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du Fer à moulin

Development & plasticity of the nervous system



Fiona Francis, Director
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Institut du Fer à Moulin

The *Institut du Fer à Moulin* (IFM) is a Neuroscience research Institute affiliated with Inserm (French National institute for health and medical research) and Sorbonne University, one of the best scientific and medical faculties in France. It is located in central Paris within walking distance from the Pierre and Marie Curie university campus and the Pitié-Salpêtrière hospital.

The IFM teams focus on nervous system development and plasticity. Their projects involve basic research and translational aspects of neurological and psychiatric diseases. The IFM has been part of various Parisian research networks providing strong links between teaching, clinical psychiatry and basic research.

The IFM was created in 2007 and currently hosts 7 independent research groups, including five whose leaders joined the Institute as young scientists (ATIP-AVENIR laureates). Excellent common facilities and equipment ensure efficiency. A strong emphasis is placed on interactions between scientists and students with weekly progress reports and invited seminars, each in English. The atmosphere is international and highly collaborative giving students and post-docs the opportunity for scientific networking and project development. In addition, one-day international IFM colloquiums are organized covering important and timely Neuroscience topics.

IFM members have received national and international grants and awards, including starting and advanced ERC grants. The IFM benefits from the advice of an international Scientific Advisory Board which is also involved in the selection of new teams.

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Education and training

IFM scientists include six lecturers, two full professors at Sorbonne University, and Inserm or CNRS scientists actively involved in teaching. Several Master courses are organized at the IFM each year. The IFM provides a special support for PhD students, with a personalized PhD committee.

Research groups

Neurotransmission and signaling (PI, Jean-Antoine Girault)

This group studies the signal transduction mechanisms by which neurotransmitters exert long-lasting effects. This is investigated in the striatum in the context of incentive procedural learning, drug addiction, and movement disorders (Parkinson's disease and dystonia). Research focuses on core signaling mechanisms shared in these different conditions.

Cortical development and pathology (PIs, Fiona Francis and Laurence Goutebroze)

Using genetics, biochemistry, molecular and cellular biology, and physiology, this group investigates cytoskeletal-associated proteins which are mutated in human cortical development abnormalities, associated with epilepsy, intellectual disability and neuropsychiatric disorders. They focus their studies on cell proliferation and migration, axonal outgrowth, and synaptogenesis, investigated in different genetic models (e.g. Eml1, Lis1, Dcx and Cntnap2), and related to human mutations. Pathophysiology is also studied for hippocampal malformations. Techniques used include *in utero* electroporation and viral infection, time-lapse imaging, RNA interference, morphological and behavioral studies.

Plasticity in cortical networks and epilepsy (PI, Jean Christophe Poncer)

The team explores the pathophysiology of focal epilepsies, with a specific focus on the function and plasticity of cortical synapses and networks. Their recent work has focused on alterations of neuronal chloride homeostasis in focal epilepsies and the functional impact of mutations associated with epileptic encephalopathies. By combining advanced electrophysiology and optical imaging techniques in cellular and animal models, as well as post-operative tissues from epileptic patients, our aim is to resolve the cellular architecture of epileptic networks and identify key cellular determinants that could represent novel therapeutic targets for drug-resistant epilepsies.

Serotonin signaling in plasticity and disease (PIs, Anne Roumier and Corentin Le Magueresse)

Serotonin (5-hydroxytryptamine, 5-HT) participates in many physiological functions in the central nervous system and at the periphery, including during development. This group discovered the role of $5HT_{2B}$ as an auto-receptor positively regulating the release of serotonin, which is relevant for impulsivity, depression and addiction. Current projects investigate the role of 5HT2B in the control of serotonin and dopamine neurons and in the modulation of neuroinflammation, and its consequences in psychiatric conditions. The group studies how mechanisms of immunity, in particular microglial cells, shape the construction of brain circuits and how their dysregulation favors the emergence of neurodevelopmental and psychiatric disorders.

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Sleep and emotional memory (PI, Gabrielle Girardeau)
The "Sleep and emotional memory" group is interested in the neurophysiological processes of emotional regulation (memory, learning, reactivity, plasticity) that take place during the different sleep phases. For this, they use a combination of correlational and causal approaches with multi-structure electrophysiological recordings and optogenetics in the behaving rat (learning/sleep).

Stem cells in neurodevelopment (PI, Stéphane Nédelec)
This lab studies the molecular and cellular basis of human nervous system development in health and disease using organoid approaches. They seek to decode: 1) the principles controlling morphogenesis and formation of cell type diversity in the hindbrain and spinal cord, 2) how genetic mutations perturb these events to cause neurodevelopmental disorders such as spinal muscular atrophies or juvenile forms of amyotrophic lateral sclerosis. To approach these questions, in vitro models derived from human induced pluripotent stem cells are coupled with live imaging, genomic analyses and histological analyses performed on organoids and human embryos.

Pleiotropy of morphogens (PI, Julien Ferent)
During embryonic development, secreted molecules, or morphogens, instruct the shape and organization of the nervous system, by acting on proliferation, cell fate, migration or axonal growth. Thus, differentiating neurons need to change their molecular responses to morphogens to achieve the precise sequence of correct behaviors. Using *in vitro* models (microfluidic chambers) as well as 3D imaging, this group investigates how a single (and then multiple) morphogenic signal(s) act at multiple steps of neuronal development to induce the different responses.

Core facilities and shared equipment

The IFM is organized in such a way that most of the scientific equipment is located in common facilities easily accessible to all teams. In addition to shared equipment and facilities for cell culture, biochemistry, histology, and molecular biology, three major core facilities comprise dedicated personnel:

Cell and tissue imaging core facility. This facility offers state-of-the-art microscopy equipment and image processing tools (e.g., SP5 confocal, FV10i compact confocal, spinning disk, 2-photon, and PALM/STORM microscopes...) as well as electron microscopy.

Mouse breeding and experimentation facility. An entirely renovated SPF facility equipped for surgery, behavioral studies, and optogenetics.

Cell and tissue engineering. This facility differentiates neurons from induced pluripotent stem cells to aid in basic and disease-oriented projects.

Selected recent publications

Gribaudo et al. (2023) Self-organizing models of human trunk organogenesis recapitulate spinal cord and spine co-morphogenesis. ***Nat Biotechnol.*** *doi: 10.1038/s41587-023-01956-9*

Simonnet et al. (2023) Silencing KCC2 in mouse dorsal hippocampus compromises spatial and contextual memory. ***Neuropsychopharmacology*** *48:1067-1077*

Albertini G et al. (2023) Serotonin sensing by microglia conditions the proper development of neuronal circuits and of social and adaptive skills. ***Mol Psychiatry*** doi: 10.1038/s41380-023-02048-5.

Romero DM et al. (2022) Novel role of the synaptic scaffold protein Dlgap4 in ventricular surface integrity and neuronal migration during cortical development. ***Nat Commun*** *13(1):2746*

Girardeau and Lopes-Dos-Santos V (2021) Brain neural patterns and the memory function of sleep. ***Science*** *374(6567):560-564*

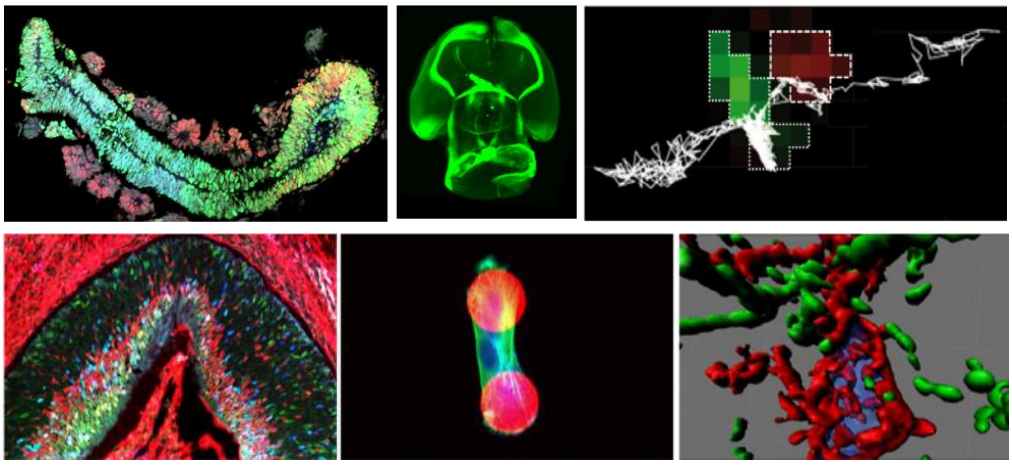
Mouilleau V et al. (2021) Dynamic extrinsic pacing of the HOX clock in human axial progenitors controls motor neuron subtype specification. ***Development*** *148(6):dev194514*

Druart M et al. (2021) Elevated expression of complement C4 in the mouse prefrontal cortex causes schizophrenia-associated phenotypes. ***Mol Psychiatry*** 26(7):3489-3501.

Goutierre M et al. (2019) KCC2 Regulates Neuronal Excitability and Hippocampal Activity via Interaction with Task-3 Channels. ***Cell Reports*** *28(1):91-103.e7.*

Uzquiano A et al. (2019) Mutations in the Heterotopia Gene Eml1/EML1 Severely Disrupt the Formation of Primary Cilia. ***Cell Reports*** *28(6):1596-1611.e10.*

Ferent J et al. (2019) Boc Acts via Numb as a Shh-Dependent Endocytic Platform for Ptch1 Internalization and Shh-Mediated Axon Guidance. ***Neuron*** *102(6):1157-1171.e5*



Applications for new groups and positions

Applications should be sent directly to Fiona Francis and Jean-Christophe Poncer. Post-doctoral applicants and students should contact directly the relevant group leader.

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