INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE

BRAIN & SPINE INSTITUTE - PARIS

ANNUAL REPORT 2014

SEARCH, FIND, CURE, FOR YOU & WITH YOU

ICM
Brain & Spine Institute

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EDITORIAL

Hope. It's the key word for 2014, thanks to the enthusiasm and achievements of our researchers and our partners, growing in numbers by our side.

The year 2013 was encouraging, and 2014 has been rich in discoveries and progress thanks to all those who take part in the daily life of the ICM. To progress it is necessary to **take risks and try approaches that might lead to breakthroughs** at the interface between different scientific fields. In order to advance it is necessary to **develop new unconventional approaches and new methodologies**. This is what we have done every day since the inauguration of the ICM in September 2010.

Many of these discoveries and projects allowed us to progress in our understanding of the diseases of the brain and spinal cord:

- The discovery of a peptide of viral origin gives **new hope for patients with Parkinson's** and other neurodegenerative diseases. The research, conducted on mice, demonstrated the existence of a peptide that can protect against degeneration of neurons implicated in Parkinson's disease. This discovery gives hope for for the future of preventing neurodegenerative diseases.

- The INSIGHT study was launched in collaboration with the Institute of Memory and Alzheimer's Disease (I2MA) and the Pfizer research laboratory in the IHU-A-ICM. The aim of this five to six year study is to **observe and understand the evolution of Alzheimer's Disease in a cohort of at-risk people in order to identify the factors that initiate the disease**. 400 healthy subjects will be selected to participate in the study. All of these players are motivated to better understand and hope to ultimately treat the disease

Since 2012, the ICM has published more than **1000 scientific articles**, with a significant increase in impact factor over time. Additionally, **five** researchers were honored with prizes: Claire Wyart for the Irene Joliot-Curie prize, Mohammed El Behi for the Foundation Bouvet-Labruyère prize, Luc Mallet for the Marcel Dassault prize, Mathias Pessiglione and Lionel Naccache for the prize of the Academy of Science. All of this attests to the excellence of the 600 researchers, engineers, and technicians at the institute.

With six new companies joining in 2014, the business incubator iPEPS-ICM now hosts 20 companies in partnership with the institute.

This year, the first international companies arrived at the ICM: Neoventure Technologies (Ontario), which develops new biomarkers for Alzheimer's disease and PathMaker (Boston), which is developing a method for electrical stimulation of the spinal cord.

The iPEPS-ICM obtained seven new patents, and three projects developed at the iPEPS-ICM won worldwide innovation competitions: DREEM, Brain-e-NOVATION, which is creating e-health solutions, and Bio serenity, which is developing an "intelligent health" solution for tracking and diagnosing epilepsy.

Several events also marked the year 2014. A new publicity campaign was launched, and new supporters have joined in this formidable human and scientific adventure.

Finally, I wish to acknowledge the loyalty of our partners, sponsors, companies, and regular donors, large and small, who contribute every day to build the medicine of tomorrow.

The year 2015 will be very important for the institute, which will celebrate its 5th anniversary since opening. 2015 will also be the moment for a first evaluation, which we owe to all those who accompanied the development of this center of reference for diseases of the nervous system. We will be mobilized so that this year will also be synonymous with new discoveries and rich in challenges. My thanks to all of you who made the adventure of the ICM possible and who have stood alongside us to overcome the diseases of the brain and spinal cord.

Professor
Gérard Saillant
President of the ICM

EDITORIAL

The ICM is on the right track. Already recognized as a **major contributor to research on the nervous system and its pathologies,** both on the national and international scale, the major achievements of 2014 illustrate the medical and scientific advances made in a number of domains and bear witness to the creativity and engagement of our researchers and personnel.

Our new ICM research unit, created on January 1, 2014 with our institutional partners, CNRS, INSERM, Pierre and Marie Curie University, is composed of **25 teams that have been renewed**. These teams cover numerous domains, both fundamental and translational. In order to reinforce and vitalize the institute, the ICM and the IHU-A-ICM launched an **international call for projects** to recruit one or more new teams. Almost a hundred applicants submitted projects and several members of our Scientific Advisory Board came to the ICM to interview a dozen that were preselected on the basis of their scientific excellence. Following this procedure, the team directed by **Bassem Hassan** was chosen and will join the institute in 2016. We have optimized and reconfigured different parts of the building in order to house all of the teams. The organization of the platforms has also evolved with the creation of a **Platform Committee** for greater reactivity and better coordination and to anticipate the needs of the researchers by participating in the technological development of the Institute. **The first day dedicated to institute platforms** allowed us to communicate the capability of these platforms to researchers and enterprises, both within and outside the Institute. Additionally, new platforms were created, such as **PRISME** for the study of behaviors in ecological situations or virtual reality, and other platforms were reinforced, such as with the development of **optogenetics** in vivo and the creation of a **therapeutic evaluation center (CET)** associated with our Clinical Investigations Center (CIC).

The **first institute retreat** was a moment of discussion and conviviality during which all personnel could discover the multiple facets of the institute. The retreat was also the occasion to accelerate the **ICM 2020** program, a strategic program involving all members of the institute. Another emphasis was **scientific strategy** and transversal projects associating the technology and expertise of the teams and platforms in order to advance further at the interfaces between disciplines. Given the success of these interactions, it was decided to launch a call for **joint projects** by the ICM and the IHU-A-ICM to support the most innovative and original transversal projects in 2015. In parallel, work groups have been created to make proposals as to how to better live and work together, increase the influence of the institute, and develop a feeling of belonging. Concrete measures have already been taken thanks to the broad participation of the vital forces of the Institute.

The ICM is now **recognized internationally in the neuroscience community**. This has led to the establishment of strategic alliances with the Institute of Neurology (UCL, London, UK) and the DZNE (Helmholtz, Germany), with which the ICM participates in joint European projects. Exchanges are developing with the Sandler Institute (USCF, San Francisco, USA), Yale University (New Haven, USA), and the Florey Institute (Melbourne, Australia), primarily among students. A joint workshop was held this year in Montreal with the Montreal Neurological Institute and Hospital (McGill, Montreal, Canada). Fundraising has also become international, the first international fundraising event took place in London in April 2014.

The quality of the **scientific events of the institute** is now established. Prestigious lectures by eminent international figures are complemented by monthly lectures on the arts, culture, and science that bring together donors and the personnel of the ICM. The institute is an unique place for training and is associated with Pierre and Marie Curie University. Furthermore, thanks to "les Ajités," an association of students and post-doctoral fellows that organizes numerous events, a new dynamic of discussions and scientific reflection for the youngest members of the Institute has been ushered in.

Finally, interaction with the business world is accelerating thanks to the 20 start-ups incubated in the iPEPS-ICM that collaborate with local teams, four of which originated in the ICM. In addition, we organized meetings with entrepreneurs, and the ICM hosted many events dedicated to innovation and technology transfer. In this context, **the commercialization of the first licenses for patents** generated in the ICM is an encouraging sign.

All the elements are thus in place to make the original ecosystem of the ICM a terrain for **very high level research** that will not only advance the frontiers of knowledge but will also develop applications for the **benefit of patients**.

I wish to thank most sincerely all those who have had faith in us and have supported us including founding members, the Friends Circle of the ICM, donors, sponsors, institutional partners, and others for their faith and their loyalty at our sides so that we can work together to succeed in expanding the ambition of the ICM to new frontiers.

Professor
Alexis Brice
Director General of the ICM

ORGANIZATION OF RESEARCH IN THE ICM

TEAM LEADERS	PRINCIPAL INVESTIGATORS

AXIS: "NEURODEGENERATIVE DISEASES"

TEAM "CAUSES OF ALS AND THE MECHANISMS OF MOTOR NEURON DEGENERATION"

Séverine Boillée	Christian Lobsiger Delphine Bohl Stephanie Millecamps Danielle Seilhean Vincent Meininger François Salachas

The team was supported by the: Agence Nationale de Recherche, Association pour l'étude de la culture d'embryon, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autre maladies du motoneurone, Association France Parkinson, Aide à la recherche des Maladies du Cerveau, Institut Pasteur/Labex REVIVE consortium, Institut Pasteur/Association Française contre les Myopathies

TEAM: "MOLECULAR BASES, PHYSIOPATHOLOGY, AND TREATMENT OF NEURODEGENERATIVE DISEASES"

Alexis Brice	Morwena Latouche Hartmann Alexandra Durr Annie Sittler Fanny Mochel Christel Depienne Isabelle Le Ber Olga Corti Suzanne Lesage Giovanni Stevanin Jean-Christophe Corvol Frédéric Darios Caroline Nava

The team was supported by the: Agence Nationale de la Recherche, APHP, École de Neurosciences Paris Ile de France, INSERM (Cossec), Université de Toulouse, Agence Nationale de Sécurité du Médicament et des Produits de Santé, European Commission,UCL University et Fondation High Q. USA, University Hospital of ULM, Association Française de l'Ataxie de Friedreich, Association Française contre les Myopathies, Association des personnes concernées par le tremblement essentiel, Association Strümpell-Lorrain, Association Connaître les Syndromes Cérébelleux, Fondation de France, Fondation Maladies Rares, Fondation Plan Alzheimer, Association France Alzheimer, Association France Parkinson, Association PSP France, Fondation pour la Recherche Médicale, Prix Académie des sciences, Elisabeth Badinter, Insituto de Biologia Molecular e Cellular, Prix Fondation Roger de Spoelberch Suisse,The Michael J Fox Foundation, Fondation Carlo Besta (contrat doctoral), Fondation Jacques et Gloria Gossweiler, VERUM Fondation, Baylor Research Institute BRI, CHDI Foundation, SERVIER, SANOFI-AVENTIS, IPSEN Innovation, Pfizer Pharmanet Suisse, Pfizer, ULTRAGENIX, UCB Pharma S.A. France, Fondation EDF

TEAM: "ALZHEIMER'S AND PRION DISEASES"

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TEAM LEADERS	PRINCIPAL INVESTIGATORS

TEAM: "NEUROGENETICS AND PHYSIOLOGY"

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Sophie Nicole	Mohamed El Behi
	Bruno Eymard
	Isabelle Rebeix
	Laure Strochlic

The team was supported by the: Agence Nationale de Recherche, Assistance Publique-Hôpitaux de Paris, Association Française de l'Hémiplégie Alternante, Association contre les Myopathies, ARSEP - Aide à la Recherche sur la Sclérose en Plaques, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone, Fondation de France (Prix Bouvet-Labruyère-ICM 2013), Fondation Maladies Rares, OSEO (defi), BIOGEN, OCIRP, Pharnext

TEAM: "EXPERIMENTAL THERAPEUTICS FOR PARKINSON'S DISEASE"

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	Stéphane Hunot
	Rita Raisman
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The team was supported by the: Agence Nationale de la Recherche, INSERM (contrat d'interface), INSERM (ITMO), CHU Pointe à Pitre, ICM, European Commission, PSP France, Association pour la recherche sur les Nicotianées, Fondation RATP, Air Liquide, BOIRON, SERVIER, KLESIA, INTERNATIONAL ESSENTIAL TREMOR FOUNDATION

TEAM: "TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS: FROM GENETICS TO ZEBRAFISH"

Edor Kabashi

The team was supported by: Inserm Atip Avenir, European Commission, DOF (Department Of Defense), Université de Montréal via SLA, IHU-The Johns Hopkins University, Association France Alzheimer, Fédération pour la Recherche sur le Cerveau, Institut de Recherche sur la Moelle Epinière et l'Encéphale, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone, Fondation Cognac Jay, KLESIA

TEAM: "EXPERIMENTAL NEUROSURGERY"

Brian Lau	Carine Karachi

The team was supported by: INSERM ATIP Avenir, Agence Nationale de Recherche, European Commission, Association France Parkinson, Institut de France, Simons Foundation, SANOFI-AVENTIS, Jean-Louis and Marie Cécile Dufloux

TEAM: "ABNORMAL MOVEMENTS AND THE BASAL GANGLIA: PHYSIOPATHOLOGY AND EXPERIMENTAL THERAPEUTICS"

Stéphane Lehericy	Isabelle Arnulf
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This team was supported by the: Agence Nationale de la Recherche, INSERM, INSERM (COSSEC), CNRS (Contrat d'interface), ICM, Association Française de l'Hémiplégie Alternante, Association Française du Syndrome de Gilles de La Tourette, Association des personnes concernées par le tremblement essentiel, Association France Parkinson, Fondation Bettencourt Schueller / Projet Ultrabrain, Fondation de l'avenir, Fondation Groupama, Fondation Maladies Rares, Fondation Pierre Gilles de Gennes pour la Recherche, Fédération pour la Recherche sur le Cerveau, Fondation pour la Recherche Médicale, 2ne contract (PI Sabine Meunier): January 1 2014-April 30 Avril 2015 (80 000Đ en 2014), NEB (Naturalia et Biologia), Prix Fondation NRJ, Genzyme France, GSK Glaxosmithkline, IP SANT2, IPSEN Innovation, LILLY, Merz Pharma, Novartis Pharma, ROCHE, SERVIER, TEVA France, UCB Pharma France S.A, Fonds Patrick de Brou de Laurière, Fonds de dotation Pierre Bergé, Fondation AREVA / projet Gamma, Fondation EDF

TEAM LEADERS	PRINCIPAL INVESTIGATORS

AXIS: "NEURONAL EXCITABILITY, NERVE TRANSMISSION, AND DISEASES ASSOCIATED WITH EPILEPSY"

TEAM: "SYNAPTIC INHIBITION AND AUTO-MODULATION OF MICROCIRCUITS OF THE CEREBRAL CORTEX"

Alberto Bacci

The team was supported by the: Cette équipe a bénéficié du soutien de : Agence Nationale de Recherche, European Commission, Ministère de l'Egalité des Territoires et du Logement, Ecole des Neurosciences Paris Ile de France, Brain and Behavior Foundation (ex Narsad), Telethon Italia, ICM

TEAM: "DYNAMICS AND PHYSIOPATHOLOGY OF NEURONAL NETWORKS"

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Team: "NEUROGENETICS AND PHYSIOLOGY"

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TEAM: "GENETICS OF EPILEPSY"

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TEAM: "OPTOGENETIC DISSECTION OF SPINAL CIRCUITS UNDERLYING LOCOMOTION"

Claire Wyart

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The team was supported by the: Ecole des Neurosciences Paris Ile de France (contrat doctoral), Ville de Paris, European Commission, Fondation Campus Paris Saclay, The Human Frontier Science Program Organization, EMBO, Wings for Life, SERVIER, CARCEPT PREV, Fondation Bettencourt Schueller, Philippe Foundation

TEAM LEADERS	PRINCIPAL INVESTIGATORS

AXIS: "DEVELOPMENT, GLIAL PATHOLOGY, AND REPAIR"

Team: "NEUROGENETICS AND PHYSIOLOGY"

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TEAM: "CELLULAR AND MOLECULAR MECHANISMS IN THE DEVELOPMENT OF GLIOMAS"

Emmanuelle Huillard

The team was supported by: INSERM ATIP Avenir, European Commission, Association pour la Recherche sur le Cancer, La Ligue Nationale contre le Cancer

TEAM: "MECHANISMS OF MYELINATION AND REMYELINATION IN THE CENTRAL NERVOUS SYSTEM"

Catherine Lubetzki
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The team was supported by the: Agence Nationale de Recherche, 2ème contrat (PI Catherine Lubetzki) : 1er Mars 2013-29 Août 2016 (84 976e en 2014), Inserm (contrat d'interface), Aide à la Recherche sur la Sclérose en Plaques, Multiple Sclerosis International Federation, Genzyme, VERTEX, MERCK SORONO, Prix Marie-Ange Bouvet Labruyère, NOVARTIS

TEAM: "MOLECULAR AND CELLULAR APPROACHES TO MYELIN REPAIR"

Anne Baron Van Evercooren
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The team was supported by the: Inca Groupement d'Intérêt Public Cancéropôle, La Ligue Nationale contre le Cancer, Fondation pour la Recherche Médicale, Association pour la Recherche sur le Cancer, Beta Innov

TEAM: "OLIGODENDROCYTE DEVELOPMENT AND NEUROVASCUAR INTERACTIONS"

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The team was supported by the: Agence Nationale de la Recherche, Agence Nationale de Sécurité Sanitaire de l'Alimentation de l'Environnement et du Travail, Aide à la Recherche sur la Sclérose en Plaques, National Multiple Sclérosis Scoiety via Children's national organisation, Novartis Pharma, TEVA

TEAM LEADERS	PRINCIPAL INVESTIGATORS

AXIS: "COGNITION, EMOTION, ACTION"

TEAM: "PICNIC LAB: PHYSIOLOGICAL EVALUATION IN HEALTHY SUBJECTS AND PATIENTS WITH COGNITIVE DISORDERS"

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The team was supported by: Agence Nationale de Recherche, INSERM, Ecole des neurosciences Paris Ile de France (contrat doctoral), European Commission, Fondation Voir et Entendre, Association France Alzheimer, Fondation pour la Recherche Médicale, LesHanot Haim Foundation, McDonnell Foundation, AXA Research Fund

TEAM: "FRONTLAB - FRONTAL SYSTEMS: FUNCTIONS AND DYSFUNCTIONS"

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TEAM: "STUDY OF EMOTIONS AND SOCIAL INTERACTIONS"

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TEAM: "BEHAVIOR, EMOTION, AND THE BASAL GANGLIA"

Luc Mallet
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The team was supported by the: Agence Nationale de Recherche, Fondation Fondamentale, Christian Poquet

TEAM: "BIOLOGICAL, PSYCHOLOGICAL, AND COMPUTATIONAL BASES OF MOTIVATION"

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The team was supported by the: Ville de Paris, Direction Générale pour l'Armement, European Commission, Fondation Coopérative scientifique Sorbonne Université, Fondation pour la Recherche Médicale, SERVIER

TEAM LEADERS	PRINCIPAL INVESTIGATORS

AXIS: "MODELS AND METHODS FOR NEUROSCIENCE" (TRANSVERSAL AXIS)

TEAM: "OPTOGENETIC DISSECTION OF SPINAL CIRCUITS UNDERLYING LOCOMOTION"

Claire Wyart	Pierre-Luc Bardet Hugues-Pascal Mousselard

The team was supported by the: Ecole des Neurosciences Paris Ile de France (contrat doctoral), Ville de Paris, European Commission, Fondation Campus Paris Saclay, The Human Frontier Science Program Organization, EMBO, Wings for Life, SERVIER, CARCEPT PREV, Fondation Bettencourt Schueller, Philippe Foundation

TEAM: "ARAMIS: MATHEMATICAL MODELS AND ALGORITHMS FOR IMAGE AND SIGNAL PROCESSING IN THE HUMAN BRAIN"

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The team was supported by the: Agence Nationale de Recherche, European Commission, Fondation Plan Alzheimer (projet CATI, multi-tutelles)

TEAM: "BIOTECHNOLOGY AND BIOTHERAPY"

Philippe Ravassard	Rolando Meloni

The team was supported by the: Agence Nationale de Recherche, Région Ile de France, European Commission, Fondation pour la Recherche Médicale

2014 IN REVIEW

RESEARCH

Over the course of the year, the 600 researchers, engineers, and technicians of the Institute were mobilized to try to find new therapeutic avenues to better understand and treat the diseases of the brain and spinal cord. This chapter will present the major advances made by the teams.

1 NEURODEGENERATIVE DISEASES

Neurodegenerative diseases, like **Alzheimer's disease**, **Parkinson's disease,** and **Amyotrophic lateral sclerosis** are **chronic** and **often disabling**. These diseases present a **problem for public health** because of **patients' handicaps**, **impact on their families,** and the cost of care, particularly in view of an **aging population**.

What are the **genetic and environmental bases** of these disorders and what **determines their progression**? What **mechanisms** are responsible for **progressive and selective neuronal loss**? How can one **recognize and distinguish among these diseases** at an **early stage?**

To answer these questions, the teams of the ICM are working to determine the **molecular bases** of certain **hereditary forms** of these diseases and identify the most frequent **risk factors**. They are also identifying **biological markers** in order to **detect these diseases early** in patients.

Neuronal death can affect different regions of the brain associated either with **intellectual and emotional functions, such as in** Alzheimer's disease and Creutzfeldt-Jakob disease or with **motor system function** (Parkinson's disease, Amyotrophic lateral sclerosis or Charcot disease).

The great challenge for neurodegenerative diseases is to develop **treatments that stop their progression. Researchers in the ICM work at different scales to address this challenge,** from **identification of diseases in simple models** in the laboratories to **therapeutic trials** in patients in the **Clinical Investigation Center** of the ICM.

Because of the excellence of ICM researchers and clinicians, this rich scientific environment benefits patients fully through the development of **personalized medicine** adapted to each case.

1. Alzheimer's disease and other pathologies that cause intellectual disability

With about **860,000 people** in France and **35 million people worldwide** who suffer from Alzheimer-type dementias, Alzheimer's disease is at the center of our attention.

Alzheimer's disease is characterized by the **slow degeneration of neurons**, beginning with the **hippocampus** then expanding to other regions of the brain. This degeneration is the result of the

concomitant progression of **two types of damage**, the abnormal accumulation outside nerve cells of a protein called **ß-amyloid peptide (Aß-peptide)** leading to the formation of **"amyloid plaques,"** also called **"senile plaques,"** and the abnormal accumulation of the **tau protein** in neurons, leading to their **degeneration** and simultaneous **cognitive deterioration**.

Understand the mechanisms

As in many neurodegenerative diseases, **lipid metabolism** plays a central role in Alzheimer's disease. In 2014, **Stéphane Haïk** and **Marie-Claude Potier** 's team showed that the **increase** in **membrane cholesterol** in neuronal cultures led to an increase in the production and secretion of amyloid peptide, replicating early changes observed in Alzheimer's disease[1]. These observations have opened new avenues for understanding the **mechanisms of Alzheimer's disease** and identification of therapeutic targets.

In the team of **Stéphane Haïk** and **Marie-Claude Potier**, **Benoît Delatour** and his collaborators showed that when **amyloid peptides** are injected into normal mice, they diffuse rapidly in the brain and induce **transitory cognitive deficits**. These results confirm *in vivo* the **toxicity** and pathogenicity of the Aß-peptides, which will be a prime **therapeutic target**[2].

The team of **Stéphane Haïk** and **Marie-Claude Potier** studies both Alzheimer disease and prion diseases such as **Creutzfeld-Jakob** disease because of their important biological analogies. They are interested in the **molecular mechanisms** implicated in the **propagation of prions** and, more precisely, the **conversion of normal proteins into toxic malformed proteins** that accumulate and cause **neuronal death**. The researchers have developed methods for **amplifying the malformed proteins** *in vitro* in order to observe the process of **misfolding** (abnormal folding of the proteins) and **understand the mechanisms of neuronal death**. These methods permit the study of the **mechanisms of propagation** and also allow **modeling of the barriers to prion transmission**[3] and also to **test therapeutic molecules** and develop **diagnostic approaches** with **excellent sensitivity and specificity**[4]. The phenomenon of propagation has been observed in other neurodegenerative diseases, and studies are underway to transfer these findings to other **proteinopathies** of the central nervous system, neurodegenerative diseases characterized by the abnormal accumulation of certain proteins that include **Alzheimer'sDisease** (aggregation of **ß-amyloid** and **Tau**) and **Parkinson's Disease** (aggregation of **α-synuclein**). Understanding this represents a **major challenge:** try to **block propagation** and **find treatments adapted** to these pathologies.

Cécile Delarasse, from the team of **Bertrand Fontaine** and **Sophie Nicole**, studies the role of the purinergic receptor **P2X7R** in **Alzheimer's Disease**. This receptor is implicated in the maturation of the precursor of the ß-amyloid protein. When activated, it cleaves the ß-amyloid protein in the middle of the sequence of the Aß peptide, which **prevents** the formation of **neurotoxic Aß peptides** and produces a soluble fragment that has neuroprotective properties. **P2X7R** is also implicated in the

release of **pro-inflammatory factors** by microglial cells, **innate immune system** cells present in the brain. An excessive inflammatory reaction can be harmful. **P2X7R**, because of its **role in inflammation** and the cleavage **of the ß-amyloid protein,** could have a double effect in Alzheimer's disease **depending on the stage**. **Cécile Delarasse's** project also aims at understanding the role of **microglial cells, potential targets for the treatment of Alzheimer'sDisease**.

Identify risk factors

People with **trisomy 21** have a higher risk of developing Alzheimer's Disease; approximately 45% of people with **trisomy 21** have an Alzheimer's-type dementia by age 60. In these patients, the protein **DYRK1A** encoded by a gene on chromosome 21, is **overexpressed** in the brain. In 2014, the team of **Marie-Claude Potier** showed that this protein is also **overexpressed** in the **brains** of patients with Alzheimer's Disease[5]. The protein could thus be both an **early marker** of and a **risk factor** for Alzheimer's Disease. In collaboration with **Bruno Dubois**, clinical trials are underway in the **INSIGHT** cohort to determine whether the variation in expression of this protein appears before patients show symptoms and whether this could be used as a predictive marker of the disease.

In a study of 2600 Islanders, Harald Hampel, in **Bruno Dubois'** team, and his colleagues **demonstrated a correlation between the presence of a mutation in the *ABCA7* gene and Alzheimer's Disease**[6]. The **ABCA7** protein is strongly expressed in the central nervous system and belongs to the family of proteins implicated in **membrane transport**. An alteration in the gene encoding this protein is a **risk factor** for Alzheimer disease. These studies open the way for **new methods for diagnosing** Alzheimer disease as well as other neurodegenerative disorders.

Recently, **Harald Hampel** and his colleagues demonstrated that **interactions between two genes** *(APOE and PICALM)* are associated with both **brain atrophy** and **cognitive deterioration** in patients with Alzheimer's Disease[7].

Visualize the inside of the brain

The team of **Stéphane Haïk and Marie-Claude Potier** developed **CLARITY**, a method that **allows visualization** of the inside the brain of patients with Alzheimer's disease in 3-D[8]. This technique, applied for the first time to samples of brain from patients with Alzheimer's disease from the brain bank of the Salpêtrière Hospital **GIE NeuroCEB** directed by **Charles Duyckaerts**, permits the study of the **organization of senile plaques**, **axon trajectories,** and **neurofibrillary degeneration** on brain slices.

Redefine disease criteria

Since 2007, **Bruno Dubois,** in collaboration with a group of international experts (International Working Group, IWG), is trying to **define the diagnostic criteria for Alzheimer's Disease** in order to better identify the disease's different forms and integrate biomarkers in diagnosis. In 2014, the investigators **refined diagnostic criteria**[9] to **improve detection** of Alzheimer's based on physiopathological biomarkers, including quantification of ß-amyloid deposits by PET-SCAN and their amount in the cerebrospinal fluid. They have also defined **specific criteria** for **atypical forms** and **preclinical stages** of Alzheimer's Disease.

Follow the evolution of disease

In 2014, the collaborative research performed by **Harald Hampel** and **Michel Thiebaut de Schotten** in the team of **Bruno Dubois** was honored by the review ***Alzheimer's & Dementia***.[10] They work on **early markers** of Alzheimer disease and measures of **brain connectivity** using novel methods of advanced **neuroimaging** to discover **new makers** specific to the different stages of Alzheimer disease such as damaged nerve networks. These markers, specific to the patient at a given moment, could enable the **early detection** and **effective treatment** of Alzheimer disease.

Test treatment efficacy

The team of **Bruno** Dubois measured the effect of a pharmacological agent, donepezil, on the size of the hippocampus in patients with **Alzheimer's disease** using a **new technique** of image analysis developed by the team of **Olivier Colliot** and **Didier Dormont**. This clinical study of **more than 200 patients** from **28 centers** throughout France showed that treatment for a year **reduced hippocampal atrophy in the patients by 45%**[9]. This is the first large scale multi-centrer study of a treatment in patients with mild cognitive deficit and also the first time that a statistically significant effect of a treatment on hippocampal atrophy has been obtained in patients.

2. Parkinson's Disease and other pathologies that cause a motor handicap

Parkinson's Disease is the second most common neurodegenerative disease. Parkinson's affects 1.5% of people over 60 years of age and 4% of people over 85. The disease is caused by the **progressive death of neurons** in a deep region of the brain, the ***substantia nigra***. These **neurons**, which use the molecule **dopamine** to communicate with other neurons, play an essential role in the control of movement. Symptoms of the **disease** include **slowing of gestures**, **limbs and trunk rigidity,** limb **tremors**, loss of dexterity, and **gait disorders**.

Physicians know partially how to **treat the motor symptoms** of the patients with drugs that replace dopamine but do not know how to prevent **neuronal death** itself. Furthermore, neurodegeneration is not limited to dopaminergic neurons or the motor system and affects brain regions other than the *substantial nigra*.

Identification of genetic factors

Alexis Brice's group is developing an integrated approach to Parkinson's Disease using a variety of experimental methods *in vivo* and *in vitro* to investigate from genetic bases of the disorder to its **physiopathological mechanisms.** One challenge is to study early stages of the disease in order to find predictive biomarkers such as gene mutations before the disease can be detected clinically.

With this goal in mind, the **team of Alexis Brice with Suzanne Lesage,** is part of an **international consortium** that has the aim of defining the **genetic profile of Parkinson's disease**. This project has led to the **identification of six new risk factors** for **Parkinson's disease**[12] and confirmed the **implication of 19 already known genetic risk factors**. The analysis was performed on data from more than **100,000 individuals and** represents a major scientific advance in our **understanding of the process by which the disease appears** in patients as well as the development of new therapies.

In collaboration with this international consortium, the team of **Alexis Brice** has also found a correlation between **polygenic risk**, mutations in several genes, and the age of onset for the disease[13]. The **early forms** of Parkinson's disease are not only caused by the most penetrant mutations, homozygous mutations in *PARK2* for example, but can also be caused by a **polygenic accumulation of more common** and less penetrant mutations. The identification of polygenic risk facilitates **understanding of gene interactions** and interactions of the genes with their environment in the increased risk of developing the disease.

The team of **Philippe Ravassard** works on **dopaminergic neurons**. Ongoing

studies in a mouse model aim at determining **the role of *GPR88*, a gene** already implicated in schizophrenia (see V-Cognition), in the **motor and non-motor symptoms** of **Parkinson's disease**.

Prevent neurodegeneration

The team of **Etienne Hirsch** studies the **progression of lesions** caused by **neuronal death** and tests the **protective effect** of various molecules on **dopaminergic neurons**. In his team, **Stéphane Hunot** and collaborators have identified a **small peptide** of viral origin that **protects the neurons** implicated in Parkinson's disease **against degeneration**[14]. This peptide is part of the **X protein of the Borna virus**, which infects nerve cells. The X protein **inhibits neuronal death** to ensure the **survival of the virus**. The peptide was shown to have neuroprotective effects in mice when administered intranasally. This relatively non-invasive method is very promising for future treatments of **neurodegenerative diseases**.

The X protein works by protecting mitochondria, which are the "power plants" of cells and are essential for energy production, which is an essential physiological process. When **mitochondria** are **altered**, **axons degenerate and disappear progressively leading to neuronal death**. **Olga Corti** in **Alexis Brice**'s team has recently described a **natural mechanism for protecting mitochondria** in an **experimental model of Parkinson's disease**[15]. This mechanism involves **maintenance of the expression of a mitochondrial enzyme**, called **HSD17B10**, by **Parkin** (mutations in the *Parkin* gene are implicated in parkinsonian syndromes). **Loss of this protective mechanism** could contribute to **mitochondrial dysfunction** and **neurodegeneration** in Parkinson's disease.

Treat balance and gait disorders

Etienne Hirsch and his team also study **the death of non-dopaminergic neurons** in **Parkinson's disease**. In **Parkinson's, symptoms caused by non-dopaminergic neurons**, such as gait and balance disorders**, are not corrected by treatment**. These symptoms are **severe** in parkinsonian patients and indicate a poor prognosis for the evolution of the disease.

In collaboration with the team of **Brian Lau**, they confirmed that the **pedunculopontine nucleus** (PPN), a region of the **brainstem**, is implicated in **gait control** in humans and that **stimulation** of the PPN **reduces gait and balance disorders** in patients with Parkinson's disease[16].

The clinical Neurology and Neurosurgery team of the Pitié-Salpêtrière Hospital followed six patients implanted with electrodes in the PPN for **deep brain stimulation**. The double-blind study showed a **decrease in "freezing" and falls** in three patients and an **improvement** in their **postural control**[17]. The patients also described an **improvement** in their **quality of life**. These results are tremendously encouraging and open the way for the development of **new treatments for severe forms of Parkinson's disease**. However, they should be regarded with caution because of risks related to the technique that were observed during the study.

As a consequence of this study, **Marie-Laure Welter** in **Etienne Hirsch**'s team obtained a grant from the **Michael J. Fox**

Foundation to perform a larger scale therapeutic trial targeting the PPN with **Carine Karachi**.

Identify predictive and prognostic markers

The **PPN** is also implicated in **sleep regulation**. The team of **Etienne Hirsch** and that of **Marie Vidailhet and Stéphane Lehéricy** showed that **lesions** of the PPN could be **implicated in sleep disorders** observed in parkinsonian patients[18]. This discovery is quite interesting because **sleep disorders** characterized by **great agitation** are part of the **early symptoms** of patients with **Parkinson's disease**.

The team of **Marie Vidailhet and Stéphane Lehéricy** are at the forefront of recent technical advances in **magnetic resonance imaging** (MRI), which allows **diagnosis of parkinsonian syndromes**, **detection of the progression of the disease,** and **understanding the physiopathology of movement disorders**[19]. The aim is to **detect biomarkers** of the disease to **better understand** it and **make diagnoses as early as possible** thanks to a multimodal physiological, clinical, and imaging study in patients with Parkinson's disease.

The team has made enormous advances in the understanding of the lesions underlying symptoms. With **new analytical techniques,** they have detected **small abnormalities** in the ***locus coeruleus***, which is a structure implicated in **sleep**[20]. The team has recently shown that these abnormalities can be detected even **before symptoms of Parkinson's disease appear**. These very particular **sleep disorders** are not only **prognostic markers** of the evolution of the disease but also **predictive markers that allow a better understanding of its physiology**. A certain number of collaborations have been established with international teams to **identify other risk factors** implicated in Parkinson disease[21].

Other structures in the brainstem, in particular the ***substantia nigra***, a region that degenerates in Parkinson's disease, have anomalies in pre-symptomatic carriers of a mutation responsible for Parkinson diseases[22].

The identification of these **predictive markers** allows researchers to **follow patients** and try to **slow the emergence of their symptoms**. It's also a way to study the compensatory circuits that mask symptoms in spite of the lesions.

Studies using the same strategy are underway on the **brainstem circuits** implicated in **gait and cognitive disorders** in Parkinson's disease.

In collaboration with **Jean-Christophe Corvol**, the team of **Marie Vidailhet and Stéphane Lehéricy** are involved at the **national level** in clinical studies aimed at determining the **efficacy of certain treatments**[23] or to evaluate the **factors predicting response to treatment**[24] in patients with **Parkinson's disease**.

Understanding movement disorders

The team of **Marie Vidailhet and Stéphane Lehéricy** is also interested in other less frequent diseases that affect movement, such as **essential tremor**, **Gilles de la Tourette syndrome**, **dystonia,** or **mirror movement disorder**, which are studied from the points of view of the **circuits involved** and their **physiopathological mechanisms**. **Neuronal circuits** link both the **cerebral cortex and the cerebellum,** situated at the back of the brain, as well as the **cortex and the basal ganglia** situated deep in the brain under the cortex. The team uses an integrated approach combining **genetic, metabolic, physiological, and behavioral information** as well as **imaging data** (MRI and MEG, see the technical platforms of the ICM) and **clinical examinations**.

In their group, **Cécile Gallea** and her collaborators have recently analyzed the implication of the **cerebello-thalamo-cortical circuit** (cerebellum-thalamus-cortex) in **essential tremor**[25].

C**ortical functions are altered i**n **dystonia,** a neurological motor disorder causing abnormal muscle tone. Researchers have identified a **genetic form** of dystonia, myoclonic dystonia, which is distinguished from other forms of dystonia by its unique **physiopathological mechanisms**[26].Additionally, the team demonstrated an increase in **cortico-striatal connectivity** (cortex-basal ganglia) during motor training in a **learning task**, which contributes to the **consolidation of motor memory**.[27]

Gilles de la Tourette syndrome is characterized by **motor and vocal tics**, which can be associated with behavioral disorders, obsessive compulsive disorders, attentional deficits etc., involving **motor, emotional, and limbic circuits**. **Yulia Worbe** and her collaborators have shown not only an **alteration in the connectivity**[28] of these circuits but also a **structural anomaly**[29] at the level of the sulci.

Patients with congenital **mirror movement disorder** make involuntary movements on one side of the body that reproduce intentional movements made on the other side of the body. This disease was **identified clinically and genetically** by ICM researchers **Emmanuel Roze,** from the team of **Marie Vidailhet and Stéphane Lehéricy,** and **Christel Depienne,** from the team of **Alexis Brice**. In 2014, different forms of the disease were characterized and **mutations were identified in the genes responsible for the disease, RAD51 and DCC**[30].

3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), or Charcot disease, affects the **motor neurons**, neurons in the brain and spinal cord that **innervate muscles**. Patients with ALS (4/100,000) suffer in consequence from a **progressive motor handicap** that leads to **paralysis** and death in an average of 2 to 5 years after the first symptoms appear.

Slow the progression of ALS

The team of **Séverine Boillée** works with the ICM in its fight against this disease. This team is particularly interested in the role of **inflammatory processes** in the **degeneration of motor neurons**. As in all neurodegenerative diseases, an **immune response** is observed in the central nervous system in ALS. A major question is how the **immune reaction,** implicated in the defense of the organism, becomes **deleterious** and **contributes to neuronal death**.

Microglial cells and macrophages are activated over the course of the disease and produce **neurotoxic factors** implicated in motor neuron degeneration. In 2014, the team of **Séverine Boillée** demonstrated the role of "**system xC-**" in the progression of ALS[31]. **System xC-** is a **transporter** that mediates the release of **glutamate,** an excitatory neurotransmitter, by microglial cells and macrophages. The increase in the level of glutamate is related to what is called **excitotoxicity**, hypothesized to be responsible for **the degeneration of motor neurons** in ALS. Consequently, **system xC-** contributes to the **toxic activity of microglial cells**. Thus, **blocking** system xC- might therefore be of **therapeutic interest** to **slow the progression of ALS**.

In 2014, **Gaelle Bruneteau**, member of the team of **Bertrand Fontaine and Sophie Nicole**, established a link between the **overexpression of the protein Nogo-A** and denervation of muscles in ALS at the level of the **neuromuscular junction**[32]. This protein could be both a **biomarke**r that facilitates **diagnosis of the disease** and a **therapeutic target**. A phase 2 study aimed at testing the efficacy and the safety of a **monoclonal antibody directed against Nogo-A** is underway in patients with ALS.

Identify risk factors

The teams of **Séverine Boillée** and **Edor Kabashi** are involved in the search for **new mutations** in order to **create models** of ALS and elucidate the mechanisms underlying its progression.

In collaboration with an **international consortium**, **Stéphanie Millecamps** in the **team** of **Séverine Boillée** contributed to the discovery of a **new gene related to the immune system and autophagy,**

TBK1, related to the immune system and autophagy, implicated in **ALS and frontotemporal dementias**[33] (FTD), a neurological pathology frequently associated with ALS.

Over the course of the last years, **29 genes** have been implicated in ALS, notably the **gene C9orf72** that is the **most frequent genetic cause of ALS**[34] and **frontotemporal dementias**[35] (FTD). These 2 studies have led to the definition of clinical criteria that allow rapid molecular diagnosis of patients with a mutation in *C9orf72*.

In collaboration with the team of **Edor Kabashi**, the teams of **Séverine Boillée** and **Alexis Brice** have determined the frequency of several **genetic causes**, including ***SQSTM1***, in populations of patients with ALS[36] and/or FTD[37]. Furthermore, the analysis of sections of spinal cord from autopsied patients allowed **Stéphanie Millecamps** and **Danielle Seilhean** to compare the **neuropathological signs associated with the presence of these mutations**[37].

After a study of a cohort of more than **1500 patients**, these three teams demonstrated in 2014 that a long glutamine repeat (polyQ) in the gene ***ATXN2*** was a **risk factor** for the development of **ALS** and **FTD-ALS**. Furthermore, the concomitance of repeats in ***C9orf72*** and ***ATXN2*** could have an influence on the **type of the disease** (ALS or ALS-FTD rather than FTD), the age of disease onset, and the **life expectancy** of the patients[38].

Understand the mechanisms and treat disease

The team of **Edor Kabashi** developed the first vertebrate animal model of this genetic deficiency, a **knock-down** of ***C9orf72*** expression in the **zebrafish**. In 2014, the researchers developed a **new zebrafish model** in which the ***SQSTM1*** **gene was inactivated**. In this model, they observed the **loss of the fish's motor functions** associated with a **deficit in motor neurons**, which **mimics the symptoms of ALS**[39]. They also showed that stimulation of **autophagy,** the degradation of abnormal proteins, reestablished **normal motor behavior in the fish**. Autophagy dysregulation may thus be involved in ALS. These results are very encouraging and might present **therapeutic perspectives** for patients with ALS.

2 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is the **number one cause of severe non-traumatic handicap** in young adults. It affects about **80,000** people in France (1 in 1000 people), more than **540,000** people in Europe, and about **2.8 million worldwide**.

MS is an **inflammatory disease of the central nervous system** in which the **immune system**, normally implicated in the fight against viruses and bacteria, is activated and **attacks itself**.

In MS, the inflammatory reaction **destroys the protective myelin sheath** that surrounds neuronal projections, the **axons**. The main role of this protection is to **assure rapid conduction of the nerve impulse** so that **information** leaving the brain rapidly **reaches the muscles**. **Myelin** also plays an important role in maintaining the **integrity of the axons**. Repeated **inflammatory attacks** alter the transfer of information and cause **motor, sensory, balance, and visual disorders.** Although myelin has the **capacity to renew itself -** called remyelination - this process is **ineffective** in MS and **decreases as the disease progresses**.

ICM researchers are therefore trying to **understand the mechanisms of de- and remyelination**, not only to **prevent destruction** of the myelin, but also to **stimulate its repair**.

Identify risk factors

The team of **Bertrand Fontaine and Sophie Nicole** (see also Alzheimer's disease, Amyotrophic lateral sclerosis, and rare diseases) identified **five new groups of genes** associated with a **predisposition to MS**[40]. These **gene networks** are involved in the **adhesion** and **migration of immune system cells**, the **T lymphocytes**, in the brain. The entry of T lymphocytes into the brain is a crucial step in the **development of MS** because these cells are **responsible for the destruction** of the **myelin sheath**. By **blocking the migration of T lymphocytes** into the nervous system, **degradation** of the myelin sheath decreases, **favoring repair of the myelin sheath** and **restoration of nerve functions**. One of the gene networks identified in this analysis is of major interest for the **identification of new therapeutic targets** in MS.

Understand mechanisms

The team of **Brahim Nait Oumesmar and Anne Baron-Van Evercooren** have demonstrated the **beneficial effect of several molecules** on **myelin repair**. The latest advance was the identification of the effect of a pro-myelinating factor called **Olig2**[41]. Overexpression of this factor stimulates the **regeneration of oligodendrocytes**, the cells responsible for the **production of myelin**. This discovery could have repercussions on the development of **therapeutic**

strategies aimed at **stimulating repair** of the damages caused by MS.

The researchers also demonstrated the presence of **synaptic connections** between **neurons and oligodendrocyte progenitors** in demyelinating lesions. Their studies indicate that these connections **control remyelination**[42] by regulating the state of proliferation of the oligodendrocyte progenitors. This mechanism allows **the process of myelination to adapt to the activity of the neuronal circuit**.

The researchers also participated in the demonstration that the molecule **endothelin**[43] **inhibits remyelination** via activation of the Notch receptor. These studies open the way to a **pharmacological approach** to remyelination and the identification of **new therapeutic targets**.

The team is also interested in the **cellular aspects** of de- and remyelination and demonstrated the **contribution** of **cells from the peripheral nervous system** to **remyelination in the central nervous system**. Recently, they identified a **group of stem cells in the peripheral nervous system**[44]. These stem cells/progenitors can generate **Schwann cells**, cells that ensure the myelination in the peripheral nervous system in **response to demyelination** in the central nervous system. These Schwann cells are of interest because they are not a target of the immune system in MS, thus **remyelination by these cells** could have a **beneficial effect**.

The research of the team of **Catherine Lubetzki and Bruno Stankoff** also focuses on the **cellular and molecular mechanisms** of de-/remyelination, notably those that control the **migration** and **recruitment of oligodendrocyte precursors** in demyelinating lesions. The researchers have recently shown that **oligodendrocyte progenitors** are **activated**, become **more motile,** and **express inflammatory factors (CcL2 and IL1b)** that **increase their mobilization and differentiation** during demyelination[45].

In collaboration with the teams of **Brahim Nait Oumesmar** and **Philippe Ravassard**, researchers in the team of **Catherine Lubetzki and Bruno Stankoff** demonstrated the role of a **guidance molecule, netrin**, *in vivo* in a mouse model. This molecule **inhibits** the **recruitment of oligodendrocyte precursors** to MS lesions. By **blocking this molecule**, the researchers obtained an acceleration of myelination[46]. This research on **guidance molecules** is extremely important because **acceleration of recruitment** of progenitor cells and remyelination permits **axon repair** during a period of time when the **lesions are still reversible**.

Another research axis of the team of **Catherine Lubetzki and Bruno Stankoff** focuses on the **early mechanisms** of the **formation of nodes of Ranvier**, regions of the axon that are not myelinated and which **permit rapid conductance of nerve impulses**. The researchers showed that structures called **pre-nodes**, which resemble nodes of Ranvier, appear **before the beginning of myelination**[47]. The aggregation of these structures along the axon is induced by a still unknown factor produced by the oligodendrocytes. These pre-nodes play a **functional role**, **accelerating conductance of the nerve impulse** along the axon. The fact that another element in addition to myelin can accelerate

the nerve impulse is an **innovative concept**. A study is underway to determine the role of these pre-nodes during remyelination.

Measure the evolution of the disease

The team of **Catherine Lubetzki and Bruno Stankoff** wants to measure what cannot be seen by MRI, notably the evolution of the disease. To do this, they developed an **innovative program of multimodal imaging** by positron emission tomography (PET-SCAN) of demyelination/remyelination. A pilot study was performed with a tracer that attaches to white matter, PIB, labelled with carbon 11 (PIB is also a marker of amyloid plaques in Alzheimer disease), followed by a PET-SCAN coupled with MRI[48]. With this method, **the kinetics of demyelination/remyelination can be followed and** patients identified according to their capacity to remyelinate. This new methodology could serve as a **predictive marker** for the evolution of the disease.

By combining **several MRI techniques** and analyzing the **functional connectivity** of fiber tracts in the brain, the researchers showed that certain **tracts** are particularly **disconnected** in patients with cognitive disorders, **notably** default networks and attentional networks. This disconnection is related to **neurodegeneration** in specific regions of the cortex, which causes the **loss of cognitive faculties**[49].

The team also works on a project of **imaging specific to neurodegeneration**. Although MS is a myelin disease, the degeneration of neurons is what causes the handicap. By using a PET-SCAN tracer (flumazenil), the researchers were able to **quantify and localize neuronal degeneration and measure inflammation in patients**[50, 51].

These methods allow prediction of the evolution of patients, **understand why they progress,** and **evaluate therapies targeting remyelination, neurodegeneration, or neuro-inflammation.**

3 BRAIN TUMORS

Around **5000 people** are diagnosed each year in France with a **primary malignant brain tumor**. The symptoms depend on the localization of the tumor, its size, and rate of development. Neurons are not the only cells in the brain. They are supported structurally and functionally by **glial cells** such as **oligodendrocytes** that produce the myelin that surrounds neurons. Like lymphocytes of the immune system, glial cells are the **origin of the most aggressive and frequent tumors**, **lymphomas,** and **gliomas**, respectively.

Develop diagnostic and prognostic tools

Working with samples from one of the most important brain tumor banks, the **OncoNeuroTek,** directed by **Jean-Yves Delattre**, the Experimental Neuro-oncology team of **Marc Sanson** uses **molecular biology** to detect genetic mutations that cause these tumors, analyze their contribution to the **prognosis,** or **predict response to a treatment**, providing **useful informations for clinicians**. A molecular prognosis classification has thus been proposed starting from a small number of key alterations, notably in the ***IDH1*** and ***TERT*** genes[52,53].

The mutation in ***IDH1*** has an additional interest. The mutations leads to the **accumulation** of a specific metabolite, **D-2HG**. In collaboration with the **CENIR**, the team of Marc Sanson is developing a **diagnostic tool based on the detection of D-2HG** by **magnetic resonance spectroscopy**.

Identify the causes and mechanisms

Two **"rare tumor" networks** are coordinated by the Neuro-oncology team. The first concerns **oligodendrogliomas** (**POLA** network) and is coordinated by **Jean-Yves Delattre**. Thanks to **high-throughput sequencing**, research has made **great advances in our understanding of the development of tumors and the identification of their causes**. Working on the **largest collection of oligodendrogliomas ever studied** by **high-throughput technology**, the team of **Marc Sanson,** in collaboration with the group of Richard Houlston in London and the team of **Emmanuelle Huillard, recipient of the ATIP/Avenir grant** (Inserm and CNRS), confirmed the implication of several genes and identified **new genes**, including ***TCF12*** in the development of these **oligodendrogliomas**[54]. A mutation in the ***TCF12*** gene compromises **transcriptional activity** and is **associated with a more aggressive form of the tumor**. **Sixty percent** of **oligodendrogliomas** have a mutation in another gene, **CIC**, which is a transcriptional repressor. **Vincent Gleize** in **Marc Sanson**'s team has just deciphered the **mechanism of action** of this gene in tumor cells[55]. Identifying the mechanism means identifying potential therapeutic targets.

The other "rare tumors" network concerns **primary brain lymphomas** (**LOC** network) and is coordinated by **Khe Hoang-Xuan**. The team of Khe Hoang-Xuan showed for the first time **specific mutations** in these **rare tumors**[56].

This opens perspectives for **targeted therapy**.

Develop personalized therapies

In collaboration with the team of Antonio Iavarone at Columbia University, the team of **Marc Sanson** characterized a cohort of gliomas carrying a **highly oncogenic fusion gene** and showed the patients with these tumors, although rare, can benefit from a **specific treatment**[57]. This preliminary study has led to a **clinical trial** coordinated by **Marc Sanson**, which will begin **nationally** next September then expand to the rest of **Europe**.

The aim of the Experimental Therapeutics platform **Gliotex**, supported by the **Association for Research on Cancer (ARC)** and directed by **Ahmed Idbaih**, is to develop **specific treatments** according to **the mutation profile of the tumor** using **cell cultures** and **grafts** in mice. The team has tested an i**nhibitor** targeting an oncogene, ***MDM2***, that is amplified in certain tumors. Cells containing this mutation respond selectively to this inhibitor. A **phase 1** trial with an **MDM2 inhibitor** was initiated following this study. This approach inspires hope in the long term of **personalized treatments for every patient** based on the **genetic profile** of his or her tumor.

4 EPILEPSIES

Epilepsy is one of the most frequent neurological diseases, affecting almost 1% of the population. An epileptic seizure is a very brief period of **abnormal electrical activity** in a **group of cortical neurons**. This electrical discharge can be circumscribed to a region of the cortex, focal epilepsy, or spread throughout the entire cortex, generalized epilepsy.

As with other brain diseases, researchers prefer to use the plural in reference to epilepsies defined by a variety of features that makes their classification complex: the **type of seizure** (tonic-clonic seizures with a phase of contractions and a phase of spasms-, absences in children, partial seizures, etc.), the **cause of the epilepsy** (tumor, infection, malformation, metabolism, genetics, etc.), and the association of **other neurological** signs, such as the profile of the electroencephalogram.

A third type of epilepsy in the population **resists medical treatment.** These forms of epilepsy constitute the **main target** of ICM researchers and clinicians.

Identify the responsible genes

The team of **Eric Leguern** and **Stéphanie Baulac** are interested in the **genetic** origins of epilepsies. Their aim is to **identify new genes** responsible for hereditary (genetically determined) epilepsies and to develop **experimental models** *in vitro* and *in vivo* in order to elucidate the **mechanisms** of epilepsy and **test new treatments** to improve care of the patients.

After the identification of a new gene, ***DEPDC5,*** associated with an **hereditary form** of focal epilepsy, the researchers discovered that in certain cases mutations in this gene also cause a **malformation of the cortex**[58]. This lesion might be due to a **somatic mutation** that occurs in brain cells during the life of the patient in ***DEPDC5*** **in addition to the mutation inherited** from the parents. These results are the first example of this type of **mechanism** being described in a focal epilepsy.

The team of **Eric Leguern** and **Stéphanie Baulac** identified another gene, ***FIG4,*** implicated in a **hereditary epilepsy associated with cortical malformations**[59]. **This gene** has already been **implicated in other pathologies, including** a **peripheral neuropathy (Charcot-Marie-Tooth disease)** and a malformation syndrome in newborns. The team showed that one of these three syndromes will develop, depending on the **localization and type of the mutation**.

Caroline Nava and **Christel Depienne**, in collaboration with the **electrophysiology platform** and a **European consortium**, recently discovered that ***de novo*** **mutations,** not present in the parents, of the ***HCN1*** **gene** are implicated in **Dravet syndrome**, a **severe epilepsy** in newborns[60]. At first, these children have recurrent febrile convulsions that resist treatment followed by epileptic seizures that also resist treatment. Towards their second year of life, these infants develop **cognitive disorders**. The **HCN1** gene is very interesting because it encodes a protein that contributes to the

formation of a **neural channel, the** HCN channel,which controls **rhythmic activity of neurons**. This discovery confirms the **crucial role of HCN channels** in the mechanisms implicated in human epilepsies. The discovery of a **new genetic cause** of this disease will additionally help refine **diagnosis.**

Via their participation in the **EuroEPINOMICS** consortium, the team of Eric Leguern and Stéphanie Baulac, associated with **Christel Depienne,** also identified another gene **implicated in severe epileptic encephalopathies, KCNA2**[61].

The team is also interested in the **pathogenic mechanisms** caused by mutations in the ***Lgi1*** gene. In order to **determine the population of neurons implicated** in focal familial epilepsies caused by mutations in ***Lgi1,*** the researchers developed a **mouse model** in which the gene could be mutated **specifically** in certain subpopulations of neurons. They could thus show that epilepsy is linked to **excitatory glutamatergic neurons** (neurons that use glutamate as a neurotransmitter)[62] .

Study the dynamics of the brain

The team of **Stéphane Charpier** studies the **dynamics of activity in neuronal networks in the brain** and the **excitability of individual neurons**. Information is encoded in the **electrical activity** of the neurons. Each neuron receives, processes, and sends electrical messages to other neurons. At this level, certain keys to epilepsy can be found. **Abnormal electrical activity** prevents information processing in epilepsy, and thus electrophysiological probing can provide keys to understanding the disease. The team of **Stéphane Charpier** uses electrophysiology to study the electrical activity of the brain on all spatial scales and in real time, from global electrical activity measured on the **surface with** EEG, to the **intracellular** activity of **individual neurons**. In close interaction with **neurologists**, this team explores both focal and generalized epilepsies, notably childhood absence epilepsies. They showed that there are **zones of high frequency** activity in the **epileptogenic regions** of the brains of patients with focal epilepsies. These rapid rhythms thus become electrophysiological markers of an epileptogenic region because they are **specific to the region in which the seizure begins** and are recorded before the seizure occurs[63]. This discovery is important because it provides a link to the **mechanisms upstream of the epileptic seizure, which could help researchers understand** how to **predict** and **anticipate seizures**.

Understand the mechanisms

The team of **Richard Miles** works on **dysfunctions related to focal epilepsies,**

those with a localized epileptic center. The focus is often situated in the **hippocampus**, a region hidden deep in the temporal cortex. **Richard Miles** and his collaborators seek to understand how **anomalies of synaptic signaling** between neurons can lead to epileptic activity.

Brain cancers, or **gliomas**, are often associated with epilepsy. In the **cortical area around the tumor**, researchers detected differences in the expression of **chloride transporters**[64] that modify synaptic signaling in the hippocampus of patients with focal epilepsies.

The team of Richard Miles developed a technique to **maintain slices of brain tissues** from patients with **focal epilepsy of the temporal lobe in culture**[65]. These human tissues conserve their **morphological characteristics** and their **epileptic activity** for 4 to 6 weeks. The maintenance in culture of these cells enables researchers to **transfect them** with viral vectors that express **probes of neuronal activity** or **test** the long term **effect of treatments**.

The team of **Richard Miles** also explores the **sclerosis** or **neuronal death** that causes focal epilepsies. They work in particular on the **role of lipids in neuronal death, including cholesterol**. In collaboration with **Nathalie Cartier**, the team of **Richard Miles** showed that **by inhibiting the extrusion of cholesterol from neurons**, **epileptic activity** and **neuronal death** increase in the hippocampus of mice[66].

5 COGNITION, BEHAVIOR, AND PSYCHIATRIC DISEASES

The brain is a astounding machine for **processing information**, an activity that underlies **cognition** (perception, reflection, memorization, decisions, speaking, etc.), from which emerges **consciousness** of **ourselves** and the **world** around us.

The mechanisms that underlie **mental functions**, whether **motor**, **intellectual**, or emotional, are at the origin of **human behaviors**. Why do we do what we do? What are the bases of normal or altered **motivation**? How do our **intentions** produce behaviors? How do our **intellectual and emotional functions** combine to **determine our actions**? How do we become **conscious of the world** around us and **ourselves**? What is consciousness? How do we communicate with **language**?

To answer these questions, ICM researchers study how neuronal networks perform **information processing** using a variety of tools, from the most subtle **clinical analyses** to **electrophysiological examination**, as well as **neuroimaging**. The data obtained are essential for understanding and better treating the **functions altered** in patients, whether they have **intellectual** (memory loss, language disorders, perceptions, notably visual, etc.) or **psychiatric disorders** (depression, anxiety, schizophrenia, autism, obsessive compulsive disorders, etc.).

1. Emotions, depression, and social interactions

The team of **Nathalie George and Philippe Fossati** is interested in the mechanisms by which **social processes** activate and regulate the **emotional brain**.

Thanks to the high temporal resolution of **magnetoenphalography** (MEG), which operates on the order of the millisecond, and electroencephalography (EEG), the team of **Nathalie George and Philippe Fossati** showed an **early perceptional bias** in **anxious subjects**[67]. These people are **hypervigilant** and **react faster** than others when they are presented photographs of human faces showing fear or happiness, negative or positive stimuli. Anxiety is **not simply felt,** it also has an **impact** on the **way the subjects perceive the world**. This study opens **new avenues** to the **understanding of anxiety**.

A study of **epileptic subjects** treated by electrodes implanted in their brain showed that a region implicated in emotions, the **amygdala**, is activated **early** when the patients look at **photographs of faces**[68]. These experiments help understand the **speed of**

information processing by the "**emotional brain**."

A meta-analysis performed by the team demonstrated the contribution of a region of the brain, the **anterior cingulate cortex**, to **social distress related to exclusion**. The same region is dysfunctional in **depressed patients**[69]. This study underlines the importance of social exclusion in the **physiopathology of depression** and will help define **new therapeutic targets for this disorder**.

Bruno Millet, who joined the team of **Nathalie George and Philippe Fossati** in 2014, is specialized in deep brain and magnetic transcranial stimulation, both of which he uses to treat depression that is resistant to pharmacological treatments[70] and obsessive compulsive disorders[71].

2. Autism

The team of **Nathalie Georges and Philippe Fossati** showed that being imitated improved the **social behavior** of **autistic patients** by modulating specific regions of the brain, notably a region called the **insula,** which plays a central role in **social behaviors** and the **development of emotions.**[72] These results open new perspectives for the treatment of **autism.**

3. Motivation and decision making

The team of **Mathias Pessiglione, Sébastien Bouret, and Jean Daunizeau** is interested in **apathy** and thus in the processes involved in human **motivation**.

Treatments for apathy target **dopaminergic and noradrenergic** (use noradrenaline as their neurotransmitter) **neurons**, which play an important role in **motivation**. To **determine the respective roles** of these two types of neurons, the team of **Sébastien Bouret** performed a **behavioral study**. **Motivation determines many aspects of our behavior, including the choice of our actions** and the **mobilization of the energy needed for these actions**. The researchers showed that **dopaminergic neurons** intervene in the **decision to act**, whereas **noradrenergic neurons** contribute to the **mobilization of the energy** needed to perform the action[73]. This is a **major** discovery because one or the other of these **two aspects of a behavior** can be **preferentially targeted** in **apathetic patients**.

The team of **Mathias Pessiglione, Sébastien Bouret, and Jean Daunizeau** demonstrated the **effect of context** on our value judgements[74]. The region of the brain responsible for the attribution of value is the **orbito-medial prefrontal cortex, which has increased activation** when something pleases us. An experiment in healthy subjects showed that when background music is agreeable, subjects better appreciate a painting they are shown. Thus pleasant music increases the activity of the **orbito-medial prefrontal cortex**, predisposing the person to appreciate the painting presented. **Judgements** are therefore **influenced by context**. By affecting the state of our orbito-medial cortex, the **context** will influence our

value judgements. The team was able to **distinguish the main properties** of the **system for attributing values**, which is conserved in primates. This also leads to an increasingly precise **cartography** of the **different regions of the brain** implicated in **motivation** and **decision-making**.

Of course, motivation is not localized in a region of the brain but emerges from **cooperation among several regions organized in networks**. The researchers thus **invented a mathematical method** to describe the **way that the activity of the brain systems are coordinated to control behavior**[75]. Applied to recordings of brain activity of healthy subjects making a series of decisions, this method will allow us to both understand how pertinent **information** is processed and transformed through the **neuronal networks** to produce a **behavioral response** and also to predict the kinds of functional deficits that are induced by lesions of the brain.

The team of **Paolo Bartolomeo, Laurent Cohen**, **and Lionel Naccache** (see **Language and mechanisms of consciousness**) is interested in the way we attribute **values and meanings to our choices**. The researchers asked healthy subjects to evaluate vacation sites then asked them to choose among the sites they preferred. Finally, they were required to reconsider the sites. Subjects had a tendency to prefer the sites they had already chosen and showed less preference towards those that they had eliminated. This demonstrated that the human beings are in **internal conflict with themselves;** this is called **cognitive dissonance**, and the best way to resolve this conflict is to **change our values**. To relieve internal conflicts and obtain **coherence between our values and our actions**, we tend to give **more value to our choices**. Thus **our values influence our actions**, but, **our actions also influence our values**. We thus have a **mechanism for internal coherence that is related to the memory of our actions**[76].

Thanks to the **PRISME** platform (see Platforms), the team **of Bruno Dubois and Richard Lévy** (see **Creativity and reasoning**) is developing an **innovative project**, **EcoCapture**, for an **ecological study** of **apathy**. Using body sensors, **the behavior** of **apathetic patients** will be analyzed in a semi-ecological situation. This project will be carried out **in collaboration** with the company **ERDF**. The aim is to use the data obtained to allow **patients suffering from a neurological deficit,** who have disorders of decision-making or behavior, to go back to work.

4. Creativity and reasoning

Bruno Dubois and Richard Lévy, in their laboratory **FRONTlab**, are interested in the **mental functions** of the **frontal lobes**. These functions construct and control our most **complex behaviors,** such as **decision-making**, **creativity** and **analogical reasoning**, the generation of **voluntary behaviors,** and the organization of **language.**

In studies of patients with lesions of the frontal lobe, the team of **Bruno Dubois and Richard Lévy** showed that **cognitive control** in the **frontal lobe** is organized **hierarchically;** a cascade of controls is exerted from anterior regions towards posterior regions[77]. The researchers also related the **capacity for analogical reasoning** with different structures of the **prefrontal cortex** and showed that **variability** in these capacities is **correlated** with the **volume of certain subregions of the frontal lobe**[78]. The researchers in this team showed that **categorization** involves **distinct functions,** both the **capacity to collect information** and the **capacity to abstract**. These **two mechanisms** depend on **specific regions** in the **frontal lobes**[79].

Creativity is greatly **affected** in patients with **lesions of the frontal lobe**, contrary to what has been published in the literature that suggests that this type of lesion increased creativity. It is thus due to **control** and the **capacity to elaborate new rules** that creativity can be expressed[80].

These discoveries show the **heterogeneity of the frontal lobe.** The aim of the team is to **dissect the multiple processes** involved in **creativity**, their interrelationship, and the underlying brain **regions**.

In the team of **Bruno Dubois and Richard Lévy**, **Antoni Valero-Cabré**, in collaboration with the **team of Paolo Bartolomeo** (see Language and Mechanisms of consciousness), uses **non-invasive stimulation** to **modify the oscillatory activity of the frontal lobe** and **improve visio-spatial cognition** in patients with brain lesions. Studies are underway at present in patients with progressive supranuclear palsy (PSP).

5. Language and networks

In the team of **Bruno Dubois and Richard Lévy**, **Marc Teichman** identified a **new network** linking **Broca's area with the basal ganglia**, a network that is critical for the **syntactic organization of language**[81].

Using diffusion MRI to **trace white matter fibers connecting different regions of the brain**, **the team of Paolo Bartolomeo, Laurent Cohen, and Lionel Naccache** (see Mechanisms of consciousness) demonstrated the existence of **privileged connections** between the **region of letter recognition** and **language areas**[82]. The same **small region of the visual cortex in the left hemisphere** enables us to identify the letters we see, thus the anatomy of communication pathways in the brain is key for determining brain functions.

6. Mechanisms of consciousness

Paolo Bartolomeo, Laurent Cohen, and Lionel Naccache seek in their patients, answers to basic questions not only concerning **visual attention** and l**anguage**, but also **consciousness**. They explore the **brain mechanisms and the psychological properties of conscious mental operations**.

Using **EEG**, they recently identified **neuro-markers of levels of consciousness** in **patients incapable of communicating**. Approximately **100 brain signatures** of consciousness have been identified, which have permitted distinguishing a patient in a vegetative state from a patient with minimal consciousness[83]. An algorithm integrating all these signatures makes it possible not only to make a **diagnosis**, but also to **predict the evolution** of the patient. This is the first time that an **algorithm** has had **prognostic value**. These studies aim at developing new tools for diagnosing the level of consciousness of patients who cannot communicate.

The researchers also detected different **brain signatures** of the **processing of the meaning of words.** Certain of these signatures are not conscious and can appear if the patient is in a coma, others are **specific to a state of consciousness**[84].

Consciousness is not related to the function of a single brain region but to **communication between regions**. One of the many signatures of the level of consciousness is the **way in which regions communicate with each other**[85]. In 2014, **Lionel Naccache** and **Laurent Cohen** applied for a **patent** for this discovery.

The group of **Lionel Naccache** recently showed in a collaboration why we are **not conscious of external noises during sleep**[86]. They found that even if sounds penetrate the auditory cortex, sleep disturbs the capacity of the brain to anticipate the sounds.

The team also studies the question of **conscious perception**. The team showed that **unconscious treatment** of sounds takes place in auditory areas of the temporal lobe, but that **consciousness** of the regularity of sounds requires **communication between different regions of the brain** including the **frontal lobe**[87]. Another study concerned processing **of the meaning of words** in conscious subjects[88]. The researchers have also shown that when a person is asked to pay attention to something, the person becomes conscious of what was presented just before. **Conscious perception** is thus **restrospective**[89].

The team of **Stéphane Charpier** (see **Epilepsies**) studies the **mechanisms** underlying consciousness. In a normal brain, there is a **constant background activity** in **each individual neuron** called **synaptic noise**. In an experimental

model, the team of **Stéphane Charpier** completely **suppressed this activity** in the brain, which remains normal from a connectivity point of view. The brain is then in an **isoelectric, electrically neutral state, and its response to a given stimulation is always identical**. Consequently, the **endogenous activity** of the brain (produced by the brain) **creates variability in the way neurons respond to stimulations**[90]. This background brain activity at the origin of the **variability of neuronal responses** to exogenous **stimulations** (outside the brain) is probably related to the **mechanisms of consciousness**. What creates the significance of a stimulation is both the **stimulation itself** and the **endogenous activity of the brain**. This discovery has led the team of **Stéphane Charpier** to begin a **study of patients in deep comas**.

7. Clinical cases and compensatory strategies of the brain

The study of **patients** with **neurological dysfunctions** permits researchers to understand the basic **mechanisms of brain function** and adapt diagnoses. Following a **stroke** in the right hemisphere, certain patients act as if the left side of the world no longer exists; they suffer from **unilateral spatial neglect**. Some of these patients recover with time, but spontaneous improvement of neglect is far from the rule; at least one third of patients in the acute phase of this disorder will continue to present signs more than a year after their lesion. By following the evolution of **45 patients** with this pathology by diffusion MRI, the team of **Paolo Bartolomeo** showed that the **neglect persists** when it is associated with **destruction of the fibers of the *corpus callosum*** that mediate **dialogue between the two brain hemispheres**[91]. If the fibers aren't affected, the two hemispheres can compensate in part for one another thanks to mechanisms of **brain plasticity**, which are not well known. The **identification of factors that predict the persistence of neglect is an major clinical challenge because this identification would enable patients to take advantage of a program of reeducation adapted to the disorder, which can become chronic**.

Another clinical case concerns an **extremely rare and formidable genetic disease, Ondine syndrome,** which **prevents patients from breathing** because of a severe dysfunction of the part of the brainstem responsible for **automatic respiration**. In the most severe forms, the patients die asphyxiated as soon as they fall asleep. Current treatment consists of an **external ventilator** that patients use when they sleep, even during a short nap. When they are awake, they must **breathe voluntarily**. The team of **Lionel Naccache, Laurent Cohen, and Paolo Bartolomeo** performed a study in a young woman awake and suffering from this syndrome and compared brain activity when she either breathed voluntarily or with external ventilation. **The researchers showed that she was more effective in carrying out intellectual activities with assisted respiration. Her cortex was available for other activities when it no longer had to manage her respiration** [92].

The team of **Lionel Naccache, Laurent Cohen, and Paolo Bartolomeo** also recently demonstrated the existence of a **new pathway for the treatment of visual information by the brain**[93].The posterior part of the ***corpus callosum*** **transfers information between the two hemispheres of the brain**. A patient with lesions at this level developed the **capacity** to transfer information through the **anterior region of the brain, the** frontal lobe, which is not normally implicated in this type of activity.

8. Obsessive compulsive disorders

The team of **Luc Mallet** is specialized in the study of the basal ganglia, a group of deep subcortical regions of the brain. The team showed the implication of one of these regions, the **subthalamic nucleus**, in a pathological behavior, **obsessive compulsive disorder** (OCD)[94]. Patients with this disorder suffer notably from the need to reassure themselves repeatedly and exaggeratedly with respect to their acts ("Did I turn off the gas?" etc...).The results of the team confirmed that this region is a good target for **therapeutic stimulation**. With the **recent recruitment of the researcher Eric Burguière**, the team set up a translational approach using experimental models of this pathology, in which they can use **optogenetics to specifically modulate the activity of neurons implicated in the compulsive behaviors**. The objective is to better **identify the brain circuits** at the origin of the **symptoms of the OCD** and better understand the origin and the functional relationship between compulsions and obsessions. These complementary approaches allow adapting **different therapeutic strategies** according to the neurobiological origin of this disorder, which is inaccessible to classical clinical approaches.

Overall, the aim of these **translational approaches** is to better understand the mechanism of action of brain stimulation and optimize the safety of this procedure in patients. At the therapeutic level, the team, a recognized leader in the field, recently completed a comparative study of stimulation targets in patients with severe OCDs and began a clinical study of severe cocaine addiction.

9. Schizophrenia

The team of **Philippe Ravassard and Rolando Meloni** studies **schizophrenia**, a severe and disabling mental disease that affects about 1% of the population. The team has recently identified a **new therapeutic target** for the treatment of this disease[95], the receptor **Gpr88**, present on the surface of cells and localized exclusively in the brain. The researchers showed that **local inactivation** of Gpr88 in the ***nucleus accumbens***, situated in the ventral striatum, a structure the function of which is altered in schizophrenia, **normalizes cognitive behaviors** in a model of schizophrenia. These behaviors are **resistant to treatments commonly used in patients**. This study represents an **important advance** in the validation of a new **therapeutic target** and an innovative experimental approach. For these studies, Manuela Ingallinessi was awarded the **Louis FOREST** Life Sciences **thesis prize** offered by the **Chancellery** of the Universities of Paris.

6 MODELING

Different imaging techniques (EEG, MEG, MRI) are complementary, but their **integration** is difficult because of their heterogeneity. Integration is a problem for all data obtained in patients. One of the challenges for the team of **Olivier Colliot and Didier Dormont** is to **combine this varied and complex data in a form that is useful for research**, a contemporary problem typical of "**Big Data**" produced by the new digital technologies. The ARAMIS team was created in 2013. Because of its unique thematic situation in the Institute, it is a joint team with Inria (National Institute for Research in Informatics and Applied Mathematics). More generally, the aim of the team is to develop **better methods of image analysis** to **characterize the numerous neurodegenerative diseases** (Alzheimer's disease, frontotemporal dementia, etc.), **epilepsy**, and **cerebrovascular pathologies** (vascular dementia, stroke).

With new **image analysis technology** developed by the team, the researchers were able **to measure the effect of a pharmacological agent** on the size of the hippocampus in patients with **Alzheimer's disease** in collaboration with the team of **Bruno Dubois**[96]. This is the first time that this technology was used in a clinical study of this magnitude (see Alzheimer's disease).

The researchers also developed a **model that enables understanding of the organization of the brain by graph theory**[97]. This model provides neuroscience researchers with practical information for the **study of brain networks**.

In collaboration with the team of **Claire Wyart**, **Fabrizio De Vico Fallani** developed a **mathematical model** to **characterize neuronal networks in the** zebrafish[98] (see Basic mechanisms). This effective method is useful for studying functional abnormalities in the nervous system during development or under pathological conditions.

A new statistical method was developed to **analyze grey matter and white matter tracts** simultaneously **in the brain**. With this tool, **variations in connectivity as a function of the morphology of the brain can be visualized**. In collaboration with the team of **Marie Vidailhet and Stéphane Lehéricy**, the researchers studied patients with **Gilles de la Tourette syndrome and confirmed in vivo the presence of abnormal connections between the central grey matter and the cortex**[99] (see Parkinson's disease and other pathologies that cause motor handicaps).

7 RARE DISEASES

Several teams in the ICM are mobilized in the fight against **rare neurodegenerative diseases** such as **Huntington disease**, **cerebellar ataxias**, **spastic paraplegias**, **channelopathies,** and **alternating hemiplegia of childhood**.

1. Huntington disease

Huntington disease is a **neurodegenerative disease** linked to a **genetic mutation**. The signs of the diseases often develop in people between 30 and 50 years old with the appearance of progressive **motor, behavioral, and psychiatric disorders**, which lead to dependency and affect the rest of the family. , Even though the genetic anomaly was discovered in 1993, there is still no treatment that can change the course of the disease. In the team of **Alexis Brice**, **Fanny Mochel** and **Alexandra Dürr** have recently demonstrated the **therapeutic potential** of a synthetic oil, **triheptanoin**.

A study on **10 patients with Huntington disease** showed that this **treatment improves brain energy metabolism, which is abnormal in patients and contributes to the progression of their symptoms**[100]. This result represents a major advance for the discovery of **new treatments and a license was obtained from ULTRAGENYX, the company that commercializes triheptanoin**. On the basis of these results, a one-year clinical study has been initiated in France and the Netherlands on about one hundred patients using clinical parameters and imaging as evaluation criteria.

2. Cerebellar ataxias

Research on the **spinocerebellar ataxias (SCA),** which interests the team of **Alexis Brice**, has made major advances this year. A **neurodegenerative disease of the cerebellum that is characterized by specific motor symptoms such as balance disorders, SCA can be very disabling**. SCA are caused in half of cases by mutations in about thirty genes, but many cases cannot yet be explained.

The advances are the result of ambitious **international projects** to which the team of **Alexis Brice** contributes. **Alexandra Dürr, Giovanni Stevanin**, and their colleagues of the international **SPATAX** network helped **identify two new genes** that are responsible for **autosomal dominant forms of spinocerebellar ataxia when mutated**.

One of these genes, ***ELOVL5/SCA38***[101], encodes an enzyme involved in lipid metabolism, opening the way for a **diagnosis by assay of polyunsaturated fatty acids** in the **plasma** of patients. The second gene, ***TMEM240/SCA21,***[102]

encodes an membrane protein that is abundant in synapses, though its role is unknown. Mutations in this gene are associated with complex phenotypes including **cognitive dysfunction** or slowly evolving **mental retardation**. The discovery of these genes represents hope for the identification of **new potential therapeutic targets**.

In a genetic study of **144 patients** with **congenital ataxia**, **Alexandra Dürr** and her collaborators also showed that different mutations in the ***GRID2*** gene, which encodes a glutamate receptor, are implicated in the development of more or less severe **cerebellar ataxias**[103]. Finally, a gene responsible for a severe form of the disease **associating ataxia and dystonia** was identified in one family by the group of **Giovanni Stevanin** in collaboration with a team of the AFM[104]. The protein encoded by this gene interacts with a major gene implicated in dystonias, establishing a link between these rare diseases.

In a **vast international study** associating 12 countries (**EUROSCA and Giovanni Stevanin**, the analysis of genetic data from the **largest cohort ever studied in the field of SCA** (1931 patients), a correlation was discovered between the **age at which SCA appears** and a trinucleotide (CAG) repeat in different genes[105]. This discovery is a step further in our **understanding of SCA**. The identification of **genes** that can **modulate the severity of the pathology** (age of symptoms onset, associated signs, rate of deterioration, etc.) could permit the application of **alternative therapeutic strategies** aimed at **slowing the progression** of the disease. In a large cohort of patients with SCA (types 1, 2, 3 and 4), **Fanny Mochel** and her collaborators identified early **brain energy dysfunctions** by MRI spectroscopy that were correlated with clinical parameters[106]. The analysis of an experimental model and the brains of patients with a severe form of ataxia associated with retinal degeneration enabled the group of **Annie Sittler** to show that the pathogenesis could be explained in part by an **alteration in the pathways involved in the degradation/recycling of proteins**[107].

3. Spastic paraplegias

Hereditary spastic paraplegias are clinically and genetically **heterogeneous neurological disorders** that affect people of all ages. The clinical signs appear progressively and are characterized by severely **disabling gait disorders** due to stiffness, or spasticity, of the lower limbs.
The team of **Alexis Brice** participated in an **international study** that led to the identification of **18 new genes** implicated in **hereditary spastic paraplegias**

(HSP)[108]. This study is based on the initial genetic analysis of **55 families** from several countries and **200 families** from the **SPATAX** network as well as models of the effects of the mutations in the zebrafish and a bioinformatics analysis that showed **interconnections** between these genes and more than 500 other genes. This study brings the number of genes potentially mutated in HSPs to 74. These discoveries will lead to the identification of **new cellular mechanisms** implicated in the development of the disease and new potential **therapeutic targets**.

Frédéric Darios, Giovanni Stevanin, and their collaborators discovered a **new gene, REEP2,** implicated in HSP. This gene encodes a protein in the endoplasmic reticulum, a network of intracellular membranes with various functions including the synthesis of proteins and lipids and the production of membranes. The REEP2 gene increases the number of genes implicated in HSP in relation to the functions of the endoplasmic reticulum, underlining the importance of this intracellular network. The aim of the researchers is to better understand the **correlation between the anomalies of the endoplasmic reticulum and neurodegeneration** in order to develop therapeutic strategies that could be common to several forms of HSP.

4. Diseases of neuromuscular excitability

Congenital myasthenic syndromes are a group of **genetic disorders** that disrupt the functioning of the **neuromuscular junction, the zone of communication between the motor nerve that commands a movement and the muscle on which it acts**. These syndromes are characterized by muscle weakness that affects, depending on the form, the trunk, the limbs, or the face, notably with ocular problems. The most severe forms cause motor or respiratory deficits requiring mechanical ventilation.

The team of **Sophie Nicole and Bertrand Fontaine** has shown that mutations in the ***agrin*** gene are **responsible** for a form of **congenital myasthenic syndrome** characterized by weakness and atrophy of the distal muscles[109]. **Agrin** plays an important role in the f**ormation** and **maintenance** of the neuromuscular junction. This discovery has **major implications** for the **care of patients**, already allowing a **molecular diagnosis** and the possibility of **new therapeutic approaches**. This publication also opens the way to more basic research on **the mechanisms of action of agrin** in the pre- and postsynaptic compartments upstream and downstream of the synapse.

Muscle channelopathies constitute another heterogeneous group of **genetic disorders** that are associated with **mutations in genes** encoding **ion channels**. The ion channels that are altered in muscular channelopathies are voltage-dependent channels, channels that are sensitive to variations in membrane potential. Voltage-dependent ion channels play a determining role in the contraction and relaxation of muscles. **Muscle channelopathies** are characterized by attacks of **muscle stiffness** (non-dystrophic motonia) or **paralysis.** The **diagnosis is** complicated by

the periodic nature of the symptoms, but is **important for the prevention of the disease** because certain factors can worsen the attacks. The team has also shown that **mutations in the gene encoding the muscle chloride channel**, at the origin of a form of congenital motonia, can modify the phenotype of motonia caused by mutations in the muscle sodium channel.[110]

5. Alternating hemiplegia of childhood

The team of **Sophie Nicole and Bertrand Fontaine** is interested in another rare disease, **alternating hemiplegia of childhood**. This neurodevelopmental disease is characterized by periodic hemiplegia and paroxystic disorders, persistent developmental retardation, and a cognitive deficit. The disease appears before 18 months of age. The earliest sign is the occurrence of repeated episodes of hemiplegia lasting a few minutes or several days, affecting one side or the other. An **international collaboration** among researchers, clinicians, and patient associations has led to the identification of mutations in the ***ATP1A3*** **gene** responsible for the disease[111]. This gene, mutated in 75% of cases of alternating hemiplegia of childhood, encodes the alpha subunit of a sodium/potassium pump expressed in neurons, which plays a **major role** in the **regulation of neuronal excitability** and is also responsible for rapid onset **dystonia parkinsonism**[112]. In collaboration with the team of **Marie Vidailhet and Stéphane Lehéricy**, the team of **Sophie Nicole and Bertrand Fontaine** showed that a mutation in the ***ATP1A3*** gene is not the only determinant of clinical signs of the disease and can lead to dystonia parkinsonism or alternating hemiplegia of childhood in different individuals in the same family. This implies that in addition to genetic factors, **epigenetic and environmental factors** play an essential role in the **expression of the clinical symptoms**[113]. Altogether, these discoveries have led to both the development of a **genetic diagnostic tool** for alternating hemiplegia of childhood and also to the possibility of **new therapeutic strategies**.

The researchers also showed that a special diet decreased the frequency and the severity of the paroxysmal attacks associated with the disease[114].

These results are very encouraging and open the way to other energy-related therapeutic approaches like those of **Emmanuel Flamand-Roze** in the team of **Marie Vidailhet** and **Fanny Mochel** in the team of **Alexis Brice**.

8 BASIC MECHANISMS UNDERLYING THE DEVELOPMENT AND FUNCTION OF THE NERVOUS SYSTEM

Understanding the basic mechanisms of the development and functioning of and the prevention of the appearance of neurological diseases.

1. Glial cell development

The research of the team of **Jean-Léon Thomas and Bernard Zalc** concerns the development of **glial cells**. Glial cells **assist** the **neurons** of the central nervous system (CNS) structurally and functionally and are extremely heterogeneous. The most immature are the **neural stem cells** that produce neurons, astrocytes, and oligodendrocytes, the **myelinating cells** of the central nervous system. Astrocytes and **oligodendrocytes** are differentiated cells derived from neural stem cells. A third population of glial cells in the central nervous system consists of **microglial cells**, which are non-neural in origin and infiltrate into brain tissue.

The aim of the team is twofold: on the one hand, **identify molecules necessary for the production, maintenance, and differentiation** of stem cells and glial cells, and on the other hand, **test the therapeutic potential** of these **molecules** in models of developmental and neurodegenerative diseases and during aging.

Michel Mallat and **Bernard Zalc** studied the process of de-/remyelination of the **optic nerve** in **Xenopus** and showed that the **response of microglia** to **demyelination** is due to **oligodendrocyte precursors** residing in the nerve, which are responsible for **remyelination**[115].

Carlos Parras has shown the contribution of the transcription factors **Olig2** and **Mash1** to the **development** of oligodendrocytes and the process of **demyelination**[116,117] .

Charles-Félix Calvo has established the **importance of a molecule, VEGFR3**, in the **activation of neural stem cells and consequently the production of new neurons**[118]. This **molecule is the receptor for a growth factor (VEGF)**. Throughout life, an adult is able to generate new neurons from neural stem cells in order to maintain cognitive function. This **neurogenesis** takes place in the **hippocampus**, a structure of the brain that plays a central role in **memory**. Experiments *in vivo* in a mouse model confirm that **VEGFR3 signaling specifically activates neural stem cells** in the brain. It not only participates in but is absolutely necessary for the "awakening" of the neuronal stem cells and thus the **creation of new neurons** without provoking vascular proliferation. These results, reproduced **in vitro** in human cells, bring **new hope** for the **development of therapies** that

improve the production of neurons to **alleviate cognitive decline** in persons with **Alzheimer's disease**. In effect, the **decline of the mechanism of neurogenesis** during aging could be implicated in the **emergence of neurodegenerative pathologies** such as Alzheimer's disease.

The team has **also** collaborated in several studies by partners of Jean-Léon Thomas, at Yale University, on the **epigenetic control of embryonic neurogenesis**[119,120,121] and the **function of VEGFR3 signaling**[122,123].

2. Cortical networks

The **cerebral cortex** is the structure of the brain where **sensory information** is **processed, stored, and used** to **generate elaborate behaviors** and for **cognitive functions**. The coordinated activity of a myriad of different neurons connected in **complex functional networks** enables the brain to accomplish this. The **activity of cortical neurons**, brain cells responsible for memory and consciousness, requires the **precise integration of nerve impulses that they receive**, excitatory or inhibitory. **Dysfunction** of these neurons causes **neurological and psychiatric disorders, including** epilepsy, autism, schizophrenia (see Cognition and psychiatric disorders). Understanding how the cortical neurons integrate the multitude of signals they receive is the first step in the detection of anomalies and eventually in the prevention of neurological diseases. The studies of the team of **Alberto Bacci** concern the **regulation of neuronal microcircuits in the healthy brain** at the origin of normal cortical function. The researchers recently identified a **process of auto-modulation** of the principle cortical neurons, pyramidal neurons, by a retrograde mechanism that **affects their own electrical activity**[124]. The **excitation/inhibition (E/I) ratio** of these neurons must remain constant in time and in intensity to regulate complex cognitive functions and **prevent the appearance of neurological and psychiatric diseases**. The pyramidal neurons can **block the E/I ratio** by increasing the intensity of their own inhibition by specific **interneurons,** small neurons that project locally, characterized by the expression of a molecule called parvalbumin.

These studies reveal the existence of a **selective inhibitory mechanism of neuronal plasticity by interneurons**. They also help to better understand the regulation of the neuronal circuits that underlie cortical functions. The **modulation of electrical signals** can play a **crucial role in cortical activity** and the **treatment and integration of sensory information**.

3. Locomotor circuits

In the **spinal cord**, the **central pattern generator for walking** allows one to move naturally without having to think. Nevertheless, when there is a **medullary lesion**, new means of **reactivating the spinal circuits** (circuits of the spinal cord) must be found. The team of **Claire Wyart, Pierre-Luc Bardet, and Hugues Pascal Moussellard** seeks to understand how **spinal cord circuits** are **recruited** during **locomotion**, how they **develop,** and how they can be **stimulated** or reactivated when lesioned.

In order to study the **morphology and the role of genetically identified neurons** in vivo, this team makes use of the **transparency of the zebrafish**. In particular, the team studies the **role of local sensory information** that **communicates with spinal circuits** about the state of muscle contraction and **posture** during a **movement**. The group has characterized a **new sensorimotor loop** in the spinal cord **conserved** across **vertebrate species**[125]. The implicated sensory neurons are localized at the level of the **central canal of the spinal cord** and contact the cerebrospinal fluid. When they are activated, either by a chemical or mechanical stimulus, they send **information** to other **neurons involved in locomotion**. This previously unknown neuronal pathway, conserved among vertebrates, links **the internal state of a person**, via the cerebrospinal fluid, with the **central pattern generator for walking**. This discovery opens a new field of investigation on the possibilities of **modulating pharmacologically** the motor circuits of the spinal cord in case of a **lesion** or a **neurodegenerative disease**.

In collaboration with **Fabrizio De Vico Fallani** and **Mario Chavez** of the ARAMIS team of **Olivier Colliot and Didier Dormont**, the researchers have developed a **mathematical model** to characterize the connectivity of motor networks in the zebrafish[126] (see Modeling).

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GLOSSARY

Axon: nerve fiber conducting electric signals from the neuron's cell body towards its target to transmit the signals at synaptic terminals.

Basal ganglia: grey matter (composed of neuronal cell bodies) situated deep in the brain, which intervenes in particular in the control of movement and voluntary movements through interactions with cortical areas.

Brainstem: part of the brain situated between the brain hemispheres and the spinal cord. It controls vital functions including swallowing, respiration, cardiac rhythm, and wakefulness, and contains the motor and sensory nuclei of the head and the neck.

Central nervous system: composed of the brain and the spinal cord.

Cerebellum: located behind the brainstem. It is implicated in the control of balance and the coordination of movements.

Cerebrospinal fluid: liquid that circulates in the brain. It transmits nutrients to nerve cells and eliminates debris.

Cortex: the outermost part of the brain, also called grey matter. Part of the information transmitted by the neurons arrives and leaves at the level of the cortex.

Dendrites: Nerve fibers that receive electrical messages sent by other neurons to transmit them to the cell body.

DNA: molecule present in all cells that contains the information needed for the development and the functioning of living beings. It is the molecule that contains genetic information.

Gene: sequence of DNA containing the code for the production of one or more proteins (or regulation of protein expression level).

Genotype: the collection of genes of an individual.

Glial cells: cells that form the environment of the neurons. These include several subtypes. Oligodendrocytes produce myelin, astrocytes have protective and support functions and supply nutrients and oxygen, and microglial cells eliminate dead cells and fight against pathologies.

Hippocampus: structure of the brain that plays a central role in memory.

Medullar: concerning the spinal cord

Microglial cells: Immune cells responsible for the defense of the central nervous system.

Mutation: modification of genetic information causing a genetic disease.

Myelin: insulating and protective sheath around nerve fibers that facilitates transmission of signals in the nervous system

Neural stem cells or progenitors: cells that can differentiate into neurons or glial cells.

Neuron: nerve cell assuring the transmission of the nerve impulse. It is composed of receptive elements called dendrites, a cell body that integrates information,and an axon that transforms information in the form of an electric signal.

Neurotransmitter: chemical substance used by neurons to communicate with each other or another cell in the organism, such as a muscle cell

Oligodendrocyte: myelin producing cell.

Oncogene: a gene that favors development of a cancer when expressed.

Peripheral nervous system: part of the nervous system formed by the ganglia and nerves outside the brain and the spinal cord. Its principle function is to transmit information between limbs and organs and the central nervous system.

Pharmacologically: based on the use of a medication.

Phenotype: the morphological, physiological, and behavioral characteristics of an individual.

Spinal: concerning the spinal cord.

Spinal cord: directly connected to muscles by the nerve roots then the nerves. It transmits information from the brain to muscles and the viscera. The spinal cord transmits sensory information from the limbs, the trunk, and the viscera to the brain in return.

Striatum: brain structure situated under the cortex that is part of the basal ganglia.

Synapse: functional contact zone between two neurons or a neuron and another type of cell (muscle cell, sensory cell, etc.).

Transcription: first step of the process that transforms the information encoded in genes into proteins.


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THE IHU-A-ICM

2

1 Major achievements

2 Major publications

The mission of the IHU-A-ICM is to conduct projects of excellence in care, training, and technology transfer in the field of research on the diseases of the nervous system. Its priority is to favor the development of innovative diagnostic and therapeutic products and procedures. The objectives of the IHU-A-ICM, Paris Institute of Translational Neurosciences, are: development of international level research in the field of the diseases of the nervous system (neurology and psychiatry), creation of advanced technical platforms, promotion of research results, research partnerships with industry, training of future professionals in health, health administration and heath industries, improvement of care, and transfer of care from the hospital to the homes of patients.

EDITORIAL
FREDERIC SALAT-BAROUX, PRESIDENT OF THE IHU-A-ICM

Since its creation in February 2012, the role of the IHU-A-ICM has been to understand the function and dysfunction of the nervous system, which is a major challenge for research. It has benefited to that end from an unprecedented financial effort on the part of government that has engaged us and encourages us to advance in response to the confidence placed in our institution.

Faithful to the spirit of its founders and its missions, the IHU-A-ICM has continued its efforts to favor the emergence of new results and new concepts thanks to an interdisciplinary scientific strategy based on the most innovative techniques and close to the patients.

At the end of the institute's third year of existence, I want to acknowledge the first very promising results obtained.

These results are due first of all to you, your work, and your engagement, your faith in progress at the service of those who suffer and their families.

I also want to acknowledge the quality of our collaboration with our founding members and first of all the ICM. We are engaged with them in a wonderful collective adventure.

I want to acknowledge most of all the new impetus given to the institute by its Director General, Prof. Bertrand Fontaine, with the launching of ever more innovative transversal research programs, which will permit the institute to mobilize its resources in the service of strategic scientific orientations.

Constant engagement, innovative spirit, cohesion of the teams, such are the key words and the principles that, this year again, will guide each of us and the IHU-A-ICM as a whole.

Thank all you again.

EDITORIAL
BERTRAND FONTAINE, DIRECTOR GENERAL OF THE IHU-A-ICM

The IHU-A-ICM unites a critical mass of clinicians and talented researchers capable of major discoveries in a synergistic ensemble and is today able to attract the best international researchers. The Paris Institute of Translational Neuroscience, the IHU-A-ICM, the fruit of a governmental program of investments for the future, celebrates its three years of existence. In this year, which will see the first evaluation of our work by the international jury that selected us, we are proud to present a very positive appraisal and promising results.

In matters of care, the IHU-A-ICM has made spectacular advances with the activity of the Behavioral Neuropsychiatry Unit. Since its opening, 250 patients have been examined, 80% benefitted from receiving a diagnosis at the end of their stay, and 77% had a treatment adapted to their condition that was different from their treatment when they entered the unit. The IHU also showed its ability to constitute large cohorts with the recruitment of 400 subjects for the INSIGHT study, an innovative study on Alzheimer's disease, one of the first studies to follow healthy at-risk subjects with great ambitions for understanding the disease, performed in partnership with Pfizer.

In 2014, the acquisition of major equipment foreseen since the beginning was finalized. The IHU-A-ICM has acquired a mixed PET-MRI system thanks to an exceptional fundraising campaign and sponsors in collaboration with two of its founding members, the APHP and the Foundation for Research on Alzheimer's disease. It's the first mixed PET-MRI system for the clinic and research on a French site. It will contribute both to research on neurodegenerative diseases and the improvement of care.

The institute has finalized, in the context of a joint action with the ICM, the recruitment of a foreign senior researcher, selected by the International scientific advisory board common to the IHU-A-ICM and the ICM. His scientific project is aimed at understanding the mechanisms of genetic control from cell specification to the molecules implicated in neurodegenerative diseases such as Alzheimer's disease. This recruitment confirms the attractiveness of our Institute, made possible by the IHU program of investments for the future.

Finally, the ICM and IHU announced in June 2015, the launching of the "Big Brain Theory" program. This new program will permit the attribution of grants for new innovative and interdisciplinary projects in neuroscience for the researchers and clinicians of the Institute. This call for projects emphasizes originality and risk-taking, and will free the researchers from administrative duties by financing completely the projects selected by the international scientific advisory board of the IHU-A-ICM and ICM.

I wish to warmly thank the patients, researchers, clinicians, support teams, and our partners that have made the dreams of the IHU a reality, and also our founders, the AP-HP, the UPMC, INSERM, the CNRS, the FRA, and the ICM, for their constant support. The year 2015 opens with strong achievements and ambitious and creative perspectives to accelerate research and the discovery of new treatments for our patients.

1 MAJOR ACHIEVEMENTS

The IHU has assembled a critical mass of **talented,** well-integrated **clinicians and researchers** and is capable of attracting international participants. The IHU finalized negotiations with a senior foreign candidate selected by the International scientific advisory board. He was ranked first in an international call for projects, "New Teams," with a scientific project aimed at understanding the mechanisms of genetic control starting with cell specification. The IHU-A-ICM **acquired a mixed PET-MRI system** thanks to an exceptional fundraising campaign and patronage in collaboration with the support of two of its founding members, the AP-HP and the *Fondation pour la Recherche sur Alzheimer.* It is the first mixed PET-MRI system for research and the clinic on a French site. In the context of its industrial strategy, the IHU has established a partnership with a **French company, Medtech**, for the acquisition of a ROSA robot for neurosurgery. In 2014, the IHU finalized the acquisition of major equipment planned from the beginning of the program. The IHU-A-ICM began a major reorganization of its platforms in order to optimize its fees and offer a diversity of services for industrial users. The IHU-A-ICM has recruited 18 staff members for the platforms, mostly with permanent contracts. In terms of care, the IHU-A-ICM has also made spectacular advances since the opening of the Behavioral Neuropsychiatry Unit. Since it opened, **250 patients** have been examined, 80% of whom received a diagnosis and 77% a treatment adapted to their condition that differed from the treatment they were receiving when they entered the unit. Finally, the IHU has demonstrated its ability to constitute **large cohorts** with the recruitment of 343 subjects included in the INSIGHT study in partnership with Pfizer.

The Paris Institute of Translational Neuroscience (IHU-A-ICM) has pursued the pilot procedures it established at the start of the program.

In 2014, reflection was begun on **scientific policy** jointly with the Brain and Spine Institute (ICM). This analysis consists of evaluating the first results of the IHU-A-ICM, in order to propose a new joint and transversal scientific organization of the two foundations and to develop new initiatives and ambitious projects. For the first time, a joint meeting of the Boards of Directors of the IHU and the ICM took place in September 2014.

The IHU-A-ICM acquired a mixed PET-MRI system thanks to sponsorship, in collaboration with the support of two of its founding members the AP-HP and the *Fondation pour la Recherche sur Alzheimer.* This equipment will be functional in the fall of 2015. The ability to acquire perfectly recorded images in two modalities in a single imaging session while maximizing the quantitative and clinical information is a unique contribution to research on neurological diseases and the constitution of cohorts

in the framework of the IHU-A-ICM. It is the first mixed PET-MRI machine for the clinic (used by the APHP) and research (used by the IHU-A-ICM) on a hospital site. The informatics connections required for research were established between the site of image acquisition and the research laboratories.

In 2014, the acquisition of major equipment planned by the program was finalized. The IHU-A-ICM in conjunction with the ICM began a major reorganization in order to optimize the functioning of the technical platforms, establish an optimal price scale, and standardize all procedures.

Finally, the IHU-A-ICM, as the UPMC winner of the European public-private program KIC (Knowledge and innovation communities), is a partner in the neuroscience and innovation program KIC-Innolife (Healthy aging) The IHU-A-ICM was strongly involved in this application through the action of its Director General, a member of the pilot committee of the French sector. He developed partnerships with the AP-HP and Air Liquide, and was one of the French representatives in the "education" and "brain" groups during the development of the project.

The team of the **Parkinson Project** continued including patients in the ICEBERG cohort at the center of the clinical project of the IHU: study of factors predicting the conversion to and the progression of Parkinson disease. The rhythm of recruitments is as expected. The team also identified a viral peptide that is neuroprotective in models of Parkinsonian diseases, this led to a publication in *Nature Communications* and a patent.

The team of the **Alzheimer Project** has continued its efforts to develop the INSIGHT cohort in collaboration with Pfizer. The objective of including in the INSIGHT cohort 90 subjects over 70 years of age with PET AV45-positive amyloid was reached in 2014. This required the successful inclusion of a total of 343 subjects in the study. The multimodal database is being developed and the first analyses have begun.

The teams of the **Multiple Sclerosis Project** demonstrated the inhibitory role of endothelin1 in remyelination and showed, in collaboration with the Children's Hospital, Washington, D.C., that this molecule constitutes a new pharmacological target to initiate remyelination (publication in the prestigious journal Neuron).

The **Motivation Project** chose, in conformity with the IHU concept, to create long-lasting structures that could not have been developed with just the usual financing: the Behavioral Neuropsychiatry Unit (UNPC) in the clinical domain, the PRISME platform for the study of human behavior in the research domain, and diverse academic and societal initiatives in the educational domain. Since the opening of the UNPC in November 2013, 250 patients have been examined. The diagnoses most frequently made are degenerative diseases and severe depressive disorders that mimic dementia; 80% of the patients had a new or confirmed diagnosis after their stay in the unit and 77% had a treatment adapted to their situation that differed from their treatment when they entered the unit.

Among the major achievements of the **Epilepsy Project**, the teams pursued and further developed a new translational

project in patients and in a rodent model aimed at exploring the excitability of cortical neurons and cortical responses to sensory stimulation during isoelectric comas. The team also identified a de novo mutation in the HCN1 ion channel gene in children with fever-sensitive epileptic encephalopathies. The intrinsic properties of the mutated channels were studied by the electrophysiology platform of the IHU leading to a publication in Nature Genetics.

The **Bioinformatics/Biostatistics Project** began in 2013 with the recruitment of its scientific coordinator. This platform develops methods dedicated to the analysis of multimodal data (RGCCA): genetic, genomic, transcriptomic, epigenomic, metabolomic, clinical, and neuroimaging. The team created a pole "Databases and Datawarehouse" and recruited its director in June 2014. The team also developed a complete pipeline (treatment, analysis, interpretation, visualization) of data concerning genetic variants (gene panel, whole-exome sequencing), in relation with the Genotyping-Sequencing platform. The project has been completed and has led to the existence of platforms with an associated management unit and the development of technological research.

The members of the **Clinical Research Project** have successfully continued the activities of the Clinical research platform dedicated to neuroscience. In 2014, the CIC and CET received 2904 patients (consultations or one-day hospitalisations) participating in 62 studies: 43 studies in the CIC and 19 in the CET. Privileged partnerships with the private sector are continuing or being initiated.

The **Care Project** has continued its efforts with the recruitment of a coordinator to create, with ARS Ile-de-France, a pole "Handicap Ile-de-France." Three working groups were formed and have begun their activity, which should be finished in July 2015.

The actions of the **Educational Project** are described among the socioeconomic impacts (actions undertaken for sharing knowledge, teaching).

The plan of action of the **Strategy Project** was pursued during 2014. The IHU finalized negotiations with Dr. Bassem Hassan (VIB, Leuven, Belgium), who was ranked first in the international call for projects "New Teams." The scientific project of this team is to understand the mechanisms underlying the genetic control of cell specification and to transpose these basic approaches to disease models. What is new is the senior status of the candidate, until now the Institute has only attracted junior researchers.

The IHU also launched calls for "Clinic and Care" projects and structural projects in 2013. The first results of this strategy can be appreciated by the success of two PHRIP projects concerning care. As for internal collaborative projects, the IHU notably financed a project aimed at understanding the role

of the CIC, a gene frequently mutated in oligodendrogliomas, in the development of oligodendrocytes and in the genesis of these tumors. Characterization of the function of CIC is underway.

We also wish to describe the advancement of the transversal projects that have reached maturity:

The **Imaging Project** has enabled the development of the imaging silo platforms in the framework of the IHU in association with the ICM. These platforms are now completely operational with an associated management unit and are developing technological research in the following domains: multimodal imaging, gait analysis, imaging in primates, integrated MEG/EEG electrophysiology. During 2014, the imaging silo organized a series of courses that were a success. The program will be repeated in 2015. These platforms also led to the publication of many articles reflecting the efficacy of the translational research program of the IHU.

Among the major achievements of the **Animal Model Project** in 2014 was the installation of a platform for in vivo neurophysiology on small animals. The platform has developed methods for exploring the central and peripheral nervous system (electroneuromyogram, electromyogram, somatosensory evoked potentials), which have led to the development of five projects. In association with the Epilepsy project, this platform also offers the possibility of long-duration video electroencephalograms. The project is now completed and has led to the existence of platforms with an associated management unit and the development of technological research.

The **Cell Culture Project** is now completed and has led to the creation of platforms with an associated management unit and the development of technical research. Three platforms have developed services (fee-based) and technologies: cell culture and screening, culture of iPS cells, electrophysiology, and screening. The technical offer has now been increased with the installation of a second electrophysiology rig for extracellular recordings of electrical field potentials on brain slices *(in vitro)* or in the zebrafish *(in vivo).*

2 MAJOR PUBLICATIONS

1. Szelechowski et al. A viral peptide that targets mitochondria protects against neuronal degeneration in models of Parkinson's disease. Nature Communication 2014.

2. O'Bryant SE et al. Guidelines for the standardization of preanalytic variables for blood-based biomarker studies in Alzheimer's disease research. . Alzheimers Dement. 2014

3. Hammond et al. Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. Neuron, 2014.

4. Lagarde et al. Why do patients with neurodegenerative frontal syndrome fail to answer the following question: "In what way are an orange and a banana alike?" Brain, 2014.

5. Nava C et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet. 46(6):640-5, 2014.

6. El Mendili MM, Cohen-Adad J, Pelegrini-Issac M, Rossignol S, Morizot-Koutlidis R, Marchand-Pauvert V, Iglesias C, Sangari S, Katz R, Lehericy S, Benali H, Pradat PF. Multi-parametric spinal cord MRI as potential progression marker in amyotrophic lateral sclerosis. PLoS One. 2014 Apr 22;9(4):e95516.

7. Laouchedi M, Galanaud D, Delmaire C, Fernandez-Vidal S, Messé A, Mesmoudi S, Oulebsir Boumghar F, Pélégrini-Issac M, Puybasset L, Benali H, Perlbarg V Deafferentation in thalamic and pontine areas in severe traumatic brain injury. J Neuroradiol. 2014

8. Mesci et al. System xC- is a mediator of microglial function and its deletion slows symptoms in amyotrophic lateral sclerosis mice. Brain 2014

9. Esteves T, (2014). Loss of association of REEP2 to membranes leads to hereditary spastic paraplegia. Am J Hum Genet 94:268-277.

10 Boxer AL et al. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. Lancet Neurol. 2014.


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Patient Applications Transfer Edit View Settings Orientation Type Image Tools System Options Help
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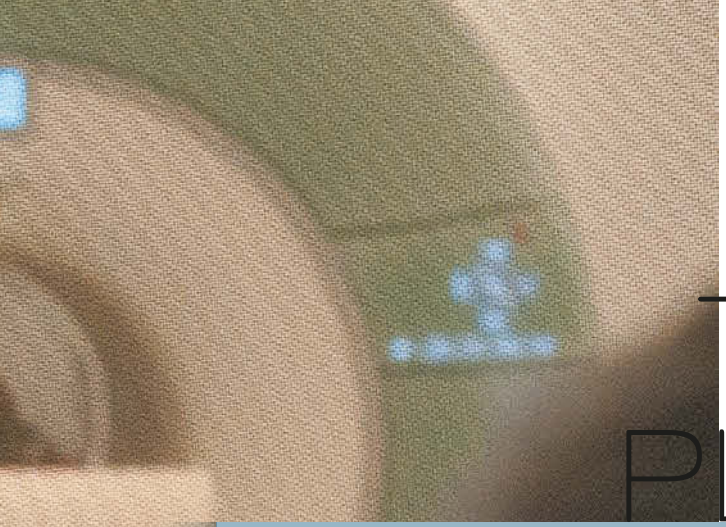
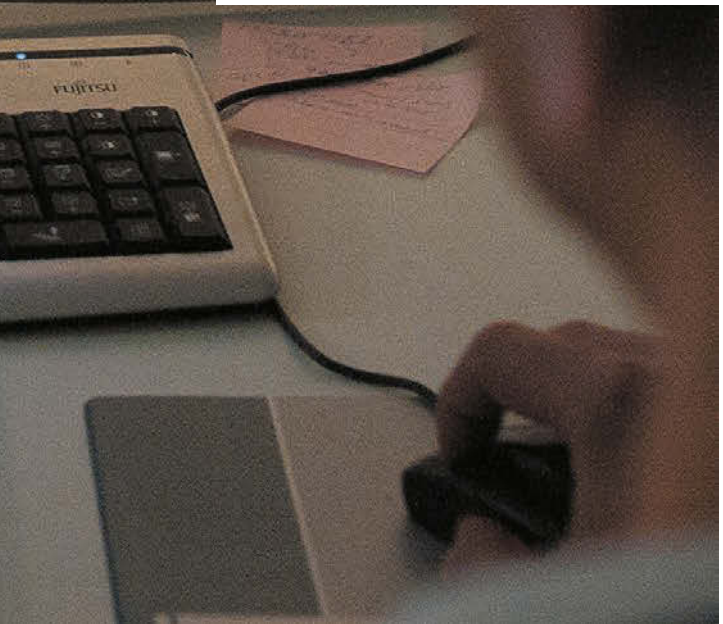


TECHNICAL PLATFORMS

3

1. Molecular exploration
2. Cellular exploration
3. Cellular imaging
4. Functional exploration
5. Preclinical functional exploration - phenoparc
6. Bioinformatics and biostatistics – iconics
7. Biological resource center

The quality of scientific discoveries depends on the performance of the technical platforms on which the discoveries are performed. Revolutionary in its conception, innovative in its organization, the ICM is also unique because of its advanced technical equipment.



1 MOLECULAR EXPLORATION

The molecular exploration silo consists of two platforms: iGenSeq and iVector. The role of the first, iGenSeq, is dedicated to sequencing and genotyping the genome, i.e. reading the long molecules of DNA that form chromosomes. The aim is to analyze the genome and detect possible mutations and associations between these mutations and neurological diseases. The second platform, iVector, constructs molecular tools for gene transfer so that researchers can perform experiments using genetic manipulations *in vitro* (outside the organism) or *in vivo* (after injection in the organism like a vaccine). These tools are derived notably from innocuous modified viruses, converted into gene transporters. This type of technology is the basis of gene therapy, therapies that act on genes, which ICM researchers hope to use to "repair" the abnormal DNA of patients.

1- iGenSeq – GENOTYPING AND SEQUENCING PLATFORM

YANNICK MARIE AND GIOVANNI STEVANIN

iGenSeq offers tools and services for the analysis of the genome to academic and industrial researchers. More specifically, the services include real-time PCR, sequencing, as well as the purification and analysis of nucleic acids. Each project submitted to the platform is discussed with the researcher in order to evaluate its feasibility and optimize its design. This platform offers researchers high-throughput sequencing and PCR accompanied by biostatistics services. iGenSeq is part of the network of platforms of the ICM , including vectorology, histology, microscopy, cell culture, etc. that facilitates translational research.

ACTIVITIES

- Real-time PCR: with SybrGreen technology or specific probes, quantification of RNA, digital PCR, HRM
- Sequencing: medium-throughput with GS junior and Miseq Illumina systems, including multiplex amplicon (Fluidigm ACCESS ARRAY), long-range and ultra-deep sequencing applications and Capture (DNA and RNA): high-throughput with the NextSeq Illumina system for EXOLE applications RNAseq and MethylSeq
- Genotyping
- Purification and analysis of PCR products: PCR or purification of sequences and quantitative analyses of DNA and RNA

PUBLICATIONS

Coutelier M et al. GRID2 mutations span from congenital to mild adult onset cerebellar ataxia. Neurology 2015 (advance online April 3rd).

Hopfner F* et al. The impact of rare variants in FUS in essential tremor. Mov Disord 2015 (advance online January 28).

Lossos A* et al. Fe/S Protein Assembly Gene IBA57 Mutation Causes Hereditary Spastic Paraplegia. Neurology 2015, 84:659-667.

Baulac S1 et al. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. Ann Neurol. 2015 Apr;77(4):675-83.

Millecamps S et al. Genetic analysis of matrin 3 gene in French amyotrophic lateral sclerosis patients and frontotemporal lobar degeneration with amyotrophic lateral sclerosis patients. Neurobiol Aging. 2014 Dec;35(12):2882.e13-5.

Nava C et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet. 2014 Jun;46(6):640-5.

Méneret A et al. Congenital mirror movements: mutational analysis of RAD51 and DCC in 26 cases. Neurology. 2014 Jun 3;82(22):1999-2002.

Gillet E1 et al. TP53 and p53 statuses and their clinical impact in diffuse low grade gliomas. J Neurooncol. 2014 May;118(1):131-9.

Picard F et al. DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. Neurology. 2014 Jun 10;82(23):2101-6.

Esteves T et al. Loss of association of REEP2 with membranes leads to hereditary spastic paraplegia. Am J Hum Genet. 2014 Feb 6;94(2):268-77.

Boillot M et al. Glutamatergic neuron-targeted loss of LGI1 epilepsy gene results in seizures. Brain. 2014 Nov;137(Pt 11):2984-96.

2 - iVector – VECTOROLOGY PLATFORM

PHILIPPE RAVASSARD AND ANDRE SOBCZYK

The vectorology platform (iVector) produces a large number of lots of lentiviral vectors every year. These viral vectors are the tools of choice for gene transfer in applications *in vitro* and *in vivo* for basic research, cellular engineering, gene therapy, cell therapy, immunotherapy, and vaccines. The platform's BSL2 and BSL3 confinement laboratories satisfy all demands for virus production. iVector constructs recombinant viruses, which form viral particles.

There are different scales of production, and high-titer viruses (a mean of 109 functional viral particles/mL) are delivered after purification. The platform team, in close collaboration with the Biotechnology and Biotherapy team, proposes a wide variety of empty lentiviral vectors ready to accept any gene of interest. These two teams ensure the continual improvement and evolution of these vectors. iVector is integrated in the network of ICM platforms (genotyping, histology, microscopy, cell culture, etc.).

3

TECHNICAL PLATFORMS

MOLECULAR EXPLORATION

ACTIVITIES

- Design and construction of viral and non-viral vectors.
- Maxi and Giga preparations, amplification/purification of plasmid DNA (endotoxin-free).
- Production of recombinant Lv (3rd generation "ΔU3" or "SIN") and Rv (retroviral) vectors.
- A variety of control lentiviral vectors (GFP, miRneg, etc.) are available.
- Development of transduced cell lines and mini-banking (after feasibility analysis in the laboratory).
- Quality control: determine of the titer of functional viral vectors (FACS, qPCR), measure the concentration of physical viral particles (Elisa p24)
- Technical and regulatory advice for the design, production, and use of viral vectors.
- Development of new viral tools (CAV-2 and rAAV) with serotypes specific for research in neurobiology.

PUBLICATIONS

Sepulveda-Diaz JE et al. HS3ST2 expression is critical for the abnormal phosphorylation of tau in Alzheimer's disease-related tau pathology. Brain 138, 1339–1354. Brain. 2015 May;138(Pt 5):1339-54.

Gleize V et al. CIC inactivating mutations identify aggressive subset of 1p19q codeleted gliomas. Ann Neurol. Ann Neurol. 2015 May 27.

Ingallinesi M et al. Local inactivation of Gpr88 in the nucleus accumbens attenuates behavioral deficits elicited by the neonatal administration of phencyclidine in rats. Mol Psychiatry. 2014 Aug 26.

Tepavčević V et al. Early netrin-1 expression impairs central nervous system remyelination. Ann Neurol. 2014 Aug;76(2):252-68.

Morán I et al.Human beta cell transcriptome analysis uncovers lncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. Cell Metab. 2012 Oct 3;16(4):435-48.

Courtney M et al.The inactivation of Arx in pancreatic alpha-cells triggers their neogenesis and conversion into functional beta-like cells. PLoS Genet. 2013 Oct;9(10):e1003934.

Al-Hasani et al. Adult duct-lining cells can reprogram into beta-like cells able to counter repeated cycles of toxin-induced diabetes. Dev Cell. 2013 Jul 15;26(1):86-100.

2 CELLULAR EXPLORATION

ICM researchers work on different scales from molecules such as DNA and proteins to the organism, as well as the cell, which is midway between these two extremes. In the brain and its continuation, the spinal cord, several types of cells coexist:

- Neurons are the active element of nervous tissue and play a major role in the transmission of information. This involves successive electrical and chemical events. Neurons form an incredibly complex and dense network. Each neuron is composed of a cell body, which includes the nucleus that contains the DNA, an axon that transmits information, and dendrites which receive information.
- Glial cells, more numerous than neurons, have specialized functions. Several cell types can be distinguished:

– Microglial cells that act as sentinels and preserve the integrity of neurons faced with different types of attacks.

– Astrocytes that have support, protective, and nutritional functions.

– Oligodendrocytes that produce the myelin sheath, an envelope that insulates the axons of certain neurons, accelerating propagation of the nerve impulse.

Research in the ICM requires the availability of easily manipulated cell cultures to reproduce the mechanisms of nervous system pathologies in a simplified manner. These studies require recording the activity of neuronal cells in order to evaluate possible anomalies in the transmission of the electrical signal, manipulation of stem cells to produce authentic nerve cells or glia, and also analysis of pathological cellular dysfunctions by quantitative fluorescent microscopy. Recently, it has become possible to perform this type of analysis on living cells in the ICM thanks to automated microscopes.

Histological techniques on tissue sections enable evaluation of the integrity of populations of neurons and glial cells in different regions of the brain in order to understand the function or dysfunction of the brain as a whole. These techniques need prior labeling with antibodies or specific dyes to be effective.

All these activities are possible thanks to four cellular exploration platforms.

3

TECHNICAL PLATFORMS

CELLULAR EXPLORATION

1 - CELIS – ADVANCED CELL CULTURE EQUIPMENT

PATRICK-PIERRE MICHEL AND LAETITIA STREHL

This platform offers a large range of cellular models as well as advanced technologies to academic and industrial researchers who:

1 – wish to perform experiments on pathologies of the brain and the spinal cord

2 – wish to screen small molecules to discover promising treatments for these pathologies

Other activities include the production and characterization of pluripotent stem cells (iPS) and electrophysiological recordings in cultured cells or brain slices. This platform is part of the network of ICM platforms (sequencing, vectorology, histology, microscopy, etc.) and is supported by the IHU-ICM.

ACTIVITIES

- Study pathologies of the brain, spinal cord, and skeletal muscle on cell cultures or tissue sections.
- Screen for treatments for neuronal or glial pathologies, including brain tumors
- Automated cell culture
- Molecular and cellular pharmacology
- Conventional or automated fluorescence imaging, infrared fluorescence imaging
- Real-time measurements of cell proliferation
- Electrophysiological characterization of ion channel dysfunction
- Conventional ELISA and immunological assays by electrochemiluminescence.
- Flow cytometry

PUBLICATIONS

Bertolin G et al. Parkin maintains mitochondrial levels of the protective Parkinson's disease-related enzyme 17-ß hydroxysteroid dehydrogenase type 10. Cell Death Differ.

Freeman SA et al. Acceleration of conduction velocity linked to clustering of nodal components precedes myelination. Proc Natl Acad Sci U S A. 112:E321-8.

Guerreiro S et al. The sleep-modulating Peptide orexin-B protects midbrain dopamine neurons from degeneration, alone or in cooperation with nicotine. Mol Pharmacol. 87:525-32.

Esteves T et al. Loss of association of REEP2 to membranes leads to hereditary spastic paraplegia. Am J Hum Genet 94:268-277.

Marquer C et al. Increasing membrane cholesterol of neurons in culture recapitulates Alzheimer's disease early phenotypes. Mol Neurodegener. 9:60.

Tepavčević V et al. Early netrin-1 expression impairs central nervous system remyelination. Ann Neurol. 76:252-68.

2 - CELIS - E-PHYS – ELECTROPHYSIOLOGY PLATFORM

CARINE DALLE AND PATRICK-PIERRE MICHEL

CELIS-E-PHYS offers high level services to academic and industrial researchers needing electrophysiological data *in vitro* and *in vivo* (zebrafish). This type of data is essential for all neuroscience studies concerning the biophysical properties of ion channels, the functional characterization of all types of cells, and the study of synaptic and electrical activity in the nervous system in general. The platform is thus important for numerous research projects ranging from the functional characterization of channelopathies to that of neurons derived from human induced pluripotent stem cells (iPSC). CELIS-PHYS is part of the network of ICM platforms (sequencing, vectorology, cell culture, iPS...) that facilitate translational research. CELIS-PHYS is supported by the IHU-A-ICM.

ACTIVITIES

- Generation of electrophysiological data (including experimental design, data acquisition, analysis, and interpretation)
- Electrophysiology rigs with technical support
- Preliminary studies to evaluate the feasibility of research projects
- Specialized advice on electrophysiology
- Training of students and engineers in electrophysiological techniques

PUBLICATIONS

Nava C et al. De novo mutations of the hyperpolarization-activated cyclic nucleotide-gated channel 1 gene (HCN1) are responsible for early infantile epileptic encephalopathy. Nature Genetics, 2014 Jun;46(6):640-5

3 - CELIS – IPS – PLATFORM FOR THE PRODUCTION OF HUMAN INDUCED PLURIPOTENT STEM CELLS

DELPHINE BOHL, PATRICK-PIERRE MICHEL AND SOPHIE DUFFAURE

Human induced pluripotent stem cells, iPSc, are produced in order model degenerative diseases of the brain and spinal cord in a culture dish. The aim is to study the molecular and cellular mechanisms at the origin of these diseases and develop a screening system to identify molecules of therapeutic interest.

The objectives of the platform are to provide a service to generate human induced pluripotent stem cells (iPS) as well as to offer training and advice for cell culture.

This activity is part of the cell culture platform of the ICM and is supported by the IHU-A-ICM.

ACTIVITIES

- **Services**

  Reprogramming of human somatic cells into iPSc

  Molecular and functional characterization of iPSc

  Culture and storage of iPSc

- **Provide** equipment for independent users

- **Scientific and technical advice for users**

  Optimization and improvement of protocols

- **Development**

  Generation and characterization of neural stem cells derived from iPSc

  Genetic modification of iPSc

4 - HISTOMICS – HISTOLOGY PLATFORM (study of normal and pathological tissues)

BENOIT DELATOUR AND ANNICK PRIGENT

Histomics is a technical support center open to ICM researchers and academic and industrial partners. The center rents equipment or provides services and uses standardized protocols and advanced material (ultramicrotomes, cryostats, freezing microtomes, etc.) for treating histological samples. The platform team offers technical and scientific services, trains users in histological methods, and also works on independent projects. Histomics is part of the network of platforms of the ICM (genotyping-sequencing, vectorology, cellular exploration, etc.) that facilitate translational research.

ACTIVITIES

- Infrastructure rental: equipment and reagents are available for independent users
- Training: histological techniques (cutting, staining immuno- or histochemistry)
- Technical advice, help with developing new protocols
- Histological services: paraffin inclusion, sectioning, histo- or immunohistochemical staining

PUBLICATIONS

Epelbaum S et al. Acute amnestic encephalopathy in amyloid-ß oligomer-injected mice is due to their widespread diffusion in vivo. Neurobiol Aging. 2015 Jun;36(6):2043-52.

3 CELLULAR IMAGING

A group of ICM platforms is entirely dedicated to cell and tissue imaging. These platforms provide access to the most recent techniques thanks to advanced imaging material:

- Classical microscopy: observation of microscopic samples by incident illumination

- Video microscopy to follow cellular movement in real time

- Fluorescence microscopy: observation of molecules, cells, or tissue sections by fluorescence and phosphorescence. This includes classical fluorescence microscopy, confocal microscopy, two-photon microscopy, and spinning disk confocal microscopy

- Transmission electronic microscopy to observe different cellular compartments (organelles, viruses, crystals, molecules) at high resolution

1 - IMAGE ACQUISITION

ANNE BARON-VAN EVERCOOREN AND CORINNE BACHELIN

iGenSeq offers tools and services to academic researchers and industrial partners for analyzing the genome. These services include real-time PCR and sequencing, as well as purification and nucleic acid analysis. Each project submitted to the platform is discussed with the researchers in order to evaluate its feasibility and to optimize its design. This platform also provides techniques such as high speed real-time PCR and sequencing with biostatistics services. iGenSeq is part of the network of ICM platforms (vectorology, histology, microscopy, cell culture, etc.) that facilitates translational research.

2 - OPTOGENETIC TWO-PHOTON MICROSCOPY

CLAIRE WYART

3 - PICPS – PITIE-SALPETRIERE CELL IMAGING PLATFORM

ANNE BARON-VAN EVERCOOREN AND CLAUDE-MARIE BACHELET

4 FUNCTIONAL EXPLORATION

The functional exploration platforms permits carrying out of experiments on living organisms *(in vivo)* in a non-invasive manner that respects the integrity of the subject. These platforms are particularly adapted to human subjects – patients or healthy volunteers.

These platforms support three main research axes:

- Clinical research: study of the evolution of the major pathologies of the nervous system and development of treatments
- Research in the cognitive sciences: understand brain function and study the neural bases of thought, behavior, and aging.
- Research on signal and image analysis: development of new methods for processing brain imaging data

The functional exploration platforms offer techniques for recording brain activity and high resolution imaging such as magnetic resonance imagery (MRI), electroencephalography (EEG), and magnetoencephalography (MEG).

1 - CENIR-human MRI – NEUROIMAGING FOR RESEARCH

STEPHANE LEHERICY AND ERIC BARDINET

The CENIR (Neuroimaging research center) is the main MRI platform for imaging *in vivo.* With expertise in the fields of neurodegenerative diseases, cognitive neuroscience, and image analysis, the CENIR proposes high quality imaging tools for research on the brain and spinal cord to academic and industrial researchers. The CENIR human MRI team, composed of 15 people, has complementary skills (neuroimaging, neuroscience, image analysis, stimulation, physics of MRI, data analysis) and helps carry out research protocols (more than 80 projects in 2014) thanks to the imaging equipment. The use of 3T MRI and MRI-compatible EEG creates a perfect environment for carrying out neuroimaging projects.

3

TECHNICAL PLATFORMS

FUNCTIONAL EXPLORATION

ACTIVITIES

- Clinical research: integrated studies of the physiopathology of neurological and psychiatric diseases, including clinical and therapeutic care. The protocols concern all of the major pathologies of the nervous system: neurodegenerative diseases, white matter pathologies, epilepsy, motor disorders, psychiatry, brain plasticity, and functional recovery.
- Cognitive neuroscience: brain function, neural bases of cognition and behavior, aging
- Image processing: development of methods for processing data as well as tools for structural and functional imaging
- Support for researchers: development of stimulation programs, acquisition protocols, and help with different stages of data analysis

PUBLICATIONS

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Worbe Y et al. Reinforcement learning and Gilles de la Tourette syndrome: dissociation of clinical phenotypes and pharmacological treatments. Arch Gen Psychiatry. 2011 Dec;68(12):1257-66

Charron S et al. Divided representation of concur- rent goals in the human frontal lobes. Science. 2010 Apr 16;328(5976):360-3

2 - CENIR-MEG/EEG – MEG AND EEG PLATFORM FOR RESEARCH PROJECTS IN NEUROSCIENCE

NATHALIE GEORGE AND DENIS SCHWARTZ

The CENIR-MEG/EEG platform is part of the Neuroimaging research center (CENIR). The platform is dedicated to the development of non-invasive methods that allow visualization of brain activity under normal or pathological conditions with a temporal resolution on the order of a millisecond. Thanks to its advanced equipment, the CENIR-MEG/EEG team helps its academic and industrial partners design and perform their clinical or basic research projects and analyze results. CENIR-MEG/EEG is part of the network of ICM platforms (MRI, PANAM, PRISME...) that facilitate translational research.

ACTIVITIES

- Clinical and basic research on the normal and pathological brain
- Development of methods for the integrated analysis of electrophysiological data at several levels (EEG, MEG, deep recordings, peripheral neurophysiological recordings)
- Creation of software for data processing, statistical analysis, and visualization

PUBLICATIONS

Huijgen J et al. Amygdala processing of social cues from faces: an intracerebral EEG study. Soc Cogn Affect Neurosci. 2015 May 11. pii: nsv048. [Epub ahead of print]

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Dumas J et al. Revisiting mu suppression in autism spectrum disorder. Brain Research – 2014 - 108-119 10.1016/j.brainres.2014.08.035

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Park HD et al. Spontaneous fluctuations in neural responses to heartbeats predict visual detection, Nature Neuroscience 17, 612–618.

Morel S et al. ERP evidence for an early emotional bias towards happy faces in trait anxiety, Biological Psychology, 99, 183-192.

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3 - PLATFORM FOR THE EXPLORATION OF HUMAN BEHAVIOR

MATHIAS PESSIGLIONE, PHILIPPE FOSSATI, AND PIERRE LEBOUCHER

PRISME is the ICM platform dedicated to the functional exploration of human behavior. It is composed of two entities:

1 – PRISME-Virtual Reality has recognized expertise in the modeling of virtual worlds. This platform develops and adapts new virtual reality paradigms for behavioral and cognitive neuroscience. The platform also develops new equipment and therapeutic protocols adapted to neuropsychiatric diseases.

2 – PRISME-Real Life is intended for the study of cognitive functions, human behavior, and social interactions in ecological conditions, so that the results obtained are not limited to the laboratory context. The aim is to 1) test a large number of subjects so that they will be as representative as possible of the general population, 2) set up environments close to those found in everyday life, and 3) use wireless recording systems so that the patients are free to move.

Academic and industrial partners can use the equipment and are assisted by the team to develop appropriate protocols. PRISME is part of the network of ICM platforms (MRI, MEG/EEG, TMS...) that facilitate translational research.

ACTIVITIES

PRISME-Virtual Reality

- Cognitive reeducation program, including web-therapy and therapy by virtual reality
- Walking and fear of falling, spatial cognition, and interpersonal space
- Social interactions: embodied conversational agent
- Virtual reality: environments and creation of avatars

PRISME-Real Life

- Test cognitive functions
- Evaluate competency for sports
- Study social interactions
- Automatic analysis of behavior
- Freely moving subjects
- Multimodal recordings
- Brain stimulation

4 - CENIR-STIM – STEREOTAXIS PLATFORM (TECHNIQUES, IMAGES, MODELS)

JEROME YELNIK, CARINE KARACHI, AND SARA FERNANDEZ VIDAL

STIM is part of the Neuroimaging research center (CENIR). STIM offers support for the analysis and development of computer programs for treating stereotactic imaging data (used, for deep brain stimulation, pharmaco-resistent epilepsies, and radiosurgery). It offers clinicians tools for the stereotactic localization of deep brain structures. The YeB Atlas, developed by Jérôme Yelnik and Eric Bardinet, is a powerful support for data analysis.

The platform is involved in several deep brain stimulation (DBS) protocols in collaboration with other research institutes and industry. Other departments of the Pitié-Salpêtrière Hospital, including Neuroradiology, Neurosurgery, and Neurology contribute their expertise to the platform. The network of ICM platforms (more than 20) facilitates translational research.

ACTIVITIES

- Pre-surgical determination of targets for DBS
- Pre- and post-operative localization of DBS electrodes
- Optimization of MRI sequences for DBS protocols
- Data analysis with the YeB Atlas
- Development of computer programs for DBS and epilepsy

- Expertise:

Evaluation of new MRI sequences by researchers and engineers in order to discover previously unknown brain regions

Close collaboration between researchers and clinicians

5 - CENIR-PANAM – PHYSIOLOGY AND MOVEMENT Analysis PLATFORM

JEAN-CHARLES LAMY AND MARIE-LAURE WELTER

The PANAM platform is part of the Neuroimaging research center (CENIR). Its mission is twofold:

1 – Clinical and therapeutic research with non-invasive brain stimulation on neurological and psychiatric disorders

2 – The study of movement, gait, and balance in patients with neurological disorders.

In addition, the platform develops new non-invasive techniques based on transcranial magnetic stimulation (TMS) that safely alters electrical activity through the skull with strong temporary magnetic fields and coupled recordings LFP/EEG (LFP=Local field Potential). The platform is part of the network of ICM platforms (preclinical models, neuroimagery, MEG/EEG, deep brain stimulation, etc.) that facilitate translational research.

This Platform received support from the RATP Foundation.

3

TECHNICAL PLATFORMS

FUNCTIONAL EXPLORATION

ACTIVITIES

- Electrophysiological studies (TMS, EMG, EEG, LFP...)
- Clinical research and experimental therapeutics using non-invasive stimulation
- Mapping of cortical organization/disorganization in neuropsychiatric pathologies (Parkinson's disease, ALS, essential tremor, congenital mirror movements, primary orthostatic tremor, dystonia, autism...)
- Effects of "virtual" brain lesions on cognitive and motor tasks
- Development of experimental therapeutics for neuropsychiatric disorders with high and low frequency rTMS and tDCS,
- Development of non-invasive stimulation of the cerebellum (TMS, tDCS, tACS...)
- Development of coupled recordings:TMS/MRI, TMS/EEG, and LFP/EEG
- Evaluation of therapeutic treatments on patients with motor and behavioral disorders, including gait and balance problems
- Development of intracerebral recordings coupled with biomechanical/cinematic/EEG parameters, including when walking

PUBLICATIONS

Quentin R et al. Cereb Cortex. Visual Contrast Sensitivity Improvement by Right Frontal High-Beta Activity Is Mediated by Contrast Gain Mechanisms and Influenced by Fronto-Parietal White Matter Microstructure. J Neurol. 2015 Jun;262(6):1515-25.

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Kishore A, Popa T, James P, Yahia-Cherif L, Backer F, Varughese Chacko L, Govind P, Pradeep S, Meunier S. Age-related decline in the responsiveness of motor cortex to plastic forces reverses with levodopa or cerebellar stimulation. Neurobiol Aging. 2014 Nov;35(11):2541-51.

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Demain A et al. High-level gait and balance disorders in the elderly: a midbrain disease? J Neurol. 2014 Jan;261(1):196-206.

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6 - CENIR-small animal MRI – MRI PLATFORM FOR SMALL ANIMALS

ALEXANDRA PETIET AND MATHIEU SANTIN

The small animal MRI platform is part of the Neuroimaging research center (CENIR). The platform is dedicated to imaging of experimental disease models in rodents. A very strong magnetic field associated with high quality radio-frequency antennas (Cryoprobe™ for the mouse) and a large variety of imaging and data analysis protocols offer a high-quality platform for imaging in small animals. The small animal CENIR-MRI is part of the network of platforms that facilitate translational research.

ACTIVITIES

- Basic neuroscience: neuroanatomy of the brain, evaluation of new biomarkers
- Applied neuroscience: characterization and evaluation of experimental models, study of disease progression, effects of therapeutic molecules
- MRI microscopy: high resolution images of post-mortem biological samples
- Image processing: development of methods for data processing and of tools for functional and structural neuroimaging in small animals

PUBLICATIONS

Kundu P et al. Differentiating BOLD and non-BOLD signals in 11.7 Tesla Rat Resting State fMRI. Neuroimage 2014, Nov 15;102 Pt 2:861-74.

Santin MD et al. "In vivo (1) H MRS study in microlitre voxels in the hippocampus of a mouse model of Down syndrome at 11.7T", NMR Biomed 2014, Oct;27(10):1143-50.

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M . Vandenberghe et al. "High-throughput 3D whole-brain quantitative histopathology in rodents", Nature Scientific Reports, 2015, in press

5 PRECLINICAL FUNCTIONAL EXPLORATION – PHENOPARC

The preclinical functional exploration platform has 3000m^2 of space for the housing of animal models for research projects and experimentation. Studies can be carried out on various models using multiple techniques, including behavioral, surgical, and electrophysiological approaches. The platform's equipment and experts offer high quality support for teams within and outside the ICM.

1 - PHENO-ZFish – PLATFORM FOR EXPERIMENTATION ON THE ZEBRAFISH

CLAIRE WYART AND SOPHIE NUNES-FIGUEIREDO

This platform is dedicated to preclinical research on the zebrafish.

The zebrafish is a vertebrate with a rapidly developing nervous system that enables quick testing of the potential of therapeutic molecules before studying the therapeutics in detail in higher species.

The platform has aquariums that that can house more than 20,000 adult fish and advanced equipment, including an automated robot for feeding and 6 injection systems for transgenesis.

Furthermore, the platform proposes imaging, optogenetics, an advanced technique for activating target neurons at a distance with light, and behavioral experiments on mutant and transgenic lines. The users of the platform have access to specific training, for example in fish handling, including breeding, egg collection, transgenesis, screening and sperm freezing. Highly qualified technicians are responsible for care, breeding, and health. PHENO-Zfish is part of the network of ICM platforms (vectorology, genotyping, cell culture, electrophysiology...) that facilitate translational research.

ACTIVITIES

- Production and maintenance of transgenic and mutant lines
- Genotyping by PCR
- Transgenesis (Tol2/CRISPR/TALEN)
- Fluorescence in situ hybridization (FISH)
- Fluorescence immunohistochemistry on embryos/larvae in toto or on sections
- Confocal, two-photon, and spinning disk imaging
- Quantification of immunoreactive regions on images
- Behavioral analysis, interpretation of results obtained with mutant models and drug screening
- Sperm freezing
- Electron microscopy on embryos or larvae (1-3 days)
- Calcium imaging and optogenetics
- New lines for use with probes and activators of neuronal activity *in vivo*

PUBLICATIONS

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Wegener A et al. Gain of Olig2 function in oligodendrocyte progenitors promotes remyelination. 2015. Brain 138 (Pt 1):120-35.

Tepavčević V et al. Early netrin-1 expression impairs central nervous system remyelination. 2014. Ann Neurol 76(2):252-68.

Hammond TR et al.. Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. 2014. Neuron 81(3):588-602.

2 - PHENO-ICMice – RODENT PRECLINICAL PHENOTYPING SERVICE

MAGALI DUMONT AND BRAHIM NAIT OUMESMAR

This platform has a 1500 m^2 infrastructure equipped with advanced equipment (7000 ventilated SOPF/SPF cages and 40 rooms equipped for experimentation). It offers academic and industrial teams advanced material supervised by experts in the field. An external company is responsible for the breeding, care, and well-being of the experimental models. PHENO-Mice is part of the ICM network of platforms (small animal MRI, sequencing, vectorology, histology, microscopy...) that facilitate translational research.

PRECLINICAL FUNCTIONAL EXPLORATION – PHENOPARC

ACTIVITIES

- Behavior: locomotion, anxiety, depression, memory, sociability, motor coordination, etc.
- Surgery: stereotactic surgery, imaging in vivo, electroporation, resection
- Neurophysiology: EEG, EMG, evoked potentials, optogenetics, etc.
- Room rental for experimentation
- Services offered for the use of experimental models

PLATFORM FOR *IN VIVO* NEUROPHYSIOLOGY ON SMALL ANIMALS

SOPHIE NICOLE, VINCENT NAVARRO, AND DELPHINE ROUSSEL

This platform promotes neurophysiological exploration of central nervous system pathologies in rodent models. Its aim is to fulfill the needs of academic and industrial researchers who want to detect electrophysiological alterations and the effects of therapeutic strategies.

These approaches permit the characterization of phenotypes of experimental animals for:

- Peripheral neuropathies (axon degeneration, demyelination)
- Myopathy, muscle atrophy, sarcopenia
- Myasthenia (neuromuscular transmission)
- Epilepsy (presence/type/severity of the seizures)
- Physiological behavior (sleep-wake cycles)
- Brain dysfunction (encephalopathy, etc.)

ACTIVITIES

- Advice: the platform offers expertise for developing projects and experimental protocols, the choice of the most pertinent neurophysiological tests, data analysis, manuscript preparation, and ethics protocols.
- User training: the platform trains users in the use of the equipment, software, and data analysis
- Rental of space/equipment: Two recording units are available:
- A unit for electromyography (EMG) and evoked potentials (EP) (Neuro- Mep- Micro-Neurosoft)
- A unit for long-duration video electroencephalography (EEG) in which 5 mice or 3 rats can be recorded simultaneously (Deltamed-Natus)
- Services: the platform offers expertise for carrying out research projects

3 - PHENO-ICMaze – RODENT BEHAVIOR PLATFORM

MAGALI DUMONT AND NADEGE SARRAZIN

This platform assists academic and industrial researchers in the design and carrying out of research projects requiring behavioral testing to characterize new transgenic lines and identify therapeutic targets. More than 30 tests are available for mice and rats in order to ensure the success of the research projects. PHENO-ICMaze is part of the network of ICM platforms (small animal MRI, sequencing, histology, microscopy...) that facilitate translational research.

ACTIVITIES

- Advice: the team offers its expertise for the elaboration of projects and experimental protocols, the choice of the most pertinent behavioral tests, data analysis, manuscript preparation and ethics protocols.
- User training: the team offers training sessions in the use of equipment and software
- Rental of rooms/equipment: 12 rooms can be rented for carrying out of over 30 behavioral tests.
- Services: the team offers its expertise for carrying out of research projects

PUBLICATIONS

Ingallinesi M et al. Local inactivation of Gpr88 in the nucleus accumbens attenuates behavioral deficits elicited by the neonatal administration of phencyclidine in rats. Mol Psychiatry. 2014 Aug 26.

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6 BIOINFORMATICS AND BIOSTATISTICS - ICONICS

Over the course of the last two decades, research in neuroscience has witnessed a spectacular explosion of data collected in laboratories. Collecting the information is one thing, analyzing and understanding it in order to develop new treatments is another. The role of the iCONICS Bioinformatics silo is to ensure the collection of data from different sources, then storing and organizing the data.

The iCONICS silo also offers tools for managing the data for analysis and interpretation with specialized methods and complex statistics.

The iCONICS silo is composed of two platforms. It offers researchers and clinicians help with data analysis and creates innovative computer programs.

1 - DATABASES AND DATAWAREHOUSE

LAURE SEUX AND BERTRAND FONTAINE

The Databases and Datawarehouse team stores data in databases, all of which are designed on the same model. This permits daily formatting and management of information (clinical, genetic, imaging, diagnoses, neuropsychology, environment, images, disease evolution, raw and analyzed data, etc.) obtained on healthy or diseased subjects.

The team then prepares the data in the datawarehouse for statistical analysis and provides the teams with tools for the first steps of analysis.

ACTIVITIES

- Design the architecture of the databases and associated files
- Installation and configuration of the databases
- Development of secured Web interfaces
- Conception of datawarehouses and datamarts
- Development of dynamic reports (BI)

2 - BIOINFORMATICS/BIOSTATISTICS

IVAN MOSZER AND BERTRAND FONTAINE

The Bioinformatics/Biostatistics team develops two kinds of expertise:

- processing of genetic/omics (genomic, transcriptomic, epigenomic) data, primarily derived from high-throughput sequencing, by offering computer programs and accompanying research projects;
- biostatistics, with an emphasis on the design and implementation of advanced methodologies for the integration of multimodal data (clinical observations, genetics/omics and neuroimaging).

ACTIVITIES

- Offer methodological advice and expertise in the design of and interpretation of biomedical studies.
- Define, apply, and offer procedures for treating high-throughput -omics data
- Design and apply biostatistical methods, in particular strategies for the integrated analysis of multimodal data

7 BIOLOGICAL RESOURCE CENTER

Samples taken from patients, including blood, biopsies, and surgical resections, are an extremely precious source of information for disease research. The ICM hosts three biobanks that collect, record, process, conserve, and distribute biological resources, including samples and associated data. This activity is strictly regulated by bioethics laws to respect patients and requires the approval of a Committee of Protection of Persons (CPP). Quality control of the three ICM Biological Resource Centers (BRC) is certified in conformity with the norm AFNOR NF S96-900. The biobanks are also part of the BRC network of biocollections for neuroscience which benefits from sharing resources and promotes the collections, as well as the national BioBank infrastructure.

3

TECHNICAL PLATFORMS

BIOLOGICAL RESOURCE CENTER

1 - THE DNA AND CELL BANK

ALEXIS BRICE, ALEXANDRA DURR, AND SYLVIE FORLANI

The DNA and Cell Bank – ICM amasses and manages collections of samples from medical research projects, mainly concerning neurological and psychiatric pathologies. In 2014, these collections contained about 182,000 samples of biological resources, including DNA, cells, blood cells, and fluids, and fibroblaststaken from more than 52,000 people, including patients, relatives, and controls, since the creation of the bank in 1990 and increased by an average of 3500 new samples each year.

These samples represent one of the most important collections worldwide, notably for pathologies such as Parkinson's disease, frontotemporal dementias, autism, and certain rare diseases such as spinocerebellar degeneration. In 2014, the bank was involved in 34 national and international research projects. The bank is equipped with important equipment, including an automated DNA extractor. Its quality control system was certified in conformity with the norm NF S96-900 in 2009.

PUBLICATIONS

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Tezenas du Montcel S et al. Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes. Brain. 2014 Sep;137(Pt 9):2444-55.

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Noreau A et al. SYNE1 mutations in autosomal recessive cerebellar ataxia. JAMA Neurol 2013, 70: 1296-1301

2 - BIOLOGICAL RESOURCE CENTER FOR MULTIPLE SCLEROSIS

BERTRAND FONTAINE AND ISABELLE REBEIX

This resource center is a bank of samples from patients with multiple sclerosis (MS), a disease with a strong socio-economic impact. Like the other ICM banks, the samples are distributed to researchers who work to better understand the physiopathology of the disease, improve existing treatments, identify new curative treatments, and refine the prognosis of the evolution of the handicap. Over the course of the last 6 years, the center has distributed 200,000 samples. The samples come from families that are either simplex, one affected child and his two parents, or multiplex, several affected members of a sibship, as well as sporadic cases and healthy subjects that serve as controls to determine what is specific to the disease.

To date, the DNA of 27,000 patients, 1739 visibly healthy relatives and 700 control patients is at the disposal of the scientific community. Each DNA sample is associated with detailed clinical data specific to MS as well as genetic data.

The center is also certified in conformity with the norm NF S96-900, specific to biological resource centers. A national project aimed at collecting biological resources from 30,000 MS patients was recently launched. In the context of this project, the center was selected to manage the DNA of these patients

3 - THE Tumor BANK: OncoNeuroTek

JEAN-YVES DELATTRE, MARC SANSON AND YANNICK MARIE

he tumor bank, OncoNeuroTek, is a biological resource center (APHP) specialized in samples from patients with brain tumors. It's the largest biobank of brain tumors in Europe and contains samples from about 15,000 patients. The large size is thanks to its location in the Pitié-Salpêtrière Hospital.The bank receives samples locally, and the hospital is one of the largest European centers for the diagnosis and treatment of brain tumors.

OncoNeuroTek collects, annotates, and conserves samples from patients with brain tumors. For over 15 years, it has collected tissues and also tumor DNA and RNA as well as patient DNA and plasma. The location of the samples and associated clinico-biological data are stored in a unique database, permitting the identification and extraction of samples necessary for projects associated with the tumor bank.

To promote the quality of its services and the professionalism of its personnel, the OncoNeuroTek tumor bank adheres to the principles and requirements of the French norm NF S96-900, specific to biological resource centers since 2012. After a two year period during which a correct and viable quality control system was implemented, the tumor bank was certified by AFNOR, the national organization for

standardization, certification, industry press, and training.

Since the OncoNeuroTek tumor bank was set up in the ICM, 16 collaborations have been established with research teams from all horizons: regional, national, and international.

PUBLICATIONS

Labreche K et al. TCF12 is mutated in anaplastic oligodendroglioma. Nature Comm, in press.

Di Stefano et al. Detection, characterization and inhibition of FGFR-TACC fusions in IDH wild type glioma. Clin Cancer Res. 2015 [Epub ahead of print]

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Gonzalez-Aguilar A1 et al. Recurrent Mutations of MYD88 and TBL1XR1 in Primary Central Nervous System Lymphomas. Clin Cancer Res. 2012 Oct 1;18(19):5203-11.

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Kristen Severi
Team of Claire Wyart

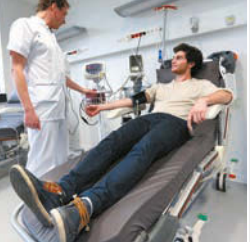
Transgenic
Gad1b:GFP
(Higashihima Lab)
zebrafish larva

CLINICAL INVESTIGATION CENTER

4

1. Parkinson's disease
2. Neurogenetics
3. Alzheimer's disease
4. Multiple sclerosis
5. Amyotrophic lateral sclerosis
6. Rare diseases
7. Understanding brain function: motivation
8. Participatory medicine

In 2014, 77 studies were ongoing in the ICM Clinical Investigation Center (CIC), directed by Pr. Jean-Christophe Corvol. The clinical trials concerned Parkinson's disease, Alzheimer's disease, multiple sclerosis, neurogenetics, neuropsychiatry, amyotrophic lateral sclerosis, peripheral neuropathies, epilepsy, and other neurological diseases.



4

CLINICAL INVESTIGATION CENTER

1 PARKINSON'S DISEASE

Deep brain stimulation of the subthalamic nucleus is a treatment that has beneficial effects for the motor symptoms of Parkinson's disease, however, it does not improve balance problems or falls. A therapeutic trial conducted at the CIC by an ICM team (Carine Karachi and David Grabli) showed that **stimulation of another deep brain nucleus, the pedunculopontine nucleus** (PPN), improves **gait and balance disorders** that resist pharmacological treatment in certain patients. The double-blind study, performed in six patients, showed a **decrease in "freezing" and falls** in three patients, as well as an **improvement in postural control** and **quality of life**. These results are very encouraging and open the way to the development of **new treatments for severe forms of Parkinson's disease**. However, they must be regarded with caution because of surgical complications observed during the study. Following this study, a grant was obtained from the **Michael J. Fox Foundation** for a larger scale **therapeutic trial** targeting the PPN.

The CIC also participates in the **evaluation of new pharmacological treatments** for Parkinson's disease. Trials of treatments for the **motor complications** of the disease, motor fluctuations and dyskinesias, were completed in 2014 or are ongoing (Jean-Christophe Corvol). Current treatments are not effective on "**non-motor**" symptoms of the disease, such as cognitive, sleep, or behavioral disorders or problems with the autonomous nervous system. Studies are being performed in the CIC to better understand these symptoms. For example, a very detailed imaging study of the brainstem has revealed brain **structures implicated in sleep and balance disorders** in certain patients (Marie Vidailhet and Isabelle Arnulf). A therapeutic study is also under way to try to improve **hypersalivation** (Marie Vidailhet).

Finally, an important effort has been made to progress in the **personalization** of treatments thanks to progress in genetics. A cohort of more than 400 patients is being followed at the CIC to identify predictive factors, and another study is under way in 400 patients, half of which have behavioral disorders induced by their anti-parkinson's treatment, which are dopaminergic agonists.

The major challenge for the coming years is to **stop the evolution of the disease** or even **prevent the appearance of symptoms** in **at-risk subjects**. The present phase remains the search for biomarkers that enable the progression of the disease to be followed or markers **preceding the appearance of symptoms**. To rise to the challenge, a study has just begun at the CIC on a cohort of **300 patients** (Jean-Christophe and Marie Vidailhet). The effort is shared with European (Sweden, Germany, Spain, AETIONOMY project) and **American** (Michael J. Fox Foundation) partners.

A **therapeutic trial** testing the **efficacy of bee venom** as a **neuroprotective treatment** was completed and the results are being analyzed (Andreas Hartmann). In addition, several new **potentially neuroprotective drugs** are being tested ex vivo, on blood from Parkinsonian patients or subjects at risk for developing the disease in partnership with the pharmaceutical industry.

2 NEUROGENETICS

The ICM (Alexis Brice and Suzanne Lesage) is an active partner in an **international consortium** that aims to define the **genetic profile of Parkinson's disease**. This project gave access to **whole exome sequencing,** sequencing all genes, in thousands of parkinsonian patients and recently identified **six new genetic risk factors** for Parkinson disease. The studies identified 24 genetic risk factors implicated in the disease, six of which had not been described. This great step forward in the story of this neurodegenerative pathology is the result of meta-analysis of all existing pan-genomic association studies performed on data from more than 100,000 people. Additionally, analysis of data from families of patients followed at the Pitié-Salpêtrière by the neurogenetics team led to the identification of new genes responsible for the disease, opening the way to new therapeutic strategies.

3 ALZHEIMER'S DISEASE

The first therapeutic trial aimed at **preventing the onset of Alzheimer's disease** is under way (Bruno Dubois, Isabelle Le Ber), the aim of which is to test the efficacy of a **neuroprotective agent** in **rare genetic forms** of Alzheimer disease with international industrial and academic partners. The study is original in that it also proposes to treat **asymptomatic people that are at-risk for the disease because they carry a mutation responsible for the disorder**. This is the **first neuroprotective therapeutic trial** to be undertaken in humans.

Other pharmaceutical agents are being tested at the CIC or the Memory and Alzheimer Disease Center (IM2A) coordinated by Bruno Dubois.

4

CLINICAL INVESTIGATION CENTER

4 MULTIPLE SCLEROSIS

Three new treatments already tested in the CIC are **now commercially available**, including a treatment to improve gait disorders, fampridine, and two new treatments for inflammatory forms of multiple sclerosis (Catherine Lubetzki, Isabelle Papeix, Maya Tchikiladze).

Research concerning **progressive forms** of the disease is ongoing. CIC teams hope to discover **differential biomarkers** of inflammation, myelin destruction, and neurodegeneration (Bruno Stankoff). Studies aimed at testing agents to slow the **progression** of the disease, two studies, and **promoting remyelination,** one study, are ongoing. A **pre-clinical** study to test the **efficacy of a new treatment** was performed on 70 patients with different types of multiple sclerosis.

Finally, the CIC participated in two therapeutic trials aimed at developing a new treatment for multiple sclerosis symptoms developed by MedDay, a company incubated in the ICM. The **efficacy of MD1003**, a new agent against the progressive form of MS was just confirmed by a Phase III study involving 154 patients. This treatment not only slows the progression of the disease but also improves the health status of certain patients.

5 AMYOTROPHIC LATERAL SCLEROSIS

The results, unfortunately negative, of a therapeutic trial in which the CIC participated were announced in 2014. The fight continues, however, with **several therapeutic trials** now underway in the CIC (François Salachas, Pierre-François Pradat). The CIC is also contributing to a better understanding of the **mechanisms implicated** in this disease by combining **clinical analysis**, **electrophysiological approaches**, **imaging of the spinal cord,** and **biomarkers in blood or biopsies** (Pierre-François Pradat, François Salachas, Lucette Lacomblez, Thomas Lenglet). Additionally, the CIC contributes to the development of a **tool for writing with the eyes** for patients with severe motor disorders (in collaboration with Jean Lorenceau).

6 RARE DISEASES

Aside from Parkinson's disease, the CIC also contributes to a better understanding of and the development of new treatments for **related rare diseases**. The CIC participated in one of the first international therapeutic assays in **progressive supranuclear palsy** (Jean-Christophe Corvol). Although the results of the trial were unfortunately negative, they nonetheless provided information on the disease progression, which will facilitate development of future clinical trials.

On the occasion of the 50 years of the discovery of this disease, the CIC, in conjunction with the **French association of PSP patients,** organized a workshop in which clinicians, researchers, and industry reflected on the best way to identify new pharmaceutical agents for this disease in June 2014.

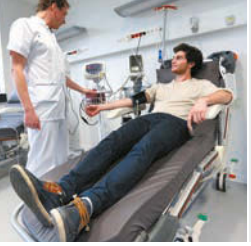
The gene responsible for a very rare disorder of bimanual motor coordination was identified thanks to a collaboration of ICM researchers (Christel Depienne and Emmanuel Roze). The physiopathology of this disease was then studied in experimental models and the results were confirmed in humans.

A therapeutic trial was conducted at the CIC to test the **efficacy of an anti-epileptic drug** in the treatment of dystonias with **myoclonus** (Emmanuel Roze). The results are being analyzed.

Other pathophysiological studies or therapeutic assays are being performed in several rare diseases, including cerebellar ataxias, channelopathies, metabolic disorders, and others (Alexandra Dürr, Fanny Mochel, Bertrand Fontaine, Savine Vicart).

7 UNDERSTANDING BRAIN FUNCTION: MOTIVATION

In addition to therapeutic trials and studies aimed at better understanding the mechanisms of certain pathologies, the CIC is also at the service of ICM researchers who try to better **understand the function of the human brain**. For example, a series of studies were carried out in **healthy volunteers** to determine which neurotransmitters are implicated in the **phenomenon of motivation** (Mathias Pessiglione).



4

CLINICAL INVESTIGATION CENTER

8 PARTICIPATORY MEDICINE

The CIC has begun to **evaluate patients** at home in order to study the evolution of the disease in an ecological environment via **intelligent applications**. Tools for evaluation and also reeducation through intelligent games are being used, notably for gait disorders in parkinsonian patients. Various tools for the follow-up of patients are also being used, notably for epilepsy. In collaboration with **Alexis Genin** (the IHU-A-ICM and the Pitié-Salpêtrière Hospital), a work group ("living lab") is being set up in which **patients**, **developers,** and **health professionals** meet together to generate ideas and apply them in order to best respond to the needs of patients.

The Clinical Investigation Center received support from the EDF Foundation


ICM

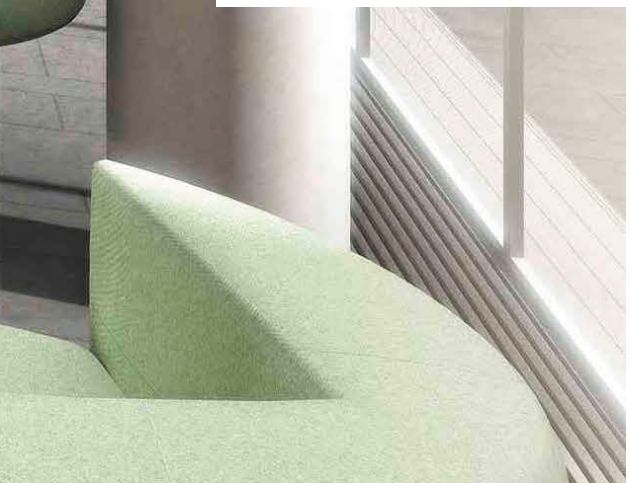
RESEARCH APPLICATIONS

5

1 Transform knowledge and promote research

2 iPEPS-ICM companies

The ambition of the ICM is not only to perform excellent research, but above all to use the knowledge and abilities of researchers for the development of new treatments. To achieve this aim, the "Research Applications" team is composed of people with doctoral degrees in science who have worked in industry and specialists in innovation and the creation of start-ups. The team detects scientific results that inspire hope, creates partnerships with the most active companies in the health field, protects discoveries by patents, and initiates work on projects to develop new treatments. To promote all the work of the institute and permit researchers at the institute to create their start-ups, the iPEPS-ICM incubator establishes a bridge between research and concrete applications. This promotion of knowledge and know-how permits the rapid transformation of creation of the fruits of research into medical applications. It should ensure the autonomy and competitive status of the ICM.



5

1 TRANSFORM KNOWLEDGE AND PROMOTE RESEARCH

The ICM has been awarded the prestigious "Carnot Institute" label, which supports its strategy of establishing industrial partnerships. Thanks to this support, the Research Applications team utilizes a proactive approach to detect innovation resulting from ICM research and to establish **collaborations with industry.**

In 2014, **70 partnerships** were established, including **20 new scientific collaborations.** For example the ICM established a partnership with the Californian company **Ultragenyx** for a clinical Phase II study of a molecule identified by the ICM and Inserm against **Huntington disease.** A particular effort was made to ensure the quality of the management of the partnership in order to encourage teamwork and retain loyalty on the part of the industrial partners, more than half of which are international.

2 IPEPS-ICM COMPANIES

iPEPS-ICM stands for "Paris-Salpêtrière Business Incubator." This structure, created in 2012, is the **first accelerator of innovation dedicated to diseases of the brain in France**. This incubator/accelerator facilitates the relationships of companies with both **investors** and **clinical experts** and helps them to establish research collaborations with **ICM** teams.

2014 WAS THE YEAR OF SUCCESSFUL START-UPS IN THE iPEPS-ICM

The **efficacy of a new agent, MD1003**, against the **progressive form of multiple sclerosis** was just confirmed by a **clinical Phase III trial**. This treatment not only slows the progression of the disease but also improves the state of health of the patients. At the origin of this treatment is **MedDay**, a start-up founded by the neurologist Frédéric Sedel and Guillaume Biron. This company has been incubated at the ICM since its creation.

Three projects incubated at the iPEPS-ICM or derived from research in the institute **won prizes at the world innovation competition**: **DREEM**, a connected headband that optimizes sleep, **Brain e-NOVATION** that creates **e-health solutions** on the basis of video games, and **Bio serenity** that develops an **intelligent health** solution for the **follow-up** and **diagnosis of epilepsy**.

Ad Scientiam has developed **two smartphone applications** to **both measure motivation** and also to **follow the "on" and "off" phases of patients with Parkinson disease**. **Ad Scientiam was included in a ranking of the 100 most innovative start-ups in France**.

SIX NEW COMPANIES

With the addition of **six new start-ups in 2014**, the **iPEPS-ICM** now hosts **20 industrial partners** of the institute and is now full.

This year, the first **international companies** established offices in the ICM: **Neoventures Technologies (Ontario)** that develops **new biomarkers of Alzheimer's disease** and **PathMaker (Boston)** that works on a **program of electrical stimulation of the spinal cord to facilitate walking**.

THREE NEW PATENTS

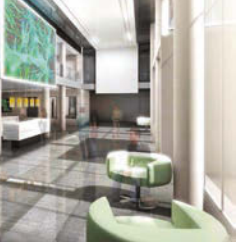
Three new patents were obtained:

Hand me, a life agenda for **epileptic patients** in the form of a **smartphone application**, **ZebraZoom**, software for the **automatic tracking of zebrafish behavior** developed in collaboration with **Claire Wyart**, **triheptanoin**, a molecule for treating **Huntington disease**.

TWO NEW PROTOTYPES

Toap Run, a video game for the prevention of falls in patients with **Parkinson's disease** was finalized and the first clinical trial is underway.

The prototype of the **Melomind headset**, created by **My Brain Technologies**, was presented at the **CES 2015 in Las Vegas**. The connected headset that induces



relaxation through the use of specific sounds.

The iPEPS-ICM INFRASTRUCTURE

In addition to supporting young companies in terms of support and logistics, the iPEPS-ICM offers more than 1000m^2 of offices, laboratories, open space and meeting rooms. It also offers the use of **advanced technology platforms** in the central part of the building, which favors encounters.

iPEPS-ICM hosts both companies that develop **new pharmacological treatments** and companies that specialize in **medical technologies**. The structure also houses start-ups developing **new diagnostic solutions** in order to treat diseases earlier, and **"connected health" tools**, such as video games, to help the elderly maintain their autonomy. Here again, **openness** is a source of **potential partnerships** and **creativity** at the **service of patients**. Life in the incubator has also evolved, notably due to "**Lift sessions**" that are the occasion for regular discussions and dialogue among the different members of the structure.

THE FUTURE

Over the course of these last years, **medicine has been radically transformed**. **Digital solutions** are now integrated to help patients **remain autonomous** thanks to tools like tablets or smartphones and **medical technology**. Great developments will also occur in the field of **prevention**, the best treatment being to remain well. The next great ambition of the ICM is to ally itself with partners to develop **research programs** aimed at developing new strategies to **prevent or delay the development of diseases**. These strategies could include nutritional approaches, physical activity, "bio-feedback" and more.

You will find all the companies of the iPEPS-ICM on the site icm-institute.org

You will find all the companies of the iPEPS-ICM on the site icm-institute.org

KEY FIGURES

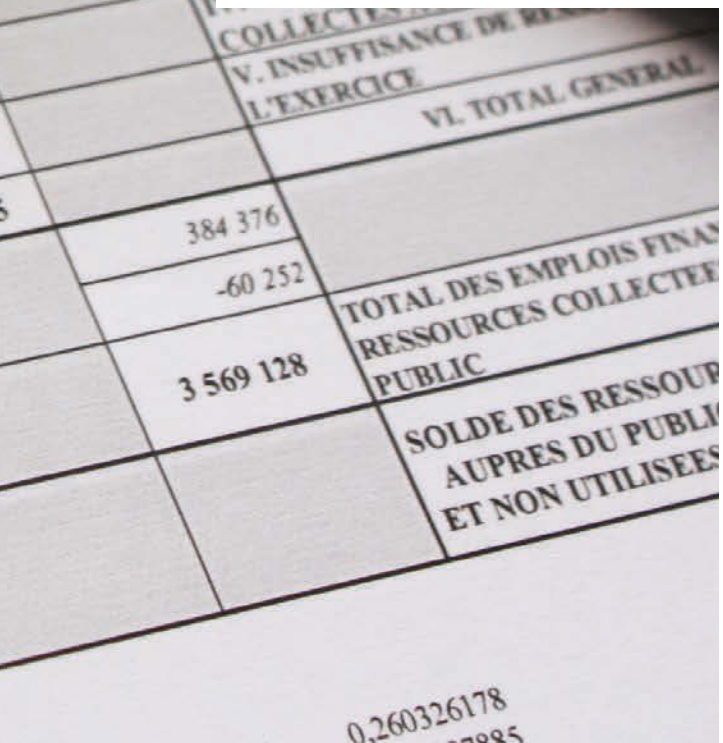
6

1 Fundraising

2 Use of Resources Statement

3 Balance sheet

All the acts and discoveries of the ICM were made in total transparency; the "Comité de la Charte du Don en Confiance" (Charter committee for donating with confidence) awarded the ICM its approval in 2010 and again in 2014. The last report attests that the ICM Foundation accepts the principles of the Charter committee, statutory functioning and disinterested management, rigorous management, high quality communication and fundraising campaigns, and financial transparency. You will find below the use of resources statement and a detailed presentation of the accounts of the ICM for the fiscal year.



1 FUNDRAISING

Revenue from fundraising in 2014 reached 11.1 M€ at the end of the fiscal year. More than 76.8 M€ in accumulated donations and pledges have been raised since the creation of the ICM.

In 2014, three important contracts with sponsors were signed over the course of the year with:

- Fondation EDF to support a research program studying the mechanisms of the appearance of Parkinson's disease.
- Fonds de dotation Pierre Bergé to finance upgrading of the 3T MRI
- Fondation AREVA to support research on cerebral dystonia.

On July 4, 2014, the Friends of the ICM Circle was launched. It assembles donors who were engaged in the adventure of the ICM from the beginning and who have donated large sums of money (10,000€ or more).

The Circle was created to specifically thank important donors who have been active all throughout the financing campaign launched by the ICM in 2008.

The Circle now has 447 members. To express our gratitude, exclusive activities are proposed including encounters and discussions between donors and researchers to keep donors updated on research perspectives and the use of donations.

The Circle is presided over by Mr. Maurice Lévy and Mr. David de Rothschild, Founding Members of the ICM.

In the context of the development of the Circle beyond our borders, the ICM organized a charity dinner in London for potentially important donors in April 2014.

In order to increase its donor base, the ICM has pursued its strategy of direct marketing initiated in 2010. An investment of 2.3 M€ divided among 11 fundraising campaigns yielded 4.5 M€ for the fiscal year and increased the donor base by more than 26,000 people for a total of 85,000 donors at the end of 2014.

Finally the ICM is particularly grateful to families who collected donations in memoriam for the benefit of the Institute.

DONATIONS IN KIND AND SPONSORSHIPS

Many companies have offered their support by contributing know-how in their field of activity or by offering products free of charge.

The ICM has benefited from

- Media space offered by Amaury média, Europe 1, Lagardère Publicité, Canal+, NRJ, Médiavision, FigaroMédias, TF1 Publicity, France Télévisions, Clear Cjannel, Metrobus, A nous Paris, Figaro.fr, Liberation.fr, Au féminin.com, Skype, CCM Benchmarck, Doctissimo, Orange, GMC Factory, AOD, HiMedia Group, RMC, AB, L'EQUIPE, TMC, A ir France, Credit Agricole Center Ouest.
- Free services: Publicis, 1000 Mercis, Samsung, Orrick Rambaud Martel, VH 15, Quaterback, E-makina, IDEC, E-Art Sup.

THE ICM IN FRANCE

The ICM has continued its regional expansion. In 2014, three regional antennae were organized around the following objectives:

- Reinforce the visibility, reputation, and attractiveness of the ICM for donors, the general public, and economic and political figures
- Contribute to the development of financial resources of the ICM to accelerate scientific advances with its own research teams and their regional, national, and international partners
- Bring together ICM and regional researchers in neuroscience and promote these collaborations.

This approach will be progressively extended to other regions on different themes related to nervous system diseases.

2

THE USE OF RESOURCES STATEMENT – 2014

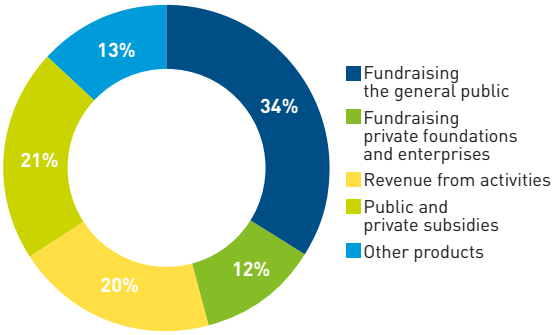
THE FISCAL YEAR ENDED ON DECEMBER 31, 2014

USES	Uses N-Profit and loss statement	Allocation of resources by use
Social Missions	**18 965 223**	**6 916 634**
ACTIONS DIRECTLY CARRIED OUT		
Research program	11 013 534	2 214 343
Technological platforms	5 615 960	2 765 179
Other (including research applications, incubator and events/ international partnerships)	2 335 729	1 937 112
Costs of fundraising	**3 370 951**	**2 622 523**
Costs of appeals to the generosity of the general public	2 621 283	2 620 112
Costs of the search for other private funds	304 600	0
Costs related to the search for subsidies and other public competitions		
Costs of communication	445 069	2 411
Costs of functioning of the organism	**1 824 796**	**197 826**
I. TOTAL USES IN THE PROFIT AND LOSS STATEMENT	**24 160 971**	**9 736 983**
II. PROVISIONS	**15 600**	
III. EXPENSES TO BE CARRIED OUT ON ALLOCATED RESOURCES	**3 063 917**	
IV. SURPLUS RESOURCES OF THE FISCAL YEAR	**0**	
V. GRAND TOTAL	**27 240 488**	
Part of fixed assets acquired during the fiscal year financed by funds collected		
Neutralization of the provisions for depreciation of fixed assets financed by funds collected		-140 563
TOTAL USES FINANCED BY FUNDS COLLECTED FROM THE PUBLIC		**9 596 420**

RESOURCES	Resources collected- profit and loss statement	Resources collected and used
Carryover of resources collected from the public not allocated and not used at the beginning of the fiscal year		**1 922 760**
Resources collected from the general public	**8 195 737**	**8 195 737**
Unallocated monetary donations	7 374 482	7 374 482
Allocated monetary donations	153 880	153 880
Unallocated bequests and other gifts	507 248	507 248
Allocated bequests and other gifts	0	0
Other products related to public generosity	160 126	160 126
Other private funds	**7 330 572**	
Patronage	2 937 934	
Partnership	2 568 326	
Private grants	1 824 312	
Subsidies and resources from public competitions	**3 277 873**	
Other products	**5 190 670**	
Financial products	272 423	
Services offered	2 193 039	
Other products	2 725 208	
I. TOTAL RESOURCES FROM THE PROFIT AND LOSS STATEMENT	**23 994 851**	
II. CARRYOVER OF PROVISIONS	**0**	
III. CARRYOVER OF UNUSED ALLOCATED RESOURCES FROM PREVIOUS FISCAL YEARS	**2 253 667**	
IV. VARIATION OF ALLOCATED FUNDS COLLECTED FROM THE PUBLIC		**37 698**
V. RESOURCES LACKING FOR THE FISCAL YEAR	**991 969**	
VI. GRAND TOTAL	**27 240 488**	**10 156 195**
TOTAL OF USES FINANCED BY RESOURCES COLLECTED FROM THE PUBLIC		**9 596 420**
BALANCE OF RESOURCES COLLECTED FROM THE PUBLIC NOT AFFECTED OR USED AT THE END OF THE FISCAL YEAR		**559 775**

EVALUATION OF VOLONTARY CONTRIBUTIONS IN KIND			
Social missions	44 818	Volunteers	44 818
Costs of fundraising		Services in kind	
Costs of functioning		Contributions in kind	

RESOURCES 2014



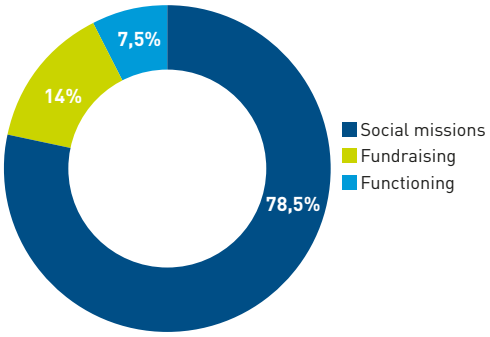
The resources for 2014 reached **26.2 M€**. They include 24 M€ of products of the fiscal year and a carryover of 2.2 M€ affected but not used during previous fiscal years.

The products of the fiscal year correspond essentially to revenues from fundraising (46%), either from the general public (34%) or private foundations and companies (12%).

They also include:

- Revenues from the activity of the technical platforms (2.2 M€) and research collaborations with industrial partners (2.6 M€).
- Public (3.3 M€) and private (1.8 M€) subsidies.

USES 2014



The grand total of uses for 2014 reached **27.2 M€**: 24.1 M€ used in 2014 and 3.1 M€ affected for later use. Among uses in 2014, the amount dedicated to social projects reached 19 M€, which represents 78.5% of the total uses for the fiscal year. The social projects include:

- Research projects (58%)
- Technical platforms (30%)
- Scientific events and international partnerships (9%)
- Incubation of innovative enterprises (3%)

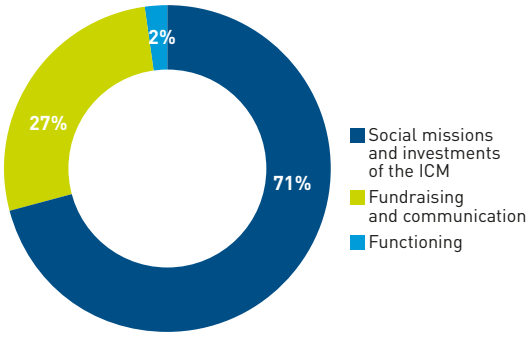
The research projects financed were dedicated to neurodegenerative diseases and spinal cord injury. The technical platforms (neuroimaging, vectorology, sequencing, genotyping, cell culture, and histology) contribute to these projects.

The costs of fundraising correspond to expenses related to the collection of funds from private people (donations and bequests) and private companies and foundations (sponsorship and support). They represent 14% of the uses.

The costs of functioning correspond to the expenses of the support teams (finance, personnel, informatics and logistics), which represent 7.5% of the total uses for the fiscal year. Uses to be carried out on affected resources (3.1 M€) correspond principally to donations from companies and foundations received during the year to be used later for specific pluriannual research programs.

USE OF RESOURCES STATEMENT

USE OF RESOURCES COLLECTED FROM THE PUBLIC



Resources collected from the public at large and used in 2014 reached 9.6 M€.

In brief, out of 100 € of resources collected from the general public, 71 € were used to finance the social projects and investments of the institute, 27 € were used for fundraising, and 2 € covered the costs of functioning of the ICM.

3 BALANCE SHEET

SIMPLIFIED BALANCE SHEET

ASSETS (In K€)	31.12.14	31.12.13
Net immobilized assets	10 168	11 778
Realizable and available assets	32 678	27 822
Total	**42 846**	**39 600**

LIABILITIES (IN K€)	31.12.14	31.12.13
Association funds	20 418	23 720
Results of the fiscal year	-992	-3 112
Dedicated funds	4 694	3 884
Debts	18 726	15 108
Total	**42 846**	**39 600**

The total amount of investments by the ICM since its creation has reached nearly 21 M€, mainly dedicated to the technical platforms that support research.

Investments during the fiscal year reached 1.1 M€:

The ICM acquired a cryoprobe for imaging, completed its equipment for the functional experimentation platform, and finished the installation of its business incubator.

The net immobilized assets reached 10.1 M€. As of December 31, 2014, the treasury amounted to 18.4 M€.

The equity of the ICM was 19.4 M€. It included 11.7 M€ of association funds plus 2.6 M€ of subsidies for investments and a carryover of 5.1 M€. The non-expendable endowment of the ICM is 1.2 M€.

At the end of the fiscal year, dedicated funds (funds remaining to be used for specified programs) reached 4.7 M€.

EXCERPT FROM THE 2014 REPORT OF THE CONTROLLER OF THE *COMITE DE LA CHARTE POUR LE DON EN CONFIANCE*

"The last three year period saw the rapid and courageous launching of the social missions of the Foundation, which set up high level teams and their equipment in a superb building. The foundation offered its researchers facilities that they did not previously have access to and reinforced perspectives for the internationalization of their work in a variety of ways.

The new period that is starting is characterized by the desire to set up a stable organization based on a rational and concerted public/private partnership endowed with balanced financial bases, while maintaining the same ambitions for high level performance in the sphere of national and international scientific research."

LIFE IN THE ICM

7

1 Scientific and extra-scientific lectures

2 Fundraising events and the publicity campaign

The ICM has developed a strategy of scientific and extra-scientific activates that include both numerous exchanges among the research teams and also encounters with high level scientists and personalities from society. Additionally, in 2014, the ICM developed communication programs consisting of cultural and sporting events in partnership with associations and enterprises. These events are initiated by the ICM or organized for its benefit in order to raise funds and for it to become better known. In parallel, the institute benefited from an ambitious publicity campaign conceived by Publicis Conseil, along-term partner of the ICM.

1 SCIENTIFIC AND EXTRA-SCIENTIFIC LECTURES

Twenty-eight events of scientific interest took place during the year at the ICM, including 3 prestige lectures: Prof. Richard Frackowiak of the Vaudois University Hospital Center with a lecture entitled, "The nosology of brain diseases – an informatics and data lead approach," Sten Grillner, of the Neuroscience Department of the Karolinska Institute in Stockholm, with a lecture entitled, "The logistics of network in motion – from microcircuits to selection of behavior," Eve Marder, of the University of San Diego, in California, with a lecture entitled, "Variability, robustness, and homeostasis in neurons and networks." The inaugural lecture of Brain Awareness Week was given by Philippe Vernier, Director of the Alfred Fessard Institute of Neurobiology, CNRS, on the question, "Evolution of intelligence and the size of the brain: is there a relation?"

ICM researchers organized numerous colloquia at the ICM. The institute hosted the 1st International colloquium on the cellular Imaging Network of Pierre and Marie Curie University, the European Congress on Gilles de la Tourette Syndrome, the 4th International Symposium on the Biology of Decision-Making, the 1st International Colloquium on Neuroethics, the 1st Colloquium on Neuroimmunology; Neuropsychology Day that brought together many clinicians, Scientific Day of the Life Sciences Section of the *Ecole Pratique des Hautes Etudes*.

The six extra-scientific lectures were also the occasion to expand the field of discussion. This year, Jean-Claude Ameisen, President of the National consultative committee on ethics – Professor at the University of Paris (erreur dans la version française. MR) – Diderot, reflected on memory: "What is left of what has disappeared?" Actress Dominique Blancread texts by Marguerite Duras. Stage director Bruno Abraham-Kremer gave a reading based on the correspondence and works of Anton P. Tchekov. Laurent Cohen, Professor of neurology and researcher at the ICM, debated the subject of neuropsychology, "The brain as spare parts." John Harris, professor of bioethics at the University of Manchester, participated in the 1st Colloquium on Neuroethics. Eric Burguière, ICM researcher, and Yves Sarfati, psychiatrist, presented a scientific show. Mathieu Lehanneur, creator/designer, gave a lecture, Architecture that combines design, science, art and

technology to improve the lives of its users." And finally, Jean D'Ormesson gave a lecture entitled, "Why do we write?"

The ICM also hosted the inaugural lecture of the 50 years of INSERM, given by Prof. Yves Agid, Honorary Professor of Neurology and Neuroscience and Founding Member of the ICM, on the subject, "Normal and pathological subconsciousness."

Each month, convivial moments are organized to permit researchers, teams, and companies to meet together and discuss their projects and research results.

Finally, each year the ICM participates in pedagogical activities with two programs directed toward young people, in collaboration with INSERM, the Rectorat of Paris and life science teachers in junior and senior high schools, as well as elementary schools. In the program *"Chercheurs en herbe"* (Budding researchers), students are immersed in the life of the laboratory and carry out a research project during the school year, assisted by young researchers. "Destination labo" provides the occasion to bring young people into the laboratories in order to familiarize them with research-related professions.

Finally, the research teams of the ICM participated in the encounter "Patients-Researchers" organized by Inserm in October.

THE ASSOCIATION OF YOUNG RESEARCHERS: LES AJITES

The association "les Ajités" was born of an initiative of a group of young researchers who identified the need for a framework in which to meet together to discuss their work when the ICM was created. They organized the first retreat of young researchers in 2010 and initiated the first socio-cultural activities of the future institute.

Since then, this group of young researchers has become official with the citation of the association in the JO (Official Journal) in February 2012. The annual retreat, organized with the help of the Communications Department, has become an essential event on the ICM's scientific calendar.

This three-day retreat not only gives rise to high level scientific discussions, but is also the occasion for the young researchers to develop a "spirit of the institute" through the social relations they establish. This year, they inaugurated the first edition of the Brain Booster Challenge. This unique workshop offers the participants the possibility of developing their capacity to create innovative and interdisciplinary research projects and thus assimilate, in an original way, the obligations of their profession.

Throughout the year, the association organizes scientific and cultural events, which serve to maintain scientific interactions among the young researchers of the Institute, thanks to the financial aid and logistics of the ICM. The monthly "Science Pizza" provides the possibility of continuing discussions in a more informal setting than a seminar. This date has become a staple of the young scientific community, an average of 80 people participate each month. The

7 SCIENTIFIC AND EXTRA-SCIENTIFIC LECTURES

Ajités also organizes informal lunches for young researchers with the weekly lecturer as part of the scientific events of the Institute; the youngest members of the institute thus have the possibility of privileged discussions with internationally renowned researchers. In addition, the association organizes oral training sessions in which the participants learn the basic techniques of handling stress and using their voice, with the aim of improving their oral presentations.

The "Happy Hours," to which all members of the personnel of the Institute are invited, encourage the creation of a social fabric in the building. The first Scientific Photography Competition in the Institute was a real success. The winning photographs were exhibited in the hall and on the social networks.

Finally, the association offers an extra-scientific framework for diverse activities open to all the personnel of the Institute.

2 FUNDRAISING EVENTS AND THE PUBLICITY CAMPAIGN

SPORTING AND CULTURAL EVENTS

This year, **nineteen sporting** events supported ICM research, such as the operation "Un chrono pour un Don," the meeting of the automobile association "Fée rarissime," Classic Days, the association Sogno Di Cavallino, the "Teufs Teufs du Coeur" organized by the Lions Club of Essarts le Roi, or the women's tennis internationals of Strasbourg. All of these partners, new or faithful to us, enabled the collection of funds for the benefit of the ICM while associating pleasure and generosity everywhere in France. The **universe of sailing**

was honored, notably by the support of Francis Joyon who started on the "Route du Rhum" aboard the trimaran IDEC flying the colours of the ICM. The navigator also crossed the finish line at Rio de Janeiro by starting on the "Route de l'Amitié." The Institute was also present at the competition "Les Voiles de St. Barth," a regatta in the heart of the

Caribbean, with a Gala for the profit of the ICM. In 2014, **our faithful partners** once again associated the ICM with sporting events such as "La tête c'est le pied," the Golf trophy "les Echos" and the "20 KM de Paris." The ICM also benefited from an auction organized by the Porsche Club France.

A year full of challenges was highlighted by the engagements of athletes proudly wearing the colors of the ICM to help research, like Christel Chinour, who ran the Paris, Moscow, and New York marathons, but also Blandine Tissot and her solitary race in Grenoble. The institute and its research teams also participated in the "Marche Solidaire Main dans la Main," in order to increase awareness of ALS (amyotrophic lateral sclerosis) and the work of ICM teams on this subject. **Lovers of vintage automobiles** were also mobilized by a new event, the "Classic Festival."

Fourteen cultural events took place inside and outside the walls of the ICM, such as the projection, to thank donors, of the film LUCY in the presence of **Luc Besson,** a French film maker, producer, scriptwriter, and Founding Member of the ICM, followed by a debate/discussion with Prof. Yves Agid. **Liz McComb,** gospel diva, enabled the ICM to organize its first gala of the season, a concert at the Olympia music hall. In addition, the **extra-scientific lectures** at the ICM

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were also moments in which music made itself heard, with concerts such as: the jazz concert of the group led by Jérôme Yelnik, an ICM researcher, the concert of **Quatuor Quad,** the concert of the soloists of the Paris Symphonic Orchestra under the direction of Cyril Diederich, the concert of the Groupe AOURA.

And the link between the ICM and music does not stop there! Several musical events took place for the benefit of the ICM, notably with one of its most faithful partners, the association **Music Passion Parkinson,** but also the Lions Club that offered a concert/show about the life of Barbara, in Limoges, in addition to charity events such as the one organized by IDEC.

For the fourth consecutive year, the **FIAC** supported the ICM on the occasion of the breakfast "Happening Créatif et de Collecte" around a creation of the artist

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FUNDRAISING EVENTS AND THE PUBLICITY CAMPAIGN

Emmanuelle Antille, photographer, video and filmmaker, in collaboration with the **teams** of Stéphane Charpier and Michel le Van Quyen. The aim was to design an operation mixing Art and Science.

The ICM also participated in other **events mixing science and culture** such as: **Conf'&Sciences** organized by the student association IndeSciences, the Festival Pint of Science where one discusses science in a bar, a concept just imported from London, or yet the permanent **"neuro-playful" exhibition "C3RV34U"** at the Cité des Sciences et de l'Industrie in Paris. In addition, the ICM organized a lecture on Jean-Martin Charcot by **Catherine Bouchara** and **Lionel Naccache** during Brain Awareness Week that also included amusing and creative workshops. Within the same context, the ICM participated in the projection of a choreographic documentary **"Eloge du Movement,"** derived from a neuroscience research protocol, developed by the ICM, to evaluate the role of dance in the hospital. The principal investigator is Alexandra Durr.

Additionally, the ICM profited from **auctions,** including the sale of prestigious automobiles of Puymirol, organized by the **Lions Club d'Agen of Val de Garonne,** and also a bottle **offered for charity** by the **Château du Clos de Vougeot** at the 53rd wine sale of the Hospices de Nuits-Saint-Georges, presided over by the actor Patrick Timsit, faithful to the ICM. Particularly moved by research conducted at the ICM, **F.P. Journe celebrated, this year, the 10 years of his association with the Institute,** and continues to offer 30% of the profits from the sale of each Centigraphe to the ICM. Since 2008, 525 Centifgraphe Souverains and Centigraphe Sports have been sold and contributed to the advancement of research at the Institute.

Each of the **Journées Mondiales** (Alzheimer, Parkinson, multiple sclerosis, epilepsy, ALS, etc.) is an important date in the life of the ICM. The institute never misses an occasion to publish and present the numerous studies and advances of its research. Every trimester, the **"Rendez-vous ICM"** are the occasion for donors to meet with the different members of the research community and discuss the latest advances.

THE PUBLICITY CAMPAIGN

The ICM is based on an original financial model combining public and private funds for faster reactivity. Support and donations are essential. The ICM therefore launched a **new campaign to attract donations** by placing the heart of the association, medical research, at the center of its communication.

It's the message that the Institute wanted to transmit in order to remind the public of the importance of helping research on nervous system disorders and accelerate progress.

With humor, the publicity film **imagined by Publicis Group, a long-term partner of the ICM,** created a surprise by addressing a broad public. On a bluesy background, four researchers, among their test tubes, begin a clumsy strip tease to collect funds to advance their work. With this publicity film and its simple setting, the ICM sought to address the public at large with the fundamental question: "Is this the only way to finance research on the brain and the spinal cord?" Far from a guilt-inducing sermon, the campaign counted on the emotion aroused to share a very positive message: by contributing to the ICM you are giving researchers the means to carry out their ambitions.

This multimedia campaign (TV, movies, web) was supplemented by poster and press campaigns with same humor and wacky tone. On the model "Save our planet, the ICM, with "Save our brain, help researchers protect it", continues to try to surprise readers by proposing a catchy phrase and an unexpected response in two new typographic messages of high intensity.

GOVERNANCE, OVERSITE, AND TRANSPARENCY

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GOVERNANCE, OVERSITE, AND TRANSPARENCY

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GOVERNANCE AND OVERSIGHT

GOVERNANCE, OVERSITE, AND TRANSPARENCY

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THE FRIENDS OF THE ICM CIRCLE

CERCLE DES AMIS DE L'ICM

The Friends of the ICM Circle brings together the grand donors of the institute: individuals, companies, foundations, and associations. Strong partners of the ICM, they have placed the force of their philanthropy at the service of research on the nervous system.

- From the beginning, the "founding grand donors" supported the ambitious idea of creating a neuroscience institute in the heart of the Pitié-Salpêtrière Hospital in Paris.
- Mobilized by the Campaign Committee between 2008 and 2012, the pioneer grand donors helped concretize this unique and innovative research model.
- The grand donors joined them in relation with the members of the Committee of the Friends of the ICM or from different horizons.

The Friends of the ICM Circle is open to all people, companies, foundations or associations wishing to support the ICM. The office of the Friends of the ICM Circle is present to accompany the grand donors, advise them, put together custom made projects and define sponsorship strategies that reflect the wishes of each.

The Circle is meant to grow.

The mission of the Committee of Friends of the ICM is to invite new donors to join the Circle in order reinforce the resources of the ICM and thus permit researchers to pursue their ambitious work.

The Committee of Friends of the ICM is composed of:

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The Friends of the ICM Circle is international.

The ICM has established a relationship with Transnational Giving Europe (TGE), a partnership of European foundations and associations that allows a donor who pays taxes in one of the partner countries of the TGE to support the ICM while benefitting from the fiscal advantages offered by his country of residence.

The ICM shows its gratitude to the members of the Circle of Friends of the ICM.

The Donors' Wall is located in the hall of the ICM to pay homage to all of its major supporters. The Grand Donors are also mentioned, if they so desire, in the activity reports of the ICM and its researchers.

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GOVERNANCE, OVERSITE, AND TRANSPARENCY

FRIENDS OF THE ICM CIRCLE ACTIVITIES

Throughout the year, members are invited for private visits of laboratories, scientific and cultural lectures, and meetings with researchers.

- **April 3, 2014 – LONDON – dinner at the Rothschild Bank**

The first evening in support of the ICM in Great Britain.

- **July 4, 2014 - Lecture inaugurating the Friends of the ICM Circle**

Grand donors met at the ICM and were introduced to life at the institute, the great scientific advances, the challenges for research, and how donations are used. Donors then visited the laboratories, the incubator, and met with several research teams.

Launch of the Friends of the ICM Circle

The **FIAC (International Contemporary Art Fair)** supported the ICM for the fourth consecutive year. An artistic performance was organized at the Petit Palais the day of the inauguration of the FIAC. Emmanuelle Antille, a Swiss artist, created a video in collaboration with the team of Stéphane Charpier that progressed thanks to the concentration of the public and their donations.

October 22, 2014: FIAC: Breakfast and performance, "Art-Science"

- **November 18, 2014: Breakfast at the Rothschild Ban**

Dr. Marie-Laure Welter, neurologist and neurophysiologist, presented her research to the members of the Circle.

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