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AGE WELL

The global health challenge of nervous system diseases can only be tackled by an innovative and multidisciplinary center of excellence that unites the best researchers.

Thus it has been 5 years since the ICM opened its doors and 650 researchers, engineers, and technicians work together every day towards a common goal: allow people to remain free of their movements and their thoughts. In thinking of the people around us, our friends, our parents, our close ones, we ask ourselves today not only how long we will live, but also in what conditions. Today, the fight of the researchers at the ICM is based on finding new solutions for these diseases, for quality of life, and on the way in which we understand “aging”.

Today, the ambition of the institute is to become a major neuroscience research center on the international scale that is at the origin of new therapies capable of treating diseases of the brain and spinal cord while maintaining brain function to age better.

In order to provide researchers with the means for their ambitions, we need everyone’s support: personal, businesses, and the community. Extending life and related pathologies associated with aging are problems that concern us all without exception.

Thank you for supporting the ICM and standing at our side in this unprecedented human and scientific adventure.

Mr. David de Rothschild
Founding Member

A DOOR BETWEEN TWO WORLDS

When Gérard Cogno-Bourdieu was diagnosed with Parkinson’s Disease in 2009 he decided to commit himself completely to music with his musician friend, Sylvia Renard. Together, the duo opened a “door between two worlds,” building a bridge between classically-inspired piano music and electroacoustic spaces of electronic music. Gérard Cogno-Bourdieu and his music partner are organizing a benefit concert on Sunday, November 15, 2015 at 5pm at the theatre of the Bretonneau Hospital. All proceeds will be donated to the ICM. Places are limited, tickets are on sale on the production’s website “Le Murmure des Anges” at the address www.le-murmure-des-anges.com.

FIAC

In the exceptional setting of the MiniPalais within the Grand Palais, the major donors of the ICM enjoyed the opportunity to experience research for the opening day of the FIAC through the eyes of Mehdi Cibille, a mysterious and anonymous artist. A 60 minute creative performance brought together creativity and generosity, benefiting work on brain and the spinal cord diseases.

THE PITIÉ-SALPÉTRIÈRE LABELED “REGIONAL CENTER OF EXCELLENCE”

In the scope of the new national plan for neurodegenerative diseases (2014-2019), seven regional centers of excellence were named in the field of neurodegenerative disorders, including the site of the Pitié-Salpêtrière. In a single location, the Pitié-Salpêtrière groups together forces of excellence in basic and clinical research, technology transfer, and organization of treatment plans, further expanded by institutional connections with UPMC and Sorbonne-Université and related teams in neuroscience and human and social sciences with a focus on neurodegenerative diseases.

PARTNERS: KLÉSIA

The Klésia group, sponsor of the ICM from the beginning, invited two startups incubated at the ICM to the Klésia Space at the MEDEF Summer School that took place August 26-27, 2015.

With “formidable youth” as the theme, the MEDEF Summer School wanted to address the great French and worldwide challenges to offer youths all possible chances to succeed in their professional future. Prof. Gérard Saillant, President of the ICM, spoke for the closing plenary lecture and provided an account of the experience of the ICM, which brings together not only researchers and clinicians, but also startups in the iPEPs incubator. Two young companies, BRAIN e-NOVATION and Melomind also brought together creativity and generosity, benefiting work on brain and the spinal cord diseases.


NEWS

Seen on the web

• icm-institute.org/en/alzheimer-en/
  A special report on Alzheimer’s disease

• icm-institute.org/fr/actualite/m-a-tactique-etait-loc-les-troubles-obsessionnels-compulsifs-aujourd’hui/
  An column on OCD from Margot Morgièvre, researcher at the ICM.

• icm-institute.org/fr/lesconferences-de-icm/
  Find the last two seminars dedicated to multiple sclerosis and amyotrophic lateral sclerosis

CALENDAR

●●● November 15, 2015
  – Concert for Hope organized by the Lions Club of Verrières le Buisson

●●● November 17, 2015
  – Concert “A door between two worlds”

●●● November 21, 2015
  – National Epilepsy Day

●●● November 21, 2015
  – “Music Passion Parkinson” Concert
**EPILEPSY: IDENTIFY, STUDY, AND UNDERSTAND**

Epilepsy is the most common neurological disorder after migraine. 500,000 people in France and 50 million people in the world are affected, of which half are younger than twenty years old. This disorder impacts both society and families tremendously. An epileptic seizure corresponds to brief abnormal electrical activity in a network of cortical neurons. This discharge can be confined to a region of the cortex (focal epilepsy) or spread out over the cortex (generalized epilepsy). As for other brain disorders, researchers prefer to speak of epilepsies in the plural form as the disorder has many forms that make classification complex, including the type of seizures (tonic-clonic seizures with a contraction phase and a spasm phase, childhood absence epilepsy, partial seizures), the cause (tumor, infection, malformation, metabolic, genetic), the association with other neurological signs, and the electroencephalogram trace. Among the different forms of epilepsy found in the population, one-third of cases are resistant to medical treatments and constitute the major target of researchers and clinicians at the ICM.

At the heart of the institute, three teams are devoted to this disorder and link their work around three essential approaches.

1/IDENTIFY THE GENES RESPONSIBLE

Eric Leguern and Stephanie Baulac’s team is interested in the genetic origins of epilepsies. Their objective is to identify new genes responsible for inherited (genetically determined) epilepsies, then to develop experimental models to understand the mechanisms of the disorder and to test new medicines to improve treatment for patients.

After identifying a new gene, DEPD5, associated with a hereditary focal epilepsy, the researchers discovered that mutations (modifications) of this gene caused a cerebral malformation in certain cases. This malformation is a result of a second mutation in the DEPD5 gene that survives in brain cells over the life of the patient and is added to the mutation inherited from the parents. This discovery is the first time that such a mechanism has been described for a form of focal epilepsy.

This team identified another gene, FIG4, implicated in a hereditary epilepsy associated with cerebral malformation. The gene has already been implicated in other pathologies: a peripheral neuropathy (Charcot-Marie-Tooth disease) and in a malformation syndrome of newborns. The team brought to light the fact that where and what type of mutation occurs determines which of these three syndromes will develop.

Caroline Nava and Christel Depienne, in collaboration with the electrophysiology platform and a European consortium, recently discovered that de novo mutations (not present in the parents of affected individuals) of the HCN1 gene are implicated in Dravet syndrome, a severe form of epilepsy occurring in infants. At first, these infants have recurring febrile convulsions that are resistant to medication, which are succeeded by epileptic seizures also resistant to medication. Around their second year of life, these infants develop cognitive deficits. The HCN1 gene allows a protein to be produced that contributes to production of an ion channel. Ion channels regulate the excitability of a cell and thus control the activity of neurons. The discovery of a new genetic cause responsible for this severe form of epilepsy allows new diagnoses and a better explanation of the disease for patients and their families.

The modification of another gene, Lgi1, is implicated in familial focal epilepsies. In order to study the mechanisms responsible for triggering a seizure, the researchers developed a rodent model in which the gene Lgi1 is modified in certain sub-populations of neurons. The researchers were thus able to show that the epilepsy is related to the excitation of a certain type of neuron and that Lgi1 plays a key role in regulating excitability.

2/ STUDY BRAIN DYNAMICS

Stéphane Charpier’s team studies the activity dynamics within the neuronal networks of the cortex and the excitability of individual neurons. The transmission of nerve impulses propagates in the form of an electrical signal. Each neuron must receive, process, and send out electrical signals to other neurons. Certain keys to understanding epilepsy are found at this level of study, in which abnormal electrical activity prevents proper treatment of information. Stephane Charpier’s team utilizes electrophysiology to study the electrical activity of the brain at all spatial scales and in real time: from the global surface electrical activity (EEG) to the intracellular activity of an individual neuron. In close collaboration with clinical neurology teams, this team explores both focal and generalized epilepsies, notably childhood absence epilepsy. They showed that in patients with focal epilepsy, the epileptogenic region of the brain showed high frequency activity. These rapid rhythms become thus electrophysiological markers of a epileptogenic region because they are specific to the region giving rise to the seizure and are recorded before a seizure arises. This important discovery allows understanding of the mechanisms in advance of an epileptic seizure and could allow prediction of seizures before they occur, an important advance for treating epileptic patients. The same team recently identified neurons triggering absence seizures, which are common in young children and result in a temporary loss of consciousness.

Stéphane Charpier’s team is continuing its work to understand the brain mechanisms that are responsible for these consciousness problems that are associated with epileptic seizures.
3/UNDERSTAND THE MECHANISMS
Richard Miles’ team is focused on dysfunction related to focal epilepsies localized in a precise area of the brain. This location is often found in the hippocampus, a deep hidden region of the brain at the level of the temple. Richard Miles and his collaborators seek to understand how aberrations in communication between neurons could lead to epileptic events.

Patients suffering from brain cancer often have epilepsy associated with the cancer. In the region of the brain around the tumor, researchers detected aberrations in communication between neurons due to a modification of a certain type of ion channel (chloride channels). Their effect is to modify the signaling between neurons as in the hippocampus of patients suffering from focal epilepsies.

Richard Miles’ team also developed a technique to conserve in culture brain slices taken from patients suffering from focal epilepsy of the temporal lobe. These human tissues conserve their morphological characteristics and their epileptic activity for four to six weeks. The ability to maintain these tissues in culture for such a long time is a major advance for understanding the mechanisms of epilepsy and to test the effect of treatments in the long term.

Richard Miles’ team also explores the sclerosis or neuronal death that is at the origin of focal epilepsies. The team works in particular on the role of lipids, including cholesterol, in this neuronal death. In collaboration with Nathalie Cartier, the team showed the role of cholesterol in increasing epileptic activity and neuronal death in the hippocampus of the mouse.

AND ON THE INCUBATOR SIDE?
The number of epileptic patients in Europe is up to 6 million, and only half of these patients receive adequate treatment. The diagnosis of epilepsy to allow for appropriate and individualized treatment requires frequent hospital stays in order to follow the many clinical protocols. Unfortunately, these stays are restrictive and are not always sufficient for recording epileptic seizures in real-time, a prerequisite for defining the right treatment. Today, establishing a correct diagnosis can take two or three years. An adequate treatment is thus possible much faster. Additionally, the doctor can analyze the patient’s reactions to a given treatment and adapt the dose in real-time. Thanks to this technology, costs are reduced and monitoring epilepsy is accessible to more doctors and patients. Furthermore, if patients provide agreement, the anonymous data are available to the researchers of the Brain and Spine Institute to model different types of epilepsy.

The data, collected and analyzed by a smartphone application, are sent to a secure medical “cloud”. The data can be reviewed at any time by the treating physician who has a stable and systematic updated base in order to establish the right diagnostic that can then be established in 2 to 3 weeks. An adequate treatment is thus possible much faster. Additionally, the doctor can analyze the patient’s reactions to a given treatment and adapt the dose in real-time. Thanks to this technology, costs are reduced and monitoring epilepsy is accessible to more doctors and patients. Furthermore, if patients provide agreement, the anonymous data are available to the researchers of the Brain and Spine Institute to model different types of epilepsy.
Everything started 13 years ago, during a road accident. I was cycling, and I was knocked over by a van. The shock was so violent that my brain was affected; this is certainly the origin of my epilepsy.

My first seizure took place one evening, some time after, while I was in a car with my mother. It was nighttime, and I remember the headlights from the cars next to us, black, and the contrast with the lights. I felt incredibly fatigued. It seemed that I stopped speaking and fainted. My mother was very afraid, she helped to lay me out on the ground while waiting for emergency help. The doctors then made the formal diagnosis of epilepsy, a huge shock for me.

My second seizure occurred during a road accident while I was cycling, and I was knocked over by a van. The shock was so violent that my brain was affected; this is certainly the origin of my epilepsy.

After several months, I wanted to change to a new neurologist and was directed to Professor Navarro at the Pitié-Salpêtrière Hospital. We took a long time to discuss together, and he prescribed a new medicine that considerably reduced my seizures, and thanks to which I feel much better. The seizures are now partial, meaning I no longer become unconscious. I always had a strong sentiment at the cardiac level, but now I remain present. Before meeting Prof. Navarro, I had up to 10 seizures per day. Now, I have 1 to 2 consistently each day. It’s fewer but still enormous for me.


*Name changed for privacy reasons

AND IF HAVING CONFIDENCE INFLUENCED OUR JUDGEMENTS?

A study led by the team of Mathias Pessiglione and Jean Daunizeau showed that the region of the cortex responsible for value attribution also integrates the degree of confidence that we have in our judgements. This work, published in the journal Nature Neuroscience, represents significant progress in the understanding of how the brain functions and opens new perspectives on neuro-economics.

From the choice of a restaurant to that of a partner, our propensity to compare and evaluate is constantly present in our lives everyday. How do we attribute value to things? What are the parameters that influence our judgements? And what if the confidence that we place in our judgement affected these things?

In order to test this hypothesis, researchers in the team searched for healthy subjects to evaluate their attraction to photographs (faces, scenes), then to evaluate their degree of confidence in their judgement. The result was very clear: the more that people are certain of themselves, the more their judgements are deep-seated!

In parallel, the team used fMRI to show that the activity of the medial prefrontal cortex, a region of the brain responsible for attributing value, is proportional to the value attributed to the objects and also the degree of confidence. The integration of value and confidence in the same region of the brain could explain some irrational behavior. Someone who feels very confident and finds themselves in an agreeable context could have erroneous judgement and would thus be more easily manipulated. This work opens new perspectives in the understanding of the brain mechanisms underlying our choices and decision-making.

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MAKE THE BRAIN TRANSPARENT TO BETTER UNDERSTAND ALZHEIMER’S DISEASE

For the first time, Kunie Ando, Benoit Delatour, and Charles Duyskaerts, in Marie-Claude Potier and Stéphane Haïk’s team at the ICM, used a method called CLARITY in the brains of Alzheimer’s patients, allowing visualization of the interior of the human brain in three dimensions.

With almost 860,000 people in France and 35 million people worldwide suffering from Alzheimer’s-type dementias, Alzheimer’s disease is a center of concern.

Alzheimer’s disease is accompanied by a progressive decline of several cognitive functions resulting from a concomitant progression of two types of lesions. On one level, the abnormal accumulation of a protein called amyloid-beta peptide on the exterior of neurons drives the formation of “amyloid plaques”, also called “senile plaques”. On another level, the abnormal accumulation of TAU protein inside neurons drives their neurofibrillary degeneration, synonymous with cognitive decline.

Thanks to the CLARITY technique, the team was able to visualize these lesions and study the brain organization of patients with Alzheimer’s disease. The post-mortem samples come from the Salpêtrière GIE NeuroCEB brain bank, financed by the Associations de Malades France Alzheimer, France Parkinson, Fondation ARSEP, and CSC.

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This technique, developed at Stanford, allows maintenance of internal structure while making the brain transparent. It consists of removing the lipids (fat) and replacing them with a transparent gel. Thanks to fluorescent probes that attach to certain types of molecules, the researchers visualized the organization of senile plaques, axonal trajectories, and the neurofibrillary degeneration in a post-mortem sample.
PARKISON’S: TREAT WALKING PROBLEMS WITH DEEP BRAIN STIMULATION

Walking troubles related to balance and the falls associated with these troubles that are caused by Parkinson’s disease are a major public health problem.

Researchers at the ICM recently showed that the pedunculopontine nucleus, a region of the brainstem, is involved in the control of walking, and stimulating this nucleus reduces the troubles that can arise. In certain advanced forms of Parkinson’s disease, medical and surgical treatments have been shown to be less effective, and the patient starts to experience walking troubles, freezing*, and falls, confining these patients to a wheelchair. Recent hypotheses suggest that the troubles might be caused by neuronal death in the pedunculopontine nucleus (PPN), a brain region involved in the control of walking and balance.

In order to verify this hypothesis, ICM researchers used a multidisciplinary experimental approach that consisted of an electrophysiological study during a neurosurgery procedure.

The results obtained confirmed the dominant role of the PPN in the control of walking. Additionally, a second study showed that deep brain stimulation of the PPN improved the walking and balance problems in certain Parkinsonian patients. However, this procedure is risky and cannot be performed in all patients. These preliminary results strengthen the understanding of the PPN in the control of walking. Additionally, a second study showed that deep brain stimulation of the PPN improves the walking and balance problems in certain Parkinsonian patients. However, this procedure is risky and cannot be performed in all patients.

The company PathMaker Neurosystems Inc., which develops non-invasive treatments for patients with neuromotor difficulties, joined the IPEPS-ICM incubator.

More than 27 million of patients in the United States and Europe suffer from motor problems resulting from cerebrovascular accidents, cerebral paralyses, multiple sclerosis, Parkinson’s disease, or other neurodegenerative diseases. Non-invasive stimulation technology for the spinal cord developed by PathMaker offers new methods for treating these patients.

“By establishing our European offices and our operations in a state of the art neuroscience institute, we have the opportunity not only to work with the best specialists and researchers in the field, but also to take advantage of the research infrastructure and the Clinical Investigation Center at the ICM.”

PathMaker was created to commercialize recent advances in development and clinical applications of transcutaneous spinal direct current stimulation (tDCS) for patients suffering from motor difficulties of neurological origin. tDCS is a new non-invasive neuromodulation technique. Its development was possible thanks to recent advances in the understanding of neural circuits in the spinal cord by scientific advisors of the company and thanks to their clinical activity in treating patients suffering from paralyses, muscle weakness, and from loss of muscular tonicity.

* Sudden and brief immobility usually accompanied by stamping in public health problem.

THE ICM IN FRANCE

To reinforce its proximity to donors and to accelerate research, the ICM is active in the regions of France. Three regional delegations were created. These delegations function thanks to the involvement of numerous volunteers and work in line with the seat of the ICM. Collaborative research programs are led locally with national centers of scientific excellence. Each region is organized around a regional delegate who drives actions of the ICM and leads communication actions with the support of a local ambassador.

Nearly 70,000 euros were for example raised by the ICM delegation in Limousin since the beginning of 2015 for the benefit of research on neurodegenerative disorders. Since the beginning of the year, athletes, presidents of associations, and company heads have been active in bringing together a network of dynamic and committed players alongside researchers. This past September 24, the five-year anniversary of the institute, an event was organized in Limoges to thank them. The financially supported scientific project focuses specifically on ALS (amyotrophic lateral sclerosis). It is associated with a research team at the ICM (Severine Boillée) and the CHU of Limoges with Philippe Coriat, neurologist, and Benoît Main, epidemiologist. Mr. Jean-Claude Boisdevèys, ICM regional delegate, brings together a network of ambassadors who get together for events such as the Tour du Limousin, the Vassivière half-marathon, and makes possible the support and commitment of organizations such as the Inner Wheel Club, of athletes, or of companies such as Smuggler.
I am a French citizen living abroad, how can my donation to the ICM be tax-deductible?

I am a non-French citizen and living outside France, how can my donation to the ICM be tax-deductible?

The ICM, certified by the Fondation de France, can now receive donations through the Transnational Giving Europe (TGE) network. ICM donors residing in a selection of European countries are now eligible to receive tax benefits in their country of tax residence.

A donor resident in one of the participating countries and wishing to make a gift to the ICM can contact the foundation in the country of his/her residence. The home foundation establishes contact with the foundation in the recipient country for an assessment of the intended beneficiary: the ICM. If the evaluation is positive, the donor makes the gift to his home-country foundation which then provides the donor with a tax receipt and transfers the gift to the ICM.

To see the list of the country member of the TGE network, please visit the ICM website: http://icm-institute.org/en/make-donation-outside-france/

For any questions regarding this process, please contact Capucine de Kervenoael of the ICM at:
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+33 (0)1 57 27 40 38

NOWADAYS 1 IN 8 PEOPLE IS LIKELY TO DEVELOP A NEURODEGENERATIVE DISEASE INSIDE THE BRAIN HEMISPHERES.