the imperfect multimodal data (clinical, biological and movement). We address the classification problem by focusing on a careful dealing with the uncertainties in the recorded data. Uncertainty is related to the reliability of the sensors, but it is also related to the variability of human movement/physiology/biology and its evolution over time. Here, it is essential to have the most faithful representation of the data, including its imperfection, to feed the medical strategy.

9 AUTOMATIC HONEYBEE COLONY SOCIOMETRY

A combination of environmental stresses is producing, on a global scale, an undeniable decline in bee colonies. The «SuperBeeLive» project that we are conducting is based on the real-time monitoring of a bee colony, from its birth to its death, in order to monitor in detail its homeostasis and its health status. From the videos of each frame, multiples classes of data could be extracted going from individual bee behaviors to the nature of each cell. The master project consists in conceiving a method of daily analysis of the cells in an automatic way to annotate their contents, to describe the distribution of the contents and their location on the frame. Beside these sociometric data, demographic data of the bee colony will be also automatically follow in real time. The methods to be developed will be done in the form of an analysis software and a method of data visualization. The demographic part of the work will require deploying a neural network capable of annotating each bee and a machine learning approach to count them.

ÉQUIPES

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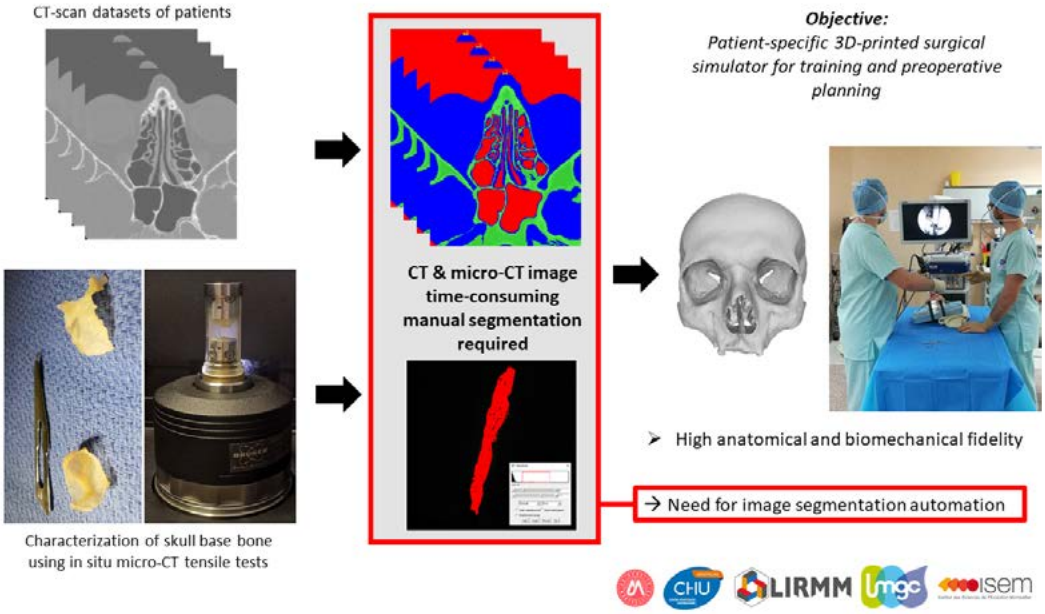
10 A PREREQUISITE TO 3D PRINT OF PATIENT-SPECIFIC SURGICAL SIMULATORS OF ENDOSCOPIC ENDONASAL SKULL BASE SURGERY: AUTOMATION OF THE SEGMENTATION OF CT AND MICROCT 3D IMAGES

The segmentation of 3D CT scan images – to 3D print patient-specific surgical simulators of endoscopic endonasal skull base surgery – remains largely time-consuming. The partial volume effect on thin bone structures (100 µm) avoids to use the common segmentation methods such as global thresholding. These simulators have to reproduce the mechanical behavior of human tissues which are not known. To study these mechanical properties, we developed mechanical tests during microCT scanning to follow the shape deformation of material samples under stress. a traction microCT data. This high-resolution exam allows to differentiate bone layers of different intensity but it makes difficult to separate the layers from the support material during segmentation. The aim of this project is then to study and develop new automated segmentation algorithms for 3D images from both CT and microCT data set to allow patient-specific design of skull base surgical simulators.

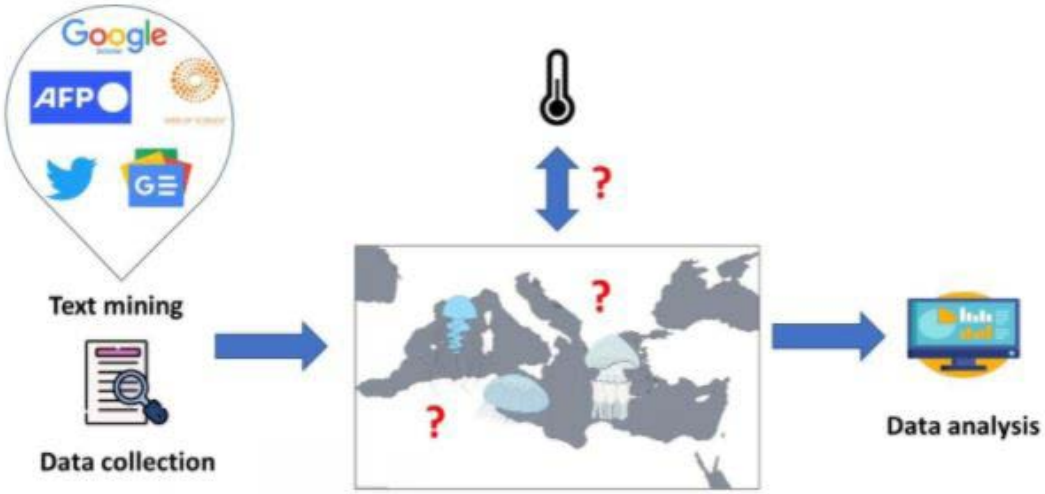


11 DECIPHERING SPACE-TIME JELLYFISH DIVERSITY BLOOMS IN THE MEDITERRANEAN SEA THROUGH TEXT MINING

In recent decades, massive blooms of jellyfish observed in temperate and subtropical regions have altered coastal ecosystems biodiversity and economic activities, such as tourism and fishing.

Jellyfish can be considered as suitable ecological indicators of the ecosystems state, since much of the observed variability can be explained with few descriptors. The unpredictable nature of blooms challenges traditional scientific approaches to monitor jellyfish species, and scientific monitoring cannot alone allows depicting their biodiversity changes at a basin scale. Data collection from social networks and mass media could provide valuable data on spatial and temporal coverage. We here propose a complementary approach based on data gathered through text mining, which is the process of automatically deriving information from large amounts of text, and data mining to depict patterns and trends in collected data.

Our goals are to map space-time patterns of stranded jellyfish in the Mediterranean basin, and to assess their diversity in the context of tropicalization and meridionalisation phenomena.



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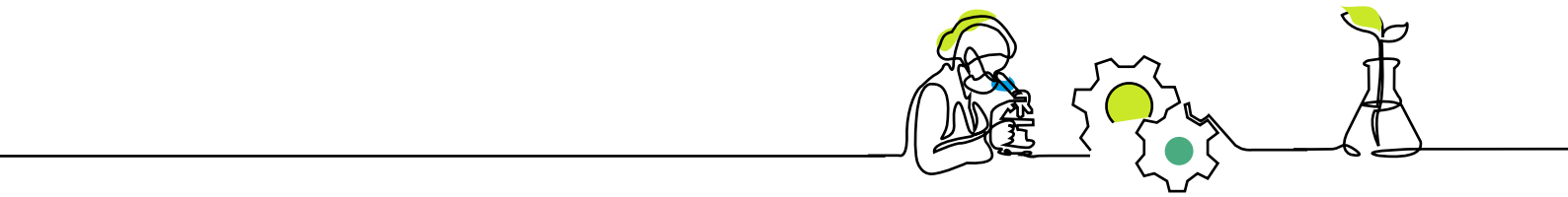
Encadrant : Sandra Bringay (LIRMM : Laboratoire d'Informatique, de Robotique et de Microélectronique de Montpellier)

Encadrant : Arnaud Sallaberry (LIRMM : Laboratoire d'Informatique, de Robotique et de Microélectronique de Montpellier)

Encadrant : Pascal Poncelet (LIRMM : Laboratoire d'Informatique, de Robotique et de Microélectronique de Montpellier)

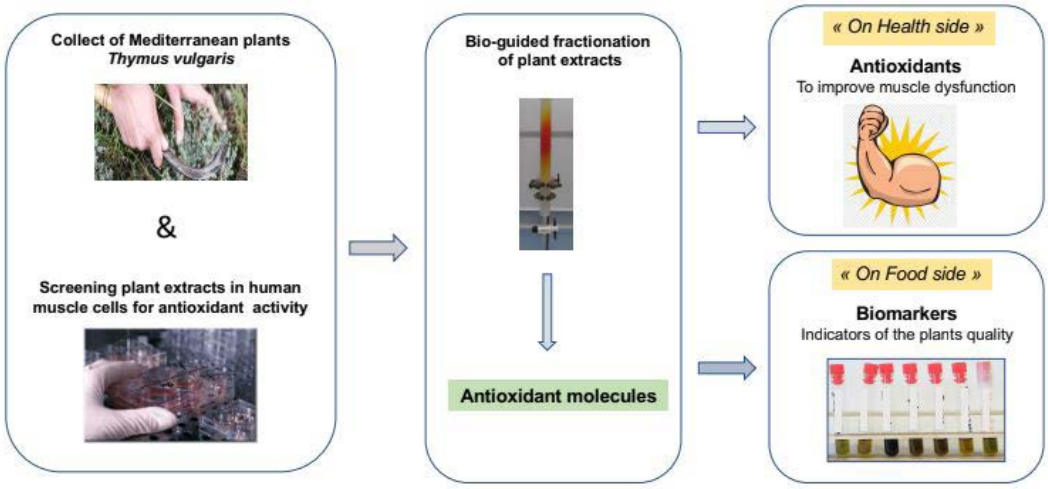
ABSTRACTS DES PROJETS LAURÉATS

KIM FOOD & HEALTH



1 ISOLATION OF COMPOUNDS OF *THYMUS VULGARIS* AS THERAPEUTIC ANTIOXIDANTS FOR MUSCLE DISORDERS AND BIOMARKERS FOR NUTRITION

In the PhyMedExp laboratory in Montpellier, we are working on the establishment of cellular and animal models to improve the understanding of physio-pathological mechanisms involved in pathologies affecting muscles. These pathologies are now clearly linked to mechanisms involving oxidative stress and action of free radicals. In this context, we propose to investigate on antioxidant properties of a Mediterranean plant, *Thymus vulgaris*, in a human muscle cells model exposed to H_2O_2 oxidative stress. We will identify bioactive molecule(s) having antioxidant properties from extracts of T. vulgaris, using a bioassay-guided fractionation combined to NMR analysis, in collaboration with the phyto-chemists from the CEFE laboratory at the Pharmacy Faculty in Montpellier. The first objective of this project is to discover natural antioxidant compound(s) that could be tested in future preclinical studies. The second objective is to identify antioxidant molecules as biomarkers of this Mediterranean plant.



ÉQUIPES

ÉQUIPE

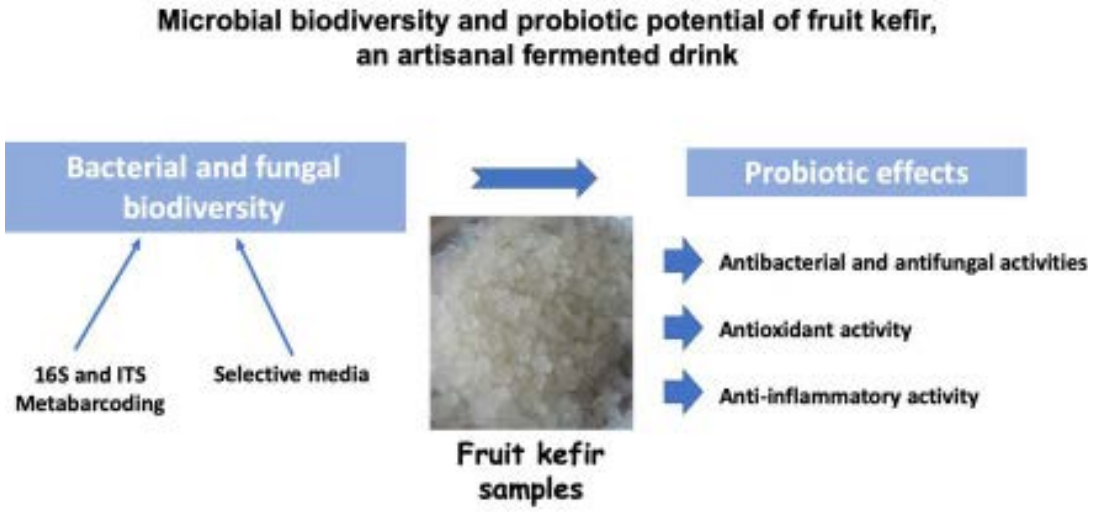
Encadrant : Nathalie Saint (PhyMedExp)

ÉQUIPE

Encadrant : Sylvie Morel
Centre d'Ecologie Fonctionnelle et Evolutive (CEFE)

2 MICROBIAL BIODIVERSITY AND PROBIOTIC POTENTIAL OF FRUIT KEFIR, AN ARTISANAL FERMENTED DRINK

Kefir is a fermented drink of natural origin, renowned for its beneficial effects on health linked to the presence of probiotic microorganisms. Indeed, kefir grains contain a complex symbiotic microbial community consisting of lactic acid bacteria, acetic acid bacteria and yeasts, embedded in an insoluble exopolysaccharide matrix. The composition of the ferments is likely to influence the organoleptic and probiotic quality of the finished product. We therefore propose to take an interest, using samples of kefir from fruits of different origins, in the microbial biodiversity and the probiotic potential of kefir grains. First, microbial communities will be studied by cultural and molecular (metabarcoding) approaches. Then, the probiotic potential of the isolated strains will be evaluated by antimicrobial tests against food microbial pathogens or contaminants. Finally, the antioxidant and anti-inflammatory activities will be analyzed *in vitro*.



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Encadrant : Frédéric Boudard
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UMR TransVIHMI

3

Balancing our lipid intake by regulating our intake of omega-6 fatty acids and increasing our intake of omega-3 fatty acids is a strong nutritional recommendation from the WHO. Indeed, exposure to unbalanced diets that are too rich in omega-6 can promote the onset of chronic inflammatory diseases. In order to rebalance intakes, in addition to the traditional intakes of fish and certain oilseeds, microalgae constitute new sustainable sources of omega-3 fatty acids, under a specific form i.e., glycolipids more precisely of galactolipids. These galactolipids are not digested like classical lipids (triacylglycerols) and very likely modulate the digestion of these lipids. In this project we propose to study the microalga Chlorella sorokiniana as a source of galactolipids and to characterise the modulations of lipid bioaccessibility induced by this microalgae galactolipid extracts. To do so, we will adopt a transdisciplinary research approach, ranging from biophysics to food and health applications and gathering the expertise of the biotechnology platform and team working on macronutrients bioaccessibility of the UMR IATE, of the CBS in membrane integrative biophysics, of The UMR Qualisud's «Sensory Functionalities of Foods» on oxidation and antioxidants and of IBMM's Synthesis of Bioactive Lipids team on non-enzymatic oxidized derivatives of polyunsaturated fatty acids (NEO-PUFAs) characterization.

ÉQUIPES

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Encadrant : Claire Vigor
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Encadrant : Pierre-Emmanuel Milhiet & Véronique Vie
Affiliation : Centre de Biologie Structurale (CBS)

4 METABOLIC PROPERTIES OF GREEN GRAPE EXTRACTS

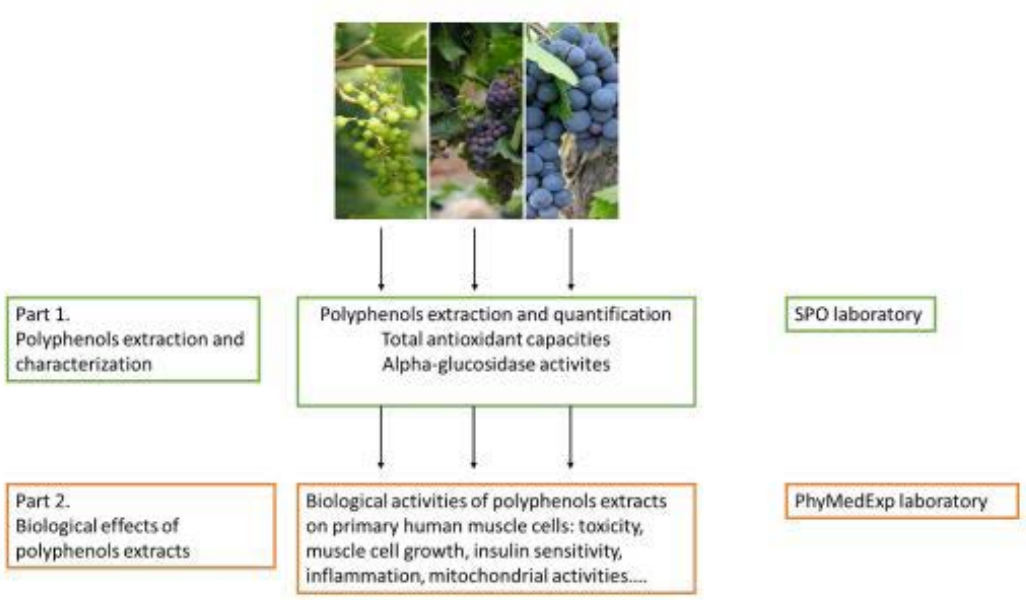
ÉQUIPES

ÉQUIPE

Encadrant :
Karen Lambert-Cordillac (PhyMedExp)

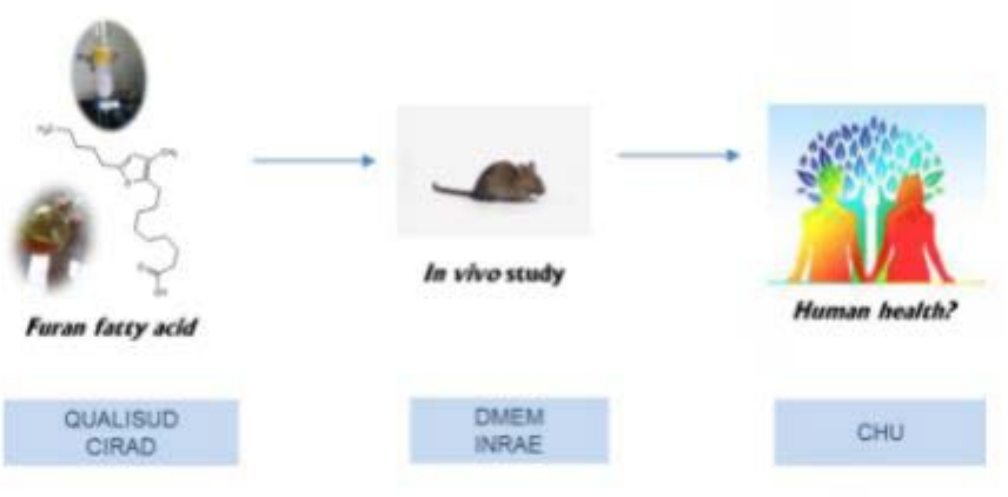
Encadrant : Cédric Saucier (Laboratoire d'oenologie SPO)

We previously demonstrate that a mixture of polyphenols from red grapes at a nutritional dose reduces or counters several risk factors for metabolic syndrome in animals and human studies. However, the recent study carried out in the SPO laboratory shows an inhibition of the entry of glucose into the body, more important with green grape extracts compared to mature red grapes. This result suggests a major role of the stage of ripening of grapes in their biological effects. In this study, we propose to investigate the biological effects of grape extracts at different ripening stages (green and red (mature)) on human skeletal muscle cells. Syrah and Grenache grape varieties will be used as they are the most widely planted grape in Occitanie. The perspective of this word, will be to identify the most active compound of the extracts in order to propose new therapeutics against metabolic syndrome.



5 METABOLIC EVALUATION OF FURAN FATTY ACID SUPPLEMENTATION IN OBESE MICE

Obesity is a major, international public health problem, qualified by the WHO as the first non-infectious epidemic in history. Furan fatty acids (FuFAs) are lipids present in small quantities in plants, microorganisms, and animals. Several studies suggest that FuFAs from our diet could have beneficial effects against metabolic disorders associated with a Western-style diet.
However, the data concerning the health effects of FuFAs are to date only very partial (in particular because of the absence of a potential economically exploitable source) and it is necessary to better characterize the biological and health effects of these molecules.
The objective of this project is to explore the metabolic changes induced by supplementation with furanic acid of obese and insulin-resistant mice (HFD mice).



ÉQUIPES

ÉQUIPE

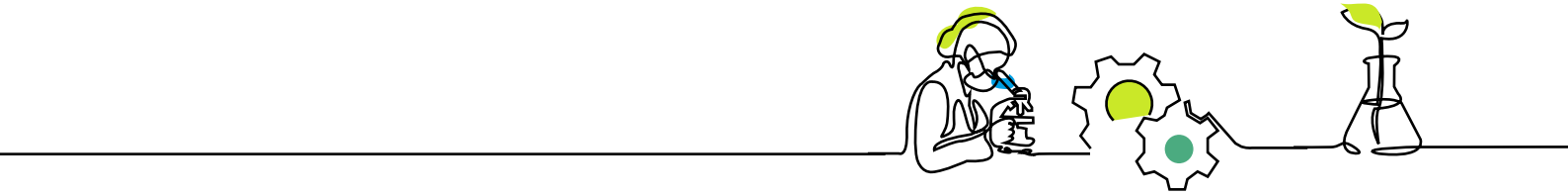
Encadrant : Christine Feillet Coudray (INRAE)

Encadrant : Ariane Sultan (CHU de Montpellier)

Encadrant : François Casas (INRAE)

Encadrant : Erwann Durand (CIRAD)

AUTRES ABSTRACTS



1 MULTI-PHASE MICROFLUIDICS TO DETERMINE LOCAL FLOW-RATE DETECTION

Microfluidics represents the utilisation of micro-scale channels that provide numerous analytical advantages such as: i) faster reaction time, ii) reduced reagent consumption and iii) parallel high-throughput screening. In order to be used for on-chip detection however, it is vital to understand the on-chip local channel flow-rate. While industrial options such as time- of-flight and coriolis sensors exist, they remain too expensive for low-cost prototyping systems.
Therefore, the aim of this project is to develop a low-cost multi-phase (liquid/gas) system to perform local flow rate measurements within microfluidic channels. Firstly, using automatic image detection and from this, integrating photonic detection modules to provide a low-cost flow rate detection alternative.

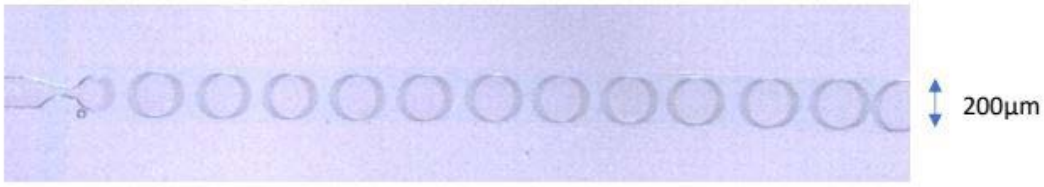


Figure 1: Example of multi-phase, liquid/gas flow within a microfluidic channel

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ÉQUIPE

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ÉQUIPES

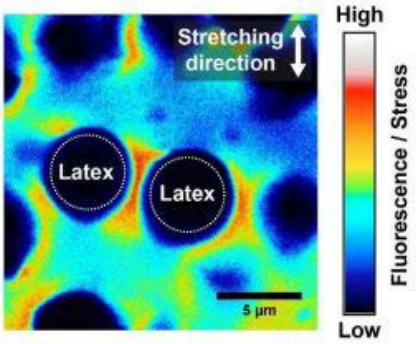
Encadrant :
Rémi Mérindol, Laboratoire Charles Coulomb (L2C)

Encadrant :
Daniel Bouvard, Centre de Recherche en Biologie cellulaire de Montpellier (CRBM)

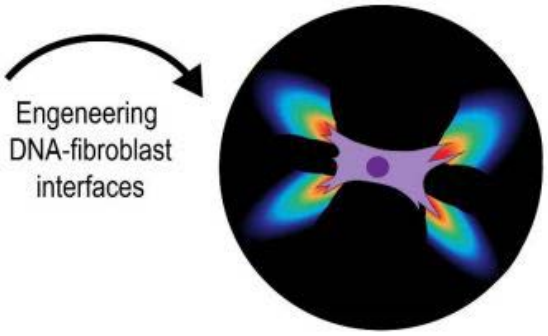
2 ENGINEERING DNA-FIBROBLAST INTERFACES

The mechanical properties of the extracellular matrix (ECM) play a critical role on numerous physiological processes. In particular, during tumour development, ECM rigidification by cancer associated fibroblast is known to be a bad prognosis factor. Yet, current synthetic ECM do not allow to visualize cell-ECM interactions at the sub-cellular level. We recently developed materials made of DNA that change fluorescence under stress (Figure).[1] Such materials are promising synthetic ECM allowing to visualize the forces exerted by cells, in addition DNA provides an exceptional control over the material architecture, reorganisation and functionalization. This project aims to test and optimise strategies allowing fibroblasts to adhere and interact with DNA hydrogels. The student will prepare and characterize functionalized DNA hydrogels at the L2C under the supervision of R. Merindol, and test fibroblast adhesion and spreading at the CRBM under the supervision of D. Bouvard.

[1] R. Merindol, G. Delechiave, L. Heinen, L. H. Catalani, A. Walther, Nat. Commun. 2019, 10, 528.



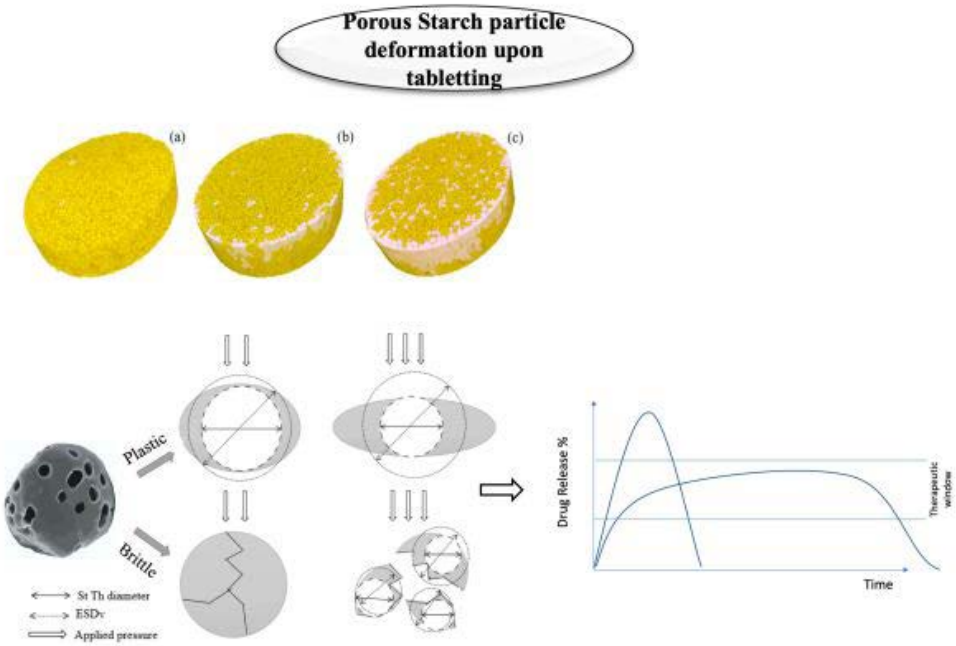
Confocal fluorescent immaging of mechanofluorescent DNA hydrogels showing inhomogeneous stress distribution around latex particles.



Schematic representation of the forces exerted by a cell on a mechanofluorescent DNA hydrogel.

3 POROUS STARCH PARTICLES AS A FUNCTIONAL PHARMACEUTICAL TABLETING EXCIPIENT USED FOR CONTROLLED DRUG DELIVERY

Recently, porous starch particles have gained interest as potential matrixes with high surface area that can be used as carriers by loading small particles or molecules in this porous network. The present project proposes to establish a proof of concept of porous starch particles for oral drug delivery applications through the investigation of particle production processes and their use as a functional controlled drug delivery excipient for tableting. The internship will focus on three different activities associated with the specific expertise of the different partners: 1) Porous starch particles will be produced through both extrusion, freeze drying cycles and spray drying processes within the UMR IATE plant agro-ressources processing plateform (Planet) 2) Drug loading and release, compression and physical testing of the porous starch compacts will be performed within the UMR ICGM Pharmaceutical tableting platform and 3) X-Ray Micro-Computed Tomography evaluation of the compacts will be performed within the UMR Qualisud XMT platform.



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Encadrant :
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Bernard Cuq (UMR IATE)

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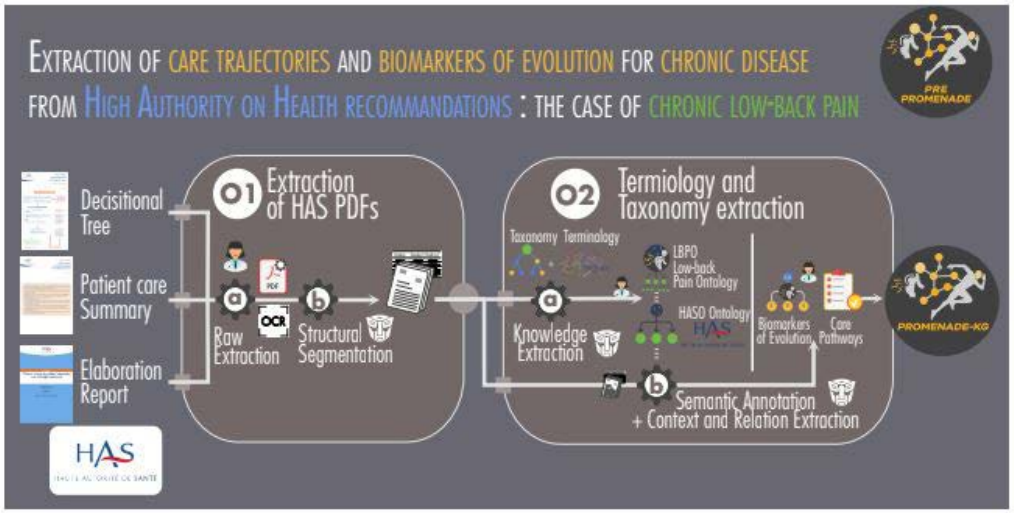
Encadrant :
Andon Tchechmedjiev, IMT Mines Alès

Encadrant :
Arnaud Dupeyron, CHU Nîmes

4 PRE-PROMENADE -- EXTRACTION OF CARE TRAJECTORIES AND BIOMARKERS OF EVOLUTION FOR CHRONIC DISEASE FROM HAS (HAUTE AUTORITÉ POUR LA SANTÉ) RECOMMENDATIONS: THE CASE OF CHRONIC LOW-BACK PAIN

Low-back pain (LBP) is the leading non-transmissible disability in the world since 1997. In France half of the population suffers from LBP episodes and is the second leading cause of consultations with general practitioners (GPs), which amounts to a yearly cost of 1 billion euros. 10% of patients develop a chronic form with severe consequences. This internship will aim at extracting knowledge from clinical reports from patient consultations in order to characterize typical care pathways and their outcomes, and to compare these observational pathways with official treatment protocols of the Haute Autorité pour la Santé in order to identify biomarkers instrumental in preventing chronicity. The candidate will extract knowledge (terminology + taxonomy extraction, semantic annotation, context identification) contained in HAS recommendation documents in the form of a knowledge graph (KG) that can be exploited to confront the recommendations to observational knowledge.



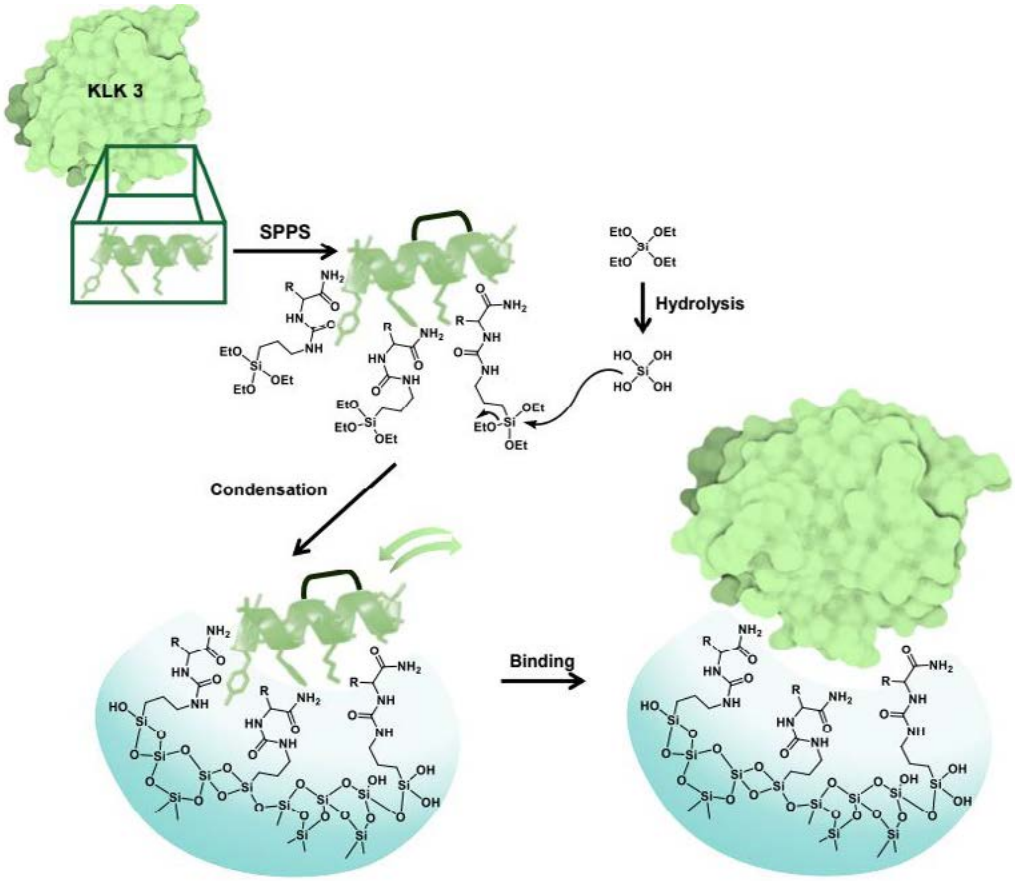
5 EPITOPE IMPRINTING OR HOW TO DEVELOP MATERIALS RECOGNIZING PROTEIN IN BIOLOGICAL MEDIA

ÉQUIPES

Encadrant :
Gilles Subra (IBMM)

Encadrant : Margaux Clavié

Molecularly Imprinted Polymers (MIPs) can be the considered as artificial antibodies mimics. A 'molecular imprint' is a cavity created within a synthetic polymer matrix, which may capture a target molecule, ideally a relevant protein with a certain selectivity. The shape, but importantly, the chemical functions of the imprint are crucial to the efficiency of the capture. Protein imprinting presents some challenges. First, the lack of commercially available functional monomers limits the diversity of interactions between the imprint and the protein. We propose to synthesize silylated amino acids derivatives as functional monomers to recapitulate the diversity of protein-protein interactions. Then, proteins have a weak chemical stability and can be degraded during the imprint synthesis. To avoid this, we propose to develop epitope imprints, by synthesizing a stapled peptide recapitulating an accessible helix of the native target protein.



ÉQUIPES

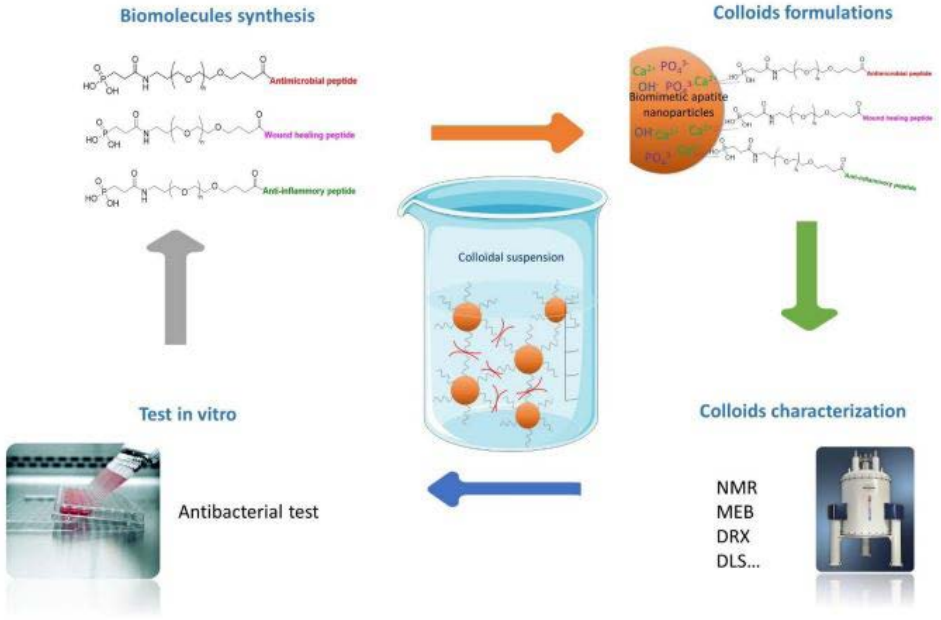
Encadrant :
Gilles subra (IBMM)

Encadrant :
Mathilde Guérin

6 SYNTHÈSE DE NANOPARTICULES HYBRIDES D'APATITE POUR LE TRAITEMENT DES PLAIES COMPLEXES À FORT RISQUE INFECTIEUX

Open wounds which are frequently found in all health services (maxillofacial, orthopedic, plastic surgery...) have a major risk of infection, especially in the most fragile subjects such as the elderly, diabetics, immunodepressed or burn victims. Innovative solutions must be developed for the most complex wounds where coordinated effects (antibacterial and pro-healing) are necessary to obtain optimal healing. Moreover, current solutions are usually based on systemic antibiotic therapy, but microbial resistance is becoming a major public health problem, and alternative solutions are needed.

In this context, the project aims at designing an alternative solution to conventional dressings and systemic antibiotic treatments by developing submicron colloidal peptide-apatite hybrid particles for the controlled release of active agents. These biocompatible and biodegradable apatite particles are used as (nano)carriers for the transport of therapeutic agents for targeted treatment. During this internship, the student will have the opportunity to synthesize hybrid apatite particles with anti-bacterial agents and to perform biological tests.



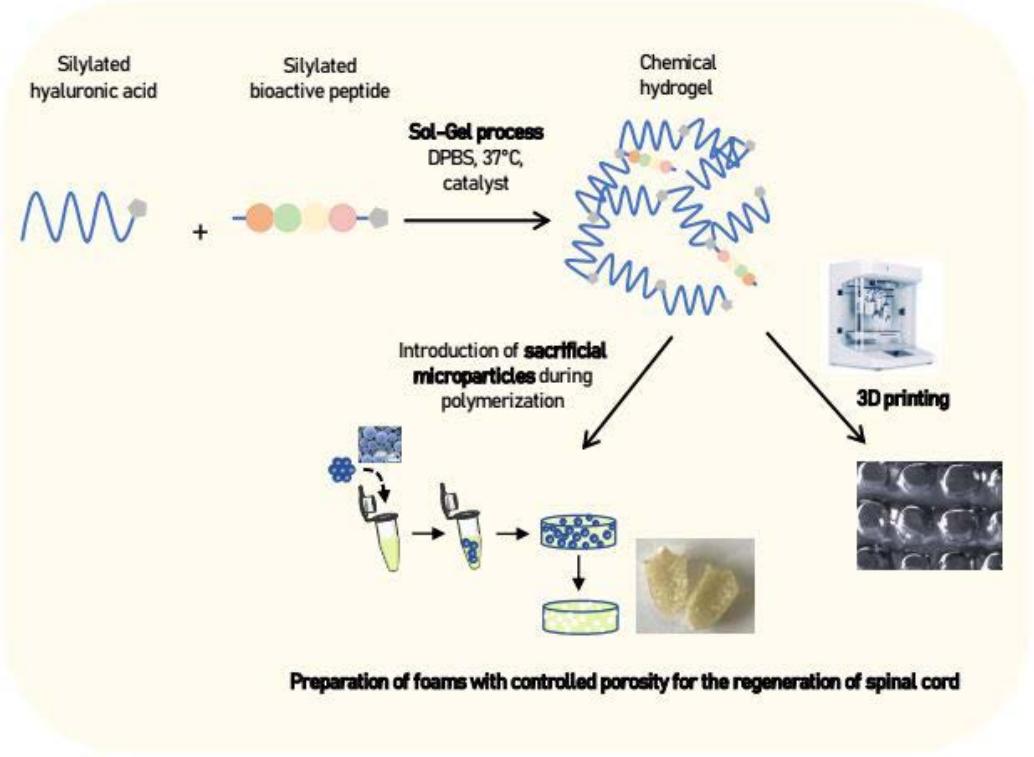
7 HYDROGELS BASED ON SILYLATED HYALURONIC ACID FOR THE REGENERATION OF THE SPINAL CORD

ÉQUIPES

Encadrant :
Gilles Subra (IBMM)

Encadrant : Cécile Echalier

The Sol-Gel process is a mild polymerization that our group uses to prepare biomaterials for regenerative medicine applications. This method requires the functionalization of biomolecules, e.g. natural polymers and bioactive peptides, with silylated groups. These groups allow the formation of a covalent 3-dimensional network under mild conditions compatible with fragile molecules and live cells.
In collaboration with Nanyang Technological University (Singapour), we are developing hydrogels based on silylated hyaluronic acid for the repair of spinal cord lesions. Processing of these mat rials, in particular to create and control porosity, is critical for the biological application. Therefore, we are looking for a student to take part into the synthesis and processing of biomaterials capable to enhance the regeneration of the spinal cord. During this internship, the student will have the opportunity to perform functionalization reactions on hyaluronic acid and investigate the use of 3D printing techniques and sacrificial materials to obtain scaffolds with a controlled porosity.



Preparation of foams with controlled porosity for the regeneration of spinal cord

ÉQUIPES

Encadrant :
Xavier Bantreil (IBMM)

Encadrant :
Julien Pinaud (Institut Charles Gerhardt Montpellier)

8 SURFACE FUNCTIONALIZATION AND REACTIVITY IN MECHANOCHEMISTRY - TOWARDS EVEN MORE SUSTAINABLE CHEMISTRY

In 2019, IUPAC recognized mechanochemistry as one of 10 innovative technologies that would change the world.[1] This technology, and more specifically ball milling, offers many benefits related to environmentally friendly chemistry (short reaction times, solvent-free reactions, different selectivity of the solution...).[2] However, purifications are necessary when the organic reactions are performed in the presence of additives or catalysts, thus diminishing the «green» aspect of the technique.

A collaboration between the IBMM (Dr. X. Bantreil) and ICGM (Dr. J. Pinaud) has recently led to the development of reactors whose surface could be functionalized. In this context, the trainee will have the mission to fabricate other reactors and to study their mechanical properties. In parallel, the synthesis of a reactive functionality will permit to anchor a palladium catalyst to the surface of the reactors. The reactivity of this surface palladium will be studied in Pd-catalyzed cross-coupling reactions.

1 Gomolloń-Bel, F. Chem. Int. 2019, 41, 12−17.

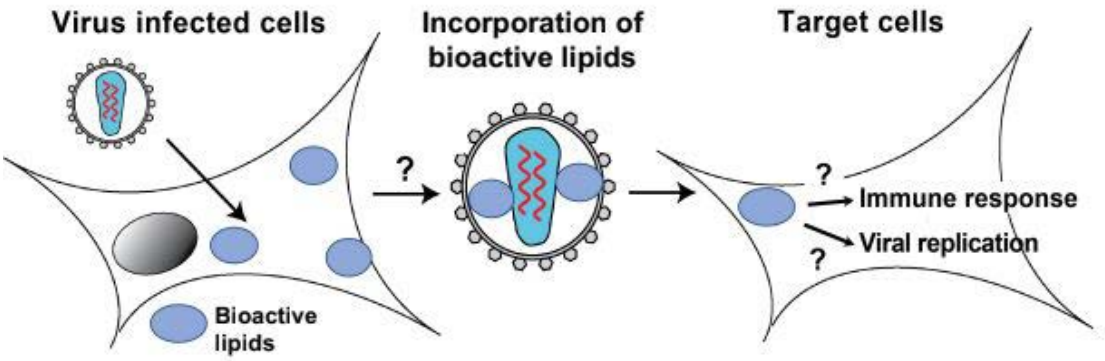
2 a) Howard, J. L.; Cao, Q.; Browne, D. L. Chem. Sci. 2018, 9, 3080−3094. b) Beillard, A.; Bantreil, X.; Métro, T. X.; Martinez, J.; Lamaty, F. Chem. Rev. 2019, 119, 7529−7609. c) Friscic, T.; Mottillo, C.; Titi, H. M. Angew. Chem., Int. Ed. 2020, 59, 1018−1029.

9 INCORPORATION OF BIOACTIVE LIPIDS IN VIRAL PARTICLES OF HIV

ÉQUIPES

Encadrant :
Lise Chauveau (IRIM : Institut de Recherche en Infectiologie de Montpellier)

Bioactive lipids such as eicosanoids (including prostaglandins and leukotrienes), phospholipids and fatty acids, play a very complex and important role in modulating virus replication and antiviral immune responses. Virus particles from enveloped viruses such as HIV can contain various proteins, nucleic acids or other molecules coming from the infected cell that produced them. In this project, we will look at incorporation of these important bioactive lipids within virus particles. We will then interrogate how this incorporation influences viral replication and the antiviral immune response in the new infected cell. Viruses will be produced in cells expressing or not crucial enzymes for the production of lipids of interest and will be analysed by mass spectrometry with help from our collaborators at the MAMMA facility. The effect of this incorporation on virus replication and antiviral immune responses will then be studied in the main HIV target cells: primary CD4 T lymphocytes.



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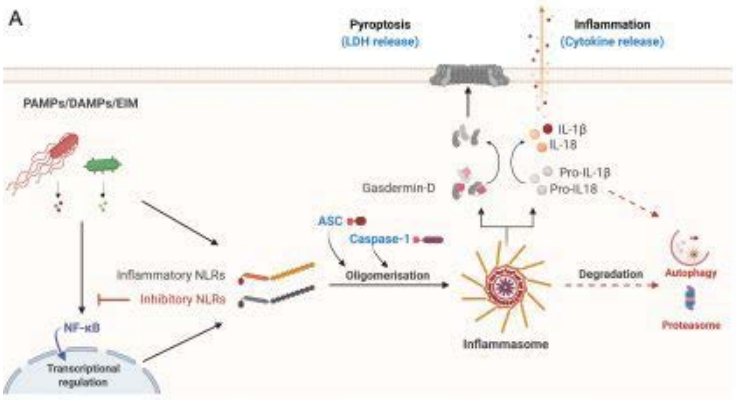
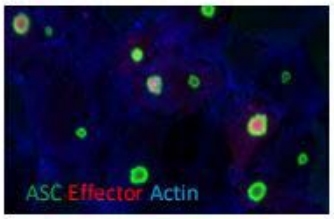
10 MANIPULATION OF INFLAMMASOMES BY THE STEALTH PATHOGEN *COXIELLA BURNETII*

Encadrant :
Eric Martinez, Institut de Recherche en Infectiologie de Montpellier (IRIM)

Coxiella burnetii is a highly infectious class 3 pathogen that causes Q fever zoonosis. Upon infection, *Coxiella* diverts multiple intracellular trafficking pathways to form a replicative vacuole and inhibit cell death by apoptosis. These processes are hijacked by effector proteins secreted by the bacteria into the cytoplasm of the host cell via a type 4 secretion system (T4SS). In addition, *Coxiella* may attenuate the inflammatory response of infected cells allowing it to persist chronically in the host. Indeed, *Coxiella* modulates the signaling pathways of innate immunity, in part thanks to the effectors NopA and IcaA which play a role in the disruption of the nuclear transport of NF-κB and the inhibition of the non-canonical inflammasome. Recently, we have identified a new *Coxiella* effector protein capable of interacting with canonical inflammasomes. These inflammasomes play an essential role in the detection of intracellular pathogens and the inflammatory response of immune and placental cells. It is therefore essential to understand how *Coxiella* manipulates them and inhibits inflammation in infected cells. The objective of the internship will be to characterize the function of the *Coxiella* effector protein by biochemical and microscopic methods.





11 IDENTIFICATION OF PATTERNS IN ELECTROENCEPHALOGRAPHY SIGNALS FOR THE ASSESSMENT OF DISORDERS OF CONSCIOUSNESS

Encadrant :
Gérard Dray (IMT Mines Alès)

Mots clés : EEG, task-related brain activity dynamics, optical flow, disorders of consciousness

In this project, we wish to develop an original and multidisciplinary approach to processing neurophysiological electroencephalography (EEG) signals to help clinicians in their assessment of disorders of consciousness . Currently, the analysis of EEG signals is primarily performed using signal-processing techniques to extract signals of interest that are classified in a supervised or unsupervised manner. The extraction of informative features and the precise classification of these combined signals are considerably difficult due to physiological non-stationarity, low signal-to-noise ratio, and interference from various noises etc. On the other hand, the temporal aspect is poorly acknowledged in the literature, under the assumption that the signals of interest have the same patterns, which may not be the case in reality. The objective of our approach is to improve the spatiotemporal synchronization of EEG signals by conjointly setting-up digital propagation models and machine learning approaches.

ÉQUIPES

Encadrant :
Charles Lecellier (IGMM)

12 ASSESSING THE LINK BETWEEN THE CLINICAL IMPACT OF GENETIC VARIANTS AND THEIR EFFECT ON TRANSCRIPTION INITIATION AT MI-CROSATELLITES.

As part of the international FANTOM consortium, whose aims at better characterizing the human non-coding transcriptome, our team has recently discovered that a significant fraction of Transcription Start Sites, as mapped by cap analysis of gene expression (CAGE), initiates at microsatellites [1], also called short tandem repeats (STRs). STRs correspond to repeated DNA motifs of 2 to 6 bp and constitute one of the most polymorphic and abundant repetitive elements, with wide impact on gene expression[2] through various molecular mechanisms[3] . We trained sequence-based convolu- tional neural networks (CNNs) able to predict transcription initiation at STRs with high accuracy 1, providing an unprecedented mean to evaluate the impact of genetic variants on this process. On the other hand, we showed that genetic variants linked to human diseases are preferentially found at STRs with high transcription initiation level 1, supporting the biological relevance of transcription initiation at STRs in clinics. The candidate will (i) validate the link between the pathogenicity of genetic variants and their impact on transcription initiation at STRs integrating and interpreting the output of our models with the ClinVar database [4] and (ii) develop a user-friendly web interface that will facilitate the interrogation of genetic variants observed in patient genomes for clinical routine.

1 Grapotte, M. et al. Discovery of widespread transcription initiation at microsatellites predictable by sequence-based deep neural network. Nature communications 12, 1–18 (2021).
2 Gymrek, M. et al. Abundant contribution of short tandem repeats to gene expression variation in humans. Nat. Genet. 48, 22–29 (2016).
3 Bagshaw, A. T. Functional mechanisms of microsatellite dna in eukaryotic genomes. Genome biology and evolution 9, 2428–2443 (2017).
4 Landrum, M. J. et al. ClinVar: public archive of interpretations of clinically relevant variants. Nucleic Acids Res. 44, D862–868 (2016).

13 ANALYSIS OF VIRAL INTEGRATIONS OF THE BADNAVIRUS GENUS (CACAO SWOLLEN SHOOT VIRUS GROUP) WITHIN THE DIVERSITY OF COCOA GENOMES (*THEOBROMA CACAO)*

Recently, we have detected viral sequences of species of the genus Badnavirus, within different genomes of healthy cocoa trees. The partial sequences obtained are divided into 13 subgroups or types corresponding to the species S (or eTCBV1 for endogenous Theobroma cacao bacilliform virus 1) or S prim (or eTCBV2). Bioinformatics analyses on recently available cocoa genomes confirmed the integration hypothesis and were followed by molecular biology confirmation for the type (type VI) and resulted in a publication. In addition to the need for further study of the structure of these integrations in cocoa genomes, these results raise several questions. It is not known whether these integrated viral sequences have viral equivalents encapsidated and replicating in the plant and as already observed for other viruses, the integration of these badnaviral species into the cocoa genome could modify their resistance to some viral species of the swollen shoot associated species complex (CSSV) via processes that may involve siRNAs.

ÉQUIPES

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Encadrant :
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Institut des Biomolécules
Max Mousseron (IBMM,
CNRS) & Catherine Oiry-Cuq

14 *IN VITRO* PHARMACOLOGICAL CHARACTERIZATION OF BIVALENT GPCR LIGANDS AIMED AT SELECTIVELY TARGETING THE GHRELIN-DOPAMINE HETEROMER

The ghrelin GHSR and the dopaminergic D2R receptors are druggable cell targets playing a key role in health and disease. We and others reported that these G-protein coupled receptors physically interact *in vitro* and *in vivo* to form heteromer structures with unique modes of function. In order to selectively target these functional edifices, we have synthesized bivalent ligands consisting of two pharmacophores of each receptor tethered by a linker. The aim of the project is to explore the pharmacological properties of these new bivalent compounds using in vitro biological models. The trainee will have to delineate the pharmacological profiles of the ligands – binding affinity, activation of G proteins, production of second messengers, and recruitment of arrestin - using cell lines expressing the different combinations of receptors. The fellow will have to perform ligand binding and signaling protein activation experiments using fluorescence transfer methods (FRET, HTRF), essentially.

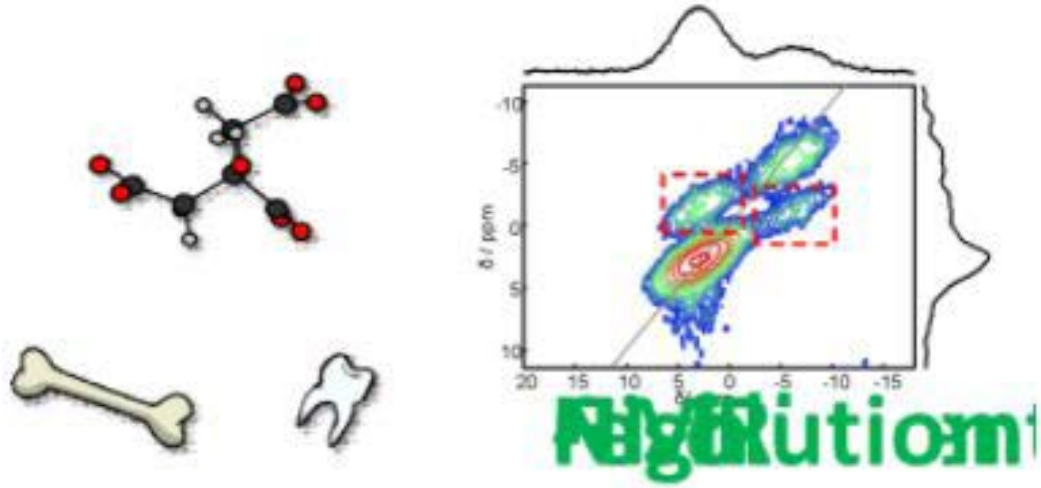
15 DEVELOPMENT OF INNOVATIVE STRATEGIES FOR ISOTOPIC ENRICHMENT OF BIOMOLECULES IN SEARCH OF NEW BIOMINERALIZATION MECHANISMS

ÉQUIPES

Encadrant :
Danielle Laurencin (CNRS, ICGM, UM)

Encadrant :
Thomas-Xavier Métro CNRS, IBMM, UM)

Whether for the detailed understanding of physiological phenomena or to elucidate the structure of complex biomolecules, the use of isotopic labeling of biomolecules is a frequent and efficient strategy. For example, the enrichment of amino acids in stable isotopes (13C, 15N, 2H, 18O…) has allowed to elucidate the structure of many membrane proteins. However, the preparation of 17O enriched molecules for high resolution NMR analysis has been the subject of only a handful of studies, due to the very high costs of isotope labeling. On the basis of recent results obtained in the laboratory, the objective of this internship will be to develop novel strategies for 17O enrichment of biomolecules, using mechanochemistry. The idea will then be to use them for advanced NMR characterizations of biomimetic systems, in order to better understand the phenomena involved during biomineralization.



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ÉQUIPES

ÉQUIPE

Encadrant :
Véronique Alary (CIRAD/ ICARDA)

Encadrant : Lina Amsidder (CIRAD)

Encadrant : Guillaume Duteurtre (CIRAD)

16 SOCIO-ECONOMIC- CONTRIBUTIONS OF CAMEL MILK PRODUCTS IN NORTH-AFRICAN DRYLANDS: THE CASE OF MOROCCO

Over the last two decades, camel herding has known a renewed interest in North Africa as a socio-economic development factor in dry areas. Based on a systemic approach, we conducted an empirical field study in East and South Morocco, to assess the different goods and services provided by camel herding and other camel-related activities in these arid and semi-arid zones. Semi-structured survey questionnaires were submitted to 40 herders, 34 traders, 30 consumers, local authorities and other stakeholders of the camel sector in East provinces and South-East provinces of Morocco. Socioeconomic contributions at both households and territorial level were considered. Results at the household level reveals the multi-use of camel products in the local food system and the traditional medicine practices even if the camel income generation come mainly from the sale of live animals. Overall 70% and 32% of surveyed households were used to transform camel meat and milk, respectively, for home-consumption. Milk marketing mainly goes through short social chain from the camel herder to the end-users at the local level. Milk marketing is more practiced by the young herders with a small camel herd. At the territorial level, the camel milk processing sector is still in its infancy with low-scale units and needs innovation and management support in order to boost milk collection, processing and marketing through business. Young camel herders expressed the most interest in this development of camel milk value chains that could contribute to the sustainable development of North-African drylands.

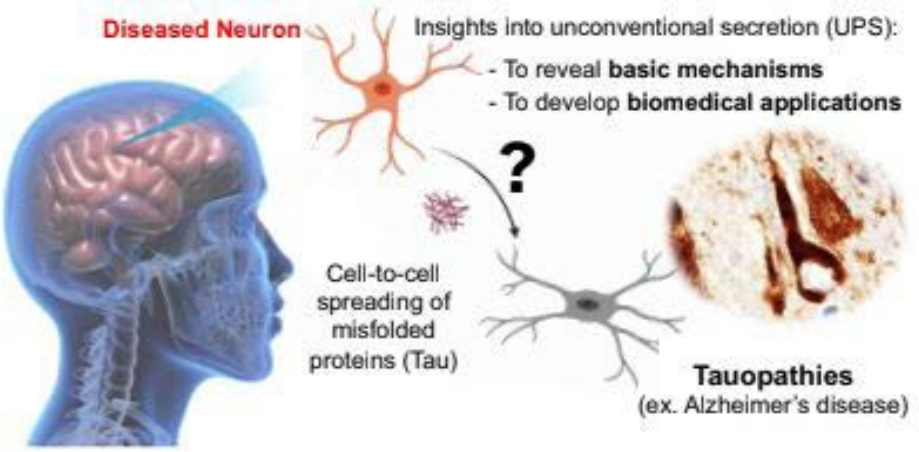
17 UNCOVER MECHANISMS OF UNCONVENTIONAL PROTEIN SECRETION – FROM BASIC RESEARCH TO NEURODEGENERATIVE DISEASE THERAPEUTICS

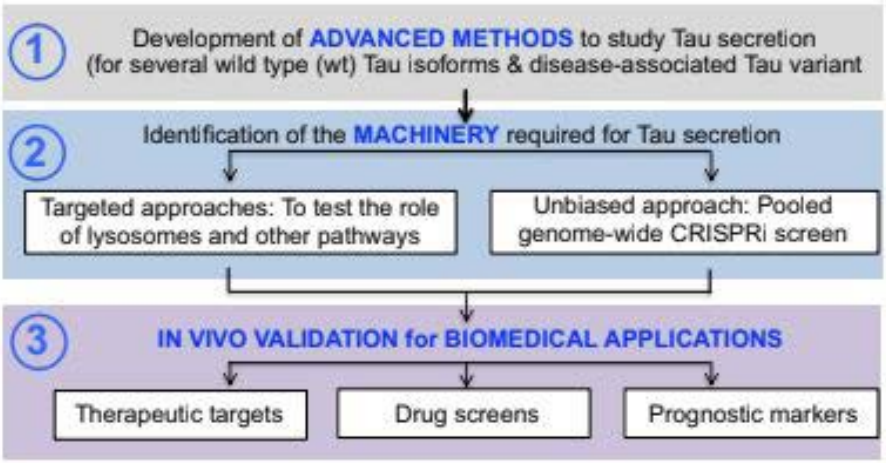
ÉQUIPES

Encadrant :
Julien Villeneuve (IGF : Institut de Génomique Fonctionnelle)

In eukaryotic cells, cytosolic proteins can be exported out of cells even though they lack a signal sequence to enter the endoplasmic reticulum. This fundamental process that remains poorly understood is called Unconventional Protein Secretion (UPS). During aging, UPS of misfolded proteins promotes their transmission from neuron to neuron, and thus is critical in neurodegenerative diseases (NDs) progression. Within the proposed project, we will study the secretion of misfolded proteins with the objectives to uncover new UPS mechanisms and to pave the way for new strategies for therapeutic approaches of NDs. To this end, we will use a multidisciplinary approach by combining biochemical, high-throughput and in vivo approaches, as well as state-of-the-art imaging and genomic technologies.

At the crossroad of critical challenges, the project will can make important advances into basic mechanisms that will then be exploited for biomedical applications.





18 STRUCTURE AND ACTIVATION OF THE RGA4/ RGA5 IMMUNE RECEPTORS FROM RICE

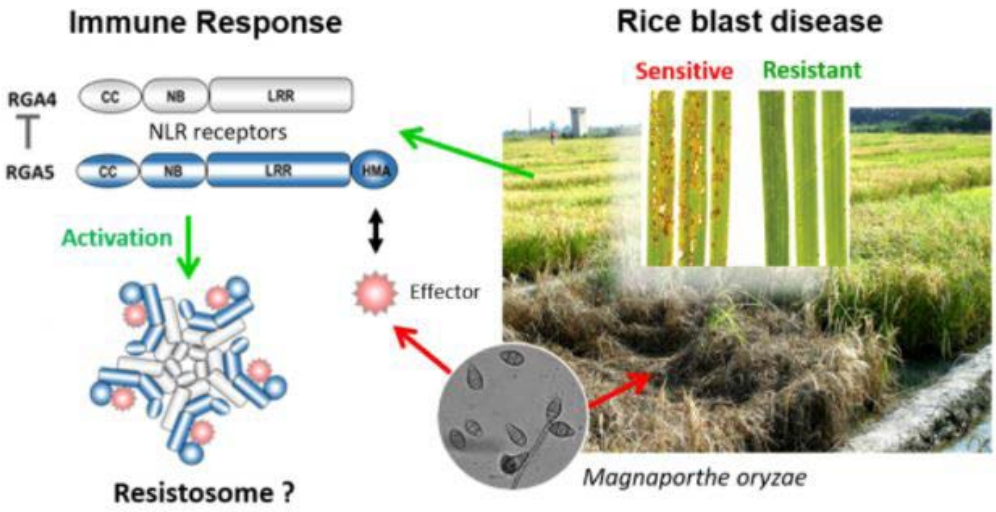
ÉQUIPES

ÉQUIPE

Encadrant :
Nathalie Declerck (CBS : Centre de Biochimie Structurale)

Encadrant : Karine DE GUILLEN (CBS : Centre de Biochimie Structurale)

The Master's student will join the group "Structural basis of plant immunity" which has been collaborating for many years with INRAE to study the NLR-type immune receptors RGA4 and RGA5 from rice, with the aim of engineering novel receptors providing improved resistance to crop disease. The work is based on a strongly interdisciplinary and integrative approach combining protein biochemistry, structural biology and biophysics, bioinformatics and plant molecular genetics. Current efforts are focused on the production of whole proteins and complexes for structural studies of the macromolecular assembly (resistosome) formed by RGA4 and RGA5 upon infection by a fungal pathogen. During the internship, the Master's student will contribute to different aspects of the ongoing work and use different experimental techniques for the production and structural characterization of recombinant proteins. This project is supported by an ANR grant that includes funding for a PhD fellowship starting September 2022.



19 CONCEPTION D'UNE FORMULATION POUR LA REMINÉRALISATION DENTAIRE

Le phénomène d'érosion de l'émail dentaire est un phénomène fréquent qui peut toucher n'importe quelle population, à n'importe quel âge. C'est l'un des facteurs à l'origine de nombreux problèmes dentaires dont l'apparition de caries, la fragilisation des dents, voire l'apparition d'infections lorsque la pulpe dentaire est atteinte... L'émail, une fois érodé, n'est pas capable de s'auto-réparer et il n'existe à l'heure actuelle aucun traitement permettant de le régénérer. Dans ce contexte, un partenariat entre les laboratoires Pierre Fabre, dont la branche Oral Care est spécialisée dans le soin dentaire, l'équipe de recherche « Polymères pour la Santé et les Biomatériaux » de l'IBMM et la Plateforme de Protéomique Clinique du CHU de Montpellier, a été initié afin de bénéficier de l'expertise de ces équipes pour certains aspects de ce projet pluridisciplinaire autour de la reminéralisation de l'émail dentaire dans le contexte physiologique de la sphère buccale. Le candidat devra avoir de solides compétences en chimie organique/inorganique. Des connaissances en chimie du vivant/biologie, chimie des substances naturelles, chimie analytique (spectrométrie de masse), chimie des polymères et/ou en formulation galénique seront un plus. Le projet sera réalisé au sein du Département des « Polymères pour la Santé et les Biomatériaux » de l'IBMM (http://ibmmpolymerbiomaterials.com/) sous l'encadrement d'Hélène Van Den Berghe et de la Plateforme de Protéomique Clinique du CHU de Montpellier, sous l'encadrement du Pr Christophe Hirtz. Des séjours dans la société Pierre Fabre, basée à Castres et à Toulouse, seront également à prévoir durant le stage.

ÉQUIPES

Encadrant :
Hélène Van Den Berghe / Pôle Chimie Balard Montpellier

Encadrant :
Christophe Hirtz / Plateforme de Protéomique Clinique CHU Montpellier

Encadrant :
Mélanie Souyris / Pierre Fabre Castres

20 SYNTHÈSE PAR MÉCANOCHIMIE DE CHIMIOTHÈQUES CIBLANT LES RÉCEPTEURS 5HT$_6$

ÉQUIPES

ÉQUIPE

Encadrants :
Frédéric Lamaty, Xavier Bantreil (Institut des Biomolécules Max Mousseron : IBMM)

Encadrant : Séverine Chaumont-Dubel (Institut de Génomique Fonctionnelle : IGF)

Le projet EcoSero6TSA est à l'interface chimie-biologie. Son objectif est de mettre au point l'utilisation d'un outil éco-compatible innovant en chimie de synthèse, la mécanochimie, pour une application en chimie médicinale avec la synthèse de molécules traitant les symptômes associés aux troubles du spectre autistique (TSA) pour lesquels le récepteur 5-HT$_6$ de la sérotonine est une cible thérapeutique prometteuse. La mécanochimie, avec l'utilisation de broyeurs à billes, permet d'effectuer des réactions chimiques en l'absence de solvant organique en faisant appel à des forces mécaniques. Cette approche, novatrice en chimie médicinale, permet la préparation rapide de chimiothèques ciblant le récepteur 5-HT$_6$ de la sérotonine.
Nous nous inspirerons des structures que nous avons synthétisées précédemment, validées comme actives dans d'autres pathologies (voir schéma ci-contre), pour concevoir de nouveaux ligands potentiels d'intérêt pour le projet. Le stage consistera à préparer par mécanochimie cette nouvelle famille de molécules hétérocycliques. Ces molécules seront ensuite testées in vitro et in vivo pour évaluer leur efficacité à inhiber les voies de signalisation liées au récepteur 5-HT$_6$.

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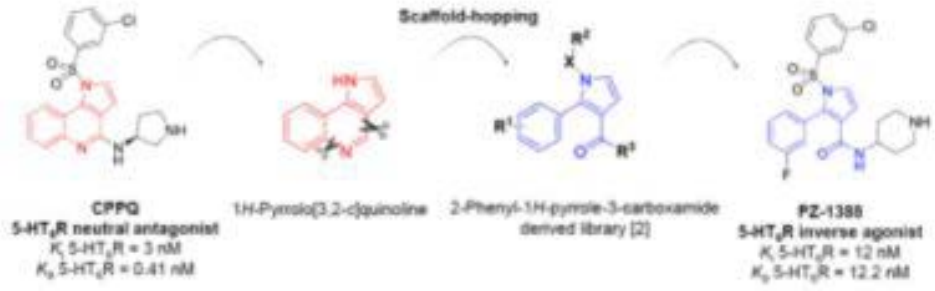

21 DESIGN AND SYNTHESIS OF KALLIKREIN 6 INHIBITORS AGAINST MULTIPLE SCLEROSIS

ÉQUIPES

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease on the central nervous system. MS affects more than two million worldwide, including 100 000 in France, with 3 000 to 5 000 new cases reported each year. The consequences of this demyelination are multiple and result in severe motor, sensory and cognitive decline. So far, disease-modifying drugs in the market are mainly targeting the inflammatory component of the pathology, but have little impact on remyelination. The identification of new therapeutic compounds enhancing myelin repair in MS is thus a critical public health issue. Recently, we identified potent inhibitors of kallikrein 6 (KLK6), a serine protease involved in the process of dymyelination/remyelination of axons.[1] These compounds showed pro-myelinating potential in vitro and ex-vivo. In collaboration with Pr El Amri (Sorbonne University) and Dr Nait Oumesmar (Brain Institute, Paris, the project supported by the ANR, aims to study this family of compounds (SAR studies) and to enhance the potency and the selectivity of the first identified hits.

Encadrant :
Nicolas Masurier : Institut des Biomolécules Max Mousseron (IBMM)

1 S. AÏt Amiri et al., J. Med. Chem., 2021, 64, 5667-5688

ÉQUIPES

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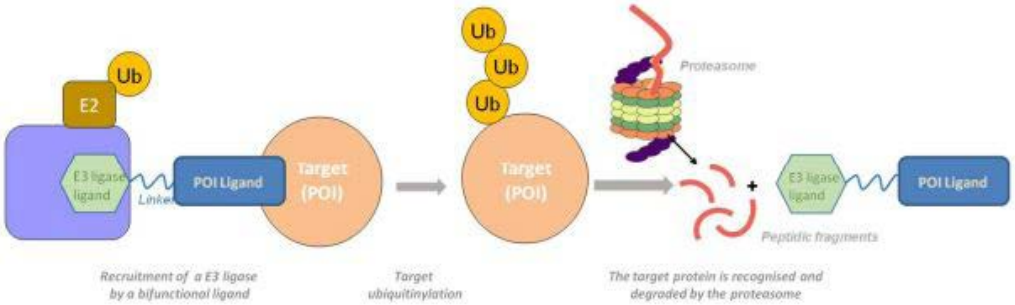
Encadrant : Jean-Marc Brondello (Institute for Regenerative Medicine and Biotherapy (IRMB)

21 SENOPROTAC: SYNTHESIS OF PROTACS TARGETING SENESCENT CELLS TO INDUCE THEIR SPECIFIC ELIMINATION

Osteoarthritis (OA) is the most common articular disease. More than a third of the population after 60 years display radiographic signs for knee OA. To date, no curative treatment is available for OA patients and there is a huge unmet need before prosthetic surgical joint replacement. Recent works reveal the central role of cellular senescence as driving force in OA development. In this project, we aim to synthesize and then evaluate the senotherapeutic activity of PROTACs (PROteolysis TArgetting Chimeras) compounds able to target senescence-regulatory factors (POI) that we have identified. PROTACs are bifunctional molecules that simultaneously bind a target protein and an E3 ubiquitin ligase. This leads to the poly-ubiquitination of the target protein, which is then degraded into small peptides and amino-acids by the proteasome complex. The first step of the project will consist of synthesizing bifunctional molecules at IBMM. Then, the effect of the different constructs will be evaluated within IRMB on a cellular model in order to assess their activities on senescence.



EN PARTENARIAT AVEC

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