# LIST OF PROJECTS (14)

## INTERNATIONAL PHD CONTRACTS

**MARCH 2023**

## 1. BLOUIN Jean (LNC): Cutaneous control of voluntary finger movements

**State of the art**
Touch is paramount for our interaction with the physical world. Indeed, the mechanical deformation of the skin when touching objects stimulate different types of skin mechanoreceptors providing the central nervous system with various information about the properties of the touched objects (e.g., size, texture, compliance, shape, …, see Johnson 2001 for a review). The cutaneous system also provides information about the relative motion between the skin and the objects (e.g., direction and speed, Aimonetti et al. 2007; Chancel et al. 2016). Most of the studies on the function of the cutaneous information have focused on perceptual outcome of touch. Very few studies have addressed the motor functions of cutaneous information other than its functions in grip force adjustments for preventing slippage of handheld objects (see Johansson & Flanagan 2019 for a review).

Our team has recently discovered that when tracing the contour of a shape with the fingertip with biased visual feedback of the finger motion, the tracing performance is more degraded when finger tactile information is available during the tracing than when it is not (Vlachou et al. 2023). Because the processing of somatosensory information in the context of a conflict between visual and somatosensory feedbacks worsens tracing performance (Bernier et al. 2019), this finding indicates that cutaneous information contributes to the control of tracing movements, even when visual feedback is available.

**Objectives**
The goal of the present thesis proposal is to investigate the neural bases of the cutaneous control of finger movements. In particular, a thorough exploration of the adaptability of the cutaneo-motor system and of the effect of this adaptation on the peripheral and central processing of cutaneous inputs will be undertaken.

**Expected results**
Because the cutaneous cues contribute to the control of movement, we predict that the relationship between cutaneous input and motor output is adaptable. This adaptation should have both behavioural and neurophysiological signatures.

**Feasibility**
Research from our team focuses on the neural bases of voluntary movements. We have the knowhow and all the required materials to start and complete the projects of this thesis proposal. Some experimental protocols have already been accepted by the CERSTAPS ethic committee (no. IRB00012476-2021-09-12-140).

**Expected candidate profile**
Master degree in Neuroscience, Psychology or Sport sciences; Research experience in sensory and/or motor systems; valued team worker; good reading and writing skills in English.

**References**
Aimonetti, Hospod, Roll, Ribot-Ciscar et al. (2007) J Physiol 580.2 : 649–658
Bernier, Burle, Vidal, Hasbroucq, Blouin (2009) Cereb Cortex 19: 2106-2113
Chancel, Blanchard, Guerraz, Montagnini, Kavounoudias (2016) J Neurophysiol 116: 1522–1535 Johnson (2001). Curr Opin Neurobiol 11 : 455-461.
Vlachou, Legros, Sellin, Simoneau, Mouchnino, Blouin (2023). 15ème Journée de la Recherche en Neurosciences, Québec 6 février 2023

## Laboratory and team

Laboratoire de Neurosciences Cognitives (UMR 7291)
3 place Victor-Hugo 13331, Marseille

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Team : Neural bases of sensorimotor behavior
Team leader: Jean Blouin

## PhD supervisor

Jean BLOUIN, CNRS researcher (DR)

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**Currently supervised PhD student(s) :**

Benjamin Mathieu (expected defense July 2023)

**Previously supervised PhD students :**

G. Manson (2019, Ass. professor Queens Univ.)
N. Lebar (2016, Physiotherapist)
R. Chaumillon (2015, Researcher Airbus)
P.-M. Bernier (2009, Professor, Univ Sherbrooke)
E. Guillaud (2006, CNRS research engineer)
F. Sarlegna (2004, CNRS researcher)
J.-P. Bresciani (2003, Professor Univ. Fribourg)

**Publications of supervised PhD students**

Mathieu B, Abillama A, Martinez M, Mouchnino L, Blouin J (2022) Keeping in touch with our hidden side. Neuroscience Letters 136693

Blouin J, Saradjian AH, Pialasse J-P, Manson GA, Mouchnino L, Simoneau M (2019) Two neural circuits to point towards home position after passive body displacements. *Frontiers in Neural Circuits* 13:70.

Manson GA, Tremblay L, Lebar N, de Grosbois J, Mouchnino L, Blouin J (2019) Auditory cues for somatosensory targets invoke visuomotor transformations: Behavioral and electrophysiological evidence. *Plos One* 14(5): e0215518.

Manson GA, Blouin J, Kumawat AS, Crainic CA, Tremblay L (2019) Rapid online corrections for upper limb reaches to perturbed somatosensory targets: Evidence for nonvisual sensorimotor transformation processes. *Experimental Brain Research* 237: 839-853

Chaumillon R, Blouin J, Guillaume A (2018) Interhemispheric transfer time asymmetry of visual information depends on eye dominance: an electrophysiological study. *Frontiers in Neuroscience 11,72*

Lebar N, Danna J, Moré S, Mouchnino L, Blouin J (2017) On the neural basis of sensory weighting: Alpha, beta and gamma modulations during complex movements. *Neuroimage* 150: 200-212.

Chaumillon R, Alahyane N, Senot P, Vergne J, Lemoine-Lardennois C, Blouin J, Doré-Mazars K, Guillaume A, Vergilino-Perez D. (2017). Asymmetry in visual information processing depends on the strength of eye dominance. Neuropsychologia 96: 129-136

For a complete list, see: https://hal.science/search/index/q/*/authIdHal _s/jean-blouin

## 2. BROVELLI Andrea (INT): Higher-order interactions in human brain networks supporting causal learning

**State of the art.** A central hypothesis in neuroscience posits that cognitive functions arise from the coordinated activity of neural populations distributed over large-scale brain networks. Goal-directed learning, which supports the acquisition of causal relations between our behaviors and their consequences, is no exception, and it is thought to emerge from interactions between neural populations distributed over the associative fronto-striatal circuit and limbic "reward" system. Although central, this hypothesis has never been fully tested, yet. Indeed, progress has been limited by the lack of approaches for studying brain interactions beyond pairwise relations, the so-called higher order interactions (HOIs).

**Objectives.** The aim of the proposed PhD thesis in computational neuroscience is twofold. The first objective is to develop new functional connectivity (FC) approaches to analyze HOIs and their relation with cognitive processes. The second aim is to investigate the role of HOIs in cortical brain networks supporting goal-directed causal learning.

**Methods.** To achieve the first goal, we will exploit recent advances in information theory and network science. We will test novel measures that allow the characterisation of statistical interdependencies within multiplets of three and more neural signals, such as the O-information, and measures of redundant and synergistic interactions, based on the Partial Information Decomposition framework. Recent network science approaches will also be used to represent and analyze the structure and dynamics of the observed HOIs. To achieve the second goal, we will analyze a unique dataset collected from the BraiNets team that includes cortical high-gamma activities (HGA, from 50-150 Hz) estimated from MEG and intracranial SEEG data collected from human participants performing a causal action-outcome learning task. Model-based analyses of HGA will be used to map learning computations predicted by Bayesian or reinforcement learning models onto cortico-cortical HOIs.

**Expected results.** We expect to provide a novel FC framework for the analysis of HOIs in cognitive brain networks. We expect to find HOIs in brain circuits mediating goal-directed learning including the parietal, temporal, dorsolateral and dorsomedial prefrontal cortex and orbitofrontal cortical systems. We expect to reveal choice- and outcome-related learning signals (e.g., reward prediction errors) to be mapped onto higher-order cortico-cortical interactions.

**Feasibility.** The theoretical foundations for the analysis of HOIs are present in the literature and the brain data has already been collected. Although the project has an explorative nature, feasibility is good.

**Expected candidate profile.** We search for a candidate with a strong interest in computational neuroscience, the study of complex systems and cognitive

neuroscience questions related to the neural bases of learning. Prior experience in network neuroscience and Python is a plus.

## Laboratory and team

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Team : Brain Networks (BraiNets), https://brainets.github.io/

Team leader: Andrea Brovelli

## PhD supervisor

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**Currently supervised PhD student(s)**

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Yorgos Bardanikas (50%) - EU Innovative Training Network

**Previously supervised PhD students**

Ruggero Basanisi (2017-2021)

Laetitia Lalla (2014-2017)

**Publications of previously supervised PhD students**

Combrisson E, Allegra M, Basanisi R, Ince RAA, Giordano BL, Bastin J, Brovelli A (2022). Group-level inference of information-based measures for the analyses of cognitive brain networks from neurophysiological data. *Neuroimage*, 258:119347.

Basanisi R, Brovelli A, Cartoni E, Baldassarre G (2020). A spiking neural-network model of goal-directed behaviour. *PLoS Comput Biol* 16(12): e1007579

Lalla L, Rueda Orozco PE, Jurado-Parras M-T, Brovelli A*, Robbe D* (2017). Local or Not Local: Investigating the Nature of Striatal Theta Oscillations in Behaving Rats. *eNeuro*, 4(5) e0128-17.2017 1–14

## 3. CHARROUX Bernard, CAVEY Matthieu (IBDM): Neuronal bases of behavior evolution in Drosophila

**State of the art:** A central question in neurobiology is to understand at the genetic, molecular and cellular levels how neuronal circuits generate behaviors. Higher brain functions such as multi-sensory integration and decision-making processes are particularly poorly understood. In addition, how these functions are modified during evolution to promote the appearance of novel behaviors remains largely unknown. Which functional characteristics and circuit wiring principles evolve to change behavioral outputs? We can now address these questions by investigating the evolution of decision-making processes in *Drosophila* models.

We have developed a simple paradigm taking advantage of a divergence in egg-laying behavior (oviposition) between two genetically tractable fruit fly species. Most species including the model *Drosophila melanogaster* prefer to lay their eggs in rotten fruits, but the invasive pest *Drosophila suzukii* has evolved a novel preference for ripening fruits instead, causing important damage to the fruit industry worldwide. Using quantitative behavioral assays, chemically-defined oviposition substrates, neurogenetic tools and functional imaging approaches (calcium imaging), we have demonstrated that behavioral divergence is linked to differences in how sensory information is processed in the Central Nervous Systems (CNS) of these two species. More precisely, neuronal circuits controlling oviposition decisions in response to perception of fruit sugars appear to be tuned to different levels of activation in the two species.

**Objectives:** Our aim is to identify the molecular, cellular and circuit-level bases of differential sensory processing contributing to inter-species behavioral divergence. To that end, the proposed project will use new transgenic tools in *D. suzukii* to manipulate populations of CNS neurons homologous to those controlling oviposition behavior in *D. melanogaster*. We will then compare the physiological properties and functional role of these CNS circuits in oviposition decisions across species.

**Methods and feasibility:** Oviposition neurons can be targeted in *D. melanogaster* via expression of the Gal4 transcriptional activator under the control of specific gene regulatory elements. We will use these regulatory sequences and standard transgenesis approaches to generate Gal4 transgenic lines in *D. suzukii* targeting similar sets of neurons. We will then compare anatomical features of these neurons across species using available fluorescent UAS reporters and compare their function in oviposition behavior assays using neuronal silencing and activating transgenes. Neuronal physiological properties will be assessed via calcium imaging

(GCaMP reporter) upon stimulation of the sugar-sensory neurons. All resources, methodologies, equipment and expertise are available in the host institute and team.

**Expected results:** We expect to observe anatomical, physiological and/or functional differences between species in CNS oviposition neuronal circuits providing a functional basis for inter-species divergence of behavior.

**Candidate profile:** The candidate should have solid background in neurobiology, microscopy and quantitative analyses. Expertise in dissection, genetics and behavioral studies will be an asset.

## Laboratory and team

Institut de Biologie du Développement de Marseille (IBDM)

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Team: Evolution and development of morphology and behavior

Team leader: Benjamin Prud'homme

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**Previously supervised PhD students**

Florence Capo

**Publications of supervised PhD students**

Cytosolic and Secreted Peptidoglycan-Degrading Enzymes in Drosophila Respectively Control Local and Systemic Immune Responses to Microbiota. Charroux B*, Capo F, Kurz CL, Peslier S, Chaduli D, Viallat-Lieutaud A, Royet J*. * Co-corresponding authors. **Cell Host Microbe. 2018 Feb 14;23(2):215-228.**

Oligopeptide Transporters of the SLC15 Family Are Dispensable for Peptidoglycan Sensing and Transport in Drosophila. Capo F, Chaduli D, Viallat-Lieutaud A, Charroux B*, Royet J*. **Co-corresponding authors*. **J Innate Immun. 2017;9(5):483-492.**

Bacteria sensing mechanisms in Drosophila gut: Local and systemic consequences. Capo F, Charroux B, Royet. J.Dev **Comp Immunol. 2016 Nov;64:11-21.**

Tissue-Specific Regulation of Drosophila NF-kB Pathway Activation by Peptidoglycan Recognition Protein SC. Costechareyre D, Capo F, Fabre A, Chaduli D, Kellenberger C, Roussel A, Charroux B*, Royet J*. **Co-corresponding authors*. **J Innate Immun. 2016 8(1):67-80.**

## PhD co-supervisor

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## 4. DEBANNE Dominique (UNIS): Plasticity of intrinsic neuronal excitability in visual thalamic neurons

**State of the art**. The dorsal lateral geniculate nucleus (dLGN), a primary recipient structure of retinal inputs, is traditionally considered to be just a relay of visual information. However, recent works indicate that dLGN expresses functional plasticity following monocular deprivation (MD; Jaepel et al., Nat Neurosci 2017; Sommeijer et al., Nat Neurosci 2017). The cellular and molecular substrate of this plasticity has not been idendified.

**Objectives**. Our proposal therefore consists in testing whether visual and spiking activity may modify neuronal excitability in dLGN neurons. We propose to i) determine the mechanisms of long-term potentiation of intrinsic excitability (LTP-IE) in dLGN relay cells and GABAergic interneurons, and ii) define the structural correlate and the molecular mechanisms of the homeostatic plasticity of intrinsic excitability observed following MD.

**Methods**. To characterize the induction and expression mechanisms of LTP-IE in dLGN neurons, a combination of electrophysiological recordings in acute or cultured slices and of pharmacological tools, CRISPR/Cas9, calcium imaging and calcium uncaging will be used.

**Expected results**. Homeostatic plasticity may regulate both voltage-gated channels at the AIS and/or passive membrane properties. We will therefore analyze the changes in spike threshold and passive membrane properties (input resistance and membrane capacitance) of the neurons after various delays of MD on the deprived and spared regions of the dLGN. A lower spike threshold is expected for homeostatic compensation whereas a higher spike threshold is expected for Hebbian plasticity. No change in passive properties is expected after homeostatic and Hebbian plasticity.

**Feasibility**. This research project is largely feasible as we already obtained preliminary results showing that homeostatic regulation of neuronal excitability is observed after 4 days of MD but that Hebbian regulation is found after 10 days of MD. To understand whether LTP-IE and MD-induced plasticity of IE share common expression mechanisms in dLGN neurons, we will test whether the magnitude of LTP-IE is changed after MD. In particular, we will check LTP-IE magnitude in neurons from the deprived and spared regions of the dLGN after 4 and 10 days of MD. An increase in LTP-IE is expected in neurons that underwent a reduction in IE (i.e. open side at 4 days of MD or deprived side at 10 days of MD) and the opposite effect in neurons that underwent an increase in IE.

**Expected candidate profile**. For this project, the candidate will have to be interested in cellular physiology and should have at least a theoretical background in electrophysiology. Skills in immunohistochemistry, molecular biology and cellular biology may be a plus.

## Laboratory and team

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Team: Plasticité de l'excitabilité neuronale et épilepsie

Team leader: Dominique Debanne

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Maria-Laura Musella (50%)

Konstantina Mylonaki

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Valérie Sourdet (100%) Thèse soutenue en 2002

Sami Boudkkazi (100%) Thèse soutenue en 2006

Philippe Gastrein (100%) Thèses outenue en 2007

Emilie Campanac (100%) Thèse soutenue en 2008

Andrzej Bialowas (100%) Thèse soutenue en 2008

Celia Gasselin (100%) Thèse soutenue en 2013

Franck Dubruc (50%) Thèse soutenue en 2013

Mickael Zbili (100%) Thèse soutenue en 2016

Aurelie Fekete (100%) Thèse soutenue en 2018

Esther Steidl (50%) Thèse soutenue en 2019

Yanis Inglebert (100%) Thèse soutenue en 2018

Johanna Extremet (50%) Thèse soutenue en 2022

## Publications of supervised PhD students

2023 – Debanne D & Inglebert Y. Spike-timing dependent plasticity and memory. **Current Opinion in Neurobiology** (in press)

2022 - Ramirez-Franco JJ, Debreux K, Extrémet J, Maulet Y, Belghazi M, Villard C, Sangiardi M, Youssouf F, El Far L, Lévêque C, Debarnot C, Marchot P, Debanne D, Russier M, Seagar M, Irani S, El Far O. Patient-derived antibodies reveal the subcellular distribution and heterogeneous interactome of LGI1. **Brain**, doi: 10.1093/brain/awac218

2022 - Extrémet J, El Far O, Ankri N, Irani SR, Debanne D, Russier M. An Epitope-Specific LGI1-Autoantibody Enhances Neuronal Excitability by Modulating Kv1.1 Channel. **Cells**, 11: 2713

2022 - Sammari M, Inglebert Y, Ankri N, Russier M, Incontro S, Debanne D. Theta patterns of stimulation induce synaptic and intrinsic potentiation in O-LM interneurons. **Proceedings of the National Academy of Sciences USA**, 119: e2205264119

2021 - Fékété A, Ankri N, Brette R, Debanne D. Neural excitability increases with axonal resistance between soma and axon initial segment. **Proceedings of the National Academy of Sciences USA**, 118: e2102217118

2021 - Inglebert Y, Debanne D. Calcium and spike timing-dependent plasticity. **Frontiers in Cellular Neuroscience**, 15: 727336

2021 - Incontro S, Sammari M, Azzaz F, Inglebert Y, Ankri N, Russier M, Fantini J, Debanne D. Endocannabinoids tune intrinsic excitability in O-LM interneurons by direct modulation of post-synaptic Kv7 channels. **Journal of Neuroscience**, 41: 9521-9538

2021 - Zbili M, Rama S, Benitez MJ, Fronzaroli-Molinieres L, Bialowas A, Boumedine N, Garrido JJ, Debanne D. Homeostatic regulation of axonal Kv1.1 channels accounts for both synaptic and intrinsic modifications in the hippocampal CA3 circuit. **Proceedings of the National Academy of Sciences USA**, 118: e2110601118

2020 - Zbili M, Rama S, Yger P, Inglebert Y, Boumedine N, Fronzaroli-Molinieres L, Brette R, Russier M, Debanne D. Axonal Na+ channels detect and transmit levels of input synchrony in local brain circuits. **Science Advances**, 6: eaay4313

2020 - Zbili M, Debanne D. Myelination Increases the Spatial Extent of Analog-Digital Modulation of Synaptic Transmission: A Modeling Study. **Frontiers in Cellular Neuroscience**, 14: 40

2020 - Inglebert Y, Aljadeff J, Brunel N, Debanne D. Synaptic plasticity rules with physiological calcium levels. **Proceedings of the National Academy of Sciences USA**, 117: 33639-33648

2019 - Debanne D, Inglebert Y, Russier M. Plasticity of intrinsic neuronal excitability. **Current Opinion in Neurobiology**, 54: 73-82

2019 - Zbili M, Debanne D. Past and future of analog-digital modulation of synaptic transmission. **Frontiers in Cellular Neuroscience**, 13: 160

2019 - Steidl E, Gleyzes M, Maddalena F, Debanne D, Buisson B.

Neuroservice proconvulsive (NS-PC) set: A new platform of electrophysiology-based assays to determine the proconvulsive potential of lead compounds. **Journal of Pharmacological and Toxicological Methods**

2018 - Rama S, Zbili M, Debanne D. Signal propagation along the axon. **Current Opinion in Neurobiology**, 51: 37-44

2018 - Fékété A, Debanne D. Somatic modulation of ectopic action potential initiation in distal axons. **Journal of Physiology (London)**, 596: 5067-5068

2017 - Rama S, Zbili M, Fékété A, Tapia M, Benitez MJ, Boumedine N, Garrido JJ, Debanne D. The role of axonal Kv1 channels in CA3 pyramidal cell excitability. **Scientific Reports**, 7: 315

2017 - Seagar M, Russier M, Caillard O, Maulet Y, Fronzaroli-Molinieres L, De San Feliciano M, Boumedine N, Rodriguez L, Zbili M, Usseglio F, Formisano-Treziny C, Youssouf F, Sangiardi M, Boillot M, Baulac S, Benitez MJ, Garrido JJ, Debanne D, El Far O. LGI1 tunes intrinsic excitability by regulating the density of axonal Kv1 channels. **Proceedings of the National Academy of Sciences USA**, 114: 7719-7724

2017 - Gasselin C*, Inglebert Y*, Ankri N, Debanne D. Plasticity of intrinsic excitability during LTD is mediated by bidirectional changes in h-channel activity. **Scientific Reports**, 7: 14418

2016 - Zbili M, Rama S & Debanne D. Dynamic control of neurotransmitter release by presynaptic potential. **Frontiers in Cellular Neuroscience**. 10: 278

2015 - Rama S*, Zbili M*, Bialowas A, Fronzaroli-Molinieres L, Ankri N, Carlier E, Marra V & Debanne D. Presynaptic hyperpolarization induces a fast analogue modulation of spike-evoked transmission mediated by axonal sodium channels. **Nature Communications** 6:10163.

2015 - Gasselin C, Inglebert Y & Debanne. Homeostatic regulation of h-conductance controls intrinsic excitability and stabilizes the threshold for synaptic modification in CA1 neurons. **Journal of Physiology (London)** 593: 4855-4869

2015 - Bialowas A*, Rama S*, Zbili M, Marra V, Fronzaroli-Molinieres L, Ankri N, Carlier E & Debanne D. Analog modulation of spike-evoked transmission in CA3 circuits is determines by axonal Kv1.1 channels in a time-dependent manner. **European Journal of Neuroscience** 41: 293-304

2013 - Campanac E*, Gasselin C*, Baude A, Rama S, Ankri N & Debanne D. Enhanced intrinsic excitability in basket cells maintains excitatory-inhibitory balance in hippocampal circuits. **Neuron** 77: 712-722.

2023 - Dubruc F, Dupret D & Caillard O (2013) Self-tuning of inhibition by endocannabinoids shapes spike-time precision in CA1 pyramidal neurons. **Journal of Neurophysiology** 110: 1930-1944

2013 –Debanne D, Bialowas A, Rama S. What are the mechanisms for analogue and digital signaling in the brain? **Nature Reviews Neuroscience** 14: 63-69

**Complete list on https://unis-neuro.com/4-equipe-debanne-dominique.html**

## 5. DEVRED François (INP): Tau droplets inhibitors: a new class of anti-neurodegenerative disease compounds

***State of the art*** - Reduced microtubule stability, which plays an important role in axonal transport has been observed in several neurodegenerative diseases (ND) such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis. It is often associated with dissociation of tau protein, which stabilizes microtubules. Under pathological conditions tau is hyperphosphorylated and aggregates in the form of paired helical filaments, the main component of neurofibrillary tangles found in many NDs. Thus, one of the main strategies of fighting these currently uncurable diseases consists in finding efficient inhibitors of tau aggregation. Recently it was demonstrated that formation of droplets during liquid-liquid phase separation (LLPS) of tau could be the first step that trigger tau aggregation. In our lab, we have developed a new high throughput assay that allow to follow LLPS formation using nanoDSF instrument.

***Objectives*** - Thus, the objective of the proposed PhD project is to identify anti-neurodegenerative disease compounds by targeting inhibition of tau LLPS using our newly developed screening assay.

***Methods*** - This will be achieved through several steps using *in vitro*, *in cells* and ultimately *in vivo* approaches that PhD student will learn and apply at Institute of neurophysiopathology. *First*, we will screen a protein-protein interaction inhibitors library to identify potential candidates. *Second*, found inhibitors will be investigated in detail to rank them for their ability to inhibit both LLPS and paired helical filaments formation. Their interaction with tau will be characterized using biophysical methods such as isothermal titration calorimetry, analytical ultracentrifugation, surface plasmon resonance and mass spectrometry to understand the molecular mechanism of inhibition. *Third*, the ability of the compounds to inhibit tau LLPS will be investigated using neuronal cell models. For that purpose, intracellular droplets formation and the impact of inhibitors on this process will be followed using fluorescence microscopy and cell that overexpress tau-EGFP. *Finally*, compounds that exhibit strong propensity to inhibit LLPS formation in cells will be tested on mice models of tauopathies.

***Expected results*** – By the end of PhD project we expect to identify several scaffolds able to inhibit LLPS of tau in cells and obtain preliminary results of its efficiency on mice models.

***Feasibility*** - Institute of neurophysiopathology possesses all necessary infrastructure, facilities, and expertise for successful accomplishment of the project. All in vitro experiments including screening will be performed at platform PINT of INP which has all necessary instrument and already performed nanoDSF screenings. In cell experiments will be performed on the facilities of team 9 "Cytoskeleton and Neurophysiopathology" that has an experience to follow tau aggregation in cellular models. Finally, in vitro experiments will be carried out at

animal facilities of INP which also has a solid background in experimentation on mice models of neurodegenerative diseases.

***Expected candidate profile*** – We expect to find highly dynamic and motivated candidate for this project, who willing to acquire a broad range of methods from *in vitro* biophysical and cellular methods to *in vivo* methods. Strong background in molecular and cell biology is required.

## Laboratory and team

Institute of NeuroPhysiopathology (INP) UMR 7051

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Team: Cytoskeleton and Neurophysiopathology

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## PhD supervisor

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### Previously supervised PhD students

**Dahia Yatoui** (2019-2022)

**Romain La Rocca** (2017-2020)

**Andrei Roman** (2014-2017)

### Publications of supervised PhD students

**Dahbia Yatoui**, Philipp O. Tsvetkov, **Romain La Rocca**, Viktoriia E. Baksheeva, Diane Allegro, Gilles Breuzard, Géraldine Ferracci, Deborah Byrne, François Devred. Binding of two zinc ions promotes liquid liquid phase separation of Tau. International Journal of Biological Macromolecules 2022

**Romain La Rocca**, Philipp O. Tsvetkov, Andrey V. Golovin, Géraldine Ferracci, Diane Allegro, Pascale Barbier, Soazig Malesinski, Françoise Guerlesquin, François Devred. Identification of Zinc-binding sites of tau. International Journal of Biological Molecules 2022

Viktoriia E Baksheeva, Andrei Y Roman, Claude Villard, François Devred, Deborah Byrne, **Dahbia Yatoui,** Arthur O Zalevsky, Andrey V Golovin, Gary S Shaw, Philipp O Tsvetkov*, Evgeni Y Zernii*. Mechanism of Zn2+ and Ca2+ Binding to Human S100A1. Biomolecules 2022

Andrey Golovin, François Devred, **Dahbia Yatoui, Andrei Roman,** Arthur Zalevsky, Rémy Puppo, Régine Lebrun, Françoise Guerlesquin, Philipp Tsvetkov. Zinc binds to RRM2 peptide of TDP-43. International Journal of Molecular Sciences 2020

Philipp O. Tsvetkov, **Romain La Rocca,** Soazig Malesinski, François Devred. Characterization of Microtubule-associated proteins and tubulin interactions by isothermal titration calorimetry. Microcalorimetry of Biological Molecules: Methods and Protocols, Methods in Molecular Biology, (chap. 12) vol. 1964, 2019

**Andrei Roman,** François Devred*, **Romain La Rocca,** Cyrille Garnier, Deborah Byrne, Evgeni Yu. Zernii, Vincent Peyrot, Philipp O. Tsvetkov. Zinc-dependent reversible self-assembly of tau. J Mol Biol 2018

Philipp O. Tsvetkov, **Andrei Roman**, Viktoriia E. Baksheeva, Aliya A. Nazipova, Marina P. Shevelyova, Vasiliy I. Vladimirov, Michelle F. Buyanova, Dmitry V. Zinchenko, Andrey A. Zamyatnin Jr., François Devred, Andrey V. Golovin, Sergei E. Permyakov, Evgeni Yu. Zernii. Functional status of neuronal calcium sensor-1 is modulated by zinc binding. Frontiers in Molecular Neuroscience. 2018

Philipp O. Tsvetkov, Emeline Tabouret, **Andrei Roman**, Sylvie Romain, Céline Bequet, Olga Ishimbaeva, Stéphane Honoré, Dominique Figarella-Branger, Olivier Chinot, Francois Devred Differential Scanning Calorimetry of plasma in glioblastoma: toward a new prognostic / monitoring tool. Oncotarget. 2018

Cyrille Garnier, Francois Devred, Deborah Byrne, Rémy Puppo, **Andrei Roman**, Soazig Malesinski, Andrey Golovin, Régine Lebrun, Natalia Ninkina, Philipp O. Tsvetkov, Zinc binding to RNA recognition motif of TDP-43 induces the formation of amyloid-like aggregates. Scientific Reports 2017

**Andrei Roman**, Francois Devred, Alexander A. Makarov Aslan A. Kubatiev, Vincent Peyrot, Philipp O. Tsvetkov. Sequential binding of calcium ions to B-repeat domain of SdrD from Staphylococcus aureus. Canadian Journal of Microbiology 2016

## 6. FASANO Laurent (IBDM): Towards a potential therapy of a rare form of autism spectrum disorder: Genetic rescue of Tshz3

- **State of the art**

Autism spectrum disorder (ASD) is characterized by abnormalities in two core behavioral domains, namely deficit in social interactions and restrictive, repetitive patterns of behavior. We identified the gene *TSHZ3* as the minimal region of overlap for 19q12 heterozygous deletions in patients with a new syndrome including autistic features and provided evidence, from studies in mouse models, for a link between heterozygous *Tshz3* deletion, defects in cortical projection neurons (CPNs), striatal cholinergic interneurons (CINs) and ASD-like deficits. Our data also suggest that the post-natal *CamK2-Cre*-mediated deletion of *Tshz3* leads to ASD behavioral deficits without affecting the viability of the CPNs and CINs[1-4]. These observations are the ground of this project.

- **Objectives**

Determine if restoring *Tshz3* expression after birth improves ASD-like deficits.

- **Methods**

To test this possibility, we generated a conditional rescue mouse model (*Tshz3*$^{+/STOP}$) allowing restoring *Tshz3* expression following Cre-mediated excision of the STOP cassette inserted in the unique intron of *Tshz3* upstream of the exon 2. To restore *Tshz3* expression we will use the *CamK2-Cre* mouse line. In this scheme, *Tshz3*$^{+/STOP}$; *CamK2-Cre* (*Tshz3-rescued*) embryos will be heterozygous for *Tshz3*, thus mimicking the condition of *TSHZ3* patients with ASD, until after birth when *Tshz3* expression will be restored following *CamK2-Cre*-mediated excision of the STOP cassette. Behavioral testing of *Tshz3*$^{+/STOP}$ and *Tshz3*-rescued mice will be performed using a live mouse tracker system (LMT), enabling automatic live tracking, identification and characterization through behavioral labelling of up to four mice in an enriched environment with no time limit. Further characterization of these models will include molecular transcriptomics (scRNAseq) to analyze/compare gene expression in *Tshz3*$^{+/STOP}$, *Tshz3*-rescued and control mice to identify the molecular pathways involved in ASD behavior.

- **Expected results**

There are no medications currently approved for the treatment of the main core symptom in ASD. This project is a new approach to identify novel treatment options for ASD. Indeed, if *Tshz3*-associated dysfunctions can be reversed, transcriptomic analysis might identify novel disease genes, including "druggable" differentially expressed genes e.g. encoding a receptor or an enzyme.

- **Feasibility**

Mouse lines and operating LMT are available.

- **Expected candidate profile**

Master's degree in biology. Strong interest in neurosciences and mouse behavior. Experience in model organisms; Cell and molecular biology; English writing and speaking; data analysis; team working.


1. Caubit, X. *et al.* TSHZ3 deletion causes an autism syndrome and defects in cortical projection neurons. *Nat Genet* **48**, 1359-1369 (2016).
2. Chabbert, D. *et al.* Postnatal Tshz3 Deletion Drives Altered Corticostriatal Function and Autism Spectrum Disorder-like Behavior. *Biol Psychiatry* **86**, 274-285 (2019).
3. Caubit, X. *et al.* Camk2a-Cre and Tshz3 Expression in Mouse Striatal Cholinergic Interneurons: Implications for Autism Spectrum Disorder. *Front Genet* **12**, 683959 (2021).
4. Caubit, X. *et al.* Targeted Tshz3 deletion in corticostriatal circuit components segregates core autistic behaviors. *Transl Psychiatry* **12**, 106 (2022).


## Laboratory and team

Marseille Developmental Biology Institute (IBDM), UMR7288

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https://www.ibdm.univ-amu.fr/team/transcriptional-regulatory-networks-in-development-and-diseases/

Team: Transcriptional regulatory networks in development and diseases

Team leader:Laurent FASANO

## PhD supervisor


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### Currently supervised PhD student(s)

Raul SILVA (co-supervised with Séverine Dubuisson, LIS) – from 02/2023 to 01/2026

### Previously supervised PhD students

M. Armel Gallet 1996-1999 ; Soutenance le 17 Février 1999

Mlle Corinne Angelats 2000-2001 ; Soutenance 23/02/2000

Mme Ouarda Taghli-Lamalem 1997-2001 ; Soutenance 22/06/2001.

M. Hervé Faralli 2006-2009 ; Soutenance 18/06/2010.

Mlle Elise Martin 2006-2010 ; Soutenance 24/09/2010

Mlle Silvia Pimentel 2006-2010 ; Soutenance 10/02/2011 à Lisbonne (Portugal).

Mlle Irene Sanchez-Martin 2015-2018 ; Soutenance 18/12/2018

**Publications of supervised PhD students**


1. Sanchez-Martin I, Magalhães P, Ranjzad P, Fatmi A, Richard F, Thien Phong Vu Manh T, Saurin A, Feuillet G, Denis C, Woolf A.S, Schanstra J.P, Zürbig P, Caubit X, Fasano L. (2021) PMID 34919690
2. Fasano L, Sanchez-Martin I, Caubit X. (2019) PMID 30742275
3. Martin E, Caubit X, Airik R, Vola C, Fatmi A, Kispert A, Fasano L. (2013) PMID 23671695
4. "Teashirt in cell proliferation "; Silvia Pimentel, Rui Gomes and Laurent Fasano. LAP Lambert Academic Publishing (2012). ISBN 978-3-8484-2850-2
5. Faralli H, Martin E, Coré N, Liu QC, Filippi P, Dilworth FJ, Caubit X, Fasano L. (2011) PMID 21543328.
6. Caubit X, Lye CM, Martin E, Coré N, Long DA, Vola C, Jenkins D, Garratt AN, Skaer H, Woolf AS, Fasano L. (2008) PMID 18776146
7. Taghli-Lamallem O, Gallet A, Leroy F, Malapert P, Vola C, Kerridge S, Fasano L. (2007) PMID: 17524390.
8. Angelats C, Gallet A, Therond P, Fasano L, Kerridge S. (2002) PMID 11784100
9. Erkner A, Roure A, Charroux B, Delaage M, Holway N, Core N, Vola C, Angelats C, Pages F, Fasano L, Kerridge S. (2002) PMID 11874908
10. Gallet, A, Angelats C, Erkner A, Charroux B, Fasano L, Kerridge S (1999). PMID 10205174
11. Charroux B, Angelats C, Fasano L, Kerridge S, Vola C (1999). PMID 10523673
12. Erkner A, Gallet A, Angelats C, Fasano L, Kerridge S (1999). PMID 10545232
13. Gallet A, Erkner A, Charroux B, Fasano L, Kerridge S (1998). PMID 9707400
14. E. Alexandre, Y. Graba, L. Fasano, A. Gallet, L. Perrin, P. de Zulueta, J. Pradel, S. Kerridge and B. Jacq. (1996). PMID 8951796

## 7. IBOS Guilhem, CHAVANE Frédéric (INT): Inferring and modelling large scale cortical interactions during comparative decision making in non-human primates

Frédéric Chavane (head of the Neopto team in the Institut de Neurosciences de la Timone INT, Marseille France), would like to encourage applications for a PhD position with Dr Guilhem Ibos. Candidates should apply to the 2023 PhD scholarship for international students of Marseille's Neuroschool.

The research group of Guilhem Ibos studies cortical mechanisms of cognitive control in non-human primates (NHP, macaque and marmoset monkeys). We specialize in training NHP to perform sets of cognitive tasks and recording/analyzing extra cellular neuronal activity in large populations of distributed cortical networks. Adapting our behavior to ever changing environment requires to constantly confront sensory representation and internally generated, goal-directed representations of our needs and expectations. For example, when looking for a friend in a crowd, we compare visual representation of each object (extracted within the hierarchy of visual areas) to internally generated representation of our friend. Such behavior engages a large set of cortical and sub cortical areas, and involves several cognitive processes such as working memory and decision making. Our research group aims at understanding how different sources of information are integrated and compared in order to facilitate decision making processes. We recently proposed that a network of cortical areas, including parietal and prefrontal cortices, interact with sensory visual cortex when comparing what we are looking at (sensory information), to what we are looking for (working memory information)(1–4). We recently recorded simultaneously the activity of populations of PFC, V4 and LIP neurons in macaque monkeys.

The goal of the project is composed of 2 complementary approach: 1. Analyzing and modelling the activity of prefrontal, parietal and visual cortical areas interact during comparative decision making. The student will use deep learning approaches to model cortical interactions between each area and predict the impact of cortical inactivation of specific neurons on the state of the rest of the network. 2. Directly test these predictions in vivo during experiments consisting of simultaneous inactivations/recordings in PFC/LIP/V4 networks.

The selected student will fully participate to data acquisition (single and multiple point electrodes in behaving monkeys), analysis (spiking pattern dynamics) and modeling (deep learning).

Candidates should:

(a) have notions of cognitive neurosciences and show record of highest grades. Experience in animal research in general and with NHP in particular will be a plus but is not mandatory.

(b) have a solid experience in programming (Matlab, Python), statistics and data analysis.
(c) be able to collaborate with other students/post docs.

She/he will integrate the NeuroSchool PhD Program of Aix-Marseille Université which organizes post-graduate studies in Neurosciences with theoretical courses and soft skills. Starting date is Fall 2023. For administrative reasons, applications must be addressed to Dr Chavane via the Neuroschool website, but candidates must contact Guilhem Ibos (guilhem.ibos@univ-amu.fr) who will supervise the project.

Reference list:


1. *G. Ibos, D. J. Freedman, Sequential sensory and decision processing in posterior parietal cortex. Elife. 6 (2017), doi:10.7554/eLife.23743.*
2. *G. Ibos, D. J. Freedman, Interaction between Spatial and Feature Attention in Posterior Parietal Cortex. Neuron. 91, 931–943 (2016).*
3. *G. Ibos, D. J. Freedman, Dynamic Integration of Task-Relevant Visual Features in Posterior Parietal Cortex. Neuron. 83, 1468–80 (2014).*
4. *D. J. Freedman, G. Ibos, An Integrative Framework for Sensory, Motor, and Cognitive Functions of the Posterior Parietal Cortex. Neuron. 97, 1219–1234 (2018).*


## Laboratory and team

Institut de Neurosciences de la Timone, UMR 7289
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Team: InVibe (Inference in Visual Behaviours)
Team leader: Guillaume Masson

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### Currently supervised PhD student(s)

Alexis Monnet-Aimard
Cléo Schoeffel

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## Currently supervised PhD student(s)

Salvatore Giancani (co-supervised, start 2021)
Florent Missey (co-supervised 2018)

## Previously supervised PhD students

I. Racicot (19-22)
G. Benvenuti (09-15)
Q Montardy (08-12)
A Reynaud (05-10)
S Chemla (06-10)
F. Matonti (09-13)
L Hoffart (05-10)

## Publications of supervised PhD students

Selected (last 5 years)

Bourbousson M, Racicot I, Muslimov E, Behaghel T, Blaize K, Bourdet A, Chemla S, Hugot E, Jahn W, Roux S, Vanzetta I, Weber P, Sauvage J-F, Chavane F, Ferrari M. 2020. Imaging multiple cortical areas with high spatio-temporal resolution using innovative wide-field imaging system. *NeuroPhotonics*. doi:https://doi.org/10.1117/12.2556793

Racicot I, Muslimov E, Degiovanni X, Baurberg J, Blaize K, Sauvage J-F, Ferrari M, Chavane F. 2021. Optical system with a curved detector for wide-field high-resolution cortical imaging at meso-scale. *Opt Instrum Sci Technology Appl Ii* 6. doi:10.1117/12.2597067

Hahn G, Ponce-Alvarez A, Monier C, Benvenuti G, Kumar A, Chavane F, Deco G, Frégnac Y. 2017. Spontaneous cortical activity is transiently poised close to criticality. *PLoS Computational Biology* **13**:e1005543. doi:10.1371/journal.pcbi.1005543

Chemla S, Reynaud A, Volo M di, Zerlaut Y, Perrinet L, Destexhe A, Chavane F. 2019. Suppressive Traveling Waves Shape Representations of Illusory Motion in Primary Visual Cortex of Awake Primate. *Journal of Neuroscience* **39**:4282– 4298. doi:10.1523/jneurosci.2792-18.2019

Chemla S, Muller L, Reynaud A, Takerkart S, Destexhe A, Chavane F. 2017. Improving voltage-sensitive dye imaging: with a little help from computational approaches. *Neurophotonics* **4**:031215. doi:10.1117/1.nph.4.3.031215

## 8. KRAHN Martin, Gorokhova Svetlana (MMG): Plasma profiling as a novel biomarker for a rare neuromuscular disease

- **State of the art**

LAMA2-related dystrophies are caused by a complete or partial deficiency of laminin-211. LAMA2-RD patents have mild to profound muscle weakness that can also be associated with central nervous system abnormalities, such as white matter changes and seizures. Disease biomarkers are critical to effectively detect and follow the potential changes in patients involved in therapeutic trials. Unfortunately, there are currently no validated biomarkers available for LAMA2-related dystrophies. A novel way to follow and diagnose various pathologies based on denaturation profiling of plasma using nanoDSF (Differential Scanning Fluorimetry) has recently been described for glioma by researchers of The INteractome Timone Platform (PINT). Similar approaches have also shown reproducible disease-specific profiles in various other pathologies. It is therefore possible that the nanoDSF could detect plasma profile patterns specific to LAMA2-RD patients, thus identifying a novel minimally invasive way to diagnose and follow patients.

- **Objectives**

The two objectives of our project are to:

1. test if denaturation profiling of plasma from patients can be used as a biomarker in LAMA2-RD disease population.

2. explore the molecular processes leading to changes in plasma signature by analysing the extracellular environment of cultured cells from LAMA2-RD patients

- **Methods**

Frozen plasma samples from LAMA2-RD patients and from age-matched controls will be analysed by nanoDSF instrument at the The INteractome Timone Platform (PINT) in the Institute of NeuroPhysiopathology (INP), Aix-Marseille University. The denaturation profiles obtained from plasma samples from LAMA2-RD patients will be compared to that of control samples using advanced AI methods in order to detect the differences that could serve as non-invasive disease biomarkers. To further explore the identified differences in plasma signatures between LAMA2-RD patients and controls, the changes in the extracellular environment of patient-derived cell cultures will be analysed by nanoDSF instrument.

- **Expected results**

We expect to observe differences between the patient and the control plasma profiles, thus helping to develop a non-invasive LAMA2-RD biomarker for future clinical studies. We also expect to see the effect of extracellular matrix changes typically present in LAMA2-RD patient-derived cell cultures on denaturing profiles of extracellular media. By controlling the different aspects of cell culture, we plan to identify the molecular changes that affect the denaturing profile.

- **Feasibility**

Our "Translational Neuromyology" group in the Nerve and Muscle department of the Marseille Medical Genetics institute as well as our collaborators at The

INteractome Timone Platform (PINT) in the Institute of NeuroPhysiopathology (INP) have all necessary equipment and infrastructure to accomplish the proposed research project.

- **Expected candidate profile**

We are looking for a curious and motivated candidate with a solid fundamental background in molecular biology and biochemistry. Experience in cell culture would also be a plus.

## Laboratory and team

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Team: Translational Neuromyology, Nerve and Muscle,

Team leader: Marc Bartoli

## PhD supervisor

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### Previously supervised PhD students

André Maues de Paula 2011-2016

Mathieu Cerino 2016-2021

Khaoula Rochdi 2017-2022

### Publications of supervised PhD students

Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Aymane Bouzidi, Halima Nahili, Ghizlane Zouiri, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin Krahn "Identification of novel mutations by targeted NGS in Moroccan families clinically diagnosed with a neuromuscular disorder" Clinica Chimica Acta 2022 524, 51-58

Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Halima Nahili, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin

Krahn "First characterization of congenital myasthenic syndrome type 5 in North Africa" *Mol Biol Rep 2021 Sep 22. doi: 10.1007/s11033-021-06530-7*

Cerino M, Gorokhova S, Béhin A, Urtizberea JA, Kergourlay V, Salvo E, Bernard R, Lévy N, Bartoli M, Krahn M. Novel Pathogenic Variants in a French Cohort Widen the Mutational Spectrum of GNE Myopathy. *J Neuromuscul Dis. 2015 Jun 4;2(2):131-136.*

Mathieu Cerino, Svetlana Gorokhova, Pascal Laforet, Rabah Ben Yaou, Emmanuelle Salort-Campana, Jean Pouget, Shahram Attarian, Bruno Eymard, Jean-François Deleuze, Anne Boland, Anthony Behin, Tanya Stojkovic, Gisele Bonne, Nicolas Levy, Marc Bartoli, Martin Krahn. "Genetic Characterization of a French Cohort of GNE mutation negative inclusion body myopathy patients with exome sequencing". *Muscle Nerve, 2017 Nov;56(5):993-997*

Mathieu Cerino, Emmanuelle Campana-Salort, Pascal Cintas, Dimitri Renard, Alexandra Salvi, Raul Juntas Morales, Céline Tard, France Leturcq, Tanya Stojkovic, Nathalie Bonello-Palot, Svetlana Gorokhova et J Mortreux, A Maues De Paula, N Lévy, J Pouget, M Cossée, M Bartoli, M Krahn, S Attarian, "Novel deleterious CAPN3 variant associated with an autosomal dominant calpainopathy". Neuropathology and Applied Neurobiology, 2020 Oct;46(6):564-578 (Impact Factor 6,88)

Mathieu Cerino, Emmanuelle Campana-Salort, Svetlana Gorokhova, Amandine Sevy, Nathalie Bonello-Palot, Nicolas Lévy, Shahram Attarian, Marc Bartoli and Martin Krahn "Refining NGS diagnosis of muscular disorders" *Journal of Neurology, Neurosurgery, and Psychiatry 2020, Volume 92, Issue 2*

De Paula AM, Bartoli M, Courrier S, Pouget J, Levy N, Pellissier JF, Figarella-Branger D, Krahn M, Attarian S. Further heterogeneity in myopathy with tubular aggregates? Muscle Nerve. 2012 Dec;46(6):984-5.

Böhm J, Chevessier F, Maues De Paula A, Koch C, Attarian S, Feger C, Hantaï D, Laforêt P, Ghorab K, Vallat JM, Fardeau M, Figarella-Branger D, Pouget J, Romero NB, Koch M, Ebel C, Levy N, Krahn M, Eymard B, Bartoli M, Laporte Constitutive activation of the calcium sensor STIM1 causes tubular-aggregate myopathy. *J.Am J Hum Genet. 2013 Feb 7;92(2):271-8.*

## PhD co-supervisor

GOROKHOVA Svetlana, AHU

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### Previously supervised PhD students

Khaoula Rochdi 2017-2022 (co-supervision with Abdelhamid Barakat and Martin Krahn)

### Publications of supervised PhD students

Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Aymane Bouzidi, Halima Nahili, Ghizlane Zouiri, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin Krahn

"Identification of novel mutations by targeted NGS in Moroccan families clinically diagnosed with a neuromuscular disorder" Clinica Chimica Acta 2022 524, 51-58

Khaoula Rochdi, Mathieu Cerino, Nathalie Da Silva, Valerie Delague, Halima Nahili, Yamna Kriouile, Svetlana Gorokhova, Marc Bartoli, Rachid Saïle, Abdelhamid Barakat, Martin Krahn "First characterization of congenital myasthenic syndrome type 5 in North Africa" *Mol Biol Rep 2021 Sep 22. doi: 10.1007/s11033-021-06530-7*

## 9. KHRESTCHATISKY Michel (INP): Vector-based targeting of RNA therapeutics to the brain for the development of novel treatments for neurodegenerative disorders

The Blood Brain Barrier (BBB) is a highly impermeable and protective cell barrier consisting of tightly sealed endothelial cells. To date, the BBB represents the main hurdle in the development of brain-specific therapeutics, in particular of biologics, such as antisense oligonucleotides (ASOs) and antibodies. Many approaches have been investigated to promote drug transport across the BBB into the parenchyma of the central nervous system (CNS). Notably, receptor mediated transcytosis (RMT) pathways are being exploited, for instance by the engagement of Transferrin Receptors (TfR), Insulin Receptors, and/or Low-density Lipoprotein receptors (LDLR). In our laboratory, we have developed and patented a family of TfR-targeting nanobodies (nTfRs) with efficient BBB-crossing features that have been used for the brain delivery of specific ASOs.

The objectives of this project are: i) to use the existing nTfR technology to target genes involved in the pathobiology of neurological disorders (e.g., BACE1 in Alzheimer's disease, AD); ii) to improve the BBB-crossing features of the existing nTfR through protein engineering methods.

To accomplish these objectives, ASOs will be designed for selected AD genetic risk factors and synthetized using standard methodology based on solid-phase synthesis and deprotection. Real time qPCR (RT-qPCR) performed on transfected cells overexpressing the targeted gene of interest will be used for *in vitro* validation of the newly developed ASOs. Molecular cloning techniques and mammalian cell systems (e.g., HEK239T) will be used for the expression of the nTfRs as well as newly engineered nTfR versions. Analytical methods, such as fast protein liquid chromatography (FPLC), will be used for protein purification, while ELISA and surface plasmon resonance (SPR) will be used for binding assessment studies. The best nTfR-ASOs validated *in vitro* will be injected systemically in wild type mice. RT-qPCR and Western Blot on brain extracts will be used to assess *in vivo* knock down activity and protein expression, respectively. *In situ* hybridization will be used to assess ASOs distribution into the brain. The final objective is to test the conjugates in mouse models of AD.

This project is expected to deliver one or more nTfR-ASO conjugates that can effectively cross the BBB and regulate the expression of selected AD genetic risk factors. Therefore, this project will contribute to foster the development of ASOs-based therapeutics that can be used for the treatment of neurodegenerative diseases, such as AD.

The BBB and Neuroinflammation Team of the Institute for Neurophysio-pathology (INP) has a long-standing experience in understanding the role of the BBB during physiological and neuroinflammation conditions. Moreover, with our biotech partner company Vect-Horus we have developed several vector molecules,

based on peptides or nanobodies, that facilitate drug transport across the BBB. The INP, is well equipped with all the-state-of-art technological platforms for molecular cloning, cell cultures, fluorescence imaging, molecular interactions assessments, and a new animal facility. The team consists of scientists with all the expertise in BBB physiology and development of brain delivery systems.

The project will be carried by a highly motivated Master student with a degree in biotechnology, biochemistry, molecular sciences, neuroscience, or related fields. The candidate will be required to work in a multicultural and multidisciplinary environment. The candidate is expected to have a strong theoretical knowledge in molecular biology, cell culture (mammalian and bacterial), protein expression and purification, and antibody-antigen biophysical characterization. Computational knowledge for protein modelling and programming skills (e.g., Python) are a plus.

## Laboratory and team

Institute of NeuroPhysiopathology (INP)

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Team: BBB & Neuroinflammation

Team leader: Dr. Michel KHRESTCHATISKY

## PhD supervisor

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### Currently supervised PhD student(s)

Marion DAVID; Baptiste BROC

### Previously supervised PhD students

Lotfi FERHAT; Amina RAFIKI; Patrick BASSAND; Oualid SBAI; Yatma GUEY; Yves MOLINO; Karine VARINI (2015); Amandine BONNET (2016); Giuseppina IACHETTA (co-direction, 2016); Romy COHEN (2018); Grigorios KYRIATZIS (2020); Xue YANG (co-direction, 2020)

**Publications of the last 5 years involving PhD students of the team (underlined)**

1: Girard SD, Julien-Gau I, Molino Y, Combes BF, Greetham L, Khrestchatisky M, Nivet E. High and low permeability of human pluripotent stem cell-derived blood-brain barrier models depend on epithelial or endothelial features. FASEB J. 2023 Feb;37(2):e22770. doi: 10.1096/fj.202201422R. PMID: 36688807.

2: Kyriatzis G, Bernard A, Bôle A, Pflieger G, Chalas P, Masse M, Lécorché P, Jacquot G, Ferhat L, Khrestchatisky M. Neurotensin receptor 2 is induced in astrocytes and brain endothelial cells in relation to neuroinflammation following pilocarpine-induced seizures in rats. Glia. 2021 Nov;69(11):2618-2643. doi: 10.1002/glia.24062. Epub 2021 Jul 26. PMID: 34310753.

3: Sbai O, Soussi R, Bole A, Khrestchatisky M, Esclapez M, Ferhat L. The actin binding protein α-actinin-2 expression is associated with dendritic spine plasticity and migrating granule cells in the rat dentate gyrus following pilocarpine-induced seizures. Exp Neurol. 2021 Jan;335:113512. doi: 10.1016/j.expneurol.2020.113512. Epub 2020 Oct 22. PMID: 33098872.

4: Varini K, Lécorché P, Sonnette R, Gassiot F, Broc B, Godard M, David M, Faucon A, Abouzid K, Ferracci G, Temsamani J, Khrestchatisky M, Jacquot G. Target engagement and intracellular delivery of mono- and bivalent LDL receptor-binding peptide-cargo conjugates: Implications for the rational design of new targeted drug therapies. J Control Release. 2019 Nov 28;314:141-161. doi: 10.1016/j.jconrel.2019.10.033. Epub 2019 Oct 20. PMID: 31644939.

5: Iachetta G, Falanga A, Molino Y, Masse M, Jabès F, Mechioukhi Y, Laforgia V, Khrestchatisky M, Galdiero S, Valiante S. gH625-liposomes as tool for pituitary adenylate cyclase-activating polypeptide brain delivery. Sci Rep. 2019 Jun 24;9(1):9183. doi: 10.1038/s41598-019-45137-8. PMID: 31235716; PMCID: PMC6591382.

6: David M, Lécorché P, Masse M, Faucon A, Abouzid K, Gaudin N, Varini K, Gassiot F, Ferracci G, Jacquot G, Vlieghe P, Khrestchatisky M. Identification and characterization of highly versatile peptide-vectors that bind non-competitively to the low-density lipoprotein receptor for in vivo targeting and delivery of small molecules and protein cargos. PLoS One. 2018 Feb 27;13(2):e0191052. doi: 10.1371/journal.pone.0191052. PMID: 29485998; PMCID: PMC5828360.

7: Stamegna JC, Sadelli K, Escoffier G, Girard SD, Veron AD, Bonnet A, Khrestchatisky M, Gauthier P, Roman FS. Grafts of Olfactory Stem Cells Restore Breathing and Motor Functions after Rat Spinal Cord Injury. J Neurotrauma. 2018 Aug 1;35(15):1765-1780. doi: 10.1089/neu.2017.5383. Epub 2018 Apr 30. PMID: 29357739.

8: Theret L, Jeanne A, Langlois B, Hachet C, David M, Khrestchatisky M, Devy J, Hervé E, Almagro S, Dedieu S. Identification of LRP-1 as an endocytosis and recycling receptor for β1-integrin in thyroid cancer cells. Oncotarget. 2017 Aug 10;8(45):78614-78632. doi: 10.18632/oncotarget.20201. PMID: 29108253; PMCID:

PMC5667986.

9: Girard SD, Virard I, Lacassagne E, Paumier JM, Lahlou H, Jabes F, Molino Y, Stephan D, Baranger K, Belghazi M, Deveze A, Khrestchatisky M, Nivet E, Roman FS, Féron F. From Blood to Lesioned Brain: An In Vitro Study on Migration Mechanisms of Human Nasal Olfactory Stem Cells. Stem Cells Int. 2017;2017:1478606. doi: 10.1155/2017/1478606. Epub 2017 Jun 18. PMID: 28698717; PMCID: PMC5494110.

10: Baranger K, Bonnet AE, Girard SD, Paumier JM, García-González L, Elmanaa W, Bernard A, Charrat E, Stephan D, Bauer C, Moschke K, Lichtenthaler SF, Roman FS, Checler F, Khrestchatisky M, Rivera S. MT5-MMP Promotes Alzheimer's Pathogenesis in the Frontal Cortex of 5xFAD Mice and APP Trafficking in vitro. Front Mol Neurosci. 2017 Jan 10;9:163. doi: 10.3389/fnmol.2016.00163. PMID: 28119565; PMCID: PMC5223243.

11: Molino Y, David M, Varini K, Jabès F, Gaudin N, Fortoul A, Bakloul K, Masse M, Bernard A, Drobecq L, Lécorché P, Temsamani J, Jacquot G, Khrestchatisky M. Use of LDL receptor-targeting peptide vectors for in vitro and in vivo cargo transport across the blood-brain barrier. FASEB J. 2017 May;31(5):1807-1827. doi: 10.1096/fj.201600827R. Epub 2017 Jan 20. PMID: 28108572.

## 10. MANENT Jean-Bernard (INMED): Identifying early signs of circuit dysfunction before epilepsy onset in murine models of cortical malformations

**State of the art**

Epilepsies are progressive brain network disorders, and especially those arising in childhood as a consequence of malformations of cortical development (MCDs). Seizures are known to result from abnormal circuit activity; however, circuit-level changes that progressively "render epileptic" developing brains with MCDs remain poorly understood. It is equally unclear how MCDs could interfere with the proper wiring of cortical circuits, and whether signs of circuit dysfunction could be detected at early pre-epileptic stages before epilepsy onset.

Neuroimaging studies in patients with MCDs have highlighted the presence of widespread circuit-level defects extending beyond the macroscopically visible malformation. Through studying murine models of MCDs, the present project aims at identifying and characterizing these early circuit changes, and evaluating their potential impact for cortical operation.

**Methods**

in vivo and in vitro electrophysiological and functional imaging approaches; histology and morphometric methods; in vivo genetic manipulations to induce MCDs (in utero electroporation); in vivo stereotactic injection of viral vectors to express fluorescent reporters or activity sensors.

**Expected results**

This project has the ambition to identify early circuit changes, detectable at early pre-symptomatic stages prior to epilepsy onset, and that may serve as biomarkers or predictors of epilepsy outcomes.

**Feasibility**

3 murine models with cortical malformations; equipped in vivo setups for head-fixed and freely moving recordings; in-house in vivo imaging facility; project authorization for animal research (APAFIS#26835-2020080610441911 v2); ongoing local and international collaborations.

**Expected candidate profile**

Prior experience with rodent handling and surgeries; in vivo recordings including electrode preparation and stereotactic implantation; stereotactic viral injections; histology and microscopy; data analysis

**Bibliography**

Petit, Jalabert et al *Ann Neurol* 2014; Sahu et al *Epilepsia* 2019; Plantier et al *Cereb Cortex* 2019; Hardy, Buhler, Suchkov et al *Neurobiol Dis* 2023.

## Laboratory and team

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Team leader: Dr Carlos Cardoso

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F Martineau (PhD defense 2017)

**Publications of supervised PhD students**


- Petit LF, Jalabert M, Buhler E, Malvache A, Peret A, Chauvin Y, Watrin F, Represa A, Manent JB. Normotopic cortex is the major contributor to epilepsy in experimental double cortex. Ann Neurol. 2014 Sep;76(3):428-42.
- Plantier V, Watrin F, Buhler E, Martineau FS, Sahu S, Manent JB, Bureau I, Represa A. Direct and Collateral Alterations of Functional Cortical Circuits in a Rat Model of Subcortical Band Heterotopia. Cereb Cortex. 2018 Dec 7.
- Martineau FS, Sahu S, Plantier V, Buhler E, Schaller F, Fournier L, Chazal G, Kawasaki H, Represa A, Watrin F, Manent JB. Correct Laminar Positioning in the Neocortex Influences Proper Dendritic and Synaptic Development. Cereb Cortex. 2018 Aug 1;28(8):2976-2990
- Martineau FS, Fournier L, Buhler E, Watrin F, Sargolini F, Manent JB, Poucet B, Represa A. Spared cognitive and behavioral functions prior to epilepsy onset in a rat model of subcortical band heteropia. Brain Res. 2019 Jan 25. pii:S0006-8993(19)30052-6.

## 11. PERRINET Laurent (INT): An efficient modelling approach for the detection of spiking motifs in neurobiological data

*State of the art.* Neuroscience has recently undergone a scientific and technological revolution. The scales at which neuronal activity can be experimentally recorded has considerably expanded. One striking example is the use of photonic imaging approaches to simultaneously sample the activity of thousands of neurons in vivo. Such novel experimental evidence shows that information processing in the brain is not a purely feed-forward process but relies also on internally generated activity in recurrent networks forming complex dynamical systems. Interestingly, it has been recently shown that neural information can be carried by way of series of spikes distributed on neurons of large networks and forming precise spiking spatio-temporal motifs.

*Objectives.* The goal of this project is to bring an interdisciplinary perspective to the detection of precise spike motifs in neurobiological data. In particular, inspired by neurobiological observations, we will mathematically formalize a representation in an assembly of neurons based on a set of motifs with different relative spike times. The main innovative aspect is to consider a representation based on repetitions of these spiking motifs at precise times of occurrence, thus extending the capabilities of analog representations based on vectors of instantaneous firing rate.

*Methods.* In preliminary work, we showed that this dedicated artificial neural network outperforms classical covariance-based methods in recognizing spiking motif timing and identity. This machine learning algorithm is particularly powerful when there is a large number of overlapping motifs as the temporal depth of the motifs increases. We used the *pyTorch* deep learning library, which is well suited for high-performance computing architectures such as GPUs, making it a viable option for high-throughput analysis of neurobiological data.

*Expected results.* An added value of this algorithm is that it can be used to learn precise spiking motifs in an unsupervised manner. It is a powerful tool for the detection of sequential activation of motifs in neurobiological data. In particular, the motifs may take the form of elementary waves and we will challenge the hypothesis that neural activity drives computations thanks to traveling waves, an aspect in which the collaboration with the team of Frédéric Chavane, an expert on their functional role in the visual cortex, will be crucial.

*Feasibility.* Thanks to our preliminary work, we have validated this algorithm on synthetic data for which the ground truth is known. The method will be applied on existing data by our group, notably from cats, macaques or marmosets. The availability of this material makes the project highly feasible.

*Expected candidate profile, specifying at least 4 skills.* The candidate should have a strong inter-disciplinary profile in 1/ computational neuroscience, 2/ biological neuroscience, 3/ machine learning, and 4/ open science (FAIR principles).

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### Previously supervised PhD students

Mina Khoei, Victor Boutin, Angelo Franciosini

### Publications of supervised PhD students


- Victor Boutin, Angelo Franciosini, Frédéric Chavane, Laurent U Perrinet (2022). Pooling in a predictive model of V1 explains functional and structural diversity across species. PLoS Computational Biology.
- Victor Boutin, Angelo Franciosini, Frédéric Chavane, Franck Ruffier, Laurent U Perrinet (2021). Sparse Deep Predictive Coding captures contour integration capabilities of the early visual system. PLoS Computational Biology.
- Victor Boutin, Angelo Franciosini, Franck Ruffier, Laurent U Perrinet (2020). Effect of top-down connections in Hierarchical Sparse Coding. Neural Computation.
- Mina A Khoei, Guillaume S Masson, Laurent U Perrinet (2017). The flash-lag effect as a motion-based predictive shift. PLoS Computational Biology.
- Mina A Khoei, Guillaume S Masson, Laurent U Perrinet (2013). Motion-based prediction explains the role of tracking in motion extrapolation. Journal of Physiology-Paris.

## 12. PICARDO Michel, BAUDE Agnès (INMED): Hippocampal dynamics in health and ASD during the first two postnatal weeks

- **State of the art**

The human hippocampus is crucial for the storage of events into episodic memory. The fact that human episodic memory improves with development and is only partially functional in infancy suggests that hippocampal representations may be very different at early postnatal age. Indeed, it has been suggested that the hippocampus, in addition to being a cognitive region, should also be considered as a sensorimotor structure (Bland and Oddie, 2001; Del Rio-Bermudez and Blumberg, 2021). We and others, have recently shown that this is particularly true during development, when self-triggered sensorimotor inputs (in the form of spontaneous myoclonic movements, such as twitches) drive CA1 dynamics (Mohns and Blumberg, 2008; Dard et al., 2022) and may contribute to the development and maturation of the hippocampal circuitry. More specifically, my group has shown that the first postnatal week ends with a change in the hippocampal representation of sensorimotor inputs with most pyramidal cells switching from being activated to being inhibited by self-generated spontaneous movements whereas interneurons remain activated. We also demonstrated that this change is mediated by the rapid anatomical sprouting of peri-somatic GABAergic innervation of pyramidal cells by parvalbumin basket cells (PVBC, Figure 1, bottom panels represented in red), in agreement with theoretical predictions from a computational model. Furthermore, unpublished data from my group indicate that around P9: 1- the frequency of spontaneous myoclonic movements is reduced in an animal model of ASD; 2- PVBC perisomatic innervation is reduced in the same model of ASD. Of note, this stage (P9) marks a salient checkpoint when both parameters significantly impact CA1 dynamics. Based on these findings, our project is well positioned to address **how hippocampal development is affected in mouse models of ASD** ("outstanding question" in a recent review (Banker et al., 2021)).

- **Objectives**

Since the diagnosis of autism is largely based on behavioral assessment, **we first plan to quantify several aspects of mouse behavior in ASD during development**. **Then, we will test the hypothesis that the transition observed between the first two postnatal weeks is affected in mouse models of ASD. Finally, we will probe the circuit mechanisms supporting this transition both in wild type and ASD mouse model**.

- **Methods**

To address these questions, we will use a combination of *in-vivo* two-photon microscopy, behavioral and electrophysiological recordings, and anatomical characterization during the first two postnatal weeks.

- **Expected candidate profile**

We are looking for a motivated student with either a neurobiology background with a keen interest in computational neuroscience or a physics student with interest in neurobiology and experimentation.

## Laboratory and team

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Team: Developmental scaffolding of adult hippocampal circuits
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Robin Dard (2019-2022)

**Publications of supervised PhD students**

- Leprince E*., Dard RF*., […] Picardo MA, Bocchio M., Baude A., Rosa Cossart R. *Extrinsic control of the early postnatal CA1 hippocampal circuits*. Neuron. 2023 Dec 28:S0896-6273(22)01086-8.

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-Denis J, Dard RF, Quiroli E, Cossart R, Picardo MA. *DeepCINAC: A Deep-Learning-Based Python Toolbox for Inferring Calcium Imaging Neuronal Activity Based on Movie Visualization.* eNeuro. 2020 Aug 17;7(4):ENEURO.0038-20.2020.

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Yannick Bollman 2016-2018

**Publications of supervised PhD students**

https://pubmed.ncbi.nlm.nih.gov/?term=Baude+A&cauthor_id=35856497

Leprince E, Dard RF, Mortet S, Filippi C, Giorgi-Kurz M, Bourboulou R, Lenck-Santini PP, Picardo MA, Bocchio M, Baude A, Cossart R. Extrinsic control of the early postnatal CA1 hippocampal circuits. Neuron. 2022 Dec 28:S0896-6273(22)01086-8. doi: 10.1016/j.neuron.2022.12.013.

Cavalieri D, Angelova A, Islah A, Lopez C, Bocchio M, Bollmann Y, Baude A, Cossart R. CA1 pyramidal cell diversity is rooted in the time of neurogenesis. Elife. 2021 Nov 1;10:e69270. doi: 10.7554/eLife.69270.

Bollmann Y, Modol L, Tressard T, Baude A, Che A, Duan ZRS, Babij R, De Marco García NV, Cossart R. Assemblies of Perisomatic GABAergic Neurons in the Developing Barrel Cortex. Neuron. 2020 Jan 8;105(1):93-105.e4. doi: 10.1016/j.neuron.2019.10.007.

Villette V, Guigue P, Picardo MA, Sousa VH, Leprince E, Lachamp P, Malvache A, Tressard T, Cossart R, Baude A. Development of early-born γ-Aminobutyric acid hub neurons in mouse hippocampus from embryogenesis to adulthood. J Comp Neurol. 2016 Aug 15;524(12):2440-61. doi: 10.1002/cne.23961.

## 13. RIVERA BAEZA Claudio, MINLEBAEV Marat (INMED): Role of surround inhibition in generalization and propagation of epileptic activity in the neonatal brain in vivo

**Summary:** Epilepsy is a neurological disease involving recurrent seizures, which affects up to 1.5% of human neonates (Sheth et al., 1999; Solomon et al., 1984). The neonatal focal seizures may often propagate and degenerate into generalized seizures (Pisani et al., 2021). In the mature brain there are mechanisms preventing the progression of focal epileptic activity to generalized seizure. One of them is epileptic surround inhibition (ESI) that limits the interictal-to-ictal transition and spread of epileptic activity (Prince & Wilder, 1967). ESI arise from i) modulations of blood flow and oxygen delivery, ii) long-range and local inhibitory circuitry. Neonatal nervous system is characterized by the low level of the neurovascular coupling maturation (Kozberg et al., 2013; Zehendner et al., 2013) and immaturity of the interneuronal based inhibition (Daw et al., 2007; Doischer et al., 2008; Minlebaev et al., 2011) putting the question about the efficiency and existence of those mechanisms early in development.
**Our hypothesis** *is that immature neurovascular coupling and inhibitory circuits are inefficient to generate surround inhibition resulting in easily propagating epileptic discharges and their degeneration into the epileptic activity in the developing cortex*. Our PhD project is to test this hypothesis using a combination of sophisticated imaging and electrophysiological recordings from rodent models of epileptic activity *in vivo*.
In the **Task 1.1 we will evaluate the efficiency of GABAergic inhibition during the neonatal and juvenile periods of development.** We will characterize the developmental changes in chloride homeostasis and derived functional changes in GABAA mediated transmission using the combination of electrophysiological recordings and the optical intrinsic signal imaging (OIS). Our preliminary results show the efficiency of GABAergic inhibition starting early in development, we plan to validate our results using the selective pharmacological antagonists (bumetanide and VU0463271, respectively).

In the **Task 1.2 we will characterize the contribution of the interneurons in suppression of the neuronal activity during the epileptic conditions** using OIS and intracellular calcium imaging in transgenic mice expressing the calcium sensor GCamp6 in interneurons. The spatial and temporal crosscorrelation of the epileptic signal and interneurons activity will validate the interneuronal contribution in mechanisms of ESI.

In the **Task 2 we will answer the question of the inadequate metabolic supply as an antiepileptic mechanism** by characterizing the blood flow changes in the developing rat neocortex using multiwavelength OIS imaging. The result will be detailed description of the hemovascular changes and oxygenation

of the neuronal tissue over extended cortical surface during epileptic activity in the immature nervous system.

All the resources required for realization of these objectives are available in INMED. These complementary sets of expertise will therefore allow us to explore the mechanisms underlying the generalization and propagation of epileptic activity in the neonatal brain *in vivo*.

The PhD student to be recruited should be highly motivated and versatile, with a background in experimental biology, especially in neuroimaging (using OIS), electrophysiology (extra- and intracellular recordings) in vivo and appropriate analytic skills.

## Laboratory and team

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Marine Tessier 12/2021
Amina Rezzag Lebza 07/2021
Emmanuelle Goubert 12/2017
Nazim Kourdougli 12/2015

**Publications of supervised PhD students**

1. **Tessier M**, Saez Garcia M, **Goubert E**, Blasco E, **Consumi A**, Dehapiot B, Tian L, MolinariF, Laurin J, Guillemot F, Hübner CA, Pellegrino C, Rivera C.Bumetanide induces post-traumatic microgliainterneuron contact to promote neurogenesis and recovery. **Brain**, conditionally accepted.

2. Khirug S, Soni S, Saez Garcia M, **Tessier M,** Zhou L, Kulesskaya N, Rauvala H, Lindholm D, Ludwig A,

Molinari F, Rivera C. Protective Role of Low Ethanol Administration Following Ischemic Stroke via Recovery of KCC2 and p75NTR Expression. **Mol Neurobiol**. 2021 Mar;58(3):1145-1161. doi: 10.1007/s12035-020-02176-x.

3. **Goubert E,** Altvater M, Rovira MN, Khalilov I, Mazzarino M, Sebastiani A, Schaefer MKE, Rivera C, Pellegrino C.Bumetanide Prevents Brain TraumaInduced Depressive-Like Behavior. **Front Mol Neurosci.** 2019 Feb 5;12:12. doi: 10.3389/fnmol.2019.00012.

4. Di Scala C, **Tessier M**, Sapet C, Poulhes F, Sicard F, Zelphati O, Pellegrino C. A new polymer-based approach for in vivo transfection in postnatal brain. **J Neurosci Methods.** 2019 Jan 1;311:295-306. doi: 10.1016/j.jneumeth.2018.11.004.

Riffault B, **Kourdougli N**, Dumon C, Ferrand N, Buhler E, Schaller F, Chambon C, Rivera C, Gaiarsa JL, Porcher C. Pro-Brain-Derived Neurotrophic Factor (proBDNF)-Mediated p75NTR Activation Promotes Depolarizing Actions of GABA and Increases Susceptibility to Epileptic Seizures. **Cereb Cortex.** 2018 Feb 1;28(2):510-527. doi: 10.1093/cercor/bhw385.

6. **Kourdougli N,** Pellegrino C, Renko JM, Khirug S, Chazal G, Kukko-Lukjanov TK, Lauri SE, Gaiarsa JL, Zhou L, Peret A, Castrén E, Tuominen RK, Crépel V, Rivera C. Depolarizing γ-aminobutyric acid contributes to glutamatergic network rewiring in epilepsy. **Ann Neurol.** 2017 Feb;81(2):251-265. doi: 10.1002/ana.24870.

7. Blauwblomme T, Dossi E, Pellegrino C, **Goubert E**, Iglesias BG, Sainte-Rose C, Rouach N, Nabbout R, Huberfeld G. Gamma-aminobutyric acidergic transmission underlies interictal epileptogenicity in pediatric focal cortical dysplasia. **Ann Neurol.** 2019 Feb;85(2):204-217. doi: 10.1002/ana.25403. Epub 2019 Jan 17.

8. **Kourdougli N**, Varpula S, Chazal G, Rivera C. Detrimental effect of post Status Epilepticus treatment with ROCK inhibitor Y-27632 in a pilocarpine model of temporal lobe epilepsy. **Front Cell Neurosci**. 2015 Oct 23;9:413. doi: 10.3389/fncel.2015.00413.

9. Saarikangas J, **Kourdougli N**, Senju Y, Chazal G, Segerstråle M, Minkeviciene R, Kuurne J, Mattila PK, Garrett L, Hölter SM, Becker L, Racz I, Hans W, Klopstock T, Wurst W, Zimmer A, Fuchs H, GailusDurner V, Hrabě de Angelis M, von Ossowski L, Taira T, Lappalainen P, Rivera C, Hotulainen P. MIMInduced Membrane Bending Promotes Dendritic Spine Initiation. **Dev Cell.** 2015 Jun 22;33(6):644-59. doi: 10.1016/j.devcel.2015.04.014.

10. Pallud J, Le Van Quyen M, Bielle F, Pellegrino C, Varlet P, Cresto N, Baulac M, Duyckaerts C, **Kourdougli N**, Chazal G, Devaux B, Rivera C, Miles R, Capelle L, Huberfeld G. Cortical GABAergic excitation contributes to epileptic activities around human glioma. **Sci Transl Med**. 2014 Jul 9;6(244):244ra89. doi: 10.1126/scitranslmed.3008065.

11. Medina I, Friedel P, Rivera C, Kahle KT, **Kourdougli N**, Uvarov P, Pellegrino C. Current view on the functional regulation of the neuronal K(+)-Cl(-) cotransporter KCC2. **Front Cell Neurosci.** 2014 Feb 6;8:27. doi: 10.3389/fncel.2014.00027.

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**Publications of supervised PhD students**

1: Hardy D, Buhler E, **Suchkov D**, Vinck A, Fortoul A, Watrin F, Represa A, Minlebaev M, Manent JB. Early suppression of excitability in subcortical band heterotopia modifies epileptogenesis in rats. Neurobiol Dis. 2023 Feb;177:106002.

2: **Suchkov D**, Shumkova V, Sitdikova V, Minlebaev M. Simple and Efficient 3D-Printed Superfusion Chamber for Electrophysiological and Neuroimaging Recordings In Vivo. eNeuro. 2022 Oct 5;9(5):ENEURO.0305-22.2022.

3: Dard RF, Leprince E, Denis J, Rao Balappa S, **Suchkov D**, Boyce R, Lopez C, Giorgi-Kurz M, Szwagier T, Dumont T, Rouault H, Minlebaev M, Baude A, Cossart R, Picardo MA. The rapid developmental rise of somatic inhibition disengages hippocampal dynamics from selfmotion. Elife. 2022 Jul 20;11:e78116.

4: **Suchkov D**, Sharipzyanova L, Minlebaev M. Horizontal Synchronization of Neuronal Activity in the Barrel Cortex of the Neonatal Rat by Spindle-Burst Oscillations. Front Cell Neurosci. 2018 Jan 19;12:5.

5: Sintsov M, **Suchkov D**, Khazipov R, Minlebaev M. Developmental Changes in Sensory-Evoked Optical Intrinsic Signals in the Rat Barrel Cortex. Front Cell Neurosci. 2017

6: Khazipov R, Zaynutdinova D, Ogievetsky E, Valeeva G, **Mitrukhina O**, Manent JB, Represa A. Atlas of the Postnatal Rat Brain in Stereotaxic Coordinates. Front Neuroanat. 2015 Dec 23;9:161.

7: **Mitrukhina O, Suchkov D,** Khazipov R, Minlebaev M. Imprecise Whisker Map in the Neonatal Rat Barrel Cortex. Cereb Cortex. 2015 Oct;25(10):3458-67.

## 14. RIVERA Santiago (INP): Mechanisms of action of MT5-MMP in Alzheimer's disease and therapeutic modulation using viral-mediated transgenic strategies

- **State of the art**

We found that the proteinase MT5-MMP (MT5 thereafter) promotes amyloidosis and neuroinflammation, while MT5 KO prevents the latter as well as LTP and cognitive deficits in the 5xFAD transgenic mouse model of Alzheimer's disease (AD) early in the disease. Similarly, MT5 KO in neural cell cultures of 5xFAD mice and in iPS-derived neural cells of AD patients reduces neuroinflammation and the accumulation of neurotoxic products of APP metabolism. Most interestingly, we found that expression of mutated/truncated forms of MT5 in AD cell models reduces APP/amyloid pathology. Together, this suggests that pre-symptomatic AD pathology begin much earlier than expected and that MT5 modulation may alleviate this pathology. The underlying **hypothesis** is that mutant MT5 forms interfere with the detrimental mechanisms driven by endogenous MT5, thus preconfiguring MT5-based biomolecules with therapeutic potential for AD.

- **Objectives**

To test this hypothesis, we plan three objectives to determine the therapeutic potential and the mechanisms of action of mutated forms of MT5 in: 1) Neural cell cultures from the 5xFAD mouse model of AD.
2) Human iPS-derived neurons carrying genetic mutations
3) 5xFAD mice at pre-symptomatic and symptomatic phases of the disease

***Models*:** a) primary cultures of neurones/astrocytes from 5xFAD mice; b) human iPS-derived neurons with AD mutations; c) *5xFAD* mice for *in vivo* studies

**Techniques**

MT5 activity will be modulated by transducing cultured cells and mouse brains with AAVs coding for MT5 mutated variants. We will assess the impact of these modulations using biochemistry (WB, immunoprecipitation, ELISA), molecular and cell biology (qPCR, mutagenesis, immunocytochemistry), advanced microscopy (SIM, HCS), electrophysiology (patch clamp), anatomopathology and mouse behaviour. Particular attention will be paid to pathways involved in the control of APP/amyloid metabolism, neuroinflammation and synaptic activity.

- **Expected results**

- Identify **novel neurodegeneration pathways** driven by MT5.
- Set the basis for generating MT5-based biomolecules with therapeutic potential.
- Take a further step to validate MT5 as a new potential target in AD.

- **Feasibility**

The project is supported by 2 senior scientists and 2 technical staff. All the technical expertise and state-of-the-art equipment is available at the INP. The project is funded for 4 years by French national agencies (i.e., FRM, ANR).

- **Expected candidate profile**

Be willing to learn (or already have a grounding in) one of the following areas: biochemistry, molecular and cell biology, electrophysiology, microscopy or neuroanatomy of the brain. Theoretical knowledge of AD or at least neuroscience/neuropathology. Comfortable working with mice and a passion for scientific research. Ethical conduct, teamwork, motivation, curiosity and critical thinking skills.

## Laboratory and team

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Team: Neural Plasticity and Degeneration
Team leader: Santiago RIVERA

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Pedro Belio Mairal (4th year). He is cosupervised with Dr. Emmanuel Nivet

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Laura Garcia-Gonzalez 2016-2020
Jean-Michel PAUMIER 2015-2018
Nathalie Py 2011-2014
Adlane Ould-yahoui 2007-2011
Crystel Ogier 2002-2005
Jérôme Jourquin 1999-2002

**Publications of supervised PhD students**

**Pilat P, Paumier J-M, García-González L**,
Louis L, Stephan D, Manrique C, Khrestchatisky M, Di Pasquale E, Baranger K and Rivera S (2022). MT5-MMP promotes neuroinflammation, neuronal excitability and Ab production in primary neuron/astrocyte cultures from the 5xFAD mouse model of

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