INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE

BRAIN & SPINE INSTITUTE - PARIS

ANNUAL REPORT 2013

SEARCH, FIND, CURE, FOR YOU & WITH YOU

ICM
Brain & Spine Institute

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EDITORIAL

2013 was a year rich in advances across all of our sectors of activity.

This was made possible by the mobilization of everyone: donors, researchers, deciders. The ICM is a reality: we have concentrated in the daily management of research and its applications, while remaining focused on our future objectives.

Together, we continue our **fight against the diseases of the brain and spinal cord.**

• Translational research has developed thanks to the 600 researchers of the Institute, and **important scientific advances concerning the neurodegenerative diseases** have been made. The mutual commitment of the researchers to the fight against neurological diseases has continued and the quality of their work, the awards they have won and the French and European financing they have obtained attest to the scientific excellence of the Institute. In 2013, for example, an ICM team identified a protein permitting a better diagnosis of amyotrophic lateral sclerosis and the development of a treatment. Another team significantly advanced our understanding of multiple sclerosis and myelin repair by identifying a compound essential for communication between neurons, which when altered causes this disease (1). Researchers of the ICM have also identified a new gene associated with a hereditary form of epilepsy (24). Finally, one team has identified a means for predicting the onset of epileptic seizures in patients (36). **These are major advances and will, in the end, help repair the brain and solve the immense puzzle that it represents.**

• 2013 was also a major year in terms of **clinical trials,** which involved 400 patients in 77 research protocols. At the end of 2013, the clinical trial of an innovative neuroprotective medication for the treatment of Parkinson's disease based on bee venom was completed. The Clinical Investigation Centre of the ICM participated in the development of a tool for writing with the eyes; this system could improve life for patients with paralyzed limbs. Finally, a special effort was made for rare diseases: Pompe disease, Huntington disease, cerebellar ataxias, channelopathies...

We are convinced that concurrent studies and multidisciplinary research will enable us to prevent, cure and repair all of the diseases of the brain and spinal cord.

In addition, in June 2012, we had the pleasure of inaugurating the iPEPS-ICM, a start-up incubator and nursery. This structure takes advantage of the presence of researchers, clinicians and enterprises within the same ecosystem in order to accelerate research and develop of new treatments. The iPEPS-ICM accommodates companies working on therapeutics and medical devices, as well as e-health and diagnostics. Here again, the absence of barriers is a source of potentially creative partnerships, with the same objective: **improve patient care and propose new treatments in the shortest time possible.** The ICM thus unites the forces of the most important institutions devoted to the neurosciences in France, the Brain and Spinal Cord Institute (ICM), the IHU-A-ICM, Pierre and Marie Curie University (UPMC), the *Assistance Publique - Hôpitaux de Paris* (AP-HP), the National Institute of Health and Medical Research (Inserm) and the National Centre for Scientific Research (CNRS), with those of young companies and major actors in the field of biomedical innovation.

All of these discoveries and actions were made with the greatest possible **transparency.** The Committee for the protection of donors accorded its approval to the ICM as early as 2010. Its latest report confirms that the ICM acts in accordance with its principles: statutory functioning and disinterested and rigorous management, high-quality publicity and fundraising, transparent finances. You will find in this annual report the use of resources statement and a detailed balance sheet presenting the accounts of the Institute for the fiscal year 2013.

1 person out of 8 will one day suffer from a disease of the brain of spinal cord. Faced with such a challenge, only a model of open and multidisciplinary innovation will increase our chances of success. The founding vision of the Brain and Spinal Cord Institute is that the road to new solutions pour the diseases must come from a successful marriage between the best of both institutional and private research.

Thank you for being faithfully at our side and imagining with us tomorrow's medicine.

Professor
Gérard Saillant
President of the ICM

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EDITORIAL

In just a few years, the ICM has become a key player in research on the nervous system and its diseases, attested by the numerous scientific and medical advances summarized in the outstanding discoveries of the year 2013.

In 2013, the Institute was evaluated by AERES *(Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur)* and our academic sponsors (CNRS, Inserm, Pierre and Marie Curie University), following the visit of our International Scientific Advisory Board. I am pleased with the very favourable judgements of these authorities, which led, in 2014, to the creation of a new ICM research unit comprising 25 teams. The new Institute has thus reinforced certain subjects, such as research on the degenerative diseases (amyotrophic lateral sclerosis), cognition (social interactions and psychiatry) or neuroimagery (computational anatomy). This dynamic will continue in 2014-2015 with the recruitment of one or more new teams in response to an international call for projects in conjunction with the IHU-A-ICM (Institute of Translational Neurosciences). Thanks to the latter, the technological platforms at the service of the researchers have been reinforced with the creation of a platform of bioinformatics and biostatistics, an electrophysiology platform to rapidly test the consequences of mutations in ion channels, for example, or the acquisition of new systems for analyzing behaviour in rodents.

At the end of the year, we launched the ICM 2020 program to elaborate a strategic vision shared by all members of the Institute. The objective is to finalize, in 2014, a road map with 3 axes: scientific strategy, mobilisation of all participants and stabilization of the economic model of the Institute. We already know that all the participants share the vision of an institute engaged in research on the nervous system and the fight against its diseases founded on **excellence, innovation, efficacity, pluridisciplinarity, internal collaborations and high quality technological platforms.** We now hope to reinforce internal interactions within the Institute and the sense of belonging and to increase the prestige of the Institute and its influence internationally.

Our policy of European alliances is beginning to bear its fruits, with an increased participation in European projects with our principal strategic partners, the *Institute of Neurology* (UCL, London, United Kingdom) and the *DZNE* (Helmholz, Germany). Our international exchanges and collaborations are developing, with the *Sandler Neuroscience Center* (UCSF, San Francisco, USA), the *Montreal Neurological Institute and Hospital* (McGill University, Montreal, Canada) or the *Florey Institute* (Melbourne, Australia), to name a few.

In addition, our researchers benefit from very high-level scientific and cultural events including numerous lectures and prestigious guests. With the IHU-A-ICM, a yearly Summer School is being created that will reinforce the international influence and the pedagogic activity of the Institute.

The success of the ICM incubator (iPEPS-ICM) is also growing; about fifteen innovative enterprises were already installed at the end of the year working in collaboration with the researchers of the Institute in a wide variety of fields. This ecosystem favouring local innovation combined with an increasing number of industrial partnerships should accelerate the arrival on the market of applications of the Institute's research.

The ICM is thus on the way to becoming **a research institute that can't be ignored,** capable of going beyond the frontiers of knowledge to transform innovations in research to applications to the greatest benefit of patients.

I would like to warmly thank all those who trusted in us for their support (Founders, Friends of the ICM, donors, sponsors, institutions, partners ...), their faithful presence at our side, and their contribution to the development of a scientific policy that we are determined will be ambitious.

Professor
Alexis Brice
Director General of the ICM

OUTSTANDING EVENTS OF THE YEAR 2013

I. NEURODEGENERATIVE DISEASES

The neurodegenerative diseases are chronic diseases that are often a cause of handicap. These diseases represent a public health problem because of the handicaps of patients, the impact on their families and the cost of their care; in particular, the ageing of the population is increasing the number of patients with neurodegenerative diseases. The challenge that these diseases represents resides in their complexity and variability. The use of the singular is often misleading. For example, the term "Parkinson disease" corresponds to disorders that, of course, have common features, but which, nevertheless, vary greatly from one patient to another. The greatest force of the Brain and Spine Institute is to combine **multiple approaches** (genetics, biochemistry, electrophysiology, imagery, etc.) that allow for the most detailed analysis possible of the different mechanisms underlying these diseases. In addition, the integration of the Institute in the heart of La Pitié-Salpêtrière Hospital gives access to very large clinical databases that permit us to **apprehend the variability of these mechanisms.** The objective is to develop personalized medicine that is adapted to each case for maximal efficacy. **The excellence of ICM researchers and clinicians creates a rich scientific environment that will benefit patients.**

1. PARKINSON DISEASE AND OTHER PATHOLOGIES CAUSING MOTOR HANDICAPS

All neurodegenerative diseases have share the fact that they directly affect neurons rather than the cells that constitute their structural and metabolic environment. Those presented here affect, more specifically, the neuronal systems responsible for movement, even if other cognitive functions can also be affected (language, memory ...). Amyotrophic lateral sclerosis (ALS) - or Charcot disease (eponymous disease; Jean-Martin Charcot, the founder of modern neurology, was one of the most illustrious French physicians at the end of the 19th century) - affects motoneurons, i.e. the neurons that project from the brain and spinal cord to muscles. Patients with ALS (4/100000) suffer, in consequence, from a motor handicap that leads to paralysis and death within 2 to 5 years after the first symptoms. In 2013, the team of **Bertrand Fontaine and Sophie Nicole** established a link between the expression of a protein in muscles and the rapidity of the progression of the paralysis caused by ALS. This protein can serve both as a biomarker permitting better diagnosis of the disease and a target for treatment (1). The team of **Sévérine Boillée** accompanies the ICM in its fight against the disease. This team is especially interested in the role of inflammatory processes. In ALS as

in all the neurodegenerative diseases, an immune response is observed in the central nervous system. However, in all of these diseases, a primordial question has not been elucidated: how does this immune reaction become deleterious and thus contribute to neuronal death. Knowing that immune cells are implicated in the progressive phase of the disease, a better understanding of the interactions between these cells and motoneurons could be of therapeutic value in stopping the progression of ALS. For this project, the team of **Sévérine Boillée** uses genetic data from patients in order to study in detail the mutations and the associated mechanisms by creating animal models of the disease. The team also uses tissues and cells from patients in order to confirm the pertinence of these mechanisms for the human disease. Notably, they develop models in culture using pluripotent stem cells derived from skin cells of ALS patients transformed in motoneurons or their surrounding cells in order to identify the factors that influence their survival.

In 2013, the team successfully clarified the role of the protein C1q, one of the initiating factors of the complement system involved in the immune response. Numerous previous studies had suggested that this protein played a deleterious role, but the team has shown that this pathway was not implicated in the neurotoxicity associated with the disease. On the contrary, it could have neuroprotective properties. These researchers have shown that in mouse models of ALS genetically modified to not express C1q, their condition worsened rather than improved (2). These studies bring into question the hypothesis of the deleterious effects of the protein.

The team also identified 4 new mutations in the gene SQSTM1 (encoding the protein p62) implicated in the disease (3), and also established the link between the mutated genes and the accumulation of the protein in motoneurons (4). These studies open new doors for our understanding of the pathological processes of ALS.

During the past few years, major advances have been made in the genetics of ALS, notably the discovery that the gene C9orf72 represents the most frequent genetic cause of ALS and frontotemporal dementia (DFT), a neurological pathology frequently associated with ALS. In 2013, the team of **Edor Kabashi** demonstrated that the levels of C9orf72 are reduced in ALS patients carrying expanded repetitions in the same gene (5). Furthermore, his team contributed crucially to the field by developing the first vertebrate model of the genetic deficiency, i.e. a knock-down of the expression of C9orf72 in the zebra fish (6). In collaboration with the laboratory of **Alexis Brice,** the team of **Edor Kabashi** determined the frequency of several genetic causes, including SQSTM1, in ALS patients with frontotemporal dementia. In addition, his laboratory characterized the genetic causes of pathologies affecting motoneurons, including GBA2 and VAPB (7). Finally, the team of Edor Kabashi identified endoplasmic reticulum (ER) stress as a major molecular

mechanism underlying ALS. Consequently, compounds known for an inhibitory effect on ER stress, for example salubrinal and guanabenz, attenuated toxicity in zebra fish models of the disease (8,9,10).

Parkinson disease also affects movement. It concerns 1% of persons over 65 years of age. It is most of all associated with specific motor symptoms that are not caused by the loss of motoneurons as in ALS, but by the progressive death of neurons in a deep region of the brain, the *substantia nigra*. These neurons, termed dopaminergic, produce and use the molecule dopamine (a neurotransmitter) to communicate with each other. If physicians know in part how to treat the motor symptoms of patients with substances that replace dopamine, these treatments remain symptomatic; how to prevent neuronal death is still unknown. Furthermore, neuronal degeneration does not only affect the *substantia nigra* and is unfortunately not limited to the dopaminergic neurons or the motor system. The teams of the ICM have performed an enormous amount of basic research to better understand the mechanisms of neuronal death in order to find efficacious treatments. The group of **Alexis Brice** has developed an integrated approach to Parkinson disease, from its genetic bases to it physiopathological mechanisms. The team uses a large panel of experimental methods *in vivo* and *in vitro* (outside the organism) in cellular systems (neurons are a specific type of cell). One of the challenges facing the team is to study the earliest phases of the disease, even before it becomes clinically detectable, in order to find predictive biomarkers, such as genetic mutations. These biomarkers allow the problem to be approached at its source, to better understand the disease and protect the patients as early as possible. Another challenge concerns the variability of the causes and consequences of Parkinson disease, each patient being a case in itself. In 2013, the researchers with **Suzanne Lesage** thus discovered a genetic mutation associated with a severe variant of the disease, which evolves rapidly and affects deep sub-cortical regions, including the *substantia nigra* and the basal ganglia, as well as in a motor region of the cortex (surface of the brain consisting of gray matter like the deep regions) (11). The genetic code is one of the bases of cellular, thus neuronal, function; genes permit the production of the proteins that regulate the functions. This type of study associating a gene with a disease can thus lead to the elucidation of the mechanisms by which the disease develops. It was precisely in 2013 that the team of **Olga Corti** contributed a better understanding of the proteins produced by genes mutated in Parkinson disease. These genes regulate "quality control" in mitochondria, small organelles in the cell that convert the oxygen we breathe into energy; the team identified a new mechanism implicated in the maintenance of this function. When mutated, these proteins induce the accumulation of defective mitochondria causing

neuronal death (12). The team of **Etienne Hirsch** is also interested in Parkinson disease. During 2013, they were able to show the protective effect of two molecules on dopaminergic neurons, lactoferrine and apamine (13, 14). The case of apamine illustrates the accidental nature of research: apamine was derived from bee venom suspected to have neuroprotective properties because of a patient who improved after being stung by bees. The team of **Philippe Ravassard** also studies dopaminergic neurons. Work is in progress to determine the role of a gene (GRPR88) on dopaminergic networks in an animal model of Parkinson disease.

The team of **Etienne Hirsch** is interested in the death of non-dopaminergic neurons in Parkinson disease. For example, degeneration of the small pedunculopontine nucleus that uses acetylcholine as its neurotransmitter leads to specific disorders of gait and equilibrium (15). In collaboration with Brian Lau (ICM), the team tries to eliminate the associated symptoms by electrical stimulation of cholinergic brain regions. Finally, the team is continuing its partnership with Air Liquide testing the neuroprotective effects of rare gases in the neurodegenerative disease; they are already known to have beneficial effects in stroke.

Motricity is affected not only in amyotrophic lateral sclerosis and Parkinson disease, but also in the spino-cerebellar ataxias. These diseases affect the cerebellum (the "little brain" located at the posterior bases of the brain) causing problems with coordination. In 2013, **Annie Sittler,** in the team of **Alexis Brice,** showed the neuroprotective role of a molecule already used to the multiple sclerosis. This molecule, beta-interferon, improved the symptoms of mice genetically modified to model the disease (16). **Familial spastic paraplegia** is another example of a motor disease. **Alexis Brice and his colleagues Frédéric Darios, Alexandra Dürr and Giovanni Stevanin** showed, in 2013, that this pathology is associated with certain genes implicated in the metabolism of lipids (17, 18). Lipid metabolism is more and more frequently shown to be implicated in neurodegenerative diseases (Parkinson, Alzheimer, frontotemporal dementia, etc.).

Other rare diseases, such as **essential tremor, Gilles de la Tourette syndrome, dystonia or mirror movements,** also cause motor handicap. The team of **Marie Vidailhet and Stéphane Lehéricy** has made Parkinson disease their target. Unlike the other groups that are focused on cellular and molecular mechanisms, this group works on a more global scale, that of the neuronal circuits that link, on the one hand, the cerebral cortex and the cerebellum (at the back of the brain) and, on the other, the cortex and the basal ganglia located in the deep brain (under the cortex). The team also uses, however, an integrated approach using genetic, metabolic, physiological and behavioural information, as well as imagery (MRI and MEG - see the technological platforms of the ICM). Here also, the aim is to detect

biomarkers of the disease that permit a better understanding and the earliest possible diagnosis. In 2013, the team for example elucidated the functional anatomy of the brain of patients with the mirror movements syndrome, which obliges them to make symmetric movements (ex: left and right hands) even when they try to make an asymmetric movement (of the right hand only). The patients, who have a mutation in the gene RAD51, abnormally activate both motor cortices symmetrically during movements made with one hand (19). The team also seeks to develop new treatments, essentially based on stimulation (electric or magnetic, intracranial or transcranial). Last year they showed the therapeutic value of **transcranial magnetic stimulation** (TMS) in patients with essential tremor (essential because unaccompanied by other signs or causes as in Parkinson disease). After 5 days of stimulation, the tremor decreased for 3 weeks with no other treatment, thus indicating a beneficial, long term modulation of the activity of the dysfunctional neuronal networks (20).

The precise mechanism of action of treatment by stimulation is unknown. This is also the case for other types of stimulation-based therapies. The team of **Brian Lau** (recipient of an ATIP/AVENIR 2013), works on deep brain stimulation (intracranial), which is known to improve the motor symptoms of patients with Parkinson disease. The group seeks to understand the physiopathology of Parkinson disease, in particular the functions of the targets of deep brain stimulation, notably the subthalamic nucleus. The team recently contributed to the localisation of these targets.

2. ALZHEIMER DISEASE AND OTHER PATHOLOGIES CAUSING AN INTELLECTUAL HANDICAP

It is not evident how to classify neurodegenerative diseases; **amyotrophic lateral sclerosis** is often associated with **fronto-temporal dementia, Parkinson disease** can alter intellectual functions after affecting motricity... The diseases evoked below also resist too strict classification. One can consider, however, that they principally concern cognition (memory, language, etc.) and the emotions, before motricity. Current knowledge indicates that there is a parallel between at least two of them: **Alzheimer disease and prion diseases such as Creutzfeldt-Jakob disease. Alzheimer disease** affects close to a million people in France, victims of memory disorders, mental confusion, etc. **Creutzfeldt-Jakob disease,** much less frequent, causes a dementia that evolves more rapidly. Why consider these two diseases together? The prion proteins are, in their normal state, present throughout the brain. In prion diseases, such as Creutzfeldt-Jakob disease, some of these proteins adopt a pathological three-dimensional form (despite a normal

chemical composition). This abnormal form can be propagated by a phenomenon of conversion of the normal protein into the abnormal protein, which leads to the death of the neurons, a mechanism of propagation that has been observed in other neurodegenerative disease such as Alzheimer disease. The team of **Stéphane Haïk and Marie-Claude Potier** is interested in the molecular mechanisms involved in the propagation of prions. In 2013, this research group developed the first experimental model in the world permitting the replication of human prions in the laboratory, an essential step in the fight against the disease (21). The team also studies the interactions between the prion protein and other key factors implicated in Alzheimer disease: beta-amyloid peptide that forms senile plaques and tau protein that causes neuronal degeneration when it aggregates. Here, as for other neurodegenerative diseases, the metabolism of lipids is at the centre of their preoccupations: the link between cholesterol and Alzheimer disease. In 2013, the team developed a method of cartography permitting the co-localization of molecules in the brains of patients, notably beta-amyloid protein and cholesterol (22). This type of study can detect a possible relation of cause and effect between cholesterol and neuronal degeneration. The team has also shown the absence of therapeutic efficacy of a molecule hoped to be effective in Creutzfeldt-Jakob disease - doxycycline - permitting the scientific community to gain time by abandoning their research on this molecule (23).

II. MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is an inflammatory disease that results in the destruction of oligodendrocytes and the myelin that surround the nerve fibres (the axons) of the brain, the spinal cord and the optic nerve. These demyelinating lesions cause defective conduction of the nerve impulse and the loss of the axons. In fact, neurons transmit information in the form of an electrical discharge (action potentials) along the axons -insulated by a sheath of myelin, a structure rich in lipids, which protects it and accelerates transmission of the nerve impulse. These myelin sheaths around the axons form white matter, as opposed to the gray matter that contains the cell bodies of the neurons. The destruction of myelin sheath alters conduction of the nerve impulse and thus the functioning of the neuronal network. The demyelinated axon becomes vulnerable leading to neurodegeneration, the cause of the progression of invalidity in patients with MS. Although myelin has the capacity to regenerate – a process called remyelination, this process is ineffective in MS. ICM researchers are thus trying to understand the mechanisms of de- and re-myelination, not only to block destruction of the myelin, but also to repair it. In 2013, the

team of **Brahim Nait Oumesmar** and **Anne Baron-Van Evercooren** demonstrated the beneficial role of several molecules, including the endothelines (24) and a synthetic derivative of tocopherol (25), in myelin repair. This team and that of **Jean-Léon Thomas and Boris Zalc** are focused on oligodendrocytes, the cells that produce myelin. The researchers work notably on the way in which oligodendrocytes develop from neural stem cells and oligodendrocyte precursor cells. Neural stem cells generate all the cells of the central nervous system: neurons, as well as astrocytes and oligodendrocytes that support them structurally and functionally. Oligodendrocyte precursors are more differentiated than stem cells and produce the oligdendrocytes that myelinate the central nervous system. In 2013, the two teams were able to elucidate the role of several factors important for the development of oligdendrocytes and remyelination. These factors ASCL1 (26) and SOX17 (27) are transcription factors that regulate the expression of genes important for the differentiation of oligdendrocyte precursors into myelinating oligodendrocytes during development and in demyelinating lesions.

The team of **Catherine Lubetzki and Bruno Stankoff** is also interested in the cellular mechanisms of de/remyelination, particularly in those controlling the migration and recruitment of oligodendrocyte precursors into demyelinating lesions, and alterations of the nodes of Ranvier, regions of the axon which are not myelinated, and which relay conduction of the nerve impulse. The team also developed an innovative program of positon emission tomographic imaging (PET) of demyelinating lesions (in publication).

MS is an auto-immune disease, and ICM researchers are also analysing this aspect of the pathology. We know, notably, that immune cells (lymphocytes), which normally protect the organism against pathogenic agents, are implicated in MS. These lymphocytes are activated outside the brain then cross the blood-brain barrier (which protects the brain) and attack the myelin. In 2013, the team of **Bertrand Fontaine and Sophie Nicole** demonstrated an association between groups of genes implicated in passage of the blood-brain barrier and the probability of developing the disease (28). The team of **Brahim Nait-Oumesmar and Anne Baron Van Evercooren** has shown the role of the adhesion molecule CD44 in the passage of the blood-brain barrier when injected intravenously.

The study of the mechanisms of repair of the nervous system is essential not only in the fight against MS, but also in the case of traumatisms of the spinal cord and brain after an accident, for example. Clinicians specialized in the treatment of lesions of the spinal cord work in close collaboration with ICM researchers with the aim of facilitating the necessary regeneration of axons and myelin. The team directed by **Claire Wyart** developed basic approaches to myelin repair using the

zebra fish for its exceptional ability to regenerate. The team studies the locomotion of the animal in its experiments. In 2013, these researches developed a program of automated observation and analysis of locomotion in the zebra fish (30), which is potentially useful for other ICM teams using the same model.

III. BRAIN TUMOURS

Neurons are not the only cells in the brain. They are supported structurally and functionally by glial cells, such as the oligodendrocytes that produce the myelin that surrounds the neurons, protecting them and improving transmission of the nerve impulse (see the section on multiple sclerosis). With lymphocytes of the immune system, glial cells are the origin of the most aggressive and frequent brain tumours (lymphomas and gliomas, respectively). With one of the largest banks of brain tumours (Onconeurotek), the team of **Marc Sanson** uses molecular biology to detect genetic mutations that cause the tumours, analyse their value for prognosis or prediction of a response to treatment, and thus provide clinicians with useful information (31,32). The team was also able to detect some of these mutations in DNA released by the tumours into blood, providing a potentially very useful diagnostic marker for clinicians. The team is now trying to determine the impact of these mutations and the molecular mechanisms by which they contribute to the transformation of a normal cell into a tumour cell. The first problem comes from the fact that mutations don't all have the same impact; some have almost no consequences, others, on the contrary, are critical and thus constitute a target for a specific cancer treatment. The objective of the experimental therapy platform Gliotex used by the team of **Marc Sanson (directors: Ahmed Idbaih - Charlotte Schmitt)** is to initiate, from cell cultures and grafts in mice, specific therapies depending on the mutational profile of the tumour. This approach provides hope, over the long term for a personalized treatment for each patient based on the genetic profile of his tumour. **Emmanuelle Huillard,** whose team was created in 2012 and was awarded an ATIP/AVENIR (Inserm and CNRS), has reinforced the potential for research on brain tumours. She also tries to understand the molecular and cellular mechanisms involved in glioma development. She focuses more particularly on the gliomas called high-grade, i.e. severe forms, and studies the stem cells of these tumours.

IV. EPILEPSIES

Epilepsy is one of the most frequent neurological diseases and affects about 1% of the population. It is characterized by abnormal electrical activity. As for other brain diseases, researchers prefer to use the plural when speaking of epilepsies, which are defined by different features that make categorization complex: importance or not of the abnormal electrical activity in both hemispheres of the brain, appearance or not of convulsions or loss of consciousness... The studies performed by the team of **Alberto Bacci** are situated upstream of those realized by other ICM teams, because he studies the regulation of the neuronal microcircuits of the healthy cerebral cortex at the origin of normal cortical function, which when deregulated can cause epilepsy. In particular, the GABAergic interneurons, which are seriously altered in epilepsy, constitute a very heterogeneous population in terms of their anatomy, their electrical properties and their functions. Such complexity makes their study a challenge, but this is necessary in order to understand the functioning of healthy and pathological neuronal circuits. The team of **Alberto Bacci** studies specifically how these interneurons participate in different forms of synaptic transmission, synaptic plasticity and oscillations of networks underlying cognitive processes. Using an electrophysiological approach, this team has already shown that activation of the principal neurons in layers 2/3 of the cerebral cortex induces the release of endogenous cannabinoids, leading to a decrease in the release of GABA by certain interneurons. Their outstanding achievement, in 2013, was the discovery of the opposite phenomenon in layer 5 of the cerebral cortex. Indeed, similar activation of the principal neurons causes an increase rather than a decrease in the release of GABA in layer 5 via release of a gas, nitric oxide, which binds selectively to a certain type of interneuron. Since these 2 cortical layers communicate, the team will then study how this bi-directional modulation of GABAergic synapses interacts with the oscillations of cortical networks that underlie the information processing and cognitive functions (33). The team of **Eric Leguern and Stéphanie Baulac** is interested in the genetic and physiological origins of the epilepsies. In 2013, they notably identified a new gene (DEPDC5) associated with a hereditary form of focal epilepsy (i.e. limited to a part of the brain (34).

All of the major discoveries made by research at the ICM in 2013 were performed at the molecular level (DNA, proteins, lipids...) and the brain cells (neurons, oligodendrocytes...). This level is pertinent for the search for new treatments, but concerns only indirectly or partially the primary function, the raison d'être, of the brain: the processing of information from which emerges our capacity to perceive, reflect, speak, memorize,

etc. This information (for example, visual information from the retina via the optic nerve) is encoded in the form of electrical activity transmitted by the neurons. Each neuron receives, treats and retransmits electrical messages to other neurons. Ideally, it is at this level that one should study the cognitive functions mentioned above (perception, language, etc.). It is also at this level that are situated certain keys to **epilepsy;** the level at which abnormal electrical activity prevents information processing. The team of **Stéphane Charpier** studies all forms of epilepsy: from partial epilepsies to generalized seizures. The generalized seizures most often seen in children are **absences.** This form of epilepsy handicaps the young patient who becomes unconscious (for a short and often imperceptible period of time, but often up to hundreds of times a day). In 2013, these researchers demonstrated, in these children and in a genetic model of the disease, that the abnormally firing cortical neurons are still capable of integrating sensory stimuli (35), challenging the generally admitted impact of the seizures on the mechanisms of consciousness. In 2013, the team also detected a modulation of the high-frequency neuronal activities that precede certain seizures, which could constitute a new mechanism of seizure initiation and - eventually - a biomarker, i.e. a way of predicting when a seizure will occur (36).

V. COGNITION AND BEHAVIOUR

The brain is an impressive machine for processing information, an activity that underlies cognition (perceive, reflect, memorize, decide, speak...), and from which emerges the consciousness we have of ourselves and the world around us. This activity defines us as human beings, making the **dementias and psychiatric disorders** that alter these functions so distressing. If the mechanisms at work in the neurodegenerative diseases and multiple sclerosis take place at the cellular and molecular levels, these mechanisms have implications at a more integrated level of information processing by networks of neurons. Studies at this level are another way to attack the deficits associated with brain lesions. The hope that one day we will be able to repair the brain is also based on our comprehension of these neuronal networks.

More precisely, an exhaustive understanding of these networks requires, in fact, a multi-scale approach to explain large networks starting from their components, to begin with, the intrinsic electrical activity of the neuron. The team of **Stéphane Charpier** uses electrophysiology, from

surface electroencephalograms (large networks of neurons) to the intracellular activity of a neuron. In 2013, this intracellular approach led to the demonstration, in a model of "isoelectric coma", that, unexpectedly, the individual functions of the neurons were preserved although the electroencephalogram was flat (37).

The team of **Luc Mallet** is specialized in the study of the basal ganglia, a group of deep subcortical regions of the brain. In 2013, the team showed the implication of one of these regions, the subthalamic nucleus, in a pathological behaviour: obsessive compulsive disorder (OCD) (38). Patients with this disorder need to reassure themselves repeatedly and exaggeratedly with respect to their actions ("Did I shut off the gas?" etc.). The results of the team confirmed that this region is a good target for therapeutic stimulation.

This same year, **Marcin Szwed and Laurent Cohen** showed that reading words in two alphabets with very different bases (French and Chinese) uses identical regions of the brain's visual system, but that there are also specific regions for each of the alphabets in the most peripheral visual areas (V1 to V4) (39).

Ana Chica and Paolo Bartolomeo established the neural bases of interactions between spatial attention and perceptive consciousness by functional MRI (40). These results not only confirmed the existence of front-parietal networks in the right hemisphere that we know already from the study of neurological patients with deficits of perceptive consciousness, but also the participation of regions in the left hemisphere such as the frontal oculomotor field. Thanks to transcranial magnetic stimulation, the causal role of the left frontal oculomotor field in the interaction between attention and perception could then be demonstrated (41).

Jean-Rémy King, Jacobo Sitt, Stanislas Dehaene and Lionel Naccache (42) have established a new, original long-distance measure of functional connectivity by EEG. This "weighted symbolic mutual information (wSMI) has turned out be a neuronal signature of the state of consciousness: the brains of conscious control subjects, conscious or minimally conscious patients, are the seat of a coherent long-distance brain conversation, whereas this conversation seems absent in patients in a vegetative state that are awake but not conscious. The major "hub" of this long-distance brain communication is in the precuneus and the posterior cingulate cortex, regions already associated with consciousness of the self and of the outside world.

A major event, in 2013, for electrophysiological research in the ICM was the inauguration of the centre "Line Garnero". This centre directed by **Nathalie George and Denis Schwartz** offers access to two non-invasive techniques usable in humans: Electroencephalography **(EEG)** and magnetoencephalography **(MEG),** which collect electric and magnetic signals,

respectively. Thanks to the high temporal resolution of the MEG (on the order of a millisecond), the team of **Nathalie George and Philippe Fossati** was able to study the early response of a region of the brain - the amygdala - implicated in the perception of fear expressed on the face of another person (43).

If the analysis of electrical activity is essential for the understanding of cognitive functions, this analysis can also be performed indirectly by observation of signals related to blood flow. In effect, when the activity in a brain region increases, blood flow also increases and, to a lesser degree, oxygen consumption. This effect is used by magnetic resonance imaging systems to study the activity of the brain in a totally non-invasive manner. This technique - functional MRI - can be used directly on human subjects and avoids the bias introduced by animal models, which must always be validated in humans. Moreover, the method furnishes images with very good spatial resolution for a non-invasive technique. In 2013, utilisation of this technique by the team of **Mathias Pessiglione** demonstrated the implication of the hippocampus in the anticipation of profit in the long term associated with a decision (44). This result was confirmed in patients with Alzheimer disease who had both atrophy of the hippocampus and a less developed capacity for anticipation. The team also showed the role of a sensory region of the brain in the representation of the physical effort required to reach a goal (45). The team of **Bruno Dubois and Richard Levy** used MRI to study the frontal lobes responsible for the most complex aspects of cognition (decision making, planning, reasoning, creativity moral judgment, social interactions...). In 2013, the team showed in patients with focal frontal lesions that the model of the organization of the frontal lobes along a hierarchical antero-posterior axis is valid (46).

These different imaging approaches (EEG, MEG, MRI) are complementary, but their integration is difficult because of their heterogeneity. The problem of the integration of data concerns, in fact, all of the information collected from patients. One of the challenges faced by the team of **Olivier Colliot** is to combine together these varied and complex data in a form of information that is useful for research, a typical, contemporary problem created by **"Big Data",** the fruit of the new digital technologies. The team (ARAMIS) was created in 2013. Because of its unique thematic position in the Institute, the team is shared with INRIA (National Institute of Research in Informatics and Applied Mathematics). More generally, the objective of the team is to develop more powerful methods of image analysis to better characterize the many neurodegenerative diseases (Alzheimer, fronto-temporal dementia...), epilepsy and cerebrovascular diseases (vascular dementia, stroke).

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THE IHU-A-ICM

1 Outstanding events

2 Principal 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 foster the development of innovative preventive, diagnostic or therapeutic products and procedures. The objectives of the IHU-A-ICM, Paris Institute of Translational Neuroscience, are: the development of international level research on diseases of the nervous system (neurology and psychiatry), the creation of top level technological platforms, capitalization on the results of research, development of research partnerships with industry, training of future health professionals, administration of health and the health-related industries, improvement of care and transfer of care from the hospital to the home of the patients.

THE IHU-A-ICM

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

The mission of the IHU-A-ICM is to respond to the immense challenge of nervous system diseases by developing tools for diagnosis, prevention and treatment.

This is one of the major problems of the century. Thanks to a critical mass rarely reached in competency for research and care and a complete infrastructure for translational research that gives concrete expression to ties between research at the patient's bedside and in the laboratory, a new model in the field of neuroscience has come into being. At the end of the Institute's second year of existence, I wish to acknowledge the first very promising results already obtained.

We owe these results to your work, your engagement, your faith in progress at the service of those who suffer and those who are close to them.

I wish most particularly to thank Bertrand Fontaine, the Director General of the IHU-A-ICM, for his constant mobilization that makes our young institution live and progress. I also wish to thank Anne Bellod, our General Secretary, for her work and her heartfelt devotion.

I also wish to acknowledge the quality of the collaboration with our Founding Members and, above all, the ICM. We are engaged with them in a very beautiful collective adventure.

But this is only the beginning.

We must obtain outstanding results to be worthy of the considerable investment the nation has made in the IHU-A-ICM. For this, we must redouble our efforts, take risks in the noblest sense of the word, and know that each hour, each day, counts because we are invested in a mission that can never be just a job or research like any other.

Those are our obligations and our responsibility.

EDITORIAL
BERTRAND FONTAINE
DIRECTOR GENERAL OF THEIHU-A-ICM

The Paris Institute of Translational Neuroscience, the IHU-A-ICM, is celebrating its two years of existence thanks to a major program of "Investments d'Avenir". The IHU-A-ICM, created in 2012, gave new life to translational research on the nervous system. The ambition of the IHU was to continue to place at the centre of each project a continuity going from research to the patient and from the patient to research. The year 2013 saw the first fruits:

▶ Dispose of a critical mass of patients in the targeted pathologies and a system of care in coherence with the scientific projects. The IHU could thus begin to constitute cohorts of patients with Parkinson disease, epilepsy, pathologies of motivation and Alzheimer disease, 250 pre-symptomatic subjects have been recruited to date.

▶ Obtain a significant implication of clinicians in the IHU by encouraging their participation in translational research. The IHU has inaugurated a Unit of Behavioural Neuropsychiatry and a new source of recruitment of patients in need of a neuropsychiatric approach.

▶ Integrate an objective of technology transfer with the development of industrial partnerships in certain research programs, as for example the important partnership on Alzheimer's disease.

▶ Reinforce innovation and creativity with the launching of a call for projects, in the spring of 2013, to recruit new teams selected by the International Scientific Advisory Board (SAB) and the response of 83 candidates, 90% of which were of international origin. The auditions of the 11 candidates preselected by the SAB of the IHU-A-ICM permitted us to identify strategic themes and to start out with new teams.

I wish to heartily thank the patients, researchers, clinicians, support teams and our partners who have helped make the dream of the IHU a reality. The year 2014 opens with new, ambitious and creative perspectives to accelerate research and the discovery of new treatments for our patients.

1

OUTSTANDING

Several major discoveries were the fruit of studies in the **Parkinson Project.** Two candidate inflammatory targets were tested and have been eliminated from the pipeline thanks to preclinical models. The year 2013 saw the opening of the platform for functional studies. Targets identified by preclinical studies will be transposable to clinical research thanks to the creation of the Parkinson cohort ICEBERG. Recruitment of this cohort is underway and involves an important interaction with the **Bioinformatics/Biostatistics plateform** of the IHU for the development of the ClinGen database. The teams of the **Alzheimer Project** have created the INSIGHT cohort in partnership with Pfizer Laboratories, Amyvid and the *Fondation Plan-Alzheimer.* Recruitment has begun remarkably well on the national level. As of December 31, 2013, 98 subjects were included, 72 of which underwent an MRI, 66 a PET-FDG and 64 a PET-Amyloid. The objective is to recrute 400 subjects with follow-up of their conversion to Alzheimer disease. The INSIGHT team will be reinforced in 2014, so as to begin the multimodal analyses and the detection of pre-symptomatic markers. The teams of the **Multiple Sclerosis Project** are developing innovative cellular and animal models to identify and validate molecules of interest for myelin repair and neuroprotection. The **Brain Motivation Project** began during the year 2013 with three innovative initiatives: (1) the opening of the Unit of Behavioural Neuropsychiatry (UNPC), (2) the finalization and installation of the PRISME platform, and (3) a multi-level pedagogical project called the "School of Motivation." The UNPC, integrated in the Pole of Nervous System Diseases, has six hospital beds and began its activity in November 2013; 75 patients have been followed. With the creation of the UNPC, recruitment began of patients with pathologies needing a neuropsychiatric approach. The team of the Motivation Project is planning a clinical trial of the effect on apathy of a molecule already on the market (repositioning with the potential for industrial development). The Platform for Research on Social Interactions and Experimental Motivation (PRISME) is being finalized and will soon open. The research teams have begun to plan the research projects that will begin in 2014. Among the major results of the **Epilepsy Project,** the teams have identified a new gene, DEPDC5, implicated in familial focal epilepsies. This discovery was published in 2013 in the journal Nature Genetics, and a patent has been registered for a diagnostic application. These studies continued with the generation of a functional model in which DEPDC5 was invalidated. The year 2014 will be devoted to functional studies associated with electrophysiology *in vivo.* The **Imagery Project** has continued to reinforce the team of engineers on the Platform of Multimodal Clinical and Preclinical Neuroimagery and Neurophysiology. The Group of Analysis of Multimodal Neuroimagery (GANIM), which now comprises six engineers, has (1) established a catalogue of tools for

processing neuroimagery, (2) established a procedure for the realization of research projects and (3) developed a training program in imaging. The GANiM has completely fulfilled its role as a platform and undertook, this year, 87 thematically much diversified projects. The IHU also has an operational platform for medullary imaging (spinal cord studies). The team continues its industrial collaborations with, for example, the development of a man-machine interface to determine, from neurophysiological data, the characteristic parameters of the cognitive state of a person in an application of facial recognition. **The Bioinformatics/ Biostatistics Project** began during the year 2013 with the recruitment of a scientific coordinator. The platform focuses on the development, expert use and dissemination of methods dedicated to the analysis of multimodal data: genetic, genomic, transcriptomic, epigenomic, metabolomic, clinical and neuroimaging. The platform thus offers analytical support for scientific and biomedical teams and

THE IHU-A-ICM

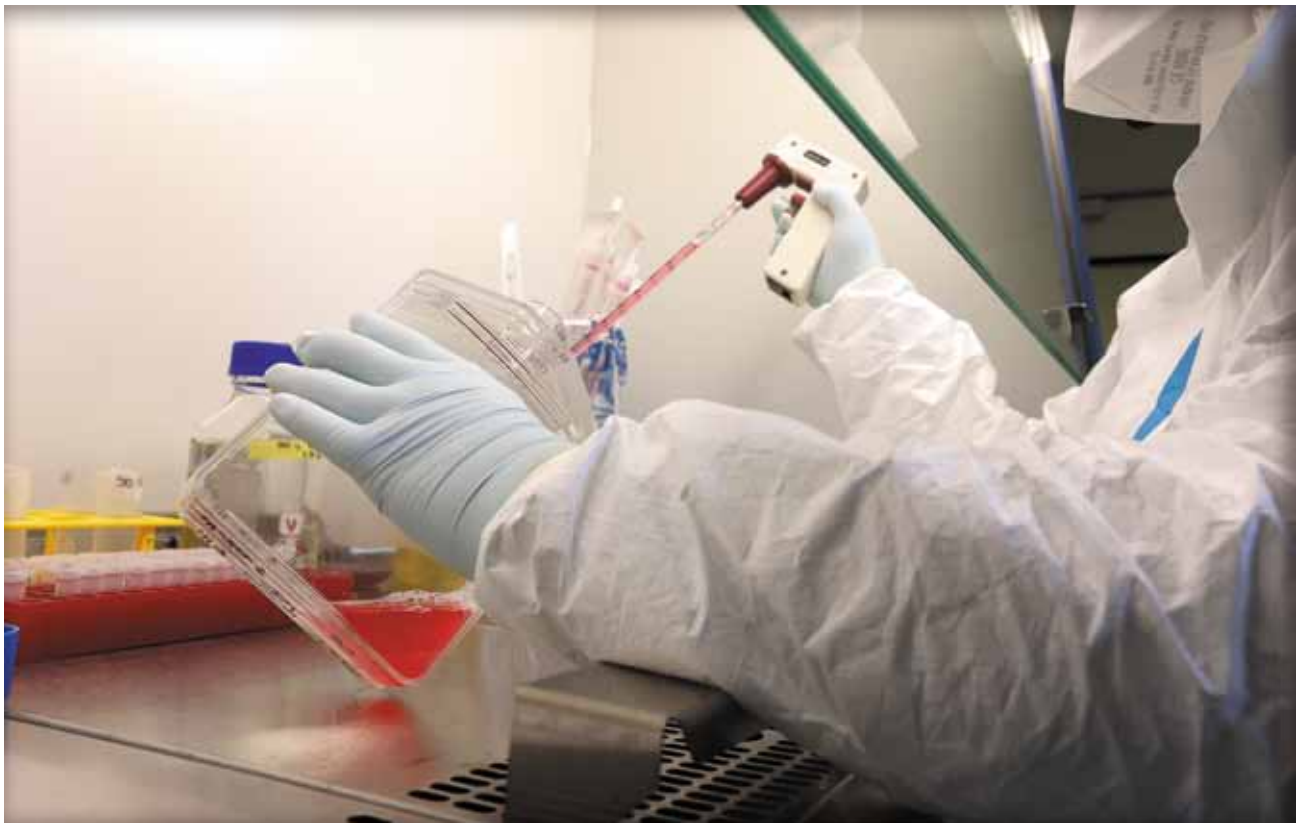
1

OUTSTANDING

develops innovative new tools. Since its beginning, the platform has recruited a pluridisciplinary team (5.5 members), determined the needs of the research teams and consolidated a strategic road map for the development of the platform. The major results obtained this year are: (1) the development of pipelines for genomic (whole-exome, whole-genome), transcriptomic (microarrays, RNA-Seq) and epigenomic (methylation) data; (2) the development of statistical methods for the integration of multimodal data (in the context of several competitive calls for projects); (3) a reflection on the definition of a Pole "Databases" within the platform. The platform has also established scientific interactions with Supélec, the IHU ICAN, the IHU imagine and INRIA. Among the outstanding realizations of the **Experimental Models Project,** the teams have developed an environment dedicated to preclinical studies based on imagery, electrophysiological recordings and behaviour. The creation of the platform has permitted preclinical studies of gait disorders and falls in Parkinsonian patients, which are a major public health problem. The patients do not respond to treatment with L-Dopa, suggesting the existence of non-dopaminergic lesions. The **Experimental Models Project** has demonstrated that the cholinergic neurons localized in the brain stem play a major role in the control of gait and posture and developed an experimental model of Parkinson disease with gait disorders and falls that do not respond to dopaminergic treatment. In the **Cell Culture Project,** the activity of the iPS platform has begun. At present, the platform maintains and characterizes iPS lines in 3 degenerative pathologies (Parkinson disease, spastic paraplegias, amyotrophic lateral sclerosis) as well as two control lines. An industrial partnership for the production of iPS lines has been initiated. **The Cell Culture and Screening Program** opened, in 2013, a platform for electrophysiological screening by patch clamp recordings on isolated cells in culture. The success of this platform has been extremely rapid, a publication was accepted, in 2013, in Nature Genetics, and a patent; they will be described in the report for 2014. The participants in the **Clinical Research Project** have successfully continued their activity on the Clinical Research Platform dedicated to the neurosciences. In 2013, 77 studies were carried out in the Clinical Investigation Centre (CIC) and the Therapeutic Evaluation Centre (CET). Half of the studies initiated in 2013 were promoted by industry the other half by academic institutions. Over the course of this second year, the **Care Project** introduced, in the Master's program "Coordination of Handicap", the coordination of cardiometabolic diseases in collaboration with the IHU ICAN. This program has become one of the tracks of the Master's in Health of the UPMC entitled "Coordination of the Health Circuit". The "Care" team was the motive force in discussions with the Ministry of Health (DGOS) for the addition of the profession of health circuit coordinator on the list of

EVENTS

new professions. Two positions of coordinators of care in the IHU led to the attribution of a permanent position in the APHP. The project Pole Handicap Ile de France with the ARS was also finalized during the year 2013. Finally, a projected partnership with a private sector partner is being developed for a Pole of Neurological Coordination in the Ile-de-France. The activities of the **Training Project** have focused on the training of paramedical personnel in research. The IHU-A-ICM has established a partnership with the Ecole des Hautes Etudes en Santé Public for the training of heads of nursing and paramedical research projects at the IHU-A-ICM. The objective is to significantly increase the number of projects presented and accepted by the Hospital Program of Nursing and Paramedical Research and to create, in the long term, a community of paramedical personnel trained to perform research. The year 2013 also saw the beginning of the plan of action of the **Strategy Project.** Several calls for projects were launched during the spring of 2013 to recruit new teams and initiate innovative projects. A call for "New Teams" received 83 applications, 90% of which came from outside



1 OUTSTANDING EVENTS

France. Auditions of the 11 candidates preselected by the SAB, the international Scientific Advisory Board, of the IHU-A-ICM were held in February 2014. A call for "Structuring and proofs of concept projects" within the IHU, with a strong focus on an innovative proof of concept and the reinforcement of pluridisciplinary connections among existing projects. Sixteen candidates were reviewed by international experts and three projects were selected. A call for "Clinic and Care" projects was launched with a strong focus on clinical research and care comprising two open projects and a project on the paramedical axis. Fifteen projects were reviewed by international experts and five projects were selected.

2 PRINCIPAL PUBLICATIONS

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2. Depienne C, Bugiani M, Dupuits C, Galanaud D, Touitou V, Postma N, van Berkel C, Polder E, Tollard E, Darios F, Brice A, de Die-Smulders CE, Vles JS, Vanderver A, Uziel G, Yalcinkaya C, Frints SG, Kalscheuer VM, Klooster J, Kamermans M, Abbink TE, Wolf NI, Sedel F, van der Knaap MS. (2013) Brain white matter oedema due to ClC-2 chloride channel deficiency: an observational analytical study. **Lancet Neurol.** 12(7):659-68

3. Pietri M, Dakowski C, Hannaoui S, Alleaume-Butaux A, Hernandez-Rapp J, Ragagnin A, Mouillet-Richard S, Haik S, Bailly Y, Peyrin JM, Launay JM, Kellermann O, Schneider B. (2013) PDK1 decreases TACE-mediated Ð-secretase activity and promotes disease progression in prion and Alzheimer's diseases. **Nat Med.** 19(9):1124-31.

4. Isabelle Le Ber, Agnès Camuzat, Rita Guerreiro, Kawtar Bouya-Ahmed, Jose Bras, Gael Nicolas, Audrey Gabelle, Mira Didic, Anne De Septenville, Stéphanie Millecamps, Timothée Lenglet, Morwena Latouche, Edor Kabashi, Dominique Campion, Didier Hannequin, John Hardy, Alexis Brice, for the French clinical and genetic research network on FTD/FTD-ALS**. SQSTM1 mutations in French FTD and FTD-ALS patients. **JAMA Neurol.** 2013 Sep 16.

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7. Peck CJ, Lau B, Salzman CD (Mar 2013). The primate amygdala combines information about space and value. **Nature Neuroscience** 16 (3):340-8

8. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, Shah TS, Spencer C, Booth D, Goris A, Oturai A, Saarela J, Fontaine B, Hemmer B, Martin C, Zipp F et al. International Multiple Sclerosis Genetics Consortium (IMSGC). Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. **Nat Genet.** 2013 Nov;45(11):1353-60.

9. Meyniel, F. Sergent, C. Rigoux, L. Daunizeau, J. Pessiglione, M. (2013) Neurocomputational account of how the human brain decides when to have a break. **Proc Natl Acad Sci** 110: 2641-6.

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SEARCH, FIND, CURE

Research axes and teams

1

- Neurodegenerative diseases
- Neuronal excitability, nerve transmission and associated diseases including epilepsy
- Development, glial pathology and repair
- Cognition, emotion, action
- Transversal

2 Technological platforms and databanks

3 The Clinical Investigation Centre - CIC

2

THE SCIENTIFIC PROGRAM OF THE ICM IS EQUAL TO THE CHALLENGE

Prevent, i.e. prevent manifestation of the disease.

Cure, i.e. slow, at best stop, the evolution of the pathological processes.

Repair, i.e. reconstruct the neuronal circuits after damage to the nervous system, and relieve to attenuate or eliminate symptoms such as memory loss, language disorders, pain, anxiety, and depression.

The objective is to do research at an international level, combining scientific creativity and therapeutic aims. The ICM's scientific program is based on the following principles: create a "combat team" for research, which implies: recruiting the best French researchers, as ranked by the National Agency for Evaluation of Research and Higher Education (AERES), and the best foreign researchers, as evaluated by the International Scientific Advisory Board; place at researcher's disposal advanced technological platforms and an efficacious Biological Resources Centre; developing multidisciplinary "translational" research in association with industrial partners and the best research centres in and outside France; and define the most important research axes.

2 1

SEARCH.
FIND.
CURE

RESEARCH AXES

AXIS 1 NEURODEGENERATIVE DISEASES

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 we recognize and distinguish these diseases from each other at an early stage? To answer these questions, the ICM is determining the molecular bases of some hereditary forms of these diseases and, especially, the most frequent genetic risk factors. A variety of experimental models of these diseases will be produced by inactivation or gene transfer, according to the nature of the responsible mutations. To detect these diseases early in their course, we are looking for biological markers in blood, urine and cerebrospinal fluid of patients, as well as from clinical examinations (neuropsychological evaluation) and brain imaging (MRI or PET-Scan, etc.). The major challenge of the neurodegenerative diseases remains the development of treatments to stop their evolution: from their identification in simple laboratory models up to therapeutic trials in patients in the Clinical Investigation Centre (CIC) of the ICM. The Institute will make a particular effort to identify the mechanisms underlying neuronal loss in Alzheimer disease and Parkinson disease and amyotrophic lateral sclerosis.

Séverine Boillée

Alexis Brice

Bertrand Fontaine and Sophie Nicole

Stéphane Haïk and Marie-Claude Potier

Étienne Hirsch

Edor Kabashi

Brian Lau

Marie Vidailhet and Stéphane Lehéricy

AND TEAMS

NEURODEGENERATIVE DISEASES

1. TEAM "CAUSES OF ALS AND MECHANISMS OF MOTONEURON DEGENERATION"

Team leader: Séverine Boillée

The team of Séverine Boillée works on amyotrophic lateral sclerosis (ALS). This disease affects the motoneurons - neurons that command the muscles. The patients suffer, consequently, from a progressive motor handicap that evolves into paralysis and causes death on the average 2 to 5 years after the first symptoms. The team is particularly interested in the role of inflammatory processes in the disease. In ALS, as in all of the neurodegenerative diseases, an immune response is observed in the central nervous system. However, in these diseases a primordial question has not been answered: how does this immune reaction become deleterious and thus contribute to neuronal death. Since these cells are implicated in the progressive phase of the disease, a better understanding of the interactions between cells of the immune system and motoneurons could have therapeutic interest in slowing the progression of ALS. For this project, the team of Sévérine Boillée uses genetic data from patients in order to characterize in detail the mutations and their associated mechanisms of action by creating animal models of the disease. The team also uses tissues and cells from patients to confirm the pertinence of these mechanisms for the human disease. They notably develop models in culture using pluripotent stem cells derived from skin cells of ALS patients transformed in motoneurons or their surrounding cells in order to identify the factors that influence their survival. The researchers also use animal models in vivo with similar objectives.

Principal investigators: Stéphanie Millecamps, Delphine Bohl, Christian Lobsiger, Danielle Seilhean, Vincent Meininger, François Salachas

The team was supported by: la Région Limousin et le CHU de Limoges, Agence Nationale de Recherche, Labex REVIVE consortium, Association pour l'étude de la culture d'embryon, Association Française contre les Myopathies, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autre maladies du motoneurone, Fondation de France, Fondation pour la Recherche sur le Cerveau, Fondation pour la Recherche Médicale, RTRA (ENP), École des Neurosciences Paris Ile de France, European Commission - Glaxosmithkline.

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2 1 RESEARCH AXES

SEARCH.
FIND.
CURE

NEURODEGENERATIVE DISEASES

2. TEAM "MOLECULAR BASES, PHYSIOPATHOLGY AND TREATMENT OF NEURODEGENERATIVE DISEASES"

Team leader: Alexis Brice

The research group of Alexis Brice, comprised of about 10 tenured researchers and clinician-researchers, focuses on three types of neurodegenerative diseases that have many clinical and physiopathological features in common: Parkinson disease, spino-cerebellar degenerations - diseases associated with specific motor symptoms, and fronto-temporal lobar degenerations that instead cause cognitive and behavioural disorders (apathy, asocial behaviours, etc.). The team has developed an integrated approach to these diseases, from their genetic bases to the underlying physiopathological mechanisms, using a large panel of experimental methods in vivo and in vitro, in cell systems or in animals or humans. One of the challenges for the team is to study the earliest phases of the disease, before they are clinically detectable, to develop predictive biomarkers. The researchers hope thus to understand and attack the problem at its root and protect the patients as soon as possible. This approach consists, for example, of finding which mutated forms of the genes are associated with degeneration, which abnormal proteins are produced from these genes, and which functions of these proteins or their absence cause cell death (toxic aggregates of proteins, dysfunction of subcellular organelles, etc.). Another challenge is presented by the variability of the causes and consequences of these diseases, each group of diseases having shared characteristics, but also features that are specific. In the end, the objective is to develop new treatments acting on the cause of the disease, knowing that existing treatments attack only the symptoms of the diseases not the process of neurodegeneration itself.

Principal investigators: Jean-Christophe Corvol, Olga Corti, Christel Depienne, Alexandra Dürr, Suzanne Lesage, Isabelle Le Ber, Fanny Mochel, Giovanni Stevanin

The team was supported by: APHP, Agence Nationale de Recherche, PSP, Association Française contre les Myopathies, Association des personnes concernées par le tremblement essentiel, Association Connaître les Syndromes Cérébelleux, Fondation de France, Fondation Carlo Besta, Fondation Plan ALZHEIMER, France Alzheimer, France Parkinson, The Michael J Fox Foundation, Prix Académie des sciences, Prix Fondation Roger de Spoelberch Suisse, École de Neurosciences Paris Il de France, VERUM FONDATION, UCL University et Fondation High Q. USA, University Hospital of ULM, European Commission, ULTRAGENIX - APHP, Ecole des Neuroscience Paris Ile de France, Fondation Jacques et Gloria Gossweiler, Fondation Plan ALZHEIMER, Fondation pour la Recherche Médicale, Ecole Pratique des Hautes Etudes, Elisabeth Badinter, ACTELION, IPSEN Innovation, Pfizer, Pfizer Pharmanet Suisse, SANOFI-AVENTIS, SERVIER.

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AND TEAMS

NEURODEGENERATIVE DISEASES / NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY / DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

3. TEAM "NEUROGENETICS AND PHYSIOLOGY"

Team leaders: Bertrand Fontaine and Sophie Nicole

The team is interested in several neuromuscular diseases, multiple sclerosis and Alzheimer disease. These diseases do not have evident points in common clinically, but share in part the same biological mechanisms, in which the researchers are specialists. The group works notably on the junction between skeletal muscles and motor neurons, called the neuromuscular junction, in the search for genes that could explain, at this level, the motor disorders of certain patients. These genes encode, for example, proteins called "receptor channels" situated on the surface of muscles the role of which is to receive chemical signals from the neuron that induces them to open. The receptor channels are present not only on the surface of muscles, they are also on neurons and play a role in Alzheimer disease. The researchers use their knowledge of these receptors to determine the role of one of them (P2X7R) in the inflammatory process implicated in the disease. For that, they use mice that model the symptoms of the disease, in which they inhibit the receptor to evaluate eventual modifications of the symptoms and deduce the underlying physiopathological mechanism. The team also applies its expertise in human genetics/ molecular biology to multiple sclerosis, an autoimmune disease that causes destruction of the myelin that protects neurons and insulates their electric activity. This destruction is determined by numerous genes the interactions of which are complex and remain to be elucidated.

Principal investigators: Gaëlle Bruneteau, Mohamed El Behi, Cécile Delarasse, Bruno Eymard, Emmanuel Fournier, Daniel Hantaï, Isabelle Rebeix, Damien Sternberg, Savine Vicart

The team was supported by: Fondation ARSEP, Prix Bouvet-Labruyère-ICM 2013, OCIRP, APHP, Agence Nationale de Recherche, Association Française de l'Hémiplégie Alternante, Association contre les Myopathies, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone, OSEO (defi), BIOGEN, Pharnext.

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NEURODEGENERATIVE DISEASES

4. TEAM "ALZHEIMER DISEASE AND PRION DISEASES"

Team leaders: Stéphane Haïk and Marie-Claude Potier

Why work at the same time on Alzheimer disease and prion diseases? Prion proteins, in their normal state, are present throughout the brain. In prion diseases like Creutzfeldt-Jakob disease, some of these proteins adopt a pathological three-dimensional form (in spite of a normal chemical composition). They can be propagated by a phenomenon of conversion of the normal protein, which leads to the death of the neurons. This mechanism of propagation has also been observed in other neurodegenerative diseases, including Alzheimer disease. The team of Stéphane Haïk and Marie-Claude Potier study the molecular mechanisms implicated in this propagation and the diversity of pathogenic agents (lineages). They study the interactions between the prion protein and other key factors implicated in Alzheimer disease: the beta-amyloid peptide that forms senile plaques and the tau protein the aggregation of which is responsible for degeneration of the neurons... The team also studies the specific features of each of the pathologies (Alzheimer disease and the prion diseases). They are interested in the links between cholesterol and Alzheimer disease and have shown that cholesterol is associated with variations in the secretion beta-amyloid. At present, there is no effective treatment available for patients with Creutzfeldt-Jakob or Alzheimer disease. With the experimental models they are developing, the team is working to identify and test in patients new therapeutic approaches.

Principal investigators: Nicolas Bizat, Benoit Delatour, Charles Duyckaerts

The team was supported by: Agence Nationale de Recherche, Alliance Biosecure, Fondation Jérôme Lejeune, France Alzheimer, Fondation pour la Recherche Médicale, Ligue Européenne contre la Maladie Alzheimer, GIS-IBISA, Don anonyme, European Commission, ROCHE - Fondation Desmarest, Prix Fondation Claude Pompidou, Elisabeth Badinter, LFB Biomedicaments, SERVIER, UMECRINE.

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AND TEAMS

NEURODEGENERATIVE DISEASES

5. TEAM "EXPERIMENTAL THERAPEUTICS OF NEURODEGENERATION"

Team leader: Etienne Hirsch

In Parkinson disease, the dopaminergic neurons (that use the molecule dopamine to communicate with each other) die progressively. If we know in part how to treat the resulting motor symptoms, we do not know how to prevent neuronal death itself. The team of Etienne Hirsch tests the protective effects of different molecules on dopaminergic neurons. Neuroprotective molecules are rare, and researchers must be alert to all opportunities. The case of apamine, studied by the team, illustrates the accidental nature of research: derived from bee venom, its neuroprotective effect was first suspected in a bee keeper. The group also has a partnership with Air Liquide to test the neuroprotective properties of rare gases in neurodegenerative diseases; gases which we already know are beneficial in the case of stroke. To fight neuronal death, Etienne Hirsch and his collaborators also study the inflammatory response it induces. In effect, if this response helps the brain eliminate dead neurons, it also has the undesirable effect of accelerating degeneration. The group is notably interested in the way this response is initiated by activation of molecular receptors present on the "clean-up team" of the brain. This basic research gives hope for new targeted treatments.

Parkinson disease also affects non-dopaminergic neurons, the destruction of which causes specific disorders of gait and equilibrium. The team of Etienne Hirsch has shown that some of these neurons use acetylcholine to communicate with each other. In collaboration with Brian Lau (ICM), the team tries to eliminate the associated symptoms by electric stimulation in cholinergic brain regions.

Principal investigators: Chantal François, David Grabli, Stéphane Hunot, Annie Lannuzel, Rita Raisman, Marie-Laure Welter, Patrick-Pierre Michel

The team was supported by: Fondation Air Liquide, Fondation RATP, RSI-Professions Libérales, KLESIA, Agence Nationale de Recherche, Ecole des Neuroscience de Paris Ile de France, France Parkinson, European Commission, Elan Pharmaceuticals, PSP, Air Liquide, BOIRON, SERVIER.

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2 1 RESEARCH AXES

SEARCH.
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NEURODEGENERATIVE DISEASES

6. TEAM "TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS / FROM GENETICS TO THE ZEBRA FISH"

Team leader: Edor Kabashi

The team of Edor Kabashi identifies the genes and cellular mechanisms implicated in amyotrophic lateral sclerosis (ALS). This disease affects the motoneurons that command the muscles, impairing voluntary movements. Not a single disease, recent research focuses on a spectrum of variants, a small minority of which correspond to "pure" ALS, i.e. with no other associated symptoms. In most patients with ALS, one observes, in addition to the symptoms of the disease, other clinical signs that vary from one patient to another, and are often characteristic of fronto-temporal dementia (due to degeneration of the frontal and temporal lobes of the brain). These variants of the disease are caused by different genes in the patients and need much research to help all those who are affected. This is the objective of the team, which carries out its experiments on the zebra fish, in which different combinations of genes can be tested. The team of Dr. Kabashi has notably developed models in this fish for all of the genes prevalent in ALS (C9ort72, TDP-43, FUS and SOD1 among others) with the aim of understanding the genetics of this disease and elucidating the physiopathological mechanisms associated with the degeneration of the motoneurons. The water in which the fish live constitutes an environment that is easy to control in the laboratory, thus facilitating testing of molecules that are potentially neuroprotective. The team of Edor Kabashi can thus test a large number of these molecules that are potentially beneficial for patients according to studies in other partner laboratories at the ICM.

The team was supported by: Philippe Foundation Inc., Fondation Cognacq-Jaÿ, KLESIA, Association Française contre les Myopathies, Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone, France Alzheimer, Institut de Recherche sur la Moelle Epinière et l'Encéphale, DOF (Department Of Defense), The Johns Hopkins University, Université de Montréal via SLA, European Commission.

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AND TEAMS

NEURODEGENERATIVE DISEASES

7. TEAM "EXPERIMENTAL NEUROSURGERY"

Team leader: Brian Lau

Several groups at the ICM have shown that brain stimulation can relieve the symptoms of patients with motor or behavioural disorders. The team of Brian Lau (with those of Marie Vidailhet and Luc Mallet) participate in this research, focusing on the motor deficits observed in Parkinson disease. This neurodegenerative disorder provokes the dysfunction of regions deep in the brain, notably the substantia nigra and the subthalamic nucleus of the basal ganglia. Brian Lau is particularly interested in the latter, because electrical stimulation can improve the motor symptoms of Parkinsonian patients. However, stimulation can also cause secondary effects and, in general, the mechanisms that underlie these different effects are not known. Brian Lau and his colleagues are working to improve understanding of these mechanisms and thus better control the therapeutic character of the stimulation. The project of the team involves electrophysiological recordings in the subthalamic nucleus during movements. These recordings are carried out in patients with Parkinson disease, but also in experimental models, to determine the role of this structure in the healthy brain (the invasive nature of the electrodes implanted deep in the brain does not allow experimentation in healthy individuals who will obtain no benefit). The team also uses experimental models to reproduce human symptoms: the researchers want to understand the evolution of the activity of the nucleus during as the disease progresses and thus demonstrate its role in the appearance of the clinical signs and the way in which they can be prevented.

Principal investigators: Carine Karachi

The team was supported by: Institut de France, INSERM, SANOFI-AVENTIS.

PRINCIPAL PUBLICATIONS

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2 1 RESEARCH AXES

SEARCH,
FIND,
CURE

NEURODEGENERATIVE DISEASES

8. TEAM "STUDY OF NORMAL AND PATHOLOGICAL MOTOR CONTROL: FROM PHYSIOPATHLOGY TO EXPERIMENTAL THERAPEUTICS"

Team leaders: Stéphane Lehéricy and Marie Vidailhet

The team is focused on the study of neuronal circuits in the normal and pathological motor system. Their work is organized along 4 axes: MRI imaging, physiology, animal models and experimental therapeutics. Thus, they develop multiple and complementary approaches to understand and treat movement disorders such as dystonia, Gilles de la Tourette syndrome, genetically-based mirror movements and Parkinson disease. They approach the mechanisms (physiology) of these disorders and develop invasive and non-invasive therapeutic applications (deep brain stimulation for dystonia, non-invasive transcranial stimulation for tremor). The results of their recent work and their projects are being developed along four principal research axes: 1) the study of normal motor control in humans and animals to better understand abnormal movements; 2) the study of abnormal motor control in human diseases, models of dysfunction of motor circuits, and behaviours (congenital mirror movements, dystonia, Gilles de la Tourette syndrome, motor disorders during paradoxical sleep, disorders of gait and eye movements, Parkinson disease which affects 1% of the population after age 65); 3) study of the physiopathology of these disorders and identification of factors that predict the evolution of the disease (Parkinson); 4) identification of new targets to improve motor function by modulating the activity of dysfunctional networks. The data obtained by the researchers is genetic, metabolic, physiological and behavioural and include imaging data (MRI and MEG -see the technological platforms of the ICM). On the basic level, this multimodal approach allows the establishment of connections between these different levels of analysis; for example, correlations between a genetic mutation, the lesion or the dysfunction of a specific brain circuit and clinical symptoms such as involuntary movements. In addition, this approach leads to the identification of biomarkers that predict the appearance and evolution of the disease. The latter permit the identification of targets for new therapeutic approaches (identification of dysfunctions in brain circuits and their modulation by electric brain stimulation). The overall aim is to propose personalized care based on better knowledge of the alterations that underlie movement disorders and on the ability to restore better motor control.

Principal investigators: Emmanuel Roze, Pierre Pouget, Isabelle Arnulf, Sabine Meunier

The team was supported by: Fondation Areva, Fonds Patrick de Brou de Laurière, APHP, Centre Hospitalier de Rennes, Agence Nationale de Recherche, Association Française du Syndrome de Gilles de La Tourette, Association des Malades Atteints de Dystonie, Association des personnes concernées par le tremblement essentiel, Dystonia Medical Research Foundation, Dystonia Coalition USA, Fondation de l'avenir, Fondation Groupama, France Parkinson, Fédération pour la Recherche sur le Cerveau, Fondation pour la Recherche Médicale, Kleine-Levin syndrome Foundation - Boston, NEB (Naturalia et Biologia), Prix Fondation NRJ, École de Neurosciences Paris Ile de France, Genzyme France, Novartis Pharma, ROCHE, Fondation Bettencourt Schueller / Projet Ultrabrain, Fondation Pierre Gilles de Gennes pour la Recherche, Lundbeck, Novartis Pharma, TEVA, UCB Pharma France S.A, Glaxosmithkline, IPSEN Innovation, LILLY, Merz Pharma, SERVIER.

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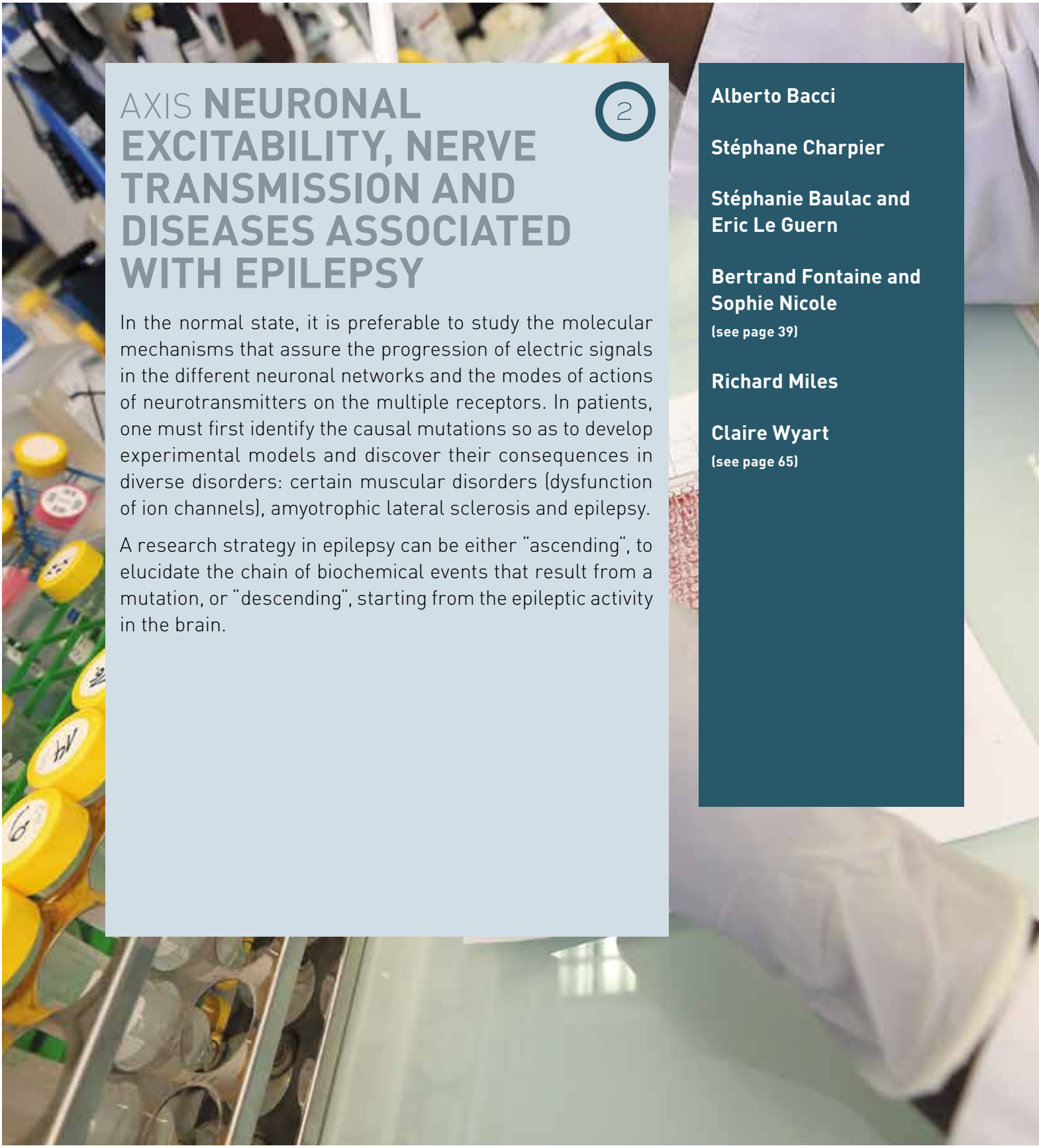
AND TEAMS



AXIS 2 NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

In the normal state, it is preferable to study the molecular mechanisms that assure the progression of electric signals in the different neuronal networks and the modes of actions of neurotransmitters on the multiple receptors. In patients, one must first identify the causal mutations so as to develop experimental models and discover their consequences in diverse disorders: certain muscular disorders (dysfunction of ion channels), amyotrophic lateral sclerosis and epilepsy.

A research strategy in epilepsy can be either "ascending", to elucidate the chain of biochemical events that result from a mutation, or "descending", starting from the epileptic activity in the brain.

Alberto Bacci

Stéphane Charpier

Stéphanie Baulac and Eric Le Guern

Bertrand Fontaine and Sophie Nicole
(see page 39)

Richard Miles

Claire Wyart
(see page 65)

2 1

RESEARCH AXES

SEARCH.
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NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

1. TEAM "CELLULAR PHYSIOLOGY OF CORTICAL MICROCIRCUITS"

Team leader: Alberto Bacci

The cerebral cortex is the brain structure in which sensory information is processed, stored and used to generate elaborate behaviours and cognitive functions. It is due to the coordinated activity of a myriad of different neurons, connected in complex functional networks that the brain is able to perform such feats. The neurons are connected together via synapses, highly specialized structures in which the presynaptic terminal of a neuron releases neurotransmitters captured by the postsynaptic structure of the neuron it contacts. The neurotransmitters are either excitatory (glutamate), inducing the contacted neuron to discharge action potentials, or inhibitory (GABA), preventing the genesis of action potentials. In the cerebral cortex, the release of the inhibitory neurotransmitter GABA is assured by neurons that often project locally, thus called interneurons. GABAergic interneurons constitute a very heterogeneous population that can be classified according to anatomical and electrophysiological criteria, and which play an important role in the control of the activity of the principal neurons.

In the team, we use an electrophysiological approach to study how specific sub-types of interneurons are at the origin of different forms of (i) synaptic transmission, (ii) synaptic plasticity and iii) oscillations of networks which are the basis of cognitive processes.

These studies will help to better understand the regulation of neuronal circuits by GABAergic interneurons underlying cortical functions that, when destabilized, are often at the origin of neurological pathologies such as epilepsy, schizophrenia and autism.

The team was supported by: TELETHON Italia, Fundaçao oara a Ciencia e a tecnologia, Caisse d'Assurance Maladie des Professions Libérales, Ministère de l'Egalité des Territoires et du Logement, European Commission.

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AND TEAMS

NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

2. TEAM "CIRCUIT DYNAMICS AND CELLULAR EXCITABILITY"

Team leader: Stéphane Charpier

The team of Stéphane Charpier uses electrophysiology to study the electrical activity of the brain at all levels, from the surface electroencephalogram (large circuits of neurons) to the intracellular activity of the neuron. This exhaustive approach allowed them to discover previously unsuspected mechanisms of memory at the intracellular level of neuronal activity, and also to study the relationships between brain activity and consciousness. It also allowed them to identify the relationships between these different levels to better apprehend and predict the initiation and propagation of epileptic seizures.

Researchers speak of epilepsy in the plural, since they are characterized by different features that make them difficult to classify: importance or not of the propagation of abnormal electrical activity in the two hemispheres of the brain, appearance or not of convulsions or loss of consciousness... The team of Stéphane Chapier is interested in all forms of epilepsy: from partial to generalized seizures. The generalized seizures most frequently encountered in children are absence seizures. This form of epilepsy is a handicap for the young patient, who loses consciousness (for a short, often imperceptible period, but up to hundreds of times a day).

Clinical hope has been provided by the team concerning: (1) improvement of the localization in the brain of epileptic foci, in which seizures begin, to be able to neutralize them; and (2) improvement of memory, by exploring new mechanisms of learning in the brain.

Principal investigators: Séverine Mahon, Vincent Navarro, Michel Le Van Quyen

The team was supported by: Fondation de France, Fédération pour la Recherche sur le Cerveau, Fondation pour la Recherche Médicale, Convergence (UPMC), Emergence (UPMC).

PRINCIPAL PUBLICATIONS

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NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

3. TEAM "GENETICS AND PHYSIOPATHOLOGY OF FAMILAL EPILEPSIES"

Team leaders: Eric Leguern and Stéphanie Baulac

The team works on epilepsy, notably the forms of epilepsy of genetic origin. The primary objective of the team is to identify new genes responsible for epilepsy by sequencing (i.e. reading) the genome (the whole of genetic information in the form of DNA) of patients who are clinically well-characterized. The researchers are particularly interested in the exome, the part of the genome that encodes the proteins that play a direct role in the cellular machinery. It's in these proteins that the characteristics of the genome are expressed. If the later is mutated in such a way as to interfere with the functions of the organism, it's often because an abnormal protein is produced or a normal protein is no longer produced. The team works not only on hereditary forms of the disease, it also looks for new mutations that appear in children of parents who do not carry the gene - as in the case of Dravet syndrome, a severe form of epilepsy in infants. To detect this new, "de novo", mutation, the researchers compare the exome of the child and his 2 parents (approach "by trios"), and look for a rare variant found only in the DNA of the child.

Beyond genetics, the team is also working to understand the function of the proteins produced by genes associated with epilepsy and the role they play in the disease. To this end, the team uses transgenic mice that lack a gene encoding one of these proteins, as well as cell lines. They also use a broad spectrum of techniques to elucidate the anatomy and function of neuronal networks at different levels, up to the behaviour of the experimental animal.

Principal investigators: Michel Baulac, Christel Depienne

The team was supported by: OSEO, BIOCODEX.

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AND TEAMS

NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

4. TEAM "CORTEX AND EPILEPSY"

Team leader: Richard Miles

The team is interested in the normal and pathological physiology of the cerebral cortex, the surface of the gray matter of the brain. The team is focused notably on the dysfunctions that lead to the so-called "focal" epilepsies, i.e. epilepsies that we know are due to a localized neuronal focus. They are often situated in the hippocampus, a deep region of the cortex (the major part of which is hidden in its folds) on which the efforts of the group are concentrated. Among the different epilepsies found in the population, a third are resistant to medical treatment and thus constitute a major target for researchers and clinicians. Richard Miles and his collaborators are trying in particular to understand the functioning of the molecular receptors present of the surface of the neurons that control transmission of the nerve impulse between neurons. Neuronal death is the other target of the team in its search for the origins of epilepsy. The researchers work, in particular, on the role of cholesterol and more generally lipids in this neuronal death. The team works directly on patients as well as on mice given a molecule that excites neuronal activity (kainic acid) to model epileptic seizures. In the patients, the team uses imagery to localize and quantify the receptors mentioned above, as well as surface electroencephalography and intracerebral recordings. These two electrophysiological approaches serve to detect potential biomarkers of incipient seizures in the form of subtle changes in electrical activity.

Principal investigator: Desdemona Fricker

The team was supported by: Agence Nationale de Recherche, Ecole des Neurosciences Paris Ile de France, Fondation Française pour la Recherche sur l'épilepsie, Fondation pour la Recherche Médicale, European Commission, OCIRP.

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2 1

SEARCH.
FIND.
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RESEARCH AXES

AXIS **DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR** 3

How are nerve cells generated, differentiated and distributed in the central nervous system? How can we identify the mechanisms of the dysfunction of glial cells and myelin, essential for the effective transmission of the nerve impulse? What are the most innovative therapeutic strategies to favour cell repair in diseases that cause a loss of myelin? One must identify the molecules and mechanisms that direct the development of the brain. One must also understand how glial cells and neurons are organized into functional networks. The greatest challenge for the ICM is the discovery of means to correct deficits caused by the dysfunction of stem cells and glial cells, such as that observed in brain tumours, multiple sclerosis, leucodystrophies and peripheral neuropathies. The ambitions of the teams of the ICM include the development of innovative therapies to repair myelin lesions by identifying new pharmacological or cellular targets to prevent demyelination and favour remyelination.

Bertrand Fontaine and Sophie Nicole
(see page 48)

Emmanuelle Huillard

Catherine Lubetzki and Bruno Stankoff

Brahim Nait Oumesmar and Anne Baron-Van Evercooren

Marc Sanson

Jean-Léon Thomas and Bernard Zalc

AND TEAMS

DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

1. TEAM "CELLULAR AND MOLECULAR MECHANISMS IN THE DEVELOPMENT OF GLIOMAS"

Team leader: Emmanuelle Huillard

The team of Emmanuelle Huillard works on the molecular and cellular mechanisms responsible for the formation of aggressive brain tumours, the high-grade gliomas. These tumours are incurable and the patients survive only a short time. This type of cancer affects not neurons but glia, the latter being a population of cells that support neurons structurally and functionally (such as oligodendrocytes, which produce the myelin that insulates the axons that connect neurons). The team makes a parallel between the normal development of glial cells and their pathological development to better understand the implication of certain genes of development in the tumoural process. Emmanuelle Huillard and her collaborators have, for example, determined the causal role in glioma formation of a transcription factor, Olig2, also implicated in normal cellular development. Transcription factors are molecules that regulate reading of the genetic code and the production, based on this reading, of the proteins that participate in cellular function. At present, the team is studying the function of the protein Id4, a modulator of Olig2, which seems to favour, or on the contrary prevent, the formation of gliomas depending on the genetic characteristics of the tumours. In addition, the team works on mice in which tumours are induced, to determine which cells in the brain are deregulated and which proteins cause the tumours develop.

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

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DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

2. TEAM "CELLULAR AND MOLECULAR APPROACHES TO REMYELINATION"

Team leaders: Brahim Nait Oumesmar and Anne Baron–Van Evercooren

The team of Brahim Nait Oumesmar and Anne Baron-Van Evercooren is focused on the diseases of myelin and more particularly multiple sclerosis and certain leucodystrophies. The neurons send information in the form of electric discharges (action potentials) along an "electrical wire" - the axon - insulated by a sheath of myelin that protects the axon and accelerates transmission of the nerve impulse. Myelin is progressively destroyed in patients with multiple sclerosis or genetic diseases such as the leucodystrophies. The team is working to better understand the mechanisms of "remyelination" that permit stem cells or progenitors to transform into myelinating cells. The team has 3 research axes: 1) the mechanisms of regeneration by oligodendrocytes, the myelinating cells of the brain and the spinal cord, and more particularly the roles of transcription factors and electrical activity in remyelination; 2) the implication of progenitor cells in the peripheral nervous system in the repair of the central nervous system; 3) the role of inflammation in remyelination; 4) the therapeutic potential of stem cells for neuroprotection and remyelination. For this research, the team develops innovative models of demyelination-remyelination, in which they can effectively test the therapeutic potential of new molecules or cells to regenerate myelin. The results of these studies should lead to the development of new therapeutic approaches to the treatment of multiple sclerosis and certain leucodystrophies.

Principal investigator: Violetta Zujovic

The team was supported by: Association Institut de Myologie, Aide à la Recherche sur la Sclérose en Plaques, ELA (research foundation), Ecole des neurosciences Paris Ile de France, Fondation pour la recherche sur le Cerveau, Fondation pour la Recherche Médicale, Institut de Recherche sur la Moelle Epinière et l'Encéphale, Ligue Française contre la Sclérose en Plaques, Multiple Sclerosis International Federation, National Multiple Sclerosis Society via Children's national organisation, GyeongGi (Bio-Center, European commission-Fondation Cluny, National Multiple Sclerosis Society via Fondazione Centro San Raffaele, OCIRP.

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AND TEAMS

DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

3. TEAM "MECHANISMS OF MYELINATION AND REMYELINATION IN THE SNC"

Team leaders: Catherine Lubetzki and Bruno Stankoff

The team of Catherine Lubetzki and Bruno Stankoff studies the cellular mechanisms of demyelination and remyelination, and the possibilities for imagery in these processes, with the aim of the translational development of remyelinating therapies in multiple sclerosis. Whereas gray matter contains the cell bodies of neurons and their connexions, white matter contains abundantly myelinated axons, which connect neurons over long distances. This team works on the formation and maintenance of the nodes of Ranvier, axonal regions in which myelin does not cover the neuron, that permit rapid propagation of the electric impulse. The team is notably identifying a factor in cells that produce myelin, the oligodendrocytes, which induces the formation of nodes of Ranvier. The molecular pathways implicated in the activation and the migration of remyelinating cells of the adult central nervous system, the precursors of oligodendrocytes, are also being identified. An important characteristic of the team is its expertise in imagery, in particular thanks to the combination of molecular imaging by through positon emission tomography (TEP) and MRI. The team has thus initiated methods for visualizing, in vivo, remyelination, neurodegeneration and microglial inflammation in multiple sclerosis. These researchers are also developing an approach using multimodal imagery in animals, combining very high-field MRI and non-conventional optical imagery, to characterize the mechanisms of myelin pathology in real time and permit the preclinical evaluation of potential promyelinating molecules.

Principal investigators: Anne Desmazières, Benedetta Bodini, Nathalie Sol Foulon

The team was supported by: Agence Nationale de Recherche, Aide à la Recherche sur la Sclérose en Plaques, Fondation pour la Recherche Médicale, Prix SOBECK - Fondation de France, Genzyme.

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DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

4. TEAM "EXPERIMENTAL NEURO-ONCOLOGY"

Team leader: Marc Sanson

Neurons are not the only cells in the brain. They are supported structurally and functionally by glial cells. With the lymphocytes of the immune system, glial cells are at the origin of the most aggressive and most frequent brain tumours (lymphomas and gliomas, respectively). With one of the largest banks of samples of brain tumours (onconeuro library), the team uses molecular biology to detect the genetic mutations that cause the tumours, analyse their prognostic value and predict their response to treatment, thus furnishing clinicians with useful information. The team also identified some mutations in DNA released by the tumours into the circulatory system, which thus provides clinicians with a potentially very useful diagnostic. The team is trying to determine the impact of these mutations and the molecular mechanism by which they contribute to the transformation of a normal cell into a tumour cell. A major problem resides in the fact that not all neurons have the same impact, some have hardly any consequences, whereas others, on the contrary, are critical and thus constitute targets for specific cancer treatments.

This is the objective of the experimental therapeutics platform Gliotex (Dr. A. Idbaih): to develop, from cell cultures and grafts on mice, specific therapies adapted to the mutational profiles of the tumours. This approach gives hope for the development of personalized treatments for each patient based on the genetic profile of his tumour.

Principal investigators: Khê Hoang-Xuan, Ahmed Idbaih, Jean-Yves Delattre

The team was supported by: Association pour la Recherche sur le Cancer, Fondation de France, La Ligue Nationale contre le Cancer, Inca, Fondation Obélisque, Beta Innov.

PRINCIPAL PUBLICATIONS

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AND TEAMS

DEVELOPMENT, GLIAL PATHOLOGY AND REPAIR

5. TEAM "OLIGODENDROCYTE DEVELOPMENT AND NEUROVASCULAR INTERACTIONS"

Team leaders: Jean-Léon Thomas and Bernard Zalc

Our research is focused on neural stem cells and oligodendrocyte precursor cells. Neural stem cells generate all of the cells of the central nervous system: neurons as well as the astrocytes and oligodendrocytes that support them structurally and functionally. Oligodendrocyte precursors are more differentiated than stem cells and only produce oligodendrocytes, which are the myelinating cells of the central nervous system. Myelin, the membrane wound around axons, assures rapid transmission of the nerve impulse. Bundles of myelinated axons form the white matter of the brain and spinal cord. The possibility of isolating and manipulating stem cells and precursors opens perspectives for the innovative treatment of neurological diseases. Our first objective is to identify the molecules necessary for the production, maintenance and differentiation of these cells. The second objective is to create models enabling us to see and manipulate these cells in the living brain. Our studies are carried out in mice, but also on the amphibian *Xenopus*, in which we introduce reporter genes expressed by oligodendrocytes and neurons. We encourage, as much as possible, the development of *in vitro* models, notably for our studies on humans, using neural stem cell lines.

Principal investigators: Charles-Félix Calvo, Michel Mallat, Carlos Parras

The team was supported by: Agence Nationale de Recherche, Aide à la Recherche sur la Sclérose en Plaques, National Multiple Sclérosis Scoiety via Children's national organisation, Agence Nationale de Sécurité Sanitaire de l'Alimentation de l'Environnement et du Travail, Ministère - Délégation de la compétitivité, de l'industrie et des services, Novartis Pharma.

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2 1

SEARCH.
FIND.
CURE

RESEARCH AXES

AXIS **COGNITION, EMOTION, ACTION** 4

The mechanisms that underlie mental functions be they motor, intellectual or emotional are at the origin of human behaviour. Why do we do what we do? What are the bases of normal and altered motivation? How do our intentions produce behaviours? How are intellectual and emotional functions combined to determine our actions? Why is what we see not always perceived by others? How do we become conscious of the world around us and of ourselves? How do we communicate with the help of language? The ICM hosts very competitive teams trying to answer these questions. These scientists work with humans, from the most subtle clinical analysis to electrophysiological examinations, including neuroimaging. The data obtained in normal subjects are indispensible for understanding and improving treatment of functions that are altered in patients, be they disorders of movement (slowness, rigidity, tremor, tic, chorea, dystonia, etc.), intellect (memory loss, language disorders, perceptual disorders, notably visual, etc.), or the psyche (depression, anxiety, schizophrenia, autism, obsessive compulsive disorders, etc.).

Laurent Cohen, Lionel Naccache and Paolo Bartolomeo

Bruno Dubois and Richard Lévy

Nathalie George and Philippe Fossati

Luc Mallet

Mathias Pessiglione, Sébastien Bouret and Jean Daunizeau

AND TEAMS

COGNITION, EMOTION, ACTION

1. TEAM "NEUROPSYCHOLGY & NEUROIMAGERY (PICNIC LAB)"

Team leaders: Paolo Bartolomeo, Laurent Cohen and Lionel Naccache

The work of the team illustrates well the dialogue between biology and medicine. Its leaders are neurologists who seek in their patients responses to their fundamental questions about visual attention, language and consciousness. A brain lesion associated with an attentional or reading disorder can indicate the localization of a brain region indispensible for these functions. The researchers use techniques of brain imaging like MRI to localise the lesion. Preserved functional activity can eventually indicate an adaptation to lesions, as well as connections between the different regions of the brain associated with the function under study or its loss. In the end, the theoretical models developed as a result of this approach should provide means to help patients recover their lost abilities.

The research group directed by Lionel Naccache explores the brain mechanisms and psychological properties of conscious mental operations. For example, his group identified, during the past few years, several brain signatures of consciousness, both in healthy subjects (ex: comparison between conscious perception and subliminal perception) and patients with brain lesions (ex: comparison between patients who are awake but not conscious (vegetative state) and patients who are awake and conscious (ex: patients in a state of minimal consciousness). These studies aim at formulating a neuronal theory of consciousness in non-communicative subjects. The group also explores the dynamics of conscious interpretations in diverse situations and the limits of non- conscious cognitive processes.

The team was supported by: Agence Nationale de Recherche, France Alzheimer, Fondation pour la Recherche Médicale, European Commission, AXA, McDonnell Foundation, AXA Research Fund.

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COGNITION, EMOTION, ACTION

2. TEAM "FRONTLAB"

Team leaders: Bruno Dubois and Richard Lévy

The researchers of the Frontlab work on the mental functions elaborated in the frontal lobes. These frontal functions are major problems for the neurosciences; they construct and control the most complex of our behaviours (decision making, planning, reasoning, creativity, moral judgement, social interactions...). A detailed knowledge of these functions is indispensible to improve treatment of the numerous neurological and psychiatric diseases affecting the frontal lobes (Alzheimer disease, frontal dementia, stroke...).

Our objectives are to: 1) better apprehend the implication of the frontal lobes in behaviour and intellectual functions; 2) transfer the knowledge acquired to medical practice.

Our research project has two essential aspects: 1) the elucidation of the implication of the frontal lobes in the generation and initiation of voluntary action, using a pathological model, apathy; 2) the clarification of their role in creative thinking and, more precisely, in the ability to inhibit automatic associations, to generate ideas and new rules.

The project is based on the study of normal human subjects and patients with brain lesions, combining: 1) experimental psychology; 2) functional imaging (fMRI) to study the activation of the brain during behavioural tasks and anatomical imaging to detect correlations between lesions in the brain and mental functions and the fibres (the "routes") that connect different parts of the brain; 3) electroencephalography to record the electrical activity of the brain; 4) neurostimulation (intraoperative intra-cerebral or non-invasive transcranial magnetic stimulation) which can activate or inactivate certain regions of the brain of the person performing an action.

Principal investigators: Marc Teichman, Michel Thiebaut de Schotten, Antoni Valerocabre, Emmanuelle Volle, Benedicte Batrancourt

The team was supported by: Agence Nationale de Recherche, AXA, Fondation pour la Recherche Médicale, IFR 49, NIH, PIR, European Commission, PSP, Ecole des Neuroscience Paris Ile de France, Pfizer AVID, ROCHE.

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AND TEAMS

COGNITION, EMOTION, ACTION

3. TEAM "STUDY OF EMOTIONS AND SOCIAL INTERACTIONS

Team leaders: Nathalie George and Philippe Fossati

Human beings are made to live in society, without which an individual cannot develop, learn or progress. The possibility to live fully within a group depends on specific capacities of the brain that teams like that of Nathalie George and Philippe Fossati are trying to understand. This research is essential for persons who have difficulty living within a group to the extent of being handicapped, like those with autism. It also has potentially important repercussions for depressed patients. The latter suffer from an abnormal regulation of their emotions, and emotions play a central role in our interactions with others. In effect, our emotions permit us to evaluate the quality of our interactions with others; conversely, interactions with others are often sources of emotion. The emotion associated with a social interaction, felt or perceived in the behaviour of the other (on his face, in his voice...) indicates to us whether our action was appropriate or not, whether our behaviour should be modified or not. The researchers thus distinguish the social brain from the emotional brain and their relationships, which they work to understand. To this end, the team compares healthy subjects and patients by functional neuroimaging. The researchers can thus determine which regions of the brain and which networks connecting these regions present an abnormal activity in patients. This research should help identify the best markers of depression and develop personalized treatments.

Principal investigators: Stéphanie Dubal

The team was supported by: Agence Nationale de Recherche, Fondation de France, Fondation RATP, Fondation pour la Recherche Médicale, CEA, Institut de recherche biomédicale des armées, Région Ile de France, ADIRR.

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COGNITION, EMOTION, ACTION

4. TEAM "BEHAVIOUR, EMOTIONS AND BASAL GANGLIA"

Team leaders: Luc Mallet and Jérôme Yelnick

The applications of the work of the team are examples of what the neurosciences can offer patients suffering from diseases of the brain. The team notably developed a unique anatomical atlas that permits accurately localized implantation of stimulatory electrodes in patients whose symptoms resist all other treatments. The patients concerned suffer from disorders such as tremor or obsessive behaviours that can be treated effectively by targeted electrical stimulation of deep brain regions (sub-cortical): the basal ganglia. What distinguishes their project is precisely their interest in these sub-cortical regions and their interactions with the cortex (surface of the brain). All aspects of cognition (language, decision making...) are associated with these cortico-sub-cortical loops. The team of Luc Mallet and Jérôme Yelnick is particularly interested in Parkinson disease, obsessive compulsive disorders, depression or addictions. Abnormal regulation of the emotions is a cause shared by several of these disorders. In effect, this applies not only to depression, but could also explain obsessive disorders and syndromes of addiction. The team carries out its research using behavioural, electrophysiological and neuroimaging data obtained in patients and animal models.

Principal investigators: Eric Burguière, Karim N'Diaye, Jérôme Yelnik

The team was supported by: Agence Nationale de Recherche, Fondation pour la Recherche Médicale, MEDTRONIC - Fondation Fondamentale, Christian Poquet.

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AND TEAMS

COGNITION, EMOTION, ACTION

5. TEAM "MOTIVATION, BRAIN, BEHAVIOURS"

Team leaders: Sébastien Bouret, Jean Daunizeau, Mathias Pessiglione

What is the relationship between Parkinson disease, depression and burnout syndrome, this modern issue of work exhaustion? The brain, of course, and most particularly the mechanisms underlying our motivations, the psychological fuel without which an active life is impossible. It is from this original angle that the team of Sébastien Bouret, Jean Daunizeau and Mathias Pessiglione propose to redefine a group of diseases and improve their treatment. The research of the team has, for example, provided new tests that inform the clinician not only of the lack of motivation of a depressed patient, but also of the nature of the deficit. Has the patient become abnormally fragile in the face of daily obligations (cooking), or less sensitive to the small pleasures they give (enjoying the dish)? Depending on the case, the optimal treatment is not the same. This type of clinical advance is based on a combination of data traditionally treated separately: biological, psychological, but also mathematical, philosophical, etc... The difficult integration of this data is rarely attempted and constitutes a major asset of the team Motivation, Brain, Behaviours. It is the basis of an ambitious program of research in humans and animals, from the cell to large-scale brain networks, leading to explanations of behaviours. The impressive list of publications of the team and its attractiveness to students attest to its success.

The team was supported by: Direction Générale pour l'Armement, Ville de Paris, European Commission, Fondation pour la Recherche Médicale, HBP (Lausanne), La société mutualiste des médecins du Département de Paris, SERVIER.

PRINCIPAL PUBLICATIONS

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- Meyniel F, Sergent C, Rigoux L, Daunizeau J, Pessiglione M. Neurocomputational account of how the human brain decides when to have a break. Proc Natl Acad Sci U S A. 2013 Feb 12;110(7):2641-6
- Le Bouc R, Pessiglione M. Imaging social motivation: distinct brain mechanisms drive effort production during collaboration versus competition. J Neurosci. 2013 Oct 2;33(40):15894-902
- Palminteri S, Serra G, Buot A, Schmidt L, Welter ML, Pessiglione M. Hemispheric dissociation of reward processing in humans: insights from deep brain stimulation. Cortex. 2013 Nov-Dec;49(10):2834-44
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RESEARCH AXES

AXIS **MODELS AND METHODS FOR THE NEUROSCIENCES (A TRANSVERSAL AXIS)** 5

From a scientific point of view, the approach of the ICM is revolutionary since its research has no barriers. The research teams are thus independent, but allied in Transversal Research Programs that favour the mutualisation of competencies. Transversal research constitutes the essential connection between basic and clinical research. It allows patients to benefit more rapidly from diagnostic and therapeutic innovations. It is the basis of research at the ICM.

Olivier Colliot

Philippe Ravassard

Claire Wyart

AND TEAMS

MODELS AND METHODS FOR THE NEUROSCIENCES

1. TEAM "ARAMIS - MATHEMATICAL MODELS AND ALGORITHMS FOR PROCESSING BRAIN IMAGES AND SIGNALS"

Team leaders: Olivier Colliot, Didier Dormont

ARAMIS is a team that performs research in informatics and mathematics applied to neuroimaging of the human brain. The objective of the team is to develop the most powerful methods of analysis to better characterize the many neurodegenerative diseases (Alzheimer disease, fronto-temporal dementia...), epilepsy and cerebrovascular diseases (vascular dementia, stroke). There are 2 categories of images: those with high spatial resolution such as MRI (Magnetic Resonance Imagery) and those with high temporal resolution such as images constructed from electrophysiological signals (magnetoencephalography or MEG and electroencephalography or EEG). Utilized correctly, these images can provide biomarkers of diseases: the team extracts from untreated images signals specifically associated with the diseases, to better understand them and detect them as early as possible, even before the appearance of clinical signs. The team is also interested in correlations between genotypes and phenotypes, for example, to establish an association between a mutated gene (genotype), a clinical sign, a lesion in a particular brain region or an abnormal electrical activity (phenotype that would be caused by the genotype). One of the challenges faced by the team is to combine this varied and complex data in a form that is useful for research, a typically modern problem of "Big Data" resulting from the new digital technologies.

Principal investigators: Marie Chupin, Stanley Durrleman, Mario Chavez, Yves Sanson, Damien Galano, Dominique Hasboun, Sophie Dupont

The team was supported by: Agence Nationale de Recherche, Fondation Plan ALZHEIMER, European Commission.

PRINCIPAL PUBLICATIONS

- Cuingnet R, Glaunès JA, Chupin M, Benali H, and Colliot O, The ADNI. Spatial and anatomical regularization of SVM: a general framework for neuroimaging data, IEEE Transactions on Pattern Analysis and Machine Intelligence, 35 (3), 682-696, 2013
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MODELS AND METHODS FOR THE NEUROSCIENCES

2. TEAM "BIOTECHNOLOGY AND BIOTHERAPY"

Team leader: Philippe Ravassard

The team is specialized in the development of gene therapies that specifically target regions of the brain responsible for the different neuropsychiatric diseases. Starting from their studies in genetics, Philippe Ravassard and his collaborators became interested in a gene encoding a protein expressed exclusively in the brain, the role of which was not well known: a receptor for molecules that signal between neurons. Inactivation of this gene throughout the brain is associated with behavioural changes resembling neurological and/or psychiatric disorders. However, the team "Biotechnology and Biotherapy" showed that local inactivation of the same gene in deep sub-cortical structure in the brain (the striatum in the basal ganglia) improves cognitive and motor deficits in models of psychiatric diseases. Since the striatum is implicated in Parkinson disease, the team is presently evaluating the role of the gene in this disease in order to develop a targeted genetic therapy for its treatment.

From a fundamental point of view, the team is also interested in a part of the DNA called "non-coding" because it does not lead to the production of proteins, but instead (long) molecules of non-coding RNA. This type of RNA is important for the regulation of genes in "coding" RNA, and can thus play a role in diseases, notably of the brain. For this work, the team potentiated its earlier, successful work on the pancreas and is capitalizing on it in association with several pharmaceutical laboratories via a start-up in the industrial nursery of the ICM.

Principal investigators: Rolando Meloni

The team was supported by: Agence Nationale de Recherche, NIH - USA-Vanderbilt University, Région Ile de France, European Commission, SERVIER.

PRINCIPAL PUBLICATIONS

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AND TEAMS

MODELS AND METHODS FOR THE NEUROSCIENCES / NEURONAL EXCITABILITY, NERVE TRANSMISSION AND DISEASES ASSOCIATED WITH EPILEPSY

3. TEAM "OPTOGENETIC DISSECTION OF SPINAL CIRCUITS UNDERLYING LOCOMOTION

Team leader: Claire Wyart

The team of Claire Wyart works to understand how the nerve networks of the spinal cord are recruited to perform a series of complex locomotor actions.

The spinal locomotor network (or central rhythm generator), which is of particular interest to the group, allows - for example - walking without thinking once the decision to move has been made. This ability to maintain a movement comes from the capacity of the network to generate electrical oscillations. Different types of data (physiological, pharmacological and anatomical) have been used in vitro (outside the living organism) to understand how these oscillations are generated. However, these approaches do not show whether the discharges of a given sub-group of neurons are necessary and sufficient to generate a movement.

To overcome this problem, the team studies the function specific spinal cells in vivo in larvae of the zebra fish. This animal model might seem very far from humans, but it has critical advantages for research that aims, long term, to repair the spinal cord and re-establish normal locomotion in patients with handicaps. In effect, the nervous system of the zebra fish evolves very rapidly, which helps gain time in the understanding of its mechanisms. In addition, the larvae are transparent, which makes them particularly adapted to optogenetics, an advanced technique that can activate target neurons at a distance by light. This new approach allows us to activate and deactivate sub-groups of neurons in order to determine their role in the movement of the animal.

Principal investigators: Pierre Luc Bardet, Hugues Pascal-Mousselard

The team was supported by: Ecole des Neurosciences Paris Ile de France, Fondation Bettencourt Schueller, Carcept Prev, Fondation Campus Paris Saclay, Région Ile de France, European Commission, SERVIER.

PRINCIPAL PUBLICATIONS

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- Cholinergic left-right asymmetry in the habenulo-interpeduncular pathway. Hong E, Santhakumar K, Akitake CA, Ahn SJ, Thisse C, Thisse B, Wyart C, Mangin JM, Halpern ME. Proc Natl Acad Sci U S A. 2013 Dec 24;110(52):21171-6
- ZebraZoom: an automated program for high-throughput behavioral analysis and categorization. Mirat O, Sternberg JR, Severi KE, Wyart C. Front Neural Circuits. 2013 Jun 12;7:107
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2

TECHNOLOGICAL

SEARCH.
FIND.
CURE

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

I. FUNCTIONAL EXPLORATION PLATFORMS

The platforms for functional exploration allow investigations *in vivo* (i.e. on the living organism) that are non-invasive and respect the integrity of the subject. They are thus particularly adapted to humans - patients or healthy volunteers. They also permit the study of animals by magnetic resonance imagery **(MRI).** These platforms support four principal axes of research: **clinical research** to study the major pathologies of the nervous system; **research in the cognitive sciences** to study the functioning of the brain and the neuronal bases of thought, behaviour and ageing; **research on signal and image processing** to develop new methods for processing brain imaging data; and the **development of experimental therapeutics** guided by imagery. These studies aim, for example, at identifying biomarkers of diseases, such as abnormal signals associated with neurodegenerative diseases that can be used to improve diagnosis and prognosis and monitor the effects of treatments.

Imaging is, in fact, at the centre of these platforms; two complementary methods are available:

▶ **MRI** offers unequalled spatial resolution (on the order of the millimetre) and yields anatomical images of very high quality permitting effective localization of lesions in brain regions that differ by their anatomy or their function. MRI also permits the detection of signals in relation to blood flow and oxygenation, an indirect functional marker of neuronal activity.

▶ This activity is also measurable with the techniques of electroencephalography (EEG) and magneto-encephalography (MEG) that detect, respectively, electrical and magnetic signals more directly associated with neurons. EEG and MEG offer lower spatial resolution than MRI, but their temporal resolution is much greater (on the order of the millisecond). MEG is more informative, but is more delicate to use. The MEG/EEG centre "Line Garnero" was inaugurated at the end of 2013.

The personnel of these platforms assist researcher-users in the elaboration and realization of their studies and analyses the imagery data obtained. The Neuroimagery Research Centre (CENIR) develops tools for image analysis, signal processing and visualisation.

Functional imagery studies that measure neuronal activity indirectly are in general associated with the study of behaviour. The later can be realized by MRI, MEG and EEG during image acquisition by recording the performance of the subjects,

PLATFORMS AND DATA BANKS

healthy volunteers or patients. However, MRI and MEG limit the use of certain metallic/electronic equipments because of the strong magnetic field generated by the MRI system and the sensitivity of the MEG system to electromagnetic fields. In addition, movements are generally limited in neuroimaging systems. Thus subjects must lie supine in the MRI system to keep their head still during image acquisition. Entire platforms dedicated to behaviour - the platforms CENIR-PRISME and CENIR-PANAM - have consequently been installed to complement the imagery studies. These platforms are also intended for the development of motor and behavioural therapies (exposure to situations that produce abnormal anxiety in certain patients, etc.). These platforms, and notably the latter, offer access to techniques of brain stimulation like TMS (transcranial magnetic stimulation) that uses a strong, temporary magnetic field to interfere - without danger - with the electrical activity of the brain. With this technique, one can determine whether stimulation of the activity of a given region of the brain affects positively or negatively a given intellectual task, induces a movement, etc. It can also be used to stop tremor in a patient. Finally, the CENIR-STIM platform offers support for data analysis and program development for stereotactic imaging (used among others for deep brain stimulation, pharmaco-resistant epilepsy, radiosurgery), offering, for example, tools for stereotactic localization of deep brain structures for clinicians. After localization of the deep brain structure, it can be stimulated electrically in patients in order to treat motor or behavioural problems that resist other treatments.

CENIR-STIM platform

2

SEARCH.
FIND.
CURE

TECHNOLOGICAL

1. CENIR (NEUROIMAGERY RESEARCH CENTRE) - MRI

TEAM

Stéphane Lehéricy: Scientific director

Eric Bardinet: Director of operations

EQUIPMENT

- Trio 3 Tesla MRI Siemens (the Tesla is a measure of the magnetic field - 3T corresponds to a field 60 000 times that of the earth's magnetic field).
- Verio 3 Tesla MRI Siemens
- Bruker 11.7 Tesla small animal MRI
- Brain Map MRI compatible EEG
- TMS (Transcranial Magnetic Stimulation)
- Optical Imagery System
- Sensory stimulation systems (visual, auditory, tactile), physiological (cardiac rhythm) and behavioural (eye movements...) recordings compatible with MRI.

The platform was supported by: Fondation Lily Safra, IPRIAC

2. CENIR – MEG/EEG CENTRE (CENTRE LINE GARNERO)

TEAM

Nathalie George: Scientific director

Denis Schwartz: Director of operations

EQUIPMENT

- Meg Elekta Neuromag TRUIX with 306 sensors and an integrated system for following eye movements. Integrated EEG system with 128 electrodes.
- 2 Brain Amp EEG systems with 64 channels
- 1 Biopac system for physiological measurements (skin conductance - correlated with an emotional state, electrical activity in muscles notably the heart
- Acoustic, visual and tactile stimulation systems

PLATFORMS AND DATA BANKS

3. CENIR-PRISME

TEAM

Mathias Pessiglione: Scientific director

Philippe Fossati: Scientific director

Pierre Leboucher: Director of operations

EQUIPMENT

- Virtual environments: 4 virtual reality helmets, 2 systems for following eye movements, several 2D / 3D virtual environments, virtual persons able to converse
- Concrete environments: 12 computer stations, indoor bicycles, treadmill and golf simulator, equipment for audio-visual recording, eye movement recording and physiological measurements (cardiac rhythm, skin conductance,...), EEG, TMS (transcranial magnetic stimulation)

4. CENIR-STIM

TEAM

Jérôme Yelnik: Scientific director

Carine Karachi: Scientific director

Sandra Fernandez Vidal: Director of operations

EQUIPMENT

- Atlas YeB - three dimensional digital anatomical atlas of the basal ganglia
- Informatics equipment for processing and storing data

5. CENIR-PANAM

TEAM

Marie-Laure Welter: Scientific director

Jean-Charles Lamy: Director of operations

EQUIPMENT

- 2 Neuronavigation systems to localize regions to be stimulated from imaging data
- 4 Transcranial magnetic stimulation (TMS) systems with 15 stimulation antennas
- 3 Transcranial electrical stimulation systems ("transcranial direct current stimulation" - tDCS)
- 2 Digitimer electrical stimulation systems
- 3 systems to record electrical activity in muscles
- AMTI platform to measure force
- 10 Vicon camera systems to capture movements
- 1 Wireless EEG system (free movements)

The platform was supported by: RATP, Fondation Areva for the acquisition of the 11.7 T MRI

6. CENIR - SMALL ANIMAL MRI

TEAM

Alexandra Petiet: Scientific director

Mathieu Santin: Director of acquisitions and image analysis

EQUIPMENT

- IBruker 11.7 Tesla MRI
- ICryoprobe for imaging in mice
- IEquipment for retention of the animal, anaesthesia and physiological control

The platform was supported by: IPRIAC

PLATFORMS AND DATA BANKS

PRINCIPAL PUBLICATIONS

CENIR IRM

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Lebreton M, Bertoux M, Boutet C, Lehericy S, Dubois B, Fossati P, Pessiglione M. A critical role for the hippocampus in the valuation of imagined outcomes. PLoS Biol. 2013 Oct;11(10):e1001684

Meyniel F, Sergent C, Rigoux L, Daunizeau J, Pessiglione M. Neurocomputational account of how the human brain decides when to have a break. Proc Natl Acad Sci U S A. 2013 Feb 12;110(7):2641-6

Worbe Y, Palminteri S, Hartmann A, Vidailhet M, Lehéricy S, Pessiglione M. Reinforcement learning and Gilles de la Tourette syndrome: dissociation of clinical phenotypes and pharmacological treatments. Arch Gen Psychiatry. 2011 Dec;68(12):1257-66

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CENIR – MEG/EEG

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Chevallier, C., Huguet, P., Happé, F., George, N. & Conty, L. (2013). Salient social cues are prioritized in Autism Spectrum Disorders despite overall decrease in social attention. Journal of Autism and Developmental Disorders, 43:1642–1651. doi: 10.1007/s10803-012-1710-x

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Fasoula A, Attal Y, Schwartz D (2013) Comparative performance evaluation of data-driven causality measures applied to brain networks. J Neurosci Methods, 215(2): 170–189. doi: 10.1016/j.jneumeth.2013.02.021

Dalal, SS., Jerbi, K., Bertrand, O., Adam, C., Ducorps, A., Schwartz, D., Garnero, L., Baillet, S., Martinerie, J., Lachaux, J-P.. Evidence for MEG detection of hippocampus oscillations and cortical gamma-band activity from simultaneous intracranial EEG. Epilepsy & Behavior (2013) 28 (2), 310-311. Doi: 10.1016/j.yebeh.2012.04.032

II. PRECLINICAL FUNCTIONAL EXPLORATION PLATFORMS

The platform for preclinical functional exploration supports scientific projects carried out in experimental models, in order to establish solid bases for optimal clinical research in patients. The platforms presented here are the equivalent in animals of the platforms for functional exploration in humans. Several species, such as the zebra fish, *Xenopus*, rodents, are used respecting current ethical rules, each species presenting a specific advantage from the point of view of research.

▶ **PHENO-ZFish Platform:** The zebra fish is a vertebrate the has the advantage of a nervous system that develops rapidly, allowing experiments that test -for example - the potential of therapeutic molecules that will be studied in more detail in higher species. The larvae of the zebra fish are also transparent and, consequently, appropriate for optogenetics, an advanced technique for activating neurons at a distance by light. The researchers also use genetic tools, video systems to record the behaviour of the fish (studies of locomotion/motricity) and different forms of microscopy (confocal, bi-photon, electronic). Finally, the aquatic environment of the fish is a medium that is easy to control in the laboratory and can be used to rapidly test numerous molecules.

PHENO-ZFish platform

PLATFORMS AND DATA BANKS

▶ **PHENO-Xen Platform:** Experimentation on aquatic models will be reinforced by the creation mid-2014 of a *"Xenopus"* (frog) platform directed by Abdeldkrim Mannioui, which will advantageously complete the preclinical functional exploration platform.

▶ **PHENO-ICMICE Platform:** Rodents, mice and rats, are mammals that are genetically close to humans, but are adapted to the laboratory because of their size and the rapidity with which they reproduce. Rodents can be manipulated genetically to model numerous neurodegenerative diseases and can thus be used to test the efficacy of new treatments. The services proposed by this platform are: equipment for behavioural studies (PHENO-ICMaze), neuronal and muscular electrophysiological recordings, as well as surgical material.

All of these research activities on experimental models are subject to regulation, and the platforms respect the European directive of 2010 on the use of animals in research ratified in France in 2013. The platforms are inspected by the Regulations Committee, which assures respect of the animals' well-being and verifies the competency of the researchers.

Direction:

▶ **Philippe Ravassard:** Scientific director

▶ **Magali Dumont:** Director of operations

1. PHENO-ZFISH

TEAM

Claire Wyart: Scientific director

EQUIPMENT

- 1000 Aquariums containing approx. 20 000 fish
- Food distribution robot
- Equipment for fertilization *in vitro*
- Equipment for genetic engineering

2. PHENO-ICMICE

TEAM

Brahim Nait Ousmesmar: Scientific director

Magali Dumont: Director of operations

EQUIPMENT

- 7000 Ventilated cages
- Automated cage cleaning system
- 40 Equipped rooms

3. PHENO-ICMAZE

TEAM

Magali Dumont: Scientific director

Doriane Foret: Director of operations

EQUIPMENT

- 12 Behaviour boxes, 20 tests
- Labyrinths for studies of memory
- Treadmill, wheels (running)
- Actimeters
- Chambered apparatus (anxiety - depression)
- Instruments for measuring metabolism

PLATFORMS AND DATA BANKS

PRINCIPAL PUBLICATIONS

Zébra Fish Zone

Hong E, Santhakumar K, Akitake CA, Ahn SJ, Thisse C, Thisse B, Wyart C, Mangin JM, Halpern ME. Cholinergic left-right asymmetry in the habenulo-interpeduncular pathway. Proc Natl Acad Sci U S A. 2013 Dec 24;110(52):21171-6

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Kabashi E, El Oussini H, Bercier V, Gros-Louis F, Valdmanis PN, McDearmid J, Mejier IA, Dion PA, Dupre N, Hollinger D, Sinniger J, Dirrig-Grosch S, Camu W, Meininger V, Loeffler JP, René F, Drapeau P, Rouleau GA, Dupuis L. Investigating the contribution of VAPB/ALS8 loss of function in amyotrophic lateral sclerosis. Hum Mol Genet. 2013 Mar 3

Rodent Zone

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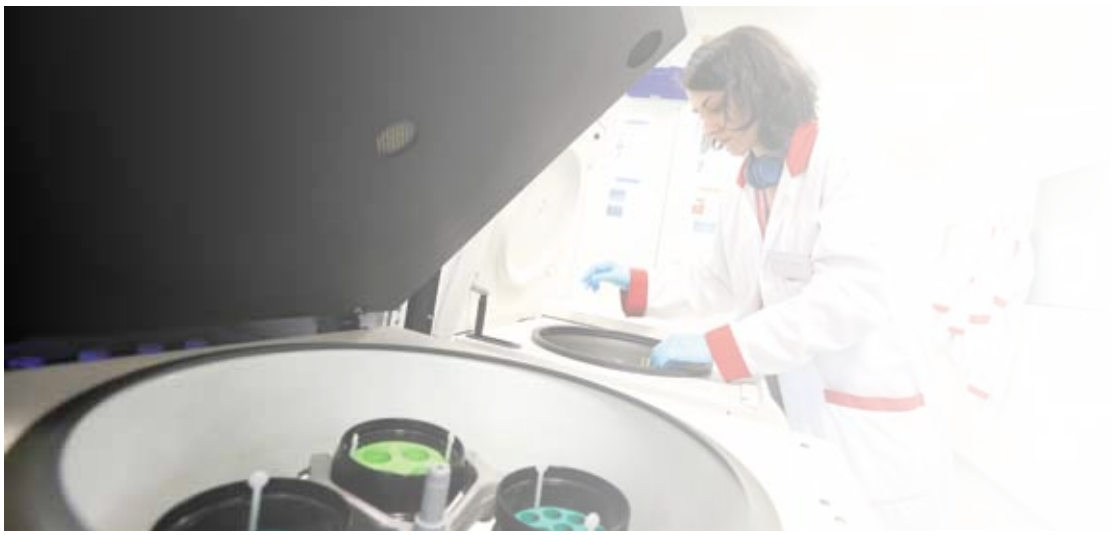
Pheno-ICMIZE platform

III. CELLULAR EXPLORATION PLATFORMS

The researchers of the ICM work on different scales, from molecules (DNA, proteins, therapeutic agents...) to the nervous system (brain, spinal cord, nerves). The scale of the cell is mid-way between these two extremes: a cell contains trillions (hundreds of thousands of billions) of molecules and the human body (on the scale of the nervous system) contains trillions of cells. The cells have been called the "bricks of life"; molecular life is organized within them (production of proteins from DNA, metabolism, etc.) and they themselves are assembled and organized to assure the functioning of organs. In the brain, the cells that have the most important role are, of course, the neurons, which exchange information in the form of electrical and chemical activity in incredibly complex networks. Other cells support the neurons structurally and functionally, notably oligodendrocytes. These cells produce the myelin sheath that insulates the "electrical wires" (axons) connecting neurons, microglial cells and astrocytes. The latter two cells are at the heart of research in the ICM in its fight to understand nervous system diseases. This research depends on cell cultures, which are more easily manipulated outside the organism, electrophysiological studies of the activity of neurons, manipulations of "stem" cells from which neurons and oligodendrocytes develop and microscopic studies (histological) that reveal the anatomy of the cells and their molecular composition. All of these activities are possible on the cellular exploration platforms.



CELIS platform

PLATFORMS AND DATA BANKS

1. CELIS PLATFORM: CELL CULTURE

TEAM

Patrick-Pierre Michel: Scientific director

Laetitia Strehl: Director of operations

EQUIPMENT

- Microscopes equipped with refrigerated CCD cameras for fluorescence observations (measurement of static or dynamic phenomena)
- Automated inverted microscope (medium-throughput screening of potentially therapeutic molecules)
- System for measuring cell proliferation in real time (evaluation of treatments for brain tumours)
- Infrared fluorescence imaging system (detection of proteins)
- Flow cytometer (cell counting)
- Incubator for cell cultures under hypoxic conditions:

PRINCIPAL PUBLICATIONS

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Michel PP, Toulorge D, Guerreiro S, Hirsch EC (2013) Specific needs of dopamine neurons for stimulation in order to survive: implication for Parkinson disease. FASEB J 27:3414-23

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2

TECHNOLOGICAL

SEARCH.
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2.CELIS-E-PHYS: ELECTROPHYSIOLOGY

TEAM

Patrick-Pierre Michel: Scientific director

Carine Dalle: Director of operations

EQUIPMENT

- Patch-clamp system for physiological recordings on cell in cultures
- System for recordings on brain slices and in the zebra fish
- System for rapid injection of pharmacological treatments onto cells
- Instrument for producing recording electrodes

3. CELIS-IPS: INDUCED PLUIPOTENT STEM CELLS

TEAM

Delphine Bolhl: Scientific director

Patrick-Pierre Michel: Scientific director

Sophie Duffaure: Director of operations

EQUIPMENT

- A culture room completely equipped for this activity
- Inverted microscopes for observation and acquisition of fluorescent images
- Dynascopes for picking clones of pluripotent cells in a sterile environment
- Cryopreservation systems

PLATFORMS AND DATA BANKS

4. HISTOMICS: HISTOLOGY (CELL LABELLING)

TEAM

Benoit Delatour: Scientific director
Annick Prigent: Director of operations

EQUIPMENT

- 23 Instruments for slicing tissue for microscopy (cryostat, microtomes, freezing microtomes, paraffin microtomes, vibratomes, ultramicrotomes)
- Histology equipment (stations for paraffin embedding, 14 work benches, a decloaking chamber, etc.)
- Equipment for the observation of histological slides (binocular microscopes, microscopes with two heads: bright field and epifluorescence)
- Microscopes, binocular magnifying glasses
- Protein labelling service

IV. CELLULAR IMAGING PLATFORMS

Microscopy is a technological world in itself, and the ICM is in the process of developing a dedicated platform that will house the advanced microscopy tools of the Institute: classical microscopy, fluorescence microscopy, bi-photonic optogenetic microscopy and, in the near future, electronic microscopy.

IMAGE ACQUISITION TEAM

Anne Baron: Scientific director
Corinne Bachelin: Director of operations

EQUIPMENT

- Classical fluorescence microscopes
- Microscopes for 3-D imaging
- Slide scanner
- Programs for 3-D reconstruction of images

BI-PHTONIC OPTOGENETIC MICROSCOPY TEAM

Claire Wyart: Scientific director

V. MOLECULAR EXPLORATION PLATFORMS

In laboratories, the term "molecular" does not refer to all molecules in general. The molecules in question here are those that carry the genetic code (the genes). DNA (deoxyribonucleic acid) can be considered to be library that contains all the information needed for the development and functioning of an organism. The expression of the information carried by the DNA is transmitted via an intermediate molecule, the RNA (ribonucleic acid). Proteins are ultimately produced from the latter. The activity of proteins determines the activity of cells (ex: neurons or support cells), which will then determine the functioning of organs and the organism.

The main role of the iGenSeq platform is the sequencing and genotyping of the genome, i.e. deciphering the long molecules of DNA that form the chromosomes. This can identify genes, eventually mutations in these genes and, finally, associations between these mutations and diseases of the nervous system. Sequencing capacity evolves very rapidly, like the processing capacity of computers, and equipment renewal is one of the preoccupations of the platform's directors.

The **iVector** platform reflects another important facet of molecular biology: genetic engineering. This is accomplished by transferring genes with the help of viruses used as transporters: these viruses, modified to be harmless, introduce the gene or genes of interest into cells in vitro (outside the organism) or *in vivo* if they are injected in an organism like a vaccine. These manipulations can be used, for example, to test on cells in culture or on mice the role of a gene identified in patients to be the origin of an acquired, degenerative or genetic disease. iVector creates, on request for basic research, vectors for gene transfer in large volumes with high titres. This type of technology is the basis of gene therapy, thanks to which researchers at the ICM hope to repair the "sick" DNA of the patients.

iVector platform

PLATFORMS AND DATA BANKS

1. IGENSEQ platform

TEAM

Giovanni Stevanin: Scientific director

Yannick Marie: Director of operations

EQUIPMENT

- 15 PCR (polymerase chain reaction) machines including 4 in "real time" - PCR is a technique for replicating in large quantities DNA and RNA to be sequenced
- 3 Medium-throughput sequencing machines: a 454-GS Jusiour system, a Miseq Illumina system
- A DNA extractor and robot for pipetting

2.IVECTOR PLATFORM

TEAM

Philippe Ravassard: Scientific director

André Sobczyk: Director of operations

EQUIPMENT

- Biological material dedicated to the design and construction of viral vectors, for the assembly of the viruses
- Equipment for the bioproduction of the viruses (CO2 incubators, large capacity centrifuges, laminar flow hoods)
- 2 Ultracentrifuges to purify the viruses
- L2 and L3 level confinement laboratories
- Double entry autoclave

2

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PRINCIPAL PUBLICATIONS

iGenSeq

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iVector

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PLATFORMS AND DATA BANKS

VI. BIOINFORMATICS AND BIOSTATISTICS PLATFORM

During the last two decades, research in neuroscience witnessed a spectacular explosion of data collected by the laboratories. In effect, molecular biology (genome sequencing, high-throughput functional analyses) and neuroimagery (visualization of the anatomy and the activity of the brain) underwent veritable technological revolutions leading to an unprecedented accumulation of data. To collect these observations is one thing, analyze and understand them in order to develop new therapies is another. The role of the platform is first to assure the collection of data from different sources, then store and organize it in order to be able to interpret it with the help of specialized methods and complex statistics.

1. Pole "Data bases and Datawarehouse"

The mission of the pole is to create data bases to collect and manage, on the one hand, data in various formats (clinical, genetic, imagery, etc.) obtained from patients with a given pathology, and, on the other hand, data of the same type on several pathologies for comparative studies. The data is stored in a "warehouse" ("datawarehouse") for statistical analysis.

2. Pole "Genomic analysis and multimodal integration"

Specialized methods are used to process the hundreds of thousands of gene mutations or tens of millions of RNA fragments obtained by last generation high-throughput sequencing. Statistical analyses associate clinical data from the patients with genetic information, brain images, etc. The teams of scientists thus benefit from a guide *"in silico"* that will help them better understand the biological mechanisms buried in the observations.

TEAM

Ivan Moszer: Scientific director and director of operations

Laure Seux: Director of operations of the Poles "Data Bases" and "Datawarehouse"

EQUIPEMENT

- The platform is based on a high-level informatics infrastructure (a cluster of several hundred computers, data base servers, etc., managed and organized in a network by the ICM Direction of Information Systems).

VII. CENTRE FOR BIOLOGICAL RESOURCES

Tissues taken from patients when blood is sampled, when biopsies are performed or during surgery are extremely precious sources of information for research on diseases. The ICM has three biobanks. Their activity consists in managing these biological resources (the samples and the associated data); i.e., to collect, record, treat, conserve and distribute them to researchers. This activity is strictly regulated to protect the patients. Two of the banks have been certified in conformity with the norm AFNOR NF-S 96-900 (Quality of Collections of Biological Resources); the third is in the process of being certified.

DNA and cell bank

PLATFORMS AND DATA BANKS

1. THE DNA AND CELL BANK

TEAM

Alexis Brice: Scientific director

Alexandra Dürr: Medical director

Sylvie Forlani: Director of operations

The DNA and Cell Bank of the ICM creates and manages collections of samples and their processing for medical research projects concerning a majority of neurological and psychiatric pathologies. In 2013, these collections contained biological resources from more than 43 000 (patients, their relatives and controls), for a total of about 155 000 samples (DNA extracts, cells, blood fluids, fibroblasts). They are among the largest collections world-wide, notably for pathologies such as Parkinson disease, the fronto-temporal dementias, autism and certain rare diseases like the spino-cerebellar degenerations. The bank has important equipment including an automated system for DNA extraction. Its quality control system was certified, in 2009, to be in conformity with the norm AFNOR NF S 96-900.

Histomics platform

2

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2. CENTRE FOR BIOLOGICAL RESOURCES FOR MULTIPLE SCLEROSIS

TEAM

Bertrand Fontaine: Scientific director

Isabelle Rebeix: Scientific and technical coordinator

The centre of resources is a bank of samples specifically dedicated to multiple sclerosis, a disease with a heavy socio-economic impact. As for the other banks of the ICM, the samples are at the disposal of researchers, so that they can better understand the physiopathology of the disease, improve existing treatments, identify new curative treatments and improve the prognosis of the evolution of the patients' handicap. During the last 6 years, the centre distributed more than 20 000 samples. The latter come from "simplex" families (an affected child and his 2 parents), multiplex families (several members of the same group of siblings affected by sclerosis), sporadic cases and healthy subjects that serve as controls so that the specific features of the disease can be determined. The centre is also certified in conformity with the norm NF-S 96-900, specific for centres of biological resources. A national project aimed at collecting biological resources from 30 000 patients with multiple sclerosis was recently launched. In the context of this project, the centre was selected to manage nationally the DNA of the 30 000 patients.

Centre of cognitive anatomy

PLATFORMS AND DATA BANKS

3. THE TUMOUR LIBRARY (ONCONEUROTEK)

TEAM

Marc Sanson: Scientific director

Jean-Yves Delattre; Scientific director

Yannick Marie: Director of operations

The tumour library is a bank of biological resources specialized in samples from patients with brain tumours. It is the largest biobank of brain tumours in Europe, and includes about 10 000 patients. Its size is due to its location on the site of La Pitié-Salpêtrière Hospital. The bank, in effect, collects samples locally, and the hospital is one of the most important European centres for the diagnosis and treatment of brain tumours. The certification of its conformity with the norm NF-S 96-900 is underway and should be validated in June 2014.

Brain tumours platform

PRINCIPAL PUBLICATIONS

Tumour library

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DNA and Cell Bank

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Mancini C, Roncaglia P, Brussino A, Stevanin G, Lo Buono N, Krmac H, Maltecca F, Gazzano E, Bartoletti Stella A, Calvaruso MA, Iommarini L, Cagnoli C, Forlani S, Le Ber I, Durr A, Brice A, Ghigo D, Casari G, Porcelli AM, Funaro A, Gasparre G, Gustincich S, Brusco A. Genome-wide expression profiling and functional characterization of SCA28 lymphoblastoid cell lines reveal impairment in cell growth and activation of apoptotic pathways. BMC Med Genomics 2013, 6:22

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2013 THE CLINICAL INVESTIGATION CENTRE - CIC

In 2013, 77 studies were ongoing at the Clinical Investigation Centre – CIC - of the ICM, directed by Jean-Christophe Corvol; 20 were new studies initiated during the year. The subjects approached were Parkinson disease and abnormal movements, multiple sclerosis, the dementias, neurogenetics, neuropsychiatry, amyotrophic lateral sclerosis, peripheral neuropathies, epilepsy and other neurological diseases. More than 400 patients were included in these studies in 2013.

Which of these studies produced outstanding results concerning the neurological diseases?

▶ **Parkinson disease:** In 2013, the Clinical Investigation Centre published the results of the study EARLYSTIM (principal investigator: Pr. Yves Agid) in the renowned New England Journal of Medicine. This study, coordinated by the CIC of La Pitié-Salpêtrière Hospital, was carried out in 17 centres in France and Germany. It shows that deep brain stimulation is effective in the early forms of Parkinson disease. The CIC also finished a proof-of-concept study on the stimulation of a new brain target (the pedonculo-pontine nucleus) in forms of Parkinson disease with falls and gait disorders, the results

of which are currently being analyzed (Dr. Grabli). At the end of 2013, a therapeutic trial of an innovative neuroprotective agent derived from bee venom (Dr. Hartmann) was finished: the definitive results are expected in 2014. The CIC also participated in the evaluation of new treatments for non-motor symptoms of the disease: a study on hypersalivation, a frequent symptom in Parkinsonian patients, is underway (Pr. Vidailhet). A unique cohort of 400 Parkinsonian patients in France will be followed for 5 years to identify markers of response to treatment (Pr. Corvol). The first results of a study on symptoms that do not respond to treatment (sleep disorders, balance problems) were published (Pr. Vidailhet). Finally, a therapeutic trial on the prevention of motor complications in the disease has begun, and partnerships were established with two pharmaceutical laboratories for the search for biomarkers to the development of innovative medications (Pr. Corvol, Dr. Lacomblez). The CIC participated in one of the very first international therapeutic trials in progressive supranuclear palsy (Pr. Corvol), a rare Parkinsonian syndrome.

▶ **Neurogenetics:** A new study of genetic forms of Parkinson disease has been initiated: new genetic risk factors have been identified thanks to a meta-analysis carried out in more than 100 000 subjects. The 21 new genetic factors will be published in 2014 by the international consortium of which the ICM is a part (Pr. Brice). Finally, the search for biomarkers of Parkinson disease and the study of pre-symptomatic subjects is ongoing in collaboration with the Michael J. Fox Foundation in the USA.

▶ **Multiple sclerosis:** Three new treatments were tested at the CIC and are now available on the market as of this year, including a treatment to improve gait disorders (fampridine) and 2 new treatments for inflammatory forms of the disease (Pr. Lubetzki, Dr. Papeix). Research concerning the progressive forms of the disease is ongoing. The teams of the CIC hope to discover differential biomarkers of inflammation, myelin and neurodegeneration (Pr. Stankoff) and develop treatments to stop progression of the disease (2 studies underway) and stimulate remyelination (1 study underway). Finally the CIC participated in two therapeutic trials of a new symptomatic treatment for multiple sclerosis developed by MedDay, an enterprise incubated at the ICM.

▶ **Dementias:** In order to treat these disorders, which considerably increase with aging of the population, earlier, the strategy of the team of Pr. Bruno Dubois aims at studying patients at the initial stage of the disease, or even the prodromal stage, a period during which a group of premonitory symptoms announce the start of the disease. In collaboration with the team of Pr. Bruno Dubois, the CIC also envisages studies on presymptomatic carriers of genetic forms of the disease; the objective is to refine the early

ESTIGATION CENTRE - CIC

or even predictive diagnosis and develop new strategies based on anti-beta-amyloid or anti-Tau therapies.

▶ **Amyotrophic lateral sclerosis:** A research program with a pharmaceutical laboratory has obtained very promising results for this neurodegenerative disease. The Clinical Investigation Centre also organized a study of the associated symptoms (balance problems, emotions) and collaborated in the development of a tool for writing with the eyes for patients with serious motor disorders.

Recently the CIC created a Centre for the Evaluation of Care and Therapeutics that is closer to the patients. This structure is dedicated to the pre-launching of new treatments, the study of cohorts of patients and the evaluation of medical practice. It exists thanks to financing from the University Hospital Institute, a partner of the ICM.

Therapeutic trials were also conducted and are ongoing to advance our understanding of epilepsy, and a special effort was made for rare diseases: Pompe disease, Huntington disease, cerebellar ataxias, channelopathies...

The Clinical Investigation Centre is part of a dynamic that is not only French but also European and consists in conducting shared therapeutic trials and research programs in close cooperation with the most prestigious French and international research centres.

RESEARCH APPLICATIONS

3

1 Transform knowledge and capitalize on research

2 iPEPS-ICM compagnies

The ambition of the ICM is not only to perform high-level research, but especially to participate in the development of new treatments capitalizing on the knowledge and competency of its researchers. To this end, the team "Research & Technology Development", composed of PhDs that have worked in industry and specialists of innovation and the creation of start-ups, detects scientific results that hold promise, creates partnerships with the most active health-selector compagnies, protects by patents the "nuggets" found by research and stimulates projects for the development of new drugs. To capitalize on the research and help Institute researchers to create their own "start-ups", the iPEPS-ICM incubator establishes a link between research and the concrete applications that can be developed. Capitalization on knowledge and know-how leads to the rapid creation of medical applications from the fruits of research. It should assure the autonomy and the competitiveness of the ICM.

3 1

TRANSFORM KNO AND CAPITALIZE

RESEARCH APPLICATIONS

The ICM has obtained the prestigious **"Institut Carnot"** seal of approval and, as such is supported in its strategy of development by industrial partnerships: the team "Research & Technology Development", thanks to this support, has initiated a proactive process to detect innovations and collaborate with industry.

In 2013, these efforts led to the signature of more than **70 contracts, 25 of which were new scientific collaborations.** A special effort was made to assure the quality of the management of the partnership, in order to encourage team work and assure the fidelity of the industrial partners (about half are international, interacting for the first time with researchers of the Institute).

In addition, **five promising new patents** were filed in 2013: a method for diagnosing epilepsy, a new modulator for the treatment of Parkinson disease, a method to detect states of consciousness, a molecular target in Alzheimer disease, neuroprotective agents for Parkinson disease. Two licences are being negotiated to permit fabrication of the products; one has already been signed with a French industrial partner.

Capitalization on the know-how of the teams and platforms is continuing to increase through the Research Applications pages on the internet site of the ICM (http://research.icm-institute.org/). The ICM has also initiated **a new approach to prospection,** by proposing well-targeted applied research projects to major international groups.

IPEPS-ICM COMPAGNIES

"iPEPS-ICM" means "the incubator and nursery of enterprises Paris-Salpêtrière." Eighteen months after it opened, the structure has become the **first accelerator of innovation dedicated to diseases of the brain in France,** and already hosts 15 partner compagnies of the Institute.

In addition to real support given to the young companies in terms of accompaniment and logistics, the incubator proposes office space, laboratories, open space, meeting rooms in more than 1000 m2; it also offers use of the advanced technological platforms in the central part of the building, facilitating interactions.

i**PEPS-ICM** not only houses enterprises that are developing new therapeutic agents but also those specialized in medical technologies, as for example EEG headsets reading electrical activity of the brain. The structure also hosts start-ups developing new diagnostic procedures so that

WLEDGE ON RESEARCH

patients can be treated sooner, or tools for "connected health", like video games that help the elderly maintain their autonomy... There again, **openness is a source of potential partnerships and creativity at the service of patients.**

Six new compagnies joined the incubator in 2013: Iltoo Pharma, Ad Scientiam, Key Neurosciences, Mediboum, Genosplice and Genious. In June, iPEPS-ICM was inaugurated by the mayor of Paris, Bertrand Delanoé and Jean-Paul Planchou, Vice-President of the Ile-de-France Region.

Life in the incubator has also evolved, notably with "Lift Sessions" that facilitate discussion and regular dialogue among the different participants in the structure. Finally, 2013 ended with the installation of BRAIN e-NOVATION, a laboratory common to the ICM and the group Genious that, thanks to support from the National Research Agency (ANR), will conceive new applications for e-health, evaluate their clinical efficacy and put these solutions on the market of tomorrows digital therapies.

Mr. Bertrand Delanoé, Mayor of Paris, and Pr. Gérard Saillant, President of the ICM, during the inauguration of the business incubator iPEPS-ICM.

E(ye)Brain is developing medical instruments to analyse eye movements for practitioners. The results obtained show that it improves and facilitates early diagnosis of certain neurological and psychiatric diseases.

MAIRIE DE PARIS ilede**France**

iPEPS-ICM enterprises in 2013

e[ye]BRAIN	Diagnostic procedures based on eye movements
CarThera – Advanced Brain Therapy Through Innovation	Therapeutic applications using ultrasound
medDay Pharmaceuticals	A treatment for multiple sclerosis
Servier – DIVER Diversité / CHIM Chimie	Tools for identifying neuroprotective molecules
3i Intelligent Imaging Innovations	Tools for cell imaging
ENDOCELLS	Innovative cell lines
Air Liquide Healthcare	Neuroprotective rare gases
MENSIA TECHNOLOGIES	Real time programs for neurophysiology

COMPAGNIES

Geno Splice	Tools for biostatistical analysis
Ilioo Pharma	A treatment for multiple sclerosis
BrainPlotting	Tools to measure permeability of the blood-brain barrier
MEDIBOUM	A treatment for neuropathic pain
GENIOUS Healthcare	Creation of serious health games, therapeutic games, e-health innovations and clinical research
Ad Scientiam Real world medical data	A smartphone application for clinical research
KEY NEUROSCIENCES	A treatment for Parkinson disease
BRAIN e-NOVATION	Creation of serious health games, therapeutic games, e-health innovation, clinical studies


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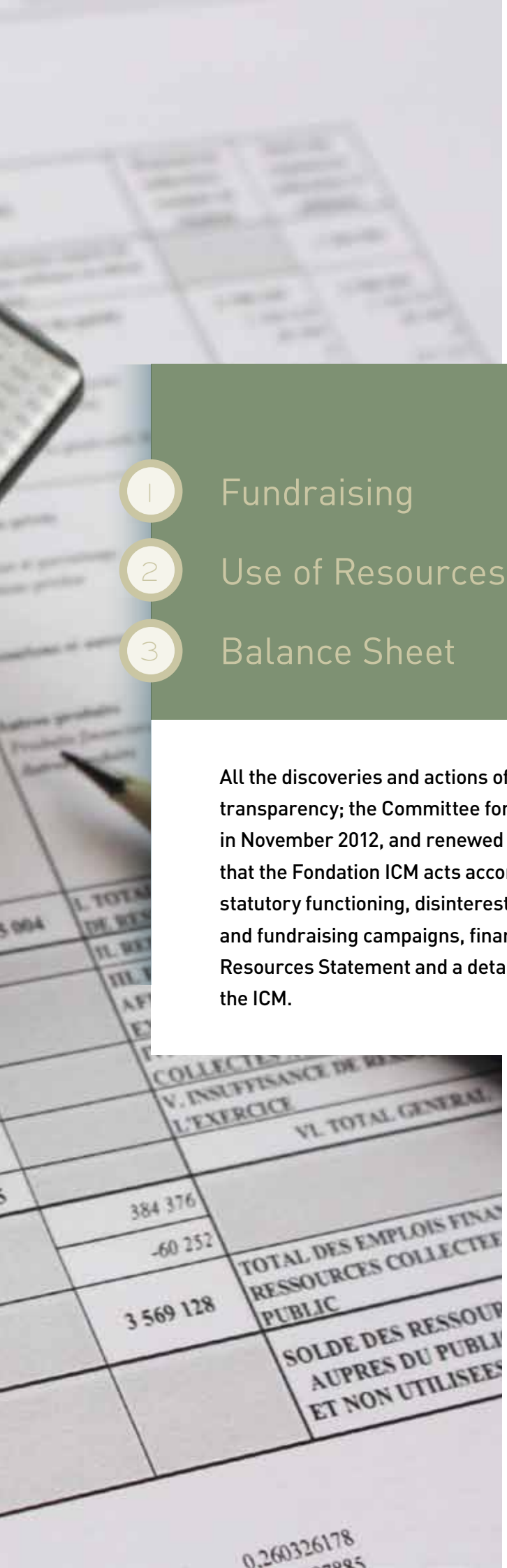
V. TOTAL GENERAL
TOTAL DES EMPLOIS FINANCES PAR LES RESSOURCES COLLECTEES AUPRES DU PUBLIC

KEY NUMBERS

4

1. Fundraising
2. Use of Resources Statement
3. Balance Sheet



All the discoveries and actions of the ICM were conducted with the greatest transparency; the Committee for the protection of donors certified the Fondation ICM in November 2012, and renewed its certification in 2013. The latest report attests that the Fondation ICM acts according to the principles of the *Comité de la Charte:* statutory functioning, disinterested and rigorous management, high-quality publicity and fundraising campaigns, financial transparency. You will find below the Use of Resources Statement and a detailed presentation of the accounts of the fiscal year of the ICM.

4 1

FUNDRAISING

KEY NUMBERS

FUNDRAISING

Income from fundraising in 2013 reached 7.8 M€. At the end of the fiscal year, almost 69 M€ (expenditures and sums engaged) were raised by the ICM since its inception.

In 2013, three important contracts for sponsorships were signed over the course of the year, with

- Fondation Cognacq-Jay, to finance 2 post-doctoral researchers working on neurodegenerative diseases,
- Group Bolloré, to support research at the ICM,
- Arkea/Groupe Crédit Mutuel wished to help the ICM by launching a financial product, the principle of which is to give part of the interests from financial investments as a donation to the ICM.

In December, the Circle of Friends of the ICM was created. It aims to bring together the donors who were engaged from the start in the ICM adventure by contributing important sums (10 000 € or more).

The Circle was created to specifically thank the Major Donors: individuals, enterprises and foundations that were active throughout the fundraising campaign launched by the ICM in 2008.

At present it includes more than 310 donors. Exclusive activities are proposed to express our gratitude, to get the donors to meet and discuss with researchers and to inform them in greater detail of the perspectives of research and the use of their contributions.

In order to increase its donor base, the ICM further developed, in 2013, the strategy of direct marketing initiated in 2010. An investment of 1.6 M€ divided among 8 major calls for donations, yielded 3.1 M€ for the fiscal year, and added 24 000 persons to the donor base for a total of 59 000 donors at the end of 2013.

Finally, the ICM is particularly grateful to and thanks the relatives of patients who organized the collection of "in memoriam" contributions to the benefit of the ICM.

IN-KIND CONTRIBUTIONS AND SPONSORING

Many enterprises have given their support by contributing their know-how in their field of activity or offering gratuitously their products and services. In the communications domain, publicity agencies and web sites have offered to the ICM space in the media free of charge.

The artists and collectors who have offered works of art to be sold for the benefit of the ICM are also included under this heading.

1000 MERCIS, Air France, Mme Bardinon, Orrick Rambaud Martel, Publicis, Quarterback, Rivington, Reedexpo – Fiac, Microsoft, TF1 publicité, RATP, Joel Winter, ANACOFI, William Christie des Arts Florissants and Jean-Philippe Pariente

ICM IN THE REGIONS

The ICM is reinforcing its presence in the different regions of France. In 2013, two regional offices were organized around the following objectives:

- reinforce the visibility, reputation and attractiveness of the ICM for donors, the public at large and personalities of the economic and political spheres;
- contribute to the development of the financial resources of the ICM, in order to accelerate scientific advances by its own research teams and regional, national and international partners;
- facilitate contacts between the ICM and neuroscience research partners in the region and capitalize on these collaborations.

This process will be extended progressively to other regions on various themes related to diseases of the nervous system.

4.2 USE OF RESOURCES STATEMENT

THE USE OF RESOURCES STATEMENT - YEAR 2013

THE FISCAL YEAR CLOSED ON DECEMBER 31, 2013

USES	Uses N-Profit and loss statement	Allocation of resources by use
Social Missions	**15 539 556**	**4 922 691**
ACTIONS REALIZED DIRECTLY		
Research program	8 165 197	2 344 782
Technological platforms	5 183 419	1 913 775
Other (including research applications, incubator and events/ international partnerships)	2 190 940	664 134
Costs of fundraising	**2 454 214**	**1 830 377**
Costs of appeals to the generosity of the general public	1 827 946	1 827 946
Costs of finding other private funds	210 648	0
Costs related to the search for subsidies and other public competitions	40 277	0
Costs of communication	375 343	2 431
Costs of organizational functioning	**1 786 884**	**181 291**
I. TOTAL USES IN THE PROFIT AND LOSS STATEMENT	**19 780 654**	**6 934 359**
II. PROVISIONS	**2 640**	
III. EXPENSES TO BE REALIZED ON ALLOCATED RESOURCES	**2 803 983**	
IV. SURPLUS RESOURCES OF THE FISCAL YEAR	**0**	
V. GRAND TOTAL	**22 587 276**	
Part of the fixed asset acquisitions for the fiscal year financed by funds collected		695 652
Neutralization of the provisions for depreciation of fixed assets financed by funds collected		-978 527
TOTAL USES FINANCED BY FUNDS COLLECTED FROM THE PUBLIC		**6 651 484**

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		**3 363 344**
Resources collected from the general public	**4 926 113**	**4 926 113**
Unallocated monetary donations	4 512 426	4 512 426
Allocated monetary donations	168 000	168 000
Unallocated bequests and other gifts	90 400	90 400
Allocated bequests and other gifts	0	0
Other products related to public generosity	155 287	155 287
Other private funds	**5 519 603**	
Patronage	2 907 300	
Partnership	1 768 158	
Private grants	844 145	
Subsidies and other public competitions	**2 654 475**	
Other products	**3 876 033**	
Financial products	238 900	
Services offered	1 798 529	
Other products	1 838 604	
I. TOTAL RESOURCES FROM THE PROFIT AND LOSS STATEMENT	**16 976 224**	
II. CARRYOVER OF PROVISIONS	**0**	
III. CARRYOVER OF UNUSED ALLOCATED RESOURCES FROM PREVIOUS FISCAL YEARS	**2 498 602**	
IV. VARIATION OF ALLOCATED FUNDS COLLECTED FROM THE PUBLIC		**284 786**
V. RESOURCES LACKING FOR THE FISCAL YEAR	**3 112 360**	
VI. GRAND TOTAL	**22 587 186**	**8 574 243**
TOTAL OF USES FINANCED BY RESOURCES COLLECTED FROM THE PUBLIC		**6 651 484**
BALANCE OF RESOURCES COLLECTED FROM THE PUBLIC NOT AFFECTED OR USED AT THE END OF THE FISCAL YEAR		**1 922 759**

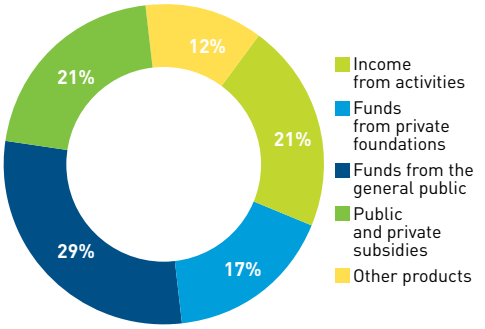
EVALUATION OF VOLUNTARY IN KIND CONTRIBUTIONS				
Social missions	59 840		Volunteers	59 840
Costs of fund raising			Services in kind	
Costs of functioning			Contributions in kind	

4 2

USE OF RESOURCES STATEMENT

KEY NUMBERS

RESOURCES 2013



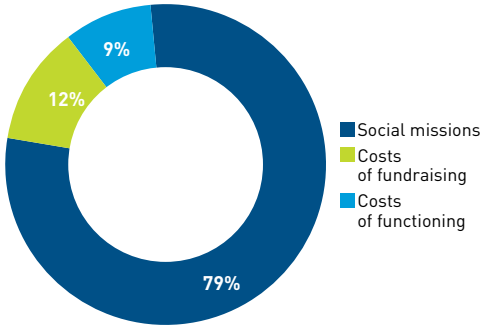
Resources in 2013 reached **19.5 M€,** and included 17 M€ of products of the financial year and 2.5 M€ of resources allocated but not used during previous financial years.

The products of the financial year were essentially revenue from fundraising (46%), either from the general public (29%) or from enterprises and private foundations (17%).

There was also:

- revenue from the activity of the technological platforms (1.8 M€), research collaborations with industrial partners (1.8 M€),
- public subsidies (European Commission and Plan Alzheimer) - 2.7 M€ and private subsidies - 0.9 M€,
- other products (rebilling of charges, rental fees from partners, financial products...) - 2.0 M€.

USES 2013



The grand total of uses in 2013 was **22.6 M€:** 19.8 M€ to be realized later from allocated resources. Among the uses 2013, the sum dedicated to social missions was 15.5 M€, and represents 79% of total uses for the fiscal year. The social missions of the ICM were:

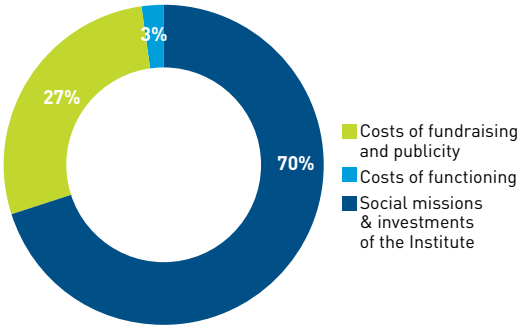
- research projects (53%),
- technological platforms (33%),
- scientific events and international partnerships (8%)
- research applications and industrial partnerships (6%)

The research projects financed principally concerned neurodegenerative diseases and trauma to the spinal cord. The technological platforms (neuroimagery, vectorology, sequencing/genotyping, cell culture and histology) contributed additional support for these projects.

The costs of fundraising correspond to the costs of collecting funds from private individuals (contributions and bequests) and enterprises (patronage and sponsoring). They represent 12% of uses.

The costs of functioning correspond to the costs of the teams-supports (finances, personnel, informatics, logistics) and represent 9% of all uses for the fiscal year. Engagements to be realized from previously allocated resources (2.8 M€) correspond mainly to contributions received during the year from enterprises and foundations, which will be used later for specific pluriannual research programs.

ALLOCATION OF RESOURCES COLLECTED FROM THE PUBLIC



Resources collected from the general public used in 2013 amounted to 6.6 M€.

In summary, out of 100 € of resources collected from the general public, 70 € were used to finance the social missions and investments of the Institute, 27 € were used for fundraising and 3 € contributed to the functioning of the organisation.

4.3 BALANCE SHEET

SIMPLIFIED BALANCE SHEET

Assets (in K€)	31.12.13	31.12.12
Net fixed assets	11 778	14 441
Realizable and available assets	27 822	20 486
Total	**39 600**	**34 927**

Liabilities (in K€)	31.12.13	31.12.12
Associated funds	23 720	24 488
Results of the fiscal year	-3 112	-1 241
Dedicated funds	3 884	3 579
Debts	15 108	8 101
Total	**39 600**	**34 927**

The total amount of investments by the ICM since its creation amounts to nearly 20 M€, mainly dedicated to the technological platforms that support research.

The **investments** for the fiscal year were **1.2 M€:**

The ICM acquired a cryostat for imagery, completed the equipment of the functional experimentation platform and finished installing the business incubator.

Fixed assets amounted to **11.8 M€.**

As of December 31, 2013, **working capital** reached **10.66 M€,** a sum similar to that of the preceding fiscal year.

The **total equity** of the ICM is **20.6 M€.** It comprises the associated funds **(11.7 M€)** to which are added investment subsidies **(2.8 M€)** and **6.1 M€ carried forward.**

The **non-expendable endowment** of the ICM is **1.2 M€.**

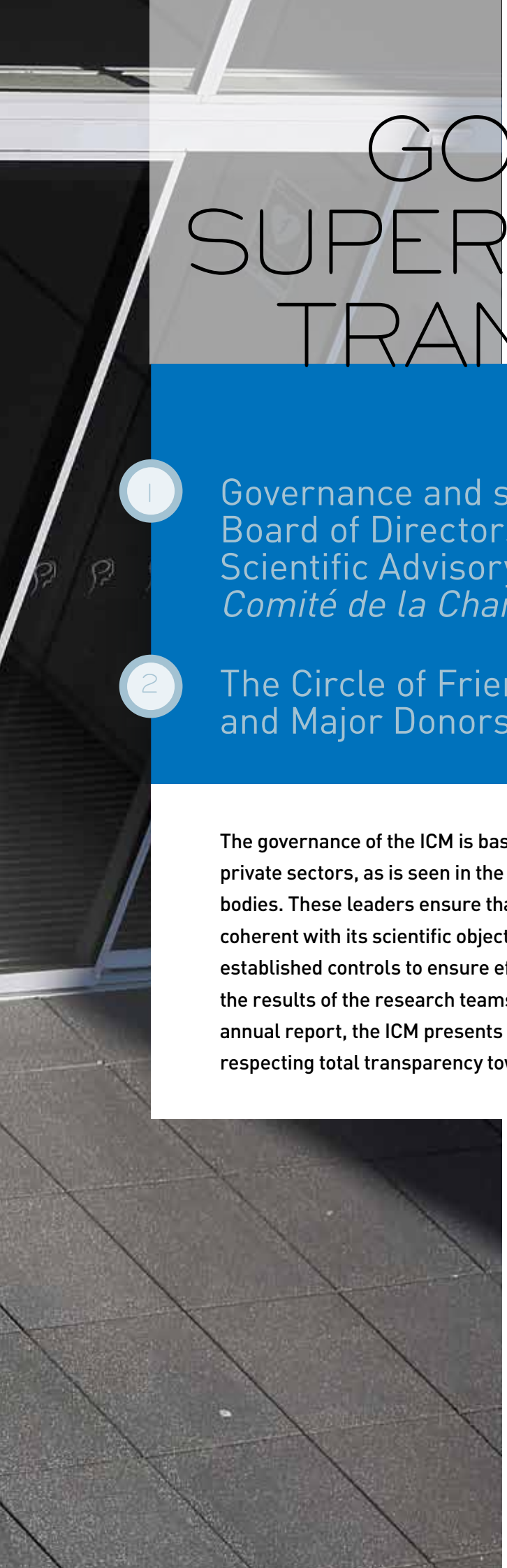
Upon closure of the fiscal year, **allocated funds** (funds remaining to be engaged in programs) amounted to **3.9 M€,** a sum close that at the end of the fiscal year 2012 **(3.6 M€).**

Excerpt from the 2014 report of the auditor of the Committee for the protection of donors.

"During the preceding three-year period, the social missions of the Foundation were deployed rapidly and courageously in a superb building that houses high-level teams and their equipment. The foundation has offered researchers facilities to which they previously had no access and reinforced, in many ways, perspectives for the internationalization of their work.

The new period that is beginning is characterized by the will to install a stable form of organization, based on a concerted public/private partnership, with balanced financial bases, while at the same time maintaining its ambitions for high-level performance in the sphere of national and international scientific research."


ICM



GOVERNANCE, SUPERVISION AND TRANSPARENCY

5

1 Governance and supervision: Board of Directors, Founding Members, Scientific Advisory Board, *Comité de la Charte*

2 The Circle of Friends of the ICM and Major Donors

The governance of the ICM is based on strong partnerships across the public and private sectors, as is seen in the composition of its Board of Directors and governing bodies. These leaders ensure that the institute's structures and resources remain coherent with its scientific objectives of the Institute. The Administration has established controls to ensure effective management and evaluates the work and the results of the research teams in order to maintain a level of excellence. In its annual report, the ICM presents its mission and the results obtained, with the view of respecting total transparency towards to its partners.

5 GOVERNANCE AND

GOVERNANCE, SUPERVISION AND TRANSPARENCY

BOARD OF DIRECTORS

Gérard Saillant, President
Jean Todt, Vice-President

College of the founders

Serge Weinberg
Jean Glavany
Jean-Pierre Martel
Gérard Saillant
Jean Todt

College of qualified personalities

Pierre Corvol, Collège de France
Alain Prochiantz, Ecole Normale Superieure
Elisabeth Tournier-Lasserve, Université Paris Diderot

College of full members

Bernard Poulain, representative of the Centre National de la Recherche Scientifique (CNRS)
Thierry Damerval, representative of the Institut National de la Santé et de la Recherche Medicale (INSERM)
Bruno Riou, representative of the Université Pierre et Marie Curie **(UPMC)**
Jean-François Sauvat, representative of the Assistance Publique-Hopitaux de Paris (APHP)

College of the Friends of the Foundation

Maurice Lévy
Lindsay Owen-Jones
David de Rothschild

Public commissioner

Philippe Ritter

SUPERVISION

FOUNDING MEMBERS

Gérard Saillant, Professor of orthopaedic surgery and traumatology, President of the ICM

Jean Todt, President of the FIA, Vice-President of the ICM

Yves Agid, Honorary Professor of Neurology and Neuroscience

Luc Besson, Filmmaker

Louis Camilleri, President of Altria

Jean Glavany, Former Minister, Executive Director of the ICM

Maurice Lévy, President of the Board of Directors of Publicis Groupe, Co-president of the Committee of the Friends of the ICM

Olivier Lyon-Caen, Professor of Neurology, ex-Director of the Pole of Nervous System Diseases of the Pitié-Salpetriere University Hospital

Jean-Pierre Martel, Lawyer

Max Mosley, ex-President of the FIA

Lindsay Owen-Jones, Honorary President of L'Oreal, Honorary President of the Committee of the Friends of the ICM

David de Rothschild, President of the Rothschild & Cie bank, Co-president of the Committee of the Friends of the ICM

Michael Schumacher, Formula 1 pilot,

Serge Weinberg, President of Weinberg Capital Partners, Treasurer of the ICM

ASSOCIATION OF THE FRIENDS OF THE ICM

Lily Safra, Honorary President, Chairwoman of the Edmond J.Safra Philanthropic Foundation

Maurice Lévy, Chairman and CEO of Publicis Groupe, Founding member and Co-president of the Committee of the Friends of the ICM

David de Rothschild, President of the Rothschild & Cie bank, Founding Member and Co-president of the Committee of the Friends of the ICM

Jean-Pierre Martel, Lawyer, Founding Member of the ICM

Serge Weinberg, President of Weinberg Capital Partners, Founding Member and Treasurer of the ICM

SPONSORS

Jean Reno, actor

Michelle Yeoh, actress

5 1

GOVERNANCE AND

GOVERNANCE, SUPERVISION AND TRANSPARENCY

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

Pr. Peter Brown, ION, University College of London, UK

Pr. Ray Dolan, FIL, University College of London, UK

Pr. Magdalena Götz, Munich Center for Neurosciences, Munich, Germany

Pr. Steve Hauser, UCSF School Med, San Francisco, USA

Pr. Heidi Johansen-Berg, FMRIB, Univ Oxford, UK

Pr. Dimitri Kullman, ION, University College of London, UK

Pr. Bertram Müller Myhsok, Max-Planck Institute, Munich, Germany

Pr. Hideyuki Okano, Keio University, Japan

Pr. William D. Richardson, University College of London, UK

Pr. Peter St-George-Hyslop, Tanz Center for Neurodegenerative Diseases, University of Toronto, Ontario, Canada

Pr. Michael Shelanski, Neuropathology, Columbia University, New York, USA

Pr. Martin E. Schwab, Brain Research Institute, University & ETH Zurich, Switzerland

Pr. Gabor Tamas, University of Szeged, Hungary

Pr. Patrick Vuilleumier, Neuroscience Center, University Hospital, Geneva, Switzerland

Pr. Hartmut Wekerle, Max Plank Institute fur Neurobiologie, Munich, Germany

Pr. Huda Y.Zoghbi, Baylor College of Medicine, Houston, USA

SUPERVISION

COMITE DE LA CHARTE

The ICM was certified by the Committee for the protection of donors on November 3, 2010; the certification was renewed on September 12, 2013. For more than 20 years, this committee has carried out the mission of the professional regulation of appeals to public generosity. Its action is based on 3 principles: accredited organizations must respect its ethics; they must exercise collective discipline with respect to donors; and accept control of their engagements. Its status allows it to combine a necessary independence of judgment and proximity with association members. The 4 fields of control exercised by the auditors of the *Comité* are: statutory functioning, disinterested and rigorous management, high-quality publicity and fundraising campaigns. So that all information furnished to the public is reliable, precise and objective, the *Comité de la Charte* recently reinforced its requirements in terms of information on management. It requires accredited organisations to agree to add a document to the Use of Resources Statement that presents, in a simplified, accessible and transparent manner, the resources collected from general public and how they were used. Like other accredited organisations, the ICM promises to respect the code of ethics of the *Comité* and submit to its oversight.

www.comitecharte.org

5 2

THE CIRCLE OF FRIE

GOVERNANCE, SUPERVISION AND TRANSPARENCY

WHY A CIRCLE OF FRIENDS?

The Circle of Friends was created in 2013, after an important fundraising campaign accomplished thanks to the Major Donors of the ICM. The Circle regroups all of the Major Donors since the creation of the ICM.

TO THANK

A those, individuals, compagnies or associations, who support research on the nervous system.

TO UNITE

the major donors and establish a dedicated and exclusive line of communication.

TO ASSOCIATE

current and future major donors in order to respond to the challenges facing the ICM.

The Circle is open to all individuals, compagnies, foundations or associations desiring to invest themselves, financially and personally, around the values of generosity, efficaciency and innovation to the benefit of the greater good. The ICM particularly wishes to show its gratitude to the donors and offers them many activities and a recognition program. The Wall of Donors is a strong located in the lobby of the ICM and updated each year, it illustration honors all of the major supporters. They are also mentioned in progress reports.

The Circle aspires to become larger; thus each member desiring to support our develoment is invited to recruit new supporters of the cause.

Since 2009, we have been collaborating an accord with Transnational Giving Europe, which is a partnership of European foundations and associations. It allows a donor who pays taxes in one of the partner countries of the TGE to support the ICM and benefit from the fiscal advantages in his country of residence. Thanks to this agreement, European donations to the ICM can transit through the European partners of the *Fondation de France* according to specific modalities for each country.

THE MEMBERS OF THE COMMITTEE OF THE FRIENDS OF THE ICM

Gérard Saillant, President of the ICM • Lindsay Owen Jones, Honorary President • Jean Todt, Honorary President • Maurice Lévy, Co-President of the Committee • David de Rothschild, Co-President of the Committee • Cédric de Bailliencourt • Jean Bousquet •Jean Burelle • Sylvain Hefes • François Henrot • Jean-Philippe Hottinguer • Eric Neubauer • Christian Schmidt de la Brelie • François Thomé • Isabelle Weill • Serge Weinberg • Alain Wicker.

NDS OF THE ICM

THE MAJOR DONORS OF THE ICM

Major Patrons

Maria Rosa Bemberg – CARCEPT PREV - FONDATION BETTENCOURT SCHUELLER - FONDATION EDF DIVERSITERRE - FIA FOUNDATION FOR THE AUTOMOBILE AND SOCIETY – IPGM - KLESIA - Docteur Léone Noelle Meyer – OCIRP - ORRICK RAMBAUD MARTEL - Lindsay Owen-Jones – PUBLICIS - Fondation Lily Safra - Michael Schumacher

Patrons

AIR FRANCE - Elisabeth Badinter - Luc Besson – BOUYGUES - Lucienne Collin - FEDERATION FRANCAISE DU SPORT AUTOMOBILE - FONDATION COGNACQ-JAY - FONDATION PHILANTHROPIQUE EDMOND J. SAFRA - FONDS DE DOTATION PIERRE BERGE - FP JOURNE INVENIT ET FECIT - François Henrot - IPRIAC - JCE HOTTINGER & CO - M. et Mme Alain Joly - Serge Kampf - Maurice Lévy - ORACLE - RACE OF CHAMPIONS – RATP - David de Rothschild - Edouard et Martine de Royere - SCHNEIDER ELECTRIC - Jean Todt et Michelle Yeoh - Serge Weinberg

Benefactors

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RAPPORT ANNUEL 2011
ICM

LIFE AT THE ICM

1 Scientific and extra-scientific lectures

2 Events and communication

6

The ICM has developed the practice of organizing scientific and extra-scientific events consisting, on the one hand, of frequent discussions among the research teams, on the other, interventions by high-level scientists or public personalities. In addition, in 2013, the ICM inaugurated a campaign of cultural and sporting events, in partnership with associations and enterprises. These actions are initiated by the ICM or organized for its benefit, to spread its reputation and raise funds. In parallel, the Institute organized a publicity campaign conceived by *Publicis Conseil,* a long-time partner of the ICM.

SCIENTIFIC AND EXT

Extra-scientific lecture
of Jean-Michel Rives, May 16, 2014

Nine important scientific events took place at the ICM this year; for example, the inaugural address of the Week of the Brain by **Philippe Vernier,** the meeting of the international consortium "Replaces" on Parkinson disease, also open to the public at large, the "Prestige" lecture "The future of Neurotrophic Factors by **Moses V. Chao,** professor and president of the American Society for Neuroscience. The international colloquium on the spino-cerebellar degenerations, the meeting of the international consortium on multiple sclerosis and the international symposium on the cerebral bases of cognition also took place at the Institute. The "Day of science" conference at the Ecole Pratique des Hautes Etudes, the Day of Neuropsychology conference on "The representation of the body and the self: the centenary of the Babinski syndrome" were also key moments in the year 2013. Finally, this year, the ICM inaugurated the MEG and invited **Jean-Pierre Changeux** to give a *"Prestige"* lecture.

Six extra-scientific lectures were also the occasion to broaden the field of debate. This year the events included a film by Caroline Pochon, "Neurochirurgie et TOCs" (Neurosurgery and OCD), the conference "The brain in love from the point of view of a brain-machine interface" presented by **Yvan Attal and Nathalie George** and the lecture by **Jérôme Yelnik** entitled "The brain - the emotions - research". **Jean-Michel Ribes** proposed a debate on the subject "Words, do they come out of the brain?" and **François Morel** read from "Hyacinthe et Rose." **André Comte-Sponville and Luc Ferry** participated in a debate on "Idealism and materialism: the statute of the Spirit."

Finally, the ICM participated, like every year, in a pedagogical event, "Chercheurs en herbe" (First-time researchers) and "Destination labo", an occasion for the Institute to invite school children to increase their awareness of research as a profession.

Distribution of diplomas, les Chercheurs en Herbe at the ICM June 5, 2013

RA-SCIENTIFIC LECTURES

THE ASSOCIATION *"LES AJITES"*

The association *"Les Ajités"* is the fruit of an initiative by a few doctoral students and post-doctoral fellows who, at the creation of the Research Centre of the Brain and Spine Institute, identified the need for a permanent framework in which the young researchers in the different teams could meet together to discuss their work. They initiated, with the help of Boris Zalc, the first retreat for young researchers in 2010 as well as the first social events in the life of the future Institute.

Since then, after publication in the *"Journal Officiel"* in 2012, this association of young scientists has acquired official existence. The scientific retreat, organized with the help of the Communications Department of the Institute, is now an essential part of the scientific year.

The three days are the occasion for scientific discussions of a high-level, from the point of view of the young researchers themselves, but also the less young. These days also help develop a spirit of belonging to the Institute and create social relations among the young scientists.

A certain number of initiatives prolong these efforts throughout the year, mainly due to support from the ICM. A monthly meeting - the SciPhi - continues scientific debate in a more informal context than in seminars (for example "live" electrophysiological recordings, behavioural experiments), whereas "happy hours" aim to encourage the development of a social fabric within the building. We are happy with the success of Sci Phi, which seems to be one of the most appreciated events at the ICM, and attracts a stable public of about 80 young scientists.

We also organized a workshop on public speaking, showed a film on Alzheimer disease followed by a discussion with those who made the film and a concert in association with the Paris Descartes Orchestra. The association also offers an administrative framework for individual initiatives, like the bi-weekly yoga and salsa courses open to all members of the personnel.

CULTURAL AND SPORTING EVENTS

This year, **fifteen sporting events** contributed support to research: the "Race of Champions", the operation *"Un chrono pour un Don"*, the *"Course en Solitaire"* of the "Figaro" newspaper, the *"Trophée de luxe"* in Geneva, the *"Bordeaux-Béziers"* bicycle race organized by Ferblanc Fundraising, the automobile event *"Fée rarissime"* and the *"Diagnonale des Fous"* in which our researchers Luc Mallet and Margot Morgiève participated. The Classic Days, the association "Sogno di Cavallino", the "*Teufs Teufs du coeur"* organized by the Lions Club of Essarts-le-Roi, and the Internationals of Strasbourg renewed their magnificent contribution to fundraising for the ICM. The year 2013 also permitted our faithful partners to associate the ICM with sporting events like the race *"La tête c'est le pied"*, the golf trophy *"Solidair's des Ormes"*, the golf trophy *"Les Echos"*, the *"Trail de la Mignonne"* of the association Naturvan and the 20 Kms of Paris. Invited by its partners CSIAM and AMC Promotion, the ICM was present at the 2013 edition of the *"Salon de la Moto"* and benefited from an auction.

Eleven cultural events took place both within and outside the walls of the ICM, such as a projection of the film *"La tête en l'air"* and a jazz concert by Jérôme Yelnik and his group. A concert by *"Les Arts Florissants"* of **William Christie** was organized in the chapel of La Pitié-Salpêtrière Hospital to thank the Grand Major Donors of the Institute. In addition the salon *Rétro-Mobile*, the distribution of the Book of J. Winter to the benefit of the ICM, the auction of the Châteauneuf du Pape

3rd edition of the Trail de la Mignonne, September 2013, for the benefit of the ICM

Concert of *"Les Arts Florissant"* directed by William Christie, September 19, 2013, in the chapel of the Pitié-Salpêtrière Hospital.

UNICATION

wine presided by Patrick Timsit, the sale of **Marie-Clair B** jewellery, the auction of prestigious automobiles of Puymirol, the Bridge tournament of the Bridge Club BC 13 were events that allowed funds to be raised to support research. For the third consecutive year, the FIAC supported the ICM on the occasion of a breakfast with a performance by **Mathieu Lehanneur.** Finally, the association *Musique, Passion Parkinson,* one of the most faithful partners of the ICM, gave several concerts to the benefit of the ICM.

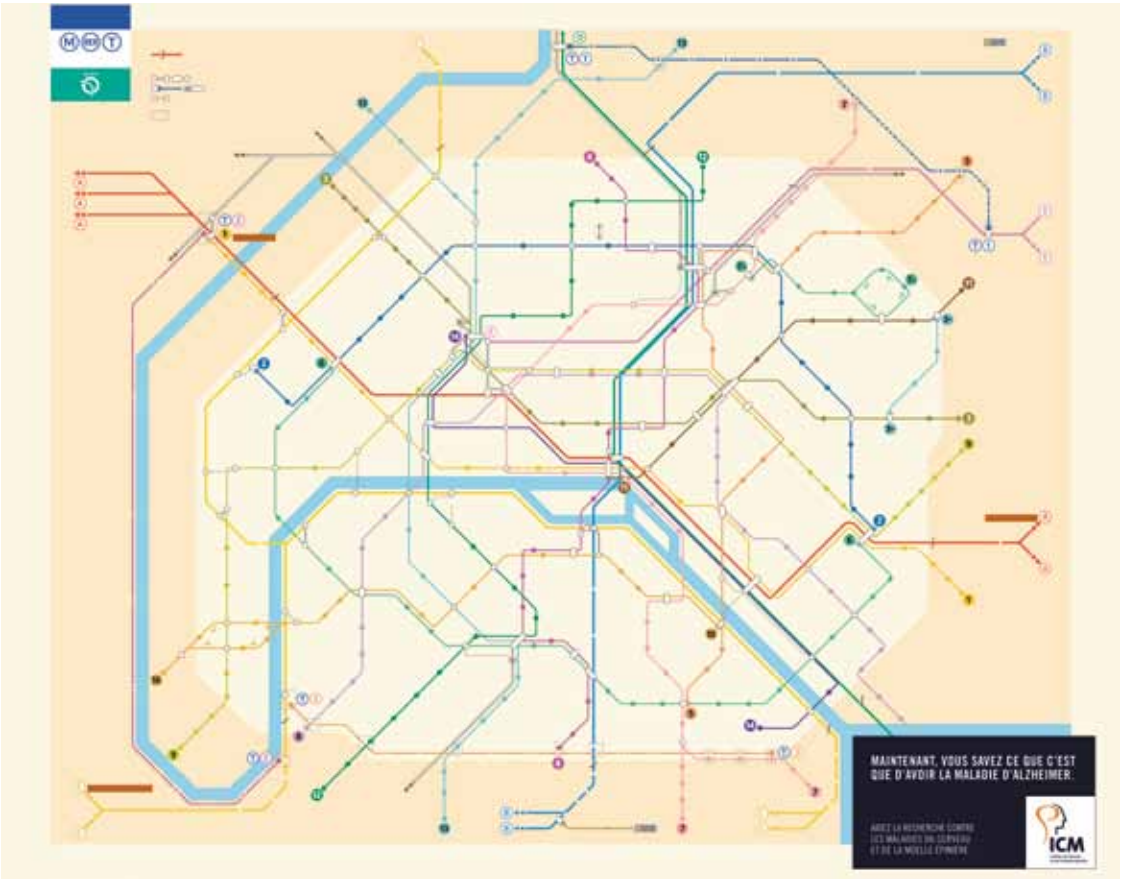
"Les Journées Mondiales" (Alzheimer, Parkinson, Multiple Sclerosis...) are important events that accompany the life of the ICM. The Institute never misses an occasion to publish and present the many studies and advances in research of the Institute.

Every trimester, the ***"Matinées ICM"*** provide the occasion for donors to meet the different members of the research community and thus share with them in their latest advances. In September, the **iPEPS business incubator** and nursery organized an open house to present to the general public the start-ups of the digital health sector.

Artistic performance by Mathieu Lehanneur during a fundraising event at the FIAC 2013: the work appeared progressively as promises of contributions by participants were announced.

THE PUBLICITY CAMPAIGN

The campaign "Lost in the metro", created in 2012 with the help of *Publicis Conseil* and the RATP, sponsor of the ICM, was repeated in 2013. It received the third prize offered by *Communication Solidaire*.



UNICATION

PUBLICATIONS

All the publications of researchers at the ICM can be consulted on the Institute's website: icm-institute.org

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