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5 YEARS ICM Brain & Spine Institute

FOR YOU & WITH YOU

The brain and spine institute donors journal

PAGE 4

SPECIAL REPORT ON RARE NEUROLOGICAL DISEASES

CONTENTS

YOUR BRAIN OUR PRIORITY

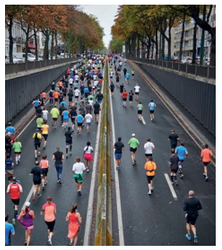
In only five years, the ICM has become a key player in research on the nervous system and associated pathologies. We exceeded our goals by far, with over 500 publications in 2015, major scientific and medical breakthroughs, and many awards for our researchers. The ICM is an attractive Institute for many researchers, both from France and abroad, as well as Visiting Professors from the world's best institutes. Foreign post-doctorate researchers make up 50% of the 26 teams of the ICM. The ICM benefits from international recognition in the field of neuroscience, giving us the opportunity to develop strategic partnerships, organize student, researcher, and clinician exchanges, and implement a summer school as well as international workshops. This international dynamic is key in encouraging successful collaboration and interaction.

Our scientific strategy aims at taking up the public health challenge that are nervous system diseases. Understanding how a healthy brain works is necessary in understanding and treating altered function in patients with diseases. Being at the forefront of the latest technological revolutions and developing innovative tools to improve diagnosis and treatment of nervous system pathologies, and finally, transforming scientific breakthroughs into treatments. Our strategy is centered around several strong pillars focused on transversal and multidisciplinary projects. I am convinced that a discovery in one disease can lead to breakthroughs for others, and that is why the ICM model promotes a seamless approach to research. We put in the same amount of energy to find ways to treat all nervous system diseases, including the rarest ones, which you will learn more about in our report. Thanks to your generous support, each and every one of these diseases is our priority.

Prof. Alexis Brice
ICM General Manager

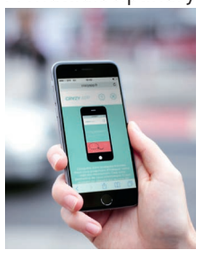
20K FOR THE ICM

On October 7, 8 and 9 2016, the Brain and Spine Institute will be part of the Paris 20K race. The partnership, in its 12th year, is a precious source of support for research activities at the Institute. The Institute will be at the race village during number pickup to raise awareness and will make Institute race shirts available. To raise funds in support of research, runners can also create a personalized fundraising page, free of charge, on Alvarum.com and invite their friends to support them in their race to raise money for research.



A NEW KIND OF TOOL FOR RESEARCH

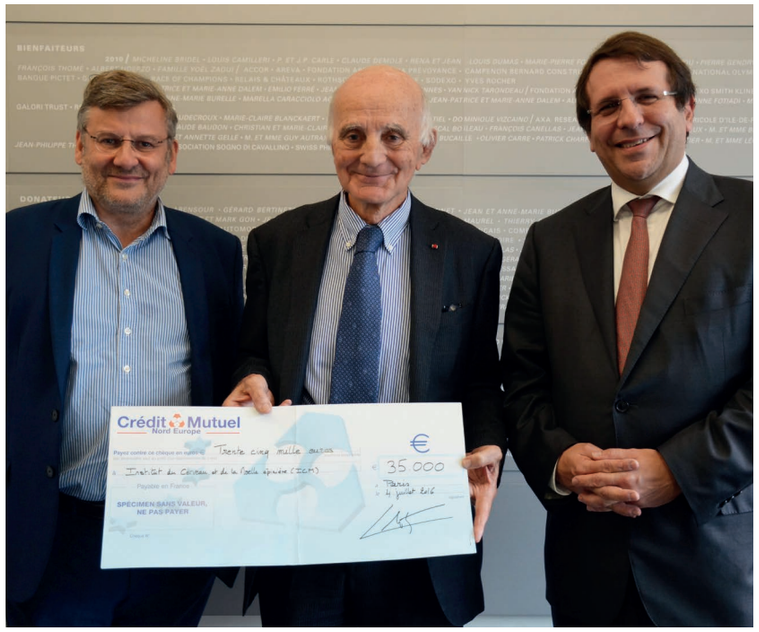
A multidisciplinary team (psychiatrists, psychologists, sociologists…) led by Prof Luc Mallet, team director at the ICM, developed an interactive science tool called Crazy'App. This web application allows users to discover patient stories of life with a psychiatric disorder, and gives them the opportunity to answer a survey that will help researchers improve their understanding of mental health disorders and change the way they are viewed by others.



More information and download:
icm-institute.org

S3ODÉON

S3Odeon is an initiative aimed at bringing Science, Health, and Society closer by promoting positive brainstorming on healthcare challenges. On September 3, 2016, notable figures and young entrepreneurs will share their vision for healthcare with the audience on the stage of the Odeon Theater in Paris. Sign-up on s3odeon.fr



PARTNERS:

A SOCIALLY RESPONSIBLE INVESTMENT PRODUCT FOR THE ICM

On July 4, the ICM received a 35,000€ endowment from the Credit Mutuel Nord Europe (CMNE) and La Française, made possible thanks to the SCPI Pierval Santé.

The Bank and its subsidiary, wishing to increase their support of medical research, decided to donate 0.70% of funds from the SCPI annual campaign, carried out by the CMNE network, to the ICM.
Pierval Santé, created in 2014 by Euryale PM, is the first SCPI with a Revenue Sharing Fund. It is a project with high social value, that aims to bring private investors and public or private healthcare organisations together to solve healthcare issues.
First quarter 2016 capitalization of Pierval Santé exceeded 50 million euros, with over 1,200 associates and 9 acquisitions (healthcare institutions, clinics, retirement homes, medical offices…). These figures illustrate Pierval Santé's relevant strategy and the proven interest of investors when it comes to diversifying their investments. Beyond basic real estate profitability, this also illustrates that investors wish to give their investment meaning through sharing.

For you & with you is the newsletter sent by the ICM to its donors. **No. 05 – June 2016**. Editor-in-chief: **Agathe Gioli-Viot**. Editorial board: **Jean-Louis Da Costa, Natacha Bitton, Carole Clément**. Design: EXCEL Production: **Louis**. Printer: **BB création** . Print run: **300 copies**. © ICM - INSERM - 20KM DE PARIS - J.P. PARIENTE - CARTHERA

Seen on the Web

icm-institute.org/en/

- World Amyotrophic Lateral Sclerosis (ALS) Day
- George Freeman MP, British Parliamentary Under Secretary of State for Life Sciences, visits the ICM
- Gene therapy: regulating gene expression with a specific diet
- A natural compound present in green tea improves cognitive capabilities in patients with Down Syndrome
- Insects have taste! and detect contaminated food
- Video: Parkinson's Disease Conference

AGENDA

- **September 3 2016** – S3Odéon - Paris
- **September 10 & 11 2016** – Fée rarissime - Toulouse
- **September 30 2016** – Alzheimer's Disease Conference at the ICM – Paris
- **October 9 2016** – Paris 20K Race

UNDERSTANDING THE BRAIN TO TREAT ALL NEUROLOGICAL DISEASES, THE RAREST INCLUDED

Diseases that go by the term rare are those that affect a small set of individuals and whose rareness leads to specific problems. In Europe, the accepted threshold is one out of 2,000 individuals. Paradoxically, there are thousands of rare diseases: six to seven thousand have been identified, and new illnesses are characterized daily in medical literature. In France, rare diseases of neurological or non-neurological origin affect 3 million individuals, 50% of them children. For these diseases, research absolutely must find an answer.

These last few years, important progress has been made and new hopes arise each day within laboratories, especially at the ICM, where several teams are involved in the fight against rare neurological diseases such as amyotrophic lateral sclerosis, Huntington's disease, cerebellar ataxia, spastic paraplegia, alternating hemiplegia of childhood, autoimmune neuropathy, congenital myasthenic syndromes, neuromuscular channelopathy, and motor disorders.

How do rare neurological diseases develop? What are the risk factors? How can we diagnose and differentiate them?

THE ICM'S ANSWER

Rare diseases are at the heart of ICM research and ambition for the future. The unique virtuous research circle offered by the ICM allows researchers to benefit from breakthroughs on a certain diseases to learn more about others. By adopting an all-encompassing view of these diseases, especially by improving understanding of nervous system function to anticipate, prevent, and treat disorders, breakthroughs will allow us to understand and, eventually, treat diseases both rare and more widespread.

A MAJOR ASSET: RARE DISEASE REFERENCE CENTERS

One of the major difficulties when studying these diseases is the very small number of patients. To remedy the lack of patients, the ICM works in close partnership with rare disease reference centers, 11 of which are at the Pitié-Salpêtrière Hospital for nervous system diseases (muscular channelopathies, intellectual deficiency with rare causes, rare diseases with psychiatric manifestations, Amyotrophic Lateral Sclerosis (ALS), Gilles de la Tourette Syndrome). This centres are organized around highly specialized teams and encourage patient care, offering treatments with all involved healthcare professionals. They are the contacts for patient organizations, families, and play an important role in developing clinical trials. The centers received national certification and are renowned for their scientific and clinical excellence. Their mission is to improve diagnostic care and quality of care. Being at the heart of a reference center hospital, for the ICM, is an opportunity to advance more quickly by pooling knowledge from researchers and clinicians and thanks to patient availability for on-site trials.

« Studying rare neurological diseases can serve as a model in understanding and identifying treatments for other nervous system diseases. » Prof. Alexis Brice

FUNDAMENTAL RESEARCH HIGHLIGHTS

AMYOTROPHIC LATERAL SCLEROSIS (ALS) OR CHARCOT DISEASE

Amyotrophic Lateral Sclerosis (ALS), or Charcot disease, affects motoneurons, neurons that travel from the brain and spinal cord to control muscles. Patients with ALS suffer from progressive motor impairment that leads to paralysis. In France, 8,000 patients are diagnosed with ALS.

• Discovery of a new gene

Many genetic factors are responsible for ALS, the most common being C9orf72 and SOD1 genes. Stephanie Millecamps, part of a team led by Séverine Boillée, participated in the discovery of TBK1, a new gene identified in familial ALS. Loss of function of the TBK1 protein, linked to the immune system and autophagy (degradation of abnormal proteins within cells), is a mechanism that could play a role in the disease and lead to neutron death. This discovery will lead to better understanding of mechanisms involved in the disease and improvement of diagnostic tools.

• Identification of a toxic factor for motoneurons

In the case of ALS, as for all neurodegenerative diseases, an immune response to protect the body is observed in the central nervous system. How does this immune reaction become harmful and involved in neutron death? A team led by Séverine Boillée found that in cases where a mutation causes ALS, cells responsible for nervous system protection secrete toxic factors that lead to motoneuron death. By blocking secretion of these factors, researchers managed to slow ALS progression in experimental modelling. Highlighting this mechanism opens up new opportunities for the development of novel treatments.

• ALS and Hereditary Spastic Paraplegia: clinical similarities create new opportunities for treatment

Hereditary spastic paraplegia is a heterogenous group of pathologies that has clinical similarities to other neurodegenerative diseases such as ALS. For the first time, Khalid H. El Hachimi and colleagues, from a team led by Alexis Brice, found neuropathological similarities (at the site of nervous system damage) between Type 11 spastic paraplegia and ALS. This discovery will allow clinicians to diagnose "atypical" ALS earlier and more precisely, via screening for SPG11 gene mutation. Additionally, understanding the mechanisms involved in these pathologies opens up opportunities for the development of new targeted treatment.

CEREBELLAR ATAXIA

Cerebellar ataxia is a degenerative disease that affects the cerebellum, a key component of the central nervous system involved in balance and coordination. Affected patients display very disabling symptoms, with impaired walking or motor skills.

• A step towards identifying a treatment?

Giovanni Stevanin, in a team led by Alexis Brice, has identified a recurring mutation in a new gene responsible for cerebellar ataxia, that codes for a calcium channel expressed in certain cerebellar neurons. Calcium channels are active participants in cell excitability and nerve information transmission. The mutation described by researchers leads to reduced activity in the channel, leading to malfunction of cerebellum neurons and symptoms of ataxia. Numerous drugs that regulate calcium channel activity are widely administered and this discovery could lead to advances in treatment for these rare disorders.

• Involvement of the calpain-1 gene

An international collaboration between Alexis Brice's team and a team led by Michel Baudry at Western University of Health Sciences, in the United States, identified calpain-1 gene alterations in 5 patients with progressive ataxia and from 4 families affected by cerebellar ataxia. Study of an experimental model rather than a murine one shows the involvement of calpain-1 proteins in ataxia and their neuroprotective activity and key role in brain development •••

••• and synaptic plasticity. This study creates new opportunities in treating neurodegenerative diseases.

GILLES DE LA TOURETTE SYNDROME: TICS, A BAD HABIT

Tics are one of the main expressions of Gilles de la Tourette syndrome. How do they appear? Why are they persistent? Yulia Worbe, part of a team led by Marie Vidailhet, and colleagues found that patients with Gilles de la Tourette syndrome are more prone to habit-forming behavior than healthy subjects of the same age. These results give new insight into how tics appear and persist; they could be, in part, learned and become automatic and could help explain the exacerbation of this behavior in patients. These results will help in the development of new treatments in the fight against Gilles de la Tourette syndrome.

CHANNELOPATHY AND CONGENITAL MYASTHENIC SYNDROME: IMPROVING DIAGNOSIS

Muscular channelopathy is a heterogeneous set of diseases in which muscle stiffness (non dystrophic myotonia) and paralysis are symptoms. Congenital myasthenia syndromes are a group of genetic disorders that disrupt proper function of the neuromuscular junction, the zone linking the commanding motor nerve and the muscle that reacts to the command with movement. They are characterised by muscular weakness. Sophie Nicole and colleagues from Bertrand Fontaine's team identified a mutation responsible for permanent muscular weakness typical of congenital myasthenic syndrome as well as periodic paralysis, typical of channelopathy. This discovery will help fine-tune the diagnosis of these two types of heterogeneous genetic diseases and pave the way for new research on therapeutic molecules to treat permanent muscle weakness.

CLINICAL RESEARCH HIGHLIGHTS

A DRUG TO COMBAT MUSCULAR DISORDERS: DYSTONIA

A study coordinated by Emmanuel Flamand-Roze tested the efficacy of zonisamide, a drug currently used to treat certain types of epilepsy, on 23 patients with a rare nervous system disease called myoclonic dystonia. Promising results show that zonisamide very significantly reduces myoclonia (muscular tremors) and the associated impairment. Dystonia, meaning abnormal posture of certain parts of the body, is also improved with treatment.

DRUG EFFECT ON MYOTONIA

Non-dystrophic myotonia is a rare disease caused by genetic mutations of ion channels in muscles leading to loss of function of these channels. Clinically, this implies difficult muscle relaxation leading to painful stiffness. The first controlled trial, conducted by Bertrand Fontaine and Savine Vicart aiming to assess efficacy and tolerance of Mexiletine for this disease, has just ended. Encouraging results are currently undergoing analysis.

IDENTIFYING MARKERS TO PREDICT ALS PROGRESSION

The national multicentric PULSE ARS1 study conducted on 1,000 patients, financed by the ARSLA and coordinated by David Devos, aims at identifying disease progression biomarkers. The study also aims at specifying the various clinical symptoms of the disease, following the specific evolution of each symptom, and determining predictive parameters and disease evolution prognoses (biomarkers). It will lead to the implementation of a nationwide databank combining characteristic parameters of patients with slowly progressing diseases and patients with rapidly progressing diseases, and eventually the prediction of disease progression for each patient.

TESTING DRUGS TO FIGHT PSP

Progressive Supranuclear Palsy is a neurodegenerative disease with a number of traits in common with Alzheimer's disease. It causes lesions in the brainstem, leading to progressive loss of balance, speech, and movement. Clinical trials for patients with PSP are set to start this year, in collaboration with the Pitié-Salpêtrière Reference Center, coordinated by Prof Bruno Dubois and Dr Isabelle Leber, and the PSP-France patients organization. The goal of the researchers is to pave the way for better patient care. This research brings new hope for PSP as well as other neurodegenerative pathologies.

INDUSTRIAL PARTNERSHIP HIGHLIGHTS

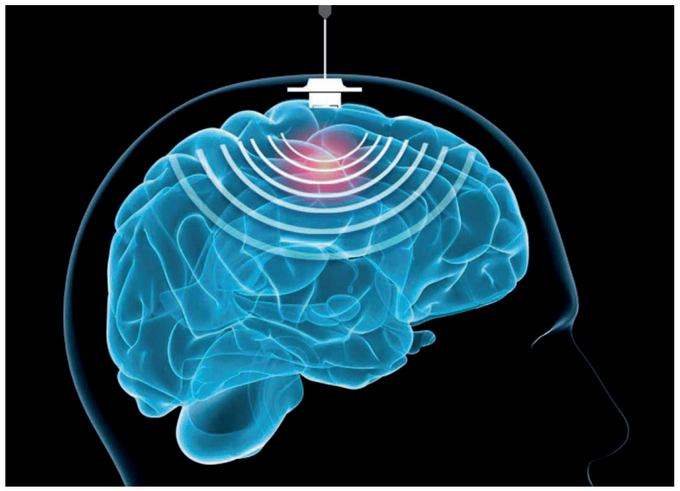
"By correcting the energy issue, we hope to slow disease progression and witness improvement in daily life of patients."

Fanny Mochel

MEDICATED OIL TO TREAT HUNTINGTON'S DISEASE

Huntington's disease is a neurodegenerative disorder linked to genetic anomaly. Symptoms of the disease often appear between ages 30 and 50, including progressive mobility, behavioral, and psychiatric impairment leading to dependency with an impact on family and relatives. Fanny Mochel and Alexandra Durr, from a team led by Alexis Brice, took up the challenge of providing energy to the brain to treat the disease. They proved the therapeutic potential of triheptanoïne, a synthetic oil, in patients with Huntington's disease. By improving the brain's energy metabolism, the drug could slow down the disease's progress. Based on these results, TRIHEP3, a European therapeutic trial coordinated by Fanny Mochel in partnership with Ultragenyx, was launched in France and in the Netherlands for one year with 100 patients. Assessment will be based on clinical and imaging parameters. Fanny Mochel has also proven the efficacy of triheptanoïne in patients with another rare disease known as GLUT-1 (Glucose transporter 1) deficiency syndrome, involving neurological and psychomotor disorders. A multi centric phase III study, in collaboration with Ultragenyx, will begin by the end of 2016.

BRAIN TUMORS: ULTRASOUNDS TO INCREASE TREATMENT DIFFUSION

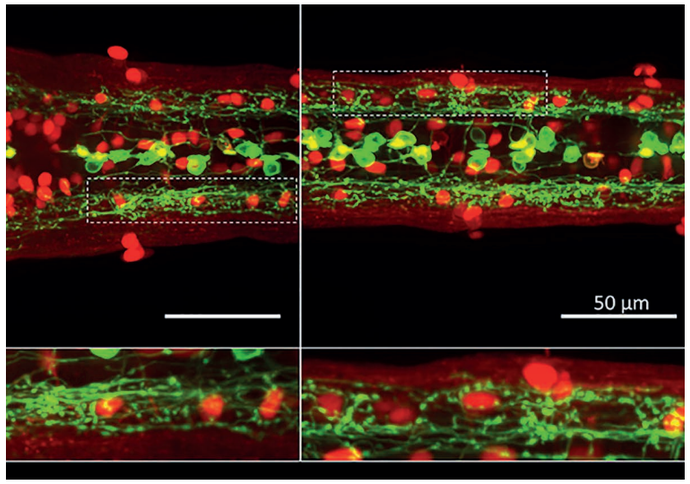


Teams from the Assistance publique - Hôpitaux de Paris, Pierre et Marie Curie University, Inserm and the CarThera company, gathered at the Brain and Spine Institute (ICM) and coordinated by Prof Alexandre Carpentier, neurosurgeon at the Pitié-Salpêtrière, AP-HP Hospital, succeeded in making blood vessels in the brain temporarily permeable in patients with a relapsed malignant brain tumor thanks to ultrasounds. This novel technique helps increase treatment diffusion, especially chemotherapy, within the brain and brings hope for other cerebral pathologies. This research was published in the international Science Translational Medicine publication's June 15 issue.

Malignant primitive brain tumour treatment currently relies on neurosurgery followed by chemotherapy and/or radiation therapy. Treatment leads to disease remission of varying durations depending on patients. The blood-brain barrier (BBB), a wall of vessels whose tightness limits neuron exposure to toxic agents, limits the passage and therefore the diffusion of treatments within the brain. In view of these observations, teams led by Prof Alexandre Carpentier, Dr Ahmed Idbaih, and the neuro-oncology group at the Pitié-Salpêtrière AP-HP Hospital, launched a Phase I/IIa clinical trial in July 2014 supported by the AP-HP for patients with relapsing malignant brain tumors. The mission is to achieve blood-brain barrier permeability to increase penetration and diffusion of chemotherapy drugs in the brain with the ultrasonic "SonoCloud®" system developed by CarThera. The device, embedded within the skull, is activated several minutes before intravenous injection of the product. Ultrasound emission for two minutes is sufficient to temporarily permeabilize the BBB for 6 hours, allowing diffusion of the therapeutic molecule in the brain that is five times more significant than usual. To date, and for the first time in the world, several repeated BBB "openings" were observed in the 20 treated patients. Tolerance has proven excellent: the technology invented by Prof Carpentier and developed by CarThera, supported by the Inserm's LabTAU physics laboratory, does not alter neurons and the BBB closes spontaneously 6 hours after intravenous perfusion.

According to Prof Alexandre Carpentier, *"this novel method gives new hope in treatment of brain cancer as well as other cerebral pathologies, potentially Alzheimer's disease, for which existing therapeutic molecules have trouble entering the brain. We must keep evaluating this technique to consider its application in clinical routine in several years."*

SENSORY NEURONS LOCATED IN THE SPINAL CORD HELP MODULATE MOVEMENT



A team led by Claire Wyart, Inserm researcher at the Brain and Spine Institute, has proven the ability of sensory neurons, located in the spinal cord, to modulate movement. In zebrafish, researchers showed that activating these neurons triggers locomotion when the animal is at rest and inhibits it when the animal is moving. These results give hope that, one day, we will be able to stimulate these circuits to generate movement in patients with spinal cord damage.

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Spinal cord lesions lead to severe paralysis and currently have no form of treatment. When communication between the brain and spinal cord is interrupted, the brain no longer voluntarily controls movement. However, within the spinal cord, autonomous circuits that generate walking ensure musculoskeletal activation when once the decision to move has been made in the brain. The aptitude to maintain movement comes from the spinal locomotor system's capacity to generate electrical oscillations.

To understand how the spinal locomotor system functions and is modulated, Claire Wyart's team studies movement in zebrafish. This transparent vertebrate is especially adapted to optogenetics, cutting-edge technology that allows stimulation of targeted neurons using light. With this method, stimulated neutrons light up and become visible.

Researchers used this technique to identify and understand how a new neural circuit, involved in control of movement, functions. By activating it at various moments (animal at rest or moving), researchers found connections with the ability to generate the oscillations that allow the fish to move. The circuit's specificity is that it relies on sensory neuron activity that, through a chain reaction, end up activating motor neurons.
Surprisingly, researchers found that locomotion regulation depends on the animal's initial state. Stimulation triggers locomotion when the animal is at rest, yet it inhibits it when the animal is already swimming. *"This type of modulation is complex and depends on context"* explains Claire Wyart, lead researcher.

In 2014, the same team proved that this circuit is present among various species of vertebrates, especially primates. This innovative work on zebrafish opens up new directions for further research to understand locomotor system modulation in humans.

Although several aspects still need to be solved, stimulating sensory circuits to activate the human musculoskeletal system that leads to walking gives hope for those with spinal cord injuries.

THE ICM IN THE LIMOUSINE REGION!

Since the launch of the collaborative research project on ALS between the ICM, the Limoges teaching hospital and Limoges University in September 2015, the ICM's Regional Delegation in the Limousine has taken up a few challenges. Let's take a look at three of them...

CROWD-FUNDING CAMPAIGN ON ULULE

The campaign, launched in February 2016, allowed Marie Nicol, Clinical Research Assistant, to join the team led by Professor Courtier and Dr Benoît Martin to research ALS hypermetabolism. Thanks to 122 donors, the starting fundraising goal was exceeded by 180%, reaching 18,000€.

THE 20TH VASSIVIÈRE LAKE CYCLING RACE

For the second consecutive year, the Limousine branch of the ICM was a partner of the Vassivière Lake Cycling Race. This year, the ICM went a step further and organized a march in support of ALS patients alongside the races (23km and 8km). The march had Daniel Cheval, former amateur sportsman from the region affected by ALS for the past two years, as its ambassador. Over 900 cyclists and 100 walkers showed up on June 26 2016 to support ALS research. The event raised nearly 15,000€ and was covered in news outlets. It was made possible thanks to ICM sponsor companies: Malinvaud, Optineris, les Granulés du Limousin, Smuggler, Lavaurs, MP Samie, Independence Royale, Ceradrop and Alair.

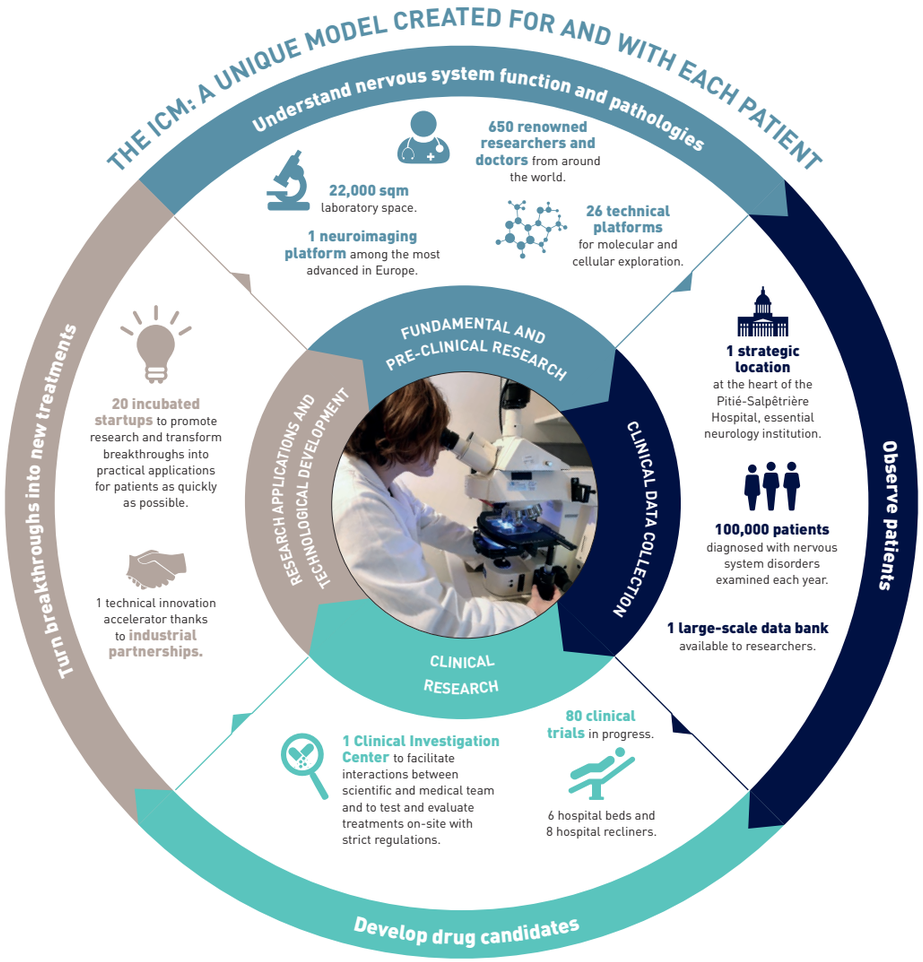
ICM/CABEX AGREEMENT SIGNING

CABEX, a company specialized in real estate diagnostics, signed a partnership agreement with the ICM on June 28 2016. From July 1 and for one year, 2€ on each of the company's invoices will be donated to the Limousine ICM. For the ICM, this is a step towards creating a corporate sponsor club and towards transversal involvement of local players to support the ALS collaborative research project.

OVERVIEW OF ICM 2015 FINANCIALS

The Brain and Spine Institute (ICM), at the heart of the Pitié-Salpêtrière Hospital, is an international-level research center, the only of its kind in the world, innovative both in design and organization. The institute's governance is based on a strong partnership between the public and private sectors. With the support of its public partners (AP-HP, CNRS, INSERM, UPMC), the ICM brings patients, doctors, and researchers together in the same place. It has the goal of allowing rapid development of treatments for nervous system lesions and administering them to patients as early as possible.

The ICM's scientific strategy is built on four research priorities: Understanding major brain functions, understanding neural interaction, deciphering cellular and molecular mechanisms of healthy and pathological brain function, and transfer knowledge to help prevent and treat nervous system diseases. From a scientific point of view, the ICM's approach is innovative: research walls come down for a multidisciplinary perspective. Major breakthroughs on brain and spine function will result from embedding these four fields in shared issues.



OVERVIEW 2015

MAJOR ACHIEVEMENTS IN 2015

ICM research developments on nervous system diseases are available in the 2015 annual report on the foundation's website (icm-institute.org) or upon written request.

RESEARCH

• Launch of the Big Brain Theory project and call for tender

A call for tender was launched conjointly by the ICM and the IHU-A-ICM in June 2015. This "Big Brain Theory" call for tender awarded grants to new projects initiated by ICM researchers, clinicians, engineers, and technicians.

• The ICM was recognized as a Neurodegenerative Diseases Center for Excellence within the greater 2014-2019 Neurodegenerative Diseases Plan.

• PRISMA MRI

Thanks to the generous support of the Pierre Bergé Foundation, the Center for Neuroimaging Research–CENIR was able to update one of its MRI machines: the Siemens Trio is now a Siemens Prisma. Prism Fit integrates three major technical innovations. One of the expected major improvements with this new machine is the signal to noise ratio (SNR).

• PLATFORM DAY

The second "Platform Day" was organized in October 2015 with over 150 participants.

• ISO 9001 certification of genotyping-sequencing and vectorology platforms

• Scientific output

In 2015, the Institute recorded a notable increase in number of publications with a significant increase with an impact factor >7. This increase in quality of ICM scientific output also appears on higher impact factors.

EUROPEAN CALLS FOR TENDER

Three ICM researchers received the ERC award in 2015: Edor Kabashi (Consolidator), Stéphane Baulac (Consolidator), and Stanley Durrleman (Starting).

INTERNATIONAL RELATIONS

• Approval of the selection for Bassem Hassan's team from VIB Belgium to join the ICM

• Continued exchanges with international research institutes the ICM established cooperation agreements with in 2014

Europe: UCL / ION (GB) – DZNE (Germany)
North America : Harvard – USA, MIT – USA, Yale – USA, Neuroscience in France Booth at the Chicago SFN, MNI –Canada
South America: USP – Brazil
Australia: Florey Institute

INDUSTRIAL PARTNERSHIPS AND RESEARCH APPLICATIONS

• Recent industrial partnerships

In 2015, the ICM signed around twenty industrial collaboration contracts with biotechnology, pharmaceutical, and medical technology companies.

• Recent patents

The "Research Applications" team at the ICM detects scientific results that can be taken a step further, creates partnerships with the most competitive healthcare companies, protects precious research with patents, and encourages projects to develop new drugs.

• Companies in the iPEPS-ICM incubator

Two new companies: NeoNeuro (Toronto) and Pathmaker (Boston) as well as 8 new candidates to entry.

• Carnot Institute

The ICM is a recipient of the prestigious "Carnot Institute" certification and, as such, receives support for technology readiness projects as well as Findmed project financing.

FUNDRAISING AND COMMUNICATION

For our donors

• Donor Morning Talks at the ICM: Parkinson's, Multiple sclerosis, Alzheimer's, Depression, Epilepsy
• Fundraising dinner in Bruxelles for patrons on May 21
• FIAC on October 21
• Friends of the ICM Circle breakfast on November 14
• Signing of the partnership agreement between the ICM and the Clermont-Ferrand Medical University, part of the ICM's regional expansion, on February 13 2015
• Brain Week: from March 16 to 21 2015
• Launch of the ICM's new website
• Screening of the film "The Theory of Everything" preceded by a presentation of current research on ALS in June
• Fête de la Science, in October

FINANCIAL REPORT

THE ICM FOUNDATION HAS BEEN RECOGNIZED AS AN OPERATING REGISTERED CHARITY SINCE 2006.

Its budget is centered on 5 key actions:

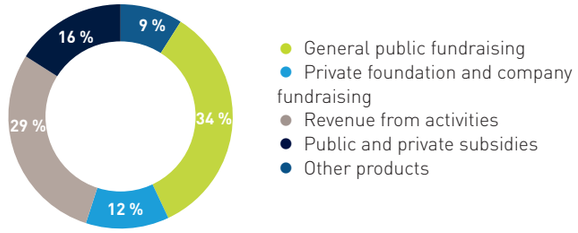
1. Fundraising: sponsorship and donors/bequests and donations;
2. Grants: public entities and private foundations (national, european, and international financing), Carnot Institute certification (ANR financing);
3. Industrial contracts, commercialization of research: partnerships with large pharmaceutical group and innovative companies (start-ups);
4. Technical platform services;
5. Various invoiced services.

These resources are essential to guarantee:

• Support for innovative research projects;
• Excellence-based researcher recruitment;
• Investment in cutting-edge equipment and technical platform operation;
• Company incubator coordination (in addition to contribution from start-ups);
• ICM operation (support for research teams / supporting functions);
• Communication and fundraising development.

1– 2015 RESOURCES

2015 resources reached 35.3 M€, including fiscal year products of 30.6 M€ and a carryover of allocated and unused resources from previous fiscal years of 4.7M€. Fiscal year profits are essentially made up of fundraising revenue (13.7 M€ or 45%), general public donations (10.4 M€ or 34%), companies and private foundations (3.3 M€ or 11%).



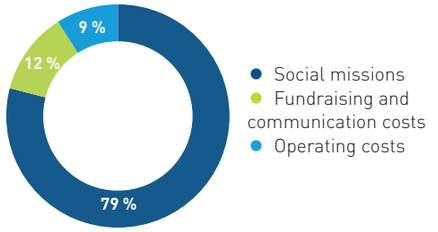
Additionally, they include:

• Revenue from technological platforms (3 M€), and research partnerships with industrial partners (5.8 M€);
• Public subsidies (3.7 M€);
• Private subsidies (1.3 M€).

2– 2015 APPLICATIONS

In 2015, the grand total of applications reached 34.5 M€: 27 M€ used in 2015 and 7.5 M€ allocated for future use. The share of applications dedicated to social missions reached 21.4 M€, 79% of total fiscal year applications. ICM social missions include:

• Research projects (55%);
• Technological platforms (33%);
• Scientific events and international partnership development (7%);
• Innovative company incubation (5%).



FINANCIAL REPORT (CONTINUED)

2– 2015 APPLICATIONS

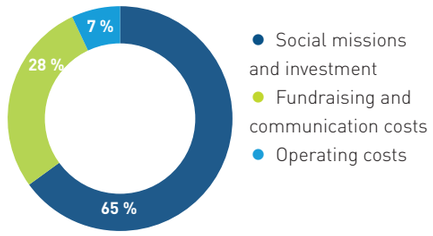
Research project financing is primarily dedicated to nervous system diseases and spinal cord trauma. Technological platforms (neuroimaging, vectorology, genotyping sequencing, cell culture and histology) support these projects. Fundraising and communication costs (12%) represent expenses in canvassing of the general public (donations and bequests) as well as companies and private foundations (patronage and sponsorship) and communication.

Operational costs (9.2%) represent support staff costs (finance, human resources, legal, IT and logistics). Applications on allocated resources (7.5 M€) primarily represent company and foundation donations received over the course of the year, to be utilized later for specific multi-year research programs.

3– ALLOCATION OF RESOURCES FROM THE GENERAL PUBLIC

Resources raised from the general public and used in 2015 totalled 10.3 M€.

In short, 65€ of every 100€ raised from the general public were used to fund social missions and investments. 28€ were used to cover fundraising and communication costs, and 7€ to cover ICM operational costs.



SIMPLIFIED BALANCE SHEET

ASSETS (K€)	31.12.15	31.12.14
Net immobilized assets	9,963	10,168
Net available and realizable assets	35,108	32,678
TOTAL	**45,071**	**42,846**
LIABILITIES (K€)	**31.12.15**	**31.12.14**
Organization funds	19,101	20,418
Fiscal year result	766	-992
Dedicated funds	7,464	4,696
Debts	17,740	18,726
TOTAL	**45,017**	**42,846**

COMMENTS

Total ICM investments since the institute's launch represent nearly 22.5 M€, dedicated primarily to technological platforms supporting research.

Fiscal year investments amounted to 2.9 M€.

Main investments:

- Key equipment acquired in 2015 is an upgrade of the 3T Trio MRI (made available by the Adrec in 2011) in Prisma fit for the Male MRI neuroimaging platform, for a total of 1.2 M€;
- Research team workspace reconfiguration and scientific equipment acquisition for 340 K€;
- Scientific IT storage capacity acquisition and calculation cluster for 225 K€.

Fixed assets amount to 10 M€. On December 31 2015, cash flow amounted to 18.5 M€, a comparable amount to the previous fiscal year. ICM equity is estimated at 19.9 M€, a 2.6% increase thanks to positive results from fiscal year 2015. This includes organization funds of 11.7 M€ as well as investment subsidies (2.3 M€) and 5.9 M€ carried forward. Nonexpendable endowments total 1.2 M€. By fiscal year end, dedicated funds (to be allocated to various programs) amounted to 7.5 M€.

Monetary Reserve Policy

The ICM was supported by an 11.7 M€ grant when it was started in 2006. The board has a very cautious policy in terms of monetary reserve preservation. ICM reserve represents 26% of the total statement of financial position in 2015. It is invested in marketable securities (long-term investment contracts with major banks, capital guaranteed and 100% in euros).

In-kind voluntary contributions

- Volunteering:

The ICM was supported by volunteering over the course of the fiscal year, especially for communication campaigns in Paris and the three regional branches. Estimated volume is 1.4 yearly full-time equivalent, i.e. 37 K€ based on hourly minimum wage.

- Equipment:

The ICM has been given access to a 3T MRI by the ADREC.

- In-kind donations:

The ICM has received in-kind support in the form of communication and fundraising:

- Media placement from Air France, Reedexpo/FIAC, Euronews;
- Complimentary services (1000 Mercis, Publicis, Ticemed, Orrick Rambaud Martel, Quaterback, Sodexo, IDEC, Axeria prévoyance).

Excellence is a top priority for the ICM. Internal and external control guarantee management discipline and efficacy: the ICM is a Comité de la Charte pour le Don en Confiance (Code of Trusted Donations Committee) member, and works with an independent financial auditor.

CODE OF TRUSTED DONATIONS COMMITTEE

On November 3, 2010, ICM received certification from the **Comité de la Charte pour le Don en Confiance** (Code of Trusted Donations Committee), renewed on September 12, 2013. For over 20 years, the Committee has been a regulator of professional fundraising from the general public. Its action is centered on 3 leading guidelines: certified organizations must respect ethics regulations, must abide by collective discipline with respect to donors, and must accept continuous monitoring of commitments.

The information presented in this document is from the 2015 Annual Report and Report on Moral and Financial Situation. The 2015 Annual Report is available on the Foundation's website (icm-institute.org) or upon written request.

DONATIONS: ANOTHER WAY OF SUPPORTING THE ICM

A donation, registered with a notary, is a way for you to transfer rights or property of personal or real estate assets to the ICM during your lifetime and help our researchers in their projects. Several options are available:

1. Full ownership donation
This is the simplest form of donation: the full ownership of an asset is transferred to the ICM.
- Pros: 66% of the amount of your donation is deducted from your earnings*.

2. Bare ownership donation
Bare ownership is conferred to the ICM, and you continue to collect earnings from the asset over your lifetime (rent, interest...).
- Pros: 66% of the amount of your donation is deducted from your earnings*.

3. Temporary usufruct donation
You will conserve ownership of your asset, and the ICM will collect earnings generated by the asset. There are specific requirements for this type of donation to be approved, including that the donation lasts at least 3 years and it contributes directly to ICM missions.
- Pros: earnings from your asset are no longer subject to income tax and its bare ownership value is no longer factored into your ISF taxable base.

Additional information on donations, bequests, life insurance and other types of donations is available at icm-institute.org/en/support

**represents a maximum of 20% of earnings.*

YOUR PERSONAL CONTACT:
Ms Claire Pennelle
+33(0)1 5727 4756
contact@icm-institute.org

WITH YOU

Suzanne, 78 years old

I am elderly and without children. As I look into estate planning, I would like to leave a trace and continue to support ICM research to improve our understanding of diseases that affect my loved ones. What can I do?
You may decide to **transfer your estate with a bequest to the ICM**. There are several types of bequests depending on whether you wish to transfer all or a part of your assets (personal or real estate). To make a bequest to the ICM, you will need to draw up a will and discuss the issue with your notary. You may also designate the ICM as a beneficiary or co-beneficiary or a life insurance policy, simply by including the Institute's contact details in the beneficiary clause.

For more information please contact
Mrs Carole Clément
Bequests and Donations Manager
+33(0)1 5727 4141

SUPPORT FORM

Thank you for sending us the completed form today with your donation to the address:
ICM – Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l'Hôpital 75013 Paris

☒ **Yes, I support the ICM in defeating diseases of the nervous system**

I am making a contribution of : ..... €

☐ By check or postal order payable to ICM

☐ By credit card (except American Express)

Your credit card number: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Last 3 digits on the back: |_|_|_|

Expiry date: |_|_|_|_| Date: ...../...../.....

Signature: *(required)*

☐ I wish to receive complimentary information on legacies and donations.

You can make a donation online at: **www.icm-institute.org**

Your donation to the ICM is deductible up to 66% of income tax (limited to 20% of your taxable income), **or up to 75% for the solidarity tax on wealth** (up to a limit of € 50,000 deducted)

Your details

☐ Mrs ☐ Miss ☐ Mr ☐ Mr & Mrs

First name: .....

Surname: .....

Address: .....

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Zip Code: |_|_|_|_|_|

Town/City: .....

Email: .....

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Phone: .....

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