BRAIN AND SPINE INSTITUTE

ANNUAL REPORT

2015

SEARCH, FIND, CURE, FOR YOU & WITH YOU.

ICM
Brain & Spine Institute

ANNUAL REPORT

2015

"The Brain and Spine Institute – ICM was created so that women and men always remain free to move and think."

Prof. Gérard Saillant, ICM President

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Prof. Gérard SAILLANT

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ICM President

“Science is the one and only priority! We must do everything for the sake of science.”

5 years after the launch of the ICM, what is your take on these first years?
It’s very positive! The ICM is now a viable concept with proven results: scientific breakthroughs and publications, and international acknowledgment as a serious partner and attractiveness despite the Institute’s young age. Financially, our books are balanced thanks to donor support. Even though we keep fighting the good fight, we can be proud of this first stage.

What’s next?
We must keep going, and speed up the ICM’s development to make it easier for our researchers, especially with our plan to merge the different organizations into a single entity. This is a crucial step in the model we have designed, and we are confident that it will be extremely beneficial to everyday research management and expected results.

You met the goals you set with the Founding Members when the project was launched. Is the ICM the Institute you had in mind ten years ago?
It sounds incredible, but the Institute is in fact a symbol of when dreams and reality meet! Scientific results have met our hopes and the viability of our “rift” model is a constant encouragement to keep going and look even further. The support of our institutional partners, the AP-HP, CNRS, INSERM and UPMC, means a lot to us as they support us daily to bring the best of public and private research in one place.
The generosity of our 100,000 donors leaves me speechless: we see them as true partners, who have supported us from the start. It’s very touching, and their precious and loyal support is truly an honor. It is very important to us as we continue on our mission: search, discover, and treat brain and spine diseases. Additionally, our research teams have started to feel “right at home” at the ICM and develop a strong sense of belonging. We are so proud to see them represent the ICM, a pride much like that of prestigious French or American universities.

Now that you have seen it in action since September 2010, do you believe that the ICM research model will one day succeed in repairing the brain?
Our greatest success and best reason to believe that we will succeed in repairing the brain is the development and implementation of translational research. Leaving the laboratory to get to the patient’s bedside, and going from the patient to the laboratory is something only a handful of centers in the world can offer. We are lucky enough to have the opportunity to develop this within a Hospital, the Pitié-Salpêtrière in Paris, birthplace of neurology that opens its doors to over 100,000 patients every year in this field alone. This rift in the way we do research has given us great hopes and breakthroughs in 5 years, and we will renew our efforts and implication to achieve our goals.

What is your ambition for the 5 years to come?
Science is the one and only priority! We must do everything for the sake of science. It is time to go from discoveries to developing effective treatments to prevent and repair brain and spine diseases.
To do so, we have to finish writing the chapter on understanding the healthy brain –how could we treat something we don’t understand?– and only then will we be able to set up the best possible treatments for diseased brains. If in 5 year’s time, an ICM team tells me “We understand how the brain works”, we will have won our first battle.

How do we get there?
We will keep growing in numbers and especially in quality of research thanks to successful recruitment, new teams and important international partnerships.

Is there anything you would like to add?
I would like to assure those who trust and support us that we are fully devoted to keeping our promises. Every single day, we do everything we can to ensure the Institute’s continued development as a reference dedicated entirely to nervous system diseases, and transparency is our priority. Finally, I hope this annual report gives you the opportunity to discover the exceptional breakthroughs of this past year, an illustration our team’s excellence, thorough work and dedications. These breakthroughs are thanks to you: they are your discoveries, and for that, I give you my most sincere thanks.

Prof. Alexis BRICE

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ICM and IHU-A-ICM General Manager

2015 marked the ICM's fifth anniversary. What are three words that could describe these past five years?

Excellence: in five years, the ICM has become a key player in research on the nervous system and its pathologies. We have gone even further than the goals we set, with over 500 publications in 2015, major scientific and medical breakthroughs you will read about in this report, and many distinctions and awards for our researchers.

Attractiveness: the ICM attracts many researchers, both from France and abroad, as well as "visiting Professors" from the most renowned institutes. Within the 26 ICM teams, 50% are foreign post-doctorate researchers. This year, we are proud to welcome world-renowned researcher Bassem Hassan as team leader.

Visibility: the ICM has an international reputation in the field of neuroscience, allowing us to create strategic partnerships, organize exchanges for our students, researchers, and clinicians, and implement a summer school and international workshops. This international dynamic is of the utmost importance to encourage successful collaboration and communication.

Search, Find, Cure, for you and with you, has been the ICM's motto since it first opened. How does this translate into everyday activities?

The ICM is located at the heart of the Pitié-Salpêtrière Hospital: such a strategic location is a major advantage when it comes to developing innovative translational research. Going back and forth between fundamental and clinical research allows patients to benefit from diagnostic and therapeutic innovations much faster. Daily collaboration with the nervous system diseases branch of the Pitié-Salpêtrière, under the direction of Prof. Jean-Yves Delattre and with nearly 100,000 patients per year, fosters intermingling and discussion between researchers and doctors. Individuals are at the very heart of the ICM's philosophy.

Our ambition is to become a leading international neuroscience research institute. What has been done to meet this goal?

This year, we created a Scientific Steering Committee with Prof. Jean-Yves Delattre as Medical Director and Alberto Bacci as Scientific Director. It brings research and clinical staff closer together and implicates them directly in the ICM's scientific approaches. Our cutting-edge technical platforms help carry out competitive research projects at the ICM. Companies in the iPEPS incubator help accelerate research, turning scientific discoveries into therapeutic applications. This unique model, the ICM ecosystem where resources and knowledge come together in one same place, helps us develop innovative solutions and make them available to patients.

What are major points of the ICM's scientific strategy?

Our strategy aims at taking up this major healthcare challenge that is nervous system illness. Understanding how a healthy brain works is key to understanding and treating its altered functions in sick patients. We are striving to be at the forefront of the latest technological revolutions, elaborate innovative instruments to improve diagnostics and treatment of nervous system pathologies, and transform scientific discoveries into therapeutic solutions. Our strategy is centered on key topics where transversal and multidisciplinary projects play a part. Because I'm convinced that a breakthrough in one disease can lead to discoveries in others, the ICM model encourages an open and seamless approach.

What are some examples of transversal projects at the ICM?

Using a collaborative approach between biologists, clinicians and scientists, the ICM neuroimmunology group works on understanding the role played by the immune system in the development of various neurodegenerative diseases like Alzheimer's, Parkinson's, amyotrophic lateral sclerosis or multiple sclerosis. With this knowledge, the hope is to eventually explore new treatment options to fight these diseases.
Another transversal project is the "prion model" used to understand biological mechanisms responsible for neurodegenerative pathologies. Most neurodegenerative diseases, from Alzheimer's to Parkinson's or amyotrophic lateral sclerosis, share commonalities with prion diseases. The idea is that they would all originate from abnormal, poorly folded protein accumulating in the brain, capable of propagating from one neuron to the next and toxic for these neurons. The "prion model" is ideal for the study of shared mechanisms amongst these various pathologies. Finally, the study of rare neurological diseases can be used as a model to better understand and identify treatments for other neurological diseases. The treatment that was shown to be most effective against progressive multiple sclerosis, for example, developed by Medday, the start-up founded by Guillaume Brion and Fréderic Sedel, was originally designed to fight a very rare form of encephalopathy.

A joint call for tender between the ICM and IHU, Big Brain Theory, is a perfect illustration of innovative and interdisciplinary research. Can you tell us more?

This was a call for tender for innovative, original, and high risk projects thanks to new collaborations between various Institute teams and platforms. 15 projects were selected and financed by the ICM and IHU to explore new research fields. Among them, partnerships between experts on Alzheimer's disease and mathematicians to model the disease's progress to improve diagnostics and treatment, and partnerships between geneticists and clinicians to develop innovative prognosis and treatment orientation instruments for multiple sclerosis.

How is research used within the ICM?

The ICM's ambition is to lead research projects that accelerate the development of new treatments. The research application team, led by Alexis Génin, detects promising scientific results, creates partnerships with companies, protects precious research with patents, and encourages projects to develop new treatments, drugs, connected objects... In order to make every project count and give researchers from the Institute the opportunity to develop their own start-up, the iPEPS-ICM incubator creates a gateway between research and consequent practical applications.

What were three high points of 2015 for you?

The recruitment of Bassem Hassan, world-renowned researcher working on the understanding of brain development and its influence on individual behavior.
The confirmation of our economic model, illustrated by our balanced books.
The development of the living lab where clinicians, researchers, patients, and developers work hand in hand to identify challenges and develop prototypes for patient care.

A challenge for 2016?

In 2016, our challenge is the development of neuroinformatics, a field centered on the application of advanced mathematics and IT to neuroscience, a field sometimes called smart data or big data. Neuroinformatics is about collecting thousands of pieces of data from patients or healthy individuals, organizing them, storing them, analyzing them, and interpreting them using innovative methods. Multimodal integration of this data will allow us to explore unchartered territory, leading to scientific breakthroughs and new instruments for the healthcare system. Comparing a patient's data to models will allow personalization of the diagnosis, prognosis, and treatment. That is the goal of precision medicine. Our Bioinformatics platforms and tech teams are at the forefront of this development, led by a team coordinated by Stanley Durrleman. Neuroinformatics is a key field in the future of medicine.

Frédéric SALAT-BAROUX

IHU-A-ICM President

IHU-A-ICM FOUNDERS

What is the IHU-A-ICM's mission?
The IHU-A-ICM is meant to lead a best practice project in care, training, and technology transfer in research on nervous system diseases. Its priority is encouraging development of innovative preventive, diagnostic, or therapeutic products and processes.

2015 was a halfway point for the IHU-A-ICM, what is your assessment of these past three years of existence?
The assessment of the past three years is extremely positive. They have allowed us to develop international-level research in the field of nervous system diseases, neurology, and psychiatry, to create cutting-edge technical platforms, to implement research partnerships with the industry, to train future healthcare professionals, and to transfer hospital care to the patient's home.

What are some major projects led by the IHU-A-ICM?
The IHU-A-ICM participated in the development and implementation of large-scale clinical trials thanks to its role in national, European, and international networks on certain diseases. The INSIGHT study in partnership with Pfizer, for example, was an innovative study on Alzheimer's disease and one of the first in the world to follow healthy subjects at risk. It will open new doors in our understanding of this illness.
The ICEBERG cohort is at the center of the IHU's clinical project on Parkinson's, aiming at studying predictive conversion and progression factors of Parkinson's disease. We pursue large-scale projects that mean a lot to us in the fields of Alzheimer's disease, Parkinson's, and multiple sclerosis to identify treatment strategies of myelin repair, epilepsy to understand and anticipate seizures and behavioral disorders shared by many neurological pathologies, especially with the launch of the Prisme platform.

How has care improved?
The IHU-A-ICM has had spectacular progress by creating the Behavioral Neuropsychiatric Unit. To better understand the origin and mechanisms of these disorders and suggest therapeutic solutions, neurologists as well as psychiatrists and researchers collaborate within the unit. The exchange between neurologists and psychiatrists is key in improving patient care, better diagnoses, and adapted therapeutic solutions.

What are the IHU-A-ICM's scientific priorities?
We've identified several fields where we need to act more strongly: neuroimmunology, stem cells, molecular biology and system biology, as well as modeling and biostatistics. Our interdisciplinary scientific strategy is based on our high-performance technical equipment, from big data to high-resolution imaging, optogenetics, electrophysiology, and brain-machine interfaces.

In 2015, the IHU-A-ICM launched the very first edition of "Brain to Market", its summer school. Can you tell us more?
"The Brain to Market" was organized by the IHU-A-ICM and the College of Engineers to bring scientists and engineers together to share knowledge and design a project together. For this first edition, the chosen topic was Multiple Sclerosis (MS). Participants had access to researchers and MS experts, but also managers from companies and startups such as Sanofi, Genzyme, Ad Scientiam as well as Brain e-Novation, incubated in the ICM. With the help of a coach, participants were grouped into multidisciplinary teams and developed a project based on main issues surrounding the illness, with marketable potential. A jury of experts evaluated each project, some of which are currently under feasibility study. The Summer School, where long-term networks are born and innovative projects are designed, was a real success and the first of many to come.

In 2015, what were the three major successes of the IHU-A-ICM?
There are many, but let's take the Big Brain Theory as an example. This joint call for tender between the ICM and IHU-A-ICM allowed fifteen innovative and original transversal projects to arise.
The arrival of the PET-MRI, first dual clinical and research equipment in a French institute, that will support research on neurodegenerative illnesses and improvement of care. This innovative imaging technique allows improvement of diagnostic performance, following of brain lesion progress, and drug efficacy testing. We were able to acquire it thanks to an exceptional round of funding in collaboration with two founding members, the AP-HP and the Foundation for Alzheimer's Research.
Closer and stronger collaboration with the ICM through the implementation of administrative management, a transfer of technology office and a shared scientific steering committee.

How do you envision the future?
Our ambition is to become a translational research Institute, an essential gateway between fundamental and clinical research, and an international leader in the field of neuroscience. We want to transform discoveries into practical applications that meet patient and medical staff needs. For that, the iPEPS company incubator and the Living Lab are two major assets. We are part of a strong collaborative network including five major neuroscience institutions: the UPMC, AP-HP, INSERM, CNRS, and FRA (Foundation for Alzheimer's Research). Thanks to this institutional and industrial cooperation, we are doing everything we possibly can to prevent and treat nervous system diseases.

Prof. Jean-Yves DELATTRE

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Director of the Pitié-Salpêtrière Nervous System Diseases Center & ICM Medical Director

"The future of medicine is predictive and tailored to informed, decision-making patients."

You are currently director of the Pitié-Salpêtrière Nervous System Diseases Center and now, additionally, ICM Medical Director. What would you like to develop in your new position?

The Nervous System Diseases Center (NSD) combines the Neurology, Psychiatry, Continuing Care and Rehabilitation, Neurophysiology and Neuropathology departments of the Pitié-Salpêtrière Hospital. It is a powerful healthcare facility with nearly 500 beds, over 1,000 staff and nearly 250 doctors.
My key priority is helping the NSD, part of the teaching hospital, and the ICM unite their expertise to help advance clinical research and therapeutic innovation. This is a unique opportunity for our patients and our country. To me, that is the ultimate priority.

How does your daily medical experience influence your research?

Daily contact with individuals affected by or dying from diseases changes our way of looking at research. On the one hand, research is a source of hope for both the patients and ourselves. We have the right to believe in it! Not so long ago, who would have thought that after decades of failure, immunotherapy would completely change the way we treat some of the most terrible forms of cancer? Who would have thought that after years of complicated development, thrombectomy would turn out to be major progress in how we care for stroke victims? There are so many examples. On the other hand, for doctors, good research is research that helps their patients! For us, there is no hierarchy in the way we do research. We need talent to understand and design, yet we also need talent to implement thorough clinical trials. If we are missing a component, we do not get anything out of it for the patient.

What are three major highlights of 2015?

For me, there is only one, and I place it above all of my topics of interest: our nation's solidarity when it comes to our values. How strong we can stand when we are united!

What are your hopes for 2016?

Getting a green light on a new building, "Paul Castaigne", bringing the whole practice of Neurology of the Pitié-Salpêtrière under one roof. It would be an opportunity to rethink our organization and create an even stronger gateway between medical care and clinical research, right by the patient's bedside. I hope we can give our paramedical and medical teams from the wing the opportunity to identify with the ICM. It is "our ICM"!

How do you envision the future? In your opinion, what does tomorrow's healthcare look like?

The future of medicine is predictive and tailored to informed, decision-making patients. Medicine has always taken steps forward by identifying different therapies for different entities in what seemed to be, at the start, shared context. I don't see why that would change.
I also believe that patients will speak up more, and taken into consideration, including when that means deciding what the future looks like in the case of terminal and disabling illness.

A typical week with Jean-Yves Delattre, even though he expects the unexpected!

Monday

- "NSD Center Administration" meeting with management staff to discuss organization
- ICM Board of Directors meeting
- Local Executive Committee meeting with fellow department directors and the Pitié-Salpêtrière Hospital board to decide on the Hospital's strategy

Tuesday

- Follow-up on organization of a national reference center on rare brain tumors
- Follow-up on current clinical trials
- Department staff meeting
- Group dedicated to developing supportive care
- Web conference with French colleagues specialized in rare brain tumors for the National multidisciplinary discussion meeting

Wednesday

- Patient appointments all day

Thursday

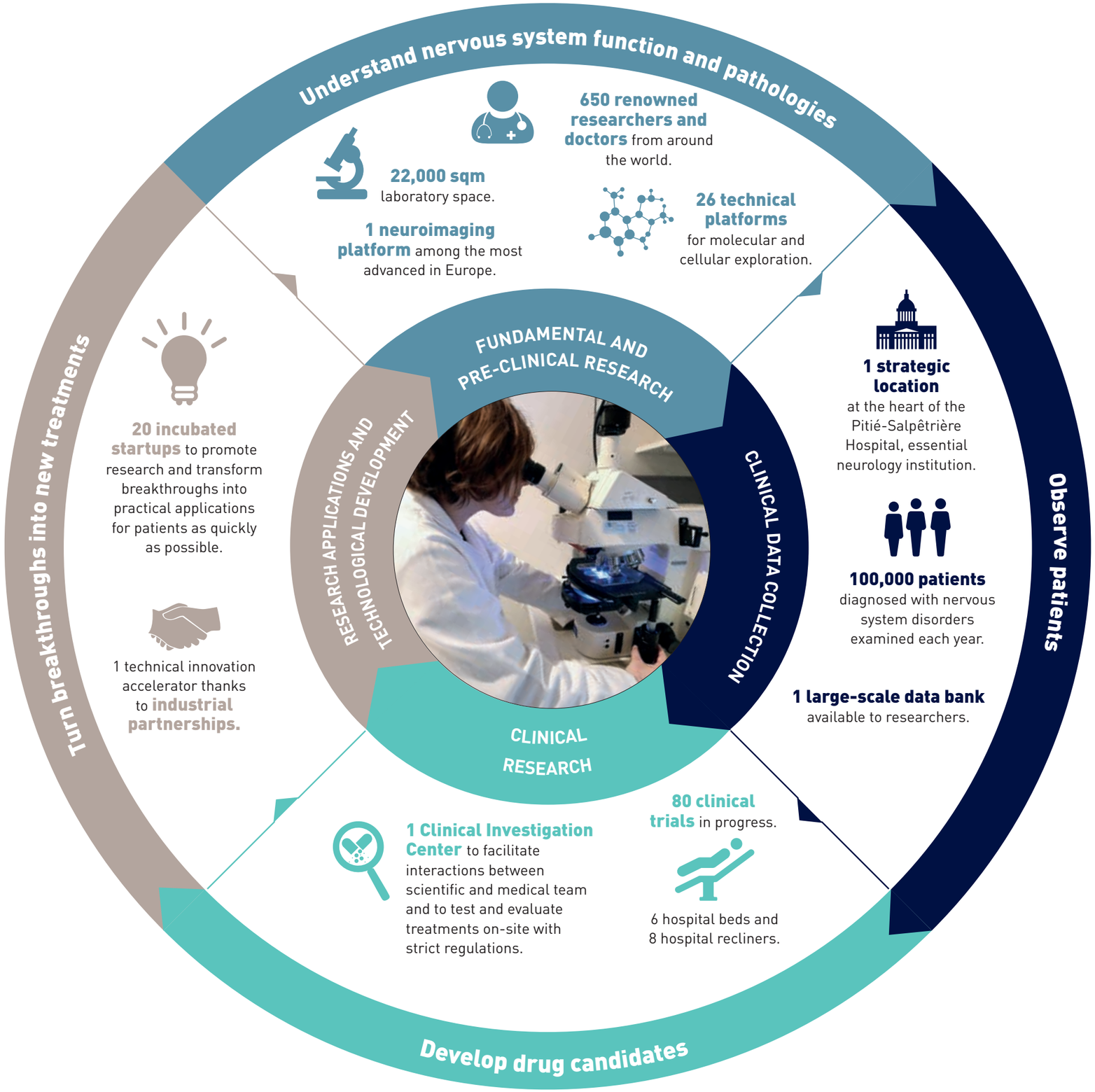
- Department physician meeting to discuss medical organization
- Department administration
- Department medical meeting
- Multidisciplinary Neuro-oncology meeting chair

Friday

- Research meeting at the experimental Neuro-oncology laboratory at the ICM
- Neuro-oncology clinical research meeting

THE ICM
A UNIQUE MODEL CREATED FOR AND WITH EACH PATIENT

The Brain and Spine Institute (ICM) in an international-level research center, the only of its kind in the world, innovative both in design and organization. Bringing patients, doctors, and researchers together in the same place has the goal of allowing rapid development of treatments for nervous system lesions and administering them to patients. The best scientists, from all horizons and countries, come to the ICM to develop the most advanced research in their field. To allow researchers to make progress in their work and give patients realistic hopes, we all need to be involved: public administration, private companies, and individuals. This is a battle that affects each and every one of us.



Research —

PATHOLOGIES AND TEAMS

Alzheimer's, Parkinson's, and Amyotrophic lateral sclerosis are all three diseases caused by degeneration of various types of neurons. What are risk factors for these pathologies? How can we detect and distinguish these diseases early on, or even predict them? Which mechanisms are responsible for neuron loss? How can we fight them to stop the disease's progression? Researchers and clinicians benefit from the ICM and its advanced technical platforms to find answers to these questions, and fight against disease.

#Alzheimer's

With nearly 860,000 individuals affected by Alzheimer's-type dementia in France, the disease is a key concern. It is characterized by slow degeneration of neurons, from a very specific area to the whole brain. How can we prevent lesion emergence and slow down the disease's progression?

THE ICM'S ANSWER:

#PREVENT EMERGENCE
#DIAGNOSE
#CLINICAL TRIALS

- **Identify risk factors to improve diagnosis or even prevent disease emergence** with a team led by Bruno Dubois.
- **Understand propagation mechanisms**, both for Alzheimer's disease and prion diseases, and develop experimental modeling to diagnose the disease and test new treatments with a team led by Marie-Claude Potier and Stéphane Haïk.
- **Study the role played by lipids in Alzheimer's disease to identify therapeutic targets** with a team led by Marie-Claude Potier and Stéphane Haïk.
- **Study the role played by the immune system** to find ways to fight against the disease with Cécile Delarasse in a team led by Bertrand Fontaine and Sophie Nicole.
- **Test new drugs** in national and international multicentric clinical trials with a team led by Bruno Dubois.

!SIGNIFICANT DEVELOPMENTS

Alzheimer's disease lesions 20 years prior to emergence[1]

Several studies have confirmed that presence of amyloid plaques can allow diagnosis of Alzheimer's disease patients and eventually help predict who will develop the disease. In an international study, Harald Hampel –AXA/UPMC head professor on Alzheimer's disease– and his team identified a silent stage or close to ten years in the disease, where there are no clinical signs yet biological markers are observable, indicating that earlier detection of Alzheimer's disease is possible. Identifying diagnostic or predictive markers of Alzheimer's disease, 20 to 30 years before the onset of dementia, has become a key challenge.

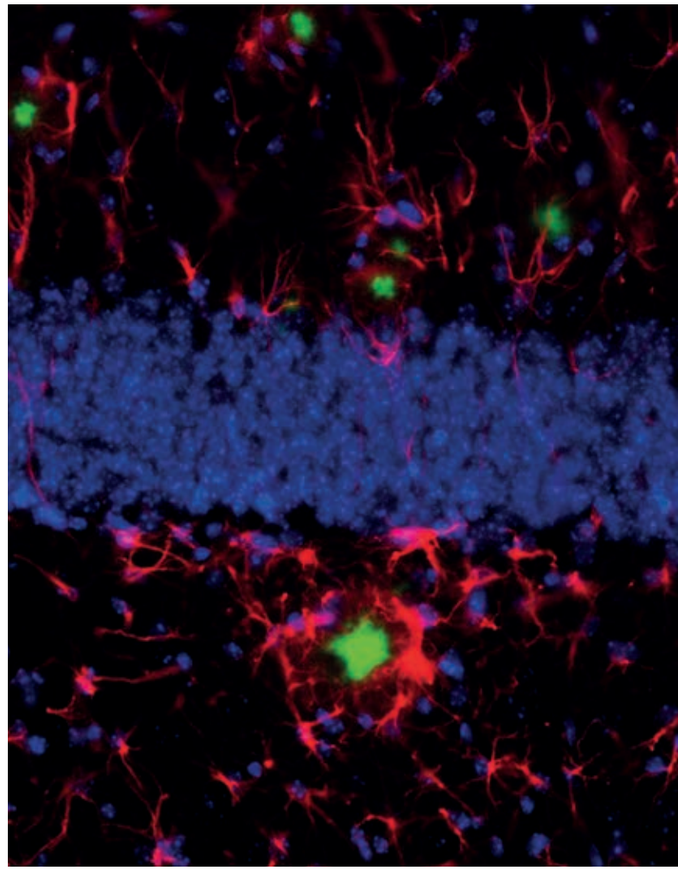
Alzheimer's disease diagnosis with blood testing?[2]

Identifying blood markers for early Alzheimer's disease diagnosis and prediction of progress is a major challenge. A study led by Marie-Claude Potier and her team showed, for the first time, that blood cells in Alzheimer's patients have specific morphological alterations. This breakthrough gives hope for diagnosis with a simple blood test.

Dementia or Alzheimer's: a simple test could tell them apart[3]

Patients diagnosed with frontotemporal dementia require specific and appropriate care. However, the disease is still often confused with Alzheimer's disease. Researchers and clinicians from the ICM and the Institute for Memory and Alzheimer's Disease (IM2A*), in collaboration with an international team, have proven that simple tests evaluating empathy could assist with diagnosis.

**The IM2A is supported in part by the Association for Alzheimer's Research.*

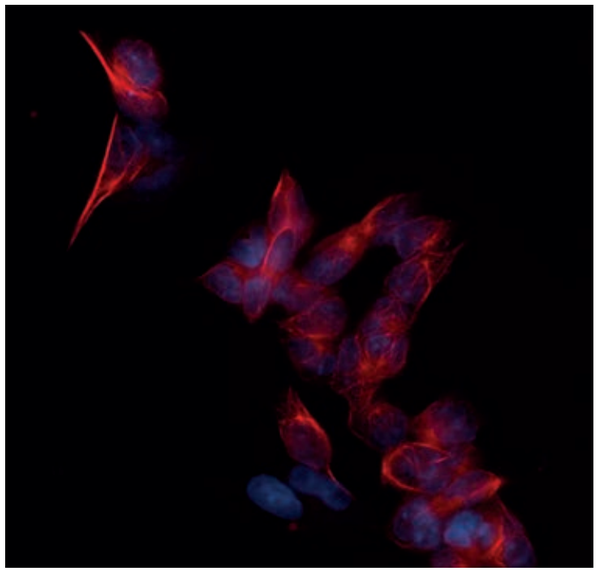


#Alzheimer's

CLINICAL RESEARCH HIGHLIGHTS

Improving understanding of disease causes

The INSIGHT study, conducted in partnership with the IHU, the Institute for Memory (IM2A), the Plan-Alzheimer Foundation, AMIVID and Pfizer and led by Prof Dubois, is an innovative look at Alzheimer's disease. It is one of the first studies worldwide to follow over 320 currently healthy at-risk individuals to understand why and how Alzheimer's disease emerges in some individuals and not others. Additionally, it aims to identify Alzheimer's triggering factors. This study brings high hopes to our understanding of the disease.



First clinical trial to prevent disease emergence

Bruno Dubois and Isabelle Le Ber, in collaboration with Prof. Hannequin at the Rouen University Hospital, are conducting an international multicentric study to test efficacy of a neuroprotective drug in rare genetic forms of Alzheimer's disease. The study's specificity lies in its protocol of offering the treatment to currently healthy yet at-risk individuals who carry a genetic mutation known to be a cause of disease. It is the first neuroprevention clinical trial with human participation.

Effects of a drug on early stage Alzheimer's disease progression

The Solane protocol, coordinated by Bruno Dubois, aims at testing the effects of solazenumab, a drug that could potentially lower or slow down amyloid plaques formation, thought to be a cause of Alzheimer's disease symptoms. The study's goal is to test drug efficacy on early stage disease progression: does it slow down mental and functional decline associated with the disease?

The immune system's early protective role[4]

A study conducted in collaboration with the Saint-Anne Hospital, the CEA, the Saint-Antoine Research Center and Roche, coordinated by Prof. Marie Sarazin, has demonstrated the beneficial and protective role of the immune system in early stages of Alzheimer's disease thanks to innovative brain imaging techniques. This study underlines the importance of early diagnosis of the disease and creates new outlooks in treatment to slow down, or even prevent its progression.

→ TAKING RESEARCH ONE STEP FURTHER

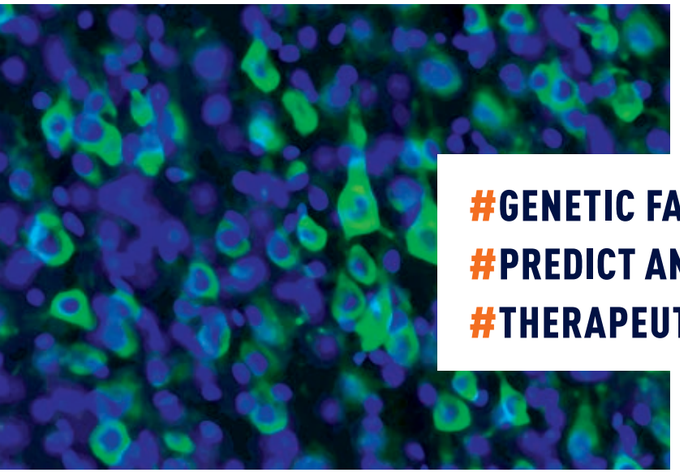
A new molecule

A research project in collaboration with MEDDAY, startup founded by Guillaume Brion and Fréderic Sedel, has launched to test therapeutic potential of a new molecule, MD1105, against Alzheimer's disease.

#Parkinson's

Parkinson's disease, with over 150,000 affected individuals in France and the second largest cause of physical handicap, is characterized by the neurodegeneration of dopaminergic neurons. These neurons produce a substance called dopamine, which plays a part in information transfer between neurons and is necessary for coordinated movements. Symptoms of the disease are slower movements, limb stiffness, shaking, as well as walking and balance disorders. How can we slow down the disease's progress and reduce its symptoms?

THE ICM'S ANSWER:



#GENETIC FACTORS
#PREDICT AND SLOW DOWN PROGRESSION
#THERAPEUTIC SOLUTIONS

♦ **Identify genetic risk factors** to improve diagnosis or even prevent disease and develop individualized treatment with a team led by Alexis Brice.

♦ **Identify prognosis and predictive markers and understand mechanisms at work** thanks to an integrated approach combining genetic, metabolic, physiological, and clinical information with a team led by Marie Vidailhet and Stéphane Lehéricy.

♦ **Develop innovative technological approaches** to identify new treatment targets with a team led by Philippe Ravassard.

♦ **Prevent neurodegeneration** and test the protective effect of various molecules with a team led by Etienne Hirsch.

♦ **Treat walking and balance disorders** thanks to deep brain stimulation with a team led by Brian Lau and Carine Karachi.

!SIGNIFICANT DEVELOPMENTS

A new gene implicated in an early and severe form of Parkinson's disease[5]

Suzanne Lesage and Olga Corti, part of a team led by Alexis Brice, have identified a new gene, VPS13C, implicated in early stage Parkinson's disease. The protein it codes is necessary for neuron protection by maintaining mitochondrial function. These results increase understanding of mechanisms leading to neurodegeneration, creating opportunities for possible therapies. Additionally, they will allow the implementation of a diagnostic instrument for these very rare and severe forms of the disease to take care of patients as early as possible.

A mechanism that protects neurons from stress[6]

Researchers from the team led by Alexis Brice have discovered a mechanism that protects neuron from cellular death. Olga Corti and colleagues have described a natural protective mechanism of mitochondria in an experimental modeling of Parkinson's disease. This mechanism implies sustaining expression of a protective mitochondrial enzyme, HSD17B10, under the influence of Parkine, whose role in damaged mitochondrial degradation has been well-described. Loss of this new protective mechanism could contribute to mitochondrial malfunction and dopaminergic neurodegeneration in the form of Parkinson's disease caused by Parkine gene mutation.

Sleep-wake cycle regulation, survival factor for dopaminergic neurons[7]

A notable fraction of hypothalamic neurons that secrete orexin, a neuropeptide implicated in sleep-wake cycle regulation, disappears in Parkinson's disease. Researchers from a team led by Etienne Hirsch have proven the existence of direct interaction between those neurons and dopaminergic neurons located within the substantia nigra whose loss causes motor skill disorders typical of the disease. The researchers also discovered that orexin acts as a survival factor for dopaminergic neurons with a mechanism involving specific receptors. These observations suggest that a therapeutic approach to restore neurotransmission capabilities to orexin in Parkinson's patients could halt the disease's progress.

Treating walking ability disorders with deep brain stimulation[8]

Walking ability and balance disorders, and consequent falling caused by Parkinson's disease are a major healthcare issue. ICM researchers recently proved that an area of the brain stem is implicated in control of walking ability in humans, and that stimulating this area could reduce consequent disorders. Deep brain stimulation of this area improves walking ability and balance disorders in some Parkinson's disease patients. These preliminary results enhance understanding of this region of the human brain stem and open the door to developing new treatments.

#Parkinson's

CLINICAL RESEARCH HIGHLIGHTS

Identify markers to follow and predict disease progression[7]

The ICEBERG study led by Marie Vidailhet and Stéphane Lehéricy, conducted at the ICM on 330 patients, at-risk individuals and healthy subjects over 7 years, aims at identifying and confirming markers that have the ability to predict and follow evolution of Parkinson's disease lesions, from the emergence of initial symptoms to the clinical expression phase. The current stage is focused on biomarker research. A marker was identified in a pre-symptomatic form of Parkinson's disease, in which patients display isolated behavioral disorders during REM sleep. With the help of brain imaging, researchers highlighted a reduction in signal in a small structure within the brain stem. The main challenge of these coming years is to:

- Slow down Parkinson's disease progression, limit disorders and develop individualized care;
- Prevent emergence of symptoms in at-risk subjects thanks to effective diagnostic instruments and targeted treatment development.

Understand causation of compulsive disorders caused by medication

The Badge-PD study conducted on 310 patients aims at researching potential genetic causes of compulsive disorders experienced by some patients, effects of antiparkinson drugs. Results of this multicentric and institutional study, coordinated by Prof Corvol, are currently undergoing analysis and will improve patient care.

→ TAKING RESEARCH ONE STEP FURTHER

Game therapy for patient rehabilitation

The TOAP RUN game developed by BRAIN e-novation, shared laboratory of the ICM and the GENIOUS group and codirected by Marie-Laure Welter and Pierre Foulon, was designed to fight against walking ability and balance disorders, and falling in Parkinson's disease. The patient's character in the game is a small animal, a sporty Toap, that needs to pick up coins on its path while avoiding obstacles. Preliminary results of the current clinical trial at the ICM are very encouraging, and show that the game is widely accepted and used with a high decrease of patient falls, an objective improvement in walking ability and instability as well as a decrease in fear of falling. This project received an award in the World Innovation Competition – Phase 1.

Fighting against involuntary movement

The ICM and CleveXel Pharma, pharmaceutical company driven by Christian Bloy, have launched a phase II clinical trial at the CIC to evaluate efficacy of molecule CVXL-0107 against motor fluctuations and involuntary movement (dyskinesia) provoked by L-Dopa, the standard Parkinson's disease treatment.

A smartphone app for daily patient monitoring

An application developed by AD SCIENTIAM, a startup incubated at the ICM and driven by Liouma Tokitsu, studies daily symptom changes in Parkinson's patients. The application is available nationwide within the NS-PARK network. The network brings 24 clinical research centers together, that all care for patients with Parkinson's disease or movement disorders. It aims at encouraging clinical trials to develop life-improving drugs for patients.

Serious game developed by BRAIN e-novation

#Amyotrophic lateral sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), also known as Charcot disease, affects motor neurons, neurons that go from the brain and spinal cord to control muscles. Patients diagnosed with ALS suffer from progressive motor disability leading to paralysis. What factors are responsible for the development and progression of ALS?

THE ICM'S ANSWER:

#GENETIC CAUSES
#DIAGNOSIS
#THERAPEUTIC OUTLOOKS

♦ **Identify risk factors** for disease modeling and explain mechanisms implicated in disease progression with teams led by Séverine Boillée and Edor Kabashi.

♦ **Identify factors involved in disease progression to design new treatment targets** with a team led by Bertrand Fontaine and Sophie Nicole.

♦ **Slow down ALS progression** thanks to understanding the role of inflammation in motor neuron degeneration with a team led by Séverine Boillée.

♦ **Discover new treatments** thanks to, on the one hand, zebrafish modeling with a team led by Edor Kabashi and, on the other hand, human motor neuron cultures generated from induced pluripotent stem cells derived from patients with a team led by Séverine Boillée. These models enable testing of different molecules to fight illness.

!SIGNIFICANT DEVELOPMENTS

Discovery of a new gene[10]

ALS is attributed to numerous genetic factors, most frequently genes *C9orf72* and *SOD1*. Stéphanie Millecamps, in a team led by Séverine Boillée, participated in the discovery of new gene TBK1, identified in familial ALS associated with frontotemporal dementia or not. Degeneration of *TBK1* protein function, related to the immune system and autophagy (degradation of abnormal proteins within cells), is a mechanism that could be present in the disease and lead to neurodegeneration. The discovery of this gene will allow improved understanding of ALS mechanisms and the opportunity to fine-tune diagnostic instruments.

Identification of a toxic factor for motor neurons[11]

ALS, like all other neurodegenerative diseases, involves an immune response in the central nervous system to protect the body. How does this immune reaction turn harmful and participate in death of neurons? A team led by Séverine Boillée proved that in cases where mutation causes ALS, cells responsible for nervous system protection liberate toxic factors leading to motor neuron death. By blocking the release of these factors, researchers managed to slow ALS progression in an experimental model. By highlighting this mechanism, researchers created a new opportunity to develop novel therapeutic strategies.

Can a defect in protein degradation cause ALS?[12]

A team led by Edor Kabashi developed the first ever zebrafish model to display *Sqstm1* gene mutation. Inactivation of the gene leads to loss of motor skills and motor neuron deficit in zebrafish, replicating symptoms of ALS. Thanks to their model, researchers proved that stimulating autophagy (degradation of abnormal proteins within cells) restores normal motor skills in zebrafish. Deregulation of autophagy could lead to ALS. These very encouraging results could represent an interesting therapeutic outlook for patients with ALS. The model also allows candidate molecule testing.

Can targeting the neuromuscular junction bring hope for ALS patients?[13]

Gaelle Bruneteau, in a team led by Bertrand Fontaine and Sophie Nicole, and colleagues have proven the existence of early morphological anomalies in neuromuscular junctions in ALS patients. These anomalies could significantly contribute to motor skill alteration. The neuromuscular junction connects motor neurons and muscle fiber, and its activation is at the source of muscle contraction. Additionally, protein overexpression in muscle, Nogo-A, is associated with stronger anomalies of neuromuscular junctions with more frequent loss of contact between motor nerves and muscles and poorer functional prognosis. Muscular buildup of Nogo-A, observed in ALS patients, could be a factor of poor prognosis.

#Amyotrophic lateral sclerosis (ALS)

CLINICAL RESEARCH HIGHLIGHTS

Identify biomarkers to predict disease 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 progressing for each patient.

Identify biomarkers to characterize motor neuron diseases

A study coordinated by Pierre-François Pradat compared muscular gene expression profiles between ALS patients, patients with various motor neuron diseases (Kennedy syndrome, spinal amyotrophia), and healthy subjects. The goal is to establish a "molecular signature" of various motor neuron disease sub-types in order to establish precise diagnoses to improve patient care.

Make human motor neurons from patient skin fibroblasts[14]

Lucette Lacomblez is coordinating a study establishing a collection of skin cells (fibroblasts) from 30 patients with ALS. Delphine Bohl from Séverine Boillée's team then generates induced pluripotent stem cells called iPS from these fibroblasts and differentiates them into pure motor neuron cultures. The goal of this study is to observe and compare motor neuron defects in patients with various genetic mutations to improve understanding of the disease and design new models to test therapeutic molecule efficacy.

Improve walking ability

A study conducted on 31 patients, coordinated by Pierre-François Pradat and in collaboration with Giovanni de Marco (CeRSM laboratory, Nanterre) evaluated walking and postural control using a multidisciplinary approach combining neurophysiological analysis and neuroimaging. The goal of this study is to develop therapeutic strategies (pharmacology, rehabilitation) to improve walking ability among ALS patients.

An instrument to write using eyes

Due to their disability, patients with ALS have difficulty speaking. A pilot study led by Timothée Lenglet in collaboration with Jean Lorenceau aims to teach patients with important motor skill disorders to write using their eyes, thanks to a device allowing users to draw and write using eye movement. The study was conducted at the Therapeutic Assessment Center.

#Multiple sclerosis (MS)

A myelin sheath surrounds neuronal projections, axons, and plays a key role in rapid conduction of nerve impulse and axon protection. In multiple sclerosis (MS), immune system malfunction, where the immune system attacks the individual's own elements, leads to destruction of the myelin sheath. Depending on its location, demyelination, that can take place in the brain as well as spinal cord, causes movement, sensation, balance, and visual impairments... How can we prevent myelin sheath destruction? How can we repair lesions? Which factors influence repair? How can we follow disease progression and predict lesion progression? How can we slow it down, or even halt it?

THE ICM'S ANSWER:

#REPAIR
#MULTIMODAL ANALYSIS
#CANDIDATE THERAPIES

♦ **Decrypt mechanisms at work in nervous system destruction** to fight the disease more effectively with a team led by Bertrand Fontaine.

♦ **Understand mechanisms in myelin sheath repair** to identify target treatments with team led by Catherine Lubetzki, Bruno Stankoff, Brahim Nait Oumesmar, and Anne Baron Van Evercooren.

♦ **Develop powerful and complementary instruments to identify neuroreparative molecules from a large pool of test molecules**, with teams led by Jean-Léon Thomas, Brahim Nait Oumesmar, and Anne Baron Van Evercooren.

♦ **Repair damage through spontaneous remyelination or via stem cells** with teams led by Catherine Lubetzki, Bruno Stankoff, Brahim Nait Oumesmar, and Anne Baron Van Evercooren.

♦ **Measure disease progression thanks to cutting-edge techniques** to predict patient progression and adapt treatment with teams led by Catherine Lubetzki, Bruno Stankoff, and Bertrand Fontaine.

!SIGNIFICANT DEVELOPMENTS

Genes that modulate MS risk[15]

A team led by Bertrand Fontaine and Sophie Nicole participated in various studies within an international consortium conducted on over 17,000 patients. Results identified genetic risk factors in MS and several protective genes. Affected genes are linked to recognition of extraneous elements by the human body. Identifying mutations or mutation combinations that modulate genetic risk is an opportunity to improve understanding of MS triggering and develop therapies. A clinical study is in progress at the Therapeutic Assessment Center, conducted on MS patients and targeted based on their genetic background.

Instruments for screening of restorative molecules[16]

Brahim Nait Oumesmar, within the NeurATRIS consortium, designed a high throughput in vitro screening of molecules that encourage differentiation of oligodendrocyte progenitor cells into mature oligodendrocytes, whose role is myelin sheath repair. Candidate molecules go through in vivo testing in a unique model developed by Bernard Zalc. The test generated a transgenic Xenopus; the Xenopus is an amphibian with myelin sheathing similar to humans, in which induced demyelination is possible. Xenopus tadpoles are transparent, allowing researchers to follow remyelination in real time and test repair potential of candidate molecules.

Repair myelin sheath lesions with skin cells[17]

A team led by Brahim Nait Oumesmar and Anne Baron Ven Evercooren has taken up a challenge: transform skin cells into nerve cells to repair damage caused by multiple sclerosis and certain leukodystrophies. Very encouraging results give hope for cell therapy using cells from the patients themselves. The team also proved that human neural stem cells have a dual therapeutic effect, both anti-inflammatory and promyelinating.

A factor of myelin repair[18]

A team led by Brahim Nait Oumesmar and Anne Baron Van Evercooren showed the beneficial effect of molecule Olig2 in myelin sheath repair. Its overexpression stimulates regeneration of oligodendrocytes, responsible for myelin production. This discovery could have a significant impact on development of treatment strategies to stimulate MS damage repair.

Progenitor cells to the rescue?[19]

The central nervous system is home to a large population of progenitor oligodendrocyte cells, or POCs. They are responsible for production of new oligodendrocytes that produce and repair myelin sheathing. A team led by Catherine Lubetzki and Bruno Stankoff used experimental modeling to prove that during demyelination, POCs are activated and express inflammatory factors (Ccl2 and IL1b) that foster migration and differentiation into oligodendrocytes in the demyelinated zone. Identification of mechanisms that control remyelination is a first step towards treatment development for patients with MS.

Measure multiple sclerosis progression with a cutting-edge technique[20]

Using an innovative multimodal positron emission tomography imaging program (PET-SCAN), the team led by Bruno Stankoff and Catherine Lubetzki was able to visualize neuron demyelination and remyelination. This method could identify patients based on their ability to renew destroyed myelin sheathing and direct the most appropriate course of treatment. Another tracer (flumazenil) in the PET SCAN allowed researchers to quantify neurodegeneration and locate it in MS patients.

#Multiple sclerosis (MS)

CLINICAL RESEARCH HIGHLIGHTS

Identifying disease biomarkers

Bruno Stankoff is coordinating a study aiming to discover differential biomarkers of inflammation, myelin destruction, and neurodegeneration thanks to advanced imaging techniques. Biomarker identification will enable disease progression prediction and patient response to tailor patient care and therapy.

A treatment for primary progressive multiple sclerosis

The Oratorio protocol, in partnership with Roche and coordinated by Caroline Papeix, texted Ocrelizumab efficacy in patients with primary progressive multiple sclerosis. Very encouraging results of this phase III study show that the drug significantly reduces impairment progression in patients, with a 24% decrease in risk of worsening impairment.

→ TAKING RESEARCH ONE STEP FURTHER

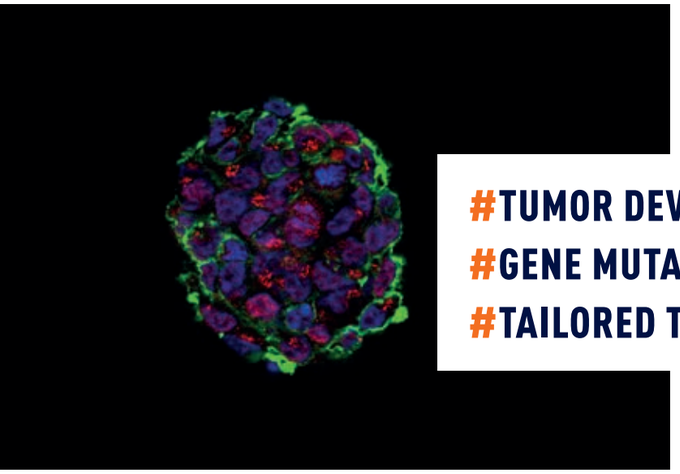
Treatment that improves general health of patients

For the first time, a drug developed by MEDDAY named MD1003 slows disease progression and improves general health of patients with primary progressive multiple sclerosis. The drug should be available soon, an encouraging development for clinicians as well as patients.

#Tumors

In France, nearly 5,000 individuals are diagnosed with early malignant brain tumors. How do these tumors develop? How can we diagnose them before it is too late? How can we predict aggressiveness more precisely? What innovative treatment strategies could allow specific targeting?

THE ICM'S ANSWER:



#TUMOR DEVELOPMENT
#GENE MUTATION
#TAILORED TREATMENT

♦ **Identify causes and understand mechanisms of tumor development** to highlight potential treatments with a team led by Emmanuelle Huillard.

♦ **Develop diagnosis and prognosis instruments** to detect genetic mutations that cause tumors, analyze prognostic and predictive value in reaction to treatment, and deliver helpful information to clinicians with a team led by Marc Sanson.

♦ **Develop tailored therapy** based on each tumor's genetic profile with a team led by Marc Sanson.

!SIGNIFICANT DEVELOPMENTS

New genes involved in oligodendrogliomas: TCF12[21]

Thanks to international collaboration and the POLA network coordinated by Prof Jean-Yves Delattre at the ICM, teams led by Emmanuelle Huillard and Marc Sanson characterized a new gene, *TCF12*, involved in development of an aggressive form of brain cancer, anaplastic oligodendrogliomas. Inactivation of the transcription factor leads to loss of tumor suppressor gene expression and could be associated with higher tumor aggressiveness. This discovery opens new pathways in understanding tumor development and identifying causal factors. It gives long-term hope for tailored treatment based on molecular alteration.

New genes involved in oligodendrogliomas: CIC[22]

60% of oligodendrogliomas have a CIC mutation, CIC being a transcription suppressor (one of the stages in the transformation of DNA to protein). Vincent Gleize, from a team led by Marc Sanson, explained the gene's mode of action within tumor cells. CIC inactivation leads to an accumulation of proteins involved in cell proliferation. This accumulation leads to tumor development. Identifying these mechanisms is a first step towards identifying potential target treatments.

Hope for tailored glioblastoma treatment[23]

Specific treatments based on tumor mutation profiles are implemented thanks to the Gliotex experimental therapy platform (supported by the ARC Foundation for Cancer Research and by the Association for Brain Tumor Research), co-directed by Ahmed Idbaih and Jean-Yves Delattre. Within this setting, a team led by Marc Sanson tested MDM2, an oncogene-targeting inhibitor that displays gene amplification in certain tumors. Results are very encouraging for future development of tailored therapies and give hope for implementation of a phase I clinical trial.

A novel preclinical meningioma model, precise copy of the human pathology[24]

Meningiomas are primitive central nervous system tumors, most frequent in adults over 35 years of age. A majority is benign, yet some can be more aggressive with multiple relapses. Michel Kalamarides and Matthieu Peyre have been developing preclinical meningioma modeling for a long time. They have just proven that inactivation of certain genes, *Nf2* and *Cdkn2ab*, as well as activation of growth factor PDGF-B in meningeal cells, generates meningiomas in mice that develop very quickly (high grade). This unique model will enable them to test new and promising therapies for patients.

New targets identified in primitive brain lymphomas[25]

Khe Hoang-Xuan has identified specific and frequent mutations in central nervous system primitive lymphomas that affect genes *MYD88* and *CD79B*. These mutations activate two signaling pathways that appear to play an important part in development of these lymphomas. They are not only diagnostic biomarkers, but also opportunities for innovative and targeted clinical trials..

#Tumors

CLINICAL RESEARCH HIGHLIGHTS

Specific and tailored therapy

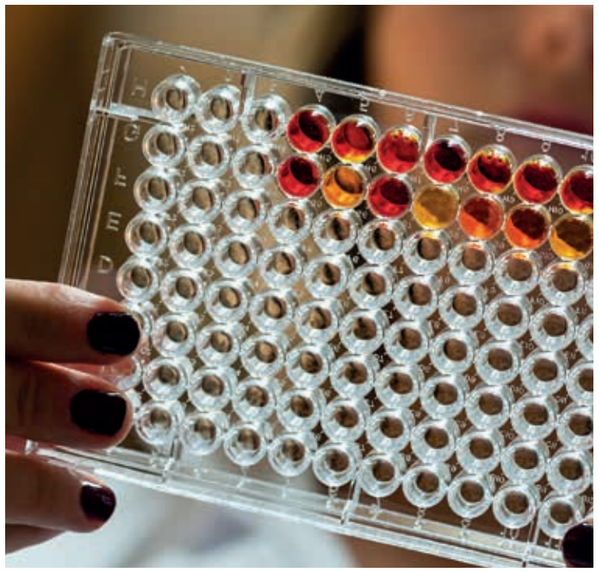
The "*TARGET*" clinical trial, coordinated by Marc Sanson, was launched nationally and could be rolled out at an international level. It aims to test specific and tailored therapy on patients with glioblastoma expressing highly oncogenic anomalies, meaning that they are responsible for tumor development. The study is conducted in partnership with Astra-Zeneca and Assistance Publique-Hôpitaux de Paris.

Oncolytic virus testing

"ONCOVIRAC" is a Phase I clinical trial led by Ahmed Idbaih testing an oncolytic virus, a virus modified to solely destroy cancerous cells in patients with glioblastoma. The trial, set to launch soon[1], is the result of a partnership between Transgène, the firm responsible for developing the virus, and Assistance Publique-Hôpitaux de Paris.

A method for non-invasive MRI diagnosis

IDH1 gene mutation is specific to gliomas and affects 40% of them. It plays a major part in tumor development and entails *D-2HG* metabolite accumulation inside the tumor. The "IDASPE" trial, coordinated by Marc Sanson and implemented in collaboration with the CENIR, developed *D-2HG* detection in tumors with MRI spectroscopy, creating a non-invasive diagnostic instrument that may soon be available to clinicians.



[1] Within the INCa Early Phase Standardized Center – Galilée, part of the Centers for Early Trials of New Drugs network.

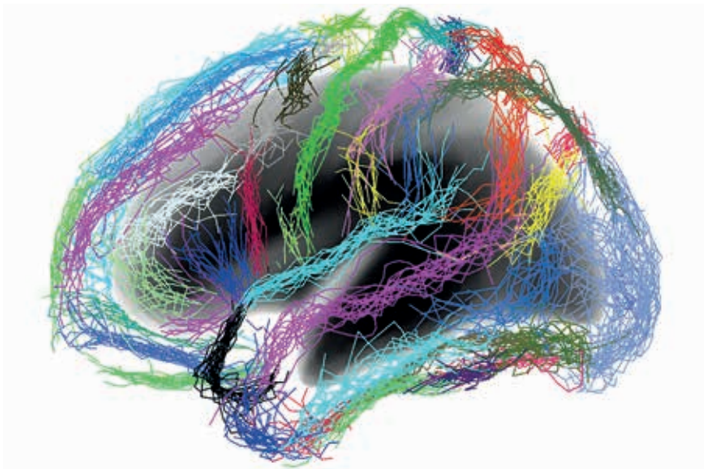
→ TAKING RESEARCH ONE STEP FURTHER

Prolonged release of anticancer molecules

GECKO BIOMEDICAL, managed by Christophe Bancel, is developing a technique for prolonged release of anticancer molecules during surgery in cases of glioblastoma.

Ultrasounds: a revolution in brain tumor treatment?

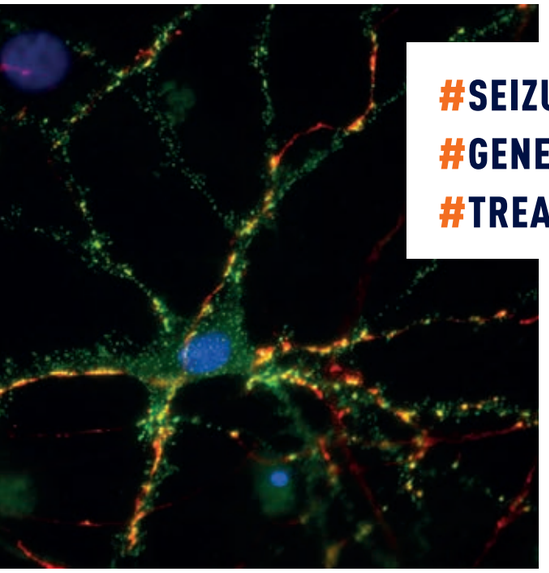
Thanks to ultrasound use, it is now possible to open the blood-brain barrier on demand to allow drugs to reach affected areas of the brain. The SonoCloud ® system was developed by CarThera, company located within the ICM, based on research by Professor Alexandre Carpentier, neurosurgeon at the Pitié-Salpêtrière Hospital. This medical breakthrough will enable significant increases in drug efficacy for drugs that do not yet manage to cross the blood-brain barrier that protects brain tissue. Brain tumor and neurodegenerative disease treatments could become much more effective. Phase I clinical trials are in progress.



#Epilepsy

Epilepsy is one of the most common neurological diseases, affecting nearly 1% of the population. An epilepsy seizure is caused by excessive and brief electrical activity in a group of cortical neurons. The surge may be limited to a certain area in the cortex (focal seizures) or may spread to the whole cortex (generalized seizures). How can we predict epilepsy seizures? Which genes are responsible for epilepsy? How does a seizure begin? How does it develop?

THE ICM'S ANSWER:



#SEIZURE ANTICIPATION
#GENETIC FACTORS
#TREATMENT EFFECTS

♦ **Identify involved genes to develop diagnostic and therapeutic instruments** with a team led by Eric Leguern and Stéphanie Baulac.

♦ **Understand underlying mechanisms of seizures and develop modeling to test new treatments** with a team led by Richard Miles.

♦ **Study brain dynamics during seizures and understand their impact on cognitive processes** with a team led by Stéphane Charpier.

→ TAKING RESEARCH ONE STEP FURTHER

Smart and connected clothing to diagnose seizures

It's revolutionary: the Neuronaute, smart and connected clothing, will offer remote diagnosis, personalized care and epileptic patient monitoring. The Neuronaute was developed by Bioserenity, a start-up run by Pierre Frouin in collaboration with Michel Le Van Quyen from a team led by Stéphane Charpier. With this technology, epilepsy monitoring will be available to a greater number of patients and doctors at a lower cost. The Neuronaute is set to launch on the market in 2016.

!SIGNIFICANT DEVELOPMENTS

Epilepsy and cortical malformation: two mutations within one single gene[26]

After identifying new gene *DEPDC5*, linked to focal seizures, the team led by Stéphanie Baulac and Eric Leguern discovered that in certain cases, *DEPDC5* gene mutations also caused focal deformity of the cerebral cortex. The lesion could be due to somatic mutation (neither inherited nor transmitted) of *DEPDC5* that takes place in brain cells during embryonic development and builds on inherited mutation. It is the first time such a process has been described in focal seizures.

Role played by lipids in regulation of epileptic activity[27]

A team led by Richard Miles is studying sclerosis, or neuronal death, that causes focal seizures. It is working more specifically on the role played by lipids, including cholesterol, in neuronal death. The team, in collaboration with Nathalie Cartier, proved that cholesterol release inhibition from neurons increases epileptic activity and neuronal death in the hippocampus of mice.

Markers for epilepsy seizures?[28]

Epilepsy seizures can occur at any time. A crucial challenge is therefore seizure prediction and anticipation. The team led by Stéphane Charpier, in close collaboration with the clinical neurology units, showed that patients with focal seizures experience specific cerebral activity before a seizure starts. Thanks to advanced electrophysiology techniques, researchers detected specific rapid rhythms in the area where the seizure starts, rhythms that were recorded before the seizure started. These rapid rhythms can be considered as electrophysiological markers that could eventually help develop seizure prediction instruments. This is a very important discovery that gives new understanding to the underlying mechanisms prior to an epilepsy seizure.

CLINICAL RESEARCH HIGHLIGHTS

Emergency treatment of convulsions in epileptic patients[29]

A patient experiencing status epilepticus, an epilepsy seizure that does not stop on its own and lasts over 5 minutes, must receive immediate care to prevent brain damage. To improve patient care, Vincent Navarro from a team led by Stéphane Charpier along with several teams from the Assistance Publique coordinated a study aiming at testing effects of adding a second antiepileptic treatment to the emergency treatment (benzodiazepines). This multicentric therapeutic trial involved 13 pre-hospital care teams from the SAMU and 26 hospital teams in charge of patients experiencing status epilepticus in France. The goal of Vincent Navarro and his colleagues is to find a way to stop convulsions in epileptic patients even faster. The study highlighted that there is no statistically significant difference between the two treatments, but aims more generally to improve diagnostic and therapeutic care in status epilepticus and to strengthen special patient care systems such as the Neurological Intensive Care Unit at the Pitié-Salpêtrière Hospital, part of the AP-HP.

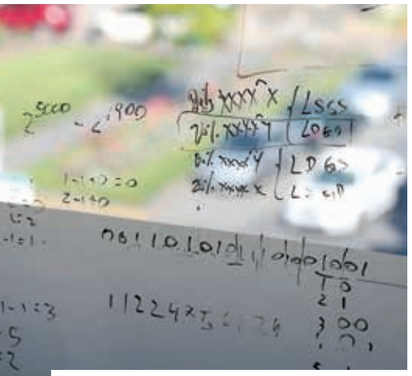
Identifying biomarkers of status epilepticus

Other studies are in progress to pinpoint relevant biomarkers in status epilepticus to identify high-risk subjects for severe neurological effects. Functional consequences of treatments used to interrupt status epilepticus are being researched thanks to collaboration between the Neurological Intensive Care Unit, the EEG Unit, and a team led by Stéphane Charpier.

#Cognition, behavior and psychiatric disorders

Understanding how a healthy brain functions is necessary to better understand and treated altered function in the case of disease. To understand underlying mechanisms of mental function, whether motor, intellectual, or emotional, ICM researchers are studying information processing by neural networks. To do so, they employ numerous instruments, including subtle clinical analysis, brain imaging and electrophysiology studies, behavioral testing, and the study of experimental modeling of pathologies. What are the foundations of normal and altered motivation? How do our intentions lead to behavior? What is conscience? What is creativity? How can we alleviate and treat depression and obsessive-compulsive disorder? How can we achieve early diagnosis and treatment of frontal lobe diseases and frontotemporal dementia that alter mental function?

THE ICM'S ANSWER:



#BEHAVIOR AND MOTIVATION
#COGNITIVE FUNCTION
#PSYCHIATRIC DISORDERS

◊ **Emotions, depression, and social interactions**: a team led by Nathalie George and Philippe Fossati is focused on how social processes activate and regulate the emotional brain. This includes, amongst other disorders, depression and autism.

◊ **Motivation and decision-making**: a team led by Mathias Pessiglione, Sébastien Bouret, and Jean Daunizeau is studying processes involved in motivation in humans.

◊ **Study of processes involved in creativity and reasoning** with a team led by Bruno Dubois and Richard Lévy. FRONTlab, their laboratory, focuses on mental function elaborated by frontal lobes. This function builds and controls our most complex behavior including decision-making, creativity, reasoning by analogy, voluntary behavior, and language.

◊ **Study of brain areas involved in language, reading, and visual perception** with a team led by Paolo Bartolomeo, Laurent Cohen and Lionel Naccache.

◊ **Study of conscience, how it works, and its disorders in neglect and non-communicating patients** with a team led by Paolo Bartolomeo, Laurent Cohen and Lionel Naccache.

◊ **Identify target treatments for schizophrenia** with a team led by Philippe Ravassard.

◊ **Understand what leads to obsessive-compulsive disorder and develop innovative treatment solutions** with a team led by Luc Mallet.

◊ **Improve diagnosis and treatment of frontotemporal dementia** with teams led by Bruno Dubois and Richard Lévy, and Isabelle Le Ber from a team led by Alexis Brice.

!SIGNIFICANT DEVELOPMENTS

Autism: can imitation have a therapeutic effect?[30]

For autistic patients, being imitated improves social behavior via activation of strategic areas in the brain. These are the findings of a study conducted by Philippe Fossati and colleagues using functional magnetic resonance imaging. When autistic patients are imitated, researchers noticed that an area of the brain strongly linked to social behavior and development of emotions is activated. Simultaneously, activity decreases in areas of the brain with overexpression in these patients. By suggesting that imitation of autistic patients has a therapeutic effect via modulation of specific brain areas, this study provides new perspectives for treatment of autism.

Can we be manipulated? When context determines tastes[31]

Why do we like a painting, or a person? Does our judgment solely depend on the painting or person's inherent value? What if other parameters came into play? The team led by Mathias Pessiglione, Sébastien Bouret and Jean Daunizeau has updated the brain mechanisms by which context influences value judgments. Using functional MRI data from healthy subjects, researchers confirmed the role played by a certain area of the cortex in assigning value: the area's activity increases when we take a liking to something. Researchers also found that when background music is enjoyable, subjects have a higher appreciation of the painting in front of them. The process is simple: enjoyable music increases activity in that particular key area, preparing it to appreciate the painting more! The team was able to highlight the main properties of this system, and results will have major implications in the field of neuroeconomics.

When the left hemisphere compensates right hemisphere lesions[32]

After a right hemispheric stroke, over 50% of patients act as if the left part of the world no longer existed: they are affected by what is known as "unilateral spatial neglect". This disorder can become chronic and extremely disabling; over one third of patients remain impaired to some extent. This could be due to visuospatial attention deficit linked to right hemisphere lesions in the brain. A team led by Paolo Bartolomeo followed 45 patients affected by this pathology with "diffusion-weighted" MRI found that the left hemisphere seems to have the ability to compensate lesions of the right hemisphere thanks to brain plasticity mechanisms that are relatively unknown. Researchers showed that this neglect is persistent when associated with damage to the connections between both hemispheres, rendering compensation impossible. A major clinical challenge is identification of factors enabling prediction of persistence of neglect in order to make appropriate rehabilitation available to patients, at risk for chronic disorder.

Concept formation: areas of the brain involved[33]

How are oranges and bananas similar? They are both fruit, of course! Patients with frontotemporal dementia (FTD) are unable to answer this question because they lack the ability to sort objects by category. Concept formation is our ability to create abstract connections between different objects and is necessary to abstraction and creativity. Researchers from a team led by Richard Lévy and Bruno Dubois studied patients with frontal cortex lesions and found that categorization in the brain involves various functions, both ability to gather information and ability for abstract thinking. Both mechanisms rely on specific areas within the frontal lobes. This study opens up new opportunities for use of concept formation testing as a means of diagnosis for FTD.

Studying language comprehension in non-communicating patients[34]

Benjamin Rohaut and Lionel Naccache took up a challenge: evaluate non-communicating patient's ability to understand language by measuring brain activity. The methodology seems simple enough: researchers had patients in persistent vegetative state or minimally conscious state listen to two connected words (for example, hive-bee or sled-snow) or unconnected words (hive-snow or sled-bee). When words were unconnected, researchers recorded two specific responses in brain activity of patients: the first is unconscious, whereas the second seems linked to awareness of meaning. This finding shows the existence of an unconscious stage in understanding of word meanings that may or may not be followed by a conscious stage. Patients in which researchers observed both responses recovered conscience and language ability within six months. Following these very encouraging results, Benjamin Rohaut and Lionel Naccache are fine-tuning the test to predict recovery of conscience as well as cognitive abilities in non-communicating patients.

#Cognition, behavior and psychiatric disorders

CLINICAL RESEARCH HIGHLIGHTS

Circuits involved in motivation

A study conducted on healthy volunteers, coordinated by Mathias Pessiglione and Jean-Christophe Corvol, aims at describing the circuits involved motivation and how they can be affected and modulated. On the long term, results from the study could improve care for patients with various neurological pathologies with altered motivation circuits.

Quantitative assessment of apathy

Apathy is defined as a loss of motivation and interest and is a frequent symptom in many pathologies such as depression, schizophrenia, as well as Parkinson's and Alzheimer's. Thanks to the PRISME platform, an innovative project called EcoCapture, developed by Richard Lévy, is focused on studying apathy. Behavior of apathetic patients will be analyzed in a semi ecological setting using wearable body sensors. The goal of this study is to use resulting data to help individuals re-enter the workplace after being affected by neurological deficit with decision-making or behavioral disorders.

Identify depression biomarkers

The challenge for the ANR SENSO project, coordinated by Philippe Fossati, is to define biological and brain imaging markers allowing easier diagnosis of depression. Markers are identified by measuring brain activity (with functional MRI and EEG) and biological activity (inflammation markers in the bloodstream) in patients with depression. Results should allow development of new, more appropriate treatment strategies. Defining biomarkers will enable closer surveillance of treatment effects, and results of the project will contribute to the ongoing development of personalized healthcare, adapted to specific needs of patients with depression.

Predict frontotemporal dementia

Frontotemporal dementia is a rare neurodegenerative disease related to Alzheimer's disease. Symptoms include behavioral changes such as apathy (loss of motivation and initiative), affective and emotional disorders, and disinhibition. Isabelle Le Ber and Bruno Dubois are conducting two studies, PHRC Predict-PGRN and ANR PrevDemAls, on 200 participants. The studies aim at finding early biomarkers in genetic forms of FTD that will allow testing of new treatments at a stage where they are most likely to be effective, before first symptoms appear. Ultimately, the challenge is to introduce preventive treatments: this is a novel, original, and promising approach in dealing with genetic forms of frontotemporal dementia.

A therapeutic trial to fight frontotemporal dementia (FTD)

This therapeutic trial is testing the effect of a drug on pre-symptomatic or early stage FTD. It is the first therapeutic trial conducted on an international level for these illnesses. It is coordinated by Dr Isabelle Le Ber representing France. Around 30 patients will be included in the first phase of the trial, with the major challenge of ultimately treating patients as well as high-risk families for this genetic variant.

Treating OCD with deep brain stimulation

Several clinical trials aiming to evaluate high-frequency brain stimulation efficacy were developed and conducted at the ICM. Carine Karachi and Luc Mallet are part of various multicentric trials and coordinated a trial aiming to compare different stimulation targets in diagnosed patients. They are also coordinating an electrophysiology research project to identify steady-state and response biomarkers in patients. With these trials, they hope to improve existing OCD treatment with deep brain stimulation.

→ TAKING RESEARCH ONE STEP FURTHER

Play for science breakthroughs

BRAiN'US is a smartphone application developed by Jean Daunizeau to collect information on how the brain works. BRAiN'US is made up of 8 games that test various cognitive abilities. Data from this unique scientific experiment is anonymous and confidential and is undergoing mathematical modeling analysis in order to create a quantitative overview of the various mental processes that come into play in decision-making. Understanding how the brain works in a normal setting will improve understanding of the nature of cognitive and behavioral disorders experienced by patients with neurological or psychiatric pathologies.
BRAiN'US 2, with new games, is in progress!

Markers of consciousness

Lionel Naccache and his team identified a group of markers (complexity, functional connectivity, evoked response, EEG activity variation, etc.) that differentiate conscious or minimally conscious patients from those in a persistent vegetative state. These markers can also predict the evolution of level of consciousness in patients in a persistent vegetative state. A European patent was filed for this consciousness monitoring method in 2015.

Treatment for apathy

The APACHE project (Apathy and Chorea in Huntington Disease Early Stage), a phase II therapeutic trial conducted in collaboration with Pfizer, was conducted at the CIC with Alexandra Durr as principal investigator. The project's goal was to assess tolerance to a treatment for Huntington's disease, PDE10A, and its efficacy on apathy in 32 patients. For the first time, the assessment was conducted by combining functional MRI, innovative apathy assessment tests developed by a team led by Mathias Pessiglione and Raphael LeBouc, and a new series of neuropsychology testing developed by Richard Levy. Results are being analyzed and already seem promising with regards to the inhibitor's effect on apathy.

#Nervous system function

Understanding the basic mechanisms of normal nervous system development and function is essential to help detect anomalies and prevent neurological diseases. How does the nervous system take shape? Which circuits come into play in motor skills? How do the different types of brain cells develop? How are new neurons produced?

THE ICM'S ANSWER:

#BRAIN DEVELOPMENT AND FUNCTION
#PRODUCTION OF NEW NEURONS
#SPINAL CORD AND LOCOMOTION

♦ **Understand genetic mechanisms that control nervous system development** with a team led by Bassem Hassan.

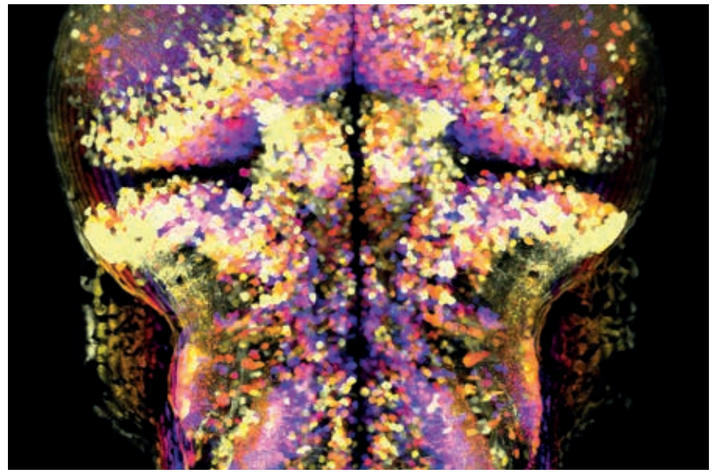
♦ **Understand the development of glial cells**, structural and functional assistants of central nervous system neurons, with a team led by Jean-Léon Thomas.

♦ **Understand brain circuits involved in locomotion** with a team led by Claire Wyart.

♦ **Understand how cerebral cortex circuits are regulated,** with a team led by Alberto Bacci.

♦ **Understand underlying mechanisms of nervous system information transmission** with a team led by Catherine Lubetzki and Bruno Stankoff.

!SIGNIFICANT DEVELOPMENTS



Brain development: discovery of a new mechanism[35]

A team led by Bassem Hassan has discovered an unprecedented mechanism, maintained among species, that regulates neurogenesis via precise temporal control of the activity of proneural proteins, essential to brain development. The mechanism relies on a simple and reversible chemical modification and is crucial in producing neurons in sufficient amounts, neuron differentiation, and nervous system implementation. Understand the role of this mechanism in neurogenesis in adults may be a promising lead in treating neurodegenerative diseases.

A new neural circuit involved in movement control[36]

Claire Wyart and her team have proven that sensory neurons in the spinal cord are able to modulate movement. In zebrafish, researchers found that sensory neuron activation triggers locomotion when the animal is at rest and inhibits it when the animal is in motion. Results open up new hope that it will eventually be possible to stimulate precise circuits to generate movement in patients with spinal cord damage.

Producing new neurons[37]

Jean-Léon Thomas and his team have identified a growth factor, *VEGF-C*, necessary to production of new neurons. Their work brings new hope in developing treatments: *VEGF-C* could be a good candidate for neuron production, compensating cognitive impairment in individuals with neurodegenerative illnesses such as Alzheimer's disease.

Mechanisms involved in transmission of nerve impulse[38]

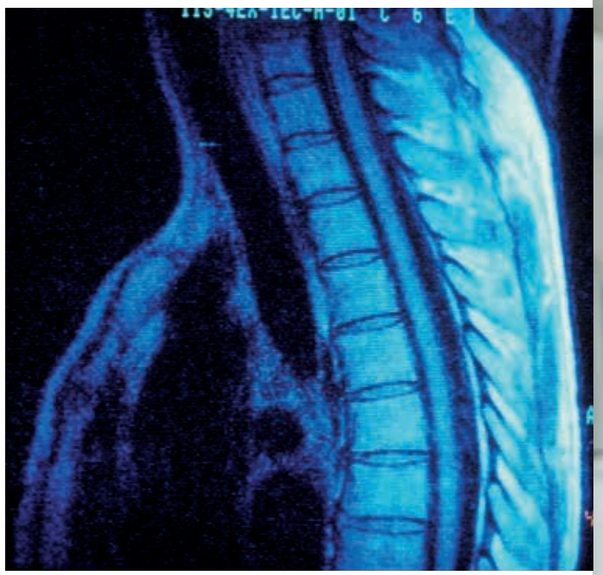
A team led by Catherine Lubetzki and Bruno Stankoff highlighted the initial mechanisms behind the creation of nodes of Ranvier, gaps in between each segment of myelin sheath, that allow conduction of rapid transmission of nerve impulse. This highly innovative research highlighted the existence of soluble factors that "aggregate" nodes of Ranvier proteins and accelerate nerve impulse conduction. These molecules could play a key part in reestablishing nerve conduction after demyelination.

#Nervous system function

CLINICAL RESEARCH HIGHLIGHTS

Treating walking and balance disorders

A therapeutic study conducted by Carine Karachi and David Grabli found that deep brain stimulation improves drug-resistant walking and balance disorders in certain patients. These highly encouraging results are an opportunity for future development of new treatment for severe forms of Parkinson's disease. The exact scope of this therapy, however, has not been fully defined yet.



→ TAKING RESEARCH ONE STEP FURTHER

A non-invasive approach to treating spasticity and paralysis

American company PATHMAKER Neurosystems, managed by Nader Yaghoubi, partnered with the ICM in 2015 to develop non-invasive systems to treat patients with paralysis, muscle weakness, and spasticity (permanent muscle contractions typically observed in stroke victims or patients with multiple sclerosis). The company's goal is to make innovative treatment based on neurostimulation of the spinal cord available on the market, where modulation of neural activity is achieved by trans-spinal direct current stimulation (tsDCS). Pathmaker has passed the engineering and security testing phase of its first product and is currently launching clinical trials at the ICM.

#Modeling

The existing imaging techniques (EEG, MRI, MEG) need more powerful image analysis methods in order to go deeper into the many neurodegenerative diseases (Alzheimer's disease, frontotemporal dementia, etc.), epilepsy, and cerebrovascular pathologies (vascular dementia, strokes). These images can be leveraged to provide biomarkers for these illnesses: from raw data, we can extract signals that are associated with specific diseases to increase our knowledge and detect them as early as possible, before any clinical symptoms. Integrating the clinical, genetic, and imaging data collected from patients is one of the major healthcare challenges of the future. How can we combine different and complex data into one useful piece of information for research? How can we correlate data from different sources to predict disease progress and adapt treatment?

THE ICM'S ANSWER:

#STATISTICAL ANALYSIS OF MULTIMODAL DATA
#NEW DIGITAL TECHNOLOGY
#BRAIN-MACHINE INTERFACE

♦ **Develop more advanced image analysis techniques** to increase description and understanding of neurodegenerative diseases and eventually predict them, with a team led by Olivier Colliot and Didier Dormont in collaboration with the ICONICS bioinformatics platform.

♦ **Correlate genetic, physiological, behavioral, clinical, and imaging data** thanks to the development of advanced mathematical instruments, with a team led by Olivier Colliot and Didier Dormont.

♦ **Develop disease modeling to predict progress and adapt treatment** with a team led by Olivier Colliot and Didier Dormont.

♦ **Write using thoughts using brain-machine interfaces** with a team led by Olivier Colliot and Didier Dormont in collaboration with the CENIR-MEG/EEG platform.

!SIGNIFICANT DEVELOPMENTS

Neuron interaction modeling to identify anomalies[39]

Specific dynamics and neural network plasticity underlie brain activity. Understanding how these networks are connected is essential in understanding how the brain is organized. Fabrizio De Vico Fallani and colleagues are developing mathematical instruments to characterize the complex networks of brain connectivity. In order to characterize the setup of neural networks in zebrafish during their development, the ARAMIS team, in collaboration with Claire Wyart and her team at the ICM, developed a mathematical model that analyzes and integrates calcium exchanges measured in vivo at the single neuron level. Calcium exchanges are a means of studying and measuring neural activity. Results show strong neural connectivity along the spinal cord and confirm that the network is organized hierarchically, characterized by rostrocaudal propagation (from head to tail) of nerve activity. This innovative approach could eventually allow detection of functional anomalies in the nervous system.

Visualizing variations in brain connectivity[40]

A novel statistical technique allows simultaneous analysis of grey matter and white matter bundles in the brain. This method is a means of visualizing variations in connectivity based on the brain's shape. Stanley Durrleman and colleagues, in collaboration with a team led by Marie Vidhaillet and Stéphane Lehéricy, conducted in vivo research on patients with Gilles de la Tourette syndrome and found connectivity anomalies between the basal ganglia and the cortex.

Measuring a drug's effect on the brain with neuroimaging[41]

Thanks to a new imaging analysis technique, developed by Olivier Colliot, Didier Dormont, and their team, researchers in collaboration with a team led by Bruno Dubois succeeded in measuring the effect of drug donepezil on the size of the hippocampus in patients with Alzheimer's disease. The clinical trial, with over 200 patients in 28 centers across France, found that the treatment reduced hippocampus atrophy by 45% if followed for a full year. It is the first large-scale multicentric trial of a treatment in patients with light cognitive impairment and is also the first time statistically significant effects of a drug are linked to the level of hippocampus atrophy in these patients.

→ TAKING RESEARCH ONE STEP FURTHER

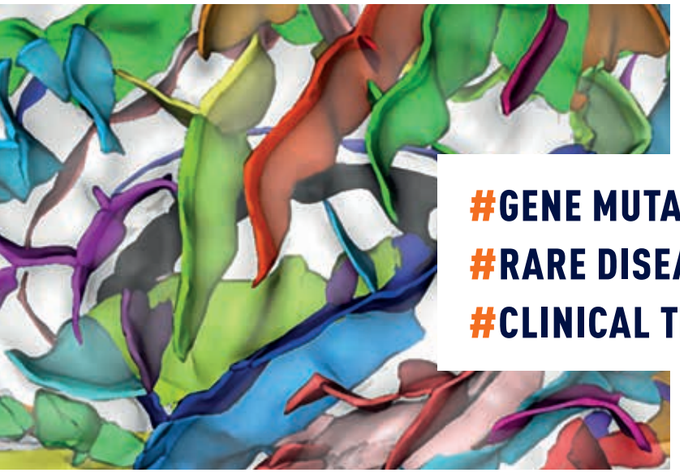
Diagnosing and predicting human stress levels

A project managed by Fabrizio de Vico Fallani and Mario Chavez, part of a team led by Olivier Colliot and Didier Dormont, has launched in collaboration with MyBrainTechnologies, a company founded by Thibaud Dumas and Yohan Attal and incubated at the ICM. The goal of the project is large-scale longitudinal monitoring of EEG data for the diagnosis and prediction of human stress levels.

#Rare diseases

Several teams from the ICM are committed to the fight against movement disorders and rare neurological diseases, including Huntington's disease, cerebellar ataxia, spastic paraplegia, childhood alternating hemiplegia, autoimmune neuropathies, congenital myasthenic syndrome, and neuromuscular channelopathy. How do these diseases develop? What are some risk factors? How are they diagnosed and differentiated?

THE ICM'S ANSWER:



#GENE MUTATIONS
#RARE DISEASE REFERENCE CENTER
#CLINICAL TRIALS

♦ **Treat Huntington's disease** by improving cerebral metabolism with a team led by Alexis Brice.

♦ **Identify genes responsible for cerebellar ataxia and hereditary spastic paraplegia and understand involved mechanisms in order to develop treatments** with Alexis Brice and his team.

♦ **Understand movement disorders (dystonia, mirror movement disorder, Gilles de la Tourette syndrome, rare tremors) to discover new treatment perspectives** with a team led by Marie Vidailhet and Stéphane Lehéricy.

♦ **Improve diagnosis and understanding of neuromuscular excitability disorders** such as muscular channelopathy, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy to improve patient care, with Laure Strochlic in a team led by Bertrand Fontaine and Sophie Nicole.

!SIGNIFICANT DEVELOPMENTS

Cerebellar ataxia: a treatment on its way?[42]

Cerebellar ataxia is a neurological disease that affects the cerebellum, a major element of the central nervous system involved in balance and coordination. Diagnosed patients have impaired walking and fine motor skills. Giovanni Stevanin, in a team led by Alexis Brice, has identified a recurrent mutation within a new gene responsible for cerebellar ataxia that encodes calcium channels expressed in certain cerebellum neurons. Many drugs that regulate calcium channel activity are currently in use; this discovery could lead to major treatment breakthroughs for these rare disorders.

Hereditary spastic paraplegia: discovery of a new mechanism[43]

Hereditary spastic paraplegias form a heterogeneous group of diseases on both a clinical and genetic level. These neurodegenerative disorders affect individuals of all ages. Clinical signs appear progressively and include highly disabling walking impairments due to stiffness (spasticity) of lower limbs. Giovanni Stevanin and his colleagues in a team led by Alexis Brice found that mutations within gene *ALDH18A1* are associated with several types of hereditary spastic paraplegias and different types of transmission. Additionally, researchers identified a new markers in the bloodstream associated with the disease that could aid in its diagnosis. These results contribute to a better understanding of the diseases and a more precise diagnosis.

Gilles de la Tourette syndrome: could tics be a bad habit?[44]

Tics are the main symptom 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 much like persistent bad habits. Alterations in certain neural networks involved in the origin of habits and increased transmission of dopamine (neurotransmitter involved in reward circuits) could explain help explain the exacerbation of 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: a new mutation in question[45]

Muscular channelopathy is a heterogeneous set of diseases with the common trait that they are all caused by gene mutations encoding ion channels that play a major role in muscular contraction and relaxation. For the first time, Sophie Nicole and colleagues from Bertrand Fontaine's team identified a recessive mutation in a sodium channel responsible for permanent muscular weakness typical of congenital myasthenic syndrome. 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 with the ability to boost sodium channel function to treat permanent muscle weakness.

#Rare diseases

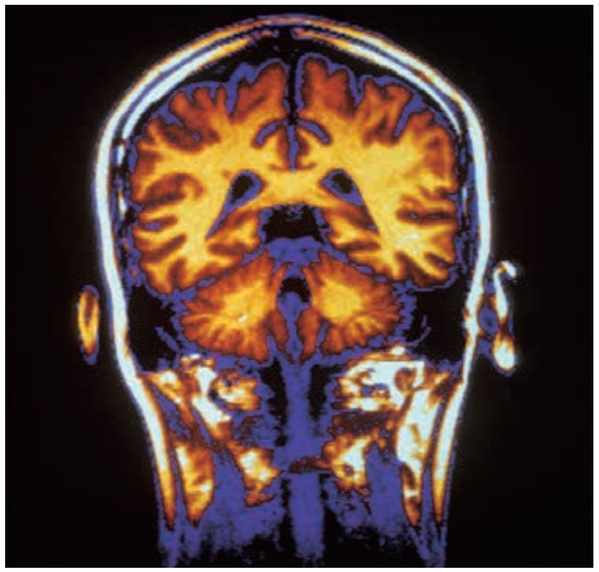
CLINICAL RESEARCH HIGHLIGHTS

A treatment for dystonia[46]

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.



Resveratrol to fight Huntington's disease

Huntington's disease is a hereditary neurodegenerative disorder whose primary symptom is the progressive appearance of movement, behavior, and psychiatric disorders. A phase II national multicentric trial, REV-HD, is coordinated by Fanny Mochel and was launched in 2015 to assess resveratrol's ability in slowing down Huntington's disease progress by improving the brain's energy metabolism. Around 100 patients will receive the treatment for one year and results will be assessed based on clinical and imaging parameters.

Medicated oil to treat metabolic abnormal involuntary movements[47]

A team led by Fanny Mochel, in collaboration with Emmanuel Flamand-Roze, tested the efficacy of triheptanoïne, a medicated oil, on patients with a GLUT-1 (Glucose transporter 1) deficit characterized by cognitive and movement disorders, namely transitory abnormal involuntary movement attacks. The treatment reduces the appearance of symptoms in child and adult patients by 90%, by restoring energy metabolism in the brain. Following these results, an international multicentric phase III study will be launched by the end of 2016 in collaboration with the Ultragenyx company.

→ TAKING RESEARCH ONE STEP FURTHER

Medicated oil to fight Huntington's disease[48]

The therapeutic potential of triheptanoïne, a synthetic oil, in patients with Huntington's disease, was proven by Fanny Mochel and Alexandra Durr from a team led by Alexis Brice. 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.

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Team

"Synaptic inhibition and auto-modulation of cerebral cortex microcircuits"

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Team

"Molecular and cellular perspectives on myelin repair"

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Aide à la Recherche sur la Sclérose en Plaques, Agence nationale de recherche ELA research foundation, ENP, Fédération pour la recherche sur le cerveau, Fondation pour la recherche médicale, Multiple Sclerosis International Federation, National Multiple Sclerosis Society via Rutgers University, OCIRP, UPMC.

Team

"Amyotrophic lateral sclerosis: causes and mechanisms of motor neuron degeneration"

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Team

"Molecular basis, physiopathology, and treatment of neurodegenerative diseases"

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Team

"Dynamics and physiopathology of neural networks"

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Team

"PICNIC Lab: Physiological assessment in healthy subjects and subjects with cognitive disorders"

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Generous support granted by:
École des neurosciences Paris Ile-de-France, EyeBrain, Fondation pour la recherche médicale, Sylvain Héfès.

Team

"ARAMIS: Mathematical modeling and algorithms in human brain signal and imaging analysis"

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Team

"FRONTlab: Frontal systems: functions and dysfunctions"

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Team

"GEN-PHYS: Neurogenetics and physiology"

Team leaders
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Team

"Survey of emotions and social interactions"

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Research teams and support

Team

"Alzheimer's disease, prion diseases"

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Team

"Experimental therapy in Parkinson's disease"

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Team

"Cellular and molecular mechanisms in glioma development"

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Team

"Treatment of amyotrophic lateral sclerosis: from genetics to zebrafish"

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Team

"Experimental neurosurgery"

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Team

"Genetics of epilepsy"

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Team

"Myelination and remyelination mechanisms in the central nervous system"

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Team

"Behavior, emotion, and basal ganglia"

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Team

"Biological, psychological, and computational foundations of motivation"

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Team

"Cortex and epilepsy"

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Team

"Biotechnology and biotherapy"

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Principal investigators
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Team

"Experimental Neuro-oncology"

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Research teams and support

Team

"Oligodendrocyte development and neurovascular interactions"

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Team

"Abnormal movement and basal ganglia: experimental physiopathology and therapy"

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Team

"Optogenetic dissection of spinal circuits underlying locomotion"

Team leader
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Principal investigators
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Hugues-Pascal Mousselard

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Research —

TECHNOLOGICAL PLATFORMS

Invaluable research discoveries are only possible with high-performance technological platforms. While it is both revolutionary in its design and innovative in its organization, the ICM is also unique in its advanced technical equipment. ICM researchers work on different scales: from studying molecules (DNA, proteins, etc.) to cells and individuals. At each scale, innovative technology is made available to researchers and clinicians. The ICM's network of platforms facilitates translational research, creating strong relationships between researchers and clinicians.

#SEQUENCING
#GENE THERAPY
#MOLECULAR INSTRUMENTS

The molecular exploration silo grants academic and industrial researchers access to instruments and services for genome analysis with the IGenSeq platform, and for viral vector production with the iVector platform. Every project submitted by researchers undergoes feasibility assessment and design optimization. Both platforms received ISO9001 standard certification in June 2015.

iGenSeq – Genotyping and sequencing platform

Yannick Marie and Giovanni Stevanin

iGenSeq is dedicated to genome genotyping and sequencing, i.e. reading the long DNA molecules that make up chromosomes. It is a means of analyzing the genome, detecting possible gene mutations, and identifying possible associations between these mutations and the appearance of neurological diseases.

ACTIVITIES
- Real-time PCR
- Sequencing
- Genotyping
- Purification and analysis of nucleic acids

— iGenSeq–genotyping and sequencing platform is supported in part by the AP-HP and the National Institute for Agronomic Research —

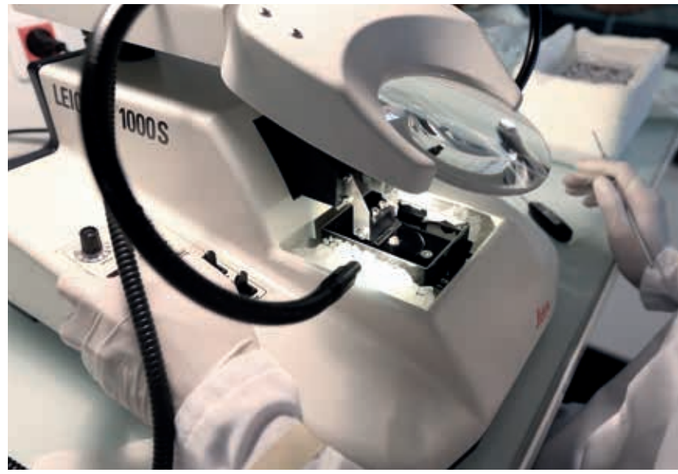
iVector – Vectorology platform

Philippe Ravassard and André Sobczyk

iVector gives researchers the opportunity to build molecular instruments for gene transfer to conduct gene manipulation experiments in vitro (outside of the body) or *in vivo* (after injection into the body, like a vaccine). These instruments are often derived from modified, harmless viruses converted into vectors for genes. This technology is the basis for gene therapy that ICM researchers hope will help "repair" DNA in patients with diseases.

WHAT IS A VIRAL VECTOR?
A viral vector is a viral particle rendered harmless that transports an artificially modified gene. Thanks to this carrier, the gene in question is integrated and expressed by the targeted cell. These vectors are often derived from modified animal or plant viruses.

WHAT IS IT USED FOR?
Basic research: viral vectors are used to created cellular or experimental models of human pathologies to study their mechanisms and improve diagnosis and treatment.
Gene therapy: viral vectors transport "repair" genes into cells or tissue of an individual with a genetic disease to treat them.
Adoptive immunotherapy: viral vectors are used to modify specific T-cells (CAR-T) ex-vivo (outside of the body) according to the type of cancer needing treatment. After obtaining a sample of the patient's cells, the patient will receive his or her own modified cells in an autologous reinjection to treat the cancer.



DRASTIC SECURITY REGULATIONS
The manipulation of viral vectors means that tight standards are enforced: laboratories are considered as level 2 and 3 biosecurity facilities (BSL2 and BSL3) to prevent any dissemination of viral particles into the environment.

ACTIVITIES
- Design and construction of viral and non-viral vectors
- Technical and regulatory advice for the design, production, and use of viral vectors

Cellular exploration

#STEM CELLS
#ACTIVITY RECORDING
#HISTOLOGY

Research at the ICM involves the development of cell cultures that are easily manipulated to reproduce mechanisms of nervous system pathologies in a simplified manner. This work requires recording neural cell activity to assess possible anomalies in electric signal transmission, manipulating "stem" cells rendered pluripotent to create true neurons or glial cells, and analyzing pathological cellular malfunction with fluorescence imaging in live or fixed cells. To facilitate their work, researchers have access to cutting-edge equipment, namely a cell culture robot and automated microscopes to acquire high-speed imaging and perform quantitative analysis. When research is focused on global brain function or malfunction, histology techniques on tissue sections enable assessment of neuron and glial cell population integrity within various brain areas. To be fully effective, these techniques require prior labeling of targeted cells with antibodies or specific stains. Brain structure visualization is now available in 3D, on brain tissue made transparent thanks to a specific technique called clarification. Four platforms make up the cellular exploration silo:

CELIS – Cell culture platform

Patrick-Pierre Michel and Laetitia Strehl

This platform offers a large range of cellular modeling as well as advanced technology to carry out experiments on brain and spinal cord pathologies, and screen small molecules to find promising treatments for these pathologies.

ACTIVITIES

- Research on neurodegenerative and demyelinating disease mechanisms and neuromuscular junction pathologies on cell culture modeling or brain tissue sections
- Automated cell culture to screen potential treatments
- Automated fluorescence imaging for in-depth cellular-scale analysis of physiopathological mechanisms

CELIS-E-PHYS, electrophysiology platform

Carine Dalle and Patrick-Pierre Michel

CELIS-E-PHYS offers high-level services to researchers and industry experts who need in vitro electrophysiological data. The platform has cutting-edge equipment used to record cellular electrical activity in various experimental conditions (isolated cells, tissue sections). It is therefore involved in many innovative research projects ranging from functional characterization of channelopathies to the functional characterization of neurons derived from human induced pluripotent cells (iPSC). This type of data is necessary in neuroscience research dealing with biophysical properties of ion channels, functional characterization of cells, and generally with the study of nervous system synaptic plasticity.

ACTIVITIES

- Production of electrophysiological data
- Expert advice in electrophysiology
- Student and engineer training in electrophysiology techniques

Cellular exploration

CELIS-iPS, Platform for the production of human inducted pluripotent stem cells

Delphine Bohl, Patrick-Pierre Michel and Stéphanie Bigou

This platform provides services in human inducted pluripotent stem cell production (iPS) as well as training and consulting services in the field of cell culture. Constant innovation is a key value for the CELIS-iPS, to keep providing advanced instruments and methods.

WHAT IS A PLURIPOTENT STEM CELL?

Stem cells occur naturally in embryos and certain adult organs or tissue. Stem cells referred to as pluripotent can infinitely multiply and differentiate into any type of cell of the body, including central nervous system cells such as neurons and astrocytes.

WHAT IS IT USED FOR?

Human inducted pluripotent stem cells, referred to as iPSc, are produced and differentiated into cells of interest to mimic brain and spinal cord degenerative diseases in a petri dish. With this technique, it is possible to generate human cells that are otherwise inaccessible (neurons, for example), improve understanding of underlying cellular and molecular mechanisms in these diseases, and identify molecules with a potential therapeutic benefit.

ACTIVITIES

- Full generation and characterization of iPSc cells
- Expert advice in electrophysiology
- Student and engineer training in electrophysiology techniques
- Scientific and technical advice for end users

Histomics

Benoit Delatour and Annick Prigent

Histomics is an open access technological platform (equipment rental) that also offers various services. Histological studies are conducted with specific instruments to cut through tissue (ultramicrotomes, cryostats, cryomicrotomes, etc.) and analyze samples (protein unmasking chamber, CLARITY process to make tissue transparent, etc.).

WHAT IS A HISTOLOGICAL SAMPLE?

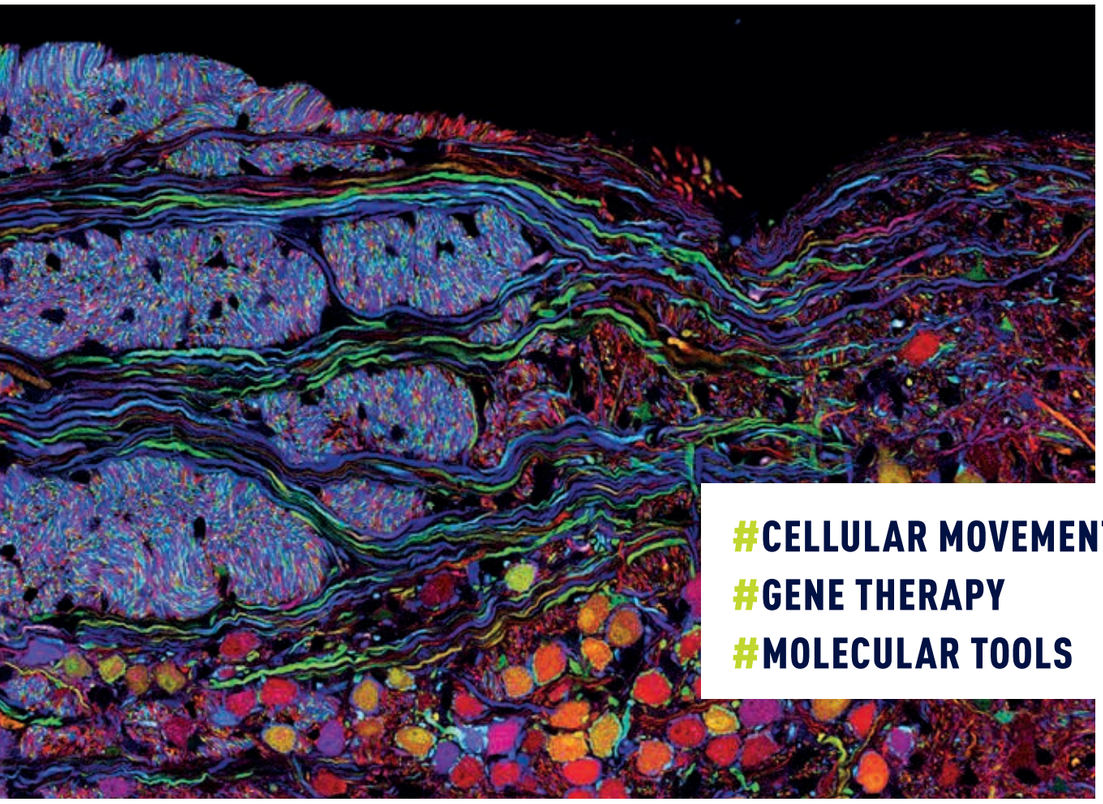
A histological sample is a biological tissue or organ sample.

APPLICATION

Microscopic analysis of the sample's structure aids in understanding normal or pathological function of the tissue or organ.

ACTIVITIES

- Equipment and reagents made available for independent users
- Training on various histological techniques
- Advice on developing experimental protocols
- Collaboration on specific projects.



#CELLULAR MOVEMENT
#GENE THERAPY
#MOLECULAR TOOLS

Within the ICM, a group of platforms is entirely dedicated to cell and tissue imaging. Image acquisition, two-photon optogenetic microscopy, and PICPS (Pitié-Salpêtrière Cell Imaging Platform) are platforms that provide access to some of the most recent techniques thanks to cutting-edge imaging equipment:
• Classic microscopy: observation of microscopic samples in tissue;
• Video microscopy to follow cell movement in real time;
• Fluorescence microscopy: observation of molecules, cells, or tissue sections by fluorescence, highlighting the desired samples. This includes classical fluorescence microscopy, confocal laser scanning microscopy, two-photon microscopy, and spinning disk confocal microscopy;
• Transmission electron microscopy to observe different cell compartments (organelles, viruses, crystals, molecules) at very high resolution.

Image acquisition

Anne Baron-Van Evercooren and Corinne Bachelin

This platform gives researchers the opportunity to use innovative technological equipment such as 3D microscopy and slide scanners.

Two-photon optogenetic microscopy

Claire Wyart

This platform develops sophisticated methods used to optically control in vivo neuron activity, called optogenetics.

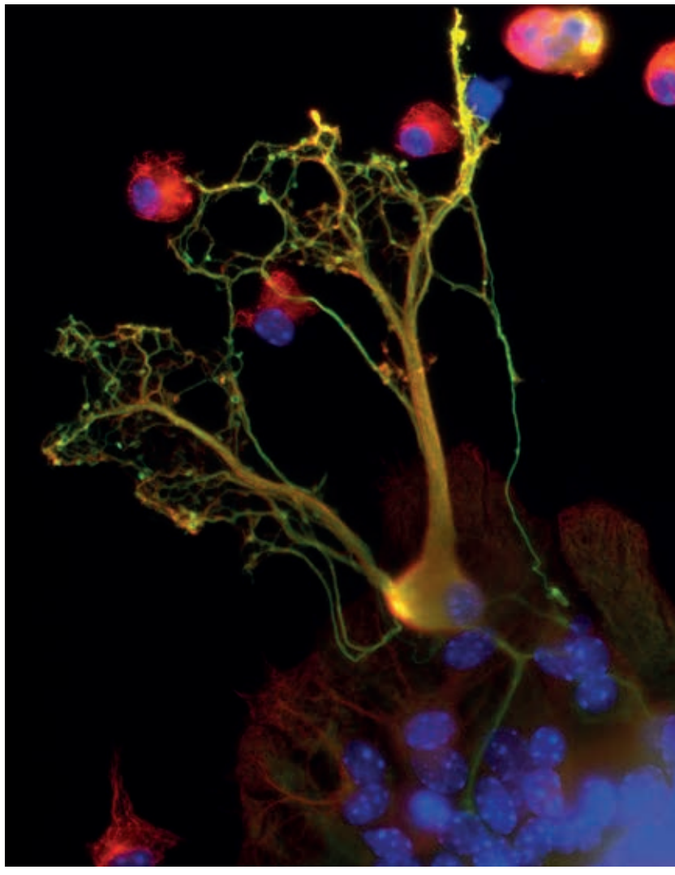
WHAT IS OPTOGENETICS?
Optogenetics is a fairly recent field of research and application that brings optics and genetics together. Combining knowledge in both genetics and optics, optogenetics allows neurons to become sensitive to light.

HOW IS IT APPLIED?
By stimulating a specific type of neurons, this method makes it possible to understand the role they play in nervous system development and function.

PICPS – Pitié-Salpêtrière Cell Imaging Platform

Anne Baron-Van Evercooren
and Claude-Marie Bachelet

Picps gives the on-site scientific community access to high-performance equipment, advice, training, and assistance in microscopy and cell imaging.



Functional exploration

#IMAGING
#BEHAVIOR
#BRAIN ACTIVITY

Functional exploration platforms enable experimentation on living organisms (in vivo) in a non-invasive manner, respecting the subject's integrity. These platforms are therefore particularly adapted to human subjects, both patients and healthy volunteers. The platforms support three main areas of research:

• Clinical research: study of the major nervous system pathologies and development of innovative treatments;
• Cognitive science research: understanding brain function and study of the neural bases of thought, behavior, and aging;
• Signal and image analysis research: development of new methods in the acquisition and processing of brain activity and imaging data.

The functional exploration platforms apply brain activity recording techniques such as extracerebral (EEG) or intracerebral (LFP) electroencephalography, magnetoencephalography (MEG), high-resolution magnetic resonance imagery (MRI), and non-invasive cerebral stimulation enabling modulation of cerebral network activity (electric stimulation, tDCS, or magnetic, TMS, transcranial).

CENIR-human MRI – Neuroimaging for research

Stéphane Lehericy and Eric Bardinet

The CENIR (Neuroimaging Research Center) is the main MRI platform for in vivo imaging. With expertise in the fields of neurodegenerative diseases, cognitive neuroscience, and image analysis, the CENIR offers academic and industrial researchers high quality imaging tools for research on the brain and spinal cord.

CENIR-MEG/EEG – MEG and EEG platform for neuroscience research

Nathalie George and Denis Schwartz

The CENIR-MEG/EEG platform is dedicated to the development of non-invasive methods that allow visualization of brain activity with millisecond timing accuracy. The equipment illustrates information flow between the different cerebral lobes, of both normal and pathological variety such as neurological or psychiatric disorders. Thanks to the platform's advanced equipment, the team helps academic and industrial partners design and perform their clinical or fundamental research projects and analyze results.

CENIR-STIM – Stereotaxis Platform

Jérome Yelnik, Carine Karachi and Sara Fernandez Vidal

STIM offers support for the analysis and development of software programs based on stereotaxic imaging data (used for deep brain stimulation, pharmacoresistant epilepsy, and radiosurgery, for example). It provides clinicians with instruments for the stereotaxic localization of deep brain structures. The YeB Atlas, developed by Jérôme Yelnik and Eric Bardinet, is a powerful tool for data analysis. The platform is involved in several deep brain stimulation (DBS) protocols in collaboration with other research institutes and the industry.

Functional exploration

CENIR-PANAM – Physiology and Movement Analysis Platform

Jean-Charles Lamy and Marie-Laure Welter

The PANAM-CENIR platform's mission is the following:
1• Clinical and therapeutic research on neurological and psychiatric disorders with non-invasive brain stimulation;
2• The study of movement, gait, and balance in association with intracranial recordings in patients with neurological disorders;
3• Multidisciplinary pairing of various techniques (i.e. TMS/EEG, tDCS/MRI, LFP/MEG...) linking variations in brain activity to movement or cognitive behavior.

CENIR-Small Animal MRI – MRI Platform for Small Animals

Alexandra Petiet and Mathieu Santin

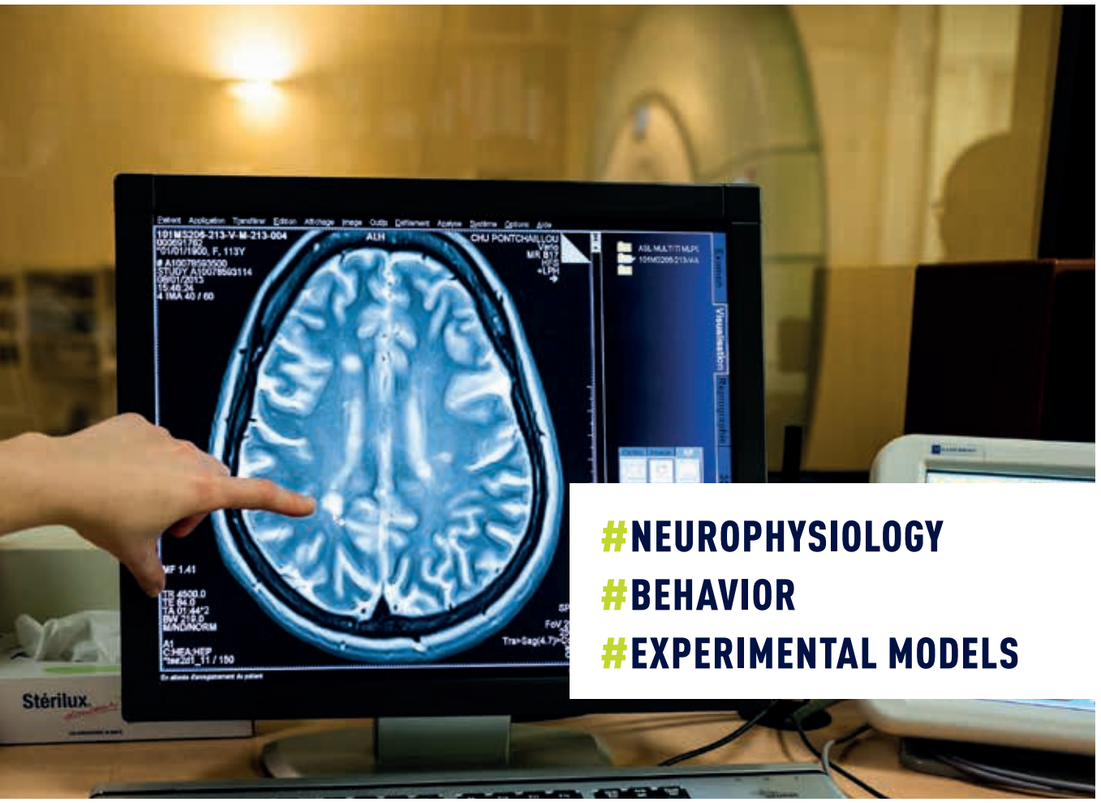
The CENIR- Small Animal MRI platform is dedicated to imaging of experimental models of disease in rodents. A very strong magnetic field associated with high quality radio-frequency antennas, with a large variety of imaging protocols and with data analysis form a high-quality platform for small animal imaging. Experimental imaging is a means of evaluating new biomarkers, studying pathological mechanisms, and evaluating new therapeutic molecules. This research is meant to be effectively transposed to human subjects to increase understanding of central nervous system diseases and accelerate treatment development.

PRISME – Platform for the Exploration of Human Behavior

Mathias Pessiglione, Philippe Fossati and Pierre Leboucher

PRISME is the ICM platform dedicated to the functional exploration of human behavior. It is comprised of two entities:
1• PRISME-Virtual Reality develops and adapts new virtual reality models for behavioral and cognitive neuroscience. The platform also develops new equipment and therapeutic protocols adapted to neuropsychiatric diseases;
2• PRISME-Real Life is intended for the study of cognitive functions, human behavior, and social interactions in ecological conditions. The purpose is to: test a large number of subjects for results as representative as possible of the general population, implement environments close to those of everyday life, and use wireless recording systems so patients are free to move around.
Academic and industrial partners have access to the equipment and are assisted by the team to develop appropriate protocols.

Preclinical Functional Exploration – Phenoparc



In a 3,000 sqm space, the PHENORPARC platform hosts scientific research projects focused on experimental modeling. Equipment and experts on-site offer high-quality research support for teams within and outside the ICM. PHENOPARC enables research on different species and has a wide scope of expertise on experimental modeling and techniques such as behavior, surgery, and electrophysiology.

PHENO-ICMice – Rodent Modeling Platform

Nadège Sarrazin and Brahim Nait Oumesmar

The PHENO-ICMice platform is housed in 1,500 sqm dedicated to phenotyping new rodent, rat, and mouse models. Research on the platform is centered on the study of Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, ALS and Huntington's disease. Scientific and technical experts as well as cutting-edge experimental equipment are on-site and available for assistance on demand to support research teams. Well-being is the focus of our concerns, and alternatives to the use of animals is always a possibility.

ACTIVITIES

- Consulting, training, and services for the public or private scientific community
- Behavior: movement, anxiety, depression, memory, pain…
- Neurophysiology: EEG recording, EMG, optogenetics…
- Other: injections, biological sampling…

PHENO-PRIM'R – Primate Modeling Platform

Morgane Weissenburger and Brian Lau

The PHENO-PRIM'R platform covers a surface of 850 m2 and hosts 3 primate species (crab-eating macaque, rhesus macaque and squirrel monkey). Research is focused on basic neuroscience research and the study of neurodegenerative diseases, namely Parkinson's disease and multiple sclerosis. Thanks to expert staff and cutting-edge equipment, the platform provides high-quality services to internal and external teams. Well-being is the focus of our concerns, and animal substitution is always a possibility.

WHY STUDY PRIMATES?

Non-human primates (NHPs) are the animals with the closest phylogenetic relation to humans. This proximity, and consequent morphological, anatomical, physiological and behavioral similarities, explains why NHPs are valuable animals in the field of human biomedical research. Thanks to primate modeling, detection and characterization of symptoms identical to those observed in patients is possible, with the goal of mitigating or eradicating these symptoms with effective and appropriate treatments.

ACTIVITIES

- Consulting, training, and services for the public and private scientific community
- Animal hosting (crab-eating macaques, rhesus macaques, and squirrel monkeys)
- Behavioral and electrophysiological studies
- Surgery and biological sampling
- MRI (in collaboration with the CENIR)

PHENO-ZFish – Zebrafish Modeling Platform

Sophie Nunes Figueiredo and Claire Wyart

This platform is dedicated to preclinical research on the zebrafish. With over 30,000 adult fish housed on the platform and cutting-edge equipment, research teams can carry out: nanoscale imaging, behavioral testing, and optogenetics (advanced technique for remote activation of target neurons with light). Highly qualified staff is responsible for daily care and animal wellbeing, and are available for services on demand. The platform has aquariums that that can house more than 20,000 adult fish and advanced equipment, including an automated robot for feeding and 6 injection systems for transgenesis. Furthermore, the platform proposes imaging, optogenetics, an advanced technique for activating target neurons at a distance with light, and behavioral experiments on mutant and transgenic lines. The users of the platform have access to specific training, for example in fish handling, including breeding, egg collection, transgenesis, screening and sperm freezing. Highly qualified technicians are responsible for care, breeding, and health.

WHY STUDY ZEBRAFISH?

The zebrafish is a vertebrate that shares 70% of its gene pool with humans. One of its many advantages is a rapidly developing nervous system that enables testing of therapeutic molecule potential. Its transparency makes this small animal particularly suitable for imaging techniques and optogenetics.

ACTIVITIES

- Consulting, training, and services for the public or private scientific community
- Fish breeding (crossbreeding, egg collection)
- Transgenesis and mutagenesis
- Immunohistochemistry and *in situ*
- *In vitro* fertilization

#DATABASE
#MULTIMODAL INTEGRATION
#BIOINFORMATICS/BIOSTATISTICS

Over the last two decades, neuroscience research has witnessed a spectacular explosion of laboratory-collected data. While collecting information is one thing, analyzing and understanding it to develop new treatments is quite another. The role of the iCONICS Bioinformatics silo is to ensure data collection from different sources, as well as data storage and organization. The silo also offers a data management toolbox, assisting data analysis and interpretation with specialized methods and complex statistics. The iCONICS silo, made up of two teams, provides researchers and clinicians with data analysis support and creates innovative software.

Database and Datawarehouse

Laure Seux and Bertrand Fontaine

The Databases and Datawarehouse team stores data in databases, all of which are designed on the same model. This allows daily formatting and management of information (clinical, genetic, imaging, diagnoses, neuropsychology, environment, images, disease evolution, raw and analyzed data, etc.) obtained on healthy or diagnosed patients. The team then prepares the data in the datawarehouse for statistical treatment and provides the teams with tools for the initial analysis.

DATAWAREHOUSE VS DATAMART?

A datawarehouse is a data storage facility that compiles most information from other databases. Its purpose is to act as a sole reference point and fuel datamarts, dedicated to targeted data analysis.

ACTIVITIES

- Implementation of database architecture and associated files
- Database installation and configuration
- Secure Web interface development
- Datawarehouse and datamart design
- Dynamic report (BI) development

Bioinformatics/Biostatistics

Ivan Moszer and Bertrand Fontaine

The Bioinformatics/Biostatistics team has a dual expertise:

- Processing of genetic/omic data (genomic, transcriptomic, epigenomic), primarily from high-throughput sequencing, by offering software and project assistance;
- Biostatistics, with an emphasis on design and implementation of advanced methods for multimodal data integration (clinical observations, genetics/-omics and neuroimaging).

ACTIVITIES

- Offer methodological advice and biomedical study design and interpretation expertise
- Define, apply, and offer high-throughput –omic data treatment procedures
- Design and apply biostatistical methodology (namely strategies for integrated analysis of multimodal data)

#DNA BANK
#BIOLOGICAL RESOURCES
#TUMOR BANK

Samples taken from patients during blood tests, biopsies, and surgery are an extremely valuable source of information for disease research. The ICM hosts three biobanks in charge of managing biological resources (biological samples and associated data) through collection, recording, processing, storage, and availability to researchers. This activity is strictly regulated by bioethics laws to respect patients and requires the approval of a Committee for the Protection of Persons (CPP). Quality control of the three ICM Biological Resource Centers (BRC) is certified under the AFNOR NF S96-900 standard. Additionally, the biobanks have partnered with the BRC BioCollections network to share and promote resource collections, and with the national BioBank infrastructure.

The DNA and Cell Bank

Alexis Brice, Alexandra Durr and Sylvie Forlani

The DNA and Cell Bank was implemented in 1990 and received NF S96-900 standard certification in 2009. It manages collections of biological resources for use in medical research projects, mainly in the field of neurological and psychiatric pathologies. The collections consolidate biological resource samples from over 52,000 patients and control groups for a total of nearly 220,000 samples (DNA, blood cells and fluids, fibroblasts) collected since the bank was created, and an additional 3,500 new samples each year. The collection is one of the largest worldwide, particularly for pathologies such as Parkinson's disease, frontotemporal dementia, autism, and certain rare diseases such as spinocerebellar ataxia. In 2015, the bank took part in 46 national and international research projects. It is equipped with powerful equipment, including an automatic DNA extractor.

French Multiple Sclerosis Genetic Research Network – Biological Resource Center (CRB-REFGENSEP) (ANR BB-0033-00019)

Bertrand Fontaine and Isabelle Rebeix

This resource center is a bank of samples dedicated to multiple sclerosis (MS), a disease with a strong socio-economic impact. Like the other ICM banks, the samples are available for researchers to better understand the disease's physiopathology, improve existing treatment, identify new curative treatments, and refine prognosis for how the impairment will evolve. Over the course of the last 6 years, the center has distributed over 20,000 samples. The samples come from trio-families (one affected child and his/her two parents), multiplex families (several siblings affected by sclerosis), sporadic cases and healthy subjects serving as a control group to determine disease specificities. In 2015, researchers had at their disposal the DNA of 2,700 patients, 1,739 healthy relatives, and 700 control group patients. Each DNA sample is linked to MS-specific and detailed clinical data as well as genetic data. The resource center has received NF-S 96-900 standard certification, applied specifically to biological resource centers. The center has been the national DNA management resource center since 2015, part of a national initiative to collect biological resources and clinical data from 30,000 MS patients.

The Tumor Bank: OncoNeuroTek

Jean-Yves Delattre, Marc Sanson and Yannik Marie

The OncoNeuroTek tumor bank is a biological resource bank (AP-HP) specialized in samples from patients with brain tumors. It is the largest brain tumor biobank in Europe, with samples from about 17,300 patients, owing to the bank's location within the Pitié-Salpêtrière Hospital. The bank receives local samples, and the hospital is one of the largest European centers for the diagnosis and treatment of brain tumors. OncoNeuroTek collects, annotates, and stores samples from patients with brain tumors. For over 15 years, it has built a collection of tissues as well as tumor DNA and RNA, patient DNA, and plasma. The samples and associated clinico-biological notes are stored in a single database, allowing the identification and extraction of criteria necessary for projects involving the tumor bank. To promote the quality of its services and its staff's professionalism, the OncoNeuroTek tumor bank has followed the guidelines and requirements of the French NF S 96-900 standard, applied specifically to biological resource centers, since 2012. After a two-year period during which the tumor bank implemented a proper and viable quality control system, it received AFNOR certification (the national organization for standardization, certification, publishing, and training). Since the OncoNeuroTek tumor bank's launch within the ICM, 16 partnerships have been developed with research teams hailing from all horizons: regional, national, and international.

Prof. Jean-Christophe CORVOL

Director of the Clinical Investigation Center at the ICM

"Thanks to the Clinical Investigation Center implemented within the ICM and the Pitié-Salpêtrière Hospital, a reference when it comes to rare and neurological diseases, we open the doors to the latest medical innovations for patients."

On the first floor of the ICM, the Clinical Investigation Center of the AP-HP (CIC) creates an exceptional path between research and care, where patients with neurological diseases are given innovative treatments. We take a closer look at the therapeutic trials of 2015 and encouraging outlooks for the future with Professor Jean-Christophe Corvol.

The CIC lies in the heart of a building dedicated to research: how is it organized? What makes it different? What is the CIC's mission?

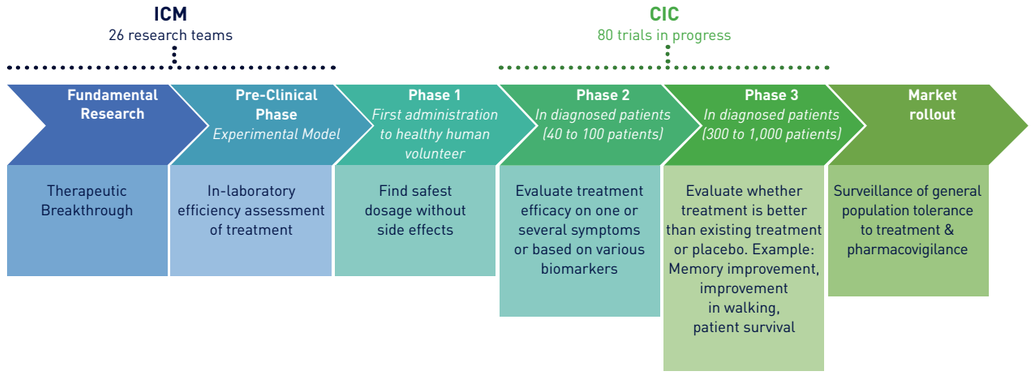
The CIC is a clinical research platform serving as an interface between ICM researchers, the hospital's neurologists, and psychiatrists. It aims at refining our understanding of brain function and pathological conditions affecting the human nervous system, as well as helping experimental research breakthroughs cross over into the human realm to improve diagnostic or therapeutic patient care.

How does having the CIC inside the ICM building, within the Pitié-Salpêtrière Hospital, affect its activity?

The CIC is housed in the ICM building, at the heart of research, and has a branch inside the Nervous System Diseases wing of the Pitié-Salpêtrière Hospital. We can therefore easily export technology from the laboratory to the patient's bedside. Thanks to this joint implementation, both in the hospital's healthcare model and the ICM's research model, doctors and researchers regularly meet to discuss various topics. Doctors and patients have access to the technical platforms and therapeutic innovations of the ICM. Patient care is facilitated by the CIC's medical and paramedical staff.

What place do clinical trials have within the scientific research process?

Clinical research is in the continuum of biomedical research that goes from understanding pathological mechanisms and identifying therapeutic solutions to evaluating efficacy of the chosen treatment in patients. Some studies also aim at improving understanding of brain function in humans. What parts of the brain play a role in motivation, in reading? What brain structures control our movements? Which neural networks communicate with one another? ICM researchers and clinicians answer these questions using the latest technology allowing us to explore the brain, such as MRI imaging, electrophysiology, and magnetoencephalography.



You are both a neurologist and director of the CIC, what is your role within the CIC?

My role is to make sure that the CIC's scientific and medical strategy is in line with that of the ICM and the hospital. It is also to share my methodological expertise on conducting studies, and ensuring that security, quality, and ethics regulations necessary in human research studies are respected.

Drastic regulation standards: responsibility, traceability, security

All studies are submitted for approval to two French bodies:

- The Comity for Protection of Individuals, in charge of delivering an opinion on the ethical nature of the study;
- The Medication Agency, ANSM, for an opinion on the security of the study.

Additionally, an internal committee within the CIC reviews all studies before launch. CIC staff is trained to respect clinical research Code of Practice.

A busy week with Jean-Christophe Corvol

- Neurology appointments pertaining to Parkinson's disease and related disorders
- Patient and evaluation inclusion in clinical studies
- Meetings with ICM researchers, Hospital doctors and industrial partners to set up new studies
- Hand in hand with paramedical staff, management of quality assurance processes and continuity of care
- Ongoing design of innovative instruments to evaluate neurological diseases

Clinical Investigation Center – CIC

The CIC in numbers

4
doctors

8
research nurses

3
nurse assistants

3
laboratory technicians

2
project managers

4
clinical study technicians

1
pharmacy residents

6
hospital beds

11
hospital recliners

6
appointment stalls

2
laboratories for storage
and analysis of biological samples

1
methodological expertise to adjust and
implement clinical studies
(selection of patients included in trial,
length of study, dosage…)

80
trials underway

Daily contact with **650** researchers

3,000
patients benefiting from clinical studies

THREE HIGHLIGHTS OF 2015 AT THE CIC

Discovery of a new gene involved in Parkinson's disease thanks to collaboration between neurologists and geneticists who collected and evaluated DNA samples in patients, and ICM teams who identified gene VPS13C and tested its relevance in experimental modeling. Project coordinated by Prof Alexis Brice and Suzanne Lesage.

Efficacy of a drug to treat symptoms of myoclonic dystonia, for which there is currently no therapy. This rare disorder, due to poor control of movements by the brain, leads to abnormal muscle contraction. The repositioned drug is currently administered to treat certain types of epilepsy. Trial centralized at ICM and coordinated by Professor Flamand-Roze.

The first drugs proven effective against progressive types of multiple sclerosis. A Phase III study on Ocrelizumab, coordinated by Dr Caroline Papeix in collaboration with Roche, proved its efficacy through modulation of the immune system. A second study on 154 patients, led by start-up MEDDAY founded by Dr Frédéric Sedel and Guillaume Brion, proved biotine efficacy on disease progression and improvement in general health of patients. These results are an encouraging sign of forthcoming availability of a treatment.

•••

What are your hopes for the coming years?

My first hope is to improve our description of the behavioral disorders shared by many neurological and psychiatric diseases. Along with Prof Richard Lévy and his team, we are doing a study to dig deeper into apathy and lowered activity levels associated with lack of motivation, thanks to the "real life" PRISME platform. The strategy is to better characterize this symptom shared by psychiatric disorders such as depression and neurodegenerative diseases like Parkinson's or dementia in order to develop specific markers, or indicators, and track the effect of new treatments. Characterizing symptoms that hinder daily life of patients in the best possible way is a crucial step that is sorely lacking in today's very technological world of neuroscience.

Transversal targeting of diseases, by their shared symptoms, is an outlook for the future and a true revolution when it comes to developing drugs.

My second hope is to carry breakthroughs in the field of rare diseases over to other diseases. Take Progressive Supranuclear Palsy, PSP, for example: it is a rare disorder caused by an accumulation of proteins, some of which are similar to the accumulation we see in Alzheimer's disease, that cause the death of neurons. The idea today is to target these proteins in two distinct diseases. 2016 should see the launch of studies to test drugs in patients with PSP thanks to the Pitié-Salpêtrière reference center coordinated by Prof. Bruno Dubois and Dr Isabelle Leber, and the very active PSP-France patient organization, run by Mr. Schang.

These projects are a source of hope not only for PSP, but also for other neurodegenerative disorders.

— The CIC is supported in part by the EDF Foundation. —

Alexis GÉNIN

Director of Research Applications

Alexis Génin, you are Director of Research Applications (DAR), what is your role within the ICM?
I am in charge of converting breakthroughs into therapeutic solutions as quickly as possible. That means, first and foremost, early detection of research results that can be converted into applications, protecting them with patents, allotting financial means for concept validation – going from an idea to a proven idea – and finally invention maturation and development of new drugs. All this is made possible in part thanks to a grant from the Institut Carnot brand, that supports research partnership development and technology transfer between public research institutions and private companies.

Research applications: creating a pathway between researchers and industrial partners

- Prove that a breakthrough or invention works and is potentially interesting
- Protect invention, in particular with a patent
- Develop a partnership with an entrepreneur or company capable of implementing the project, or create a new company ourselves and develop it within the incubator
- Develop prototypes
- Launch clinical trials

Proof of concept, or how to go from idea to proven idea

Michel Le Van Ouyen, researcher in Stéphane Charpier's team, had an idea: improve sleep quality by stimulating the brain with a connected headband. With financial aid from the DAR, the idea was tested on hospital patients at the Pitié-Salpêtrière. Researchers proved that very subtle acoustic stimulation can increase the amplitude and duration of slow sound waves during deep sleep, resulting in improved sleep quality and, potentially, memory. A patent application has been filed and a clinical study to prove effects on memorization and stress is ongoing.

Overview of ICM-Institut Carnot over the past five years

The Carnot system aims at supporting research partnership development and technology transfer between public research institutions and private companies.

- Exceptional growth
- 21 companies in the iPEPS-ICM incubator
- 180 industrial partnerships
- 1 portfolio of 50 patents
- 2joint laboratories established, winners of the "Innovation 2030" contest
  - Bio-electrics lab: Big Data analysis of EEG signals
  - Brain eNovation: Serious games
- Establishment of a "quality" division
- Certification of 2 platforms and Centers for Biological Resources

The ICM's second floor is home to a corporate incubator, the iPEPS-ICM or Paris Salpêtrière Business Incubator, the first innovation booster dedicated to brain diseases in France. In 2015, the incubator welcomed 21 national and international businesses. What is their goal? How close are they to the researchers?
These start-ups are developing therapeutic solutions, drugs, novel technology, digital instruments, to speed up research and fight against nervous system diseases. Within the ICM, they benefit from our researchers' expertise, our platforms, and our doctors to accelerate development. A third of all incubated businesses stem from ICM research and were started by researchers or doctors from the Institute. In 2015, we welcomed companies from abroad for the first time, Neoneuro (Canada) and Pathmaker (Boston), illustrating how attractive our institute is.

This year, one of our big news at the ICM is the start of the "uCIL, user-Centered Innovation Lab" where patients, researchers, clinicians and developers work hand in hand to find therapeutic solutions. Can you tell us more about how it works? What its mission is?
A living lab is built on the idea of collaborative innovation, where users are at the heart of the facility. We brainstorm on the needs of patients and medical staff together with them, in order to think up, develop, and create innovative instruments. Encouraging functional rehabilitation of patients after they leave the hospital, diagnosing the risk of impaired independence to support the elderly, improve hospital life during long-term stays to preserve patient intimacy, anticipate autistic patient crises, all these are projects in launch phase developed at the uCIL Living Lab. Our ambition is to rapidly create functional prototypes, manufactured and used thanks to collaborative innovations with a very short time to market, between 6 months and two years.

THREE HIGHLIGHTS OF 2015

First international companies enter iPEPS
Excellent end of term Carnot evaluation
Launch of the Living Lab

What are some major projects of the Department of Research Applications?

As we look to the future, *"Accelerate"* is our motto. To develop inventions even faster than before, three accelerators are currently being designed. The first, FindMED in the field of medication, was launched in January 2016. This is a project that brings 12 Carnot institutes together and aims at accelerating drug development.

The second project is NeurosensHub, in the field of medical technology, to be launched second semester of 2016. Its mission is to help design prototypes and help with clinical assessment of their benefits. Finally, the third project is in the realm of clinical research and could start in 2017. The challenge here is to evaluate, quickly and in the earlier phases, the therapeutic potential of candidate drugs. The ICM is leader, driver, and coordinator of these three projects that all have the shared goal of developing platform and expert networks to get to the proof of concept stage of an invention very quickly.

According to you, what will healthcare look like in the future?

Preventive medicine, most probably. Now, when individuals are diagnosed and arrive at the hospital, it's already very late and the toolbox we have at our disposal is limited. In the future, drugs might be a solution among many others. Nutrition, physical activity, and cognitive stimulation are means of prevention that could become increasingly important. Game-based therapy, for example, is used in rehabilitation to help patients with Parkinson's and could also help prevent falls in elderly individuals. Many neurodegenerative diseases have a metabolic aspect, meaning that there is a link with poor energy function of the brain, of metabolism, lipids, etc., making nutrition that much more important. Preventive medicine is still in its infancy, with an economic model that has yet to be built, but is probably where our health's future lies.

Neuronaute, the first connected clothing to diagnose epilepsy

Success stories

MedDay: the first effective treatment against progressive multiple sclerosis

MedDay, headed by Frédéric Sedel and Guillaume Brion, developed MD1003, first treatment proven effective against progressive MS. A clinical study on 154 patients over the course of a year in sixteen treatment centers in France showed significant improvement in patients' general heath and slower progression of the disease. The treatment should be available in the short term, encouraging news for both clinicians and those affected by the disease.

BioSerenity: Neuronaute, the first connected clothing to diagnose epilepsy

Neuronaute, developed by Bioserenity, a start-up incubated in the ICM and led by Pierre-Yves Frouin, is set to launch on the market in 2016 and offer remote personalized care and epileptic patient monitoring. Additionally, BioSerenity has acquired funding from the World Innovation Competition for a Big Data project on EEG analysis. The grant has enabled the creation of the Bioelectric Lab, a joint laboratory between the ICM and BioSerenity.

Key figures —

FUNDRAISING

14 M€ were raised in 2015, an increase in 26% compared to 2014.

Major patronage agreements signed with foundations or companies in 2015:

- HSBC-France to support research on neurodegenerative diseases;
- OCIRP for research program funding;
- Fondation d'entreprise Michelin to fund a collaborative research project between the ICM and Auvergne University;
- The Edmond J. Safra Foundation for research project funding;
- SMUGGLER to support the ICM research mission.

The Circle brings together donors who have supported the ICM from its inception, with donations of 10,000€ or more.

The Circle was created as a means of giving special thanks to important donators, individuals, companies, or foundations, who very actively participated in the Fundraising Campaign launched by the ICM in 2008. The Circle currently has 480 members. Exclusive activities are organized to thank them for their support and to help donators meet and discuss with researchers, and are also a means of giving them more in-depth information regarding research outlook and how donations are used.

Maurice Lévy and David de Rothschild, Founding Members of the ICM, currently serve as Circle co-presidents. In line with the Circle's international development strategy, the ICM organized a charity dinner in Brussels on May 20, 2015.

Over the year, the ICM continued its direct marketing strategy, initiated in 2010, to increase its donor base. Fundraising campaigns raised 5.7 M€ over the course of the fiscal year and donor base increased to 105,000 by end of year.

Finally, the ICM is especially grateful to families who collected donations in memoriam for the Institute.

IN-KIND DONATIONS AND SPONSORSHIPS

Many companies have offered their support by contributing skills from their field, or by donating products free of charge.
In this section are also featured artists and collectors who have donated works of art to be sold, benefiting the ICM.

The ICM has received support in the form of:

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

THE ICM IN FRANCE

The ICM continued its regional expansion in 2015. Three regional branches (Limousin, Basse-Normandie and Auvergne) were organized around the following goals:

- Reinforce visibility, reputation, and attractiveness of the ICM amongst donors, the general public, and economic and political figures;
- Contribute to the development of the ICM's financial resources to accelerate scientific discoveries with its own research teams and regional, national and international partnerships;
- Encourage ties between the ICM and regional neuroscience research partners and promote collaborations.

This approach will be rolled out to other regions on various topics in the field of nervous system diseases.

APPLICATIONS OF RESOURCES – 2015

APPLICATIONS	2015 Applications — Profit and Loss Statement	2015 allocation of resources by application
1. Social Missions	**21,372,369**	**6,611,803**
Actions directly carried out		
Research Programs	11,615,091	652,812
Research Technological Platforms	7,096,211	3,817,122
Aplication de la recherche et incubateur	1,059,501	666,645
Research Application and Incubator	1,601,566	1,475,224
2. Fundraising costs	**3,180,074**	**2,929,208**
Cost of appeals to the generosity of the general public	2,834,646	2,829,486
Costs related to private fund canvassing	237,164	
Costs related to prospecting for subsidies and other public aid		
Communication costs	108,263	99,723
3. Institute operation costs	**2,495,945**	**743,667**
I. TOTAL APPLICATIONS	**26,940,125**	**10,284,677**
II. PROVISIONS		
III. PLEDGES ON ALLOCATED RESOURCES	**7,464,986**	
IV. FISCAL YEAR SURPLUS	**765,690**	
V. GRAND TOTAL	**35,170,802**	
Share of fixed assets acquired during the fiscal year financed by collected funds		13,587
Neutralization of provisions for depreciation of fixed assets financed by collected funds		-2,502
TOTAL APPLICATIONS FINANCED BY FUNDS COLLECTED FROM GENERAL PUBLIC		**10,295,762**

RESOURCES	2015 Resources Collected — Profit and Loss Statement	2015 Resources Collected and Used
Carryover of resources collected from general public not allocated/used at start of fiscal year		559,776
1. Resources collected from general public	**10,400,009**	**10,400,009**
Unallocated monetary donations	9,902,339	9,902,339
Allocated monetary donations	495,506	495,506
Unallocated bequests and other gifts	2,164	2,164
Allocated bequests and other gifts		0
Other products of general public generosity		0
2. Other private funds	**10,384,825**	
Patronage	3,282,022	
Partnerships	5,817,172	
Private subsidies	1,285,632	
3. Subsidies and other public aid	**3,720,250**	
4. Other products	**6,080,715**	
Financial products	305,777	
Services rendered	2,971,969	
Other products	2,802,969	
I. TOTAL RESOURCES	**30,585,799**	
II. CARRYOVER OF PROVISIONS		
III. CARRYOVER OF ALLOCATED RESOURCES UNUSED IN PREVIOUS FISCAL YEARS	**4,693,266**	
IV. VARIATION OF ALLOCATED FUNDS COLLECTED FROM GENERAL PUBLIC		**-126,416**
V. FISCAL YEAR INSUFFICIENT RESOURCES		
V. GRAND TOTAL	**35,279,065**	**10,833,368**
TOTAL APPLICATIONS FINANCED BY FUNDS COLLECTED FROM GENERAL PUBLIC		**10,295,762**
BALANCE OF FUNDS COLLECTED FROM GENERAL PUBLIC NOT ALLOCATED/ USED END OF FISCAL YEAR		**537,606**

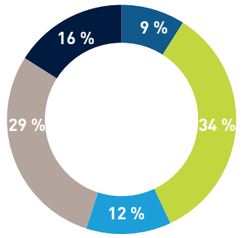
EVALUATION OF VOLUNTARY IN-KIND DONATIONS			
Social Missions	36,960	Volunteering	36,960
Fundraising costs		In-kind Services	
Operational costs		In-Kind Donations	

Balance Sheet

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€).



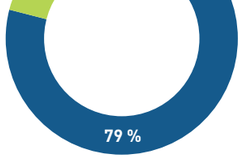
2015 APPLICATIONS
In 2015, the grand total of applications reached 34.5 M€, and 27 M€ used in 2015 and 7.5 M€ allocated for future use. The share of applications dedicated to social missions reached 21.4 M€, 79% of total fiscal year applications. ICM social missions include:

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

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.

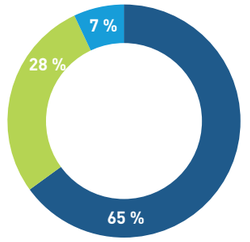
Operational costs (9.2%) represent support staff costs (finance, human resources, legal, IT and logistics).

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.



ALLOCATION OF RESOURCES FROM THE GENERAL PUBLIC
Resources raised from the general public and used in 2015 totaled 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€.

Balance Sheet

BALANCE SHEET (CONTD)

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.
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 COMMITEE

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.

Life at the ICM —

COMMUNICATION CAMPAIGN, PRESS, AND NEW WEBSITE

A communication campaign produced in 2014, with a promotional film featuring researchers removing their clothes, asked viewers *"Do we need to go this far to fund brain and spinal cord research?"* Broadcasting continued in 2015, along with two press inserts in the same humorous tone with the following message: "Save both hemispheres before it's too late" and "Make a donation, save a hippocampus". The promotional film received the Epica Prize, a European award.

World awareness days were opportunities to deploy awareness-raising communication towards Institute donors and the general public: on Parkinson's (11/04), Multiple Sclerosis (26/05), Alzheimer's (21/09), depression (08/10) and epilepsy (4/11). These initiatives consolidated the ICM's role as a major research player on nervous system diseases and a preferred contact for media outlets. Additionally, the quarterly "Meet the ICM" event where donors have the opportunity to meet researchers and the administrative team within the ICM was a continued success.

#NEW WEBSITE
#BRAiN'US
#WHO WANTS TO BE A MILLIONAIRE?

A large-scale communication campaign was launched to support the BRAiN'US project, the first interactive research project led by Jean Daunizeau, Inserm team leader at the ICM. Two appearances on TV (BFM and Magazine de la Santé on France 5) as well as articles allowed the general public to "meet" researchers from the Institute.

Another high point in the year was the broadcast of an episode of *"Who wants to be a millionaire?"* on channel TF1 with ambassadors Jean Réno and Richard Berry, ICM ambassadors.

Finally, the Institute's new website was released May 2015 with easier navigation and new sections adapted to online viewing of information.

SPORTING AND CULTURAL EVENTS, SHARED PRODUCTS

Many sporting and cultural events were organized over the course of the year to support the ICM. Some key events were a charity dinner organized in Brussels inside the Queen Elizabeth musical chapel and the Racetracks for Brains event organized on the Bresse racetrack. Additionally, the ICM invited major donors to a charity breakfast at the opening of the International Contemporary Art Fair (FIAC) at the Grand Palais in Paris.

Finally, shared products saw an increase, with 5% of all sales of the Journe Centigraphe Souverain timepiece and 10€ for every Smuggler suit and jacket donated to the ICM.

REGIONAL DELEGATIONS

ICM researchers collaborate with various regional teams in Basse-Normandie, Limousin, and Auvergne. These regional branches play an important role in supporting the ICM and organize many events benefitting the Institute. In 2015, the Limousin region organized or was a partner of over ten events, including the Tour du Lac Vassivière, a semi-marathon where 2€ from each registration were donated to the ICM. A partnership was also introduced for the 48th edition of the 2015 Tour du Limousin, a renowned cycling race. The Basse-Normandie branch organized or was a partner of three events in 2015, including the Caen Retrofestival, an event dedicated to vintage and sports cars. 5€ from each ride in a sports car were donated to the ICM. The regional Auvergne branch is the latest to join the ICM, supported in part by the Michelin Foundation.

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The Friends of the ICM Circle brings together the 480 major patrons of the Institute (individuals, companies, foundations, and non-profit organizations). They are true partners who give the ICM means to expand its research programs, hire leading scientists, attract young talent and gain access to cutting-edge technology and equipment.

The Friends of the ICM Circle is international. The ICM has an agreement with Transnational Giving Europe (TGE), a partnership of European foundations and non-profits that gives TGE member-country tax residents the opportunity to support the ICM with tax benefits as decided by their country.

Laboratory visits are offered year-round for Circle members, as well as scientific and cultural conferences and discussions with researchers.

The Friends of the ICM Committee
It aims at finding renewed support to give the ICM the means to pursue its ambitious mission.
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A few highlights from the year
May 20 2015 – Private concert followed by a benefit dinner supporting the ICM at the Queen Elizabeth Musical Chapel in Waterloo, attended by HRH Prince Lorenz of Belgium. Many guests became new members of the Circle over the course of the evening, with Jean-Philippe Thierry as ICM ambassador.

October 21 2015 – ICM benefit breakfast and "Art-science" performance at the Mini Palais on FIAC opening day. Street artist Mehdi Cibille and researcher and ICM team manager Claire Wyart collaborated to create four works of art inspired by Wyart's research on zebrafish and optogenetics. **This was the FIAC's fifth year supporting the ICM.**

November 24 2015 – Friend of the ICM Circle breakfast at PUBLICIS. Prof. Bruno Dubois, neurologist and team manager at the ICM, presented his research on Alzheimer's disease.

Scientific conferences at the ICM preceded by meet and greet sessions in the Charcot Library with the President and General Manager of the ICM. Major patrons were made aware of research advances on Parkinson's (April 9 2015), Multiple Sclerosis (May 28 2015), Amyotrophic Lateral Sclerosis (June 19 2015), Alzheimer's (October 6 2015) and Epilepsy (November 26 2015).

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WE EXTEND OUR DEEPEST THANKS TO OUR 497 PATRONS, MEMBERS OF THE FRIENDS OF THE ICM CIRCLE, FOR THEIR GENEROUS SUPPORT.

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We have verified this information numerous times to ensure it is correct. If you do, however, find an error, please accept our apologies and let us know.

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