N°	Title of the Project	Email
1	Combining proton FLASH and best-in-class DRAK1 inhibition to reduce radiation maculopathy in uveal melanoma	maeva.dufies@gmail.com,
2	Multi-Scale Molecular Rejuvenation by Cell-Type-Specific Partial Reprogramming	Dmitry.BULAVIN@univ-cotedazur.fr
3	Dynamic role of SLC3A2 variants in murine embryo development	chloe.feral@inserm.fr Matteo.RAUZI@univ-cotedazur.fr
4	Characterization and preclinical development of new ferroptosis inducers in melanoma	stephane.rocchi@univ-cotedazur.fr
5	Decoding the role of Glutamylation in Endocytic trafficking functions and liver metabolism	Jerome.GILLERON@univ-cotedazur.fr
6	STK17A as a Therapeutic Achilles' Heel in Glioblastoma and SHH-Medulloblastoma	Gilles.PAGES@univ-cotedazur.fr
7	Microbiota-derived metabolites as biomarkers and mediators of social deficits in autism: insights from mice and humans	davidovic@ipmc.cnrs.fr louis-felix.nothias@cnrs.fr
8	From Genomes to Networks: Population-Scale Rewiring of Protein Interactomes	gianni.liti@univ-cotedazur.fr Gergo.GOGL@univ-cotedazur.fr
9	Dynamics of therapy-induced tumor cell plasticity and extracellular matrix remodeling in melanoma	Sophie.tartare-deckert@inserm.fr
10	Extracellular vesicle–mediated transmission of ER stress and mitochondrial dysfunction in liver fibrosis	Beatrice.BAILLY-MAITRE@univ-cotedazur.fr mchami@ipmc.cnrs.fr
11	Deciphering the gene regulatory networks ruling plant-nematode parasitic interactions	julia.truch@inrae.fr
12	Studying a morphogenetic wave driving gut formation during embryo development	Matteo.RAUZI@univ-cotedazur.fr
13	Modeling the dynamics of a plant host exposed to multiple pathogens with artificial intelligence guided by physics	silvia.bottini@inrae.fr
14	A Physical Model of miRNA-Binding Activity in Animals and Plants	michele.trabucchi@univ-cotedazur.fr stephanie.jaubert@inrae.fr
15	Tumoroid-Guided Targeting of Ptch1 to Reverse Resistance in NSCLC	mus-veteau@ipmc.cnrs.fr valerie.vouret@univ-cotedazur.fr
16	Experimental deciphering and computational modelling of the molecular mechanisms of tumor cell invasion	luton@ipmc.cnrs.fr Rachele.ALLENA@univ-cotedazur.fr
17	Regeneration & Metabolism: Deciphering the implications of the telomerase TERT	eric.rottinger@univ-cotedazur.fr
18	DECODING OLFACTORY CONTROL OF DEVELOPMENTAL TIMING: FROM SENSORY NEURONS TO PREDICTIVE CHEMISTRY	nuria.romero@univ-cotedazur.fr
19	Experimental and theoretical analysis of ultradian rhythms	Franck.Delaunay@univ-cotedazur.fr
20	Exploring dimerization as a key mechanism of transcription factor specificity	Dominic.VAN-ESSEN@univ-cotedazur.fr Boglarka.ZAMBO@univ-cotedazur.fr
21	Lysosomal reprogramming as a driver of drug resistance in breast cancer	Sandy.GIULIANO@univ-cotedazur.fr
22	Dynamic Immune Editing of Cellular Senescence by Natural Killer Cells: Implications for Liver Fibrosis	Julien.cherfils@univ-cotedazur.fr
23	Investigating the TET2-mediated regulation of chromatin architecture in B cell lymphomas	Pilar.DOMINGUEZ@univ-cotedazur.fr Eirini.TROMPOUKI@univ-cotedazur.fr
24	A Multi-omic Integration Approach to Understand the Etiology of Fragile X Syndrome	gwizdek@ipmc.cnrs.fr
25	Homochirality Regulation and the Role of Heterochirality in Aging and Disease	agnes.banreti@univ-cotedazur.fr uwe.meierhenrich@univ-cotedazur.fr

PhD project proposal

Title of the Project: Combining proton FLASH and best-in-class DRAK1 inhibition to reduce radiation maculopathy in uveal melanoma

Research Team involved:

- Team 1 : Maeva Dufies (IRCAN – eq Gilles Pagès) https://www.ircan.org/research/teams/gilles-pages/
- Team 2 : Cyril Ronco (ICN) - https://icn.univ-cotedazur.fr/axes-de-recherche/molecules-bioactives/drug-advances-innovations/group-members
- Team 3: Johan-Petter HOFVERBERG /Jerome Doyen (Centre Antoine Lacassagne - CAL) https://www.protontherapie.fr

Consortium: IRCAN (biology, biomarkers, zebrafish/mouse), CAL (FLASH/conventional irradiation) and ICN (medicinal chemistry, DRAK1 inhibitors).

Supervisor Name (s): Maeva Dufies

Contact Person(s): Maeva Dufies, maeva.dufies@gmail.com, 0699596143

Keywords: Proton FLASH; Uveal melanoma; Ocular toxicity (radiation maculopathy); Oxidative stress; DRAK1/STK17A inhibitors; Zebrafish and murine models

Abstract (2,000 characters max including spaces):

Uveal melanoma is the most common primary intra-ocular malignancy in adults. Although ocular proton therapy achieves excellent local control, the macula/retina, cornea and ocular microvasculature are only millimetres away. A central driver of post-irradiation ocular damage is oxidative-stress signalling, which promotes endothelial dysfunction, ischemia and pathological angiogenesis—key steps toward radiation maculopathy/retinopathy. Up to 50% of patients develop these complications; progression can trigger neovascularization, neovascular glaucoma and, in severe cases, enucleation. Targeting stress-response nodes such as DRAK1, a kinase implicated in oxidative stress and cell-death pathways, offers a rational route to limit toxicity while preserving efficacy.

FLASH radiotherapy—ultra-high dose-rate delivery—may spare normal tissues without losing anti-tumor efficacy. In France, proton therapy has long been centered on two major sites (Institut Curie–Orsay and Centre Antoine Lacassagne–Nice). At Centre Antoine Lacassagne (CAL), physicists have developed an in-house proton FLASH capability (≈300 Gy/s vs ≈1 Gy/s conventional), enabling unique head-to-head comparisons.

Hypothesis: at matched physical dose, proton FLASH maintains uveal melanoma cell killing while attenuating DRAK1-linked oxidative injury in retinal, corneal and endothelial cells; combining FLASH with ICN's state-of-the-art, highly selective DRAK1 inhibitors will further enhance normal-tissue protection without compromising tumor control.

Aims: (1) compare FLASH vs conventional protons on uveal melanoma models; (2) quantify ocular safety and molecular injury pathways (oxidative stress, endothelial dysfunction, pro-angiogenic signalling) and determine the contribution of DRAK1; (3) validate in vivo safety using zebrafish then murine models, and test ICN-developed best-in-class DRAK1 inhibitors as an add-on radioprotective strategy.

Overall, this project will establish whether proton FLASH—alone or enhanced by best-in-class DRAK1 inhibition—can maintain uveal melanoma tumor control while markedly reducing vision-threatening ocular toxicity, paving the way for safer clinical translation at CAL.

PhD project proposal

Title of the Project: Multi-Scale Molecular Rejuvenation by Cell-Type-Specific Partial Reprogramming

Research Team involved:

- Team 1 : Dmitry Bulavin, https://www.ircan.org/research/teams/dmitry-bulavin/
- Team 2 : Stoyan Ivanov, https://lp2m.univ-cotedazur.fr/axes-de-recherche/cellules-myeloides-et-metabolisme

Supervisor Name (s): Dmitry Bulavin/ Stoyan Ivanov

Contact Person(s): Dmitry.Bulavin@unice.fr

Keywords: Ageing, reprogramming, rejuvenation, senescence-related molecular networks, myeloid-related molecular interactions

Abstract (2,000 characters max including spaces):

Ageing is driven by progressive disruption of molecular interactions across multiple biological scales, including epigenetic regulation, protein interaction networks, metabolic pathways, and intercellular communication. Myeloid cells are particularly susceptible to these changes, acquiring senescence-like states characterized by altered chromatin architecture, inflammatory proteomes, and rewired intracellular metabolism. These dysfunctional myeloid cells contribute to chronic inflammation, impaired tissue regeneration, and systemic loss of homeostasis during ageing.

This project aims to investigate whether cell-type-specific partial reprogramming can restore youthful molecular interactions in peripheral myeloid cells and thereby promote systemic rejuvenation. Using inducible mouse models enabling targeted expression of Yamanaka factors in p16^{High} cells and myeloid lineages, we will dissect how transient reprogramming reshapes ageing-associated molecular networks at the cellular and tissue levels.

An integrated multi-omics strategy combining transcriptomics, epigenomics, proteomics, and metabolomics will be employed to map rejuvenation across hierarchical layers of regulation. We will analyze how partial reprogramming resets transcriptional and chromatin states, remodels protein–protein and inflammatory signaling networks, and restores metabolic flexibility in aged myeloid cells. Particular emphasis will be placed on changes in the senescence-associated

secretory phenotype and myeloid-driven intercellular signaling that influence tissue microenvironments across organs.

AI-assisted network modeling and trajectory inference will be used to identify conserved molecular signatures of rejuvenation and causal interactions linking myeloid cell state to tissue-level outcomes. By focusing on molecular interaction networks rather than single pathways, this project aims to define mechanistic principles by which partial reprogramming mitigates inflammaging, restores immune homeostasis, and supports healthy ageing at the organismal level.

PhD project proposal

Title of the Project: Dynamic role of SLC3A2 variants in murine embryo development

Research Team involved:

- Team 1 : Name and website FERAL, IRCAN, https://www.ircan.org/research/teams/chloe-feral/
- Team 2 : Name and website RAUZI, IBV, http://ibv.unice.fr/research-team/rauzi/

Supervisor Name (s): FERAL Chloé & RAUZI Matteo

Contact Person(s): FERAL Chloé & RAUZI Matteo

Keywords: embryo development, mouse, compaction, mechanobiology

Abstract (2,000 characters max including spaces):

CD98hc/SLC3A2, highly expressed in proliferative cells, is a dual function transmembrane protein, modulating integrin signaling through direct interactions, and acting as a chaperone for SLC7 amino acid transporter family. Sequencing data suggests the existence of previously uncharacterized CD98hc isoform. Our preliminary experiment using CRISPR/Cas9 genome editing to selectively KO the novel isoform showed lethality as early as 8-cell-embryo (compared with E3.5-9.5 for the original isoform). **The proposed PhD project aims to characterize the expression, molecular functions, and physiological roles of this novel CD98hc isoform *in vivo* in early mouse embryogenesis.** We will pursue isoform-specific genetic approaches (KO and fluorescent tag) to generate embryos specifically deficient in the novel isoform, as well as knock-in reporter lines. Preimplantation embryos will be analyzed from the zygote to blastocyst stages to assess developmental progression, lineage specification, and cell fate decisions. We propose to characterize and study the spatial and temporal dynamics of the novel isoform, and its impact on cell division, polarity, compaction, and morphogenetic movements. To do so, we will employ multi-view light sheet microscopy for live *in toto* imaging, for minimal phototoxicity, together with 3D+time big data processing and quantitative image analysis. Quantitative analyses of mechanotransduction, integrin signaling, and extracellular matrix organization will also be performed in developing embryos using immunostaining, traction force-related readouts, and transcriptional profiling. Together, these approaches will allow the identification of isoform-specific functions of CD98hc during early embryonic development and provide insight into how integrin-mediated signaling and amino acid transport contribute to early developmental decisions. The complementarity of the teams, CD98hc expert (FERAL) and embryo live imaging expert (RAUZI) strengthen this proposal.

PhD project proposal

Title of the Project: Characterization and preclinical development of new ferroptosis inducers in melanoma

Research Team involved:
- Team 1 : INSERM U1065, C3M, Team 12. Team 12 | C3M - Centre Méditerranéen de Médecine Moléculaire
- Team 2 : UMR7272, ICN, "Bioactive Molecules" team. Bioactive Molecules - ICN

Supervisor Name (s): Stéphane Rocchi

Contact Person(s): Stéphane Rocchi (stephane.rocchi@univ-cotedazur.fr)

Keywords: Melanoma, ferroptosis, small bioactive molecules, overcoming therapy resistance

Abstract (2,000 characters max including spaces):
Melanoma is a very aggressive skin cancer causing 58,700 deaths per year. Despite dramatic improvement in the clinical management achieved by targeted- and immunotherapies, about 50% of patients with metastatic disease still face therapeutic failure due to primary or acquired resistance. The urge to identify new therapeutic approaches led us to set up a medicinal chemistry program that uncovered the *in vitro* and *in vivo* antineoplastic properties of the phenylamino-1,3,5-triazines (PATs), a new family of potent ferroptosis inducers. Ferroptosis is a programmed cell death playing a key role in tumor control. Several ferroptosis inducers are available but their development was stopped due to a lack of *in vivo* efficacy, along with unfavorable metabolic profile. There is thus a niche for the development of PATs that are structurally distinct.
Our solid preliminary data describes the efficacy and the mode of action of PATs. We now aim (1) to identify their direct targets responsible for the induction of ferroptosis by click chemistry, biological validation and crystallography ; (2) to evaluate the therapeutic potential of PATs on our collection of patient-derived melanoma cells with a focus on targeted and immuno-therapies resistant that often display an undifferentiated phenotype linked to increased sensitivity to ferroptosis ; (3) to perform a CRISPR screen to identify the susceptibility and potential resistance mechanisms to PATs ; (4) to determine the main physicochemical properties, early pharmacological profile and the efficacy of PATs in therapy resistant melanoma alone or in combination with immunotherapies.
This interdisciplinary project between a chemistry and a biology team will explore and optimize the therapeutic potential of PATs in preclinical models of melanoma. In the absence of ferroptosis inducer in late stage of development, there is an open field for PATs to exploit this tumoral liability in melanoma and other malignancies.

PhD project proposal

Title of the Project: Decoding the role of Glutamylation in Endocytic trafficking functions and liver metabolism

Research Team involved:

- Team 1 : Insulin resistance in obesity and type 2 diabetes (IROD) – C3M.
  https://www.c3m-nice.fr/en/Teams/team-07/
- Team 2 : Cellular mechanics from the molecular to the tissue scale - IPMC.
  https://www.ipmc.cnrs.fr/fr/team/mecanique-cellulaire-de-lechelle-moleculaire-a-lechelle-tissulaire/

Supervisor Name (s):
Gilleron Jérôme, PhD, HDR.
Torrino Stéphanie, PhD, HDR.

Contact Person(s):
Jerome.gilleron@univ-cotedazur.fr

Keywords: Endocytic trafficking, post-translational modifications, liver metabolism, molecular regulation

Abstract (2,000 characters max including spaces):
Endocytic trafficking arises over the last decades as a pivotal regulator of liver metabolism. Conversely, metabolic cues were found to regulates endocytic trafficking. In accordance, we recently discovered that the changes in metabolic cues that occurs between feeding and fasting states can tune very quickly the location of proteins involved in endocytic trafficking. These results suggest that hepatocytes, the main liver cells, adapt their endocytic trafficking in response to metabolites availability. Importantly, this adaptation is fast, suggesting that the proteins involved the endocytic trafficking are tuned through post-translational modifications (PTMs). Strikingly, we obtained preliminary results demonstrating that glutamylation, a PTM based on glutamate substrate, are detected on proteins involved in endocytic trafficking. However, the role of this PTM on endocytic trafficking functions and its sequential impact on hepatocyte metabolism remains ill-defined. Based on these preliminary results, we **made the hypothesis that during the feeding-to-fasting transition, when glutamate concentration increases within hepatocytes, metabolite-based PTM of proteins involved in endocytic trafficking occurs leading to a reorganization of the endocytic function that tune hepatocytes metabolic adaptation**.

To test this hypothesis, we will:

1. Identify the proteins that are glutamylated in hepatocytes *in vivo* upon feeding and fasting.
2. Determine the impact of this PTM on endocytic functionality.
3. Elucidate whether disturbing this PTM on endocytic trafficking proteins is pivotal for metabolic functions.

This project, at an exciting new interface between liver metabolism and endocytic trafficking, has the potential to identify novel mechanisms and players involved in the physiological responses to fasting and feeding. To achieve this project, our consortium combines multidisciplinary approaches from cellular and molecular biology, in a physiological context.

PhD project proposal

Title of the Project: STK17A as a Therapeutic Achilles' Heel in Glioblastoma and SHH-Medulloblastoma

Research Team involved:

- Team 1 : Gilles Pagès (IRCAN)
- Team 2 : Cyril Ronco (ICN)

Supervisor Name (s): Gilles Pagès

Contact Person(s): Gilles Pagès

Keywords: Glioblastoma; Medulloblastoma; STK17A; kinase inhibitors; TGFβ signalling; hit-to-lead/SAR; orthotopic mouse models.

Abstract (2,000 characters max including spaces):

State of the art
Malignant brain tumors rely on plastic molecular networks driving proliferation, invasion, and therapy resistance. Serine/threonine kinase 17A (STK17A) regulates apoptosis–survival decisions and actomyosin-dependent processes controlling cell division and migration. High STK17A expression correlates with poor outcome in glioblastoma (GBM) and pediatric medulloblastoma (MB). MB comprises molecular subgroups with distinct prognosis (WNT, SHH, non-WNT/non-SHH groups 3 and 4). Elevated STK17A is associated with shorter survival in SHH-MB, revealing a subgroup-specific vulnerability.

Hypothesis
STK17A orchestrates a phosphorylation-driven program linking cytoskeletal and cytokinesis modules to pro-invasive transcriptional states, including TGFβ/SMAD outputs. Selective inhibition is expected to rewire these networks and suppress malignant phenotypes in GBM and SHH-MB.

Objectives
This DYNABIO-oriented project (IRCAN–ICN) aims to establish STK17A's causal protumor role using genetic and pharmacological approaches and to build a preclinical framework for therapeutic targeting.

Methodology
1. Map STK17A signaling circuits via phosphor-proteomics and RNA-seq after genetic and chemical perturbation.
2. Validate STK17A dependency in GBM and SHH-MB cell lines and patient-derived 2D/3D cultures, assessing proliferation, apoptosis, stemness, and invasion, and linking phenotypes to molecular signatures.
3. Conduct iterative hit-to-lead/SAR program combining kinase assays, selectivity profiling (including STK17B), and cellular target-engagement readouts.
4. Test best-in-class compounds in orthotopic GBM and SHH-MB xenografts to assess tumor control, survival, and biomarker translatability.

Expected results

The project will deliver selective STK17A tool and lead compounds and a mechanistically grounded preclinical decision package supporting stratified translation in aggressive brain tumors.

PhD project proposal

Title of the Project:

Microbiota-derived metabolites as biomarkers and mediators of social deficits in autism: insights from mice and humans

Research Team involved:

- **Team 1:** Institut de Pharmacologie Moléculaire et Cellulaire (IPMC, CNRS / Université Côte d'Azur) – Team : Microbiota, Immunity and Neurodevelopment
- **Team 2:** Institut de Chimie de Nice (ICN, CNRS / Université Côte d'Azur) – Holobiomics & metabolomics group

Supervisor Name (s):

- Laetitia Davidovic (DR CNRS, HDR, IPMC) – main supervisor
- Louis-Félix Nothias (CPJ CNRS, ICN) – co-supervisor

Contact Person(s):

- Laetitia Davidovic – email: davidovic@ipmc.cnrs.fr
- Louis-Félix Nothias – email: louis-felix.nothias@cnrs.fr

Keywords:

Autism spectrum disorders; Microbiota–gut–brain axis; Microbial metabolites; Metabolomics; Social behavior; Dopamine and noradrenaline; Human cohort studies; Mouse models

Abstract (2,000 characters max including spaces):

Autism spectrum disorders (ASD) affect about 1 % of children worldwide, yet no validated biomarkers and no pharmacological treatments targets the core social deficits – the most disabling feature of the condition. The gut microbiota and its metabolites (mMet) have emerged as a key determinant of neurodevelopment that is perturbed in ASD. In particular, aromatic mMet produced from the amino acids phenylalanine and tyrosine, such as p-cresol and phenylacetate, are increased in the urine of children with ASD and correlate with social impairments.

Preclinical work from Team 1 shows that these mMet reach the brain, alter dopamine and noradrenaline signaling in social reward circuits, and are sufficient to induce long-lasting social deficits in mice. However, it remains unknown which metabolite signatures best predict social outcomes in humans and whether additional mMet contribute to social deficits in mice.

This PhD aims to (i) identify, in the French EDEN birth cohort (N=1,000 children sampled from the general population and followed from birth to 8 years), networks of mMet forming urinary signatures associated with and predictive of trajectories in social competence between ages 3 and 8 years, in interaction with perinatal and socioeconomic factors; (ii) test novel candidate mMet on mice social behavior and neuronal activity; (iii) integrate human and animal data through predictive models to prioritize relevant translational mMet biomarkers for ASD in the general population.

The project lies at the interface between neuroscience, analytical chemistry, microbiology and data science, fits within the scientific scope of DYNABIO on molecular interactions at the metabolite level, and will contribute to a better mechanistic understanding of environmental influences on neurodevelopmental trajectories. It will provide the PhD student with cutting-edge training in metabolomics, mouse models and quantitative data analysis within a highly transdisciplinary collaborative environment.

PhD project proposal

Title of the Project:

From Genomes to Networks: Population-Scale Rewiring of Protein Interactomes

Research Team involved:
- Team 1 : Population genomics & complex traits
  https://www.ircan.org/research/teams/gianni-liti/
- Team 2 : Quantitative Interactomics and Disease-Related Networks
  http://ibv.unice.fr/research-team/gogl/

Supervisor Name (s): Gergo GOGL, Gianni LITI

Contact Person(s): gianni.liti@univ-cotedazur.fr, gergo.gogl@univ-cotedazur.fr

Keywords: population genomics, interactomics, natural variants

Abstract (2,000 characters max including spaces):

Inter-individual variation in macromolecular interaction networks is a largely unexplored layer of phenotypic diversity. Here, we propose to combine population genomics and interactomics to systematically dissect how natural genetic variation reshapes protein–protein interaction networks across populations. Leveraging genomic data from thousands of wild and domesticated Saccharomyces strains, we will identify putative coding variants affecting known and previously uncharacterized interaction interfaces, with a particular focus on intrinsically disordered regions that are enriched in natural variation and frequently harbour short linear binding motifs. Missense genetic variants will be annotated for their predicted impact on function and structure. Using new-generation high-throughput interactomic assays, we will map and experimentally investigate how these variants rewire interaction networks in an individual-specific manner. This approach will reveal how natural variants perturb interaction networks by altering the thermodynamic properties of protein interactions across a continuous spectrum, ranging from subtle affinity changes to complete loss or gain of interactions absent from most of the population. By integrating these network perturbations with in vivo phenotypes related to growth, stress responses, aging and other fitness traits, we aim to elucidate how environmental pressures and domestication shape the selection of specific variants during the species evolution. Overall, this project will establish a general framework linking population-scale genetic diversity to variability in cellular networks and organismal phenotypes.

PhD project proposal

Title of the Project: Dynamics of therapy-induced tumor cell plasticity and extracellular matrix remodeling in melanoma

Research Team involved:
- Team 1: Team "Microenvironment, Signaling and Cancer" (MicroCan), C3M
- Team 2: Team "Non-coding Genome and pulmonary pathologies", IPMC

Supervisor Name (s): S. Tartare-Deckert (C3M) and B. Mari (IPMC) (50% each as co-supervisor)

Contact Person(s): S. Tartare-Deckert (Sophie.tartare-deckert@inserm.fr)

Keywords: tumor cell plasticity, extracellular matrix, functional genomics, single-cell and spatial biology

Abstract (2,000 characters max including spaces):
Cutaneous melanoma is an aggressive malignancy marked by extensive intratumoral heterogeneity and phenotypic diversity. Melanoma cells dynamically transition through a spectrum of differentiation states, each associated with distinct functional traits. Through transcriptomic reprogramming, cells adapt to stressful microenvironments and therapeutic pressure that represents a major barrier to durable treatment responses. Adaptive resistance to targeted therapy is associated with a switch from a differentiated state to a dedifferentiated, mesenchymal-like phenotype. This transition is associated with enhanced extracellular matrix (ECM) remodeling, promoting a fibrotic, mechanically altered, and drug-tolerant microenvironment that fuels resistance and tumor relapse[1,2]. Despite its clinical relevance, the molecular and cellular mechanisms driving intra-tumor fibrosis heterogeneity in response to therapy remains poorly understood. This project builds on original and compelling data from Team 1 revealing a key role for the mechanical signals in regulating melanoma cell differentiation and drug resistance[3]. To unravel the molecular circuits driving tumor mechano-phenotypic adaptation and to chart the spatial architecture of rigidity and fibrotic niches in melanoma, we will combine *in vitro* and *in vivo* models with cutting-edge multi-omics approaches including single-cell and spatial transcriptomics[4], ECM proteomics and advanced imaging technologies.

The specific objectives are to: (1) define how mechanical forces shape tumor cell behavior and plasticity; (2) map the temporal and spatial organization of mechano-phenotypic heterogeneity during response; to targeted therapy, and (3) provide preclinical proof-of-concept that targeting the cell state-dependent ECM dynamics enhances therapeutic efficacy.

This interdisciplinary project brings together Team 1, with expertise in melanoma biology,[1,2,3] and Team 2, with complementary strengths in omics and bioinformatics[4,5].

[1]Girard et al *Cancer Res* 2020
[2]Diazzi et al *EMBO Mol Med* 2022
[3]Biber et al *Cell Rep* 2025
[4]Truchi *et al. Nat. Com* 2025
[5]Peyre *et al Mol Syst Biol* 2025

PhD project proposal

Title of the Project:

Extracellular vesicle–mediated transmission of ER stress and mitochondrial dysfunction in liver fibrosis

Research Team involved:

- Team 1 : Hematometabolism and metainflammation (HEMAMETABO) and https://www.c3m-nice.fr/equipes/equipe-13/
- Team 2 : AlzPark team and https://www.ipmc.cnrs.fr/fr/member/mounia-chami/

Supervisor Name (s): Bailly-Maitre Béatrice et Mounia Chami

Contact Person(s): Bailly-Maitre Béatrice et Mounia Chami

Keywords: Liver fibrosis,

Abstract (2,000 characters max including spaces):

Metabolic dysfunction–associated steatohepatitis is a leading cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Hepatocyte injury initiates fibrogenesis, yet how stressed hepatocytes transmit pathogenic signals to neighboring cells remains poorly understood.

Work from Dr Bailly-Maitre's team shows that hepatocyte-specific inhibition of IRE1α RNase activity protects against liver fibrosis (Hazari et al, *Hepatology* 2026). In parallel, our data indicate that ER-stress components are released in the hepatocyte secretome and transferred to hepatocytes and hepatic stellate cells, promoting disease progression. Emerging evidence from Dr Chami's laboratory gain expertise in extracellular vesicles (EVs) studies in Alzheimer's disease (Lauritzen et al., J Extracellular Vesicles 2025; Eysert et al., DOI: https://doi.org/10.1101/2025.01.08.631851). They demonstrate that stressed cells export dysfunctional mitochondria through large EVs containing mitochondria, propagating metabolic stress between cells. They develop reliable protocols for small and large EVs isolation from tissues *in vivo*.

This PhD project will test whether hepatocyte-derived EVs act as vectors of ER-stress signals and mitochondrial dysfunction, thereby amplifying fibrogenesis. Using genetically engineered mouse models targeting hepatocyte IRE1α RNase activity, combined with EVs isolation and proteomic characterization, mitochondrial transfer assays, and metabolic profiling, we will define how EVs cargo reprograms recipient hepatocytes and HSCs.

The project relies on a complementary collaboration between a team specialized in liver biology, ER stress and fibrosis and a team expert in EVs and mitochondrial biology. Beyond liver pathology, we will explore whether chronic hepatocyte stress and EV-mediated mitochondrial dissemination contribute to cognitive alterations, building on Dr Chami's expertise in neurodegenerative diseases and data linking hepatocyte RNase activity to systemic inflammation.

PhD project proposal

Title of the Project:
Deciphering the gene regulatory networks ruling plant-nematode parasitic interactions

Research Team involved:
- Team 1 : ISA: Interactions Plantes-Nématodes (IPN) https://institut-sophia-agrobiotech.paca.hub.inrae.fr/equipes-isa/ipn (Dr Julia Truch) and Genomics & Adaptive Molecular Evolution (GAME) - http://www.isa-game.fr/ (Dr Etienne Danchin)
- Team 2 : INRIA : DataShape https://www.inria.fr/en/datashape (Dr Mathieu Carrière)

Supervisor Name (s): Dr Etienne Danchin (HDR), co-supervisor Dr Julia Truch

Contact Person(s): julia.truch@inrae.fr, etienne.danchin@inrae.fr

Keywords: Plant-Nematode Interactions, Gene Regulatory Network, Topological Data Analysis, Single Cell, Parasitism

Abstract (2,000 characters max including spaces):

Root-knot nematodes (RKN) are among the most destructive soil-borne crop pathogens worldwide. These highly polyphagous parasites infect plant roots at the second juvenile stage (J2), inducing the formation of specialized feeding structures composed of multinucleate giant cells and vascular tissue. The profound reprogramming of host cells differentiation is essential for nematode growth, reproduction, and gall formation, and results in severe agronomical yield losses. This parasitic interaction relies on secreted effector proteins, yet the regulatory mechanisms controlling effector expression and parasitism-related gene regulatory networks remain poorly understood.
Previous transcriptomic analyses in RKN revealed a strong stage-specific gene regulation and highlighted a conserved DNA motif enriched in promoter regions of a subset of effector genes suggesting coordinated transcriptional control of parasitism genes. In this project, we aim to decipher both the regulatory networks underlying nematode parasitism and plant host reprogramming using an integrative, trans-kingdom approach.
First, we will characterize chromatin accessibility and transcriptional dynamics, using ATAC-seq and RNA-seq data, during nematode pre- and parasitic life cycle and gall development. This strategy will enable the identification of regulatory elements, candidate transcription factors, and gene regulatory networks in both the host and the parasite. Second, *in silico* predictions of protein–DNA and protein–protein interactions will highlight putative key regulatory hubs involved in compatible interactions. Finally, time course analysis of single-nuclei transcriptomics on infective J2 will generate the first cellular atlas of RKN, uncover cell trajectories, and identify early regulators activated at the onset of parasitism. Ultimately, this work will provide new insights into the co-evolution of regulatory networks driving gall formation and nematode parasitic success.

PhD project proposal

Title of the Project: Studying a morphogenetic wave driving gut formation during embryo development

Research Team involved:

- Team 1 : Name and website RAUZI, IBV, http://ibv.unice.fr/research-team/rauzi/
- Team 2 : Name and website MORPHEME, I3S, https://team.inria.fr/morpheme/

Supervisor Name (s): RAUZI Matteo & Grégoire MALANDAIN

Contact Person(s): RAUZI Matteo

Keywords: gut formation, morphogenetic wave, planar cell polarity, tissue mechanics

Abstract (2,000 characters max including spaces):

The formation of epithelial tubes is essential to build organs responsible for directing vital factors outside-in, inside-out or within animals (e.g., food and water through the gut, air through the lungs, or blood through the blood-vessels). Therefore, tube formation is pivotal in multicellular life. Understanding the mechanisms and mechanics responsible for driving tube formation is key to understanding the emergence of complex life forms. This will provide new insights into how tubulogenesis disorders, that result from tube formation failure (e.g., spina bifida, polycystic kidney, tracheal atresia) may emerge.

To study the mechanisms driving epithelial tube formation, we will focus on the formation of the archenteron: a tubular epithelial structure that emerges from the inpocketing of the sea urchin embryo vegetal plate during gastrulation and that gives rise to the digestive tube of the sea urchin larva. Preliminary data from the Rauzi lab (based on an interdisciplinary approach) highlights a morphogenetic wave driving tissue inpocketing. Brachyury is a T-box transcription factor, which expression dynamically travels from cell-to-cell along concentric rings from the vegetal to the animal pole of the embryo during archenteron formation. Downregulation of Brachyury perturbs the formation of the animal gut. The PhD student will develop a comparative analysis between wild type and Brachyury perturbed embryos to characterize and test both the signalling and the morphometric wave. To that end the student will implement light-sheet in toto live imaging, molecular and laser manipulation and µ-aspiration to characterize and probe the inter-cell signalling dynamics, the underlying cytoskeletal remodelling, the tissue mechanics (supervision M. Rauzi) and the cell shape changes in 3D+t (supervision G. Malandain). This interdisciplinary project based on multi-modal and multidimensional analyses, will unveil new fundamental principles governing epithelial tube formation.

N.B. We are currently searching for a PhD candidate.

PhD project proposal

Title of the Project: Modeling the dynamics of a plant host exposed to multiple pathogens with artificial intelligence guided by physics

Research Team involved:

- Team 1: SMILE (Institut Sophia Agrobiotech, Sophia-Antipolis, France) https://institut-sophia-agrobiotech.paca.hub.inrae.fr/equipes-isa/smile
- Team 2: ACUMES (Inria Sophia-Antipolis, Sophia-Antipolis, France) https://team.inria.fr/acumes/
- Team 3: MaIAGE (INRAe, Jouy-en-Josas, France) https://maiage.inrae.fr/
- Team 4: Systems Biology of plant responses to stress (CRAG, Barcelona, Spain) https://www.cragenomica.es/research-groups/systems-biology-plant-responses-stress

Supervisor Name (s): Silvia Bottini

Contact Person(s): Silvia Bottini – silvia.bottini@inrae.fr

Keywords: plant-pathogens interaction – gene regulatory networks – transcriptomics time series – physics informed neural networks

Abstract (2,000 characters max including spaces):

Plant defense against biotic threats requires multiple signaling processes responsible for surveillance, perception, and immune response activation that are influenced by varying spatial and temporal factors, at different biological layers, altogether concurring for a successful or unsuccessful infection. Timely and rapid plant response to these attacks can dramatically affects plants fate. Uncovering how transcription factors (TFs) regulate their targets over time is critical to define gene regulatory networks (GRNs) in normal and infected states. Despite decades of advancement, challenges remain in GRN inference, including dynamic rewiring. Within this PhD project we aim to answer the following questions: **How is the transcriptional regulatory program dynamically reshaped in plants upon biotic stress and which are the key master regulators of plant response to different pest attacks?**

To bridge this gap, we will infer and study GRN. Reconstruction of GRNs is a fundamental aspect of genetic engineering and provides a deeper understanding of the biological processes of an organism. Here, we propose to develop a novel hybrid model inspired by the framework of Physics-Informed Neural Networks (PINNs), emerging research field in medical and biological applications. This model is based on three main ingredients: *a priori* biological information to impose biological constrains, the mathematical law (ODEs) to confer a predictive skill and guarantee interpretability, the neural network to assure the scalability to a large number of genes and interactions. This will be the first model to integrate ODEs and neural-networks to study plant-pathogen interactions and will permit to significantly advance our understanding of molecular reprogramming of plants upon biotic stress. The study of the inferred GRNs will allow to prioritize key master regulators and understand how they dynamically reshape regulatory programs in plants upon biotic stress.

PhD project proposal

Title of the Project: A Physical Model of miRNA-Binding Activity in Animals and Plants

Research Team involved:

- Team 1 : Control of Gene Expression, Team 10, C3M - Centre Méditerranéen de Médecine Moléculaire - https://www.c3m-nice.fr/equipes/equipe-10/
- Team 2 : Interactions Plantes-Nématodes, IPN, ISA - Institut Sophia Agrobiotech - https://institut-sophia-agrobiotech.paca.hub.inrae.fr/equipes-isa/ipn

Supervisor Name (s): TRABUCCHI Michele, JAUBERT Stéphanie

Contact Person(s): TRABUCCHI Michele mtrabuchi@unice.fr

Keywords: miRNA, biophysical modelling, bioinformatics, gene expression control

Abstract (2,000 characters max including spaces):

MicroRNAs (miRNAs) are about 21 nucleotide small-RNAs expressed in eukaryotes. They repress gene expression by binding to complementary sequences in target mRNAs. In animals, miRNAs bind complementarity within short seed regions (6–8 nucleotides) located in 3'UTR. In plants, miRNAs typically bind within the coding region, and efficient target cleavage requires near-perfect complementarity.

Cooperative interactions between binding sites (BS) are important and emerge from both linear along the RNA sequence and spatial proximity generated by RNA folding. Despite the abundance of computationally predicted BS in both kingdoms, only a limited subset of these sites is functionally effective.

We plan to develop a biophysical modelling framework for miRNA-binding activity that integrates multiple determinants, including the thermodynamics of each binding event, cooperation among BS on the same target RNA, and miRNA expression levels. The primary outcome of the model is the steady-state occupancy of each BS. By sampling multiple RNA folding realizations, the model yields a robust hierarchy of site occupancies, enabling discrimination between potential BS and those consistently and cooperatively occupied.

Aggregation of site occupancies into a transcript-level occupancy score provides a quantitative predictor of miRNA-mediated regulation. The use of multiple model systems (mammals and plant–nematode interactions) provides a unique opportunity to investigate the molecular basis of miRNA-mediated repression in both kingdoms and cross-kingdom RNA interference. The calculated predictions will be validated using AGO CLIP-seq, degradome profiling, and transcriptome-wide repression data in both kingdoms, as well as known bona-fide target mRNAs, using both *in-house* and publicly available datasets. This interdisciplinary project is bridging biophysics, computational sciences and molecular biology to provide a unifying mechanistic view of miRNA targeting across animals and plants.

PhD project proposal

Tumoroid-Guided Targeting of Ptch1 to Reverse Resistance in NSCLC

Research Team involved:
- Team 1 : Transport membranaire, morphologie épithéliale et cancer (https://www.ipmc.cnrs.fr/fr/team/les-proteines-arf-transport-membranaire-morphologie-epitheliale-et-cancer/)
- Team 2 : Next generation therapy in lung cancer (https://www.ircan.org/research/teams/paul-hofman/)

Supervisor Name (s):
- Team 1: Isabelle Mus-Veteau
- Team 2: Valérie Vouret-Craviari

Contact Person(s): Isabelle Mus-Veteau (mus-veteau@ipmc.cnrs.fr)
Valérie Vouret-Craviari (valerie.vouret@univ-cotedazur.fr**)**

Keywords: NSCLC, therapy resistance, Ptch1 , drug efflux, patient derived tumoroids

Abstract (2,000 characters max including spaces): (1907)

This project aims to evaluate, using patient-derived tumor organoids (tumoroids), a novel therapeutic strategy to overcome resistance to targeted therapies of non-small cell lung cancer (NSCLC) cells by inhibiting the multidrug efflux activity of the Hedgehog receptor Ptch1.

Resistance to chemotherapy and targeted therapies remains a major obstacle in NSCLC treatment. Team 1 discovered that Ptch1, overexpressed in many cancers, functions as a multidrug resistance transporter expelling anticancer drugs from tumor cells. This efflux activity depends on a cancer-specific proton gradient, conferring tumor selectivity and making Ptch1 inhibition a priori non-toxic to healthy tissues. Ptch1 therefore represents a promising therapeutic target. Team 1 demonstrated that Ptch1 inhibition enhances the efficacy of the BRAFV600E inhibitor vemurafenib in melanoma models in vitro and in vivo.
Ptch1 is also overexpressed in patient NSCLC tumors, and recently, team 1 showed that Ptch1 contributes to the resistance of NSCLC cells to targeted therapies, providing a strong rationale for evaluating Ptch1 inhibition in clinically relevant NSCLC models.

Tumoroids provide a powerful ex vivo platform to evaluate drug responses and identify predictive biomarkers guiding oncologists' therapeutic decisions in near real time. This translational approach is enabled by the IHU RespirERA through access to well-annotated patient samples from the respiratory biobank and the biopathology platform. Team 2, fully integrated within IHU RespirERA and IRCAN, is currently developing and optimizing patient-derived NSCLC tumoroids, an approach expected to enter routine clinical practice.

This PhD project will evaluate whether the Ptch1 drug efflux inhibitor can restore the efficacy of targeted therapies in NSCLC cell lines in team 1, and in NSCLC patient-derived tumoroids ensuring its clinical relevance in team 2.

PhD project proposal

Title of the Project: **Experimental deciphering and computational modelling of the molecular mechanisms of tumor cell invasion**

Research Team involved:

- Team 1 : LUTON Frédéric, IPMC (https://www.ipmc.cnrs.fr/fr/member/frederic-luton/)
- Team 2 : ALLENA Rachele, LJAD (https://math.unice.fr/~rallena/)

Supervisor Name (s): Luton Frédéric and Allena Rachele

Contact Person(s): Luton Frédéric and Allena Rachele

Keywords: Basement membrane infiltration, computational modelling, molecular dynamic, mechanical forces

Abstract (2,000 characters max including spaces):

The PhD project aims to elucidate and model how tumor cells collectively invade through the basement membrane (BM), a specialized porous protein meshwork that envelops epithelial tissues.
Using fluorescent video-microscopy, our recent observations reveal that invasive cells extend dynamic actin-based membrane protrusions through the BM, enlarging its pores sufficiently to permit cell passage via reversible nuclear deformation. In addition, our preliminary computational model uncovered the crucial role of the BM molecular component dynamic turnover in regulating filopodia penetration.
Several key questions remain unresolved, including the contribution of protease activity, the implication of cell mechanical forces, the influence of cell–cell adhesion molecules during collective invasion, and the role of the nucleus in facilitating translocation. These questions are challenging to address experimentally and will greatly benefit from computational modelling that can test simultaneously multiple parameters across a wide range of values.
The proposed PhD project will be carried out at the interface of biology and mathematics, combining wet-lab experimentation with quantitative modelling. The candidate will perform targeted experiments to record time-lapse movies of invasive cells exiting tumor cell aggregates through the BM. Fluorescent probes will be used to visualize the acto-myosin cytoskeleton, nuclei, proteases, cell–cell contacts, and the BM. Movie analyses will enable the extraction of biophysical parameters required to develop computational models, which will then be refined and validated experimentally and will allow the exploration of a broader range of invasion scenarios. This integrated approach will help identify key molecular actors and quantify the mechanical variables governing BM translocation by invasive cells.

PhD project proposal

Title of the Project: Regeneration & Metabolism: Deciphering the implications of the telomerase TERT.

Research Team involved:
- Team 1 : Regeneration, stress-response, longevity (IRCAN)
- Team 2 : Transport & metabolism (LP2M)

Supervisor Name (s): Eric RÖTTINGER (IRCAN), Marina SHKRELI (LP2M)

Contact Person(s): Eric RÖTTINGER, eric.rottinger@univ-cotedazur.fr

Keywords: Regeneration, telomerase, gene regulatory network (GRN), metabolism, cnidarian

Abstract (2,000 characters max including spaces):

Regeneration is widespread yet highly variable among animals, with mammals displaying the poorest regenerative ability. Understanding key molecular mechanisms controlling regeneration, and the forces that constrain or unleash these programs, represents a major challenge for therapeutic approaches aiming to reactivate latent regenerative responses in adulthood or with aging.

In contrast to mammals, regenerative abilities are robust in many other metazoans, with some species such as sea anemones showing whole-body regeneration. Numerous processes regulate animal regeneration, including aging, which restrains it in mammals via senescence and telomere shortening, highlighting a key role of the telomerase TERT in tissue homeostasis and repair. TERT, beyond telomere synthesis, exerts extra-telomeric effects on transcriptional/epigenetic control to modulate tissue homeostasis and regeneration. Partner 2 has shown that these non-canonical functions of TERT can unleash a regenerative program in the mouse kidney, revealing a previously underappreciated plasticity of mammalian tissues that are normally poor regenerators. Recent data further reveal that these activities of TERT potentiate the handling of injury-associated metabolic stress in this context.

Our overall objective is to define the roles of TERT in whole body regeneration in the sea anemone (studied by Partner 1), with a particular focus on transcriptional and metabolic control. Our central hypothesis is that conserved TERT-dependent mechanisms can drive regeneration in tissues and organs that have lost this capacity during evolution or during the process of aging. To test this hypothesis, we will determine whether TERT functions are required for regeneration & characterize the TERT-dependent GRN and metabolic reprograming in the sea anemone and identify evolutionary conserved modules with intrinsic pro-regenerative potential that could be harnessed to promote repair in poorly regenerating mammalian organs.

PhD project proposal

Title of the Project:

DECODING OLFACTORY CONTROL OF DEVELOPMENTAL TIMING: FROM SENSORY NEURONS TO PREDICTIVE CHEMISTRY

Research Team involved:

- Team 1: Dr Nuria ROMERO – (https://nuriaromerolab.com/)
- Team 2: Dr. Jérémie TOPIN – Institut de Chimie de Nice (https://lab.chemsensim.fr/)

Supervisor Name (s): **Dr. Nuria ROMERO and Dr. Jérémie TOPIN**

Contact Person(s): **nuria.romero@univ-cotedazur.fr**

Keywords: Development – Olfaction – Virtual screening – Chemoinformatics - Drosophila

Abstract (2,000 characters max, including spaces):

Developmental plasticity allows insects to adjust growth and life-history traits to environmental conditions. While temperature and nutrition are established modulators, the role of other environmental cues remains poorly understood. In mammals, odors can influence neuroendocrine activity, yet whether they directly gate developmental progression and the conceptual meaning of this interaction remains unknown. We have established in the fruit fly model that disrupting specific olfactory sensory neurons delays developmental timing by altering endocrine signaling. We propose, in this project, to uncover the biological significance of olfactory influences on development by identifying the responsible odorants.

Resolving this question requires a ***deeply integrated interdisciplinary approach at the interface of biology and chemistry***. We propose combining developmental neurobiology with a predictive *in silico* protocol to identify odorant–receptor interactions that modulate developmental timing. Structure-based virtual screenings, based on structure from alphafold and molecular docking, will be used to screen large chemical libraries to identify putative agonists of the olfactory receptor (OR). Prioritized hits will be experimentally validated *in vivo* (electrophysiological and developmental outputs). Beyond its conceptual scope, this work will provide a translational framework as a second objective. The identified larval OR is conserved in the agricultural pest *D. suzukii*, which is rapidly expanding and causing major crop damage. Identifying odors that bind and disrupt OR activity provides a means to delay development, thereby slowing population expansion. By integrating sensory biology and computational chemistry, this project addresses a fundamental biological question while opening a novel avenue for sustainable pest control.

PhD project proposal

Title of the Project: Experimental and theoretical analysis of ultradian rhythms

Research Team involved:

- Team 1 : Chronobiology iBV, http://ibv.unice.fr/research-team/delaunay/
- Team 2 : MACBES, INRIA, https://team.inria.fr/macbes/

Supervisor Name (s): Franck Delaunay

Contact Person(s): Franck.Delaunay@univ-cotedazur.fr

Keywords: Ultradian rhythms, Biological oscillators, Mathematical modelling, Muscle

Abstract:

The circadian clock controls oscillations at all scales, from molecules to complex physiological processes. Unexpectedly, it has recently been discovered in several species that circadian oscillations mask harmonic oscillations of 4 to 12 hours. The role of these ultradian rhythms and the mechanisms that generate them remain poorly understood. Some recent work suggests that proteostasis and metabolism are regulated by a 12-hour oscillator involving the transcription factor XBP1, a key regulator of the UPR response. We have recently initiated a collaborative project with Madalena Chaves' team at Inria, combining experimentation and mathematical modeling to better understand the characteristics, mechanisms, and dynamics of ultradian oscillations. In this context, the overall objective of the thesis project is to use skeletal muscle, a tissue with intense protein turnover, as a system for understanding ultradian oscillations. The first part will use a genomic approach to create an atlas of ultradian transcriptional oscillations in mouse muscles using ad hoc signal processing methods. The second part will aim to exploit the previous genomic data to build cellular models that enable high-resolution real-time analysis of ultradian oscillations and to analyze them quantitatively. Finally, in a third part, we will work with the Inria team to exploit the experimental data in order to refine the mathematical model of the XBP1 loop currently under construction. In return, we will test predictions proposed by numerical simulations in previously developed cellular systems. Overall, this project will contribute to advancing the field of chronobiology by providing new mechanistic and conceptual foundations for understanding the molecular interactions underlying ultradian oscillations.

DYNABio

PhD project proposal

Title of the Project:

"Exploring dimerization as a key mechanism of transcription factor specificity"

Research Team involved:

Team 1 : 'Transcription specificity' team, IRCAN www.ircan.org/research/teams/simona-saccani/

- Team 2 : 'Quantitative Interactomics and Disease-Related Networks' team, iBV http://ibv.unice.fr/research-team/gogl/

Supervisor Name (s):

Dominic van Essen (CRCN INSERM) dominic.van-essen@univ-cotedazur.fr

Boglarka Zambo (CRCN CNRS) boglarka.zambo@univ-cotedazur.fr

Contact Person(s):

Dominic van Essen, Boglarka Zambo

Keywords:

Transcription factor, Dimerization, Affinity, Interactome, Genomics, Chromatin, NF-kappa B

Abstract (2,000 characters max including spaces):

The ability of transcription factors (TFs) to bind and function at specific genomic target sites underpins gene regulation. Notably, around half of all classes of TFs in all known forms of life assemble as dimers or higher-order combinations of separate protein subunits. We hypothesize that this combinatorial assembly imparts an important layer of specificity to TF binding and function. In this project we will investigate this concept using a set of novel biochemical approaches to directly analyse individual dimers, focusing on NF-kappa B (NFkB) TFs as a model system.

NFkB is a stimulus-inducible family of TFs with evolutionarily-conserved roles in multiple processes including immune responses, cell survival/apoptosis, and differentiation, and whose misregulation is implicated in cancer and in immunological diseases. Mammalian cells co-express several NFkB subunits, which naturally assemble into multiple dimeric combinations. However, the quantitative binding specificities of distinct NFkB dimers, as well as dimer-specific gene-regulatory functions, are so far unknown.

Complementary work in the two partner teams has established a split-GFP tagging system to analyse individual NFkB dimer types, as well as the native holdup (nHU) approach to identify and quantitatively measure TF-DNA and TF-protein affinities. In this project we will combine these approaches to:

1. Quantitatively analyse the affinity-based DNA-binding preferences of different NFkB dimer combinations, using native holdup with split-GFP fluorescence and high-throughput sequencing-based readouts, and

2. Determine the protein and chromatin interactomes of NFkB dimers – both DNA-binding domains and full-length TFs - using nHU coupled to quantitative mass spectrometry.

Together, these approaches will generate an unprecedented view of the targeting and cofactor specificities of NFkB dimers, and will provide insight into the evolutionary prevalence of dimerization as a structural feature of TFs in general.

DYNABio

PhD project proposal

Title of the Project: Lysosomal reprogramming as a driver of drug resistance in breast cancer

Research Team involved:

- **Team 1 :** Dr Sandy Giuliano – Team G. Pagès (IRCAN, UMR 7284/U1081) - https://www.ircan.org/
  Dr. S. Giuliano has recognized expertise in autophagy, lysosomes, treatment resistance and metabolism.

- **Team 2 :** Dr Guillaume Robert-Team G. ROBERT (C3M, U1065) - https://www.c3m-nice.fr/equipes/equipe-02/
  Dr. G. Robert has recognized expertise in autophagy, lysosome (biology, pH, and purification), and cancer immunity .

  Supervisor Name (s): Sandy Giuliano

Contact Person(s): Sandy Giuliano, sandy.giuliano@unice.fr

Keywords: Breast cancer – Drug resistance – Lysosome – Lysosomotropic treatments – Lipid metabolism – Organelle reprogramming

Abstract (2,000 characters max including spaces):

Breast cancer (BC) treatment resistance remains a major barrier to achieving durable therapeutic efficacy and tumor control. Many anticancer drugs used in BC are lysosomotropic and accumulate in lysosomes, leading to alkalinization, impaired lipid degradation, and lipid metabolic reprogramming. However, the nature and functional consequences of this lysosome-associated lipid remodeling remain poorly characterized. How this adaptive lysosomal remodeling contributes to therapy resistance across BC subtypes therefore remains unclear.

This PhD project aims to investigate how lysosomotropic treatment (LT) induced lysosomal reprogramming promotes cancer cell survival and to determine whether restoring lysosomal acidity represents a therapeutic vulnerability.

The objectives are:

1. **Characterization of lysosomal reprogramming.** Lysosomes will be isolated from BC models exposed to LT, followed by integrated lipidomic and proteomic analyses to identify lipid species and proteins associated with adaptive lysosomal states.

2. **Functional impact on survival and cell fate.** We will investigate how lysosomal lipid remodeling modifies lysosomal stability and function, shifting the balance between adaptive survival and lysosome-dependent cell death.
3. **Therapeutic targeting by lysosomal re-acidification.** Acidifying nanoparticles and pharmacological activation of lysosomal ion channels and v-ATPase will be used to restore lysosomal acidity and evaluate effects on lipid homeostasis, lysosomal function, and sensitivity to LT.
4. **Translational relevance.** Lysosome-associated molecular signatures linked to lipid remodeling and lysosomal function will be evaluated in patient-derived samples to identify biomarkers predictive of resistance to LT and associated with clinical outcomes.

This project will reposition the lysosome from a passive drug sink to a central determinant of therapy resistance, uncovering actionable lysosome-based vulnerabilities and biomarkers in aggressive breast cancers.

PhD project proposal

Title of the Project: Dynamic Immune Editing of Cellular Senescence by Natural Killer Cells: Implications for Liver Fibrosis
(DYSEK : **DY**namic **SE**nescence Immune **E**diting by Natural **K**iller Cells)

Research Team involved:

- Team 1 : Cherfils-Vicini; Team ISAC "Immune Surveillance in Aging & Cancer", IRCAN
  https://www.ircan.org/research/teams/julien-cherfils-vicini/

- Team 2 :; Team "Équipe: Génome non-codant & Pathologies pulmonaires » IPMC
  https://www.ipmc.cnrs.fr/fr/team/genome-non-codant-pathologies-pulmonaires/

Supervisor Name (s): Cherfils-Vicini (DR2 CNRS) and Roux (CRCN CNRS/ HDR)

Contact Person(s):Cherfils-Vicini Julien; Julien.cherfils@univ-cotedazur.fr 06 03 01 96 94

Keywords: Immune–cellular interactions; Single-cell transcriptomics; Live-cell imaging; Cell-state dynamics; Systems immunology

Abstract (2,000 characters max including spaces):
The accumulation of senescent cells (SnCs) during aging and chronic diseases reflects a dynamic balance between senescence induction and immune surveillance. Natural killer (NK) cells play a key role in SnCs elimination; however, we recently revealed an active immune evasion mechanism mediated by the ganglioside GD3 (Iltis et al., Nature Aging, 2025). This PhD project, led by the ISAC team Immune Surveillance in Aging and Cancer (IRCAN, headed by J. Cherfils-Vicini) in co-supervision with Jeremie Roux (IPMC), aims **to test an original Senescence Immune Editing (SIE) hypothesis, whereby NK-cell-mediated immune pressure progressively selects SnCs states resistant to immune clearance**. The first axis relies on long-term (8-day) *in vitro* co-cultures between SnCs and human NK cells, combining bulk RNA-seq, time-resolved single-cell (sc) RNA-seq. Leveraging the ISAC team's expertise in senescence and immunosurveillance together with the quantitative live-cell imaging developed by Jeremie Roux's group, we will characterize the reciprocal transcriptional, phenotypic, and functional evolution of both populations, in the presence or absence of an anti-GD3 antibody, **to identify emerging cell states and resistance trajectories.** The second axis will assess whether SIE-associated signatures can be detected in human liver fibrosis datasets (bulk and scRNA-seq) across disease stages, age, and sex, **to evaluate the relevance of senescence immune editing in human pathology**. The third axis will use a mouse model of liver fibrosis with longitudinal bulk and sc-transcriptomic analyses **to evaluate the functional impact of immunotherapy *in vivo***. Overall, this interdisciplinary project fully aligns with DYNABIO objectives by integrating senescence biology, immunology, live cell imaging, and multi-omics approaches, and by leveraging a strong synergy between IRCAN and IPMC.

DYNABio

PhD project proposal

Title of the Project: Investigating the TET2-mediated regulation of chromatin architecture in B cell lymphomas

Research Team involved:

- Team 1 : Maria del Pilar DOMINGUEZ https://www.c3m-nice.fr/equipes/equipe-14/
- Team 2 : Eirini TROMPOUKI https://www.ircan.org/research/teams/eirini-trompouki/

Supervisor Name (s):
Maria del Pilar DOMINGUEZ; Eirini TROMPOUKI

Contact Person(s):
Maria del Pilar DOMINGUEZ; pilar.dominguez@univ-cotedazur.fr
Eirini TROMPOUKI etrompouki@unice.fr

Keywords: Epigenetics, retrotransposons, lymphoma

Abstract (2,000 characters max including spaces):

Diffuse Large B-cell Lymphoma (DLBCL) is the most common subtype of B cell non-Hodgkin lymphoma (NHL). It refers to an aggressive lymphoma that arises from germinal center (GC) B cells. Genomic analysis of DLBCLs revealed widespread alterations in the epigenome, with frequent somatic mutations in epigenetic enzymes. This stems from the key role of epigenetic modifications in regulating GC B cell plasticity. We previously demonstrated that TET2, which catalyzes the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), is a tumor suppressor in DLBCL. We focused on the role of 5hmC at highly transcribed euchromatic regions of GC B cells; however, recent studies in stem cells have unveiled a new pathway through which TET2 impedes leukaemogenesis. TET2-mediated oxidation of 5mC on chromatin-associated retrotransposon RNA inhibits the action of MBD6, which impedes H2AK119ub deubiquitination, maintaining the repression of leukemic genes. However, when TET2 is mutated, deubiquitination of H2AK119ub results in open chromatin and increased transcription of genes maintaining the malignant phenotype. Based on these results, we hypothesize that the alteration of this TET2-MBD6-DUB mechanism will drive lymphomagenesis in TET2-deficient B cells. Our project will investigate the role of TET2 as a regulator of chromatin architecture in GC B cells, analyzing the epigenetic regulation of DNA and RNA retrotransposons mediated by TET2 and its consequences on the proliferation and phenotype of B cells. We will analyze DNA methylation and chromatin accessibility on retrotransposon molecules in TET2-deficient GC B cells using genetically engineered mouse models. This analysis, combined with RNA sequencing, will allow us to pinpoint the pathways and genes whose expression is regulated by this mechanism and involved in the initiation of tumorigenesis. We expect that our findings will lead to the development of specific therapeutic approaches for TET2-mutated lymphomas.

PhD project proposal

Title of the Project: **A Multi-omic Integration Approach to Understand the Etiology of Fragile X Syndrome**

Research Team involved:

- Team 1 : RNA metabolism and neurodevelopmental diseases team. Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne Sophia Antipolis. Link.
- Team 2: Epione team. Inria Center at Université Côte d'Azur, Valbonne Sophia Antipolis. Link 1. Link2.

Supervisor Name (s):
Dr. Carole GWIZDEK (IPMC)
Dr. Irene BALLELI (Inria)

Contact Person(s):
gwizdek@ipmc.cnrs.fr

Keywords: Neurobiology, Fragile X syndrome, multi-omic integration.

Abstract (2,000 characters max including spaces):

The Fragile X syndrome (FXS) is the leading cause of hereditary intellectual disability and the first monogenic cause of Autism Spectrum Disorders. It results from the absence of the FMRP protein and the development of a therapy will require an exhaustive understanding of the cellular functions regulated by the protein and altered in the disease. FMRP is a cytoplasmic RNA binding protein controlling the local translation of several thousands of mRNAs and is now also associated to several nuclear functions. Hence, FMRP participates in multiple cellular processes and modulates a broad spectrum of mRNA targets. This positions it as a hub protein, exerting both direct and indirect regulatory control over a wide range of distinct cellular mechanisms. Consistently, numerous omics studies have been produced to evaluate the multiple perturbations of cellular homeostasis in FXS. In collaboration with the Drs. I Balelli in the INRIA team Epione, we used an AI-driven multi-omic integration approach to highlight the distortion between the transcription and the translation of mRNAs in the context of FXS. This led to lists of transcriptional and translational anomalies. Extensive bibliographic and databases analysis showed that many of our hits are proven actors in the FXS etiology while others have known key functions in the brain development. Based on these very exiting results, we will pursue by: (i) using IA driven tools to find causal links between hits, thus converting the lists into functional networks (ii) validating the hits and the connections at the bench. The PhD student will have in charge the biological part of the project and will lead the dialogue between biologists and computer scientists to define the model settings from a biological perspective and critically review the *in silico* results in order to modify the general workflow if necessary. The ideal candidate should thus have extensive experience in biology and a strong interest in bioinformatics approaches.

PhD project proposal

Title of the Project: **Homochirality Regulation and the Role of Heterochirality in Aging and Disease**

Research Team involved:
Team 1 : Agnes Banreti **http://ibv.unice.fr/research-team/banreti/**
Team 2 : Uwe Meierhenrich **https://icn.univ-cotedazur.fr**

Supervisor Name (s): Agnes Banreti, Uwe Meierhenrich

Contact Person(s): **agnes.banreti@univ-cotedazur.fr**, **uwe.meierhenrich@univ-cotedazur.fr**

Keywords: protein heterochirality; D-amino acids; epimerization; protein aggregation; neurodegeneration

Abstract (2,000 characters max including spaces):

Scientific Aim
This Ph.D. project investigates how protein heterochirality, the post-translational incorporation of non-L amino acids, contributes to neurodegeneration. It aims to identify aggregation-prone proteins affected by chiral modifications, uncover mechanisms maintaining proteome homochirality, and determine how their disruption impairs neuronal and cellular function.

Context
Protein L-homochirality is essential for proper folding and function. During stress or aging, spontaneous epimerization can introduce D-amino acids, promoting misfolding and aggregation, hallmarks of neurodegenerative diseases. Despite growing evidence, the mechanisms preserving homochirality and the consequences of its loss remain poorly understood. The Banreti team in collaboration with the Meierhenrich team (Banreti et al., 2022, Nature Communications) has shown that heterochirality induces dysfunction and shortens lifespan in vivo; this project builds directly on these findings.

Institutions & Infrastructure
The Ph.D. will be conducted at iBV (biology, genetics, molecular and cellular biology, biochemistry) and ICN (analytical chemistry). The candidate will have exclusive access to GC×GC and enantioselective HPLC-MS, developed through a long-standing iBV-ICN collaboration. This is the only site worldwide enabling D/L-amino acid separation from biological samples using these methods.

Originality & Impact
This is the first in vivo study linking protein heterochirality to neurodegeneration and identifying genes regulating proteome chirality. Combining biology, chemistry, neurobiology, and bioinformatics, it introduces heterochirality as a new dimension in protein misfolding and disease.

Feasibility
Strong pilot data, exclusive infrastructure, and established collaborations ensure this 3-year project is realistic and highly impactful.