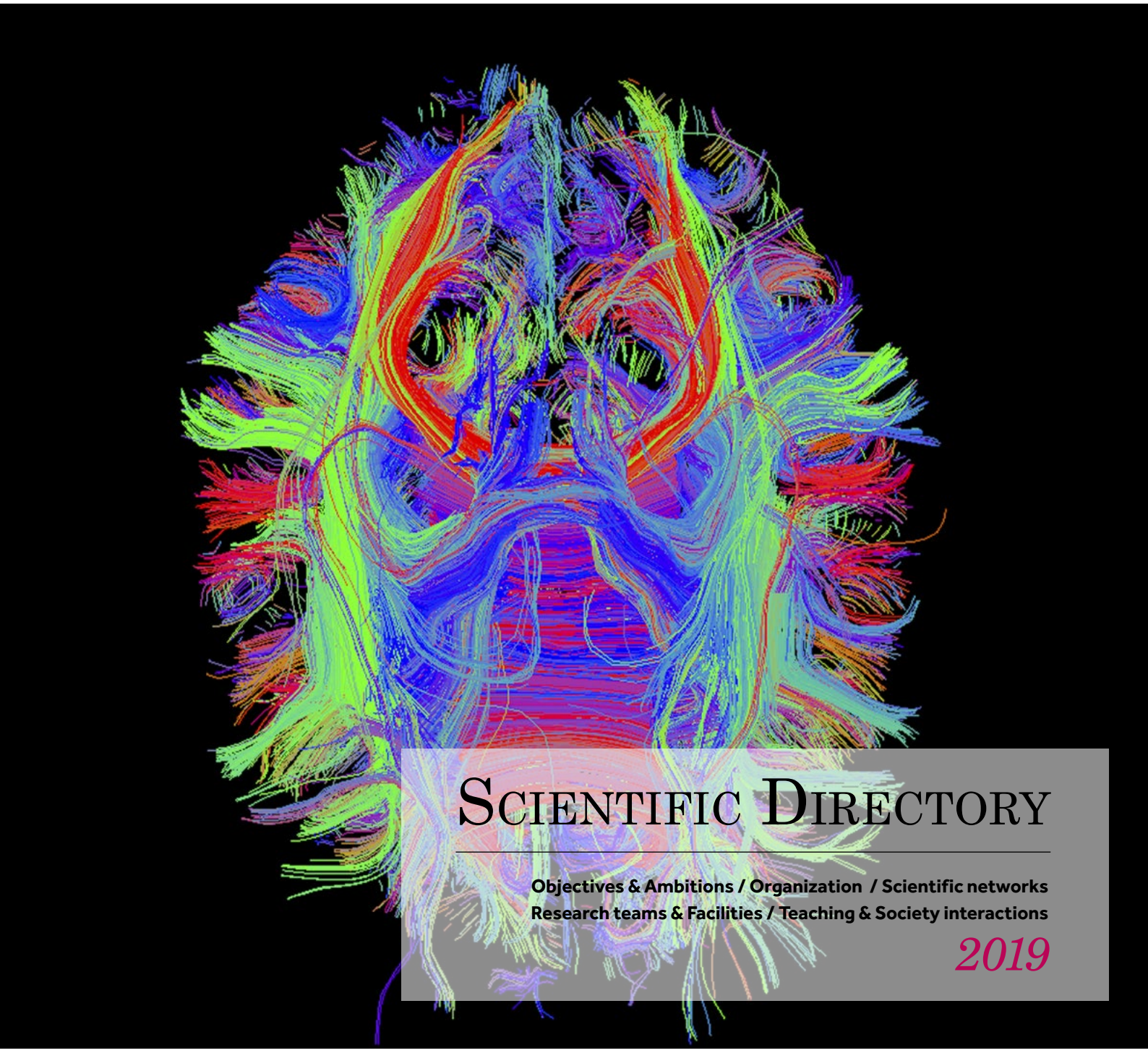
Grenoble
Institut Neurosciences



Scientific Directory

Objectives & Ambitions / Organization / Scientific networks
Research teams & Facilities / Teaching & Society interactions

2019

Université Grenoble Alpes

Inserm

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UNIVERSITÉ Grenoble Alpes

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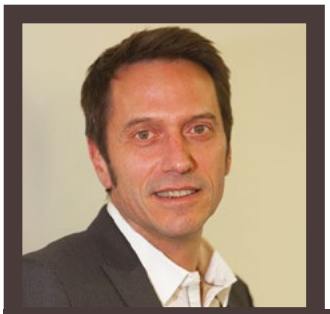
SUMMARY



Frédéric SAUDOU

Director

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EDITORIAL

Understanding molecular and cellular mechanisms involved in different physiological functions is necessary to develop new therapies. Studying these physiological functions in different organisms and pathologies is crucial in order to test their validity. In fact, many pathologies remain poorly understood and many of them do not have curative treatments, in spite of their significant impact on patients' lives and families.

Gathering expert scientists in basic and clinical neuroscience is the GIN's specialty. The 250 researchers, professors, clinicians, engineers, technicians, students and administrative personnel, who are all members of the GIN, have the following main goals:

- ***produce high-quality research in neuroscience*** *based on multidisciplinary approaches.*
- *promote translational research* ***developing, new innovative therapies*** *for pathologies refractory to existing treatments as* ***a long-term objective****.*
- ***train and educate the next generation of neuroscience researchers and clinicians*** *and thus promote the emergence and growth of young scientists and clinicians.*
- ***actively participate in creating a center of excellence in the field of neuroscience*** *at local, national and international levels.*
- ***communicate with the public****, not only to promote the research conducted by the GIN, but to also strengthen scientific communication and share knowledge.*

Marylin VANTARD

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PRESENTATION

The Grenoble Institute of Neurosciences (GIN) mission is to **understand the functioning of both central and peripheral nervous systems in order to develop new therapeutic strategies for neurological, psychiatric or neuromuscular disorders**. Currently studied pathologies of the adult nervous system include Parkinson's, Huntington's and Alzheimer's diseases, epilepsy, vascular disorders, myopathies, and mood and anxiety disorders.

The GIN develops fundamental research that spans from brain development to adult brain plasticity, from the molecular to the most integrated levels, using cell lines, animal models and clinical trials. Conversely, clinical questions (e.g. therapeutic stimulation of brain structures) are addressed through experimental approaches using animal models, thereby contributing to new conceptual findings. Neuroimaging, mainly based on NMR, in either animals or humans, also plays a role in this reciprocal interaction between basic and clinical research.

The GIN has 6.000 m^2 dedicated to research in Neuroscience in close proximity to many high level research centers, offering a unique opportunity for the development of trans-disciplinary projects. Twelve research teams host 250 researchers, clinicians, students and technicians.

The GIN operates a number of high tech platforms including MRI, animal behavior and neurophysiology facilities, electron microscopy and photonic imaging center (PIC-GIN) providing the necessary resources for high standard and innovative research.

GIN's ambition is to offer both state of the art facilities and a high-level scientific environment, and to allow attainment of the highest scientific standard. Its goal is also to encourage the emergence of promising young talents and hence to become attractive for new teams of high scientific quality in basic and translational Neuroscience.

HISTORY

2007 - Creation of the *Grenoble Institute of Neurosciences* (GIN) as a Research Centre to gather the local forces in Neurosciences organized around shared facilities. This project was jointly initiated by *Université Grenoble Alpes* (UGA) and the national research agencies dedicated to Life and Health Sciences, Inserm and CEA.

2007 - Nomination of Claude Feuerstein as Director of the GIN.

2009 - IBiSA label for electron and two-photon microscopy facilities

2012 - Creation of IRMaGe, a MRI and neurophysiology facility from small animal to human. This service unit was jointly created by *Université Grenoble Alpes* (UGA), the Grenoble Hospital and the national research agencies, Inserm and CNRS (Ibisa and Fly labeled).

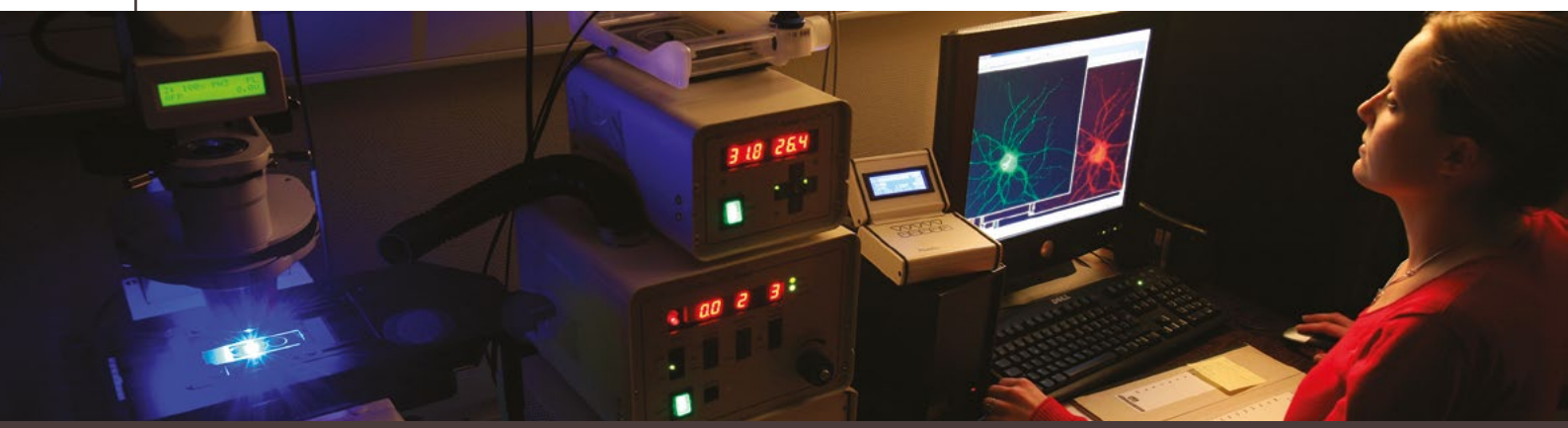
2013 - Nomination of Frédéric Saudou as Director of the GIN.

2015 - Creation of GREEN (GREnoble Excellence in Neurodegeneration). GIN is a founder member of this research structure.

2015 - Creation of a Photonic Imaging Center (PIC-GIN) devoted to molecular and cell imaging (Ibisa labeled).

2017 - Creation of the GIN foundation under the aegis of the UGA foundation.

2017 - Celebration of the ten years of the GIN.



KEY FIGURES

6,000 m²
dedicated to neuroscience research

6
facilities

250
researchers, teacher-researchers, clinicians, engineers, technicians, students and administration

BUILDING AND STAFF

13
research teams

760
original research articles or reviews in peer-reviewed journals and
42 books since 2009

12
international awards since 2011, including the Lounsbery Award 2015

RESEARCH

114 phDs
188 Masters since 2009

42 PhD students
41 HDR

8,500
hours of teaching per year

TEACHING

Collaborations with
21 countries throughout the world

340
conferences and seminars since 2009

INTERNATIONAL

13
patents with 1 license

4
start-ups created by members of the GIN since 2005

BUSINESS

5,000 people involved per year

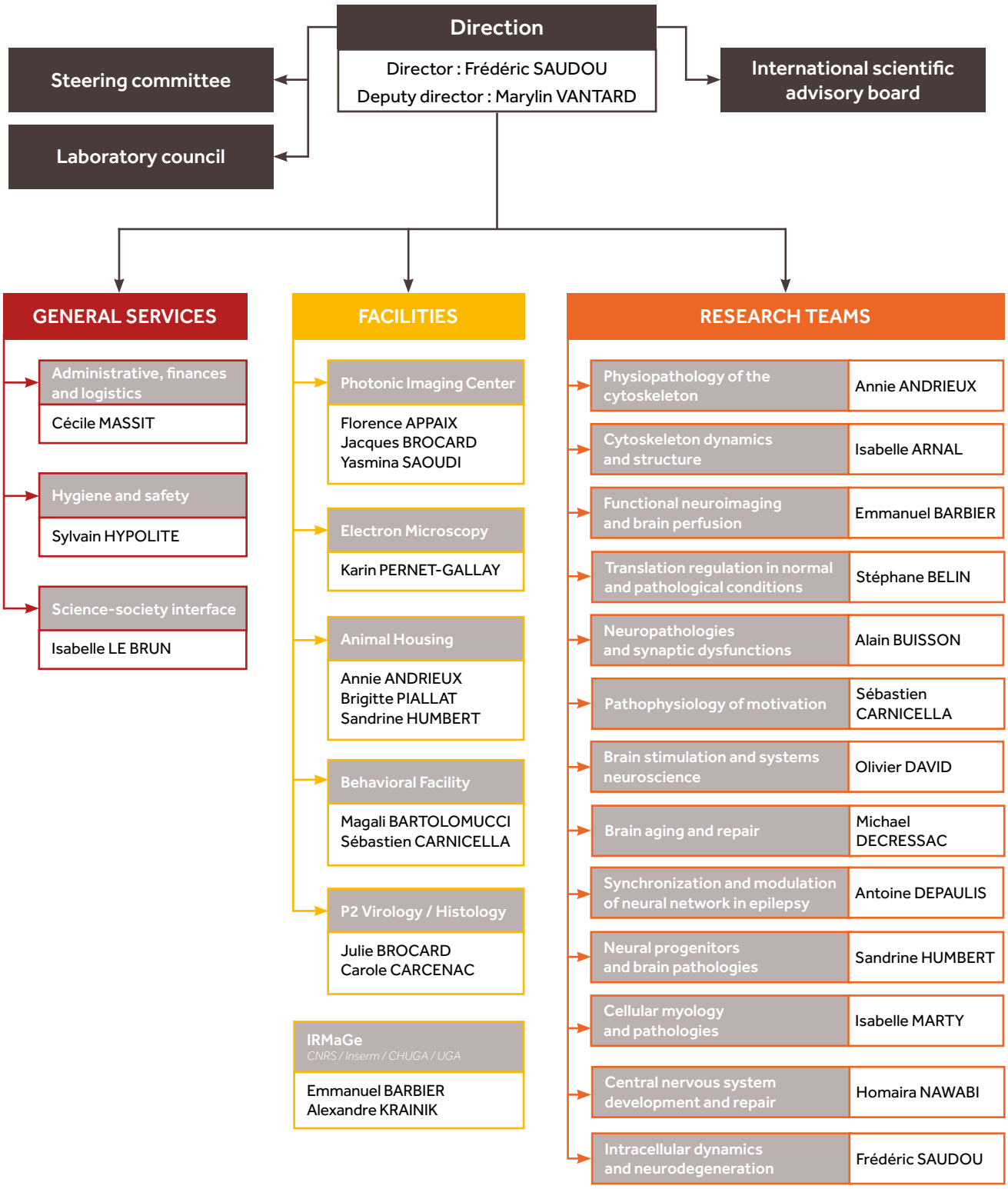
10 to **20**
visits of the institute organized every year since 2007

Participation for many years in
3 international and 1 national events*

SCIENCE-SOCIETY INTERFACE

**Brain Week, Pint of Science, Day of Epilepsy and Science Festival*

STRUCTURAL ORGANIZATION



SCIENTIFIC NETWORKS

THE GIN IN GRENOBLE AND AUVERGNE - RHÔNE - ALPES

The location of the GIN was chosen to foster interactions with clinicians of the Grenoble University Hospital (CHU Grenoble Alpes). This led to the active involvement of up to 21 clinicians in several teams and the development of translational projects.

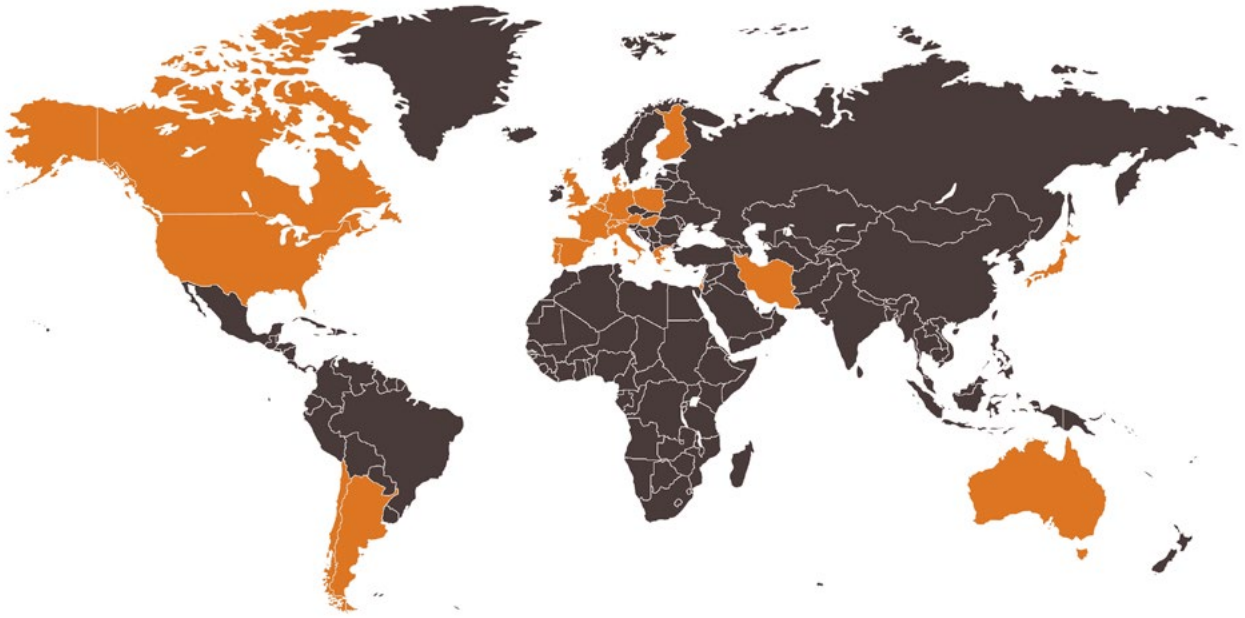
In addition, a large number of research programmes rely on the close proximity with physicists and biologists of various laboratories in Grenoble such as the European Synchrotron Research Facilities (ESRF) or renowned CNRS laboratories in physics, optics, nanosciences, engineering and cognition (LiPhy, Institut Louis Néel, Minatec, GIPSA-lab, LNPC, Clinatec, etc.). The GIN has also privileged relationships with the CEA and the Institute for Advanced Biosciences (IAB).

These interactions have led to the development of new advanced techniques that have been applied to neurobiological questions and/or new therapeutic approaches.

Within the Auvergne-Rhone-Alpes region, a powerful neuroscientific potential also exists in Lyon, Saint-Etienne, Chambéry and Archamps, all within a 1h-drive from Grenoble. In particular, The Neuroscience Federative Institute of Lyon (IFNL) is a significant partner of the GIN with several ongoing collaborations between teams of the two institutes, as well as the Institut NeuroMyoGene (INMG). Long standing interactions exist also between the GIN-associated UMS IRMaGe and Lyon's teams concerning several imaging techniques (MRI, PET scan). The current strengthening of research activities in Neuroscience between the cities of Lyon and Grenoble facilitates the organization of cross training, exchanges of teachers, ctivities for students and seminars in common.

THE GIN AT NATIONAL AND INTERNATIONAL LEVELS

Since GIN's take off, all research teams have developed close scientific collaborations with various national and international institutes involved in Neuroscience. In particular, most teams have ongoing collaborations via European or national programmes with groups of the Institute of the Brain and Spinal Cord in Paris, the École Normale Supérieure (IBENS), the Neuroscience Department of Collège de France, the Institut Curie, Neuroscience Institutes in Marseille (INMED, INT, INS), Montpellier (IGF) and Bordeaux (Magendie, IINS).



Scientific collaborations around the world.
In orange, countries with regular collaborations with GIN's scientists.

THE GIN IS PARTNER OF FEDERATIVE RESEARCH STRUCTURES

Besides collaborations of teams with various national and international laboratories, GIN is partnered with federative research structures.

GREEN, GRENOBLE EXCELLENCE IN NEURODEGENERATION

Grenoble excellence in neurodegeneration

green.univ-grenoble-alpes.fr

GIN is a founding member of the GREnoble Excellence in Neurodegeneration, GREEN. GREEN is a federative research structure recognized as a center of excellence in the field of neurodegenerative disorders by the French government in June 2015. It is integrated in the European and Canadian network of Centres Of Excellence in Neurodegeneration.

www.coen.org

GREEN assembles 26 multidisciplinary researcher teams focusing on 4 diseases (Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Multiple Sclerosis (MS)). Team expertise's range from basic to clinical research as well as in social sciences and technologies. GREEN partners are members of GIN, IAB, LPCN, Clinatec, TIMC-ThTMAS, I2BM, Medical Chemistry Dpt, Psychiatry, Neurology and Rehabilitation Dpt (CHU Grenoble), INRIA, Bioclinical Radiopharmaceutics Biocliniques, and the Grenoble Alps Health and Society Research Alliance. Research in GREEN benefits from the collaboration between its various partners and has access to large-scale facilities (ESRF, EMBL, IBS, CHU, MINATEC technology campus) and biotechnology platforms. GREEN has also developped strong relationships with local and national companies.

GREEN objectives are:

- to strive / structure and maximize / stimulate collaborative research focusing on neurodegenerative disorders in Grenoble.
- to gather multiple teams, from multiple disciplines, from basic, clinical, translational, biotechnology to social sciences research.
- to promote international recognition for Grenoble on its research in Neurosciences.
- to improve the scientific communication, networking, exchanges and education workshops to attract young scientists and Medical Doctors.
- to promote exchanges and networking with neuroscience Institutes throughout Europe.

NEUROCOG, FROM NEURONS TO SOCIAL COGNITION IN GRENOBLE

neurocog.univ-grenoble-alpes.fr

NeuroCoG
Univ. Grenoble Alpes

The GIN is a founding member of the NeuroCoG project created in 2016 at the Grenoble University (National Excellence Initiative - Idex) aims to understand the biological, neurophysiological and functional bases of behavioral and cognitive processes in normal and pathological conditions, from cells to networks and from individual to social cognition.

The NeuroCoG project is based on a wide-spectrum interdisciplinary approach (e.g. fundamental and cognitive neuroscience, chemistry, physics, cognitive and social psychology, education, language sciences, computer sciences, applied mathematics, and engineering; as well as clinical specialties such as neurology and psychiatry).

NeuroCoG brings together 46 interdisciplinary Grenoble research teams and facilities and is based on networks at local, national and international levels such as the FHU NeuroPsynov, the International excellence network on neurodegenerative disorders (GREEN), and the Pole Grenoble Cognition and Health and Society Research Alliance.

NeuroCoG project is oriented within a perspective of continuous development, and has the long-term objective of creating an Institute for Brain & Cognition in Grenoble.

NEUROPSYNOV

Fédération Hospitalo Universitaire NeuroPsyNoV

fhu-neuropsynov.chu-grenoble.fr

GIN is a founding member of NeuroPsyNov, a "Fédération Hospitalo-Universitaire (FHU)" certified in 2014, following an international evaluation. It is coordinated by Philippe Kahane, head of the Epilepsy surgery programme. The general aim of this federation is to develop a translational and multidisplinary approach to drug-resistant neurological (movement disorders, epilepsies) and psychiatric (depression, OCD) pathologies. It includes several medical units from the Grenoble University hospital (Neurology, Neurosurgery,

Psychiatry, Neuroimaging) as well as other institutes involved in Neuroscience. The development of this FHU will promote translational research in Neuroscience and will consolidate the collaborations with different local laboratories in Physics.

MYONEURALP

GIN is a member of the MyoNeurALP alliance created in 2016 to gather the community of researchers and clinicians of the Auvergne-Rhone-Alpes developing research on neuromuscular diseases.

MyoNeurALP is a reference center for rare neuromuscular diseases with expertise at all levels of the neuromuscular system (neurons, neuromuscular junction, muscle, immune cells, endothelial cells…) that associates 17 multidisciplinary teams from four research units (INMG-NeuroMyoGene Institute, Lyon, GReD Genetique Reproduction and Developpement, Clermont Ferrand, GIN Grenoble Neurosciences, LIBM (former LPE) Laboratoire Interuniversitaire de Biologie de la Motricite, Saint Etienne). MyoNeurALP aim is to gain further understanding of pathophysiological mechanisms, identify new biomarkers and propose innovative therapeutic strategies for neuromuscular disorders. The approaches are developed at multidimensional scales ranging from molecular biology, cell biology, electrophysiology to integrated human physiology.

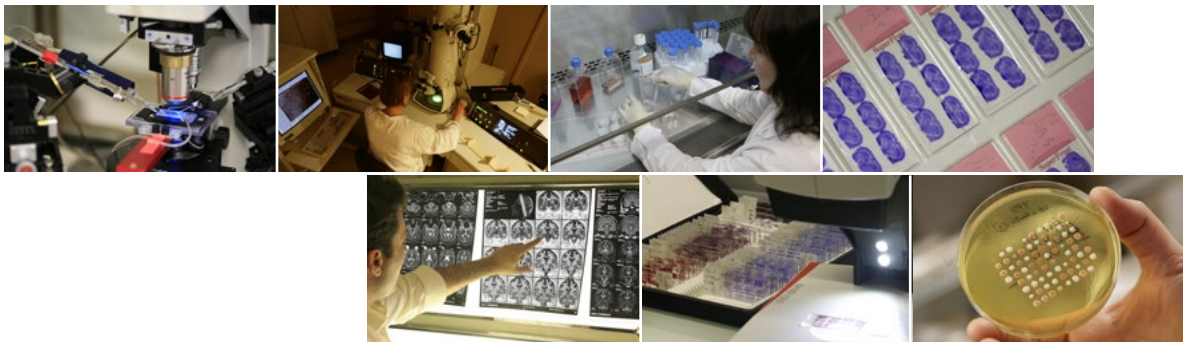
GIRC, GRENOBLE INSTITUTE OF RESEARCH ON CANCER

http://girc.ujf-grenoble.fr

GIN is a member of a Federative research structure on cancer created in 2011, GIRC, Grenoble Institute of Research on Cancer.

Cancer research is one of the most important lines of biomedical research at the UGA. Indeed, the site of Grenoble offers particular specificities for cancer research, including a whole continuum of research from studies at the molecular structure level (conducted at the Institute of Structural Biology using the locally implanted European Synchrotron Facility) up to the clinical trials carried out at the Grenoble University Hospital (CHU Grenoble Alpes). In between, fundamental research on several aspects of the mechanisms of carcinogenesis, and pre-clinical studies are run in three institutes (IAB, BIG, GIN).

RESEARCH



RESEARCH THEMES AND EXPERIMENTAL APPROACHES

The mission of the GIN is to study, understand and identify cures for neurological disorders. Its main scientific objectives are therefore the following:

- to perform research in neuroscience, based on multidisciplinary approaches and scientific excellence.
- to promote translational neuroscience research with the long-term objective of developing new therapeutic strategies for refractory or incurable neurological, psychiatric and neuromuscular disorders.
- to promote the emergence and development of promising young scientists and clinicians.
- to develop the GIN as a powerful local, national and international pole of excellence in neuroscience.

BASIC NEUROSCIENCE

FROM THE MOLECULE TO THE ORGANISM

One of the specificities of GIN is to have teams with vast expertise in the cytoskeleton, intracellular trafficking and synaptic plasticity. The mechanisms studied at this level relate to Alzheimer's disease, schizophrenia, Huntington's disease, mood disorders and myopathies.

The integration of fundamental molecular mechanisms and cellular physiology of the nervous system is the next step in order to understand the functioning of the brain. GIN develops and explores numerous animal models (C. elegans, rodents, etc.) for different pathologies such as schizophrenia, epilepsy, neuromuscular diseases, Alzheimer's disease, Huntington's, and Parkinson's. However, research in GIN is not limited to chronic diseases. Thus, tumor models, to stroke and head trauma are also studied to develop new therapeutic approaches. These research benefits from advanced tools that have been succesfuly developed by its reserachers such as imaging, functional exploration, etc.

PRE-CLINICAL AND CLINICAL NEUROSCIENCE

ANIMAL MODELS TO HUMANS

One of the GIN's strengths is the presence of many clinicians affiliated with research teams. This collaboration between medical doctors and scientists is essential for rapid development of new therapeutic strategies. It enhances transfer of basic knowledge from bench to bedside. Thus, several clinical studies are underway that implement concepts or tools developed in the GIN. Finally, the GIN is particularly involved in the proposed University Hospital Federation (FHU) Neuropsynov, the CDP-Idex NeuroCoG, and the CoEN Grenoble Excellence in Neurodegeneration (GREEN), which aims at developing and integrating pre-clinical and clinical knowledge collected on a set of neurological and psychiatric diseases.

TECHNOLOGICAL AND TREATMENT INNOVATIONS

Increasing knowledge in neuroscience and developing innovative therapies require multidisciplinary approaches and methodological developments such as those conducted in the fields of nervous system development, optogenetics, reconstitution of neural networks on chips, and the study of intracellular dynamics, electrophysiology, imaging methods, etc.

GIN also develops and evaluates new therapeutic strategies, guided by imaging around physical (nerve stimulation, TMS, synchrotron radiation) and biological (cell therapy and gene therapy, pharmacological) methods.

RESEARCH TEAMS AND FACILITIES

RESEARCH TEAMS

FACILITIES

PHYSIOPATHOLOGY OF THE CYTOSKELETON

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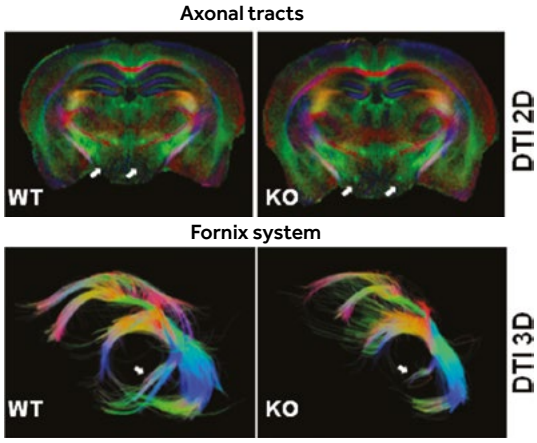
KEYWORDS: microtubules, tubulin-modifying enzymes, MAP6, neuropsychiatric diseases, cerebral plasticity.

The team *Physiopathology of the Cytoskeleton* investigates cytoskeletal microtubules. Hundreds of effectors influence the microtubules' structure or function in various neuronal processes, e.g. proliferation of neuronal progenitors, neuronal differentiation, neuronal network maturation, synaptic plasticity, etc.

Our team focuses more specifically on Microtubule-Associated Proteins of the MAP6 family on the one hand and enzymes that modify the C-terminal amino acid of tubulins (tyrosination/detyrosination cycle). These microtubular effectors are studied at various levels, from structure to whole organisms, in order to understand the various levels of microtubules' regulation:

- **Tubulin**: characterize the importance of specific C-terminal amino acids in the assembly of tubulin dimers, the formation of microtubules and their function in the yeast.
- **Tubulin-modifying enzymes**: describe the physiological impact of post-translational modifications of tubulin, such as C-terminal tyrosination / detyrosination of alpha-tubulin, on neuronal differentiation and neuronal plasticity in the adult.
- **Regulation of microtubules' dynamics in vitro**: analyze how MAP6 proteins and their partners influence the dynamic properties of microtubules and actin, in cell-free systems.
- **Neuronal differentiation and microtubule-associated protein 6 (MAP6)**: understand the contribution of these proteins and their partners in neuronal development and synaptic connectivity.
- **Development of neuronal networks and defective neuronal connectivity**: study the anatomical and physiological consequences of the absence of specific MAPs in model mice.



Axonal tracts including the fornix in WT and MAP6-KO brains, *visualized using Diffusion Tensor Imaging (DTI).*

TECHNIQUES USED

- **Molecular biology**: plasmid constructions, cloning and sub-cloning, PCR, expression of recombinant proteins, lentivirus, CRISPR/Cas9.
- **Biochemistry**: purification of proteins and antibodies, interaction of protein partners, yeast two-hybrid screening, immunoprecipitation, TIRF imaging, electronic microscopy.
- **Cellular biology**: cell lines and primary cultures of neurons, classical or confocal fluorescence imaging, videomicroscopy, FRAP and STORM high resolution imaging.
- **Animal models**: production of transgenic or conditional knockout mice, phenotypic assessment (anatomy, tractography using DTI and behavioral studies)

KEY PUBLICATIONS

- *Vasohibins/SVBP are tubulin carboxypeptidases (TCP) that regulate neuron differentiation.* **Aillaud C, Bosc C, Peris L, Bosson A, Heemeryck P**, Van Dijk J, **Le Friec J, Boulan B, Vossier F**, Sanman LE, Syed S, Amara N, Couté Y, Lafanechère L, **Denarier E, Delphin C, Pelletier L, Humbert S**, Bogyo M, **Andrieux A**, Rogowski K, **Moutin MJ**. Science. 2017 Dec 15;358(6369):1448-1453.
- *MAP6 interacts with Tctex1 and Cav 2.2/N-type calcium channels to regulate calcium signalling in neurons.* **Brocard J, Dufour F, Gory-Fauré S**, Arnoult C, **Bosc C, Denarier E, Peris L, Saoudi Y**, De Waard M, **Andrieux A**. Eur J Neurosci. 2017 Dec;46(11):2754-2767.
- *3D imaging of the brain morphology and connectivity defects in a model of psychiatric disorders: MAP6-KO mice.* **Gimenez U, Boulan B, Mauconduit F, Taurel F**, Leclercq M, **Denarier E, Brocard J, Gory-Fauré S, Andrieux A**, Lahrech H, **Deloulme JC**. Sci Rep. 2017 Sep 4;7(1):10308.
- *A role for the yeast CLIP170 ortholog, the plus-end-tracking protein Bik1, and the Rho1 GTPase in Snc1 trafficking.* **Boscheron C, Caudron F**, Loeillet S, **Peloso C, Mugnier M, Kurzawa L**, Nicolas A, **Denarier E**, Aubry L, **Andrieux A**. J Cell Sci. 2016 Sep 1;129(17):3332-41.
- *Evidence for new C-terminally truncated variants of α- and β-tubulins.* **Aillaud C, Bosc C, Saoudi Y, Denarier E, Peris L**, Sago L, Taulet N, **Cieren A**, Tort O, Magiera MM, Janke C, Redeker V, **Andrieux A, Moutin MJ**. Mol Biol Cell. 2016 Feb 15;27(4):640-53.
- *Microtubule-associated protein 6 mediates neuronal connectivity through Semaphorin 3E-dependent signalling for axonal growth.* **Deloulme JC, Gory-Fauré S, Mauconduit F**, Chauvet S, **Jonckheere J, Boulan B**, Mire E, Xue J, **Jany M, Maucler C, Deparis AA, Montigon O, Daoust A, Barbier EL, Bosc C**, Deglon N, **Brocard J, Denarier E, Le Brun I, Pernet-Gallay K**, Vilgrain I, Robinson PJ, **Lahrech H**, Mann F, **Andrieux A** (2015). Nat Commun. 6:7246.

CYTOSKELETON DYNAMICS AND STRUCTURE

Isabelle ARNAL

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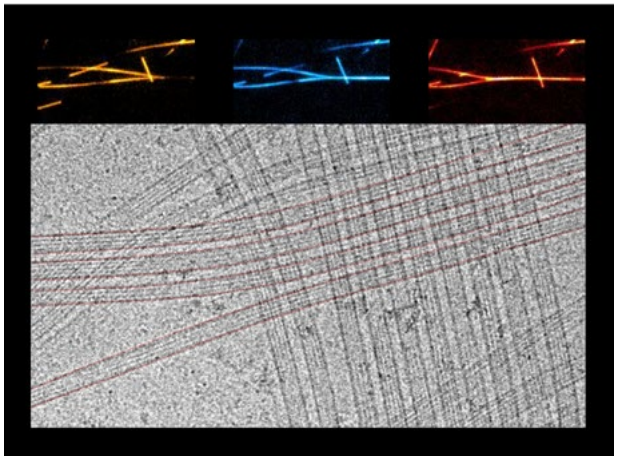
KEYWORDS: Cytoskeleton, microtubule, actin, neuronal effectors, tau, +TIPs, Alzheimer's disease

Microtubules are major components of the eukaryotic cytoskeleton and are involved in cell division, motility and morphogenesis. Important for these functions are the dynamic and structural properties of microtubules, as well as their capacity to interact with actin filaments. In vivo, numerous microtubule-associated proteins (MAPs) control microtubule behavior. Our team focuses on the molecular basis underlying the regulation of microtubules and microtubule/actin interactions by MAPs that are specifically involved in cytoskeleton organization during mitosis, neuronal differentiation and neuronal plasticity.

We use advanced-light microscopy imaging to study cytoskeleton properties in both simple cell-free systems and cellular differentiation models. In parallel, we investigate how MAPs precisely interact with microtubules and actin filaments and affect their structure and spatial arrangement by electron cryo-microscopy and cryo-tomography methods. This correlative approach combining light- and electron microscopy on various complexity level systems should help to understand at a molecular level how a MAP network elaborate complex cytoskeleton architecture in cells.



The neuronal protein tau stimulates the formation of microtubule bundles. *The colour time-lapse images (top) illustrate the formation of a bundle between growing microtubules in the presence of tau (vizualized by Total Internal Reflection Fluorescence microscopy). The bottom image represents a cryo-electron microscopy image of a microtubule bundle induced by tau. Red lines highlight microtubules that constitute the bundle (adapted from Prezel, Elie et al, 2018, Mol Biol Cell, 29: 154-165).*

TECHNIQUES USED

- **Molecular biology, biochemistry and cellular biology**: sub-cloning, protein expression and purification, study of protein interactions, spectrophotometry, stable cell line and neuronal primary cell cultures.
- **Light microscopy**: total internal reflection fluorescence microscopy, video fluorescence microscopy, single molecule imaging, confocal.
- **Electron microscopy**: negative stain, electron cryomicroscopy and cryotomography.

KEY PUBLICATIONS

- *Tau can switch microtubule network organizations: from random networks to dynamic and stable bundles*. Prezel E, Elie A, Delaroche J, Stoppin-Mellet V, Bosc C, Serre L, Fourest-Lieuvin A, Andrieux A, Vantard M and Arnal I (2017) Mol Biol Cell 29: 154-165. Article highlighted by the editor and selected for the cover.
- *α-Synuclein is a Novel Microtubule Dynamase*. Cartelli D, Aliverti A, Barbiroli A, Santambrogio C, Ragg E, Casagrande F, De Gregorio C, Pandini V, Chieregatti E, Pieraccini S, Roybon L, Pezzoli G, Grandori R, Arnal I and Cappelletti G (2016). Scientific Reports 6: 33289.
- *Tau antagonizes end-binding protein tracking at microtubule ends through a phosphorylation-dependent mechanism.* Ramirez-Rios S, Denarier E, Prezel E, Vinit A, Stoppin-Mellet V, Devred F, Barbier P, Peyrot V, Sayas CL, Avila J, Peris L, Andrieux A, Serre L, Fourest-Lieuvin A and Arnal I (2016). Mol Biol Cell 27, 2924-2934.
- *Tau co-organizes dynamic microtubule and actin networks*. **Elie A**, **Prezel E**, Guérin C, Denarier E, **Ramirez-Rios S**, **Serre L**, **Andrieux A**, **Fourest-Lieuvin A**, Blanchoin L and **Arnal I** (2015). Scientific Reports, 5:9964.
- *Tau regulates the localization and function of End binding proteins 1 and 3 (EB1/3) in neuronal cells*. Sayas CL, Tortosa E, **Bollati F**, **Ramirez-Rios S**, **Arnal I** and Avila J (2015). J. Neurochem. J Neurochem 133, 653-667.

FUNCTIONAL NEUROIMAGING AND BRAIN PERFUSION

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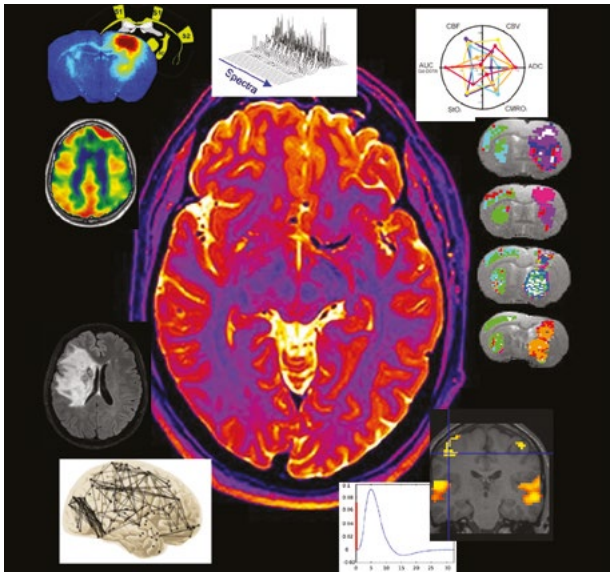
KEYWORDS: MRI, fMRI, connectivity, physiology, tumor, stroke, trauma, cognitive neuroscience.

The research field of the team F*unctional neuroimaging and brain perfusion* is in vivo biomedical magnetic resonance imaging (MRI). Our aims are the development, the validation and the application of in vivo MRI methods in the field of the clinical, biological and cognitive neuroscience.

Since 2012, the team and the MRI facility IRMaGe are members of the national infrastructures "France Life Imaging (FLI)". Advanced MRI studies, performed on a preclinical and a clinical levels, imply the coexistence of two overlapping components, one centered on the development of methods, the other on their exploitation

This duality is reflected in the multidisciplinary backgrounds of the members of the team, from physics to life sciences. More specifically, we address:

- **Development of functional and physiological imaging.** We develop new imaging tools to characterize brain microvascularization: vessel size index (VSI), permeability of the vessel wall, blood volume (CBV) and blood flow (CBF), tissue oxygen saturation (StO2, quantitative BOLD), and cerebrovascular vasoreactivity. Based on these physiological informations, we develop advanced functional MRI (fMRI) techniques (e.g. joint detection estimation, in collaboration with Inria and Neurospin) and functional connectivity MRI (e.g. graph-based approaches, in collaboration with GIPSA) to improve the use of fMRI in patients. Our expertise in fMRI serves also numerous collaborations in cognitive neuroscience (visual, motor, auditory and olfactory systems) and neurology (brain tumor, stroke, coma, brain trauma, aging).
- **Development of imaging biomarker.** To exploit the structural, metabolic and perfusion data collected with MRI, we develop innovative tools for automated information extraction. We developed the approach LOCUS, based on Markovien models in a Baysian framework, to automatically segment tissue structures and brain lesions. We also exploit multiparametric MRI using advanced statistical tools to obtain fingerprints of healthy and diseased tissues (collaboration with Inria).
- **Imaging-guided therapy.** Based on MRI, we evaluate advanced therapeutic strategies, such as microbeam X-ray therapy or anti-angiogenic therapies against brain tumors, stem cell therapy in the context of stroke and anti-edematous therapy in the context of brain trauma. Since 2012, the team is part of the national infrastructure ECELL FRANCE, which supports the development of the therapeutic strategies based on adult mesenchymal stem cells.



Imaging brain physiology and connectivity at the preclinical and clinical levels.

KEY PUBLICATIONS

- *Fully Automatic Lesion Localization and Characterization: Application to Brain Tumors using Multiparametric MRI Data.* Arnaud A, Forbes F, Coquery N, Collomb N, Lemasson B, Barbier EL. IEEE Trans Med Imaging, 37(7):1678-1689, 2018.
- *Multiparametric MRI including oxygenation mapping of experimental ischaemic stroke.* L. Simoes Braga Boisserand, B. Lemasson, L. Hirschler, A. Moisan, V. Hubert, E. L. Barbier*, C. Rémy, O. Detante. Journal of Cerebral Blood Flow and Metabolism, 37(6):2196–2207, 2017.
- *MRI of endolymphatic hydrops in patients with Meniere's disease: a case-controlled study with a simplified classification based on saccular morphology.* Attyé A, Eliezer M, Boudiaf N, Tropres I, Chechin D, Schmerber S, Dumas G, Krainik A. Eur Radiol. 27(8):3138-3146, 2017.
- *Effects of aging on low luminance contrast processing in humans.* E. Bellot, V. Coizet, J. Warnking, K. Knoblauch, E. Moro, M. Dojat. Neuroimage. 139:415-426, 2016.
- *MR Vascular Fingerprinting in Stroke and Brain Tumors Models.* B. Lemasson, N. Pannetier, N. Coquery, Ligia S. B. Boisserand, Nora Collomb, N. Schuff, M. Moseley, G. Zaharchuk, E.L. Barbier*, T. Christen. Scientific Reports, 6:37071, 2016.
- *Reliability of graph analysis of resting state fMRI using test-retest dataset from the Human.* M. Termenon, A. Jaillard, C. Delon-Martin, S. Achard. Connectome Project. Neuroimage. 142:172-187, 2016

TRANSLATION REGULATION IN NORMAL AND PATHOLOGICAL CONDITIONS

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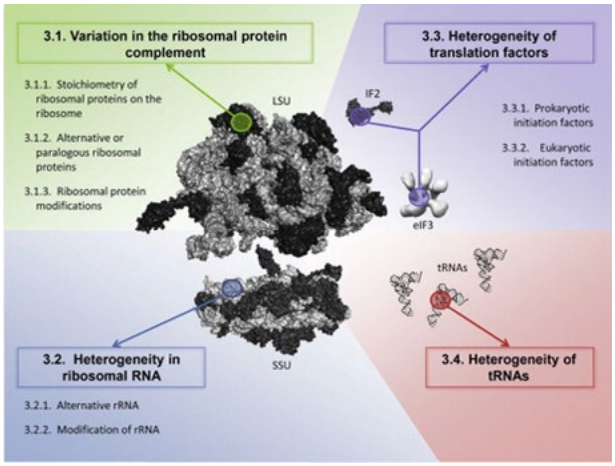
KEYWORDS: Ribosome, Traduction, Regeneration, Neuroprotection, central nervous system.

A major challenge in Biology is to understand how genes are expressed and regulated in space and time in order to ensure cell specificity, homeostasis and organism development. Genetic expression is defined by the flow DNA-RNA-Protein. Tremendous amount of work focused on gene transcription to unlock neuron survival and axon regeneration programs. Those approaches revealed interesting targets but ultimately failed to expose all the programs necessary to stimulate sufficient axonal growth in order to build full functional circuits after injury. Indeed, recent work suggests that 1) cells rely on translation to control the expression of specific sets of mRNA during critical conditions and 2) translation is directly controlled by specific compositions of the Translational Complex.

In our team, we hypothesize that translation is a key step during development and injury in order to control the expression of specific sets of mRNA involved in axonal growth and/or survival. We use combination of state-of-the-art technics such as in-vivo ribosome immunoprecipitation, proteomics analysis, molecular biology, mice models of development and injury. In particular, the objective of my project is to address:

- **Understanding how the translational complex is modified during development and after injury and which cellular programs are directly controlled by translation.**
- **Understanding how translation complex can control mRNA translation**. Based on the mRNA we identified previously, we will define the molecular mechanism underlying the specific translation regulation. We will particularly focus on IRES element regulation
- **Targeting translation will induce neuroprotection and/or regeneration in CNS after injury**.



The « specialized » ribosome. *Graphic representation of the ribosome and its potential for heterogeneity. Each component of the ribosome and the translational complex can vary in order to create a specific complex potentially associated with targeted translation regulation (from Sauert et al.).*

TECHNIQUES USED

- **In-vivo model of CNS injury**
- **Molecular biology (cloning, PCR, etc.)**
- **Virus production and handling (AAV, lentiviruses, etc.)**
- **Biochemistry (proteomics and transcriptomics, western blot, etc.)**

Cell culture (primary neuronal culture and cell lines)
Microscopy (confocal, light sheet, etc.)

KEY PUBLICATIONS

- *Evidence for rRNA 2'-O-methylation plasticity: Control of intrinsic translational capabilities of human ribosomes.* Arnaud Erales J, Marchand V, Panthu B, Gillot S, Belin S, Ghayad SE, Garcia M, Laforêts F, Marcel V, Baudin-Baillieu A, Bertin P, Couté Y, Adrait A, Meyer M, Therizols G, Yusupov M, Namy O, Ohlmann T, Motorin Y, Catez F, Diaz JJ. Proc Natl Acad Sci U S A. 2017 Dec 5;114(49):12934-12939.
- *Doublecortin-Like Kinases Promote Neuronal Survival and Induce Growth Cone Reformation via Distinct Mechanisms.* Nawabi* H, Belin* S, Cartoni* R, Williams PR, Wang C, Latremolière A, Wang X, Zhu J, Taub DG, Fu X, Yu B, Gu X, Woolf CJ, Liu JS, Gabel CV, Steen JA, He Z. Neuron. 2015 Nov 18;88(4):704-19.
- *Injury-induced decline of intrinsic regenerative ability revealed by quantitative proteomics.* Belin S*, Nawabi* H, Wang C, Tang S, Latremoliere A, Warren P, Schorle H, Uncu C, Woolf CJ, He Z, Steen JA. Neuron. 2015 May 20;86(4):1000-14. Article cited as Editor's choice in Science Signaling 26 May 2015 Vol.8 issue 378.
- *Short hairpin RNA against PTEN enhances regenerative growth of corticospinal tract axons after spinal cord injury.* E. Zukor K, Belin S, Wang C, Keelan N, Wang X, He Z. J Neurosci. 2013 Sep 25;33(39):15350-61.
- *p53 acts as a safeguard of translational control by regulating fibrillarin and rRNA methylation in cancer.* Marce*I V, Ghayad* SE, Belin* S, Therizols G, Morel AP, Solano-Gonzàlez E, Vendrell JA, Hacot S, Mertani HC, Albaret MA, Bourdon JC, Jordan L, Thompson A, Tafer Y, Cong R, Bouvet P, Saurin JC, Catez F, Prats AC, Puisieux A, Diaz JJ. Cancer Cell. 2013 Sep 9;24(3):318-30. Scientific Reports, 6:37071, 2016.

*equal contribution

NEUROPATHOLOGIES AND SYNAPTIC DYSFUNCTIONS

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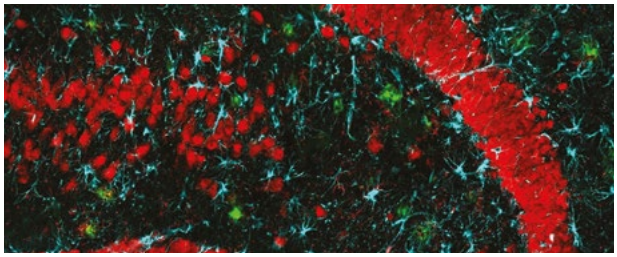
KEYWORDS: excitatory synapses, synaptic plasticity, astrocyte, calcium, Alzheimer disease, amyloid-β, NMDA receptor,glutamate.

The team *Neuropathologies and synaptic dysfunctions* develops a project aiming at characterizing the physiopathological mechanisms underlying early dysfunction induced by Alzheimer's disease by focusing on the synaptic function which represents the first target of the disease.

Alzheimer's disease is characterized at the cellular level by the accumulation of proteins outside (beta-amyloid) and inside neurons (fibrillar proteins associated with hyperphosphorylation of tau protein). Many studies have shown that the decrease in the number of dendritic spines (contact area between synaptic neurons) appears early in the disease progression and is strongly correlated with the cognitive deficits observed in patients (including memory loss). The team has developed tools to study in depth the synaptic functions and the morphology of the excitatory synapse, a pivotal structure in memory formation. To characterize the molecular mechanisms leading to alteration of synaptic plasticity potential in AD, the team focuses on the effects of pre-fribrillary forms of the Aβ peptides: the soluble oligomeric β-amyloid forms on synaptic functions to develops the following research projects:

- **Mechanisms involved in the alteration of the plasticity of glutamatergic synapses**: we aim at characterizing the conditions leading to Aβ over-production in neurons during AD; to identify the molecular targets of β-amyloid peptides in their oligomeric conformation. For these purposes, we study the consequences of exposure to soluble oligomers of Aβ on the glutamatergic neurotransmission, synaptic plasticity paradigms (LTP, LTD, PPF) with a special focus on NMDA receptors functions.
- **Structural plasticity of glutamatergic synapses**: we are studying the molecular mechanisms involved in the structural modifications observed during synaptic plasticity to further understand the consequences of β-amyloid peptide exposure on the synaptic actin cytoskeleton. Actin is the main synaptic component controlling the shape, the organization and the function of dendritic spines.
- **Involvement of astrocytes in these synaptic dysfunctions**: we are studying the modifications of the communication between astrocytes and neurons and how the structural and functional plasticity of astrocytes are linked to the synaptotoxicity and the synaptic loss in AD.



***Immunostaining of senile plaques in hippocampal slices of transgenic APP/PS1-21 mice**, an animal model of Alzheimer disease. In red, we labelled neurons, in blue astrocytes and in green Aβ deposit (senile plaques).*

TECHNIQUES USED

- **Physiology**: electrophysiology, single cell patch clamp and calcium imaging in brain slices and cell cultures.
- **Biochemistry and Cell Biology**: primary cultures of neurons and astrocytes, recombinant protein expression, purification of synaptosomes (pre- and postsynaptic fractions), purification of gliosomes, protein interaction studies, viral transfections.
- **Optical Microscopy**: live Confocal microscopy, FRAP, PALM/STORM, electronic microscopy.
- **APP/PS1-21 transgenic mice** (Alzheimer disease animal model) and APP KO mice.

KEY PUBLICATIONS

- *Synaptotoxicity in Alzheimer's Disease Involved a Dysregulation of Actin Cytoskeleton Dynamics through Cofilin 1 Phosphorylation.* **Rush T**, Martinez-Hernandez J, Dollmeyer M, **Frandemiche ML**, Borel E, **Boisseau S**, Jacquier-Sarlin M, **Buisson A**. (2018) J Neurosci., 38(48):10349-10361.
- *The amyloid-β oligomer Aβ*56 induces specific alterations in neuronal signaling that lead to tau phosphorylation and aggregation.* Amar F, Sherman MA, **Rush T**, Larson M, Boyle G, Chang L, Götz J, **Buisson A**, Lesné SE. (2017) Sci Signal. : 10(478).
- *TRPA1 channels promote astrocytic Ca^{2+} hyperactivity and synaptic dysfunction mediated by oligomeric forms of amyloid-β peptide.* **Bosson A, Paumier A, Boisseau S, Jacquier-Sarlin M, Buisson A, Albrieux M** (2017). Molecular Neurodegeneration 12 (1) : 53.
- *Disruption of dopaminergic transmission remodels tripartite synapse morphology and astrocytic calcium activity within substantia nigra pars reticulata.* **Bosson A, Boisseau S, Buisson A**, Savasta M, **Albrieux M** (2015). Glia. 63 (4): 673–68.
- *Activity dependent tau protein translocation to excitatory synapse is disrupted by exposure to Amyloid β oligomers.* **Frandemiche ML, De Seranno S, Rush T, Borel E**, Elie A, Arnal I, **Lanté F, Buisson A** (2014). J. Neurosci., 34: 6084-6097.
- *Iron overload accelerates neuronal amyloid-□ production and cognitive impairment in transgenic mice model of Alzheimer's disease.* Becerril-Ortega J, Bordji K, Fréret T, **Rush T, Buisson A.** (2014) Neurobiol Aging (10):2288-301.

PATHOPHYSIOLOGY OF MOTIVATION

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KEYWORDS: dopamine, Parkinson's disease, deep brain stimulation, psychiatry, addictions, animal behavior, translational.

The major aim of our group is to uncover the pathophysiological mechanisms underlying the development of neuropsychiatric symptoms in neurological disorders such as Parkinson's disease (PD).

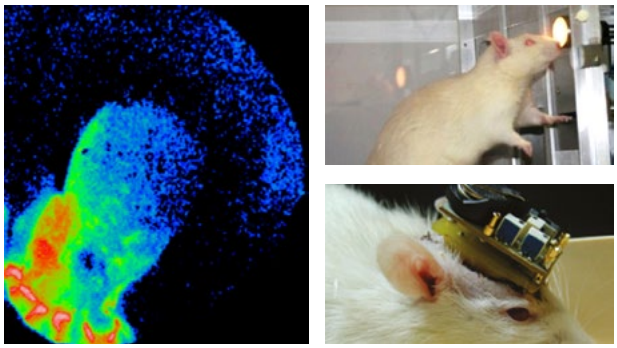
Beyond the cardinal motor features of the disease, PD is indeed associated with a plethora of behavioral complications ranging from apathy (defined as a loss of motivation), anhedonia, depression and anxiety to an heterogeneous group of impulsive-compulsive behaviors (including pathological gambling, hypersexuality, etc.) that resembles addiction in terms of phenomenology and putative psychobiological mechanisms. This cluster of symptoms, which was largely neglected in the past, severely impairs patients' quality of life and is now recognized as a major contributor to morbidity. However, their underlying neurobiological and cellular mechanisms remain unclear, as well as the influence on these symptoms of the gold-standard pharmacological and neurosurgical treatments of the disease, namely dopamine replacement therapies (DRTs) and deep brain stimulation of the subthalamic nucleus (STN-DBS). In a multidisciplinary and translational strategy, we address these questions through two main research projects:

- **Pathophysiology of apathy, depression and impulsive-compulsive behaviors in PD**

Investigating with a rodent model of non-motor symptoms of PD developed in the laboratory and experimental deep brain stimulation the implication of nigrostriatal dopamine and corticostriatal circuits dysfunctions in abnormal motivational and impulsive behaviors. Evaluating the therapeutic and side effects of DRTs on such behaviors in rats and humans..

- **Identification of transcriptomic and metabolomic markers of PD-related neuropsychiatric symptoms**

Psychiatric and neurodegenerative disorders are accompanied with profound modifications of the expression of microRNAs (small non-coding RNA sequences that powerfully regulate the translation of mRNAs) and metabolites. In a collaborative and translational project with Barbier's team, the clinical transcriptomic facility and the Movement Disorder Unit of the Grenoble University Hospital, analyzing microRNAs and metabolites levels in in specific brain regions (rats) and blood samples (rats and patients) to identify specific markers of apathy and impulsive-compulsive behaviors, in order to develop innovative predictive medical tools and therapeutic approaches.



***Autoradiography of dopamine D3 receptors in the striatum** (left).*
***Rat working in an operant, motivational task** (top right).*
***Rat with an implanted microstimulator for deep brain stimulation** (bottom right).*

TECHNIQUES USED

- **Animal behavior**: evaluation of mood-related, Pavlovian, operant and motor behaviors.
- **Experimental deep brain stimulation**: implantable microstimulators for chronic and long-term stimulation in freely-moving rats.
- **Histology and neuroanatomy**: immunohistochemistry, autoradiography, immunofluorescence, optical micro-scopy.
- **Neurochemistry and neuropharmacology**: micro-dialysis in vivo, HPLC (catecholamines), stereotaxic surgery.

KEY PUBLICATIONS

- *Implication of dorsostriatal D3 receptors in motivational processes: a potential target for neuropsychiatric symptoms in Parkinson's disease.* Favier M, **Carcenac C**, Drui G, Vachez Y, Boulet S, Savasta M, **Carnicella S** (2017). Sci Rep. 7:41589.
- *What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease?* Magnard R, Vachez Y, **Carcenac C**, Krack P, **David O**, Savasta M, **Boulet S**, **Carnicella S** (in press). Transl Psychiatry.
- *Subthalamic deep brain stimulation differently alters striatal dopaminergic receptor levels in rats.* **Carcenac C**, Favier M, Vachez Y, Lacombe E, **Carnicella S**, Savasta M, **Boulet S** (2015). Mov Disord. 30(13):1739-49.
- *Implication of dopamine D3 receptor activation in the reversion of Parkinson's disease-related motivational deficits.* **Carnicella S**, Drui G, **Boulet S**, **Carcenac C**, Favier M, Duran T, Savasta M (2014). Transl Psychiatry. 17;4:e401.
- *Pramipexole reverses Parkinson's disease-related motivational deficits in rats.* Favier M, Duran T, **Carcenac C**, Drui G, Savasta M, **Carnicella S** (2014). Mov Disord. 29(7):912-20.
- *Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease.* Drui G, **Carnicella S**, **Carcenac C**, Favier M, Bertrand A, **Boulet S**, Savasta M (2014). Mol Psychiatry. 19(3):358-67.

BRAIN STIMULATION AND SYSTEMS NEUROSCIENCE

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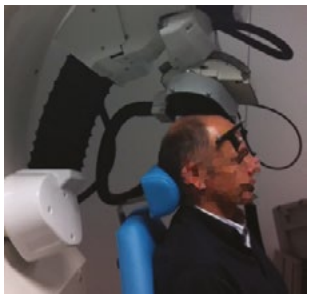
KEYWORDS: functional neurosurgery, deep brain, transcranial magnetic and vagus nerve stimulation.

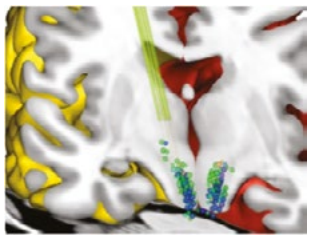
The main focus of our team is to understand the common pathophysiological mechanisms between different psychiatric and neurological diseases. For example, they are all characterized by large neuronal network dysfunction, especially within various loops linking cortical to subcortical structures. This may then explain the complexity of the clinical symptoms observed in those diseases due to its impact on multiple cognitive, motor and emotional dimensions.

In order to characterize the functional and neuro-anatomical organization of those large scale networks, establish new brain stimulation strategies and better understand their mechanisms, our team currently develops new research project combining complementary fundamental and clinical approaches:

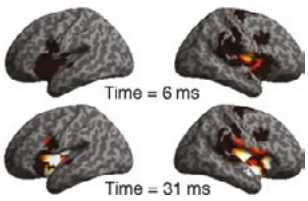
- **Deep brain stimulation and sub-cortical networks**: characterize common subcortical regions (subthalamic nucleus, anterior thalamic nucleus, locomotor mesencephalic areas) involved in various psychiatric and neurological pathologies (movement disorders, epilepsy, depression, obsessive compulsive disorders);
- **Cortical and peripheral stimulation**: mapping of neuronal circuits using anatomical (tractography) and functional (excitability) based on clinical recordings from epileptic, psychiatric and Crohn patients.



Robotised and neuronavigated transcranial magnetic stimulation.



Peroperatory mapping of subthalamic region *with micro-electrodes.*



Interhemisheric insular connectivity *as shown by electrical stimulation of the right insula.*

TECHNIQUES USED

- ***Ex vivo* imaging**: immunohistochemistry, neuronal track tracing
- ***In vivo* neurophysiology**: single and multiunit recordings, intracortical and epidural field potentials, electroencephalography (EEG), stereo-electroencephalography (SEEG), magnetoencephalography (MEG), infra-red spectroscopy (NIRS).
- **Neuroimaging**: structural and functional MRI, positron emission tomography (PET), CT scan.
- **Behavioral studies**: cognitive neurosciences, behavioral and clinical phenotype characterisations.
- **Neurostimulation**: deep brain stimulation, direct cortical stimulation, vagus nerve stimulation, transcranial magnetic stimulation (TMS).
- **Data processing**: modeling, signal and image processing.

KEY PUBLICATIONS

- *Mood and behavioural effects of subthalamic stimulation in Parkinson's disease*. **Castrioto A**, **Lhommée** E, **Moro** E, **Krack P** (2014). Lancet Neurol. 13(3):287-305.
- *Probabilistic functional tractography of the human cortex*. **David O**, **Job AS**, De Palma L, Hoffmann D, **Minotti L**, **Kahane P** (2013). NeuroImage. 80:307-17.
- *The subcortical hidden side of focal motor seizures: evidence from micro-recordings and local field potentials*. **Devergnas A**, **Piallat B**, **Prabhu S**, Torres N, Louis Benabid A, **David O**, **Chabardès S** (2012). Brain. 135(Pt 7):2263-76.
- *Imaging the seizure onset zone with stereo-electroencephalography*. **David O**, **Blauwblomme T**, **Job AS**, **Chabardès S**, Hoffmann D, **Minotti L**, **Kahane P** (2011). Brain. 134(Pt 10):2898-911.
- *Subthalamic neuronal firing in obsessive-compulsive disorder and Parkinson disease*. **Piallat B**, **Polosan M**, **Fraix V**, **Goetz L**, **David O**, Fenoy A, Torres N, Quesada JL, **Seigneuret E**, **Pollak P**, **Krack P**, Bougerol T, Benabid AL, **Chabardès S** (2011). Ann Neurol. 69(5):793-802.

BRAIN AGING AND REPAIR

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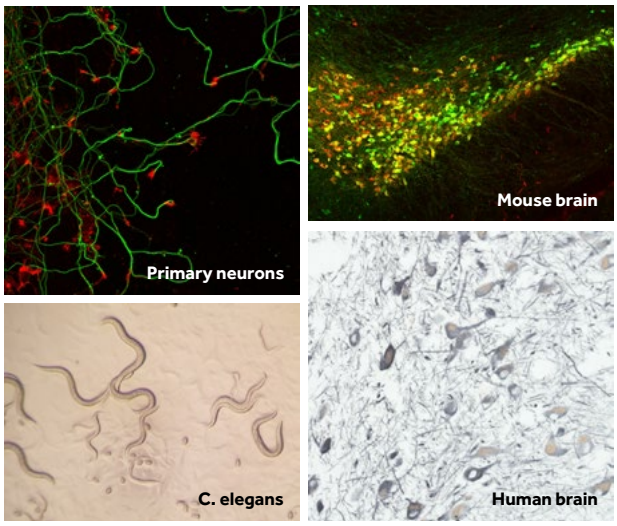
KEYWORDS: neuronal senescence, Parkinson's disease, molecular therapy, animal models, dopamine.

Age-related neurodegenerative diseases represent a major socio-economical burden for our society and a fundamental challenge for the scientific community. Ameliorating brain healthspan (i.e our lifetime spent with good cerebral function) is an unmet need and it can only be achieved by improving our knowledge on neuronal physiology.

The goal of the Neurobiology of brain aging team is to decipher the molecular signals governing neuronal senescence. Their identification would allow the elucidation of the pathogenic mechanisms underlying age-related neurodegenerative diseases such as Parkinson's disease. Addressing this critical issue would also accelerate the discovery of pertinent and effective therapies for patients.

We are particularly interested in understanding how the disease-causing protein alpha-synuclein becomes toxic and what is the sequence of the pathogenic events leading to the stochastic acceleration of nigral dopamine neurons loss in Parkinson's disease. We study the extra-cellular signals and the intra-cellular mechanisms regulating its expression level and the consequences at molecular and cellular levels when its homeostasis is perturbed. Our group is pursuing the following lines of research:

- **Pathogenic mechanisms**: we try to elucidate the signals originating from the brain or from peripheral organs that regulate cerebral aging and prime the brain towards the development of pathologies.
- **Disease modeling**: we design alternative and relevant strategies (e.g gene transfer) to mimic Parkinson's disease in cells and in in vivo.
- **Molecular therapy**: we use unbiased approaches to identify clinically approved drugs for repurposing in Parkinson's disease. By screening libraries against the druggable genome we also identify target genes to test in complementary models of pathological brain aging.



Translational approach to study pathological brain aging. *Our research models span from primary neurons (top left: cortical neurons stained for tuj1 and phalloidin) to powerful genetic models such as C.elegans (bottom left) and transgenic mice (top right: substantia nigra stained for TH in red and GFP in green). We complement the clinical relevance of our findings by the examination of post-mortem tissues from patients (bottom right: nigral dopamine visualized with neuromelanin in brown and TH staining in grey).*

TECHNIQUES USED

- **Microscopy:** immunohistochemistry, immunofluorescence confocal and live imaging, electron and super-resolution microscopy
- **Biochemistry, Molecular and cell biology**: cloning, RT-qPCR, transfection, viral transduction, ELISA, Western Blot
- **Research models**: cell lines, primary neuronal and glial cultures, C. elegans, mice, rats, humans.
- **In vivo**: viral vectors delivery, stereotaxic surgery, behavioral phenotyping

KEY PUBLICATIONS

- *Aged and diseased neurons get lost in transport.* Tamburrino A, Decressac M (2016) Trends Neurosci. 39(4):199-201.
- *Nurr1 in Parkinson's disease: from pathogenesis to therapeutic potential.* **Decressac M**, Volakakis N, Bjorklund, Perlmann T (2013) Nat. Rev. Neurol. 9(11):629-36
- *Cyclosporin promotes neurorestoration and cell replacement therapy in pre-clinical models of Parkinson's disease.* Tamburrino A, Churchill MJ, Wan OW, Colino-Sanguino Y, Ippolito R, Bergstrand S, Wolf DA, Herz NJ, Sconce MD, Bjorklund A, Meschul CK, **Decressac M** (2015) Acta Neuropathol. Commun. 3:84.
- *TFEB-mediated autophagy rescues midbrain dopamine neurons from a-synuclein toxicity.* **Decressac M**, Mattsson B, Weikop P, Lundblad M, Jakobsson J, Bjorklund A (2013). PNAS, 110(19):E1817-26.
- *a-synuclein –induced down-regulation of Nurr1 disrupts GDNF signaling in nigral dopamine neurons.* **Decressac M**, Kadkhodaei B, Mattsson B, Laguna A, Perlmann T, Bjorklund A (2012) Sci. Transl. Med. 4(163):163ra156.

SYNCHRONIZATION AND MODULATION OF NEURAL NETWORKS IN EPILEPSY

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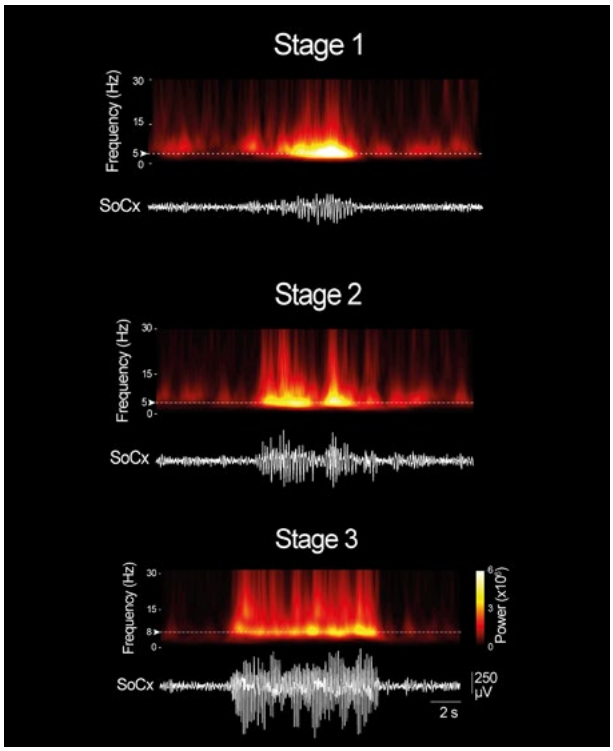
KEYWORDS: epileptogenesis, ictogenesis, seizures, oscillations, astrocytes, microglia, dopamine, cortex.

Epilepsies are neurological diseases that affect up to 1% of the population worldwide and are characterized by seizures with very different electroclinical features. These seizures result from excessive synchronization of neural networks that involve different regions of the brain depending on the type of epilepsy.
The goal of our team is to understand how an epileptic neural circuit is built and how it can switch between a physiological and a pathological activity. For this purpose, we use animal models of epilepsy in rodents and we carry out clinical studies with patients who suffer from epilepsy.

To characterize the progressive development of epilepsy (epileptogenesis) and / or to understand the mechanisms involved in the occurrence of a seizure (ictogenesis), our team aims to provide answers to the following questions:

- **How does epileptogenesis develop in genetic epilepsies or after a brain injury?** From an anatomical and functional point of view, how is a neural circuit built to gradually generate epileptic seizures, especially during brain maturation?
- **What is the link between the specific pathological oscillations recorded by deep electrodes and the tissue modifications of the epileptic network?** How the electroencephalographic (EEG) signal collected in patients who are candidate for respective surgery correlate with anatomical and neurochemical data obtained from the resected tissue.



Epileptogenesis in the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) model. *In the somatosensory cortex (SoCx), abnormal oscillations occur at the age of 15 days postnatal (Stage 1) and shape progressively into spike-wave (SW) discharges (Stage 3, 25 days postnatal).*

TECHNIQUES USED

- **Animal models of chronic epilepsy**: GAERS (Generalized Absence Epilepsy Rats from Strasbourg), KA-MTLE mice (intrahippocampal kainate);
- **Functional exploration**: Video / EEG (scalp, deep electrodes, high resolution) in patients and animal models, local multichannel field potentials, signal analysis, in vivo calcium imaging, neurostimulation, synchrotron microbeam irradiation, viral transfection.
- **Structural exploration**: Immunohistochemistry on brain sections in animals and humans, connection tracing, confocal and biphotonic microscopy.

KEY PUBLICATIONS

- *Building Up Absence Seizures in the Somatosensory Cortex: From Network to Cellular Epileptogenic Processes.* **Jarre G***, Altwegg-Boussac T*, Williams MS, **Studer F**, Chipaux M, David O, Charpier S, **Depaulis A**, Mahon S*, **Guillemain I*** (2017). Cerebral Cortex. 27:4607–4623.
- *The genetic absence epilepsy rat from Strasbourg as a model to decipher the neuronal and network mechanisms of generalized idiopathic epilepsies.* **Depaulis A**, David O, Charpier S (2016) J Neurosci Methods 260:159–174 (2016).
- *Temporal plus epilepsy is a major determinant of temporal lobe surgery failures.* Barba C, Rheims S, **Minotti L**, Guénot M, Hoffmann D, Chabardès S, Isnard J, **Kahane P**, Ryvlin P (2016). Brain. 139:444-451.
- *Synchrotron X-ray interlaced microbeams suppress paroxysmal oscillations in neuronal networks initiating generalized epilepsy.* **Pouyatos B**, Serduc R, Chipaux M, **Chabrol T**, Bräuer-Krisch E, Nemoz C, Mathieu H, **David O**, Renaud L, Prezado Y, Laissue JA, Estève F, Charpier S, **Depaulis A** (2013). Neurobiol. Dis. 51: 152–160.
- *Imaging the seizure onset zone with stereoelectro-encephalography.* David O, Blauwblomme T, **Job AS**, Chabardès S, Hoffmann D, **Minotti L**, **Kahane P** (2011). Brain. 134 : 2898-2911.

NEURAL PROGENITORS AND BRAIN PATHOLOGIES

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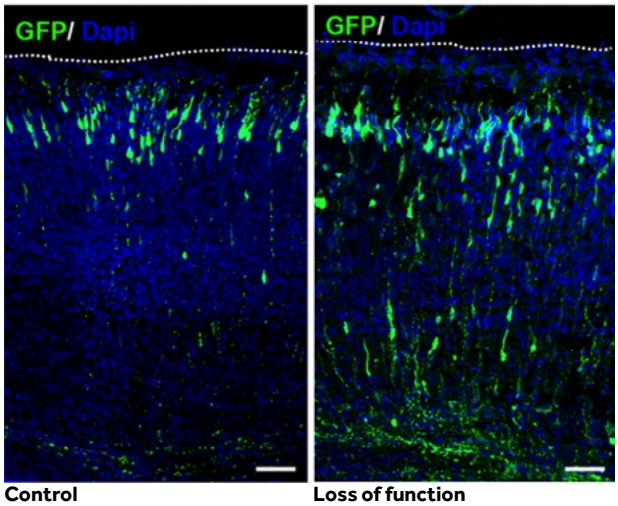
KEYWORDS: huntingtin, Huntington disease, cortical development, adult hippocampal neurogenesis, scaffold protein.

Development of the cerebral cortex and adult hippocampal neurogenesis are complex processes where huntingtin, the protein mutated in Huntington disease, plays a central role. Understanding these mechanisms will open new avenues potentially leading to treatment of Huntington disease and other neurological disorders.

More specifically, the team *Neural progenitors and brain pathologies* is studying the contribution of huntingtin to different steps of cortical development and adult hippocampal neurogenesis. We also address the questions of how these mechanisms participate in the proper establishment and maintenance of neuronal networks and whether these pathways are altered in Huntington disease.

Our working hypothesis is that abnormal development could be a predisposing factor contributing to the symptoms observed in Huntington disease. In the adult, we propose that the depressive behavior observed in patients is not just an epiphenomenon to a severe disorder with a fatal outcome, but the result of a modification in the biological function of huntingtin in adult neurogenesis.



HTT regulates neuronal migration during cortical development. *(Barnat et al. 2017). At embryonic day 18.5 (E18.5), most neurons that were labeled with the green fluorescent protein (GFP) at E14.5 by in utero electroporation have reached upper layers in control brains (left). In contrast, in absence of HTT a significant proportion of neurons failed to do so. Scale Bar, 100 µm.*

TECHNIQUES USED

- **Molecular biology and biochemistry**
- **Cell biology:** primary cultures of neurons and neural stem cells, 2D and 3D cultures, subcellular localization of proteins, analysis of cellular and intracellular dynamics
- **Microscopy:** confocal and spinning disc microscopy, live imaging
- **Mouse models:** genetic models, in utero electroporation, histology, phenotypic analysis

KEY PUBLICATIONS

- *Huntingtin-mediated Multipolar-Bipolar Transition of Newborn Cortical Neurons is Critical for their Postnatal Neuronal Morphology.* **Barnat M**, Le Friec J, Benstaali C and **Humbert S** (2017). Neuron, 93, 99-114.
- *Low cancer prevalence in polyglutamine expansion diseases.* Coarelli G, Diallo A, Thion MS, Rinaldi D, Calvas F, Boukbiza OL, Tataru A, Charles P, Tranchant C, Marelli C, Ewenczyk C, Tchikviladzé M, Monin ML, Carlander B, Anheim M, Brice A, Mochel F, Tezenas du Montcel S, **Humbert S*** and Durr A* (2017). Neurology, 88, 1114-1119.
- *Unravelling the role of huntingtin in breast cancer metastasis.* **Thion MS**, **McGuire JR**, **Sousa CM**, Fuhrmann L, Fitamant J, Leboucher S, Vacher S, Tezenas du Montcel S, Bièche I, Bernet A, Mehlen P, Vincent-Salomon A, **Humbert S** (2015). J. Natl. Cancer Inst., doi: 10.1093/jnci/djv208.
- *Huntingtin is required for epithelial polarity through RAB11A mediated apical trafficking of PAR3-aPKC.* **Elias S**, **McGuire JR**, **Yu H**, **Humbert S** (2015). Plos Biol., 13:e1002142.
- *Mutant huntingtin affects cortical progenitor cell division and development of the mouse neocortex.* **Molina-Calavita M**, **Barnat M**, **Elias S**, **Aparicio E**, Piel M, **Humbert S** (2014). J. Neurosci., 34, 10034-10040.
- *Huntingtin Regulates Mammary Stem Cell Division and Differentiation.* **Elias S**, **Thion MS**, **Yu H**, **Moreira Sousa C**, Lasgi C, Morin X, **Humbert S** (2014). Stem Cell Reports, 2, 491-506.
- *Huntingtin Mediates Anxiety/Depression-related Behaviors and Hippocampal Neurogenesis.* **Ben M'Barek K**, **Pla P**, Orvoen S, **Benstaali C**, **Godin JD**, **Gardier AM**, **Saudou F**, David DJ, **Humbert S** (2013). J. Neurosci., 33, 8608-8620.
- *The Huntington disease protein accelerates breast tumor development and metastasis through ErbB2/HER2 signaling.* **Moreira Sousa C**, **McGuire JR**, **Thion MS**, Gentien D, de la Grange P, Tezenas du Montcel S., Vincent-Salomon A, Durr A, **Humbert S** (2013). EMBO Mol. Med., 5, 309-325.

CELLULAR MYOLOGY AND PATHOLOGIES

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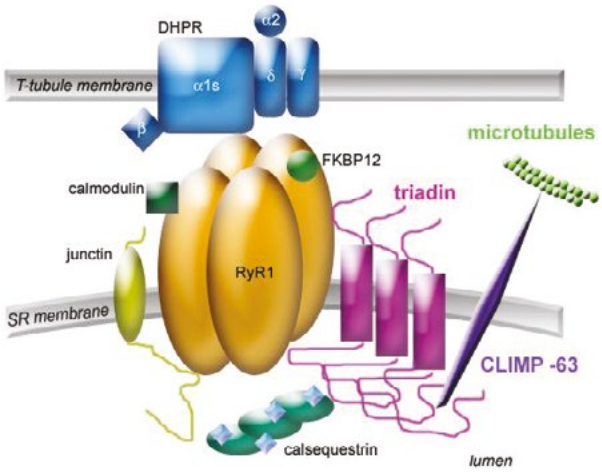
KEYWORDS: myopathies, Ryanodine receptor, calcium release complex, mutation, rare diseases.

The goals of the team *Cellular myology and Pathologies* are the understanding of the function of the calcium release complex, of the mechanisms leading to its formation, and its alterations in diseases.

Muscle stimulation at the neuromuscular junction is transformed in a huge intracellular calcium release in a specific part of muscle cell called the triad. This calcium release is performed by a large protein complex, the calcium release complex, specifically localized in the triads. The calcium release complex is organized around RyR1, the calcium release channel, and triadin. Mutations in the calcium release complex proteins (mainly in RyR1) result in a number of rare muscle disease: congenital myopathies (Central Core Disease, Multiminicore Disease), Malignant hyperthermia, etc.

The team *Cellular Myology and Pathologies* gathers basic scientists, geneticists and clinicians, working on muscle pathologies related to defect in muscle calcium release. Understanding the function of this complex, and its targeting to the triad is necessary for the development of new therapies. To reach this purpose, the team develops the following projects:

- **Development and characterization of cellular or animal models**: understand the function of proteins involved in the complex, and the pathologies related to their alteration.
- **Therapeutic development**: develop treatments to correct the mutations resulting in congenital myopathies, with a focus on RyRs and triadin mutations
- **Intracellular traffic**: study the function of proteins of the calcium release complex in the formation of the complex and in the formation of triads, in interaction with orther elements like microtubules



The Calcium release Complex in skeletal muscle. *The calcium is released from the sarcoplasmic reticulum by RyR1, upon stimulation by DHPR. triadin is able to modulate calcium release and could anchor the complex at the triad.*

TECHNIQUES USED

- **Molecular and cellular biology**: cloning, RT-q-PCR, transfection, virus production, viral transduction, production and culture of human and mouse muscle cells (primary cultures), *in vivo* transduction, etc.
- **Biochemistry**: quantitative Western blot, immunofluorescence, immunoprecipitation
- **Confocal microscopy and electron microscopy**: immunostaining, morphological analysis, calcium imaging, FRAP, photoactivation, protein dynamics.

KEY PUBLICATIONS

- *Excitation-contraction coupling alterations in myopathies.* **Marty I, Fauré J** (2016). J. Neuromuscular Diseases 3, 443-453.
- *Triadin and CLIMP-63 form a link between triads and microtubules in muscle cells.* **Osseni A, Sébastien M, Sarrault O**, Baudet M, Couté Y, **Fauré J, Fourest-Lieuvin A, Marty I** (2016). J. Cell Sci. 129, 3744-3755.
- *Exon skipping as a therapeutic strategy applied to a RyR1 mutation with pseudo-exon inclusion causing a severe core myopathy.* **Rendu J**, **Brocard J**, Denarier E, **Monnier N**, Pietri-Rouxel F, Beley C, **Roux-Buisson N**, Gilbert-Dussardier B, Perez MJ, Romero NB, Garcia L, **Lunardi J**, **Fauré J**, **Fourest-Lieuvin A**, **Marty I** (2013). Hum Gene Ther. 24,702-713.
- *Role of Triadin in the Organization of Reticulum Membrane at the Muscle Triad.* **Fourest-Lieuvin A**, **Rendu J**, **Osseni A**, **Pernet-Gallay K**, Rossi D, **Oddoux S**, **Brocard J**, Sorrentino V, **Marty I**, **Fauré J** (2012). J. Cell Science, 125, 3443-3453.
- *Absence of Triadin, a Protein of the Calcium Release Complex, is Responsible for Cardiac Arrhythmia with Sudden Death in Human.* **Roux-Buisson N**, **Cacheux M**, **Fourest-Lieuvin A**, Fauconnier J, **Brocard J**, **Monnier N**, Ray PF, Denjoy I, Durand P, Guicheney P, Kyndt F, Leenhardt A, Le Marec H, Lucet V, Mabo P, Probst V, Lacampagne A, **Fauré J**, **Lunardi J**, **Marty I** (2012) Hum. Mol. Genet. 21, 2759-2767.
- *Triadin deletion induces impaired skeletal muscle function.* **Oddoux S, Brocard J**, Schweitzer A, Szentesi P, Giannesini B, Brocard J, **Fauré J,** Pernet-Gallay K, Bendahan D, **Lunardi J**, Csernoch L, **Marty I** (2009). J Biol Chem. 284, 34918-34929.

CENTRAL NERVOUS SYSTEM DEVELOPMENT AND REPAIR

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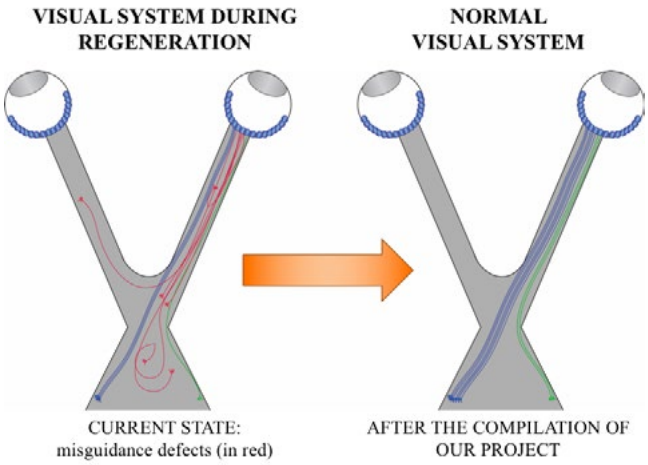
KEYWORDS: central nervous system, axon regeneration, optic nerve, axon guidance, translational control, CST.

The aim of our team is to uncover the mechanisms to build de novo circuits after insults to the central nervous system. We use the eye as a window to the brain and spinal cord.

Impairment of the CNS often affects vital functions such as vision, in the case of glaucoma, or motor function, in the cases of multiple sclerosis or spinal cord injuries. Most of the patients suffering from CNS injuries (traumatic or chronic) must endure irreversible disabilities. Moreover, injuries to the spinal cord often affect young adults, who will have to deal with severe disabilities for the rest of their lives. The main cause for a lack of efficient treatment is that unlike young neurons, mature neurons from the CNS lose the ability to regenerate their axons after injury.

Understanding the detailed mechanisms of neuronal growth, repair and functional recovery represents a major challenge for public health and society. For decades research focused on the environment of the injury to promote CNS repair. However, manipulating extrinsic factors failed to reach the expected regeneration. In contrast, modulating intrinsic pathways has shown promising results.

Our work demonstrated that the simultaneous activation of mTOR, JAK/STAT and c-myc pathways allows exceptional regeneration with axons growing close to their targets. Surprisingly we observed strong misguidance defects with potential aberrant circuit formation. We address the yet unexplored problem of the guidance of regenerating axons in adults in order to promote the formation of a functional new circuit after injury. Indeed, what are the modalities of guidance in the adult? Are axons still responsive to developmental guidance cues and are they still expressed? Can regenerative axons form connections with their targets and are these connections functional? We use the combination of state-of-the-art biochemistry, imaging, and electrophysiology in an in-vivo and ex-vivo model of the visual system to:



- **understand axon guidance** in mature system in order to properly drive regenerative axons to their brain targets and avoid aberrant projections
- **analyze the formation of a functional optic nerve circuit after injury**.

TECHNIQUES USED

- **Mice models**: transgenic mice, optic nerve and spinal cord surgeries
- **Molecular Biology/Virus engineering and production**
- **Histology**:immunohistochemistry, in situ hybridization, immunofluorescence,
- **Biochemistry**: immunoprecipitation, western-blot
- **Mass spectrometry and RNA analysis**
- **Cell Biology**: explant culture/Microfluidics chambers, primary neuron culture, cell lines culture.
- **Microscopy**: epifluorescence, spinning disc, confocal, light sheet.

KEY PUBLICATIONS

- *Doublecortin-Like Kinases Promote Neuronal Survival and Induce Growth Cone Reformation via Distinct Mechanisms.* **Nawabi H**, **Belin S**, Cartoni R, Williams PR, Wang C, Wang X, Latremolière A, Zhu J, Taub DG, Fu X, Yu B, Gu X, Woolf CJ, Liu JS, Gabel CV, Steen JA, He Z (2015). Neuron. 88(4):704-19.
- *Injury-induced decline of intrinsic regenerative ability revealed by quantitative proteomics.* **Belin S***, **Nawabi H***, Wang C, Tang S, Latremoliere A, Warren P, Schorle H, Uncu C, Woolf CJ, He Z, Steen JA (2015). Neuron. 86(4):1000-14.
- *Characterization of long descending premotor propriospinal neurons in the spinal cord.* Ni Y, **Nawabi H**, Liu X, Yang L, Miyamichi K, Tedeschi A, Xu B, Wall NR, Callaway EM, He ZJ (2014). Neurosci. 34(28):9404-17.
- *gdnf activates midline repulsion by Semaphorin3B via NCAM during commissural axon guidance.* Charoy C, **Nawabi H**, Reynaud F, Derrington E, Bozon M, Wright K, Falk J, Helmbacher F, Kindbeiter K, Castellani V (2012). Neuron. 75(6):1051-66.
- *No simpler than mammals: axon and dendrite regeneration in Drosophila.* **Nawabi H**, Zukor K, He Z (2012). Genes Dev. 26(14):1509-14. 6.
- *A midline switch of receptor processing regulates commissural axon guidance in vertebrates.* **Nawabi H**, Briançon-Marjollet A, Clark C, Sanyas I, Takamatsu H, Okuno T, Kumanogoh A, Bozon M, Takeshima K, Yoshida Y, Moret F, Abouzid K, Castellani V (2010). Genes Dev. 24(4):396-410.

INTRACELLULAR DYNAMICS AND NEURODEGENERATION

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KEYWORDS: axonal transport, cortico-striatal projections, BDNF, TrkB, synapse, energy metabolism, endoplasmic reticulum, microfluidics, videomicroscopy.

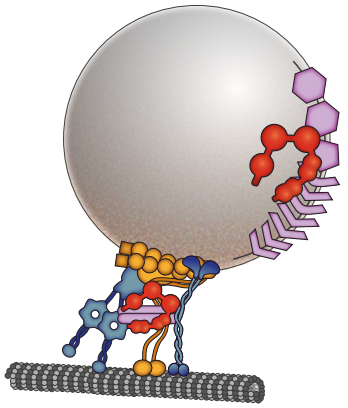
The goal of the team *Intracellular dynamics and Neurodegeneration* is to elucidate the molecular mechanisms by which mutant HTT induces neurodegeneration. In particular, our team focuses on the understanding of HTT function/dysfunction in the control of intracellular dynamics related to cell homeostasis and neurotrophin signaling.

Huntington's disease is characterized by the selective death of striatal and cortical neurons in the brain. The mechanisms by which mutant huntingtin (HTT) causes neurodegeneration remain elusive.

Over the last years, we have proposed a major role of HTT in the regulation of fast axonal transport (FAT). We found that HTT regulates efficacy and the directionality of FAT through phosphorylation and that this phosphorylation restores FAT in disease situation. The role of HTT is not restricted to vesicles in axons as HTT by regulating intracellular trafficking regulates ciliogenesis and trafficking of TrkB endosomes in striatal dendrites. By investigating the role of HTT in FAT, we unraveled a fundamental role of the whole glycolysis as the on-board provider of energy for FAT. This function is controlled by HTT.

Together these studies highlight a fundamental role of HTT in intracellular trafficking and open new avenues not only for the study of neurodegenerative disorders but also for fundamental cell biology.

We want to better understand: how control of FAT efficiency and/or directionality by HTT impacts on neuronal activity and transmission and how HTT dysfunction in FAT regulates neurodegeneration in HD but also in other neurodegenerative disorders such as Alzheimer's disease. We want to understand the consequences of specific cleavages on HTT function and neurodegeneration in health and disease. We are actively developing new physiologically relevant systems and/or tools to allow functional screening.



Huntingtin scaffolds molecular motors and glycolytic enzymes on vesicles. *The transport of vesicles in neurons, especially within axons, occurs over very long distances and requires constant energy supply. Although mitochondria generate most of the energy for the brain, they are scattered within axons. We found that the whole glycolytic machinery is present on vesicles and produce ATP to propel vesicles independently of mitochondria. This on-board energy system could be important for fast transport over long distances. HTT plays a crucial role in this process as it scaffolds the enzymes on vesicles and couple energy production to energy consumption by the motors.*

Finally, we are putting efforts in translational research by close collaborations with HD clinicians.

The achievement of these goals should lead to the development of novel therapeutic strategies for this devastating neurodegenerative disorder but might also reveal new regulatory mechanisms that are important well beyond the field of HD.

TECHNIQUES USED

- **Molecular biology and biochemistry**
- **Cell biology**: primary cultures of neurons, subcellular localization of proteins, analysis of cellular and intracellular dynamics.
- **Microfluidics, optogenetics, fluorescent reporters**, to reconstitute neuronal networks and to study axonal transport and synapse activity.
- **Microscopy**: confocal and spinning disc confocal microscopy, live super-resolution imaging.
- **Mouse models**: genetic models, lentiviral approaches, histology, phenotypic analysis.

KEY PUBLICATIONS

- *Reconstituting Corticostriatal Network On-a-Chip Reveals the Contribution of the Presynaptic Compartment to Huntington's Disease.* Virlogeux A, Moutaux E, Christaller W, Genoux A, Bruyère J, Fino E, Charlot B, Cazorla M, **Saudou F** (2018). Cell Reports, Jan 2;22(1):110-122.
- *The Biology of Huntingtin.* **Saudou F, Humbert S** (2016). Neuron., 2;89(5):910-26
- *Self-propelling vesicles define glycolysis as the minimal energy machinery for neuronal transport* . Hinckelmann MV, Virlogeux A, Niehage C, Poujol C, Choquet D, Hoflack B, Zala D and **Saudou F** (2016). Nature Communications, 7:13233.
- *Huntingtin proteolysis releases non-polyQ fragments that cause toxicity through dynamin 1 dysregulation.* **El-Daher MT**, **Hangen E**, **Bruyère J**, Poizat G, Al-Ramahi I, Pardo R, Bourg N, Souquere S, Mayet C, Pierron G, Lévêque-Fort S, Botas J, **Humbert S**, **Saudou F** (2015). EMBO J. 34(17):2255-71.
- *Vesicular glycolysis provides on-board energy for axonal transport*. Zala D, Hinckelmann MV, Yu H, Cunha M, Liot G, Cordelieres FP, Marco S and Saudou F. (2013). Cell 152:479-91.

IRMaGe
MRI AND NEUROPHYSIOLOGY FACILITY

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KEYWORDS: MRI Clinical Research, cognitive MRI, small animal MRI, EEG, transcranial magnetic stimulation, near-infrared spectroscopy.

Imaging platform for life science
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IRMaGe is a facility located within the Grenoble University Hospital and the Edmond J Safra building - Grenoble Institute of Neurosciences. It is affiliated with the *Université Grenoble Alpes*, Inserm (US 17), CNRS (UMS 3552) and the Grenoble University Hospital. IRMaGe is part of the national infrastructure 'France Life Imaging (FLI)' and is an IBiSA facility.

IRMaGe has developed expertise in the field of NMR imaging and cerebral functional explorations on humans, small and large animals. IRMaGe puts its experience to research projects within the scope of clinical, cognitive and basic neurosciences. Applications on other organs are regularly performed (lungs, liver, etc.).

IRMaGe welcomes about 50 projects per year from twenty academic teams (regional, national and international) and about 5 industrial projects. Thirty articles per year include work carried out on the facility.

TECHNIQUES USED

Anatomical MRI / MRI of tissue microstructure (diffusion, edema, necrosis, cell density, tractography) / MR Angiography / MRI of the microvasculature (blood volume, blood flow, vessel size and permeability) / Oxygenation imaging (MRI, NIRS) / Brain activity (fMRI, rsMRI, EEG) / Cellular and Molecular Imaging (MRI) / ^{1}H, ^{31}P and ^{19}F NMR spectroscopy / Brain Stimulation (TMS) / Electrophysiology (EEG)

The projects running on IRMaGe include:
Methodological developments MRI, MRS, TMS, EEG / Preclinical research (longitudinal study of experimental models of pathologies, evaluation of the effects and efficacy of new therapies, cellular and molecular imaging, evaluation of new contrast agents) / Clinical research (evaluation of new MRI imaging biomarkers for diagnostic, therapeutic orientation, and therapy follow-up of pathologies) / Research in cognitive sciences (MRI, EEG, NIRS, TMS) / Evaluation of the MR compatibility of new materials or medical devices / High resolution MR imaging of tissue samples.

EQUIPMENTS

The following equipements are available:
- a horizontal 4.7T small animal system (Bruker Biospec USR AV III) (2008)
- a horizontal 7.0T small animal system (Bruker Biospec 70/20 USR AV III) (2008)
- a horizontal 9.4T small animal system (Bruker Biospec 70/20 USR AV III) (2013)
- a four-channel, receive-only, cryoprobe to image mice on the 9.4T (2014)
- 4 small animal surgery benches, 3 physiological monitoring systems
- 2 whole-body 3.0T systems (Philips, Achieva 3T TX) (2010, 2011)
- High density EEG system with 96 active electrodes provided with an additional 16 electrode amplifier for peripheral measures (ActiveCap, BrainAmp, Germany) (2009)
- 64 electrode EEG system compatible with TMS (EasyCap, BrainAmp, Germany) (2009)
- 32 electrode EEG MRI compatible (SD32, Micromed, Italy) (2009)
- Robotized and neuronavigated TMS system (Axilum, France) (2012)
- Near Infra-Red Spectrometer (2011)

KEY PUBLICATIONS

- *Track-weighted imaging for neuroretina: Evaluations in healthy volunteers and ischemic optic neuropathy.* Attyé A, Jean C, Remond P, Peyrin C, Lecler A, Boudiaf N, Aptel F, Chiquet C, Lamalle L, **Krainik A**. J Magn Reson Imaging. In Press.
- *Permeability of Brain Tumor Vessels Induced by Uniform or Spatially Microfractionated Synchrotron Radiation Therapies.* Bouchet A, Potez M, Coquery N, Rome C, **Lemasson B**, Bräuer-Krisch E, Rémy C, Laissue J, **Barbier EL**, Djonov V, Serduc R. Int J Radiat Oncol Biol Phys. 98(5):1174-1182, 2017.
- *Effective Connectivity between Ventral Occipito-Temporal and Ventral Inferior Frontal Cortex during Lexico-Semantic Processing. A Dynamic Causal Modeling Study.* Perrone-Bertolotti M, Kauffmann L, Pichat C, Vidal JR, Baciu M. Front Hum Neurosci. 11:325, 2017.
- *3D imaging of the brain morphology and connectivity defects in a model of psychiatric disorders: MAP6-KO mice.* Gimenez U, Boulan B, Mauconduit F, Taurel F, Leclercq M, **Denarier E**, **Brocard J**, **Gory-Fauré S**, **Andrieux A**, Lahrech H, **Deloulme JC.** Sci Rep. 7(1):10308, 2017.
- *Endolymphatic hydrops imaging: Differential diagnosis in patients with Meniere disease symptoms.* Attyé A, Eliezer M, Galloux A, Pietras J, Tropres I, Schmerber S, Dumas G, **Krainik A**. Diagn Interv Imaging. 98(10):699-706, 2017.

PHOTONIC IMAGING CENTER (PIC-GIN)

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KEYWORDS: confocal microscopy, two-photon microscopy, TIRF, FRAP, high resolution, PALM, STORM, in vivo calcium imaging, optogenetics.

IBiSA Imaging platform for life science
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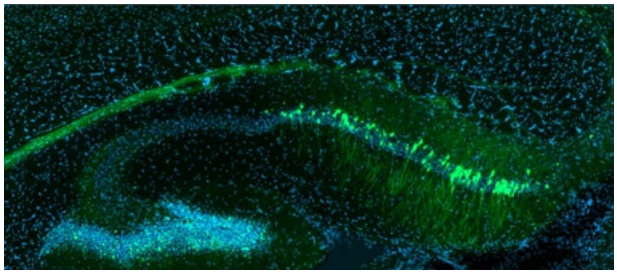
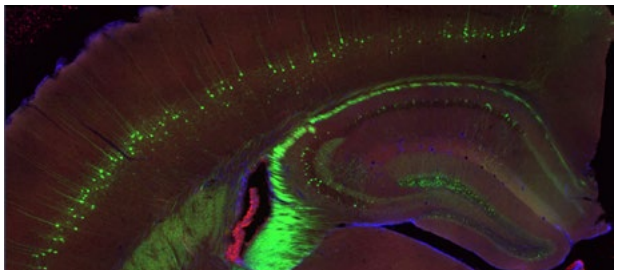
The Photonic Imaging Center of the Grenoble Institute of Neurosciences (PIC-GIN) is an optical microscopy facility that provides essential equipment and skills to support scientists in their projects in neuroscience and life science. The PIC staff consists of 3 engineers specialized in photonic microscopy (F Appaix, Y Saoudi, J. Brocard). Several fluorescence microscopy techniques are available for studies in health and disease from molecules to animal. The PIC-GIN is part of the Multidimensional Functional Microscopy Technology Network RTMFM and a member of the GDR 2588 CNRS-Functional Live Microscopy. It's also part of the imaging platform for life science (ISdV), which obtained the IBiSA (Biology, Health and Agronomy Infrastructures) label in 2016. It is therefore open to academic and private users.





Thy1-GFP Mouse Brain slices immunolabelling: *Neurons in green, cell nuclei in blue.*

SCIENTIFIC EXPERTISE

Nervous system, brain vasculature, acute brain slice, primary neuron culture, cytoskeleton, etc.

AVAILABLE EQUIPMENT

- 2 fluorescence microscopes (Nikon)
- 1 stereomicroscope (Olympus)
- 2 widefield videomicroscopes (Zeiss/Roper),
- 1 widefield videomicroscope/FRAP (Leica /Roper),
- 1 widefield microscope/TIRF (Nikon/Roper),
- 1 Spinning-Disk microscope TIRF/ FRAP/PALM/ STORM (Zeiss/Roper),
- 1 Slide scanner (Zeiss)
- 2 confocal microscopes: LSM 710/Airyscan (Zeiss), TCS SPE (Leica)
- 2 two-photon microscopes: LSM 7MP (Zeiss), TriMScope II (LaVision Biotec)

TECHNICAL EXPERTISE

High-resolution confocal microscopy (Airyscan), Super-resolution (PALM, STORM) spinning-disk microscopy, in vivo two-photon microscopy for photomanipulation (optogenetic).

KEY PUBLICATIONS

- *3D imaging of the brain morphology and connectivity defects in a model of psychiatric disorders: MAP6-KO mice.* Gimenez U, Boulan B, Mauconduit F, Taurel F, Leclercq M, Denarier E, Brocard J, Gory-Fauré S, Andrieux A, Lahrech H, Deloulme JC. Sci Rep. 2017 Sep 4;7(1):10308. doi: 10.1038/s41598-017-10544-2. .
- *Keto-polymethines: a versatile class of dyes with outstanding spectroscopic properties for in cellulo and in vivo two-photon microscopy imaging.* Pascal S, Denis-Quanquin S, Appaix F, Duperray A, Grichine A, Le Guennic B, Jacquemin D, Cuny J, Chi SH, Perry JW, van der Sanden B, Monnereau C, Andraud C, Maury O. Chem Sci. 2017 Jan 1;8(1):381-394. doi: 10.1039/c6sc02488b.
- *Carbazole-Substituted Iridium Complex as a Solid State Emitter for Two-Photon Intravital Imaging.* Lepeltier M, Appaix F, Liao YY, Dumur F, Marrot J, Le Bahers T, Andraud C, Monnereau C. Inorg Chem. 2016 Oct 3;55(19):9586-9595.
- *ALG-2 interacting protein-X (Alix) is essential for clathrin-independent endocytosis and signaling.* Mercier V, Laporte MH, Destaing O, Blot B, Blouin CM, Pernet-Gallay K, Chatellard C, Saoudi Y, Albiges-Rizo C, Lamaze C, Fraboulet S, Petiot A, Sadoul R. Sci Rep. 2016 May 31;6:26986. doi: 10.1038/srep2698.
- *Microtubule-associated protein 6 mediates neuronal connectivity through Semaphorin 3E-dependent signalling for axonal growth.* Deloulme JC, Gory-Fauré S, Mauconduit F, Chauvet S, Jonckheere J, Boulan B, Mire E, Xue J, Jany M, Maucler C, Deparis AA, Montigon O, Daoust A, Barbier EL, Bosc C, Deglon N, Brocard J, Denarier E, Le Brun I, Pernet-Gallay K, Vilgrain I, Robinson PJ, Lahrech H, Mann F, Andrieux A. Nat Commun. 2015 Jun 3;6:7246. doi: 10.1038/ncomms8246.

ELECTRON MICROSCOPY FACILTY

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KEYWORDS: transmission electron microscopy, immunogold labelling, ultrastructural morphology, high pressure freezing, synapses.

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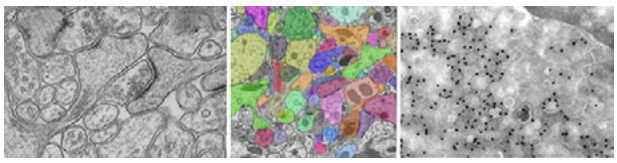
www.imagerie-grenoble.fr

The electron Microscopy facility is located in the Grenoble Institute of Neurosciences and provides access to electron microscopy instruments and sample preparation infrastructure. We also offer training for the use of equipment and guidance for specimen preparation. The access to the equipment is open to all academic users since the facility belongs to the IBiSA national biological imaging network that has funded part of the instruments.

The facility is specialized in the intracellular study of cells and tissues by transmission electron microscopy and each year around 15 projects from bio- and medical sciences are achieved with this equipment. Two thirds of these projects are research collaborations, while the others are carried by researchers themselves. The use of the instruments is on the basis of paid services and our pricing follows the principles of INSERM supported technology services.

TECHNICAL EXPERTISE

As a facility, we provide standard specimen preparation techniques for TEM morphological studies and more advanced techniques are provided through research collaboration. This includes immunogold labelling on cryosections, high-pressure freezing followed by freeze substitution, correlative light electron microscopy and 3D electron microscopy with a FIB/SEM in collaboration with the CEA. We have expertise in 2D and 3D morphometric measurements as well as in image processing and modeling of 3D datasets.



(Left) Ultrathin section of epoxy embedded hippocampus: *a spine emerges from a dendrite and contacts an axon with synaptic vesicles.* ***(Center) Segmentation of a 3D stack. (Right) Ultrathin cryosection of cultured cells:*** *immunogold labelling of MAP6 protein on vesicles.*

SCIENTIFIC EXPERTISE

Our specialization is the study of the central nervous system including vascularization, astrocytes and synapses. Morphological studies of synapses, using parameters such as the morphology of the spines, the size of the PSD, the number of synaptic vesicles or morphology of endosomes makes it possible to quantify synapse activity and adaptations in several animal model of neuropathologies. We also have a strong expertise in intracellular transport and organite morphology (mitochondrial, Golgi apparatus, endosomes etc.) in cell culture as well as in tissues like muscles, skin or reproductive organs.

AVAILABLE EQUIPMENT

- 1 transmission electron microscope (JEOL 1200EX), digital camera 2k x 2k (Veleta, SIS, Olympus),
- 1 vacuum evaporator (JEOL),
- 2 ultracryomicrotomes (Ultracut S, EM FCS and UC7, Leica),
- 1 freeze-substitution system (FCS, Leica),
- 1 high pressure freezer (HPM 100, Leica).

KEY PUBLICATIONS

- *Vascular permeability in the RG2 glioma model can be mediated by macropinocytosis and be independent of the opening of the tight junction.* **Pernet-Gallay K**, Jouneau PH, **Bertrand A, Delaroche J, Farion R, Rémy C, Barbier EL**. J Cereb Blood Flow Metab. 2017 Apr;37(4):1264-1275.
- *Synchrotron X-ray microtransections: a non invasive approach for epileptic seizures arising from eloquent cortical areas.* **Pouyatos B**, Nemoz C, Chabrol T, Potez M, Bräuer E, Renaud L, **Pernet-Gallay K, Estève F, David O, Kahane P**, Laissue JA, **Depaulis A**, Serduc R. Sci Rep. 2016 Jun 6;6:27250.
- *A critical role for VEGF and VEGFR2 in NMDA receptor synaptic function and fear-related behavior.* De Rossi P, Harde E, Dupuis JP, Martin L, Chounlamountri N, Bardin M, Watrin C, Benetollo C, **Pernet-Gallay K**, Luhmann HJ, Honnorat J, Malleret G, Groc L, Acker-Palmer A, Salin PA, Meissirel C (2016). Mol Psychiatry.
- *Regulation of postsynaptic function by the dementia-related ESCRT-III subunit CHMP2B.* **Chassefeyre R, Martínez-Hernández J**, Bertaso F, Bouquier N, **Blot B, Laporte M, Fraboulet S**, Couté Y, Devoy A, Isaacs AM, **Pernet-Gallay K, Sadoul R**, Fagni L, **Goldberg Y** (2015). J Neurosci. 35(7):3155-73.
- *Microtubule-associated protein 6 mediates neuronal connectivity through Semaphorin 3E-dependent signalling for axonal growth.* **Deloulme JC, Gory-Fauré S, Mauconduit F, Chauvet S, Jonckheere J, Boulan B**, Mire E, Xue J, Jany M, Maucler C, Deparis AA, **Montigon O, Daoust A, Barbier EL, Bosc C, Deglon N, Brocard J, Denarier E, Le Brun I, Pernet-Gallay K**, Vilgrain I, Robinson PJ, Lahrech H, Mann F, **Andrieux A** (2015). Nat Commun. 6:7246.

ANIMAL HOUSING FACILITIES *IN VIVO* EXPERIMENTATION AND BEHAVIORAL FACILITY

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KEYWORDS: mice, rats, primates, virus, behavior, electrophysiology, deep brain stimulation, Parkinson's disease, animal models of neurological disorders.

The various fields of activity of GIN are concerned by experiments on animals from the *in vivo* experimental platform. The overall goal of the experiments is to link basic research and applications in human medicine in order to better understand the functioning of cells and brain structures in either normal or pathological situations. In a scientific approach, it is essential to resort to animals in order to validate *in vivo*, data revealed *in vitro* and *in silico*. Moreover, though alternative methods have been developed, the use of animal models is still vital for most of the subjects that the Institute of Neurosciences deals with.

The GIN has two animal housing units, one dedicated to rodents and the other to primates. Within our structures, various functional explorations can be performed: behavior, electrophysiology, imaging, video-tracking. In addition, surgery, biopsies and euthanasia of animals are possible according to current regulations.

The care and use of animals (mice, rats, primates) is in full compliance with the National and European Regulation on the Protection of Vertebrate animals used for scientific purposes (Directive 2010/63; Decree 2013-118). Special attention is paid to animal welfare with the implementation of an Animal Experimentation Ethics Committee.

Ever since it was set up in 2007, GIN adopted an Ethics Committee approved by the Ministry in charge of ensuring that animal experiments are limited to those that are strictly necessary and that they take into consideration the fact that animals are sentient beings, subject to pain and with species-specific physiological and behavioral needs.

EXPERTISE AND MATERIAL

- Animal models in psychiatry, neurology, neuro-degeneration and neuro-oncology.
- Strong expertise in neuronal *in vivo* experimentation (electrophysiology, EEG, etc.) studied in correlation with analysis of behavior (integrative neurosciences).
- Technical devices for viral stereotactic injection, in utero electroporation, small animal surgery and behavioral analysis, anaesthetic bench, innovative deep brain stimulation.

Rodents can be housed in A2 zones (virus).

KEY PUBLICATIONS

- *Effect of subthalamic nucleus stimulation on penicillin induced focal motor seizures in primate.* **Prabhu S, Chabardès S, Sherdil A, Devergnas A, Michallat S, Bhattacharjee M, Mathieu H, David O, Piallat B** (2015). Brain Stimul. 8(2):177-84.
- *Multiparametric MRI as an early biomarker of individual therapy effects during concomitant treatment of brain tumours.* **Lemasson B, Bouchet A, Maisin C, Christen T, Le Duc G, Rémy C, Barbier EL, Serduc R** (2015). NMR Biomed. 28(9):1163-73.
- *Microtubule-associated protein 6 mediates neuronal connectivity through Semaphorin 3E-dependent signalling for axonal growth.* **Deloulme JC, Gory-Fauré S, Mauconduit F,** Chauvet S, **Jonckheere J, Boulan B, Mire E,** Xue J, **Jany M, Maucler C, Deparis AA, Montigon O, Daoust A, Barbier EL, Bosc C,** Deglon N, **Brocard J, Denarier E, Le Brun I, Pernet-Gallay K,** Vilgrain I, Robinson PJ, **Lahrech H,** Mann F, **Andrieux A** (2015). Nat Commun. 6:7246.
- *Activity-dependent tau protein translocation to excitatory synapse is disrupted by exposure to amyloid-beta oligomers.* **Frandemiche ML, De Seranno S, Rush T, Borel E, Elie A, Arnal I, Lanté F, Buisson A** (2014). J Neurosci.34(17):6084-97.
- *Neuronal transport defects of the MAP6 KO mouse - a model of schizophrenia - and alleviation by Epothilone D treatment, as observed using MEMRI.* **Daoust A, Bohic S, Saoudi Y, Debacker C, Gory-Fauré S, Andrieux A, Barbier EL, Deloulme JC** (2014). Neuroimage. 96:133-42.

INTERACTIONS with social, economic and cultural environments

SCIENCE-SOCIETY INTERFACE

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KEYWORDS: popularization, scientific culture, mediation, animation, neurosciences, schools.

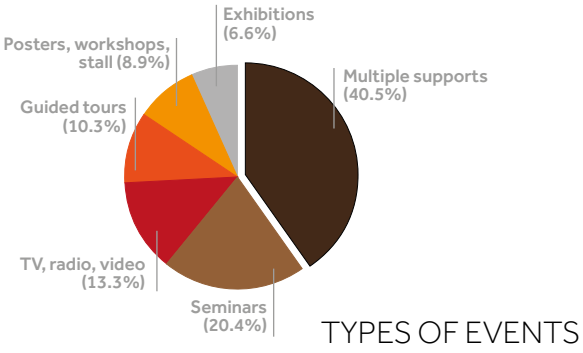
One important role for the GIN is to answer legitimate questions such as "What is scientific research? How does science develop? What advances have local and international scientists allowed?" asked by the general public. Whether formulated explicitly or not, these questions constitute major challenges to the science-society interface, especially when it comes to making science accessible to the greatest number, whether to address substantive issues or reveal the businesses surrounding the researcher.

In order to assist the direction in the diffusion of knowledge to the general public Isabelle Le Brun, assistant professor at UGA and member of GIN, coordinates the interface between science and society, since 2014. The aim of her mission is not only to develop actions in order to increase the visibility of the GIN but also to allow the public to develop a better understanding of careers in research. She is also in charge of collecting internal resources developed by GIN's members, organizing them for different audiences, and structuring actions of dissemination of existing knowledge.

SPREADING KNOWLEDGE

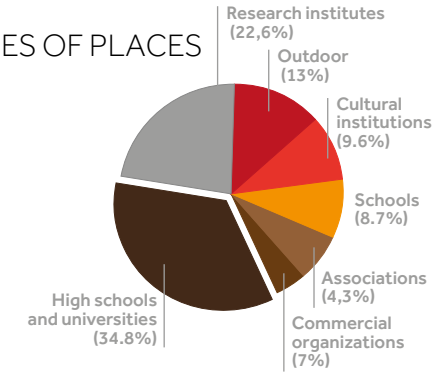
Most of GIN members are involved in scientific animation, communication or teaching. These voluntary activities show their interest in their profession and help disseminate the results of recent research to various types of audience (general public, patient associations, schools, scientists…). Taken together, all these events concern approximately 4,500 people per year.

Each year, GIN members contribute to about 20 events. 65% of these events are organized in town (exhibitions, posters, stalls and records), 52% in the country (stalls and web site), 11% in schools and 1% at the national level (workshops). Events are held either on individual initiatives, by research teams or by transversal work groups. These work groups impulse or participate in the organization of multi-site events.



TYPES OF EVENTS

TYPES OF PLACES



WEB SITE

www.atoutcerveau.fr

In 2013, the steering committee of Brain Awareness Week developed a blog with the Cultural, Scientific, Technological and Industrial Center of Grenoble, La Casemate. The aim of this website entitled "atoutcerveau" is to inform the public about scientific animations, events or articles created by local scientists. More than 2,000 hits are counted each month since its creation and several medias (in France and Québec) have recommended it.

ACTIONS

Communications in congress:

- Science and You (2015 Nancy, France):
  "What place for researchers in scientific mediation?"
  "How to create real art-science meetings?"

Ressources for people:

- Brain hat to build
- Postcards on stress research
- Booklet on ten neuromyths and on time perception
- Four mini-books on neuroscience and fantastic literature of the XIXth century

TEACHING & TRAINING

TEACHING STUDENTS

Teaching is one of the main missions of the GIN. Among GIN staff are assistant or full professors, teaching courses for the Licence (Bachelor), Master and Doctorat of different faculties of the Université Grenoble Alpes (Sports, Pharmacy, Medicine, Chemistry-Biology, Physics).

All GIN research teams welcome students of all levels or 2 week to 6 month internships. In particular, during their first semester, second-year master students follow courses given by scientists of the GIN, other Grenoble institutes, or other French and foreign universities. The next 6 months are spent with one of the teams of the GIN.

The GIN welcomes doctoral students from different French or foreign universities for a period of 3 to 4 years of research. The number of PhD students per team is limited to ensure effective supervision and future integration into research careers. The broad scientific expertise of the teams allows the students to learn the most modern techniques and methodologies to study the brain at all levels, from the molecule to behavior.

Since 2009, 114 PhD and 188 master's students prepared and graduated in the Grenoble Institute of Neurosciences. Since 2018, GIN is involved in the international graduate shool of research *Grenoble Graduate School in Chemistry, Biology and Health* which support graduate students from start to finish, and behond.

TRAINING OF THE GIN STAFF

The members of the GIN (researchers, engineers and technicians) follow many training courses especially those organized by Inserm. From 2009 to 2017, GIN scientists and technicians attended a total number of 410 courses provided by Inserm. These courses are focused on Science and specific techniques (animal experimental surgery which is now mandatory, image analysis, and statistic analyses), Scientific and Technical Information, Health and Safety, Administration, Human Resources - Personal Effectiveness, Communication – Language.

GIN staff have also followed a total of around 230 training sessions with UGA since 2009.

Beside training given by Inserm and UGA, the GIN scientists conduct training workshops and practical courses on a regular basis on their different technical facilities and are involved in clinical workshops for medecine and PhD students weekly.

GROUPS AND COMMITTEES

INTERNAL WORKSHOPS AND CLUBS

Throughout the year different groups of discussion, meetings around a scientific theme, a methodology, etc. are led by GIN staff for GIN staff.

Among the topics treated we can distinguish short classes and workshops delivered toward the GIN staff about statistics, programming and image analysis. For exemple, during the last two years, 14 sessions (i.e Philosophy of the Statistics, GraphPad Prism for newcomers and advances users, Statistical Analysis of Longitudinal Data) were organized for a total attendance of 120 people.

In parallel and in the past years, focus groups have been formed to allow experience sharing and to debate around specific and state of the art methodologies used or planned to be implemented in the institute (i.e virus generation and its use in in-vivo experiments, novel cloning approaches and the use of fusion proteins). Those informal meetings allow GIN experts on particular technic to present briefly the scientific context of the method, to explain how to it set-up in other research groups and the expected results, and allow a better understanding for the GIN community of innovative technics and their dissemination in each group. These open discussions are a unique opportunity to get feedback from someone who has already performed such experiments in order to define clearly their feasibility for other projects.

Finally, a working group called "Consciousness" where GIN researchers are founding members is dedicated to address the aspect of the «consciousness problem». The principle is to bring together a community of scientists interested in the subject and to promote interdisciplinary exchanges that feed the theme and stimulate exchanges. At the end of the year, this working group that associates experts in Humanities, Cognitive science, Biological & Medical sciences and Modelling, proposes to report on its annual reflection during a day or half-day study open to all.

These workshops and internal clubs reflect the dynamism and willingness of GIN staff to transfer their skills to their colleagues.

THE NEURODOCS

The "*NeuroDocs*" are a group created by the Ph.D. students of the GIN. The "*NeuroDocs*" organize the "*NeuroHebdos*" Ph.D. seminars,taking place every week at the Serge Kampf auditorium. Every two years, the members of the "*NeuroDocs*" organize a European meeting in Grenoble bringing together PhD students and postdocs from various European neuroscience institutes. They also take part in events such as the Brain Awareness Week and the Science Festival.

The "*NeuroDocs*" group is composed of at least one representative from each research team. The representatives change every two years.

GRENOBLE INSTITUT OF NEUROSCIENCES

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