PSI CANAUX IONIQUES

PhD project proposal

Title of the Project: Characterization of the impact of AETA-peptide-dependent NMDA receptor activation on brain endothelial cell functions.

Research Team(s) involved:

- Team 1 : Team ' Pathophysiology of Neural Circuits and Behavior' PIs: H. Marie /J. Barik – IPMC https://www.ipmc.cnrs.fr/en/team/physiopathologie-des-circuits-neuronaux-et-du-comportement

- Team 2 : Team 'Microenvironment, Signaling and Cancer (MicroCAN)' PIs: S. Tartare-Deckert/M. Deckert – C3M - https://www.c3m-nice.fr/en/Teams/en-equipe-11

Supervisor Name(s): H. Marie (IPMC) and M. Deckert (C3M) (50% each as co-supervision of PhD student)

Contact Person(s): H. Marie (IPMC)

Keywords: NMDA receptors, amyloid precursor protein, endothelial cells, extracellular matrix, blood brain barrier, neurovascular coupling

Abstract (2,000 characters max including spaces):

NMDA receptors (NMDAR) are canonical ionotropic receptors critical for synaptic function and brain information processing. However, their presence in non-excitable cells, such as cerebral endothelial cells (ECs) of the blood-brain barrier (BBB), and their role in regulating vascularization—including extracellular matrix (ECM) rigidity—remain poorly understood. Emerging evidence suggests that, in ECs, NMDAR contribute to BBB permeabilization via an atypical, ion flux-independent mechanism.

Dr Marie's team recently identified AETA, an endogenously secreted peptide derived from amyloid precursor protein (APP) cleavage, as the first molecule capable of shifting NMDAR function toward this ion flux-independent mode in excitatory neurons (Dunot et al., *Neuron* 2024). We termed this mechanism AETA-dependent NMDAR activation (ADNA). Analysis of a new mouse model (AETA-m) overexpressing secreted human AETA revealed evidence of AETA-mediated EC modulation. Bulk RNA sequencing of brain tissue showed upregulated EC-associated pathways, including ECM-linked RNAs, while immunohistochemical staining, in collaboration with Dr. Deckert, confirmed perivascular increases.

We hypothesize that ADNA regulates EC functions, including ECM rigidity, neurovascular coupling, and BBB permeability. This project will test this hypothesis through three aims:

Aim 1: Define the AETA-m mouse BBB phenotype via experimental assessment of BBB permeability, ECM rigidity, and neurovascular coupling.

Aim 2: Define the acute effects of ADNA on EC-linked ECM protein production and associated signaling pathways.

Aim 3: Rescue phenotypes observed in Aims 1 and 2 using pharmacology.

Given that AETA levels are elevated in Alzheimer's disease (AD) brains—a disorder linked to BBB dysregulation—our findings may elucidate a new mechanism underlying BBB dysfunction in AD. This project will foster a new collaboration between H. Marie's neurobiology expertise and M. Deckert's ECM know-how.

PSI CANAUX IONIQUES

PhD project proposal

Title of the Project: Role of a K+ channels its auxiliary subunits in the plasticity of cancer associated fibroblasts (CAFs) in pancreatic adenocarcinoma.

Research Team(s) involved:
Inside the PSI:

- Team 1 : **Pr Olivier SORIANI**, Team "Ion channels and Cancer", PU. http://ibv.unice.fr/research-team/soriani/
- Team 2 : **Dr Guillaume Sandoz**, Team Biology of Ion Channels; http://ibv.unice.fr/research-team/sandoz/

Outside the PSI:

- **Dr Richard Tomasini,** team "Stromal/tumour cell dialogue and metabolic reprogramming in pancreatic cancers", CRCM, Marseille; Richard Tomasini | CRCM
- **Pr Cindy Neuzillet**, Head of the Gastro-intestinal Oncology department, Curie Institute, https://institut-curie.org/person/cindy-neuzillet.

Note: *This PhD project is part of a larger project co-funded by Inca (PlBio) and Arc Fundation (Arc Pancreas) which do not cover PhD student.*

Supervisor Name(s): Olivier Soriani

Contact Person(s): Olivier Soriani; olivier.soriani@univ-cotedazur.fr

Keywords: Pancreatic adenocarcinoma; Microenvironement; CAF plasticity; Potassium channels; Signalling; intercell communication; tumor ecosystem.

Abstract (2,000 characters max including spaces):
Pancreatic ductal adenocarcinoma **(PDAC)** is one of the deadliest cancers, with a 5-year survival rate of 11%. Its progression relies on a dense fibrotic stroma caused by inflammation-induced desmoplasia, largely driven by **cancer-associated fibroblasts (CAFs)**, key players of the tumour microenvironment. CAFs form heterogeneous subpopulations that shape the tumour ecosystem, either by producing extracellular matrix (ECM) and growth factors (**myCAFs**) or by regulating tumour immunity (pro-inflammatory or immunosuppressive **iCAFs**). Because CAFs sustain tumour growth and influence therapy response, targeting their reprogramming represents a promising therapeutic approach requiring precise knowledge of the mechanisms driving CAF phenotypes and plasticity.
Building on preliminary scRNAseq, differential RNAseq, patch-clamp and in silico analyses of PDAC stroma, we found that: **(1)** human CAFs specifically express a specific K+ channel (called herein KCNx) with two auxiliary subunits, SU1 and SU2; **(2)** KCNx expression correlates with ECM organization and immunosuppression; **(3)** SU1 and SU2 expression respectively mark myCAF and iCAF subsets; **(4)** KCNx inhibition reduces cancer cell-induced CAF activation; and **(5)** SU2 expression associates with poorer overall survival.
We hypothesize that KCNx governs CAF phenotype and that its association with SU1 or SU2 drives differentiation towards myCAF or iCAF states, respectively. The thesis will **(1)** characterize SU1- and SU2-dependent KCNx regulation in CAFs (patch-clamp), **(2)** determine how SU1/SU2 expression remodels CAF

signalling and plasticity, **(3)** assess how TGF-β or IL1β-induced CAF differentiation affects KCNx/SU1/SU2 coupling and stoichiometry (SIMpull assay, collab. G. Sandoz), and **(4)** evaluate how these factors modulate CAF–induced cancer cell activation (EMT) in vitro and in vivo. This work will uncover how K+ channels control PDAC stromal plasticity and could open new therapeutic avenues targeting the tumour microenvironment.

PSI CANAUX IONIQUES

PhD project proposal

Title of the Project: ANKH channel and PPi homeostasis in joint disease

Research Team(s) involved:

- Team 1 : Ion Channel and BioMineralization – https://lp2m.univ-cotedazur.fr/axes-de-recherche/canaux-ioniques-et-biomineralisation

Supervisor Name(s): Christophe Duranton

Contact Person(s): Christophe Duranton

Christophe.duranton@univ-cotedazur.fr

Keywords: ion transport, articular disease, crystal-mediated diseases

Abstract (2,000 characters max including spaces):

Chondrocalcinosis (or calcium pyrophosphate deposition disease, **CPPD**) is a common joint disorder, affecting 10% of middle-aged adults and more than 50% of those over 80. It is characterized by the formation of **calcium pyrophosphate crystals** in joints, triggering acute inflammatory flares and chronic inflammation. Despite its frequency and clinical impact, no preventive or curative therapy exists. The mechanisms of CPP crystal formation remain poorly understood, involving ageing, metabolic disorders and factors that balance local levels of calcium, phosphate (Pi) and the key anticalcifying molecule pyrophosphate (PPi). Genetic studies identify the *ANKH* gene in early familial CPPD. *ANKH* encodes a widely **expressed plasma membrane protein** involved directly or indirectly in ATP export (a precursor of PPi) and possibly other anions such as citrate. Although *ANKH* mutations are linked to early onset CPPD, their effects on transport activity (gain or loss of function) and PPi homeostasis remain poorly defined.
The PhD project aims to study the ion transport activity of ANKH (WT and CPPD-associated mutants). We will investigate **ion transport** (ATP, PPi, citrate, etc. accumulating in supernatants using ion chromatography), assess **electrogenic properties** (patch-clamp, and lipid bilayer reconstitution) and analyze **metabolic changes** (metabolomics) using **HEK-293 cells** or **primary human cells** (patient-derived chondrocytes and fibroblasts) expressing WT and CPPD-associated variants of *ANKH*. Using established **human cohorts** (collab. with Lariboisière Rheumatology Dep., Paris), we will quantify PPi (using our **patented PPi assay**) and other metabolites in plasma, urine and synovial fluid of patients with CPPD and other joint diseases such as gout or osteoarthritis. Combining *in vitro*, *ex vivo* and clinical approaches, we aim to elucidate how ANKH mutations alter the biophysical properties of the channel and affect the local PPi homeostasis and CPP crystal formation, to pave the way for new therapeutic strategies **to prevent crystal deposition or promote dissolution.**

PSI CANAUX IONIQUES

PhD project proposal

Title of the Project: Role of the THIK1 channel in nociception and central sensitization

Research Team(s) involved:

- Team 1: Molecular physiology and pathophysiology of ion channels
- Team 2: Ion channels and pain

Supervisor Name(s): **Delphine BICHET and Anne BARON**

Contact Person(s): **Delphine BICHET**

Keywords: **chronic pain, nociception, potassium channels, inflammatory pain, central sensitization**

Abstract (2,000 characters max including spaces):

Chronic pain remains a major unmet medical need, highlighting the need to identify novel molecular mechanisms controlling both peripheral nociception and central sensitization. This PhD project addresses this challenge by focusing on the two-pore domain potassium channel THIK1, a poorly explored but highly promising regulator of pain signaling at the interface between sensory neurons and spinal neuro-immune circuits.

THIK1 is robustly expressed in nociceptors and microglial cells, positioning it as a key modulator of neuronal excitability and neuroinflammation. Strong preliminary data generated by the two teams show that THIK1 knockout mice display increased basal thermal hypersensitivity and exacerbated inflammatory pain responses, identifying THIK1 as a negative regulator of inflammatory nociception. In addition, THIK1 forms functional heteromers with THIK2 channels, raising the hypothesis that THIK1 exerts distinct functions as a homomer and within THIK1–THIK2 heteromeric complexes.

Building on these promising results and on the complementary expertise of the two teams in pain models, K2P channel biology and mouse genetics, the project will combine behavioral analyses in validated models of inflammatory (CFA) and neuropathic (SNL) pain with electrophysiological and genetic approaches using THIK1 knockout and THIK1/THIK2 double knockout mice. This strategy will allow a rigorous dissection of the respective contributions of THIK1 homomers and heteromers to neuronal excitability and pain phenotypes. Spatio-temporal modulation of THIK1 activity in peripheral nociceptors will be achieved using AAV-based approaches expressing inactive or hyperactive THIK1 variants under nociceptor-specific promoters, complemented by inducible Cre-based mouse models.

Importantly, the project aims to establish a mechanistic link between the role of THIK1 in spinal microglia, its contribution to central sensitization, and its impact on chronic inflammatory and neuropathic pain. Preliminary observations showing altered microglial morphology in the dorsal horn of THIK1-deficient mice support a role for THIK1 in microglia-dependent spinal inflammation and pain persistence.

Finally, the availability of genetic gain- and loss-of-function tools together with a THIK1 pharmacological modulators provides a strong and realistic framework to evaluate the functional and therapeutic relevance of THIK1 modulation.

PSI CANAUX IONIQUES

PhD project proposal

Title of the Project: **Excitability in the medial thalamus as a key regulator of chronic neuropathic pain**

Research Team(s) involved:
Team 1 : Neural Circuits of Emotional memories, https://www.ipmc.cnrs.fr/fr/team/circuits-neuronaux-de-la-memoire-emotionnelle/

Team 2 : Physiopathologie des Circuits Neuronaux et du Comportement
https://www.ipmc.cnrs.fr/fr/team/physiopathologie-des-circuits-neuronaux-et-du-comportement/

Supervisor Name(s): **Bianca Silva**
Contact Person(s): **Bianca Silva,** silva@ipmc.cnrs.fr

Keywords: **Thalamus, Neuronal Excitability, Chronic Neuropathic Pain, Activity mapping, HCN**

Abstract (2,000 characters max including spaces):

Chronic pain is a debilitating pathology affecting millions, yet current therapeutic options remain insufficient. While research has emphasized peripheral sensitization, the central mechanisms driving pain chronicity remain poorly understood. The thalamus serves as the primary gateway for nociceptive processing; however, research has disproportionately focused on the lateral "sensory-discriminative" pathway. The medial thalamus, which projects to limbic structures like the Anterior Cingulate Cortex (ACC), is uniquely positioned to mediate affective components of chronic pain. Preliminary data from our laboratory indicates that neurons in the medial thalamic nuclei projecting to the ACC exhibit significant hyperexcitability in a murine model of chronic neuropathic pain. Crucially, their selective ablation reverses both mechanical allodynia and associated affective-like endophenotypes. Based on these findings, we hypothesize that maladaptive plasticity within the medial thalamus-ACC axis is a core driver of pain chronicity and its emotional sequelae.

To test this hypothesis, we propose:

1. Electrophysiological fingerprinting: We will characterize the longitudinal changes in neuronal excitability using *ex vivo* patch-clamp recordings (in collaboration with S. Fernandez) and *in vivo* calcium imaging.
2. Molecular profiling: Using projection-specific single-cell RNA sequencing (scRNA-seq), we will define specific molecular alterations with a specific focus on the "channellome" of these thalamocortical neurons to identify the molecular substrates of hyperexcitability.
3. Circuit restoration: We will employ opto-chemogenetics as well as molecular manipulations to assess whether restoring homeostatic activity can reverse behavioral symptoms and normalize brain-wide functional connectivity.

PSI CANAUX IONIQUES

PhD project proposal

Title of the Project:
From Ion Channel Biophysics to Light-Driven Analgesia: Targeting TREK in the Spinal Cord

Research Team(s) involved:

- Team 1 : Sandoz http://ibv.unice.fr/research-team/sandoz/
- Team 2 : Deval-Lingueglia https://www.ipmc.cnrs.fr/fr/team/canaux-ioniques-et-douleur/

Supervisor Name(s):
Guillaume Sandoz
Contact Person(s):
Guillaume Sandoz sandoz@unice.fr / Emmanuel Deval deval@ipmc.cnrs.fr

Keywords: Pain, Two-Pore-Domain K+ channel, photopharmacology, analgesia

Abstract (2,000 characters max including spaces):

This project aims to understand and harness the role of TREK potassium channels in the spinal control of pain. We are investigating two complementary strategies: a photopharmacological approach targeting TREK channels using the light-sensitive ligand LAKI[1], and Light-Induced Analgesia (LIA), a non-pharmacological method based on UV-A activation of endogenous channels[2]. Together, these approaches provide a unique framework to modulate neuronal excitability with high spatial and temporal precision, either through reversible ligand control or direct light-dependent activation of TREK/TRAAK channels.

Our objective is to dissect the cellular and circuit mechanisms operating at the level of the spinal cord, where nociceptive information is first integrated and gated before reaching higher brain centers. We aim to determine how TREK channel activation shapes membrane excitability in primary afferents and dorsal horn neurons, how it alters synaptic transmission within spinal nociceptive circuits, and how these effects translate into changes in pain perception in vivo. By combining electrophysiology, photopharmacology, and behavioral assays, we seek to establish causal links between channel modulation, circuit function, and analgesic outcomes.

Beyond their experimental value, these findings may open new therapeutic perspectives. Targeting TREK-dependent mechanisms at the spinal level could lead to innovative strategies for chronic and neuropathic pain, based on modulation of TREK channels. Ultimately, as part of the FHU INOVPAIN, this project aims to bridge fundamental ion channel biology with translational approaches for pain control.

1. Bied M, et al, *Light-Induced Analgesia: A Drug Free Optical Method for Pain Relief via Activation of TRAAK K+ Channels*, Nature Com., 2026, 26;17(1):620.

2. Landra-Willm A et al., *A photoswitchable inhibitor of TREK channels controls pain in wild-type intact freely moving animals.* Nature Com. 2023, 1;14(1):1160