

INSTITUT DU CERVEAU  
ET DE LA MOELLE ÉPINIÈRE  
PARIS BRAIN INSTITUTE

ANNUAL REPORT 2018

SEARCH, FIND, CURE, FOR YOU & WITH YOU



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Prof Gérard Saillant,  
President of the ICM

“That each and every one of us can age in the best possible conditions and remain free of one’s thoughts and movements,” this is the medical and socio-economic challenge of the Brain and Spine Institute.

Our brain holds the biggest mysteries. Understanding it is an odyssey many scientists and doctors have embarked on. The stakes of research on brain diseases are extremely important in the context of an aging population, while society as a whole faces many challenges in order to “age well”.

Today, the innovative and singular model of our institute, which brings together patients, doctors, researchers and entrepreneurs,

proves to be a powerful accelerator of discoveries and innovations. You will discover in this annual report that 2018 was a very productive year, on a research and clinical level, in entrepreneurial valorisation and also by restructuring to improve efficiency for patient care. Finally, I would like to tell you that this progress was possible thanks to you, donors and volunteers and I would like to sincerely thank you all.

*“In order to enable researchers to progress and give real hope to patients, we must continue to involve, all of us. All, without exception, because this fight concerns each one of us.”*

## Corinne Fortin

Secretary general of the ICM

The innovative, translational and transversal model of the ICM does not only apply to research but also through an integrated administration: “A rigorous, simple, flexible and dynamic scientific and administrative organization that frees researchers from unnecessary constraints and opens financing opportunities for ambitious projects”!

The administration, and more generally all the support functions, is one of the two pillars of the ICM, the first being science, of course! These two pillars must have the same robustness so that the whole structure is solid. Facing scientific excellence, we must develop services and an administrative organization at the same level. Our mixed nature, public and private, is a source of complexity but also of real opportunities; it needs to be streamlined for optimal efficiency.



*“We have to apply “rigorous flexibility” in our procedures. We must work to lighten up the daily administrative load of the scientists, while being clear about our compliance with regulations and the requirement of excellence of our organization.”*

Prof Alexis Brice,  
Chief executive of  
the ICM



This year 2018 was rich in scientific breakthroughs and renewal for our institute. The first is that of our joint research unit, with the success of the teams presented to the HCERES evaluation, the High Council for the Evaluation of Research and Higher Education; then there was some change in our Direction, with the arrival of Corinne Fortin as Secretary General and Bassem Hassan (Inserm) as Scientific Director and Deputy Director of the Unit. 2018 was also rich in success thanks to our teams,

at national and international levels, with ever more publications and prestigious awards.

The ICM is a unique place, open to all. More than ever, we must decouple, develop creativity, rely on cooperation, collaboration, and share our expertise. A common mission serving the public interest, brings us all together to go further and faster. The advances in terms of early diagnosis is for example spectacular. Researchers can go back in time to see at which moment the dysfunctions appear, especially in regards to the genetic basis or to early warning signs of the disorder. This research axis will allow both the study of pathological processes and the development of markers at different stages of the illness, even before its manifestation; and, consequently, will permit the determination of the best time window for preventive treatments.

Regarding the more fundamental aspects of research, we are developing new approaches, aiming at novel therapeutic targets, based on molecules

*“Today, thanks to the 700 women and men who make it up, our partners, our donors and our volunteers, the ICM is now a leading neuroscience institute and major breakthroughs are and will be made there on the brain and its pathologies.”*

which modify the expression of certain genes linked to protein accumulation in neurodegenerative disorders. Preventing protein accumulation, perhaps even production, upstream represents a major hope. All these approaches are carried out at the ICM but also elsewhere. The strength of the ICM is its ecosystem which enables the association of a powerful instrument of clinical research, the Centre d’Investigation Clinique (Inserm, APHP), research teams working on the pre-clinical stage of these disorders and finally start-ups. Thanks to this cohesion, we will be able to pursue our strong ambitions in the coming years:

- To decipher the functioning and the dynamics of the healthy brain, essential to better understand and treat impaired functions in nervous system diseases but also to preserve it in its normal state;
- Accelerate the development of treatments in order to provide them to patients as soon as possible;
- Develop personalized medicine and provide doctors with new diagnostic and therapeutic tools for neurological and psychiatric diseases to give the patient the right treatment, at the right time, according to his/her profile and the evolution of his/her illness;
- Continue to disseminate a culture of neuroscience to the general public, encourage exchanges between researchers and physicians, train teachers and entrepreneurs.

2019 will be just as rich in major projects with the arrival of new research teams and the evaluation of our technology platforms; the continuation of our strategic roadmap with, among others, the development of our programmes of clinical research, neuroinformatics or teaching. Future projects also for our incubator and our communication, a new impulse for the growth of our institute to the patients’ benefit.

# THE BRAIN AND SPINE INSTITUTE, A UNIQUE AND POWERFUL ECOSYSTEM,

## A COMMUNITY DEVOTED TO NEUROSCIENCE AND PATIENT

The ICM is above all a human adventure, a community of experts who participate with passion, day in day out, in the fight against nervous system diseases. Strong interaction between basic research, applied research and hospital environment!

A multicultural, multidisciplinary environment composed of scientists (82% of researchers, clinicians and teacher-researchers, paramedics, engineers and technicians and doctoral students), administrative staff (18%) and entrepreneurs in the startup incubator of the ICM. Both private (48% of staff) and public cultures (52% of staff), successfully combined for optimum efficiency!

As a joint research unit (UMR) and with its public partners (INSERM, CNRS, Sorbonne Université, AP-HP) the institute adopts a governance based on a strong public-private partnership.





# SCIENTIFIC MISSIONS AND PRIORITIES

**Scientific missions and priorities to meet the challenges of the next decade: understanding how the brain works, preventing and curing neurological and psychiatric diseases.**

**Faced with the challenges of research on the brain and its pathologies, the ICM's objectives are clear and reaffirmed:**

- Contribute strongly to the prevention and treatment of nervous system diseases
- Participate in technological innovation and its medical applications

**To do so, the Institute must:**

- Attract the best international researchers, particularly in translational neuroscience
- Develop cutting-edge technological platforms
- Promote entrepreneurial research
- Create a unique, attractive, international and open-to-society training venue.

## A SCIENTIFIC STRATEGY TO MEET SOCIO-ECONOMIC ISSUES

Understanding the functioning and dysfunctions of the nervous system is a major challenge in neuroscience research. The central nervous system is a very complex "machinery". It is composed of a large number of heterogeneous entities interacting via molecules, cells, neural networks. It also interacts with other organs, as well as with the entire organism, and most importantly it depends on the environment. The biological mechanisms involved can last from a millisecond to several years to create anatomical structures and complex interactions between different components.

Understanding the mechanisms of the brain and its pathologies requires the ability to collect the relevant data for each level of organization, to be able to analyze them, and to correlate them with information obtained at lower and higher levels of complexity. This involves solving several technological and methodological problems.

Advances in the exploration of brain function/dysfunction therefore depend on the ability to develop an interaction between biologists/clinicians and the

disciplines of engineering, chemistry, physics, computer science and mathematics.

The aging of the population and the growing prevalence of neurodegenerative diseases have led to a massive investment by developed countries in the understanding and fight against nervous system diseases with medical objectives involving prevention, treatment and medical personalization.

To meet these challenges, the ICM supports innovative and creative approaches, led by teams bringing together both high-level researchers and renowned clinicians. Thanks to the University Hospital Institute (IHU) programme, associated with a Clinical Investigation Centre (CIC) within the ICM itself, a prolific translational research can be conducted. Both Leading-edge technological platforms and multidisciplinary expertise concentrated in a single place allow today the ICM to grasp, in an optimal way, the understanding of the nervous system. The international influence of the institute gives the opportunity to its researchers to be actors of many international research consortia, source of

fruitful collaborations. Finally, the presence of a start-up incubator at the heart of the ICM ecosystem (the iPEPS) allows on the one hand to instil an entrepreneurial spirit and on the other hand to accelerate the application of discoveries for patient care. One of the ICM's great strengths in addressing the challenges associated with the understanding of nervous system diseases is to facilitate cross-cutting and multidisciplinary research. 28 teams, 4 major domains from basic research to applied research, collaborative projects, clinical research networks, technological platforms always at the forefront of innovation.

Cross-cutting scientific approaches allow transdisciplinary and inter-pathologies collaborations such as neurogenetics, neuroimmunology, stem cells or neuroinformatics.

The creation of scientific thematic groups optimizes internal collaborations, allows the development of multidisciplinary approaches, requires technological innovation within platforms and promotes risk taking. An excellent research centre is above all a set of convergent projects towards a common mission.

## 4 DOMAINS: FROM BASIC RESEARCH TO APPLIED RESEARCH



### MOLECULAR & CELLULAR BIOLOGY DOMAIN

Understand the particularities of each cell of the brain; know their identity and identify their dysfunction



### INTEGRATED NEUROPHYSIOLOGY DOMAIN

Dissect the communication mechanisms of the cells between them; identify their networks of information exchanges within the brain and more broadly within the organism



### COGNITION DOMAIN

Understanding how communication between cells can control complex brain functions



### CLINICAL AND TRANSLATIONAL RESEARCH DOMAIN

Comparing "normal" functioning to pathological functioning, use artificial intelligence to model brain evolution during aging and during illness.

**Technological platforms : from the molecule to human behaviors**



# REACTIVE AND PERFORMING EXPERTS

## GUARANTEEING OPERATIONAL EFFICIENCY AND REGULATORY COMPLIANCE

So scientists can devote themselves to their main mission, research!



*“We ensure that research teams can be productive by providing them with maximum expertise flexibility and resources.”*

Corinne FORTIN, Secretary General of the ICM and the UMR

### DEVELOPMENTS IN 2018

The ICM supports all actors, at both human and material levels, to develop, manage and make our Quality system evolve.

#### Our Quality policy revolves around five axes:

- Ensure the highest scientific and technical quality of the work carried out within the Institute
- Develop and provide leading-edge technologies through platforms
- Optimize the functioning of the administrative and technical services of the Institute
- Support innovation by identifying innovative projects within research teams, developing partnerships with companies, carrying out actions for technology transfer, valorisation and support for business creation
- Ensure the transparency of our activities for our partners, our donors and more generally of all our funders

To do so, our Quality department raises awareness about Quality, develops the Quality management system within the Institute and our ISO9001 certified platforms. It also provides document management, as well as administrative and technical activities management on the basis of the ISO9001 standard. It also communicates the principles of internal governance within the ICM and with our external partners, implements the commitments of the “Charte du Don en Confiance”, ensuring transparency of our activities for our donors and ensuring effectiveness of public-private convergence.

### THE ICM AND THE PROTECTION OF PERSONAL DATA

The general data protection regulation, the European reference text for the protection of personal data, has been applicable since May 25th, 2018. It creates new rights for individuals and new obligations for companies and organizations that deal with these individuals' personal data. The RGPD asks us to change our working practices and implies a compliance that includes several stages - the first being the designation of a DPO, the Data Protection Officer who is the RGPD coordinator and the official correspondent with the CNIL. The ICM is currently working to implement this new regulation.



## THE ICM FOR SUSTAINABLE DEVELOPMENT

The year 2018 was an important year in the ecological approach that we have been conducting collectively for several years now (saving energy, water, etc.), with the introduction of a selective sorting solution. During the year 2018, thanks to the involvement of everyone at the ICM, we were able to recycle 31,439 kg of waste that was previously sent as unmarked, non-recovered waste.

**31 439 kg**  
OF RECYCLED WASTE

We have thus recycled:

- 10,531 Kg of cardboard
- 6,371 Kg of wood
- 5,242 kg of paper
- 3 800 kg of electronic waste
- 1,810 Kg of glass
- 1,483 Kg of plastic bottles
- 917 Kg of Polystyrene
- 437 Kg of office furniture
- 432 Kg of aluminum coffee capsules
- 416 Kg of metal cans



# THE ICM, GOVERNANCE AND FLUID ORGANIZATION

## PROMOTING A RESEARCH OF EXCELLENCE! SIMPLICITY, TRANSPARENCY, EFFICIENCY

### THE BOARD OF DIRECTORS

The Board of Directors regulates, through its deliberations, the affairs of the Institute. It decides on the strategic orientations presented by the Director General. He votes the budgets and approves the accounts. It is chaired by Professor Gérard SAILLANT, President of the ICM and composed of 15 members divided in 4 colleges: founders, qualified personalities, full members (INSERM, CNRS, Sorbonne University, AP-HP) and Friends of the Foundation.

#### MEMBERS OF THE BOARD OF DIRECTORS

##### COLLEGE OF FOUNDERS

- **Gérard Saillant**, Professor of Orthopedic and Traumatological Surgery, President of the ICM
- **Jean TODT**, President of the FIA, Vice-President of the ICM
- **Serge WEINBERG**, President of Weinberg Capital Partners, Treasurer of the ICM
- **Jean GLAVANY**, Former Minister
- **Jean-Pierre MARTEL**, Lawyer

##### COLLEGE OF QUALIFIED PERSONALITIES

- **Philippe Ménasché**, Professor of Thoracic and Cardiovascular Surgery
- **Richard Frackowiak**, Emeritus Professor at University College London
- **Elisabeth Tournier-Lasserre**, Professor of medical genetics at Université Paris Diderot

##### COLLEGE OF FULL MEMBERS

- **Bernard Poulain**, representative of the Centre National de la Recherche Scientifique (CNRS)
- **Gilles Bloch**, representative of the Institut National de la Santé et de la Recherche Médicale (INSERM)
- **Bruno Riou**, representative of the Sorbonne Université
- **Ali Ferhi**, Représentant de l'Assistance Publique – Hôpitaux de Paris (AP-HP)

##### COLLEGE OF THE FRIENDS OF THE FOUNDATION

- **Maurice Lévy**
- **Christian Schmidt de la Brélie**
- **David De Rothschild**

##### PUBLIC COMMISSIONER

- **Philippe Ritter**

### COMMITTEES OF THE BOARD

#### SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) assists the Board of Directors or the CEO on the main orientations, programmes or scientific approaches of the Institute. It is composed of the best international experts in neuroscience. Every 5 years, the ICM, as a joint research unit (in French UMR), is assessed on the quality of its research, its organization, its strategy and its five-year scientific projects. The teams' research projects are evaluated by the SAB, whose mission is to advise the Institute and assist it in defining its general orientations. After exchanges and discussions, the SAB submits an opinion that is taken into account to build the dossier submitted for evaluation by the High Council for the Evaluation of Research and Higher Education (HCERES).

- **Michael Shelanski** - President of the CSI, Columbia University, New York, USA
- **Dimitri Kullman** - ION, University College of London, UK
- **Gabor Tamas** - University of Szeged, Hungary
- **Peter Brown** - University of Oxford, UK
- **Brad Hyman** - Massachusetts Alzheimer Disease Research Center, USA
- **Stephen Hauser** - UCSF Sandler Institute, San Francisco, USA
- **Bill Richardson** - University College of London, UK
- **Helen Mayberg** - Center for Advanced Circuit Therapeutics, USA
- **Christian Buchel**, University Medical Centre Hamburg-Eppendorf - Department of Systems Neuroscience, Germany
- **Arnold Kriegstein** - UCSF, San Francisco, USA
- **Masud Husain** - University of Oxford, UK
- **Michael Heneka** - DZNE, University of Bonn, Germany



#### AUDIT COMMITTEE AND APPOINTMENTS AND REMUNERATION COMMITTEE

- **Serge Weinberg**, Chairman of the Audit Committee
- **Claire Giry**, Chairwoman of the appointments and remuneration committee
- **Jean GLAVANY**, Former Minister
- **Jean-Pierre MARTEL**, Lawyer

#### COORDINATION COMMITTEE OF THE FOUNDATION WITH ITS PUBLIC PARTNERS

- **Gérard SAILLANT**, President of the ICM
- **Ali FERHI**, Representative of AP-HP
- **Bernard POULAIN**, Representative of the CNRS
- **Gilles Bloch**, Representative of INSERM
- **Bruno RIOU**, Representative of the Sorbonne Université

#### THE ETHICS AND DEONTOLOGY COMMITTEE

The ICM Ethics and Deontology Committee was established with the dual responsibility of contributing to the ethical conduct of research and the compliance to the ethical rules of the trades that contribute to its production. It is composed of ICM staff members, appointed by the Board of Directors for 3 years, and two external personalities, one representing the patients, and the other representing the donors.





## THE MANAGEMENT COMMITTEE (CODIR)

Decisions are taken by the Director General on the basis of the CODIR members' recommendations.

### Composition :

Chief executive of the ICM and the Mixed Research Unit (UMR)

Pr Alexis BRICE

Medical Director

- Pr Jean-Yves DELATTRE

Scientific director

- Alberto BACCI until December 2018.

- Bassem HASSAN since the 1st January 2019

Deputy Director of the UMR

- Etienne HIRSH until December 2018.

- Bassem HASSAN since the 1st January 2019

Secretary General of the ICM and the Mixed Research Unit (UMR)

- Corinne FORTIN

Director of Communication and Development

- Jean-Louis DA COSTA

Director of the platforms

- Etienne HIRSCH

In addition, the Support functions management Committee (CODIS) pilots several institutional and transversal projects.



## 5 ADVISORY COMMITTEES

**They issue opinions and recommendations in their area of expertise.**

### THE SCIENTIFIC AND MEDICAL STEERING COMMITTEE (COPIL)

The Scientific and Medical COPIL enables researchers to participate in decision-making on scientific issues and financial issues that impact research.

### THE TEAMS' COUNCIL

The teams' council, made up of the Director General and all the team leaders (28 in 2018), meets once a month. It is consulted on the scientific policy, the budgetary aspects and the means to be implemented in the UMR.

### THE PLATFORMS' STEERING COMMITTEE

The platforms' steering committee is responsible for coordinating the activities of the 10 Institute's platforms and implementing the general policy guidelines of the ICM. It transmits to management evaluation elements of platforms' activity, organizational improvement proposals, and requests for resource allocations.

It is made up of scientific and operational managers of each platform's silo and representatives of support services.

### THE LABORATORY COUNCIL

The mission of the Laboratory Council is to advise the UMR management on the life of the UMR, the scientific policy, the budgetary and human resources policy, and all other questions related to the life of the UMR.

The members of the laboratory council are elected by their college (5 colleges in 2018). The number of representatives is proportional to the number of members of the college (15 members in 2018).



### THE COMMITTEE ON GENDER EQUITY

The ICM, according to the recommendations of an internal collective, the XX initiative, approved by the Scientific Advisory Board and the executive committee has formalized in 2018 a new advisory committee: the Committee for equity between men and women.

Several missions and actions of this committee have already been proposed and validated by the Management. The first step is to inform as many people as possible about the existence and the effect of gender bias in decision-making, in the behaviour adopted between colleagues but also in the way of approaching clinical research on mixed populations. These trainings will have for main goal a general awareness. Coordination with human resources management will improve the work environment and optimize research.

- Key actions were or will be carried out for the career of women at the institute, juniors or seniors, so that a men/women ratio is respected: o A workshop on leadership for young women scientists was set up with a first session in February 2018 and a second one in October 2018. These trainings will be organized on a yearly basis.

- Management Committee recommendations have been made to increase the number of women becoming team leaders as part of the ICM Joint Research Unit Renewal and for more new teams led by women to be recruited.

- The committee will ensure that more women are integrated into the various committees and councils of the institute.

In addition, the committee for equity between men and women coordinates its activities with other national committees, participates in meetings on this subject and communicates its action plan to other universities (Bordeaux, Caen).

### FOUNDERS

- Gérard SAILLANT, Professor of Orthopedic and Traumatological Surgery, 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, Film Director
- Louis CAMILLERI, CEO of Ferrari
- Jean GLAVANY, Former Minister
- Maurice LÉVY, Chairman of the Executive Board of Publicis Groupe, Co-Chair of the ICM Friends Committee
- Olivier LYON-CAEN, Professor of Neurology, former Director of the Nervous System Diseases Centre of Pitié-Salpêtrière University Hospital
- Jean-Pierre MARTEL, Lawyer
- Max MOSLEY, Former President of the FIA
- Lindsay OWEN-JONES, Honorary President of L'Oréal, Honorary President of the ICM Friends Committee
- David de ROTHSCHILD, President of Rothschild Bank & Co., Co-Chair of the ICM Friends Committee
- Michael SCHUMACHER, Formula 1 Driver
- Serge WEINBERG, President of Weinberg Capital Partners, Treasurer of the ICM

### THE ICM ASSOCIATION OF FRIENDS

- Lily SAFRA, Honorary President, President of the Edmond J. Safra Philanthropic Foundation
- Gérard SAILLANT
- Jean TODT
- Lindsay OWEN-JONES
- Maurice LÉVY
- David de ROTHSCHILD
- Jean-Pierre MARTEL
- Serge WEINBERG



# FOCUS ON THE ICM **ETHICS** AND **DEONTOLOGY COMMITTEE**

**Interview: Dr. Ségolène Aymé, geneticist doctor, rare diseases officer at the ICM and chair of the ICM Ethics and Deontology Committee.**

**You have been appointed, in 2018, Chair of the ICM Ethics and Deontology Committee (COMETH-ICM), can you summarise the background of this committee?**

The ICM committee has been established with the dual responsibility of contributing to the ethical conduct of research and respect the ethical rules of

the trades that contribute to its production. It is composed of ICM staff members, appointed by the Board of Directors for 3 years, and two external personalities, one representing the patients, and the other the donors.

Neuroscience research is one of the most controversial areas in society because it involves such important things as the basis of personality and behaviour. The anxieties and worries that this generates must be anticipated. An institute like the ICM must participate in the general debate with its expertise. It must also be exemplary in the conduct of research to meet the trust of donors and public funding agencies.

### **Ethics or deontology?**

Deontology is the set of duties and rules governing the performance of ICM's tasks, whether or not they are already translated into law. It is a code of conduct that must be respected by all.

Scientific integrity is the set of rules and values that must govern the research activity, to ensure that it is honest and scientifically rigorous, features that the ICM must promote.

The ethics of research relate to the questions posed by advances in science and their societal impacts.

### **What is the roadmap of the ethics committee?**

As a starting point, the committee should consult with the ICM staff to bring out issues that they are most concerned about and that will be given priority. We want to be as inclusive as possible in terms of reflection because the conduct of the ICM is the result of an ensemble of individual behaviours. We are going to organize debates on these topics, with training on the issues at stake, then let the opinions be said, and work towards a consensus. We also have a monitoring and training mission to raise awareness on the content of the codes of ethics and deontology already adopted.

*“Ethics are not normative but thought of as a reflexive pivot between scientific integrity and social responsibility.”*

Anybody can submit an opinion on ad hoc subjects to the COMETH-ICM, without replacing the existing regulatory committees, to which the requests will be redirected if necessary.

The biggest challenge for the COMETH-ICM will be to convince everyone that societal norms develop from those originally conceived by the research actors themselves. The world of research is not sufficiently aware of contributing directly to the evolution of norms or society's perception of science.

### **You have been appointed at the head of this committee, what is your stake in this new function?**

My goal is to include all the staff in the activities of the committee and to concretely support good practices in terms of research. Scientific output is excellent at the ICM. That's one more reason for meeting the highest ethical standards. More generally, my personal challenge is to fight against the discredit of the science that we see emerging. Confidence in science and research must be restored by showing that scientists are not only imaginative, creative, stubborn and dedicated to their mission, but also reflect on the meaning of their work and anticipate the consequences.

### **What is your vision of the future on these issues?**

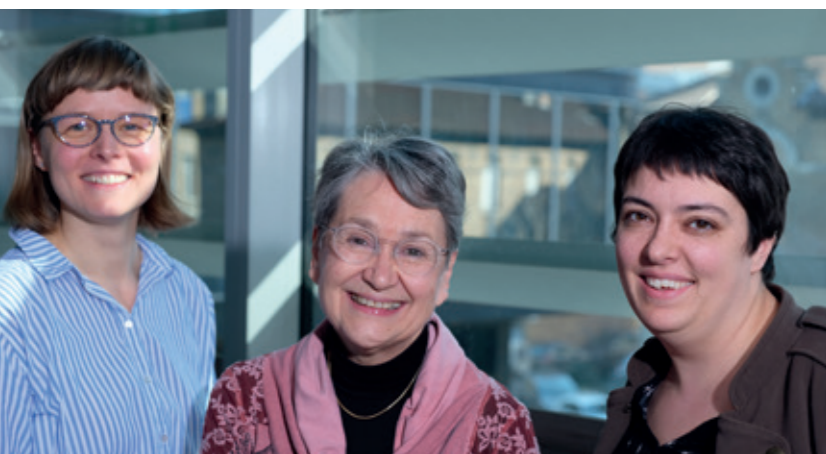
Over the past few years, we have been observing a drift of the notion of innovation compared to that of progress. But innovation is not necessarily synonymous with progress, it is synonymous with novelty but a novelty is not always a good thing. The need to innovate and be the first is such that we are no longer interested in its purpose and the societal transformations it implies. With the acceleration of technological and societal processes, the time for reflection is no longer sufficient. I think that today's struggle is to give meaning to our action for the human species and the planet in general. I trust the ICM to translate “Search, Find, Cure” into facts.

## **THE COMMITTEES OF RESEARCH INSTITUTIONS HAVE DIFFERENT AREAS OF ACTIVITY.**

The Inserm Ethics Committee is an effective player in the dialogue between the biomedical community and society as a whole. The Inserm also has a scientific integrity delegation, distinct from the ethics committee.

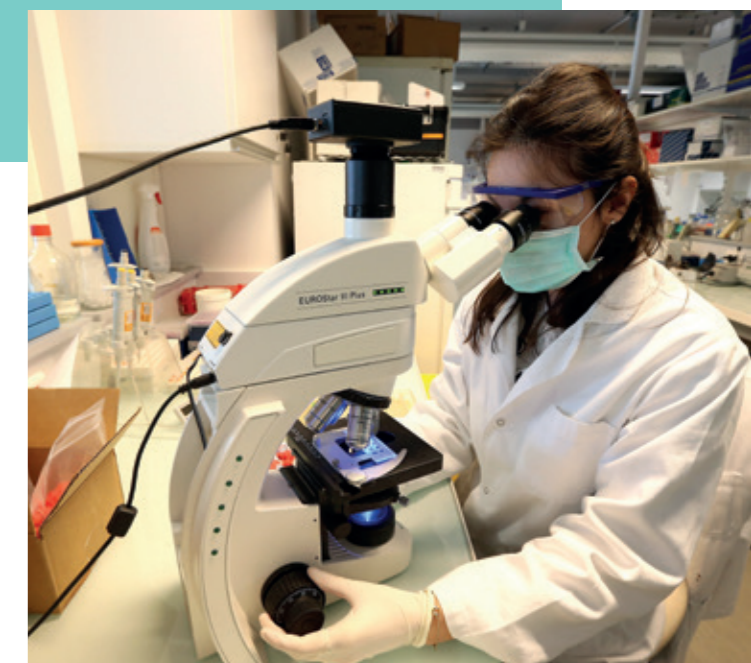
The CNRS Ethics Committee is an independent consultative body whose opinions are public. It deals with issues that are submitted by the Board of Directors, the Scientific Council or the General Director of the CNRS. It aims to enlighten the exercise of the freedom of research with regard to the duties and responsibilities of staff towards society. The CNRS also has a Referent to Scientific Integrity.

COMETH-ICM Board (from left to right) - Magali DUMONT, Ségolène AYMÉ and Mathilde GIBERT



### **CHARTERS OF ETHICS AND DEONTOLOGY IN THE FIELD OF ACTIVITY OF THE ICM**

- National charter on ethics of animal experimentation, 2014
- Allistene's Ethics of research in robotics, 2014
- National charter of ethics for the research professions, 2016
- The ethical and deontological charter of the faculties of medicine and odontology, 2017
- Code of ethics on donations with confidence, 2017
- The CNIL's report on ethical issues of algorithms and artificial intelligence, 2017
- Code of Ethics and Scientific Integrity of the National Research Agency, 2018





# PARIS TRANSLATIONAL NEUROSCIENCE INSTITUTE



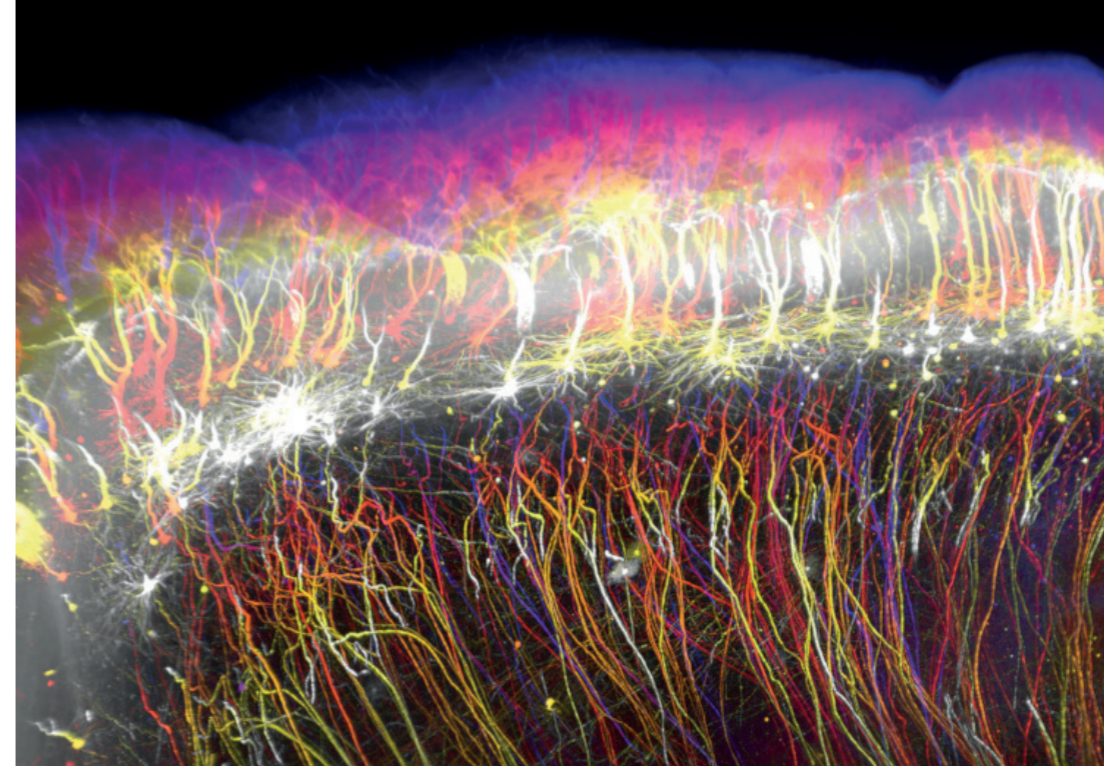
The IHU-funded initiatives created in 2012 with a budget of 850 million euros as part of the “Investissement d’avenir” program, resulted in impressive quantitative output. A network of 7 IHU, each expert in their respective domain, came out of this initiative. The funds raised since the IHU was established in 2012 provide support to scale up and structure innovative research initiatives, expand resources for the scientific and medical community, implement new technologies; develop innovative care and education initiatives.

*“Today ICM ranks 2nd in the neurology field, recruits top international group leaders, with an increasing number of key industrial partnerships, innovative start-ups and a new incubator. Building on these successes, ICM is now at a pivotal time for transformation.”*

## VERY POSITIVE RESULTS

One of the challenges of transdisciplinary multi-scale research is finding effective ways for experts from different fields to work together and take the risks necessary to step out of their comfort zones. The Big Brain Theory program grants pave the way for ICM research teams to come together to solve fundamental and hard problems in neuroscience and brain disease. A major advantage of this program is that it is both intramural and competitive at the same time. Therefore, it combines the possibility to protect the brightest most high-risk ideas of our scientists, while at the same time enabling them to work together to test these ideas. While it is certainly a challenge to recruit world-class researchers - a challenge which IHU funding helped ICM meet - it is even more challenging to retain that talent in the medium and long terms. ICM will meet this challenge in part through the increase of core funding to an internationally competitive level. The combination of core funding and intramural competitive grants ensures that our scientists have both the basic means to do their core research, as well as the competitive support to take risks and dare to cross disciplines to solve truly hard problems. The ICM has the ambition to become the clinical research wing of the “pole of nervous system diseases” at the Pitié-Salpêtrière hospital and wants to imprint a culture of research on clinical departments,

© ICM/Nicolas RENIER



young researchers, and paramedical staff. Our iCRIN (ICM Clinical research infrastructure in neuroscience) program aims to take advantage of this effort to sustain clinical research activity and develop a unique environment in the perspective of the upcoming era of precision and preventive medicine. It also aims to give access to large and high-quality data for profiling patient trajectories using state of the art of artificial intelligence and machine learning methods as part of our Neuroinformatics center.

The Neurocatalyst, Neurotrials, Living-Lab and Start-up 2.0 programs have been established to support translational neuroscience research projects at the intersection of science, engineering, innovation and medicine. The goal of the program is to encourage research that addresses unmet needs and leads to improvements in brain health, innovative care or neurosciences, and thanks to the ICM ecosystem to create products to improve care.

## THE FUTURE OF THE IHU PROGRAM

Future plans will support neuroinformatics collaborations involving biologists, computer scientists, statisticians, and engineers who want to identify fundamental principles of nervous system computation, understand how the brain’s neural network of interconnecting neurons operates and decipher the complexity of large scale brain data.

ICM will also launch a major initiative into technology development at the interface of its research teams and core facilities in highly promising areas such as cellular imaging with expansion and ultra-resolution microscopy, 3D brain reconstruction, neural activity imaging in live behaving animals, state of the art MRI and next-generation molecular and cellular approaches in animal models of brain diseases.

There has been an explosion of interest from young scientists in collaborative brain research and the

institute will need to raise fellowships to ramp up cross-disciplinary graduate, residents and postdoctoral training programs. Equally, there is interest from society, in a broader sense, and ICM’s new Open Brain School initiative is a key answer to the challenge of bringing neuroscience to the citizens.

*“Thanks to the first IHU award, ICM is uniquely positioned to become a global leader by making breakthrough discoveries of the state of the brain in health and disease, translating them into innovative applications and effective therapies, and creating a world-class center for the training of the leading scientists of the future. »*

Based on our assets the economic leverage effect of IHU funding is at 4.4 in 2018.

The ICM will present the results of the IHU to an international jury in 2019. We strongly believe that a new phase of IHU investment will allow the ICM community to transform its global positioning, advance major breakthroughs with a global, qualitative and international impact.



# HIGHLIGHTS

## ALEXANDRA DURR, WINNER OF THE LAMONICA PRIZE OF NEUROLOGY, GRAND PRIX OF THE ACADEMY OF SCIENCES

The Academy of Sciences awarded Professor Alexandra Durr the Lamonica Prize of Neurology for her work in the field of rare neurogenetic diseases. Alexandra Durr, University Professorat Sorbonne Université, Hospital Practitioner at the Pitié-Salpêtrière Hospital-APHP, ICM researcher, is a world-renowned specialist in hereditary neurological diseases.

For more than 20 years, she has been supporting patients suffering from pathologies such as Huntington's disease and spastic paraplegia, driven by the hope of being able, one day, to prevent the onset of these diseases.



## FABRIZIO DE VICO FALLANI SINGLED OUT BY THE COMPLEX SYSTEMS SOCIETY!

Fabrizio de Vico Fallani, Inria researcher in the team "ARAMIS: mathematical models and algorithms for the processing of images and signals of the human brain" at the ICM, received the Junior Scientific Award from the Complex Systems Society for "his numerous remarkable contributions to the science of complex systems, especially for these works on time series analysis and on the structure and dynamics of the brain". The Complex Systems Society aims to promote fundamental and applied research in the field of complex systems science in Europe and within the international scientific community. The Junior Scientific Award rewards the remarkable scientific advances made by young scientists who have obtained their thesis for less than 10 years.

## UNIFICATION OF THE IHU-A-ICM SCIENTIFIC COOPERATION FOUNDATION WITHIN THE ICM FOUNDATION

On the 1<sup>st</sup> January 2018, the IHU-A-ICM merged into the ICM. The intervention budget, achievements, teams, successes and hopes are now gathered to reinforce the coherence and amplify the scientific and medical project of the Institute.



## THE ICM AND THE ABEONA FOUNDATION COMMIT TO TWO ARTIFICIAL INTELLIGENCE PROJECTS TO PROMOTE GENDER EQUALITY IN THERAPY

Observation: men and women are not equal faced with the disease. Biological differences, social and cultural factors... Women are 1.5 times more affected than men by Alzheimer's disease, 3 times more by multiple sclerosis without any cause being identified today. Data science and artificial intelligence now offer the opportunity to respond to this inequality by understanding pathological mechanisms and identifying multiple and integrated causes. The Abeona Foundation and the ICM join forces on cutting-edge projects, for Multiple Sclerosis and neurodegenerative diseases such as Alzheimer's disease, through a two-year partnership.

## VISIT OF THE HIGH COUNCIL FOR THE EVALUATION OF RESEARCH AND HIGHER EDUCATION (HCERES) AND Recreation of the UMR with public partners

The Joint Research Unit (UMR) of the ICM was evaluated at the end of 2017 by the HCERES. All the research teams presented during this evaluation were renewed. The evaluation report issued in 2018 concluded that: "The UMR pursues an outstanding scientific strategy based on the development of successful research axis as well as new and riskier research areas. In just a few years, it has become internationally competitive, among a small number of world-renowned institutes." The recreation of the joint research unit (UMR) gathering INSERM, CNRS and Sorbonne University in partnership with the AHPH has been effective since the 1<sup>st</sup> January 2019.

## MICHEL THIEBAUT DE SCHOTTEN 2018 CNRS BRONZE MEDAL

The CNRS medals distinguish researchers for the originality, the quality and the importance of their work. Michel Thiebaut de Schotten, a CNRS researcher in neuropsychology and neuroimaging of brain connectivity, head of the Brain Connectivity and Behaviour (BCB) lab group in the Frontlab team led by Pr DUBOIS & LEVY at the ICM, received the 2018 CNRS bronze medal for its works.



## RECRUITMENT OF A NEW TEAM

As part of the strengthening of the neurophysiology field with an application to epilepsy and following the recommendations of the Scientific Advisory Board (SAB), the ICM launched an international call for applications in October 2017. The auditions of the candidates took place on the 13th and 14th June 2018 under the aegis of Professor Michael Shelanski, President of the SAB, and followed by meetings with ICM researchers and General Management. Jaime De Juan-Sanz, a researcher at Weill Cornell Medical College (USA), was selected as a new ICM team leader. The arrival of this new team was rendered possible thanks to the creation of the Diane Barrière Chair for epilepsy, fruit of a donation from the Desseigne family.



## MAJOR EUROPEAN FUNDING FOR RESEARCH ON RARE DISEASES

A large consortium, coordinated by the University of Tübingen (Germany), associating the Radboud University Medical Centre in Nijmegen (the Netherlands), the University of Leicester (UK), and including Eurordis, Orphanet, two major French research institutes, the ICM and the Institute of Myology, and the University Hospital of Dijon, obtained a grant of 15 million euros for the research programme SOLVE-RD. This consortium aims to improve the diagnosis of rare diseases. The researchers rely on 4 European referral networks of carers, set up to share, advance and enhance knowledge and resources available to treat rare diseases.

## SUMMER SCHOOL 2018 "THE BRAIN TO MARKET"!

The Summer School "The Brain To Market" was held from the 3rd to the 7th September 2018, at the Brain and Spine Institute (ICM) in Paris, focusing on Parkinson's disease. As every year, French and foreign researchers (Master's and Doctoral students, Post-docs), clinicians, engineers, and executives participated in the Summer School "The Brain To Market". With an unprecedented approach, this training week combines both translational neuroscience and entrepreneurial training, in order to enable participants to better understand realities and challenges of the economic and industrial world.

The Brain to Market Summer School



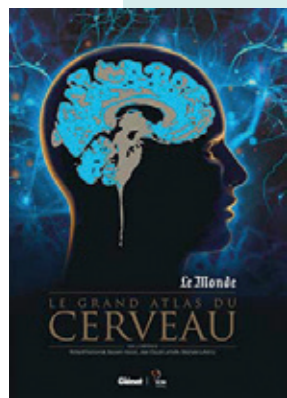


### A NEW CAMPAIGN ON PARKINSON'S DISEASE

On the occasion of World Parkinson's Disease Day, the Brain and Spine Institute has launched a new advertising film designed and offered by Publicis to raise public awareness of this disease. While revolving around a publicity film broadcast on television and on social networks, the campaign includes a mobile version of the film using an unprecedented 100% mobile technology: haptic technology. It triggers the smartphones' vibrator to recreate the tremors of Parkinson's disease during the viewing of the film. An emotional advertising campaign in total immersion: "Only our emotions should make us tremble".

### AN ATLAS DEDICATED TO THE BRAIN, PUBLISHED BY GLENAT, IN PARTNERSHIP WITH LE MONDE AND THE ICM!

This Great Atlas of the Brain was developed in collaboration with ICM researchers, French and international experts in neuroscience, with the help of the newspaper Le Monde. It reveals many new facets of the brain and allows a better understanding of the functioning of this still mysterious organ. The precise texts of the neuroscientists gathered by the ICM under the direction of Richard Frackowiak, Bassem Hassan, Jean-Claude Lamielle and Stéphane Lehericy bring clear answers to fundamental questions, always illustrated by diagrams, images from MRI or scanner and infinitely beautiful photographs produced by cutting-edge technologies in brain imaging.



### THE EXCELLENCE FRANÇAISE AWARD FOR THE ICM

The ICM has received the Excellence Française Award! Each year, this prize honours different sectors of activity in which France stands out. These sectors are represented by companies or institutions, themselves represented by their managers, or by exceptional individuals whose personal and professional success goes well beyond our borders.



### THE ICM AT THE START-UP SUMMIT – CHALLENGES

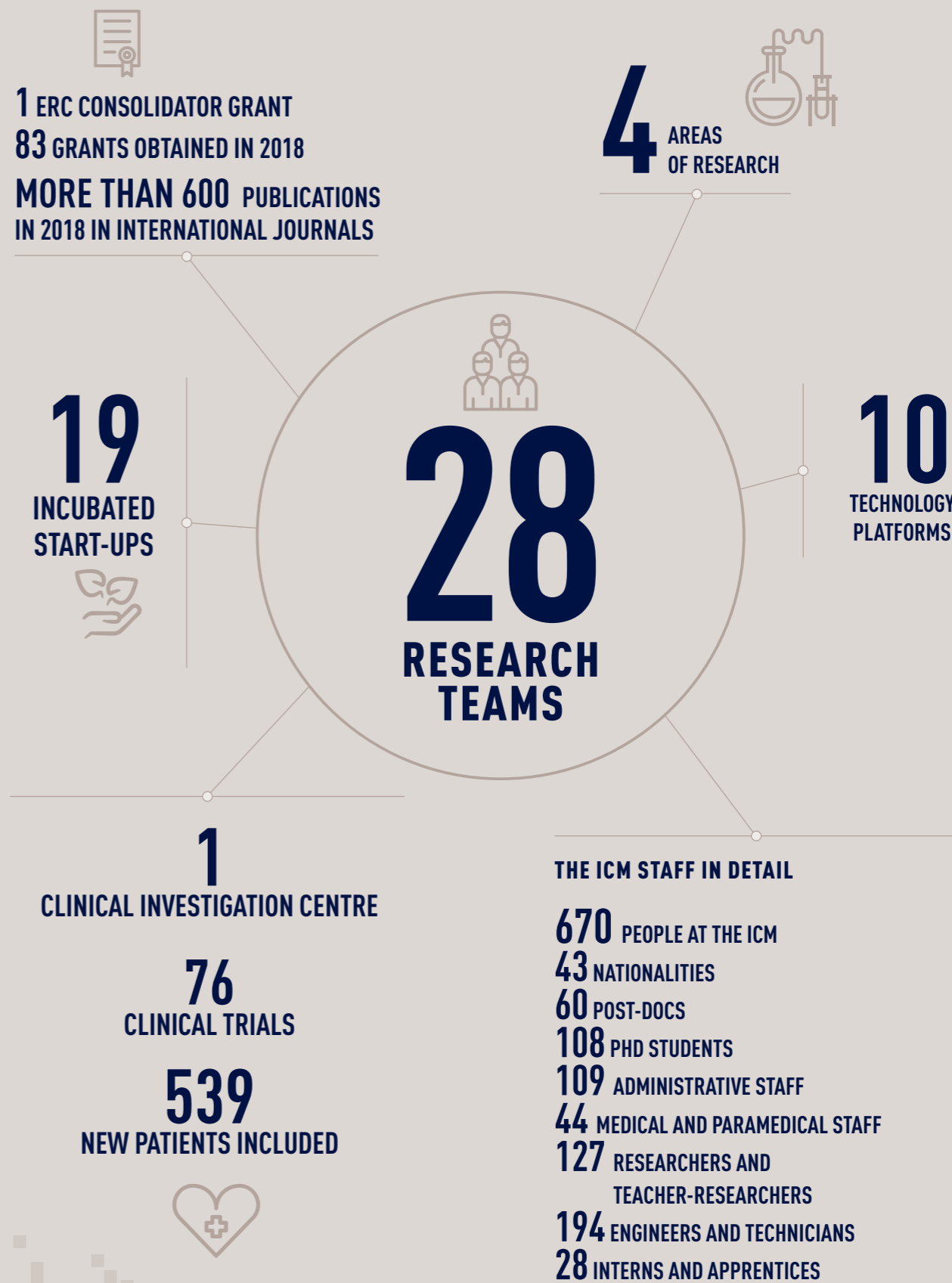
What will be tomorrow's medicine? Customized, targeted, digitalized? Will machines have a consciousness associated with their artificial intelligence, but what is consciousness? What will the connected clothes be used for and look like? These issues were approached by the ICM stakeholders at the 3rd Start-up Summit, organized by Challenges magazine, which took place in Paris in April 2018. On this occasion, Neurallys, a start-up hosted within the ICM's iPEPS incubator, was selected among the 5 winners of the "100 start-ups to invest in" in the biotech and health category.



### THE ICM WAS AT THE PARISCIENCE FESTIVAL

Pariscience has become over the years, thanks to a sharp selection and a close watch on scientific news, an unmissable event for both film and science enthusiasts and neophytes. During this festival, the Symbiose project, a 48h short films competition, was held from the 15th to the 17th October 2018. The principle is simple, young directors and young researchers divided into pairs must write, shoot, edit and release a scientific short film in 48h. This year's theme was Breaking. As part of a partnership between ICM and Pariscience, 3 PhD students and postdocs from the Institute had the opportunity to produce a short film paired with young directors, short films that were screened during the festival.

# KEY FIGURES - 2018





# RESEARCH

BY BASSEM HASSAN, TEAM LEADER AND SCIENTIFIC DIRECTOR (2019)



At ICM, neuroscientists, psychiatrists and neurologists work together to perform world class, cutting edge research to understand the brain in health and disease, to translate this understanding into products and services for patients, and to create innovative programs to share knowledge with the next generation of scientists, physicians and the general public.

**F**or neuroscience, it is the best of times and it is a key moment! Amazing advances in health care during the 20th century have resulted in lower infant mortality rates and longer life spans. Unfortunately, with this has come an increase in the incidence of brain diseases, be they neurodevelopmental, neuropsychiatric or neurodegenerative. There is also good news: the vast majority of us are not ill! Most of us live our lives without suffering a brain disorder. This means the brain of humans, and indeed all animals, has mechanisms that make it amazingly robust and able to protect and heal itself. By studying the healthy brain in humans and animals we can learn about these protective and self-healing mechanisms and use them to manage and eventually cure brain diseases. Our brain is who we are! Each of us is a unique individual because each of us has a unique brain. At the same time we all have a sense of being somehow similar in our humanity and similar to many of our animal cousins. It is an exciting challenge to understand how the brain can balance similarity and uniqueness, unity and diversity.

ICM researchers and clinicians are tackling challenges ranging from how the brain develops, how its cells work together, how its networks create behaviors and emotions and how diseases like brain cancer, Alzheimer's, Parkinson's, epilepsy and depression start, develop and might be stopped. They benefit from a large number of scientific service facilities that put the latest techniques and equipment at the service of brain science, from

**This virtuous cycle of excellence makes ICM the amazing institute that it has become less than ten years after it was founded.**

brain imaging to molecular exploration of brain cells and everything in between to understand in great detail how the brain functions and what happens under disease conditions. The work of ICM scientists and clinicians is regularly published in the best international scholarly journals, testifying to its excellence and pioneering

nature. To make this hard, long and expensive work possible, ICM scientists rely on an infrastructure of support services, including a world-class grants office, to obtain grants and prestigious awards from national and international sources.

This virtuous cycle of excellence makes ICM the amazing institute that it has become less than ten years after it was founded. It is therefore no surprise that ICM is today one of the top 3 institutes of neurology in the world!

ICM's ambition does not stop there. We have a long, hard and exciting road ahead of us. The 21st century must be the "brain health century" and investment in brain research must increase massively in order to make this happen. There has never been a more exciting and challenging time to be a neuroscientist, and there is no better place to a neuroscientist than ICM: the home of the brain!



# MOLECULAR AND CELLULAR DOMAIN

The teams whose research focuses on this field seek to decipher the influence of genetics, to dissect the molecular machinery, to establish the role of different types of cells and to understand complex cellular interactions in normal or pathological state.

## BRAIN TUMORS

### EXPERIMENTAL NEURO-ONCOLOGY

Secondary Domain: Clinical and Translational Research

**Team leader: Marc Sanson**

- Marc Sanson, Franck Bielle, Ahmed Idbaih, Michel Kalamarides, Agusti Alentorn, Jean-Yves Delattre, Khé Hoang-Xuan, Karima Mokhtari, Mathieu Peyre.
- 2 post-docs, 8 engineers & technicians, 2 PhD students
- Competitive funding obtained in 2018: Association Vaincre, ANSES, League against cancer, AP-HP, ARTC

### CELLULAR AND MOLECULAR MECHANISMS OF GLIOMAGENESIS

**- Team leader: Emmanuelle Huillard**

- Principal investigators: Emmanuelle Huillard, Isabelle Le Roux
- 1 post-doctorant, 2 ingénieurs & techniciens, 2 doctorants
- 1 post-doc, 2 engineers & technicians, 2 PhD students
- Competitive funding obtained in 2018: OLIGO NATION, RIF-Ile de France Region, League against cancer, ARC

### Towards a better characterization of gliomas

#### #BRAINTUMORS

The precise analysis of brain tumors' characteristics is a critical point to facilitate their diagnosis, their management and the setting up of new clinical trials to treat them. A study conducted by ICM and APHP researchers and clinicians focused on one type of tumor in particular, the diffuse gliomas carrying the FGFR3-TACC3 fusion gene.

These results are an important step towards a better diagnosis of these particular gliomas but also to better understand their origin and their development, with the ultimate goal of setting up personalized therapies to treat them.

— Source: Bielle et al. *Brain Pathol.* Oct 2017

A study conducted by Marc Sanson's team (APHP/Sorbonne University) in collaboration with Professor Houlston's team at the Institute of Cancer Research (United Kingdom) highlights the specific association of certain genetic variants with different subtypes of gliomas. In the past, Marc Sanson's team participated in

the identification of genetic variants present in the general population and associated with the risk of developing a glioma. These show that most of the previously identified genetic variants are specifically associated with certain subtypes of glioma, an observation that opens new paths for research on their genesis.

— Source: Labreche et al. *Acta Neuropathol.* May 2018

Chordoid gliomas are rare brain tumours that develop in the 3rd cerebral ventricle, a structure at the base of the skull. These tumours, with slow progression and well delimited, mainly affect adults, around 45 years old, predominantly women. A study conducted at the ICM by the teams of Marc Sanson and Emmanuelle Huillard has identified a constant mutation associated with this rare subtype of brain tumour, never described in any other type of human tumour. The detailed characterization of the consequences of this mutation is under way. It could provide additional information on the developmental mechanisms of these tumours and open therapeutic perspectives specifically targeting disrupted processes in this rare subtype of glioma.

— Source: Rosenberg et al. *Nature Communications*, 2018



## THE DEVELOPMENT AND PLASTICITY OF THE CENTRAL NERVOUS SYSTEM

### BRAIN DEVELOPMENT

- **Team leader:** Bassem Hassan
- Principal investigators: Bassem Hassan
- 8 post-docs, 4 engineers & technicians, 4 PhD students
- Competitive funding obtained in 2018: MSCA - IF/GF, IMI, FRM

### STRUCTURAL DYNAMICS OF NEURONAL NETWORKS

- **Team leader:** Nicolas Renier
- Principal investigators: Nicolas Renier
- 1 engineer, 1 PhD student
- Competitive funding obtained in 2018: DIM ELICIT

### How our brain develops

Brain development is a set of extremely complex processes, many of which are still little explored. Among them, sufficient neuronal production is paramount. This mechanism is based on a perfect temporal and spatial coordination of neural stem cell division during development. Bassem Hassan's team discovered a particular type of neural stem cells and demonstrated a very precise temporal control mechanism of how these cells function during brain development in *Drosophila* (fruit fly). These results pave the way for advanced molecular and genetic studies to better understand the biology of these cells.

— Source: Mora et al. *Developmental Cell*. March 2018

## REPAIR (MULTIPLE SCLEROSIS AND DEMYELINATING DISEASES)

### MOLECULAR AND CELLULAR APPROACHES OF MYELINIC REPAIR

- Secondary Domain: Clinical and Translational Research**
- **Team leaders:** Brahim Nait-Oumesmar & Anne Baron Van Evercooren
  - Principal investigators: Brahim Nait-Oumesmar, Anne Baron Van Evercooren, Violetta Zujovic, Lamia Bouslama.
  - 4 post-docs, 2 engineers & technicians, 5 PhD students
  - Competitive funding obtained in 2018: ARSEP, NMSS, NIH, NeurATRIS

### MECHANISMS OF MYELINATION AND DEMYELINATION IN THE CENTRAL NERVOUS SYSTEM

- Secondary Domain: Clinical and Translational Research**
- **Team leaders:** Catherine Lubetzki & Bruno Stankoff
  - Principal investigators: Catherine Lubetzki, Bruno Stankoff, Nathalie Sol-Foulon, Anne Desmazière, Marc Davenne, Céline Louapre, Benedetta Bodini, Caroline Papeix, Elisabeth Maillard, Géraldine Bera.
  - 1 post-doc, 1 engineer, 3 PhD students
  - Competitive funding obtained in 2018: ARSEP, FRM, NeurATRIS

### OLIGODENDROCYTE DEVELOPMENT AND NEUROVASCULAR SIGNALS

- **Team leaders:** Jean-Léon Thomas & Boris Zalc
- Principal investigators: Jean Léon Thomas, Boris Zalc, Michel Mallat, Carlos Parras.
- 2 post-docs, 4 engineers & technicians, 1 PhD student
- Competitive funding obtained in 2018: ANR-PRCI, H2020, ANSES, ARSEP, ANR-MRSEI

### MSCopilot®, Ad Scientiam's solution (Start-up incubated at the ICM) for monitoring patients with multiple sclerosis.

#### # MULTIPLE SCLEROSIS

After a proof-of-concept study in 30 patients in 2016, Ad Scientiam has just finalized a large multicentre study comparing the scores measured by the MSFC, a clinical test performed in consultation by a neurologist, with those calculated by the MSCopilot® algorithms.

Coordinated by Dr. Elisabeth MAILLART and carried out in 11 MS expert centres, this study recruited 146 patients and 76 healthy volunteers, who successively passed the standard tests on paper and then the digital tests on smartphone.

In the presence of Prof. Catherine LUBETZKI, neurologist and team leader at the ICM and Dr Elisabeth MAILLART, Ad Scientiam confirmed that with only 4 tests, the MSCopilot® score brings together infinitely more variables than the standard tests, which enriches the data provided to the clinician. MSCopilot® is today a class I, CE-marked medical device dedicated to the follow-up of patients with multiple sclerosis.

## GENETICS AND PHYSIOPATHOLOGY OF NEURODEGENERATIVE DISEASES

### ALZHEIMER'S DISEASE AND PRION DISEASES

- Secondary Domain: Clinical and Translational Research**
- **Team leaders:** Marie-Claude Potier & Stéphane Haik
  - Principal investigators: Marie-Claude Potier, Stéphane Haik, Nicolas Bizat, Benoit Delatour, Stéphane Epelbaum, Charles Duyckaerts, Serge Marty, Jean-Philippe Brandel, Véronique Sazdovitch, Jean-Maurice Delabar.
  - 6 post-docs, 8 engineers & technicians, 2 PhD students, 1 clinical research associate
  - Competitive funding obtained in 2018: France Alzheimer, Alzheimer Plan Foundation, GIS-IBISA, Alzheimer Research Foundation

### BIOTECHNOLOGY AND BIOTHERAPY

- **Team leader:** Philippe Ravassard
- Principal investigators: Philippe Ravassard, Hélène Cheval, Jacques Mallet.
- 1 post-doc, 4 engineers & technicians, 2 PhD students
- Competitive funding obtained in 2018: IMI, Fondation de France

### NEUROGENETICS AND PHYSIOLOGY

- Secondary Domain: Clinical and Translational Research**
- **Team leader:** Bertrand Fontaine
  - Principal investigators: Bertrand Fontaine, Sophie Nicole, Cécile Delarasse, Laure Strohlic, Mohamed El-Behi, Gaëlle Bruneteau, Bruno Eymart, Emmanuel Fournier, Karine Viala, Damien Sternberg, Savine Vicart.
  - 2 post-docs, 4 engineers & technicians, 2 PhD students
  - Competitive funding obtained in 2018: AFM strategic, ARSEP

### EXPERIMENTAL THERAPEUTICS OF PARKINSON'S DISEASE

- Secondary Domain: Clinical and Translational Research**
- **Team leader:** Etienne Hirsch
  - Principal investigators: Etienne Hirsch, Stéphane Hunot, Marie-Laure Welter, David Grabli, Patrick Pierre Michel, Rita Raisman-Vozari.
  - 6 post-docs, 6 engineers & technicians, 7 PhD students
  - Competitive funding obtained in 2018: IMI, France PARKINSON

### MOLECULAR BASIS, PHYSIOPATHOLOGY AND TREATMENT OF NEURODEGENERATIVE DISEASES

- Secondary Domain: Clinical and Translational Research**
- **Team leader:** Alexis Brice
  - Principal investigators: Alexis Brice, Alexandra Durr, Giovanni Stevanin, Frédéric Darios, Morwena Latouche, Isabelle Le Ber, Olga Corti, Jean-Christophe Corvol, Suzanne Lesage, Khalid Hamid El Hachimi, Caroline Nava, Claire Pujol, Fanny Mochel.
  - 9 post-docs, 9 engineers & technicians, 11 PhD students, 3 clinical research associates
  - Competitive funding obtained in 2018: ARSLA, IMI, Spastic Paraplegia Foundation, ERC PoC, H2020, France Parkinson, ANR-JPND, Institute of France, MJFOX, FRM, ASL-HSP France, ENP-School of Neuroscience Paris, Alzheimer Plan Foundation, FRM, Academy of Sciences

### TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS: FROM GENETICS TO ZEBRA FISH

- **Team leader:** Edor Kabashi
- Principal investigators: Edor Kabashi, Corinne Besnard-Guerin, Sorana Ciura
- 3 post-docs, 1 technician, 3 PhD students,
- Competitive funding obtained in 2018: ANR, PRC

### AMYOTROPHIC LATERAL SCLEROSIS (ALS) CAUSES AND MECHANISMS OF MOTOR NEURON DEGENERATION

- Secondary Domain: Clinical and Translational Research**
- **Team leader:** Séverine Boillée
  - Principal investigators: Séverine Boillée, Delphine Bohl, Stéphanie Millecamps, Christian Lobsiger, François Salachas, Danièle Seilhean
  - 1 post-doc, 3 engineers & technicians, 4 PhD students
  - Competitive funding obtained in 2018: AFM, NRJ Foundation, ARSLA, ULM-ULM University Hospital, ANSES

### A new mechanism regulating inflammation in Parkinson's disease

A study conducted by the group of Olga Corti and Jean-Christophe Corvol in Alexis Brice's team at the ICM highlights a mechanism involved in neuroinflammation, an activation of the immune system in the brain, in particular forms of Parkinson's disease. Some forms of the disease originate from mutations in the PINK1 and PARK2 genes, encoding proteins whose function is to preserve the quality of the mitochondria, the power plants of the cells. The good functioning and the survival of the neurons involve, among others, the degradation and the replacement of the defective mitochondria. The study identified an abnormal activation of a specific inflammatory mechanism, the inflammasome, in the context of PINK1 and PARK2 gene mutation. The results highlight two pathways, which normally prevent overactivation of the inflammasome and are impaired in PINK1 and PARKIN deficient cells. Through this work, the researchers show a link between the dysfunction of an essential mechanism of mitochondria and the establishment of an abnormal inflammatory response. The capacity to identify as soon as possible, among the various forms of the disease, the predominant dysfunctions, represents an important stake for personalized therapeutic approaches.

— Source: Mouton-Liger et al. *Glia*. Apr 2018



## Advances in the genetics of fronto-temporal dementia

### # FRONTO-TEMPORAL DEMENTIA

The group of Isabelle Le Ber in the team of Alexis Brice is at the origin of several advances in the genetics of fronto-temporal degenerations (FTD). This work shows, for the first time, the influence of genetics at large on the age of onset of the disease of some familial forms of FTD. Thanks to a collaboration with the team of Charles Duyckaerts, a new gene involved in this family of pathologies could be identified, the c9orf72 gene. This gene has a high number of repeats (expansion) of a DNA sequence of 6 bases, the number of repeats varying from one patient to another. This study, conducted in healthy carriers of the mutated c9orf72 gene, shows for the first time that the size of the expansion is not a predictive marker of the age of onset of the disease. These results represent a breakthrough in understanding genes that modify the age of onset of the disease and provide important information for people at risk.

— Source: Barbier et al. *Neurol Genet*. Dec 2017; Fournier et al. *Acta Neuropathologica Communications*. June 2018; Fournier et al. *Neurobiol Aging*. Sep 2018

## Identification of a key mechanism in hereditary spastic paraplegia type 11

### # HEREDITARY SPASTIC PARAPLEGIA

Hereditary spastic paraplegia type 11 and its allelic pathologies such as juvenile amyotrophic lateral sclerosis type 5 or certain cases of Charcot-Marie-Tooth disease, are rare genetic diseases affecting motor neurons, neurons responsible for the transmission of nervous information to the muscles, caused by a mutation in the SPG11 gene. Pathology is clinically characterized by progressive weakness of the lower limbs, accompanied by spasticity, a form of muscle stiffness, and loss of sensation. Cognitive and cerebellar disorders are frequently associated. A study conducted by the group of Frédéric Darios and Giovanni Stevanin in Alexis Brice's team at the ICM highlights the deleterious role of the accumulation of certain lipids on neurons in hereditary spastic paraplegia type 11, also known as juvenile amyotrophic lateral sclerosis type 5. It also suggests that targeting this mechanism could be an interesting therapeutic avenue in this pathology.

— Source: Boutry et al. *Cell Rep*. Jun 2018

# NEUROPHYSIOLOGY

## DOMAIN

The goal of the teams in this field is to better understand the physiology of neurons and networks under normal and pathological conditions. The Institute's various teams share different approaches including molecular and cellular approaches, electrophysiological and optical recordings, optogenetics and manipulation of neuronal activity by transcranial magnetic stimulation, as well as computer models linking recordings between them.

## THE SPINAL CIRCUITS UNDERLYING LOCOMOTION

### PROBING DYNAMIC SENSORY-MOTOR INTEGRATION IN SPINAL CIRCUITS

Secondary domain: Molecular and cellular biology

- Team leader: Claire Wyart

- Principal investigators: Claire Wyart, Pierre-Luc Bardet, Hugues Pascal-Mousset

- 6 Post-docs, 1 engineer, 4 PhD students

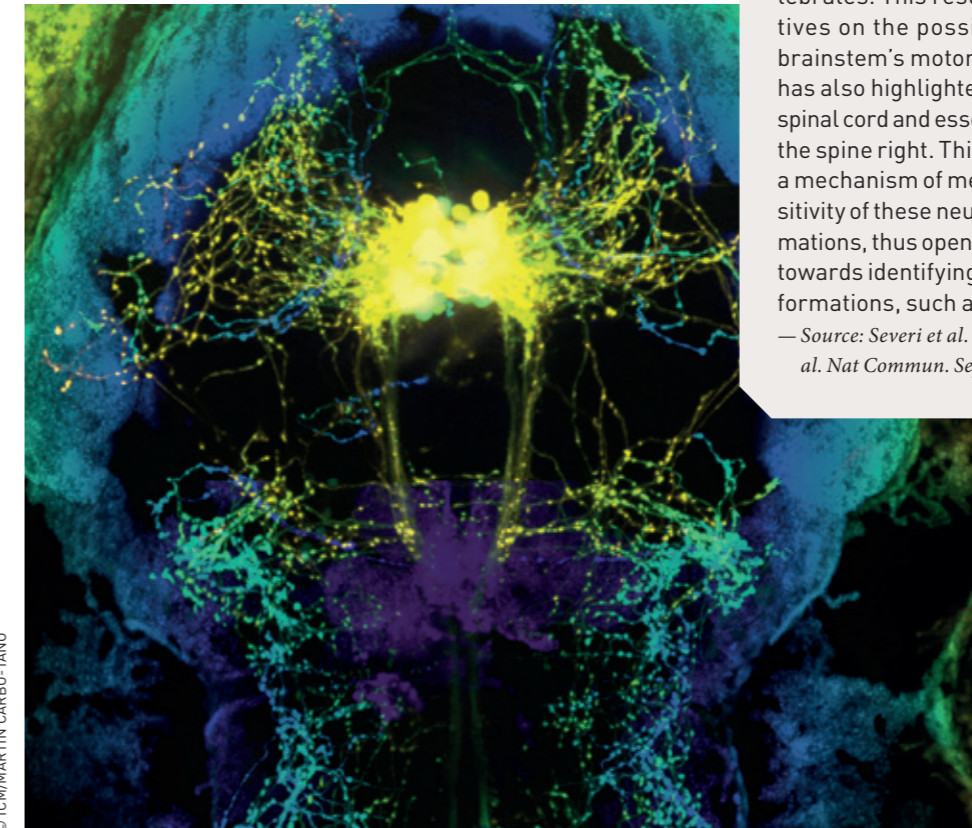
- Competitive funding obtained in 2018: HFSP, EMBO, MSCA-ITN/ETN, ERC PoC, ANR-MRSEI

### Locomotion and support of the dorsal axis

#### #LOCOMOTION

Claire Wyart's team identified, within the zebrafish's brainstem, inhibitory neurons that are essential for locomotion control of vertebrates. This result opens many perspectives on the possible role of inhibition in brainstem's motor control areas. The team has also highlighted neurons specific to the spinal cord and essential in adults to maintain the spine right. This reveals the existence of a mechanism of mechanoreception, i.e. a sensitivity of these neurons to dorsal axis deformations, thus opening new paths of research towards identifying the causes of spine malformations, such as idiopathic scoliosis.

— Source: Severi et al. *Sci Rep*. Sep 2018; Sternberg et al. *Nat Commun*. Sep 2018



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## GENETICS AND PHYSIOPATHOLOGY OF EPILEPSY

Secondary Domain: Clinical and Translational Research

- Team leaders: Stéphanie Baulac & Éric Leguern

- Principal investigators: Stéphanie Baulac, Éric Leguern, Christel Depienne, Michel Baulac, Cyril Mignot

- 4 post-doc, 2 engineers & technicians, 3 PhD students

- Competitive funding obtained in 2018: FMR (rare diseases)

### “Brain-specific” mosaic mutations in focal epilepsies associated with brain malformations

Focal epilepsies are localized in a restricted area of the brain. The DEPDC5 gene is a major gene in familial forms of this type of epilepsy. It intervenes upstream of the mTOR signaling cascade which controls in particular cell proliferation and growth and regulates brain development. These epilepsies may be associated with brain malformations, focal cortical dysplasias (FCD). A study conducted by Stéphanie Baulac's team highlights, for the first time in patients with focal epilepsies associated with cerebral malformations, the development of a mutation of the DEPDC5 gene present only in the cells constituting the seizure focus in the brain. These highly localized mutations that are not present in all the cells of the body are called mosaic mutations.

Source: Ribierre et al. *J Clin Invest*. Apr 2018

### LEXICON

AFM: French Association against myopathies

ANR - JPND: National Agency for Research - Joint programme neurodegenerative diseases

ANR - PRC: National Agency for Research - collaborative research projects between public entities in a national context

ANR-MRSEI: National Agency for Research - Setting up European or international scientific networks

ANR-PRCI: National Agency for Research - Collaborative Research Project

ANSES: National Health Security Agency

APHP: Public Assistance - Paris Hospitals

ARC: Association for Research on Cancer

ARSEP: Association for Research on Multiple Sclerosis

ARSLA: Association for Research on Amyotrophic Lateral Sclerosis

ASL-HSP France: Strumpell-Lorrain Association / Hereditary Spastic Paraplegia-France

DIM-ELICIT: Domaine d'intérêt majeur - Empowering Life Sciences with Innovative Technologies. Ile de France Region

ENP: School of Neuroscience of Paris

ERC-PoC: European Research Council - Proof of Concept

FRM: Foundation for Medical Research

H2020: Horizon 2020 European Programme

IMI: Innovative Medicines Initiative (Europe)

MJFox: The Michael J. Fox Foundation for Parkinson's Research

MSCA-IF / GF: Marie Skłodowska-Curie Actions - Individual and Global Fellowships (Europe)

NeurATRIS: Translational Research Infrastructure for Innovative Therapies in Neuroscience

NIH: National Institute of Health (USA)

NMSS: National Multiple Sclerosis Society (USA)

OLIGO NATION: American Association for Research on Oligodendrogliomas

RIF: Ile de France region ULM-University Hospital: University of ULM (Germany)



## CELLULAR PHYSIOLOGY OF CORTICAL MICROCIRCUITS

### SYNAPTIC INHIBITION AND SELF-REGULATION OF CEREBRAL CORTEX MICROCIRCUITS

- **Team leader: Alberto Bacci**
- Principal investigators: Alberto Bacci, Joana Lourenco, Laurence Cathala
- 2 Post-docs, 1 engineer, 4 PhD students
- Competitive funding obtained in 2018: Fondation Jérôme LEJEUNE, ANR-PRC, DIM ELICIT

### CELLULAR MECHANISMS IN SENSORY PROCESSING

- **Team leader: Nelson Rebola**
- Principal investigators: Nelson Rebola, Annunziato Morabito
- 1 PhD student
- Competitive funding obtained in 2018: NARSAD, DIM ELICIT

#### Unveiling the dynamics of brain plasticity

##### # BRAIN PLASTICITY

Brain plasticity, the dynamic process taking place in our brain as we learn from our experiences, varies greatly with age. Plasticity, essential in the course of development to integrate all kinds of experiences and skills, must be partially inhibited to consolidate our internal model of what we see, hear or experience. A study conducted by Alberto Bacci's team identified the mechanism underlying a reactivation of cortical plasticity that depends on peri-neuronal nets (PNNs). The results of the study suggest that after the necessary period of plasticity, the basket cells generate PNNs to protect themselves from the strong signals coming from the thalamus and thus inhibit the plasticity.

This discovery could have major implications in certain pathologies characterized by a disturbance of sensory perception such as schizophrenia or autism. Indeed, studies have shown a deficit of PNNs around the basket cells in these pathologies. Studying the role of these peri-neuronal nets in more detail could enable researchers to develop new treatments for these disorders. More generally, this would pave the way for a better understanding of the mechanisms by which cortical circuits lose their ability to form new connections and thus how we learn and store information in our memory.

— Source: Faini et al. *Elife*. Dec 2018

## DYNAMICS AND PATHOPHYSIOLOGY OF NEURAL NETWORKS, EPILEPSY

### EXCITABILITY AND DYNAMICS OF NEURONAL ASSEMBLIES

Secondary Domain: Clinical and Translational Research

- **Team leader: Stéphane Charpier**
- Principal investigators: Stéphane Charpier, Séverine Mahon, Mario Chavez, Vincent Navarro, Michel Le Van Quyen.
- 8 Post-docs, 1 technician, 2 PhD students
- Competitive funding obtained in 2018: PHRC

### CORTEX AND EPILEPSY

Domaine secondaire : Recherche clinique et translationnelle

- **Team leader: Richard Miles**
- Principal investigators: Richard Miles
- 5 Post-docs

#### Dynamics of brain immune cells in epilepsy

##### #EPILEPSY

Richard Miles' team brings new information on the variations of microglia, the immune cells of the central nervous system, in the epilepsy of the frontal lobe of the brain. They reveal the versatility of the characteristics of microglia in response to their environment: either in a region devoid of neurons or after an epileptic seizure.

— Source: Morin-Brureau et al. *Brain*. Dec 2018

## BASAL GANGLIA AND MOVEMENT DISORDERS

### NORMAL AND ABNORMAL MOTOR CONTROL: MOTOR DISORDERS AND EXPERIMENTAL THERAPIES

Secondary Domain: Clinical and Translational Research

- **Team leaders: Marie Vidailhet & Stéphane Lehericy**
- Principal investigators: Marie Vidailhet, Stéphane Lehericy, Charlotte Rosso, Yulia Worbe, Pierre Pouget, Isabelle Arnulf, Emmanuel Roze, Andréas Hartmann, Sabine Meunier, Emmanuelle Apartis-Bourdieu, Smaranda Leu-Semenescu, Elodie Hainque, Nadya Pyatigorskaya, Alexandra Petiet.
- 2 Post-docs, 2 engineers & technicians, 5 PhD students
- Competitive funding obtained in 2018: H2020, ANR-JCJC, ANR-PRC, FRM

### BEHAVIOR, EMOTION AND BASAL GANGLIA

Secondary Domain: Clinical and Translational Research

- **Team leader: Luc Mallet**
- Principal investigators: Luc Mallet, Éric Burguiere, Philippe Domenech, Jérôme Yelnik, Karim N'diaye, Christiane Schreiweis.
- 1 engineer, 4 PhD students
- Competitive funding obtained in 2018: ANR-PRCI, Fondation Fondamental

### EXPERIMENTAL NEUROSURGERY

Secondary Domain: Clinical and Translational Research

- **Team leader: Brian Lau**
- Principal investigators: Brian Lau, Carine Karachi, Éric Bardinet.
- 5 Post-docs, 1 engineer, 3 PhD students, 1 Clinical research associate
- Competitive funding obtained in 2018: Fondation de l'avenir

#### LEXICON

**ANR - JCJC:** National Agency for Research - Young Researchers  
**ANR - PRC:** National Agency for Research - collaborative research projects between public units in a national context  
**ANR-MRSEI:** National Agency for Research - Setting up European or international scientific networks  
**ANR-PRCI:** National Agency for Research - Collaborative Research Project  
**DIM-ELICIT:** Domaine d'intérêt majeur - Empowering Life Sciences with Innovative Technologies. Ile de France Region  
**EMBO:** European Molecular Biology Organization

**ERC-PoC:** European Research Council - Proof of Concept  
**FRM:** Foundation for Medical Research  
**H2020:** Horizon 2020 European Programme  
**HFSP:** Human Frontier Science Program  
**MSCA ITN / ETN:** Marie Skłodowska-Curie shares Innovative training networks / European Training Networks  
**NARSAD:** National Alliance for Research on Schizophrenia & Depression  
**NARSAD:** National Alliance for Research on Schizophrenia & Depression  
**PHRC:** Hospital Clinical Research Programme

#### Deep brain stimulation in myoclonic dystonia

##### #DYSTONIA #DEEP BRAIN STIMULATION

Myoclonus dystonia is a rare disease that usually begins in childhood or adolescence and results in two types of symptoms: muscle twitches (myoclonus) and abnormal posture of certain parts of the body (dystonia). This pathology usually also goes with various neuropsychiatric symptoms such as anxiety disorders or obsessive-compulsive disorders. This whole clinical picture often leads to difficulties of social adaptation, which is a source of suffering for patients. A study conducted by Zuzana Kozutska in the team of Marie Vidailhet and Stéphane Lehericy, showed the long-term benefit (more than 10 years of follow-up) of deep brain stimulation in the internal globus pallidus, a structure of basal ganglia in a particular form of dystonia, myoclonus dystonia, with an excellent improvement of motor functions and social adaptation.

— Source: Kosutzka et al. *Mov Disord*. Oct 2018

#### Respiratory behaviours in REM (rapid eye movement) sleep reflect mental content in lucid dreaming narcoleptics

##### #SLEEP #BRAIN FUNCTIONNING

What if it was possible to communicate with the dreamer about his dream experience at this very moment s.he was living it? A bit like communicating for the first time with an explorer describing his encounter with an unknown territory. This is the bet Isabelle Arnulf and her collaborators at the ICM won, thanks to lucid dreamers who managed to dream apnea, to signify it to researchers and to induce consequently a real respiratory change. This major advance realized with narcoleptic subjects and lucid dreamers will make it possible to study the mechanisms of breathing during sleep, the cognitive functions of paradoxical sleep and dreams, to collect data deemed not collectable, to better understand the functioning of the brain and ultimately to discover a brain signature of the dream.

— Source: Oudiette et al. *Sci Rep*. 2018 Feb.

# COGNITION DOMAIN

The teams working in this domain combine structural, electrophysiological and functional studies to understand how neural networks function across the whole brain and their importance in establishing behaviours and cognitive processes in healthy subjects and in patients with neurological and psychiatric disorders

## CONSCIOUSNESS, LANGUAGE

### PHYSIOLOGICAL INVESTIGATION OF CLINICALLY NORMAL AND IMPAIRED COGNITION

Secondary Domain: Clinical and Translational Research

- **Team leaders: Paolo Bartolomeo, Laurent Cohen & Lionel Naccache**
- Principal investigators: Paolo Bartolomeo, Laurent Cohen, Lionel Naccache, Jacobo Sitt
- 7 post-docs, 1 technician, 7 PhD students
- Competitive funding obtained in 2018: ANR-PRC

#### What do the blind see?

#VISION #BRAIN PLASTICITY

About one-third of the cerebral cortex, located furthest back in the brain, is dedicated to vision. In this region we find the area that receives the information coming from the eyes, but also all the specialized areas concerned with the identification or the location of the objects. But what is the use of all these areas for people who have never seen anything, like people blind from birth? A study conducted by Laurent Cohen and Sami Abboud shows a major reorganization of the brain in persons blind from birth, whose visual cortex takes on cognitive functions unrelated to vision. This is a remarkable example of plasticity, illustrating the brain's ability to reorganize itself functionally in an unusual situation, where a whole part of the brain is not fed by the type of information it usually receives.

— Source: Abboud et al. *Cereb Cortex*. Jan 2019

## DIRECTED BEHAVIOURS, MOTIVATION

### MOTIVATION, BRAIN AND BEHAVIOUR

Secondary Domain: Clinical and Translational Research

- **Team leaders: Mathias Pessiglione, Sébastien Bouret & Jean Daunizeau**
- Principal investigators: Mathias Pessiglione, Sébastien Bouret, Jean Daunizeau, Fabien Vinckier, Raphaël Le Bouc
- 3 Post-docs, 7 PhD students
- Competitive funding obtained in 2018: FRM, Pierre DENIKER Foundation

#### How our mood influences our decisions

#BEHAVIOUR #DECISION MAKING #MOOD

A study conducted by Fabien Vinckier identified, thanks to a computational approach, two key regions of the brain intervening in the variations of the mood and consequently on decision making. The response, at both brain and behavioural levels, is not linked to a punctual event but rather to a slower kinetics of events accumulated over time that can therefore be compared with the actual fluctuations of mood. It remains to determine to what extent this model could account for normal fluctuations but also pathological fluctuations in mood, such as those observed in patients with bipolar disorder. A better understanding of the neurobiological basis of mood disorders, may eventually allow the emergence of new therapeutic strategies.

— Source: Vinckier et al. *Nat Commun*. Apr 2018

## SOCIAL AND AFFECTIVE NEUROSCIENCE

### SOCIAL AND AFFECTIVE NEUROSCIENCE

Secondary Domain: Clinical and Translational Research

- **Team leaders: Nathalie George & Philippe Fossati**
- Principal investigators: Nathalie George, Philippe Fossati, Liane Schmidt, Bruno Millet, Jean-Yves Rotge, Hilke Plassmann
- 4 PhD students
- Competitive funding obtained in 2018: ANR, AP-HP Foundation

#### The anatomy of our brain predicts our food choices

#NEUROANATOMY #BEHAVIOUR

Rather chocolate cake or steamed vegetables? Difficult to always eat healthy! A study led by Liane Schmidt and Hilke Plassmann establishes a link between the anatomy of certain regions of our brain and the ability to control food choices. This work shows for the first time that interindividual differences in the neuroanatomy of the prefrontal dorsolateral (dlPFC) and prefrontal ventromedial (vmPFC) regions play a role in the ability to make healthy dietary decisions. These results open up prospects for a better evaluation and perhaps for the treatment of eating disorders such as bulimia or anorexia, but also to help fight the progression of obesity.

— Source: Schmidt et al. *The Journal of Neuroscience*. June 2018

#### Testosterone and consumption preferences in men

#DECISION MAKING #BEHAVIOUR

A recent study conducted by Hilke Plassmann shows that testosterone, a male sex hormone, increases men's preference for products associated with higher social status rather than products with similar perceived quality but associated with a lower status. Although the study shows that the consumption of positional goods is partly motivated by biological factors, it should not be forgotten that cultural differences may play a role in the biological foundations of status-related behaviour and that the external signs of a status are not universal. These results provide the first theoretical insights into a biological basis for preference for products associated with high status. They need to be reproduced and generalized in other populations.

— Source: Nave et al. *Nat Commun*. Jul 2018

## ROLE AND ORGANIZATION OF THE PRE-FRONTAL CORTEX

### FRONTAL SYSTEMS: FUNCTIONS AND DYSFUNCTIONS

Secondary Domain: Clinical and Translational Research

- **Team leaders: Bruno Dubois & Richard Levy**
- Principal investigators: Richard Levy, Bruno Dubois, Harald Hampel, Michel Thiebaut De Schotten, Antoni Valero-Cabre, Emmanuelle Volle, Lara Migliaccio, Bénédicte Batrancourt, Marc Teichmann
- 5 post-docs, 6 PhD students
- Competitive funding obtained in 2018: ERC-Consolidator, Pierre DENIKER foundation, FRM, Fondation Recherche Alzheimer

#### The hidden face of brain lesions

#BRAIN INJURIES #PREDICTION

What is the effect of brain injury on brain connections? Is there a link between the patients' symptoms and the interruption of brain connections due to lesion? To find out, the group of Michel Thiebaut de Schotten has developed software to observe changes in brain connections, impossible to observe on the MRI. In the long term, this tool would allow understanding the functional mechanisms of the brain and predicting the symptoms of brain-damaged patients.

— Source: Foulon et al. *GigaScience*. Feb 2018.

#### Compensation mechanisms in subjects with Alzheimer's lesions

#ALZHEIMER #PREDICTION

The INSIGHT study, led by Bruno Dubois's team, aims to observe subjects over the age of 70, who are healthy and without cognitive impairment, in order to identify early markers of the onset of Alzheimer's disease. The results of this study at 30 months of follow-up show that the presence of amyloid lesions, specific to this disease, has no impact on the cognition and behaviour of the subjects who carry them. This suggests the existence of compensatory mechanisms in subjects with Alzheimer's disease lesions to maintain their intellectual abilities and in particular the memory.

— Source: Dubois et al. *Lancet Neurology*. Feb 2018

#### LEXICON

**ANR - PRC:** National Agency for Research - collaborative research projects between public units in a national context  
**ERC-Consolidator:** European research council- Consolidator  
**Pierre Deniker Foundation:** For Research and Prevention in Mental Health  
**FRM:** Foundation for Medical Research



# CLINICAL AND TRANSLATIONAL DOMAIN



The goal of clinical and translational research is to enable the development of prediction or evolution markers and therapeutic solutions for neurological and psychiatric diseases: from their identification on simple models within laboratories, to patient trials at the Clinical Investigation Center at the ICM and throughout the Institute's clinical scope. We are talking about a cross-disciplinary, interdisciplinary field, with 18 teams attached to it in second instance. Clinical and translational research involves more and more computational neuroscience that is the joint analysis of clinical and biological data, and therefore requires the development of new mathematical and statistical approaches, neuroinformatics.

## ALGORITHMS, MODELS AND METHODS FOR IMAGES AND SIGNALS OF THE HUMAN BRAIN

- Team leaders: Olivier Colliot & Didier Dormont
- Principal investigators: Olivier Colliot, Didier Dormont, Stanley Durrleman, Fabrizio De Vico Fallani, Stéphane Epelbaum, Benjamin Charlier.
- 4 post-doc, 5 engineers, 16 PhD students
- Competitive funding obtained in 2018: H2020

### The "heart" of brain connections

#### #NETWORKS

Our brain is made up of a set of regions, connections and networks. Our cognitive and motor skills are the result of the different functionalities of these regions integrated into a complex network. Each region does not act in isolation but needs to integrate information effectively. A study conducted by Fabrizio De Vico Fallani (Inria) at the ICM, brings, through an innovative mathematical approach, new data on the organization of connections in our brain and their organization from the heart of the brain to the peripheral brain regions.

— Source: Battiston et al. *J R Soc Interface*. 2018 Sep

### Towards more reproducible research in artificial intelligence for medicine

#### #DIAGNOSTIC #ALZHEIMER

Being able to reproduce the obtained results is a major issue in biomedical research, and an essential step in drawing lasting conclusions from them. The ARAMIS team, led by Olivier Colliot and Stanley Durrleman, has developed a set of software tools allowing reproducibility in the evaluation studies of medical decision support system. At present, this software is intended for the analysis of anatomical MRI and PET (positron emission tomography) data, essential diagnostic tools for Alzheimer's disease. The researchers wish to continue developing the software platform and extend it to other types of data but also to other pathologies such as Parkinson's disease.

— Source: Samper-González et al. *Neuroimage*. Dec 2018

## CROSS-DOMAIN CLINICAL NEUROSCIENCE RESEARCH

### New early biomarker in people at risk of developing FTD/ALS

#### #PREDICT #FRONTO-TEMPORAL DEMENTIA

A study conducted by ICM researchers and clinicians identified a new early biomarker in asymptomatic individuals at risk of developing frontotemporal degeneration (FTD) or amyotrophic lateral sclerosis (ALS), as they carry a specific mutation. For the first time, researchers have measured a reduction in neurite density, reflecting the amount of axons and dendrites in specific regions of the brain, in these patients carrying the C9orf72 gene mutation. They also show that this marker is more sensitive than the previously identified standard imaging markers. This advance is very important for this pathology but also for the study of other neurodegenerative diseases in which similar phenomena can be found.

— Source: Wen et al. *J Neurol Neurosurg Psychiatry*. Oct 2018

### Brain regions associated with poor recovery after stroke (CVA)

#### #CVA #RECOVERY

A study conducted by Charlotte Rosso on data acquired by an international consortium highlights several brain regions that, when they are affected by a stroke, are associated with poorer recovery of patient autonomy. This is an important outcome for decision-making in the treatment of acute stroke. These results also focus on the important areas to be preserved or on which to intervene particularly during the re-education to strengthen them and make them functional again. The next step is to confirm this data from a new cohort, thanks to the upcoming opening of a national stroke management database.

— Source: Rosso et al. *J Neurol Neurosurg Psychiatry*. Nov 2018

### A reliable and accessible algorithm for diagnosing states of consciousness from a simple EEG

#### #DIAGNOSIS #STATES OF CONSCIOUSNESS

The clinical diagnosis of conscience disorders can be difficult and requires resorting to complementary examinations of functional neuro-imagery. In a study published in the journal *Brain*, Denis Engemann and Federico Raimondo under the direction of Jacobo Sitt, Inserm researcher at the Brain and Spine Institute, at the Pitié-Salpêtrière AP-HP hospital, propose a new electroencephalography (EEG) tool called "DoC-Forest" (DoC for Disorder of Consciousness and Forest for the name of the algorithm used). Unlike other tools developed so far and reserved for a few expert centres, "DoC-Forest" will be accessible to patients around the world.

— Source: Engemann et al. *Brain*. November 2018

### Encouraging results for therapeutic video games in Parkinson's disease

#### #PARKINSON #SERIOUS GAMES

A pilot study conducted by Marie-Laure Welter shows positive results after the use of a therapeutic video game to rehabilitate disorders of balance and walking in Parkinson's disease. The game, Toap Run, was developed by the LabCom Brain e-Novation, a collaboration between the Genius group and the ICM researchers. Larger clinical trials are still needed, but these early results already reinforce the idea of including these games - which are complementary to the reeducation of practitioners (therapists or physiotherapists) - in care plans.

Source: Nuic et al. *J Neuroeng Rehabil*. Apr 2018



# CENTER FOR NEUROINFORMATICS

## AT THE FOREFRONT OF DATA SCIENCE IN BIOMEDICAL RESEARCH

**ICM's Neuroinformatics Center aims at gathering, analysing, and making our enormous amount of scientific and medical data available to scientists. The center is firmly grounded in an open and multidisciplinary research approach.**

### BIG DATA: A CHALLENGE

Big Data, or data science, is opening new pathways in brain research and is set to provide medical care professionals with an enormous amount of precious, unexploited information. One of ICM's greatest strengths is its ability to collect all types of medical and biological data and "give them a voice" using powerful statistical tools and multidisciplinary collaborations with researchers, engineers, doctors, IT experts, and technicians. Several projects blending genomics, neuroimaging, clinical observation and data science are currently underway and rely on efficient use of artificial intelligence. These projects hope to gain a better understanding of the brain and its diseases as well as improved diagnosis and personalised treatment. Techniques such as whole genome sequencing, cutting-edge imaging (MRI, PET, etc) and electrophysiology generate datasets with millions to billions of variables for a large number of individuals. To achieve useful results and conclusions, data needs to be modelled, combined and analysed. Neuroinformatics is a field tasked with designing, developing and deploying IT and mathematical tools for joint use and processing of all these different types of data. Neuroinformatics makes it possible to develop predictive modelling to anticipate disease onset and evolution, and identify early biomarkers to allow for the earliest care possible before symptom onset. In the case of post-stroke brain lesions, these predictive models have allowed for better understanding of how brain network connections evolve to predict possible after-effects and adapt subsequent therapy.

### THE ICM CENTER OF NEUROINFORMATICS

It is a virtual center aimed at bringing together all those working in research data management and operations, and giving them a shared equipment and software infrastructure to link their data with data from other sources. As such, the center contributes to aligning and sharing best data management practices at ICM and is founded on the idea of research as a partnership and coordination between research, engineering, doctors, IT experts, and technicians.

The goal is to create a great neuroscience research data warehouse. Making this data available on an international level and enabling its use through powerful scientific tools for calculation and statistical analysis will lead to better understanding of the human brain, to new treatment strategies, and the development of decision-making tools for doctors to assist with diagnosis and therapy.

In time, it could provide doctors with new diagnostic and treatment solutions for neurological and psychiatric diseases to provide patients with the right treatment at the right time, depending on their profile and disease progression. It is an investment in the future, towards more targeted and personalised treatment.



# THE ICM'S PLATFORMS

Besides its revolutionary design and its innovative organization, the ICM is also unique in its advanced technological equipment and its high-level experts. The ICM researchers work on different scales: from the molecule (DNA, proteins...) to the person or the cell. For each of these scales, innovative technologies are made available to researchers, clinicians and start-ups. This network of ICM platforms facilitates translational and transdisciplinary research.

## MOLECULAR EXPLORATION

**iGenSeq** offers the necessary equipment for genome sequencing and genotyping of individuals, i.e. the reading of DNA, the genetic information medium. This reading makes it possible to analyze the genome, to detect possible gene mutations and to identify possible associations between these mutations and diseases of the nervous system.

**iVector** offers the opportunity to build molecular tools for gene transfer. These tools notably come from modified, harmless viruses converted into gene transporters. This type of technology is at the basis of gene therapies, which aim to overcome the absence or dysfunction of specific proteins at the origin of certain pathologies.

## CELL EXPLORATION

In the brain, there are of course the neurons that exchange information in the form of electrical and chemical activity in incredibly complex networks, but also other cells, equally essential, working to support neurons structurally and functionally such as oligodendrocytes, microglial cells and astrocytes. These different types of cells are at the heart of the ICM's research. They need to be grown "in vitro" to be more easily manipulated outside the body. Electrophysiology studies, measuring the activity of neurons, are conducted to identify internal deficits of these cells. "Stem" cell cultures, those cells whose fate can be orientated, enable to study brain cells, neurons, oligodendrocytes even though these cells are impossible to collect in humans! Finally, histological studies make it possible to analyze the brain tissues and to highlight cells' anatomy and molecular composition.

**CELIS** offers a very wide range of cellular models, as well as advanced technologies, in order on the one hand to realize experimental projects on brain and spine diseases, and on the other hand to carry out the small molecules screening, looking for drug candidates for these pathologies.

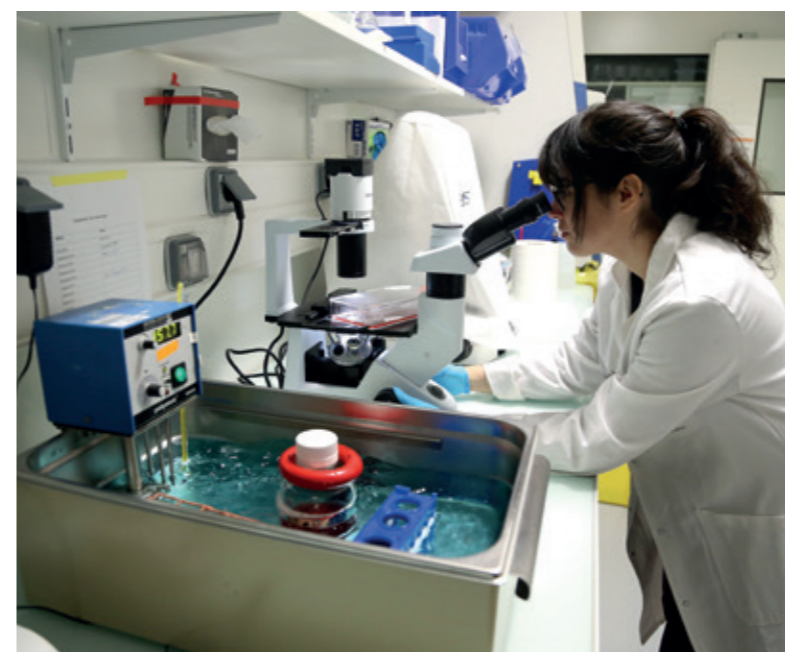
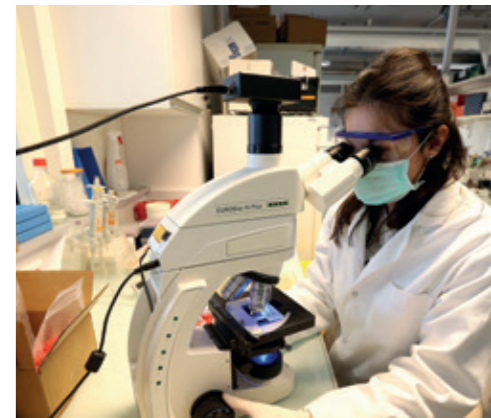
**CELIS-E-PHYS** offers high level services and equipment to record electrical activity (means of communication between neurons) of cells under different experimental conditions (isolated cells, tissue section). This type of data is essential for studies in neuroscience, for the functional characterization of any cell type and the study of the nervous system plasticity.

**CELIS-iPS** provides both a service for the generation of human induced pluripotent stem cells (iPS) and training and advice to cultivate these cells. CELIS-iPS continually innovates to offer new tools and methodologies.

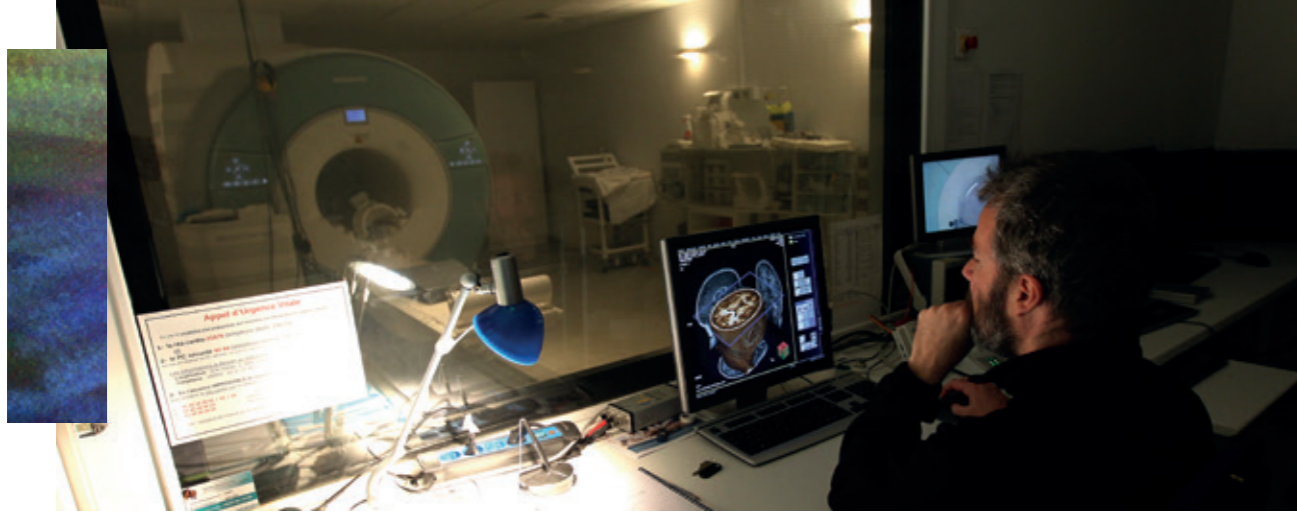
**Histomics** is an open access platform (providing equipment) and services. Histological studies are carried out using specific equipment to cut the tissues (ultramicrotomes, cryostats, freezing microtomes, etc.) and to treat the samples, for example making them transparent for a microscopy study.

## CELLULAR AND MOLECULAR IMAGING

**ICM Quant** allows access to various imaging techniques to observe cells, tissues and whole model organisms: classical microscopy, for the observation of microscopic elements in tissues; videomicroscopy to follow real-time cell movements, and fluorescence microscopy for the observation of molecules, cells or tissue sections thanks to fluorescence phenomenon that highlights the elements that we wish to observe. The latter includes conventional fluorescence microscopy, confocal laser scanning microscopy, bi-photon microscopy, confocal microscopy with rotating disk or transmission electron microscopy with very high resolution to observe the different compartments and components of the cell.







## FUNCTIONAL EXPLORATION

The functional exploration platforms enable to carry out investigations on the living organism (in vivo), in a non-invasive way respecting the integrity of the subject. The research carried out on these platforms is essential to the study of major diseases of the nervous system but also to a better understanding of normal brain function.

### THE CENIR (RESEARCH NEUROIMAGING CENTER)

#### CENIR-MRI Human

The Human MRI component of the CENIR is dedicated to in vivo imaging. With expertise in the fields of neurodegenerative diseases, cognitive neuroscience and image analysis, the CENIR offers academic researchers and industrialists high quality imaging tools for brain and spine research.

#### CENIR-MEG/EEG

The activity of Magneto and Electroencephalography (MEG/EEG) focuses on the development of non-invasive methods that allow the visualization of brain activity with a time precision on a millisecond time scale. Thanks to this equipment, it is possible to follow the information flow between different brain areas for normal or pathological processes such as neurological or psychiatric diseases. The platform team provides methodological support for developing and conducting clinical or basic research and analyzing the data obtained.

#### CENIR-PANAM

CENIR-PANAM has a double mission:

- A therapeutic mission through non-invasive brain stimulation in neurological and psychiatric diseases;
- A research mission such as the study of motor control, including gait and balance, in patients with neurological diseases;

Its specificity is multidisciplinary with the coupling of different techniques (electrical or magnetic transcranial stimulation) to associate changes in brain activity to a motor or cognitive behaviour.

#### CENIR - PET IRM

Within this structure, human brain imaging is performed using a PET-MRI, a new generation of hybrid cameras capable of simultaneously performing Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). It is thus possible to use harmless "radioactive" markers to observe particular molecules in the brain, combined with MRI. This platform is a tool of very high performance in the field of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS or multiple sclerosis, and neuro-oncology, for research, diagnosis and therapeutic monitoring.

#### CENIR-STIM

CENIR-STIM provides analysis and software development support from stereotactic imaging data (3-dimensional identification of internal brain structures) for deep brain stimulation therapies in drug-resistant epilepsies and radio surgery.

#### PRISME

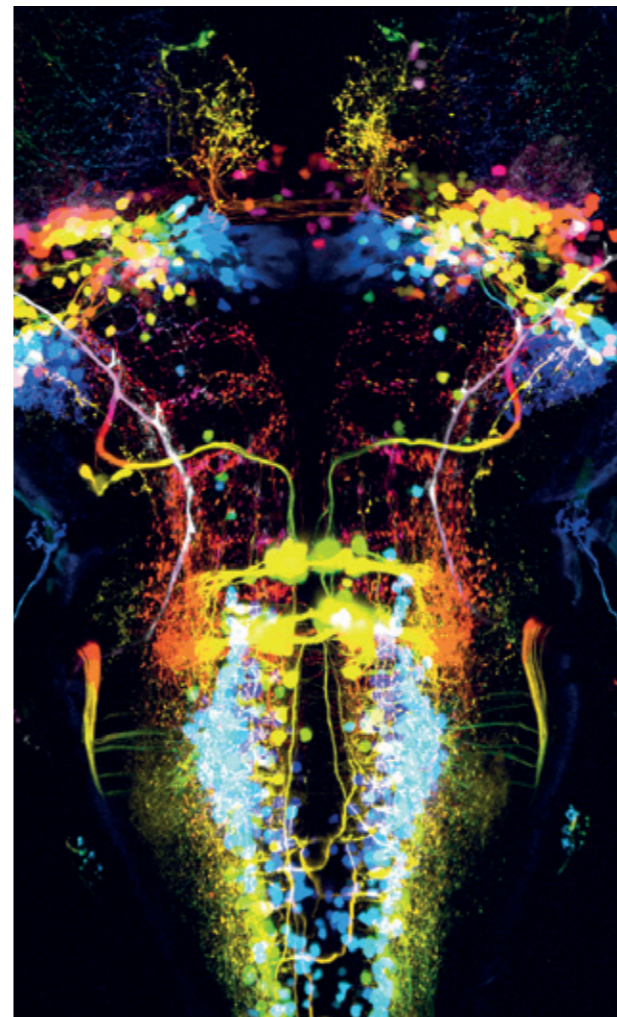
This unique platform is dedicated to study normal human and pathological behaviour thanks to a multitude of tools and sensors available in the laboratory, nearby the patient's bed, outside the walls, at home or in virtual environments (3D). It is also developing new equipment and new therapeutic protocols for neuropsychiatric diseases. One of the strengths of the platform is to be able to test a large number of subjects, under conditions close to real life, so that the results obtained are more representative of the general population.

## PRECLINICAL FUNCTIONAL EXPLORATION

The preclinical functional exploration platform enables the development of scientific projects in experimental models in order to establish essential proof of concept for relevant and safe applied research in patients.

### PHENO-ICMice

### PHENO-ZFish



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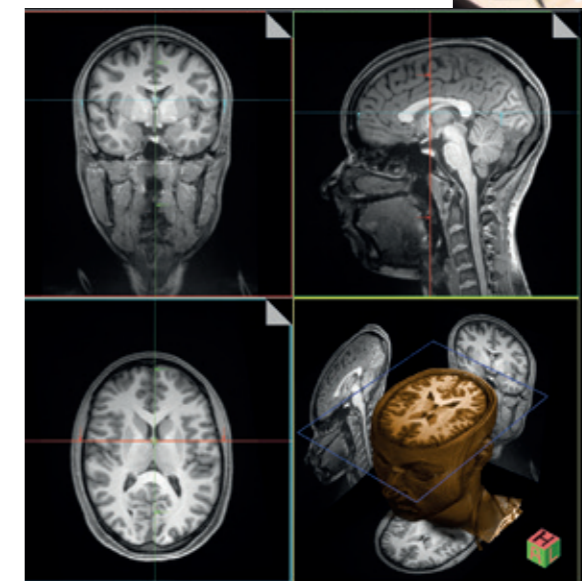
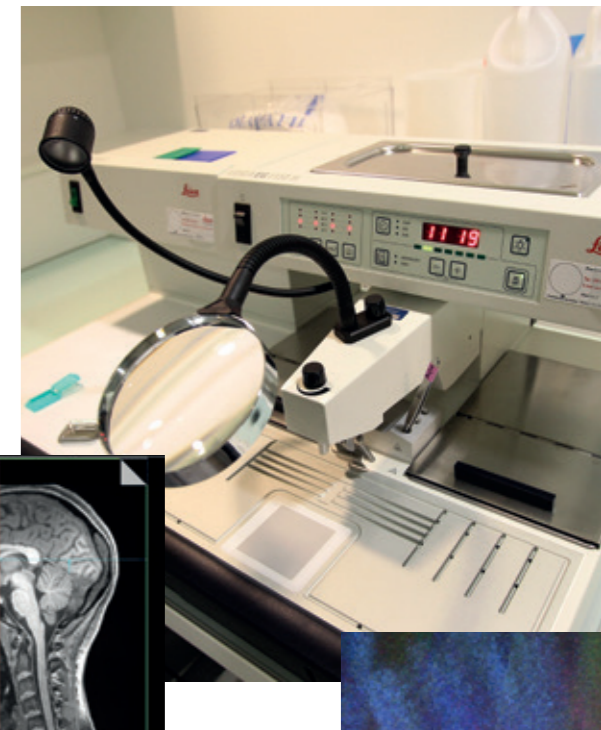
## BIOINFORMATICS AND BIOSTATISTICS

Over the past two decades, neuroscience research has witnessed a dramatic explosion in the number of data collected in laboratories. Gathering observations is one thing, analyzing and understanding them to develop new therapies is quite another. The role of this platform is to collect data from various sources, to store and organize them, so that they can be analyzed and interpreted using complex statistical methods. The iCONICS platform conducts three types of activities. The "Databases and Datawarehouse" activity develops tools to organize and gather information, on a common model, and to make them accessible through searchable interfaces. The "Genomics" division builds and implements processing chains and software for the analysis and interpretation of genetic and omic data (in particular from high-throughput sequencing: transcriptomic, epigenomic). The "Biostatistics" division provides generic support for statistical analysis and designs advanced methodologies for integrating multimodal data (from different studies) on a large scale.

## BIOLOGICAL RESOURCES CENTRES (BRC)

Samples taken from patients during blood tests, biopsies, or surgical procedures are an extremely valuable source of information for research against diseases. The activity of a BRC consists of managing these biological resources (biological samples and associated data), i.e. collecting them, recording them, processing them, keeping them and making them available for researchers.

Created in 1990 and certified according to the NF-S96-900 standard since 2009, the DNA and ICM-cell bank manages biological samples and their derivatives (cells, DNA, plasma, serum, tissues...) of 55,000 people representing 37 pathologies, mostly neurological and psychiatric.





# TECHNOLOGICAL ADVANCES

## ESSENTIAL FOR SCIENTIFIC RESEARCH

The quality of scientific discoveries depends very much on the match between research projects and the evolution of technology. Scientific and operational managers, along with the platform's steering committee, ensure a regular technological watch in order to offer the most efficient equipment and techniques as well as the best-trained personnel.

This permanent adaptation to both technological progress and ICM research requirements led to create research and development calls for tenders dedicated to technological platforms. In 2018, 4 R&D projects were supported and the cellular and

molecular imaging platform restructuring continued. All ICM technological platforms have been evaluated by an international committee of experts to open new avenues for improvement.

### CALLS FOR TENDERS "TECHNOLOGICAL DEVELOPMENT"

**For ICM's platforms to remain at the forefront in their field, technological developments are paramount.**

**Competitive calls for tenders between platforms have been set to support this approach.**

**In 2018, 4 projects were funded.**

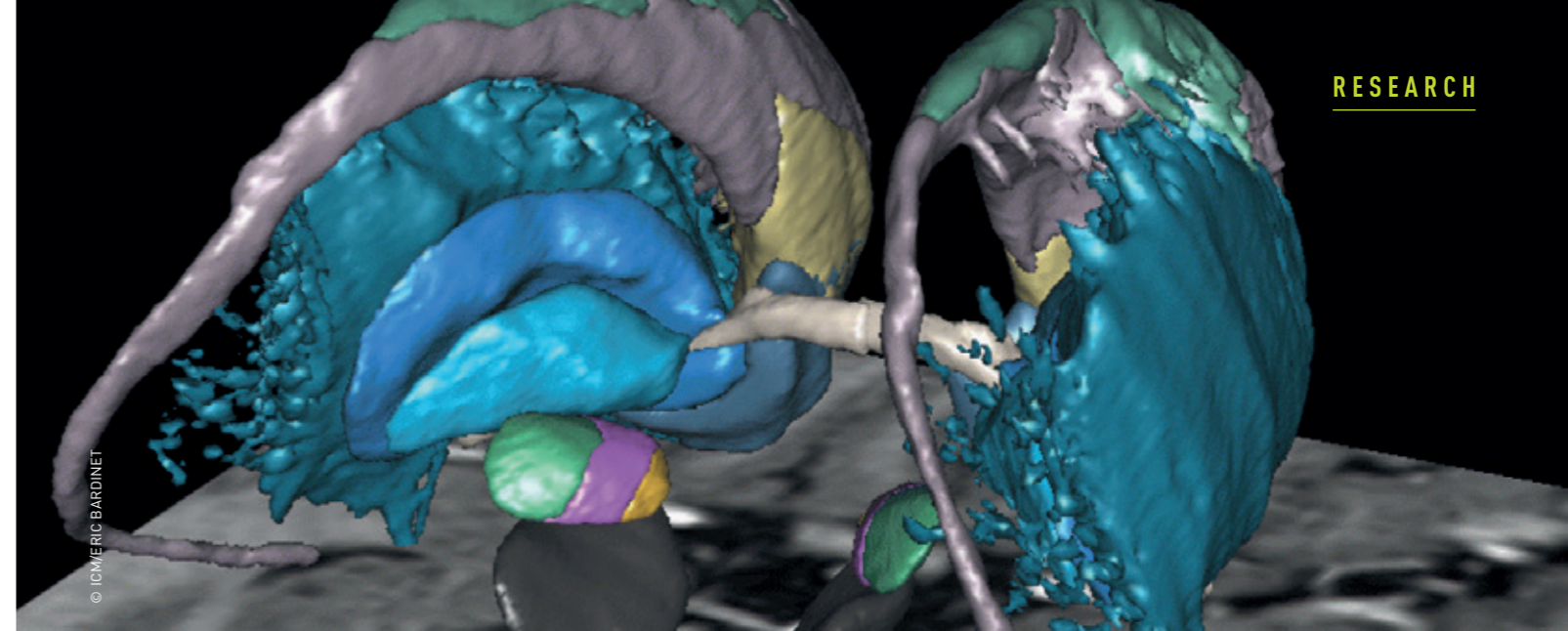
#### **Genetic manipulation by CRISPR/Cas9 in zebrafish**

Zebrafish has become one of the most important vertebrate models to study the role of genetics in development, in body normal and pathological functioning. The Crispr/Cas 9 approaches, also known as molecular scissors, which allow one gene to be replaced by another or to be modified, have radically facilitated genome engineering in various organisms. The possibilities offered by zebrafish make it an optimal option to evaluate the role of genes in the origin of human diseases. The combination of Crispr/Cas 9 technology and transgenesis

(implantation of one or more genes) in zebrafish can modulate the expression of human genes in several neurodegenerative pathologies.

#### **PRISME@Home**

PRISME@Home is part of the development of the PRISME platform and will provide quantitative measures of healthy patients or volunteers' spontaneous behaviour in their real environment, typically at home, over extended periods of time (from days to weeks). This system will include both software specifically developed to provide an easy-to-use interface and a set of connected tools (presence detectors, door detectors...). PRISME@Home will provide an "ecological" assessment of behavioural disorders (obsessive-compulsive disorder, Gilles de la Tourette syndrome, apathy) that may be confronted with evaluations conducted in laboratory or in the semi-ecological environment of the PRISME platform.



#### **Development of a statistical analysis package for magneto and electroencephalography (MEG-EEG)**

The MEG-EEG platform aims to provide software infrastructure and tools as well as scientific and technical support for the acquisition and analysis of MEG-EEG data.

Over the years, the software acquired and developed in-house has evolved to cover the majority of analysis processes. But a number of constraints are not taken into account by the tools currently available. This project aims to develop and extend, in connection with the iCONICS platform, a package dedicated to multivariate statistical analysis of electrophysiology data. It will incorporate advanced and innovative techniques adapted to the structure of MEG-EEG recordings and their experimental design.

#### **CENIR STIM web-services**

So far, the platform's strategy has been to develop advanced tools and provide support for the analysis of stereotactic imaging data that only experienced users are able to use. To overcome this restriction, the objective of this project is to develop a "SaaS" model, "Software as a Service" accessible to all through a web browser. This SaaS will allow simplified access to three tools of the platform:

- The process of characterization of basal ganglia of the YEB Atlas
- Preoperative localization of electrodes and anatomical characterization for deep brain stimulation
- Preoperative localization of electrodes for electroencephalogram exploration procedures in epilepsy

#### **FURTHER RESTRUCTURING OF CELLULAR AND MOLECULAR IMAGING**

In 2018 a new photonic microscopy specialist arrived on the platform: Claire Lovo. Actually she was back at the ICM, since she had already worked there between 2013 and 2015 within the PICPS, the "ancestor" platform of ICM.Quant.

The service of correlative microscopy (CLEM) was implemented in 2018. It was made possible by the acquisition of new equipment, financed by the ICM R&D call for tenders, won in 2017 by Asha Baskaran, engineer in electron microscopy, Serge Marty and Dominique Langui.

The platform's image processing activity has doubled between 2017 and 2018.

In order to meet the increasing demand for the use of inverted confocal microscopes (microscopes that enable to produce series of images to obtain a three-dimensional representation of the observed object), a second machine of this type has been made available to users in 2018. This system allows precise and simultaneous imaging of several fluorochromes (molecule tracers, cell-type markers) and is therefore suitable for live cell imaging.

#### **PLATFORM EVALUATION**

For the first time in 2018, the ICM platforms were evaluated by a committee chaired by Dr. Mike Schelanski, constituted of members of the ICM Scientific Advisory Board (SAB) and ad hoc experts. Following this evaluation, which took place from the 4th to the 6th December 2018, the committee made recommendations and advice to further improve platform performance and strengthen interactions with research teams.



# SUPPORT RESEARCH AND ITS FINANCING NEEDS

Research institutes have dynamically adjusted a financial strategy to better face the ever-changing public financial support constraints and industry environment, where new trends and needs emerge almost daily. The ICM medical and scientific affairs department (DAMS) hosts a unique grants office which provides a range of professional services to the ICM community and is also available to external enquiries to build collaborative proposals with ICM. The DAMS team with a large set of expertise provides assistance in sourcing and engineering national, European and international competitive research grants.

In order to best support the scientific ambitions of our researchers, the DAMS has set several tools:

**ICM Candidates' boost program:**

The team has worked on a scheme to identify that we have the right call for the right researcher. This approach also includes the search for specific prizes, awards, and support coaching for young PIs to apply to MSCA grants or ERC calls.

**Grants Skills training:**

The DAMS offer a full training set with masterclasses on how to write a grant, how to communicate the big picture of a proposal (ERC rehearsals, etc.) and training sessions on grants specific calls: ANR, H2020 collaborative frameworks, ERC, MCSA, NIH, fellowships.

**ICM grants tool box:**

The office is now able to provide full tools for applicants such as proposal templates MSCA; ERC StG, CoG, AdV, proposal check-lists based on evaluation guides, budget templates, partner description templates, information sheets on calls for proposals: ERC, MSCA, H2020 collab., IMI, procedures for application, reporting. The ICM has already developed a full database of call for proposals available to researchers.

**SINCE 2012:**

- 100 ANR national grants,
- More than 300 grants from national Associations-foundations
- 81 grants from public national funding agencies.
- 2 major international awards of 1,5 M\$ each (Allen Distinguished Investigator & New York Stem Cell Foundation Robertson Investigator) have been granted to the ICM researchers.
- No less than 46 renowned international associations' or foundations' grants among them: The Michael J Fox Foundation, National Multiple Sclerosis Society, Simons Foundation, McDonnell Foundation, EMBO, Human Frontier Science Program, etc.

- 7 NIH grants
- ICM has hosted /managed 11 ERC grants + 3 POC as a coordinator (8 are ongoing).
- ICM has managed 14 European collaborative grants (H2020, FP7, HBP...)
- Leader of one Innovative Training Networks (ITN, Zenith 4M€) and a partner of one ITN (Gliotrain).
- 15 ICM post-docs have been granted MSCA individual fellowships.

**85 M€**

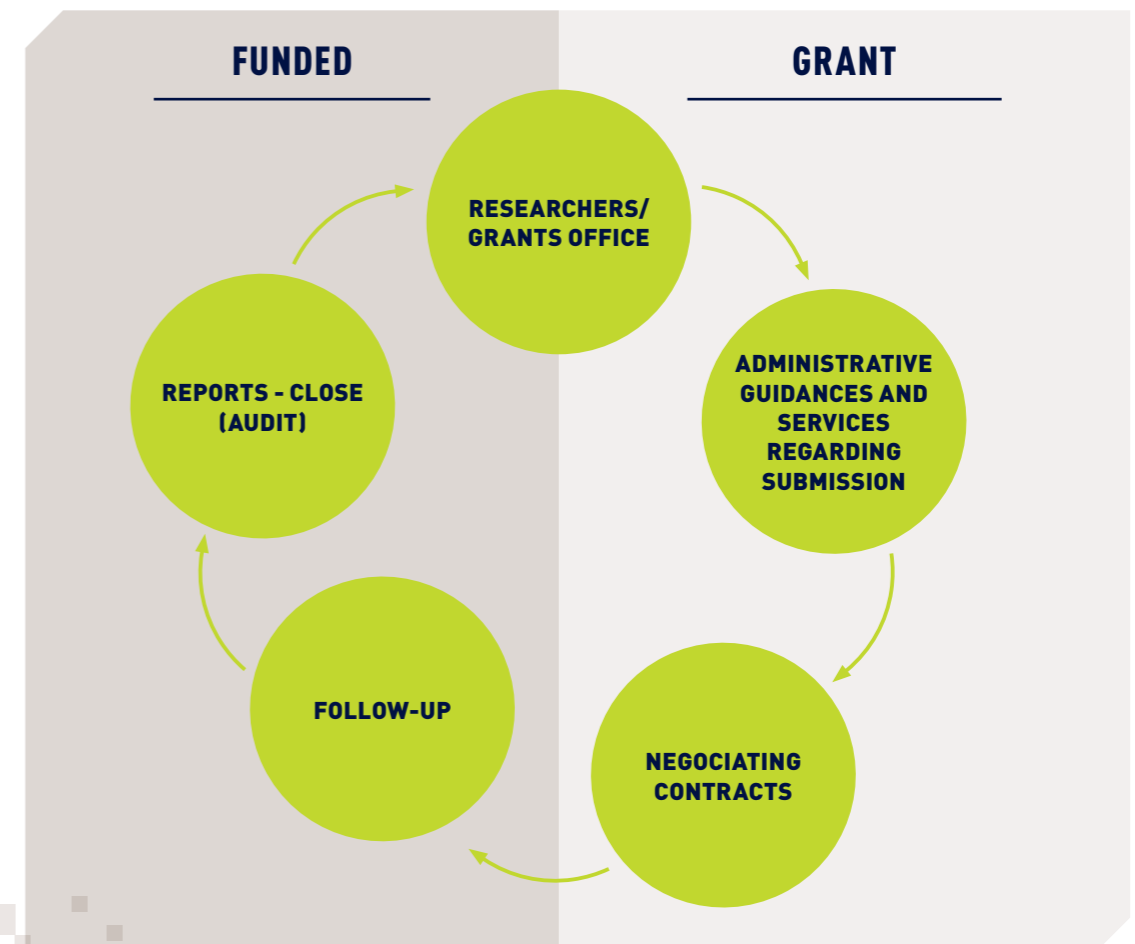
The ICM researchers have obtained 85M€ since 2012 through more than 550 grants

**10 M€**

More than of grant income on average per year

**13,5 M€**

in 2018.





# RESEARCH APPLICATIONS

BY ALEXIS GÉNIN, RESEARCH AND TECHNOLOGY OFFICE DIRECTOR

**“Transforming research into health products”.  
The year 2018 was rich in new inventions by the  
scientists of the Institute!**

**S**urprising results obtained with Brazilian colleagues have shown the interest of a drug in movement disorders associated with Parkinson’s disease. Another small molecule, genuinely new and developed with a research team from Sorbonne University, has also shown an interesting potential in multiple sclerosis. Another one, on which we have worked with one of the companies incubated at the ICM, has interesting effects for the treatment of prion diseases... Each of these discoveries was patented and R&D programmes are underway to validate their medical interest. Meanwhile, 5 other “small molecules” that could become drug candidates are being tested by the Institute research teams, thanks to a new specialised engineer.

**More than ever, the Institute’s  
innovative forces are mustered  
to create new health products  
“Made by ICM”.**

In terms of medical technologies, electroencephalography has produced the most exciting results, with three patents filed on highly innovative methods to quantify state of consciousness variations in hospitalized patients, and to develop what could become one of the most promising solutions



for the early diagnosis of Alzheimer’s disease. Thanks to new acceleration tools created by the Institute, all these projects will deepen in 2019, confirm their potential, be turned into start-ups for some or give rise to new industrial collaborations for others. In 2018, these latter gathered around the ICM actors as diverse as - for large groups - Pfizer, Genentech, Sanofi-Aventis, Abbie, UCB Biopharma, Roche, and - for start-ups and SMEs - Medday Pharmaceuticals, Tactilaptics, Mindmaze, Pathmaker, Scipio, Dynacure, Brainvectis, Minoryx.

These new joint projects will benefit from the expertise of the NEUROTRIALS® industrial clinical development team, which is now operational, and the iPEPS incubator, whose services provision has been further strengthened in 2018.

Finally, 2018 marked the launch of social and solidarity entrepreneurship programmes for the living lab cLLAPS and for the iPEPS incubator, whose goal is to create prevention or care solutions that are quickly accessible to as many people as possible, with costs as low as possible. This approach has resulted in the “Open Brain Initiative” on mental pathologies, launched by the incubator on Station F’s campus, and in the “Making Days” of the living lab. More than ever, the Institute’s innovative forces are mustered to create new health products “Made by ICM”.



# RESEARCH APPLICATIONS

The ICM Research and Technology Office aims to turn the research results into products and new solutions. This department works on 4 main axes.

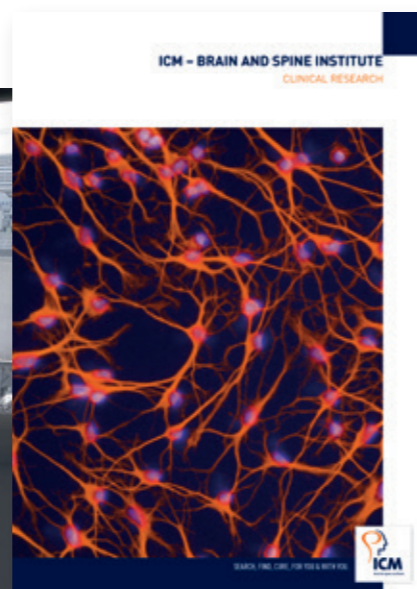


MAIRIE DE PARIS

ile de France

## HIGHLIGHTS

- Recruitment of an engineer dedicated to drug candidates evaluation
- Launch of an acceleration programme in partnership with Pfizer to support 4 digital health start-ups
- Launch of a programme to accelerate 3 start-ups involved in social and solidarity economy focusing on mental health and well-being
- 5 new molecules tested on cellular models
- Participatory Innovation Programme for the daily help of people with Parkinson's disease: 150 participants and 5 partners of the ecosystem for the development of 5 assistive devices
- 20 projects supported by the Institute Prototyping Workshop to develop new technical tools facilitating research and patient support systems
- 8 new projects supported by Living Lab
- Creation of the NEUROTRIALS team for early clinical research
- Publication of a "book" compiling ICM clinical research
- New companies joining the incubator: Ni2O, a start-up from Boston specialized in neurotechnologies and Brainvectis, dedicated to the development of gene therapies.



## BIOTECH UNIT DEVELOPMENT OF NEW DRUGS

### "Drug-hunter doctors and engineers"

In 2018, the Institute launched the "Sleeping Beauties" project, in collaboration with the best laboratories of medicinal chemistry. This enables the rational testing and development of molecules of therapeutic interest in the field of nervous system diseases. Three ICM research teams received funding and expert support from an engineer dedicated to evaluate molecules coming from, among others, the Museum National d'Histoire Naturelle and the Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN).

In terms of industrial collaborations, three ICM projects were selected for the "Sanofi iAwards" and are being funded to initiate a research plan. The selected projects focus on Parkinson's disease (Dr. Olga Corti & Prof. Jean-Christophe Corvol - Dr. Stéphane Hunot) and multiple sclerosis (Dr. Violetta Zujovic).

Other partnerships with major industrial groups have also enabled ambitious research projects to start. Support from the Merck Group, through its MSD Avenir fund, will help Dr. Philippe Ravassard develop a 3D cell culture technology that should facilitate the identification of new therapeutic tracks on Alzheimer's disease.

As for rare genetic diseases, a study conducted by Dr. Frédéric Darios and Dr. Giovanni Stevanin's group highlighted the deleterious role on neurons of the accumulation of certain lipids in hereditary spastic paraplegia type 11. This discovery was patented. In addition, thanks to a French company's support, research collaboration was set up and a young researcher was recruited to continue the project.

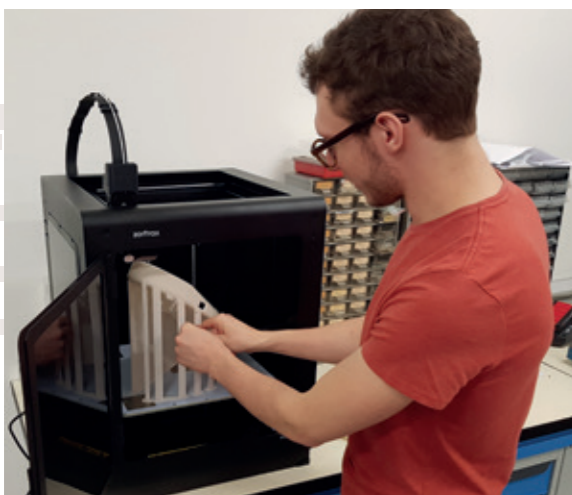
## MEDTECH UNIT DEVELOPMENT OF NEW MEDICAL TECHNOLOGIES

### "Makers" and designers, knights of participatory innovation

Federating all together doctors, paramedics, patients, engineers and designers, the Living lab has brought together 150 people in a participatory innovation approach focused on Parkinson's disease, starting with the analysis of needs and going as far as the production of innovative prototypes. The 2018 innovation programme, carried out in partnership with the France Parkinson association and the STRATE design school (and with the support of the Abbvie company), brought together the entire innovation ecosystem around the creation of technical aids for Parkinson's disease. As a result, five technical solutions were created, which will continue to be developed in 2019. In parallel, a new innovation campaign was launched in January 2019 focusing on the functional rehabilitation after brain injury.







In addition to this programme, the Living Lab is obviously open to all departments of the Nervous system diseases unit, which made two new projects emerge:

1. Neuro-Oncology: emotional mediation device to promote end-of-life support
2. Interdepartmental Sanitary Unit for Temporary Emergency Reception: Toilet Training Device for Children with Advanced Psychic and Autistic Disorders

The Living Lab continues the development of these historical projects, including:

- Physical medicine and rehabilitation: BRO robot and Cognitive Rehabilitation through Therapeutic Cooking;
- Neurology: Lumotics and motivational help to achieve Cognitive and Behavioural Therapies;

Finally 2018 launched an offer of “immersion” in participatory innovation processes. Through different formats fitting their needs, R&D and innovation managers come from different industrial groups to test the field of medical need by learning new methodologies and interacting with start-ups, engineers and healthcare staff. These programmes make it possible to detect synergies with a wide variety of R&D teams in France, to enable the joint development of new medical technologies.

#### PARKINSON INNOVATION PROGRAMME'S PROJECTS

- **Parkin'sound:** A solution to support Parkinson's patients who have difficulty with their voice;
- **Yoo:** A socializing application supporting patient care with the help of their neighbourhood;
- **Postur'up:** A connected object to improve posture and prevent falls;
- **First-Step:** A device to help trigger gait;
- **MMSS:** A support programme through adapted sports activities;



#### CLINICAL CENTRE FOR NEW THERAPEUTIC OPTIONS VALIDATED WITH PATIENTS

##### “Industrial experts’ rigor to measure the effectiveness of new drugs”

Successfully developing new therapies involves knowing how to accurately measure the impact of these therapies on sick persons, to detect the first signals of effectiveness, to identify the profiles of “markers” (in cerebral imaging, in the blood, in behaviour) that will predict the success of a new treatment option in a sick population's sub-category.

This clinical research, conducted for and with the patient, also requires teams of non-medical professionals used to organize the trials, capable of attracting the most promising companies and drug candidates. This is the mission of the NEUROTRIALS team, whose creation was one of the highlights of the year 2018. This organization type CRO (Contract Research Organization) will become the single window for clinical studies called “early” in partnership with health industry. In these studies, which follow the evaluation of drug safety, the goal is to test for the first time the therapeutic effectiveness in humans. NEUROTRIALS will therefore bring a vital operational force to the excellence of the Institute and Pitié-Salpêtrière Hospital clinician-researchers.

A team of seven persons, all from the industrial world, is already created and managing the organization (including the quality system implementation). Through this initiative, the ICM wishes to strengthen its capacity to be a first choice partner in the development of innovative therapeutic solutions, and an accelerator of their development.

#### STARTUPS UNIT INNOVATION IN START-UPS

##### “Doctors and businessmen/women specializing in orbiting innovative companies”

The year 2018 marks a new step in the incubator's development. A partnership was signed up with the pharmaceutical group Pfizer France to operate their “Pfizer Healthcare Hub” acceleration programme. This programme aims to accelerate the development of 4 start-ups in the field of digital health over a period of 9 months based on the interbred resources and expertise of ICM and Pfizer.

In parallel, iPEPS launched its first support programme dedicated to startups in the social and solidarity ecosystem. This first edition selected 3 startups offering mental health and well-being solutions. These will be hosted by STATION F for 6 months and benefit from personalized support provided by the incubator's team and external experts.

The incubator also benefited from the renewed support of the Ile de France Region as part of the call for projects “Paris Region - Incubators 2018-2020”,



#### Prizewinners of the Social and Solidarity Entrepreneurship Programme

- **Agorafolk:** A social network and tools for agoraphobic patients
- **Mila:** A social start-up who proposes re-education through music
- **Bloom Up:** An application for depressive patients monitoring



as well as the French Tech recognition through the label “French Tech Visa” aiming at facilitating mobility of foreign startups within iPEPS.

In terms of startups, Carthera has achieved a 9 million Euros' fundraising to accelerate the clinical development of its SonoCloud ultrasound mini-implant in recurrent glioblastoma and to explore its potential in other neurological indications. Bioserenity moved to Atlanta, USA, to expand its operations and was one of the 100 French companies to receive the “French Tech Pass”, which rewards start-ups with strong commercial growth. Pathmaker finally secured 10 million Euros of funding for its neuro-stimulation device co-developed with the ICM.



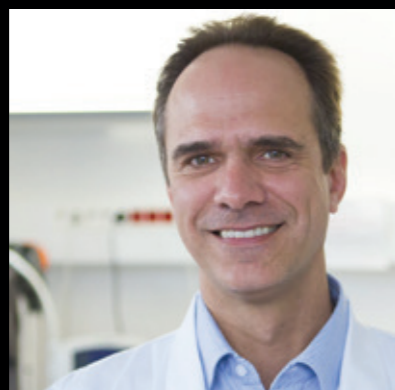
# RESEARCH AND CARE: THE PATIENT AT THE HEART OF ICM'S CONCERNS

BY **PROF JEAN-YVES DELATTRE**, ICM MEDICAL  
DIRECTOR AND DIRECTOR OF THE NERVOUS  
SYSTEM DISEASES UNIT AT  
THE PITIÉ-SALPÊTRIÈRE HOSPITAL,



Our healthcare system is currently in tension but remains considered one of the best in the world. This is true in terms of equity of access to care and our practice confirms this. On the other hand, we are less successful when it comes to the contribution to medical innovation while the big Anglo-Saxon countries provide leadership. Our challenge is to quickly join this innovation leading group while preserving our health system qualities.

AND **PROF JEAN-CHRISTOPHE CORVOL**, DIRECTOR  
OF THE ICM CLINICAL INVESTIGATION CENTRE



In the field of neuroscience, the alliance of the ICM's clinical and scientific forces and its Clinical Investigation Centre together with the Pitié-Salpêtrière hospital group meets this ambition. Every effort must be made to develop this synergy and to enable our patients to access therapeutic innovations as quickly as possible, whether these were conceived at the ICM or in any other major global laboratories. In this perspective, a major effort is currently being made to build up the "missing links" whose absence penalizes access to new therapies.

Research is a source of hope for the patient and for us. It is perfectly justified to think that major therapeutic advances are within our reach! For the doctor, good research is the one that helps his/her patient! We need brains to understand and design

but we also need brains to develop and conduct rigorous clinical trials. If one of these components is missing, there is no progress for the patient. The ICM, through the IHU programme, has become the driving force of clinical research in neuroscience on the Pitié-Salpêtrière site. The ball is in our court and we now have the tools to develop it to its highest potential, as evidenced by the numerous clinical trials conducted each year at the Clinical Investigation Centre. Some of these have produced

**The ball is in our court and we now have the tools to develop it to its highest potential, as evidenced by the numerous clinical trials conducted each year at the Clinical Investigation Centre.**

significant results in 2018, such as the DIG-PD trial on impulse control disorders in Parkinson's disease. New actions carried out by the ICM and the Nervous System Diseases Centre will be crucial to progress further, such as the creation of an ICM clinical research network with iCRIN. The union of the ICM and the Nervous System Diseases Unit has now been established and is about to give a great impulse to clinical research and care, thanks to the commitment of all, and for the best patient care.



# RESEARCH AND CARE: THE PATIENT AT THE HEART OF THE ICM'S CONCERNS

## THE CLINICAL INVESTIGATION CENTRE (CIC), TOWARDS ADAPTED AND PERSONALIZED TREATMENTS FOR EACH PATIENT

The CIC is a clinical research platform at the interface between the ICM researchers, neurologists and psychiatrists from the Nervous System Diseases-NSDs pole of the Pitié-Salpêtrière-APHP hospital. The CIC is also very involved in national and international clinical research networks. It represents an exceptional bridge between research and care and offers innovative treatments to patients affected by neurological and psychiatric diseases.

### EXPECTED RESULTS IN 2019: THE DIG-PD TEST – PARKINSON

Conducted in a cohort of 400 patients with Parkinson's disease followed for 5 years, coordinated by Pr. Jean-Christophe Corvol, this trial showed that dopamine agonists, used for the treatment of the disease, were associated with impulse control disorders, such as gambling addiction, or compulsive eating. A very significant relationship between the treatment dose and the occurrence of the disorders was observed. Since these drugs have proved to be efficient in treating the disease, the authors recommend monitoring the onset of these disorders to potentially consider another therapy.

### AN IMMUNOTHERAPY TRIAL IN PROGRESSIVE SUPRANUCLEAR PARALYSIS (PSP)

PSP is a neurodegenerative disease due to the progressive destruction of neurons from different regions of the brain. An ICM's CIC-coordinated trial was conducted to validate the therapeutic effect of an anti-TAU antibody. The TAU protein abnormally accumulates in neurodegenerative diseases such as PSP or Alzheimer's disease. The test is now completed and the results are expected by the end of 2019.

### THE ICEBERG STUDY - PARKINSON

The ICEBERG\* clinical trial relies upon the assumption that Parkinson's symptoms are only the late signs of a larger set of lesions, whose early-stage biomarkers can be detected. The study conducted on more than 300 patients identified a new marker of the progression of the loss of dopaminergic neuron through an MRI sequence detecting neuromelanin. This protein plays a protective role for neurons by capturing and isolating toxic substances such as iron.

\* with the support of the EDF FOUNDATION

### TRIALS TOWARDS PRECISION MEDICINE AMYOTROPHIC LATERAL SCLEROSIS (ALS)

In partnership with an industrialist, a therapeutic trial is under way in patients with ALS carrying a mutation on the SOD gene. SOD protein is expressed in patients, but in an abnormal configuration it leads to neuronal death. This study investigates the therapeutic role of the antisense oligonucleotides, a small molecule that, by binding to a DNA derivative, RNA, prevents the expression of the mutated SOD protein.



### PROMISING BEGINNINGS SEP BIO PROGRESS (MULTIPLE SCLEROSIS)

This study aims to identify prognostic markers of the evolution of MS, which is highly variable from one patient to another. Researchers and clinicians together analyze biological, MRI, cognitive and eye mobility data. The particularity of this study concerns the included population, consisting of brothers and sisters with multiple sclerosis. To date, 15 siblings have been included, 25 will be involved before the summer of 2019.

### REMINARY VIRTUAL REHABILITATION OF IMMOBILIZED PATIENTS

This trial concerns patients with both one limb immobilized, for example following a fracture of the shoulder, and/or suffering from a neurodegenerative disease, amyotrophic lateral sclerosis. Through mental work, the patient must succeed, in real time, to move the member of a "virtual avatar" on a screen (neurofeedback). Although the immobilized limb does not move "physically", this work activates the neural networks and keeps them in a functional state. The trial is under way on healthy subjects. The inclusion of patients should begin in 2019.

### SPAST TREATMENT OF POST-STROKE SPASTICITY

In partnership with a start-up incubated at ICM PATHMAKER NEUROSYSTEMS INC. and thanks to the technology proposed by the PANAM platform, a therapeutic clinical trial began in 2018. It aims to evaluate the effectiveness of magnetic stimulation of the spinal cord to treat spasticity, spasms and very strong and painful contractures of muscles, observed in some patients after stroke.

### A NEW NATIONAL NETWORK FOR MULTIPLE SCLEROSIS

The FCRIN-4-MS network, coordinated by Céline LOUAPRE (Paris) and Gilles EDAN (Rennes), was created in 2018. This network of experts aims to facilitate access and success of tenders for funding for all clinical research teams working on multiple sclerosis.

*"Clinical trials in France are very constrained at regulatory and administrative levels. This control, essential for patients' protection, considerably increases the time between the filing of a project and the beginning of its implementation. The F-CRIN networks facilitate the implementation of studies thanks to a project manager expert in administrative and regulatory approaches".*

*Céline LOUAPRE, CIC Referring Physician, neurologist and researcher at the ICM.*

### APPLICATION SUPPORT FOR PROMOTION FILES FOR ICM CLINICAL AND THERAPEUTIC TRIALS

In 2018, 2 project leaders, Coraline STEIN for INSERM and Sandrine SAGNES for AP-HP, joined the CIC team.

Before starting, a clinical trial must be approved by a CPP (Committee for the Protection of Individuals) and authorized by the National Agency for the Safety of Medicines (ANSM). The research must be conducted under the direction of an investigator who can be either a competent doctor or qualified persons in the field concerned by the research, and must be supervised and assured by an institutional promoter (INSERM, AP-HP...). The promoter undertakes to ensure that the persons asked to participate in a study are informed about the purpose of the research, its methodology, expected benefits, foreseeable constraints and risks, and the right to stop participating at any moment. Those who agree to participate in the study must sign with informed consent.



## 2018 CLINICAL TRIALS

**76 CLINICAL TRIALS IN PROGRESS**  
**539 NEW PATIENTS INCLUDED**

DOMAIN	NUMBER OF TRIALS	NUMBER OF INCLUSIONS
Amyotrophic lateral sclerosis	6	24
Stroke	3	10
Abnormal movements	31	347
Dementia	5	17
Epilepsy	1	0
Neurogenetics	3	7
Multiple sclerosis	18	114
Neuropsychiatry	5	17
Other pathologies	4	3
<b>Grand total</b>	<b>76</b>	<b>539</b>

### CIC BY THE NUMBERS

- 1 Doctor head of service
- 1 Deputy doctor
- 1 Health executive
- 4 Neurologist doctors
- 2 Neuropsychologists
- 6 Research nurses
- 2 Nursing auxiliaries
- 3 Laboratory technicians
- 3 Project managers
- 4 Clinical study technicians
- 1 Junior hospital doctors in pharmacy
- 1 Statistician
- 6 Clinical research associates
- 6 Hospitalization beds
- 11 Day hospital chairs
- 6 Consultation cubicles
- 1 Laboratory for storage and analysis of biological samples
- 1 Methodological expertise for the development and achievement of clinical studies (identification of patients included in the test, duration of the study, doses used, informed consents, observation books ...)

## THE NERVOUS SYSTEM DISEASES POLE, TO FACILITATE PATIENTS' ACCESS TO THE LATEST THERAPEUTIC ADVANCES

With more than 100,000 consultations per year, the nervous system diseases pole (or the MSN pole) of the APHP is the "hospital side" of the ICM. It includes all the neurology, psychiatry, follow-up care and rehabilitation services, as well as the neurophysiology and neuropathology departments of the Pitié-Salpêtrière hospital group. Diagnose, treat and rehabilitate are the three pillars of its activity.



### TOWARDS THE INVOLVEMENT OF ALL IN RESEARCH, FOR THE BENEFIT OF PATIENTS

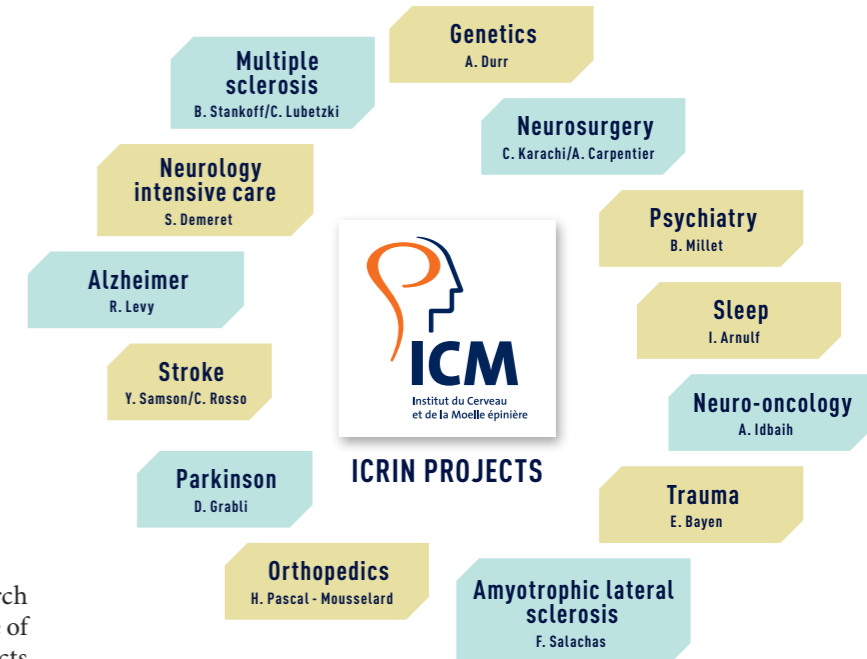
- Clinical research representation at the NSD pole's executive office & the ICM scientific steering committee
- Involvement of young people in research through goal contracts and a project bank
- Implementation of calls for internal project at the NSD pole for young doctors
- Support for paramedical research through the funding of paramedical sciences thesis and paramedical research projects
- Creation of a Methodological Committee
- Creation and continuity of iCRIN calls for projects

### ICRIN : THE ICM CLINICAL RESEARCH NETWORK

The iCRIN's goal for the "ICM Clinical Research Infrastructure Network" is to develop a culture of research right up to care services. A call for projects was launched in spring 2018 in hospital services for thematic medical and paramedical teams. The projects have been evaluated by the ICM Scientific Advisory Board on expertise, performance, quality, visibility and structure. These projects aim to develop interactions and sharing of expertise between NSD pole's actors and ICM research teams. The winners of this call for projects receive the "ICM" label associated with funding to develop their project within the hospital. Out of the 13 projects selected in 2018, 10 received a label of excellence and 3 got an emerging label.

### HOSPITAL RESTRUCTURING: APHP.6

In 2018, the creation of APHP.6 was rolled out, a group of 7 Parisian hospitals: Saint Antoine, Trousseau, Tenon, Rothschild, Roche Guyon, Pitié-Salpêtrière, Charles Foix. This represents 4000 beds and 160 000 hospitalizations a year. All adult medical specialties and paediatrics will be represented. There are also more than 16,000 employees, including 4,600 doctors and 660 professors, who will provide their service every day in this new organization. This project represents a unique potential for clinical research, with a critical mass of patients, cohorts in specific and/or rare diseases. More than 1400 clinical trials are underway with 300 dedicated staff in this group. It's an early access to innovation for thousands of patients every year.



### SUPPORT PARAMEDICAL RESEARCH

Training has been set up to develop research culture within the pole's paramedical teams (nurses, nursing auxiliaries, physiotherapists, psychologists...): it is a matter of arousing in every caring staff members their own research, especially in the field of care or quality of life, and the ICM contributes to their methodological training.

#### Two examples of projects:

- **The Neurosex project** provides patients affected by neurological pathologies with consultations with sexual health nurses. This aims to take care of concerns, difficulties, disorders or sexual dysfunctions of patients with MS (Pr Lubetzki) or glioma (Pr Khe Hoang-Xuan).
- **Docfeeling** is a study led by Pr Naccache aiming to compare the "felt" assessment of nurses about the state of consciousness of patients in a coma and assessment via a medical device. **These works apply the principle of "collective intelligence"**.

*"This work initiated by two nurses of the AP-HP hospital Pitié-Salpêtrière neurological resuscitation unit: Gwen Goudard and Karine Courcoux, and which involved more than 80 caregivers over a period of more than one year, demonstrates extraordinary motivation and huge potential for paramedical research in the unit. The support of service managers, Louise Richard-Gilis and Julie Bourmaleau, and the help of Dr. Bertrand Hermann, Inserm researcher at PICNIC-lab, for data analysis and writing the article, was determining assets to complete the study".*

Dr. Benjamin Rohaut, coordinator of the study.



# EDUCATION

BY ALEXANDRA AUFFRET, DIRECTOR OF MEDICAL AND SCIENTIFIC AFFAIRS

ICM runs, with the support of the scientific and medical affairs department (DAMS), 12 training programs with key achievements.

Since their inception in 2014, the number of programs and participants has scaled considerably with 12 programs enrolling 1500 participants in 2018. The aims of the education program were to provide trainings in state-of-the-art research fields, cutting-edge technologies, to boost clinical and paramedical qualification and sharpen transferable skills. To achieve these goals, we tested a number of pilot programs with major achievements.



Today, ICM sees a great value in putting its 12 programs under one umbrella, refining the focus of training streams, and bringing neuroscience to people and professionals outside of research and medical environments. ICM believes that much of the training that exists in continuing education could gain a lot from neuroscience-based insights and some of ICM's training programs have already been featured in research papers as case studies that prove the pedagogic efficacy of their novel approaches (The Move). We live in a time where there is an ever-growing need for continuous education. Business schools are some of the key players capitalizing on this trend with innovative masters programs in business administration, finance and more. To seize this opportunity, ICM proposes to open up neuroscience education to people outside of research as well as continue developing training for the highly-skilled professionals in research and patient care through the Open Brain School. This School will be a new international leader for neuroscience-based training for students, established researchers, clinicians, paramedical staff and professionals. The long-term goal of the ICM is to contribute to the training of both "neuro-citizens" and neuro-experts. To open neuroscience to people from diverse backgrounds interested in learning more about the brain and its role in our identity and our

behavior and to provide high-quality training to brain researchers, doctors, and medical staff.

One of the reasons for the creation of the Open Brain School is to consolidate and give more visibility to the ICM's educational programs both on national and international levels. The ICM will encourage initiatives within teams and platforms, and partnerships with various par-

## This School will be a new international leader for neuroscience-based training

tners from academia, health and care, consulting firms, incubators, charitable foundations and other types of organizations. As part of the evolution of the ICM's education activities, we have registered educational programs by creating a formal Training Organization (OF). The certification of a training program will allow ICM to deliver a certificate of knowledge, aptitude, or professional competence.

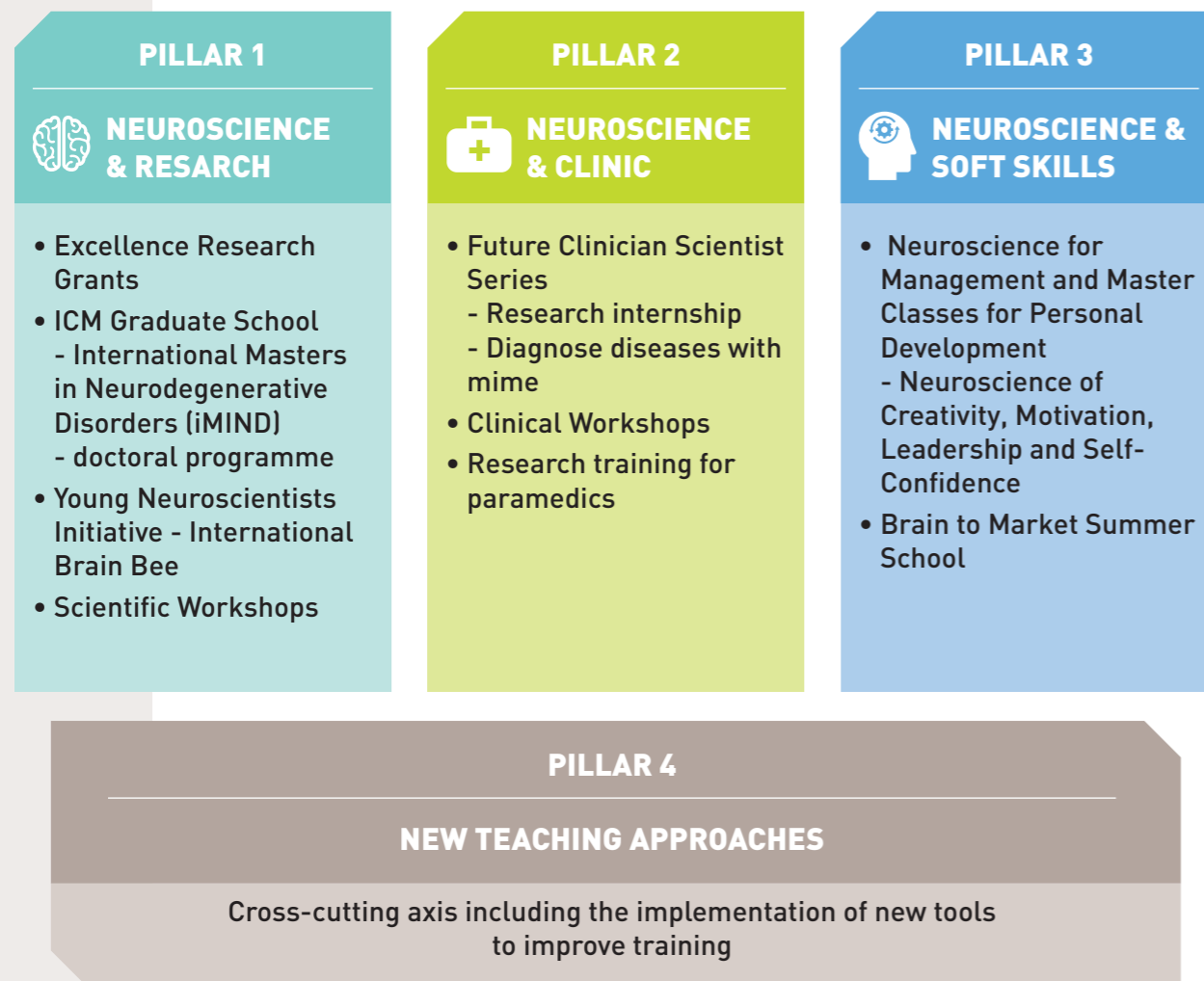


# KNOWLEDGE TRANSMISSION:

## EDUCATION AND TRAINING AT THE HEART OF THE INSTITUTE'S MISSIONS

To share knowledge at national and international levels, the ICM created a training school, the Open Brain School, with the ambition to be a new international leader in neuroscience-based training. The Open Brain School is organized around 4 pillars.

### OPEN BRAIN SCHOOL TRAINING PROGRAMMES



#### PILLAR 1: PROMOTING SCIENTIFIC EXCELLENCE

##### INTERNATIONAL BRAIN BEE PROGRAMME

This programme is an international neuroscience competition for high school students. Brain Bee's mission is to help students learn more about the brain and its core functions, neuroscience research, and misconceptions about brain disorders. The ICM will host the French national Brain Bee competition in April 2019.

##### iMIND INTERNATIONAL MASTER

The iMIND Master is an international and interdisciplinary two-year programme. Built in collaboration with the Sorbonne University and renowned foreign universities (University of Vienna, TUM, KU Leuven), this master's programme is the first of its kind dedicated to neurodegenerative diseases, one of the major societal challenges to date.

Obtaining Sorbonne University's Form'Innov funding accelerated the development of the master's degree with the official opening of M2 registrations in 2018.

#### PILLAR 2: PROMOTING CLINICAL RESEARCH

##### THE MOVE

The Move is an innovative teaching simulation-based programme that uses mime to teach medical students about neurological semiology, i.e. neurological diseases' signs. This programme is a remarkable example of innovation in terms of education. Several publications have focused on its teaching effectiveness, which is now recognized by the College of Teachers of Neurology (the highest authority for neurology teaching in France) for dissemination to all French universities.

In 2018, Vietnam joined the list of countries participating every year in the International Battle organized at the ICM.

##### PROGRAMME FOR PARAMEDICS

A set of programmes was set up to promote paramedical research with article writing workshops, courses in English, research reasoning training, two thesis scholarships and the organization of meetings between international pairs.

#### PILLAR 3: ENCOURAGING INTERDISCIPLINARITY

##### SUMMER SCHOOL: BRAIN TO MARKET

"The Brain to Market" Summer School is an annual programme combining translational neuroscience and entrepreneurial training through an intensive training formula aiming to bring out new projects, new initiatives and new approaches about neurological pathologies. In 2018, the fourth edition focused on Parkinson's disease, and has been taking on a new dimension as part of the innovation chain in close collaboration with the Living Lab and the activities carried out by the iPEPS.

##### SELF CONFIDENCE & LEADERSHIP TRAINING

A programme on leadership and self-confidence was implemented in collaboration with XX initiative. This intensive programme helps develop leadership skills and master communication tools. In 2018, 45 women (PhD students, post-docs, researchers, clinicians, support functions) have already benefited from this programme.

##### MASTERCLASS FOR CAREER DEVELOPMENT OF RESEARCHERS

Throughout the year, DAMS offers various training sessions to ICM researchers to improve their transdisciplinary know-how such as management, communication and the writing of applications for funding.

#### AND TOMORROW

- Maintain and develop Open Brain School by integrating all the institute programmes and initiatives, such as upcoming clinical workshops or training on creativity.
- Pursuing the recognition for these programmes by officially integrating them into training courses (STARE currently on a voluntary basis will be a teaching unit by 2020) and obtaining the certification of our programmes.
- Develop Pillar 4 to implement new teaching methods (MOOC, virtual reality) which will open up development opportunities with the world of EdTech.



# ICM AND ITS INTERNATIONAL NETWORK

At ICM we know that our diversity and strong ties with our collaborators all around the globe can only improve our work and make it more impactful. Our institute brings together a multinational group of people from 43 countries who are committed to advancing brain research.

Every year, ICM works with hundreds of different institutes in many different ways. In 2018, research-wise, ICM worked with institutions from 12 different countries to secure funding from national European, and international sources and our researchers published with collaborators from over 100 different institutions.

Regarding our education initiative, the ICM's Open Brain School hosted over 40 participants from outside of France to participate in its various training programmes and exchange opportunities.

To stimulate constant food for thought, our scientific conferences continue to bring in some of the best researchers in the world. In 2018 ICM was proud to host nearly one international guest lecture every week!



**MNI  
(MONTRÉAL NEUROLOGICAL  
INSTITUTE / MCGILL UNIVERSITY,  
CANADA)**

The MNI is a strong partner when it comes to publications. We have organized together several joint events and have hosted many researchers to advance a variety of topics.

**MIT,  
MASSACHUSETTS  
INSTITUTE OF TECHNOLOGY (USA)**

Every year, the ICM invites MIT students to join one of its research teams for a eight-week long internship. Our common pedagogical approach of learning through practise has rendered this a success year after year. ICM has welcomed 2 students in 2018.

**YALE UNIVERSITY  
(New Haven, USA)**

As an ongoing clinician exchange program, ICM sent two doctors to share their experience and learn from this top notch institution in the US.

**DZNE  
(German Center for  
Neurodegenerative Diseases)**

The DZNE is another long-standing partner of ICM. In 2018, we began planning our next scientific and student workshops with them. Together, our researchers secured funding for 5 prestigious grants in 2018.

**BURDENKO  
(National Medical Research  
Center of Neurosurgery, Moscow,  
Russia)**

**ISTITUTO CARLO  
BESTA (Milan, Italie)**

**UNIVERSITY COLLEGE LONDON  
(United Kingdom)**

UCL is one of ICM's key partners for scientific collaborations. Our institutes stay in close touch and organize regular workshops for our scientists and students. In 2018, ICM was thrilled to host over 40 PhDs and Post-docs from UCL.

**INTERNATIONAL BRAIN  
BEE WORLD CHAMPIONSHIP  
(DAEGU, SOUTH KOREA)**

ICM is proud to host the Brain Bee France, a neuroscience competition for high school students, which will send the winning student to the final competition in Daegu, South Korea.

*NB: Dozens of scientific collaborations are also carried out between other research centers in France and teams within the ICM.*



# LIFE AT THE ICM

## COMMUNICATE AND RAISE AWARENESS OF RESEARCH ON CENTRAL NERVOUS SYSTEM DISEASES

The main objective of the ICM Communication is to develop the image and attractiveness of the ICM in France and abroad.

To carry this out, we build relationships with media, set up partnerships, communication campaigns, events and joint actions with our academic partners (INSERM, CNRS, AP-HP, Sorbonne University, INRIA...).

Sorbonne University, INRIA).

Faced with the Institute's major challenge of treating nervous system diseases, the ICM communicates to:

- Promote and highlight its experts and the results of their work so that they can benefit from international funding opportunities and solidarity support
- Encourage the recruitment of the best experts in all fields of research in order to constantly stimulate a wind of innovation and new know-how
- Report and mobilize donors on the scientific and medical advances of the ICM
- Share and disseminate knowledge to as many people as possible

In addition, the ICM, place of education par excellence, is committed to informing as many people as possible! This is why each year the ICM organizes creative and educational events.

*The research conducted at the ICM benefits from resources from our associative partners and foundations who organize, year after year, and always with passion and hope, events for the benefit of the institute. We thank you sincerely.*

### IN 2018

#### - HEROES RACE ON 17/06

Through this initiative, our day-old heroes help advance brain and spine research. The ICM thanks them for their motivation and renewed support.

#### - AMC ISSOIS - MOTOCROSS ON 01/07

"I would like to warmly thank AMC ISSOIS for joining the ICM for the first time at the international ICM-MX we are proud to participate in. This commitment by our side is one of our great strengths. This gives us the means of our ambitions.

Pr Gérard SAILLANT

#### - CLASSIC DAYS ON 7/07

#### - RARE FAIRY, ON 12 & 13/09

#### - LES ECHOS GOLF TROPHY, ON 20/09

#### - 20KM DE PARIS, ON 14/10



▲ 20KM de Paris, on 14/10

▼ Heroes Race



Classic Days ▶





**- THE "ROUTE DU RHUM" (IDEC GROUP)**  
*"The ICM, whose President, Pr Gérard Saillant, godfather with Jean Todt of the trimaran IDEC SPORT, congratulates Francis Joyon and Patrice Lafargue, CEO of the IDEC group, who have both supported the institute for many years."*

- MUSIC PASSION PARKINSON ON 17/11
- SOLIDAIR'S
- SOGNO DI CAVALLINO

Several times a year, and thanks to the Association Sogno Di Cavallino, car races allow people with disabilities to live a magical and unforgettable moment: that of conducting tests at the wheel of sports and luxury cars.

- EVENING "ARKHELIA'S GOT TALENT" ON 18/12
- LION'S CLUB
- ROTARY CLUBS
- PORSCHE CLUB MOTORSPORT

▲ Soirée « ARKHELIA's got talent »

**- THE BRAIN WEEK**

Every March, the Brain Week takes place, coordinated by the Neuroscience Society. This is an opportunity for the ICM to open its doors and offer to all privileged moments of exchanges with researchers, clinicians, engineers and technicians of the institute through workshops and conferences (800 participants in 2018). A pedagogical and fun path proposes every year to discover the brain and its functioning.



**- THE OPEN BRAIN BAR**

The ICM has created a recurring appointment: the Open Brain Bar, friendly meetings organized every two months, dedicated to medical innovation and the future of health. (In partnership with Sciences & Avenir and Le Figaro).

These events reach audiences outside the walls of the ICM and are aimed at committed citizens who are curious to understand the involvement of science in their daily lives. These events aim to widen the audience to "younger" targets and raise awareness of the major societal challenges caused by neurological diseases.

En 2018 :

- "Multiple Sclerosis: How to measure and prevent the onset of disability?" With Professor Catherine Lubetzki, Violetta Zujovic and Saad Zinai
- "Motivation & Performance – The sportsman/woman, this brain athlete?" With Professor Gérard Saillant, Mathias Pessiglione, Antoni Valero-Cabre, Dr. Jean-François Chermann, Patrice Loko
- "Does power seriously harm the brain?" With Jean Daunizeau and Fabien Vinckier (November) - in partnership with the PARISCIENCE scientific film festival

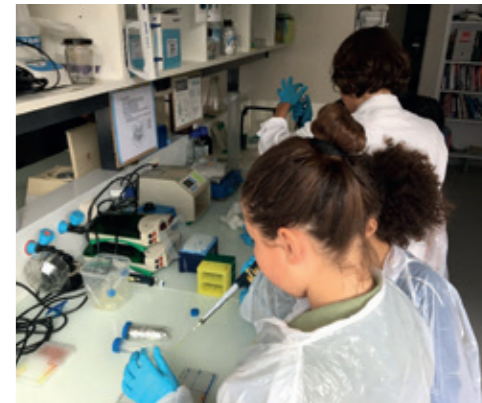
**SCIENCES, ART & CULTURE CONFERENCES**

6 conferences in 2018

- **The metamorphosis of the contemporary personality.** Marcel Gauchet Philosopher and Historian Director of studies at the EHESS and contributor at the review Le Débat
- **The conditions for maintaining life on Earth, currently very threatened by the predatory action of Man.** Gilles Bœuf, Holder the Sustainable Development, Environment, Energy and Society annual Chair. Former President of the National Museum of Natural History, Oceanographer
- **Do the presidential election and the first year of Macron's Presidency allow France to come out of its depression?** Stéphane Rozes, President of Cap (Counsel, analysis and perspectives), teacher at Sciences-po and HEC
- **The third industrial revolution:** from the collaborative economy to biotechnologies. Luc Ferry, Philosopher
- **The yawning brain:** Who? Why? How? Olivier Walusinski, Member of the French Society for Research and Medicine of Sleep. With the participation of Stéphane Lehericy
- **Life at the end**  
 Régis Aubry, Doctor Researcher, President of the National End-of-Life Observatory (ONFV), Coordinator of the national programme for the development of palliative care. Member of the National Advisory Ethics Committee.

**DESTINATION LABO**

As part of the project led by Inserm, we hosted 2 primary classes (CE2 and CM1) and opened the doors of laboratories, an exceptional opportunity to have a taste of the world of science and health research.



**BUDDING RESEARCHERS**

In partnership with INSERM and the Rectorat of Paris, ICM research teams welcome 3e (Year 10) and 1e (Year 12) students. This initiative enables these youngsters to discover research through immersion one Wednesday a month and to participate in projects. In 2018, for the 12th edition, 10 students were welcomed and presented their work to their relatives.



**THE RESEARCH OF ART**

For the first time, the ICM welcomed a young graduate from the Arles National School of Photography, Robin LOBVET, who met researchers from the Institute. This combined perspective between the photographic lens and the scientific world made it possible to highlight the artist's shots, which were exhibited in Arles during the photo festival.





# PATRONAGE, DONATION AND LEGACY

The support of our donors, individuals, corporations, foundations and associations, as well as the one from the general public is essential to enable the ICM to strengthen its research programmes, recruit the best scientists, attract young talents and provide cutting-edge equipment.

## LEGACY, DONATION AND LIFE INSURANCE

Down the road legacies, donations and life insurance will become a major pillar in the resources of the Institute. Our testators notice that the fight to understand the brain and its dysfunctions is still in its infancy. To accelerate research, prevent and cure neurological diseases, bequeath to the 28 teams working at the ICM exclusively on the brain, will make the difference.

2018 was once again marked by the development of bequests and life insurances, 790,000€ against 650,000€ in 2017 (+21%). Life insurance represents 43% of this result, thanks to the simplicity of its implementation and transmission that meets the needs of many individuals. The rest comes from general legacies and special legacies with cash, movables and immovables.

The ICM is officially recognized as “beneficial to the public at large”, and thus benefits from a total exemption from inheritance tax. This means that 100% of what we collect is used to fight against nervous system diseases.

Carole CLEMENT, in charge of the relations with testators coordinates with experts to advise testators and

manage inheritances.

Carole Clément can be reached at 01 57 27 41 41.

## THE PUBLIC COLLECTION

The public collection is an essential component to the functioning of the ICM. With more than 6.7 million Euros collected, the ICM counts on the financial support of the greatest number to help finance the institute as a whole, and through this, the research teams’ work. Day after day, the donations made by the general public allow researchers

to have ever more human, logistical and technological resources, essential to the success of their ambitious projects.

Donors are genuine partners of the ICM, which in return strives to deliver quality, up-to-date and accessible scientific information on a regular basis. Through mobilization campaigns, letters, donors’ journals and thematic conferences, donors remain informed throughout the year of the latest scientific advances, living as close as possible to the progress their commitment to us made possible. On November 2018, the ICM could count on the precious support of the actor Guillaume de Tonquédec, as ambassador of the Découvreurs d’Espoir campaign.

As a Foundation with the official status of “Recognized of Public Utility”, donations to the ICM are deductible for 66% of the Income Tax and 75% of the Real Estate Assets Tax.

The Donors Service can be reached at 01 57 27 47 56.

## PATRONAGE: PHILANTHROPY ACTING FOR RESEARCH

The *Cercle des Amis de l’ICM* brings together the major donors of the institute (individuals, companies, foundations and associations). Throughout the year, members of the circle are offered private laboratory visits, scientific and cultural conferences and meetings with researchers.

## COMMITTED AND GENEROUS PATRONS

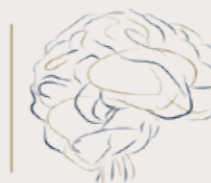
In 2018, the ICM is very proud to have been able to count on the support of particularly generous patrons. The MSDAvenir Fund joins the ranks of the institute’s sponsors by supporting an ambitious research project on Alzheimer’s disease for a period of three years. Also, the Abeona Foundation and Humanis have decided to support the ICM by funding each of the specific research programmes.

## EVENTS SUPPORTING RESEARCH

2018 was marked by the 2nd edition of the ICM Gala, which gathered more than 300 guests at the Pavillon Cambon in Paris. The evening, hosted by Nelson Monfort, raised funds to support the Institute’s researchers, through the sale of tables, donations and the auction chaired by Frédéric Chambre of the Piasa auction house. On this occasion, the prima ballerina, Léonore Baulac, offered the guests a choreographic moment on Camille Saint-Saens’ *Le Cygne*.



CERCLE  
DES AMIS  
DE L’ICM



Lily Safra,

*Honorary President of the Friends of the ICM Committee*

Lindsay Owen-Jones,

*Honorary President of the Friends of the ICM Committee*

Gérard Saillant,

*President of the ICM*

Jean Todt,

*Vice President of the ICM*

Maurice Lévy

*Co-Chair of the Friends of the ICM Committee*

David de Rothschild,

*Co-Chair of the Friends of the ICM Committee*

Jean-Luc Allavena,

Cédric de Bailliencourt,

Jean Burelle,

Sylvain Héfès,

François Henrot,

Jean-Philippe Hottinguer,

Jean-Claude Labruno,

Eddie Misrahi,

Margaux Primat,

Christian Schmidt de la Brélie,

François Thomé,

Isabelle Weill

Serge Weinberg.

*Members of the “Cercle des Amis”  
Comité on December 31st, 2018*

## THE PATRONS

- Jean RENO, Actor  
- Michèle YEOH, Actress

On the 25th September, a dinner in support of the institute was held in Geneva, hosted at its Manufacture by watchmaker F.P.Journe, a major patron of the institute. This dinner is a first step in the development of strong philanthropic ties with Switzerland.

On the 17th October 2018, thanks to the FIAC and its director Jennifer Flay, the ICM was able to organize the 8th edition of its “Art and Science” breakfast by honouring the work of Dr. Stéphane Epelbaum on Alzheimer’s disease. During this morning, run by Natacha Polony, the company 121 led by choreographer Florence Guérin and digital artist Robin Lamarche-Perrin translated, through their performance, the hopes generated by the work done at the ICM on this pathology. The 120 or so people present, along with the Founding Members of the Institute, showed a great generosity, during this morning.

Finally, at the initiative of its president, Julien Taieb, the “Sclérose en Panne” (Out of Order Sclerosis) Association organized a gala evening in Paris to support the ICM research work on multiple sclerosis. Thanks to this event, nearly 100,000 € could be collected.



# THE FINANCIAL REPORT

## RIGOUR AND TRANSPARENCY AT THE HEART OF THE ACTION

Following the amalgamation of the ICM Recognized Public Benefit Foundation and the IHU-A-ICM Scientific Cooperation Foundation, on the 31st December 2017, the ICM Foundation's accounts, closed on the 31st December 2018, have incorporated for the first time the "IHU programme", funded by the "Investissement d'Avenir" Programme through the National Research Agency (ANR). The progress and actions of the ICM were carried out in the most transparent manner. Since November 2010, "Don en confiance" has granted its approval to the ICM Foundation, and renewed it in 2016. This accreditation attests that the activities of the institute follow the principles promoted by the committee: statutory functioning and selfless management, rigorous management, quality of communication and collection actions, and financial transparency.

### FUNDRAISING

Revenue from the 2018 collection amounted to 14 M€.

In 2018, the main new sponsorship agreements signed with individuals, foundations or corporate sponsors are:

- MSD Avenir Fund: support for a project on Alzheimer's disease,
- Donase Fund: support for all research themes of the Institute,
- The "Sucres et Denrées" Company: support for all research themes of the Institute.

The Friends of the ICM Circle brings together the donors who have been involved since the beginning of the ICM adventure, accumulating large donations (€ 10,000 and more annual donation). This Circle was created to specifically thank the major donors, individuals, companies and foundations, who mobilized throughout the fundraising campaign launched by the ICM in 2008. It currently counts 533 donors. Exclusive activities are offered to express our gratitude, to make donors and researchers meet and exchange, to inform more precisely on the research prospects and the use of donations. The Circle is co-chaired by Maurice Lévy and David de Rothschild, founding members of the ICM.

In order to increase its resources, the ICM continued fundraising campaigns in 2018.

Finally, the ICM is particularly grateful and wishes to thank the relatives who have organized in memoriam donations for the benefit of the Institute.

### PATRONAGE IN KIND AND SPONSORSHIP

Many companies have supported us by bringing their know-how in their field of activity, or by offering us their products free of charge. This section also includes artists or collectors who have donated works of art to be sold for the benefit of the ICM.

The ICM benefited from in-kind patronage as part of its communication and calls for public generosity, namely:

- Media areas with Air France, Reedexpo / Fiac, ZenithOptimedia, Richard Mille, TFI, Klésia
- Works of art, products or services free of charge: Fédération Internationale Automobile, David de Rothschild, François Pinault, Maurice Lévy, Laurent Dassault, F.P. Journe Watches, Air France, Publicis Group, Richard Mille, Orrick Rambaud Martel, Hermès international, Louis Cane, Noël Dolla, Claude Viallat, Didier Chamizo, André-Pierre Arnal, Vanessa Zitzewitz, Financière LOV, Domaines Barons de Rothschild (Lafite), Champagne Laurent-Perrier, Galerie Rive Gauche, Noirmontarproduction, IDEC, ANACOFI

### FINANCIAL SITUATION 2018

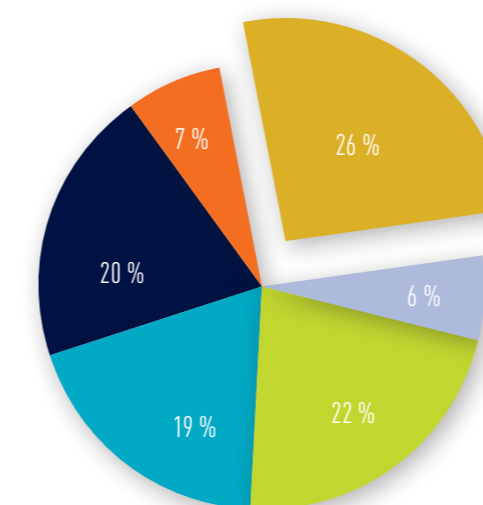
#### 2018 RESOURCES

The funding of research projects is characterized by a plurality of funding sources, anchored in a long-term perspective aiming to produce knowledge and major advances in neuroscience.

2018 resources amounted to 54.6 M€, including 43.6 M€ in revenue for the year and 10.7 M€ in allocated and unused resources in prior years. Revenues for the year essentially correspond to revenue from collections (13.9 M€ or 32%), or from the general public (11.3 M€ or 26%), or from private companies and foundations (2.6 M€ or 6%).

These also include:

- Income from technological platforms' activities (4.6 M€) and research collaborations with industrial partners (3.5 M€),
- Public and private subsidies (9.6 M €),
- The "IHU programme" financing (8.7 M €).



#### FISCAL YEAR PRODUCTS :

- General public fundraising
- Private foundation and corporate fundraising
- Public and private subsidies
- Platforms activities and industrial collaborations revenue
- IHU Programme funding
- Other revenue (rental incomes, re invoicing of charges, financial products...)

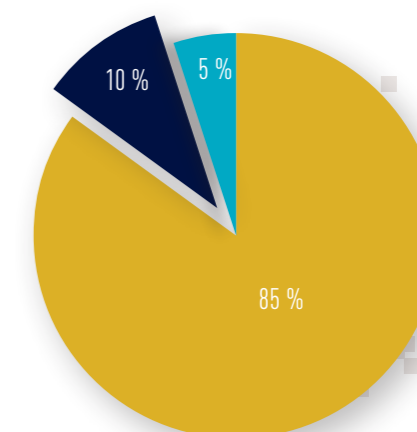
#### 2018 APPLICATIONS

The overall total of 2018 applications amounts to 54.6 M€: 43.1 M€ used in 2018 and 11.5 M€ to be subsequently realized from the allocated resources. From 2018 applications, the amount of applications devoted to social missions amounted to 36.7 M€, representing 85% of the total number of applications during the year. The social missions of the ICM concern:

- Research programmes
- Technological platforms
- Scientific animation and implementation of international alliances
- The incubation of innovative companies

Funding for research projects is dedicated primarily to nervous system diseases and spinal cord injuries. Technological platforms (neuroimaging, vectorology, genotyping sequencing, cell culture, histology and bioinformatics) support these projects. The research collection and communication costs correspond to the charges incurred to raise funds from individuals (donations and legacies) and private companies and foundations (corresponding to sponsorship and sponsorship actions), as well as to communication actions. They represent 10% of applications.

The operating expenses correspond to the costs of the support teams (general secretariat, finance, human resources, law, IT and logistics) which represent 5% of the total applications of the year. Commitments to be made from the allocated resources (11.5 M€) correspond to donations from companies or foundations and to multi-year project financing from private or public funds (ANR, etc.) received during the year that will be used later for specific multiannual research programmes.



- Social missions
- Fundraising and communication fees
- Operating costs



**ALLOCATION OF RESOURCES COLLECTED FROM THE GENERAL PUBLIC**

The resources collected from the general public used in 2018 amounted to 11.3 M€. To sum up, out of 100€ of resources collected from the general public, 66€ were used to finance social missions and investments, 26€ were used to cover the fundraising and communication costs and 8€ to cover the operating expenses of the ICM.

- Acquisition of storage capacity for scientific computing and computing cluster (€ 1,500,000).

Net fixed assets amounted to 56.1 M€. On the 31st December 2018, the amount of liquid assets was 42.5 M€. The ICM's associative funds amount to 56.1 M€. They include equity for 27.2 M€ supplemented by investment grants of 28.9 M€. The non-expendable endowment of the ICM is 1.2 M€. At the end of the financial year, dedicated funds (funds still to be committed to multi-year programmes) totalled 13 M€.

**Reserve policy**

When it was created in 2006, the ICM Foundation benefited from an allocation of 11.7 M€, of which 1.2 M€ was non-expendable. Thanks to rigorous budget management, the ICM Foundation has been balancing its expenses and revenues for four years, thus avoiding drawing on its reserves. In addition, the Board of Directors' members' policy in terms of investment is extremely cautious. The cash position of the ICM is placed in marketable securities (capitalization contract taken out with leading banks, guaranteed in capital and 100% in euro funds).

**Voluntary contributions in kind****Volunteering:**

The ICM benefited from volunteer hours during the year, particularly for communication actions. The volume is evaluated at 1.2 FTE, i.e. on the basis of an hourly wage, an amount of € 32,000.

**Patronage in kind:**

The ICM benefited from in-kind patronage as part of its communication and calls for public generosity, namely:

- Media areas with Air France, Reedexpo / Fiac, ZenithOptimedia, Richard Mille, TFI, Klésia
- Works of art, products or services free of charge: Fédération Internationale Automobile, David de Rothschild, François Pinault, Maurice Lévy, Laurent Dassault, F.P. Journe Watches, Air France, Publicis Group, Richard Mille, Orrick Rambaud Martel, Hermès international, Louis Cane, Noël

Dolla, Claude Viallat, Didier Chamizo, André-Pierre Arnal, Vanessa Zitzewitz, Financière LOV, Domaines Barons de Rothschild (Lafite), Champagne Laurent-Perrier, Galerie Rive Gauche, Noirmontarproduction, IDEC, ANACOFI

Particularly committed to maintaining its level of excellence, the ICM has set up internal and external control procedures to ensure the rigour and effectiveness of its management: it is a member of the "Don en confiance" Charter's Committee and calls in an independent auditor.

**SIMPLIFIED BALANCE SHEET**

Assets (k€)	31/12/2017	31/12/2018
Fixed net assets	58 873	56 111
Realizable and available assets	72 027	65 131
<b>Total</b>	<b>130 900</b>	<b>121 242</b>

Liabilities (k€)	31/12/2017	31/12/2018
Associative Funds	63 392	56 549
Profit for the year	1 113	-238
Dedicated funds	12 255	12 952
<b>Debts</b>	<b>54 140</b>	<b>51 979</b>
<b>Total</b>	<b>130 900</b>	<b>121 242</b>

**COMMENTS**

The total amount of the ICM's investments since its creation adds up to 30.3 M€, mainly dedicated to technological platforms that support research. Investments for the year amount to 3.5 M€.

**Main investments:**

- Scientific investments: Acquisition of a confocal microscope (400 k€) and scientific equipment (777 k€)

**"Don en confiance"**

The ICM received, on the 3rd November 2010, the approval of the "Don en confiance" Charter's Committee, which was renewed on the 6th October 2016. This committee has been regulating the call for public generosity for more than 20 years. Its action is based on 3 commitments: the accredited bodies must respect ethical rules; they must comply with a collective discipline toward the donors; and they must accept the subscribed commitments to be under continuous control.

**FINANCIAL SUMMARY**

APPLICATIONS	2018 Applications - Balance sheet	Allocation by applications of resources collected from the public in 2018
<b>1. 1. SOCIAL MISSIONS - Direct actions</b>	<b>36 742 048</b>	<b>7 429 147</b>
Research programmes	25 747 977	3 337 619
Research technological platforms	8 260 469	2 613 251
Research applications and incubator	1 593 478	645 879
Other social missions	1 140 124	832 399
<b>2. FUNDRAISING COSTS</b>	<b>4 120 827</b>	<b>2 945 733</b>
Costs of calls for public generosity	3 765 336	2 686 191
Costs of other private funds research	355 067	259 232
Communication costs	424	310
<b>3. STRUCTURE OPERATING EXPENSES</b>	<b>2 213 487</b>	<b>887 132</b>

<b>I. APPLICATIONS TOTAL IN THE BALANCE SHEET</b>	<b>43 076 362</b>	<b>11 262 013</b>
<b>II. PROVISIONS</b>	<b>56 030</b>	
<b>III. COMMITMENTS TO BE MADE FROM THE ALLOCATED RESOURCES</b>	<b>11 451 007</b>	
<b>IV. FINANCIAL YEAR RESOURCES SURPLUS</b>		
<b>V. GRAND TOTAL</b>	<b>54 583 399</b>	
Share of the fixed assets acquisition for the financial year financed by the resources collected		
Neutralization of depreciation of assets financed by the resources collected		
<b>TOTAL APPLICATIONS FINANCED BY RESOURCES COLLECTED FROM THE PUBLIC</b>		<b>11 262 013</b>

**EVALUATION OF VOLUNTARY CONTRIBUTIONS IN KIND**

Social missions		
Fundraising costs		
Operating costs		
<b>Total</b>	<b>32 368</b>	

RESOURCES	2018 Resources collected - Balance sheet	2018 Resources collected - Balance sheet
Postponement of resources collected from the public unallocated and unused at the beginning of the year		0
<b>1. RESOURCES COLLECTED FROM THE PUBLIC</b>	<b>11 303 860</b>	<b>11 303 860</b>
Unaffected manual donations	10 069 296	10 069 296
Affected manual donations	447 918	447 918
Legacies and other unallocated donations	786 645	786 645
Legacies and other allocated donations	0	0
Other revenue related to public generosity	0	0
<b>2. OTHER PRIVATE FUNDS</b>	<b>9 665 427</b>	
Patronage	2 641 708	
Partnership	3 355 493	
Private grants	3 668 225	
<b>3. GRANTS AND OTHER PUBLIC SUPPORT</b>	<b>14 633 408</b>	
<b>4. OTHER REVENUE</b>	<b>8 006 489</b>	
Financial products	629 930	
Services	4 539 320	
Other revenue	2 837 239	

<b>I. RESOURCE TOTAL IN THE BALANCE SHEET</b>	<b>43 609 183</b>	
<b>II. REVERSALS OF PROVISIONS</b>		
<b>III. POSTPONEMENT OF UNUSED ALLOCATED RESOURCES OF PREVIOUS YEARS</b>	<b>10 736 139</b>	
<b>IV. VARIATION OF DEDICATED FUNDS COLLECTED FROM THE PUBLIC</b>		-41 847
<b>V. RESOURCE SHORTFALL FOR THE YEAR</b>	<b>238 077</b>	
<b>VI. GRAND TOTAL</b>	<b>54 583 399</b>	<b>11 303 860</b>
<b>TOTAL APPLICATIONS FINANCED BY RESOURCES COLLECTED FROM THE PUBLIC</b>		<b>11 262 013</b>
<b>BALANCE OF RESOURCES COLLECTED FROM THE PUBLIC UNAFFECTED AND UNUSED AT THE END OF THE FINANCIAL YEAR</b>		<b>0</b>

Volunteering		
Services in kind		
Gifts in kind		
<b>Total</b>	<b>32 368</b>	



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