

THE ICM NEWSLETTER



Brain & Spine Institute - Paris



Five years ago, a magnificent human and scientific adventure began; the aim was to search, find and cure the diseases of the brain and spinal cord.

Since its creation, the Brain and Spine Institute chose as its mission to combat these pathologies and has not ceased to develop a research of excellence, transversal and ambitious, in the field of the neurosciences. Important technological means for molecular and cellular exploration, neuroimaging, a Clinical Investigations Centre, a Biological Resource Centre and 600 researchers and engineers were mobilized to make this institute a model without equal in the world, unique and at the heart of patient care.

From the beginning, the generosity of its sponsors and the public at large has not ceased to accompany the work of the researchers. You have placed your confidence in us from the start and continue, a little more each day, to support this combat, which is also yours. Last December, an exceptional mobilization of the "Découvreurs d'espoir" (Discoverers of hope), increased the circle of our generous donors.

But the battle is not over...

2015 is a landmark year for the Institute, which will celebrate its 5 years of existence. Faced with the challenges to public health in our society, we should redouble our efforts, become mobilized around the diseases of the nervous system and help medical research advance more rapidly.

This Newsletter is a vector of communication that enables us to focus again on the progress made.

Still too often stigmatized, mental disorders affect a large number of persons in France. This is why we wished to devote a special issue to this subject and also share with you a recent and promising advance concerning Huntington's disease.

I hope you will enjoy reading it and thank you for your support.

Serge Weinberg
Founding Member of the ICM

MENTAL HEALTH AT THE ICM: LIGHT ON DEPRESSION AND OCD



Mental health, an essential component of our health, is a state of well-being, an aptitude of the mind to function normally and respond appropriately to environmental stimuli. One speaks of **mental disorders** when the state of well-being is disturbed by specific conditions (depression, schizophrenia, bipolar disorders), in which the individual is unable to adapt to difficult or painful situations and maintain his psychic equilibrium. Today, in Europe, **165 million persons** suffer from psychiatric disorders; 75% of these disorders appear before the age of 25 years.

In France, psychiatric disorders affect more than **1 in 4 adults, 27% of the French population**. The disorders most frequently observed in the population are depression, bipolar disorders, schizophrenia, anxiety and addictions.

Research on mental health and psychiatric disorders in the ICM involves essentially **studies on cognition, the emotions and behaviour**, a voluntary choice on the part of the Institute, in order to initiate a translational research and thus make use of all its pluridisciplinary competencies, which are the strength of the ICM model and its originality.

The brain is thought to be the veritable orchestra leader of our vital functions; it enables us to respond to our primary needs, such as eating, breathing or standing upright. Nevertheless, it is also considered to be the most complex biological organ, because it is also the seat of our emotions, our thoughts. It underlies our cognitive functions and allows us to interact with our environment.

Why do we do what we do? How do our emotions influence our behaviour? What brain mechanisms are responsible when our mental health is disturbed?

Two ICM teams describe for us their research on depression and obsessive compulsive disorders.

1 What is depression?

Depression is the most frequent mental disorder; it is estimated that **5 to 15% of the French population** risk suffering from an episode of depression in the course of their life.

It is present at all ages. Today, about 3% of children are affected by this disorder. The prevalence increases to 10-15% in adolescents, and it is also high in the elderly.

The disorder is all the more serious since the **risk of death by suicide is 10 times higher in depressed persons** than in the rest of the population. In France, there are 12000 deaths by suicide each year; i.e. someone dies of suicide every hour.

The patients express *intense fatigue, profound sadness, loss of pleasure and interest, a strong feeling of worthlessness accompanied by great difficulty concentrating*. Unlike a transitory episode of sadness, the "bout of depression", a major depressive episode lasts more than 15 days without remission, in spite of external stimulation. It can lead the person to isolation, even to suicide.

Research has demonstrated the existence of a genetic vulnerability, but it is a **combination of risk factors**, such as *life situations or events* (death, a separation, loss of work, difficult childhood...) and the *recurrence of depressive episodes* (relapses), that determine the degree of severity of the disorder.

Today, there are a number of effective treatments for this pathology: **chemical treatments** (antidepressants), which relieve the symptoms of depression, often associated with **medical and psychotherapeutic care** and **physical treatments** such as deep electrical stimulation or electroconvulsive therapy (ECT, still called shock treatment) (therapeutic interventions employed in the most resistant forms).

An innovative approach to therapeutic care in psychiatry

The UNPC - **Unité de NeuroPsychiatrie Comportementale** (Behavioural Neuropsychiatry Unit) is a new clinical unit recently created thanks to the IHU-A-ICM in the framework of its "Investments for the future," in close collaboration with the APHP/Pitié-Salpêtrière.

Not yet well understood, **behavioural disorders** can be the symptomatic expression of certain diseases of the brain and disrupt the sequence of care of the patient. The objective of this clinical unit is to better understand their origin and the dysfunctional mechanisms underlying these disorders by associating neurologists, psychiatrists and researchers. The UNPC follows patients needing a neuropsychiatric approach and initiates, in parallel, clinical research projects, notably on apathy and motivation.

And research?

Several research hypotheses are under study. One of the first to be approached is *inflammation*. Depression could be due to an abnormal response of the inflammatory system or the manifestation of a chronic inflammatory disease. The existence of a *genetic background* is being explored, but the results are not yet convincing. Finally, **brain imaging** has revealed brain *dysfunctions implicated in depression*. For this reason, the team Social and Affective Neuroscience in the ICM, co-directed by **Philippe Fossati, Professor of Adult Psychiatry at the Pitié-Salpêtrière Hospital, and Nathalie George, CNRS Director of Research**, are particularly interested in the brain signatures of emotional dysfunctions and social perturbations in depressive disease. Today, with a combination of functional neuroimaging techniques and the elaboration of behavioural and cognitive tests, the team is seeking to learn how depressed patients react on the emotional or cognitive level compared to control or at-risk subjects. The aim of this research is to **identify biomarkers associated with depression**. The global aim of this research is to **propose more personalized treatments based on the biological needs of the patients**.

2 Obsessive compulsive disorders, a severe affection?

Formerly classified as a form of anxiety, obsessive compulsive disorder (OCD), a severe affection, is frequent today; **2 to 3% of the population** suffer from OCD. It represents the **4th most frequently treated disorder in psychiatry**, after phobias, addictions and depression. The disease can appear early, even in childhood, and its evolution is chronic: 65% of affected persons began the disorder before the age of 25 and 15% after age 35.

Obsessive compulsive disorders are invalidating conditions for the affected subject, but also for his entourage. They manifest as **2 large categories of symptoms: obsessions** in the form of thoughts, images with a disagreeable content that impose themselves involuntarily on the subject. These obsessions generate major anxiety that requires the performance of **repetitive behaviours**, rituals, to calm these anxiety-causing ideas.

At present, *treatments by cognitive behavioural therapy (CBT) and/or serotonergic antidepressants* can improve two thirds of the patients. However, the forms that resist classical treatments, in particular the very severe forms (20% of resistant forms), are under study, notably in the ICM, to **develop innovative therapies**.

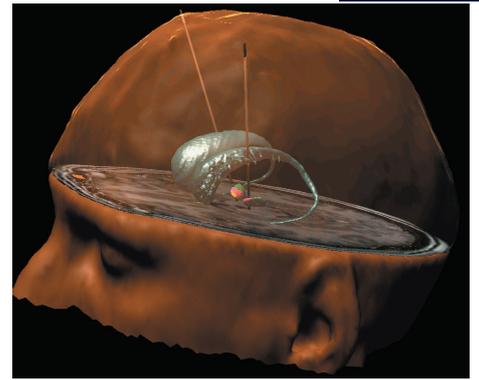


Functional imaging techniques (CENIR core facility)



Pr. Luc Mallet

Professor of Psychiatry at the Henri Mondor University Hospital, Inserm researcher in neuroscience and head of the team "Behaviour, emotion and basal ganglia" at the ICM



Intracerebral stimulation for OCD

“ Today, our objective is to develop tomorrow's treatments for a more personalized approach in terms of both therapeutics and the global care of the patient. ”

And research?

In the ICM, the research is organized along 3 major axes: **better understand** what is happening in the brains of persons suffering from obsessive compulsive disorders, **better cure** them by optimizing existing treatments and, finally, **better treat** them by developing strategies that help combat this handicap.

The team of **Luc Mallet, psychiatrist and researcher in neuroscience**, develops *basic and clinical research projects* to try to understand the brain functions implicated in the pathology by studying the behaviour both in experimental models and in humans.

With brain neuroimaging techniques, the researchers were able to identify certain regions of the cortex, **the orbito-frontal regions** (located above the eyes) implicated in

the appearance of some of the most important symptoms, notably *invasive doubt*, probably at the origin of verification behaviours.

In addition, the team aims to **propose innovative solutions**, notably in the most resistant forms, with the use of alternative therapeutic approaches, such as **experimental psychotherapies**, the use of **transcranial stimulation** or even **deep brain stimulation**.

Recently, thanks to the latter technique, the researchers discovered that by modulating the activities of very specific brain circuits, the symptoms expressed by the patients could be attenuated, or even totally suppressed. This approach consists in modulating the activity of the dysfunctional brain circuits. These networks must be better identified in the hope of increasing the therapeutic

effect. To this end, the team recently added to their research techniques optogenetic stimulation in experimental models of OCD. This translational approach between humans and experimental models is essential to **better characterize the brain circuits that are at the origin of the OCD and could eventually become a major tool to improve the treatment of patients.**

Sources : ICM, Inserm, OMS

Help researchers make your acquaintance!

BRAiN'US was born at the Brain and Spine Institute. This mobile phone application, developed by **Jean Daunizeau, Inserm chargé de recherche and co-director of the team "Motivation, brain, behaviour"** at the ICM, seeks to acquire knowledge on the way in which the normal brain functions.

Data obtained in the normal subject are indispensable to **understand and better treat the brain functions** (memory, attention intuition, etc...) **altered** in patients (e.g. anxiety, depression, schizophrenia...).

With the application BRAiN US, you **participate**, in complete confidentiality, **in a unique scientific experiment**. BRAiN'US contains 8 amusing tests, conceived as a game, to elucidate the manner in which the brain makes its decisions. Discover the different tests: the game "3 trains late" that evaluates your working memory, "the hour of the appointment" that stimulates your ability to reason, or "the difficult chicken" that evaluates you ability to learn. The behaviour of each player is then analysed along with that of the other participants, with the help of mathematical models. The more players there are, the better the researchers can determine the elementary mental mechanisms that underlie behaviours.

We can't treat what we don't understand. **Let's get acquainted.**



Upload the BRAiN'US application free of charge

UPDATE ON RESEARCH

HUNTINGTON'S DISEASE: A PROMISING TREATMENT

Studies coordinated by Dr. Fanny Mochel, Inserm researcher at the ICM, published in the January issue of *Neurology*, demonstrated the therapeutic potential of a unique synthetic oil – triheptanoin – on energy metabolism in the brains of 10 patients with Huntington's disease. By improving the brain's energy metabolism, which is abnormal in patients, this therapeutic oil might slow the evolution of the disease. This project represents an important advance in the development of new treatments.

Huntington's disease, a serious hereditary disorder that affects 5000 persons in France, is linked to an **autosomal dominant genetic anomaly**. The signs of the disease appear, often between 30 and 50 years of age, by progressive motor, behavioural and psychiatric disorders, which lead to a state of dependency that also affects the patient's entourage. The only treatments available at present act on the symptoms; there is no treatment that can change the course of

Huntington disease. At the ICM, **Dr. Fanny Mochel** has coordinated, for several years, a study aimed at validating the **hypothesis of a metabolic treatment for this disease**.

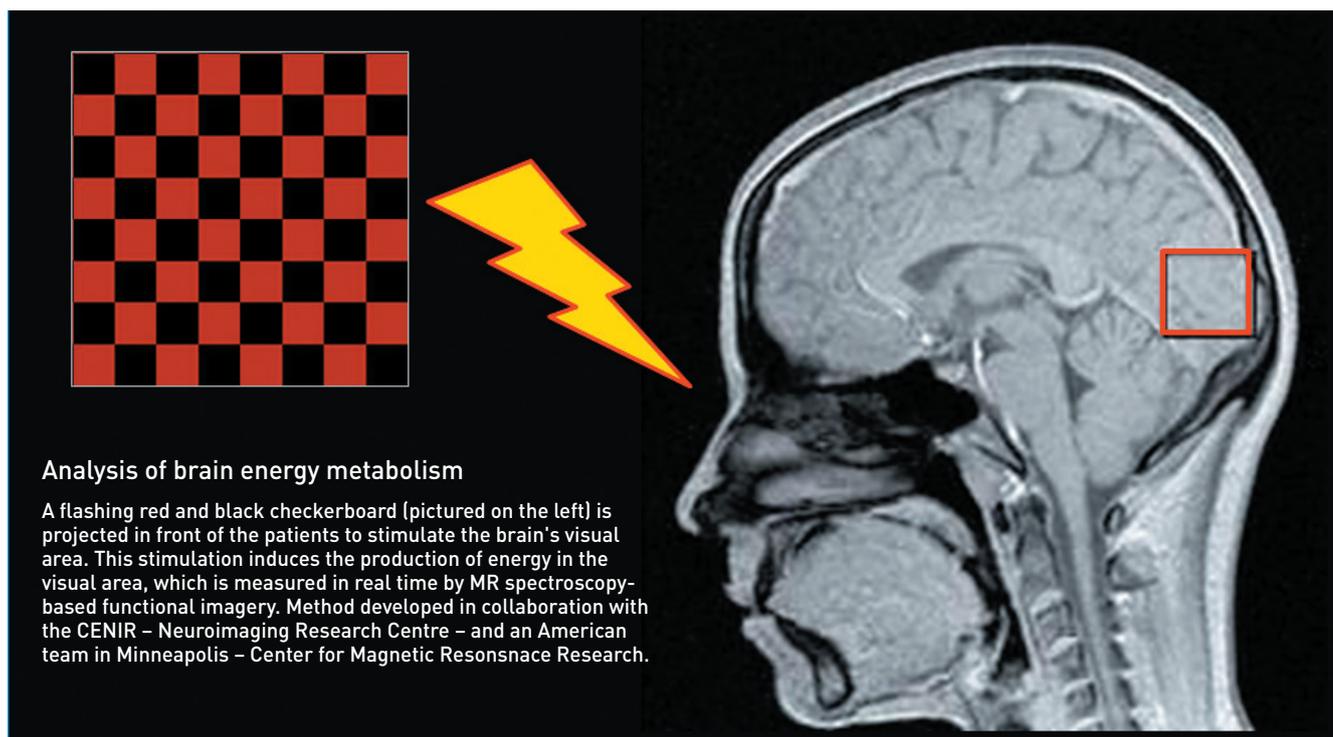
Even before the neurological symptoms of Huntington's disease appear, the energy metabolism of carriers of the genetic anomaly, which is the cause, is altered, as evidenced by weight loss, in spite of high calorie diets, and a decrease in substances in the blood that indicate an increased need for certain energy intermediates. Dr. Mochel had already shown that triheptanoin – a unique triglyceride – can furnish these intermediates. The hypothesis was thus advanced that **triheptanoin could improve, even correct, the energy deficit**, which exists both in the brain and in the periphery in Huntington's disease.

These very promising results, obtained by the researchers in the study of the benefit of this oil in 10 patients at the beginning of their disease and 13 control subjects,

show that energy metabolism in the brain was corrected after only one month of treatment. Furthermore, these preliminary observations, which need to be confirmed in a larger and longer term placebo-controlled study, raise hopes that this treatment could attenuate the motor dysfunctions of the disease.

The next step is to launch a therapeutic trial to evaluate the long-term clinical benefit in a larger number of patients. To this end, a licence was granted by ULTRAGENYX, the company that commercializes triheptanoin.

Article: Interview with Dr. Fanny Mochel of the team "Molecular bases, physiopathology and treatment of neurodegenerative diseases" directed by Pr. Alexis Brice - Adanyeguh et al., Neurology January 2015.



Analysis of brain energy metabolism

A flashing red and black checkerboard (pictured on the left) is projected in front of the patients to stimulate the brain's visual area. This stimulation induces the production of energy in the visual area, which is measured in real time by MR spectroscopy-based functional imagery. Method developed in collaboration with the CENIR – Neuroimaging Research Centre – and an American team in Minneapolis – Center for Magnetic Resonance Research.

A NEUROPROTECTIVE PEPTIDE NEW HOPE FOR PARKINSON'S DISEASE

The latest results obtained by the group of Stéphane Hunot and the team "Experimental treatments for neurodegeneration" at the ICM, in collaboration with the team of Daniel Gonzalez-Dunia of the Physiopathology Centre Toulouse Purpan and that of Jean-Michel Peyrin of the Institut de Biologie Paris Seine, represents a great leap forward in the fight against Parkinson's disease. Their studies demonstrate that a small peptide of viral origin might protect the neurons implicated in Parkinson's disease against degeneration. This major discovery appears to be very promising for the development of new therapeutic agents to prevent Parkinson's disease and, more globally, the neurodegenerative diseases.

Several research projects are underway in parallel at the ICM on different aspects of Parkinson's disease. In the team of Etienne Hirsch, Stéphane Hunot and his collaborators try to understand how neurons die in this disease, in order to find new ways to combat it by neuroprotective approaches.

There are several causes of neuronal death, one of which, an energy deficit in the neurons, interests Dr. Stéphane Hunot. The tiny energy generators of the cells – the mitochondria, the physiological role of which is primordial for neuronal function – are altered in Parkinsonian patients. These mitochondria are normally present in large numbers in the neurons and their projections – axons or dendrites – and are elongated, filamentous, in form. A sign that they are altered is their fragmentation and progressive disappearance, which leads to the degeneration of the axons followed by the death of the neuron. **Agents that protect mitochondria would therefore have great therapeutic potential for neuroprotection, the working hypothesis of these researchers.** Inspired by something that exists naturally, in particular the neurotropic virus of Borna disease or "Borna virus" - the authors have obtained spectacular results.

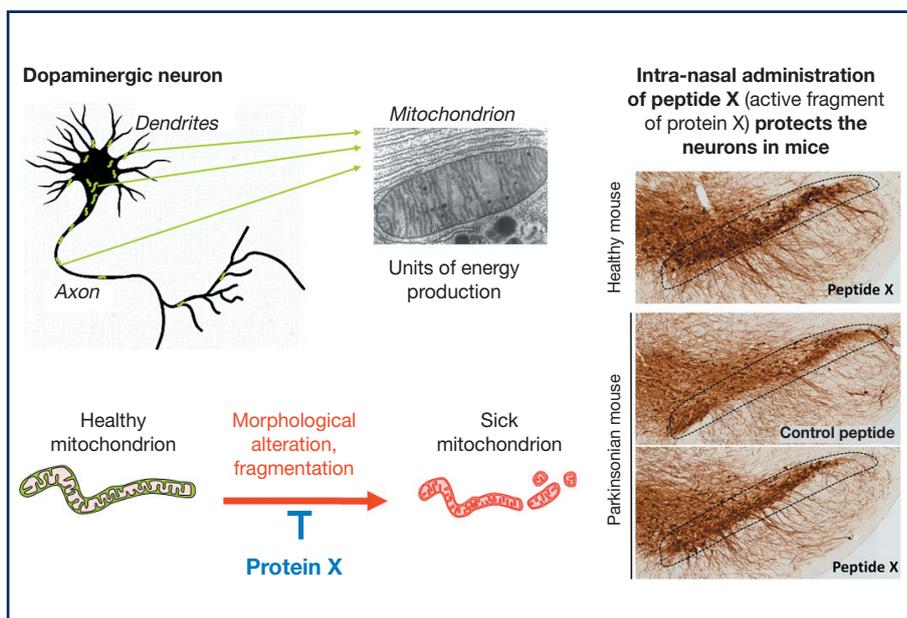
The Borna virus is known for its capacity to use the functions of the neurons it infects to its own advantage, in order to survive and multiply in its hosts without damaging the cells. To that end, it produces a protein – protein X – **that accumulates in the mitochondria** of neurons, blocking the mechanism of self-destruction of the cell (or apoptosis), a mechanism of self-defence used by the cells to limit propagation of the virus.

The researchers decided to verify the effects of protein X or peptides (small active fragments) derived from it on the maintenance of mitochondria outside the viral context. Their results show that protein X can effectively protect axons via a mechanism that maintains mitochondria, thus protecting the dopaminergic neurons at the origin of Parkinson disease from degeneration. More interestingly, these

neuroprotective effects – for the moment tested in mice – function when the peptides are administered intra-nasally. This method, which is relatively uninvasive, is very promising for the development of future treatments.

These results open the way to new therapies for neurodegenerative diseases, such as Parkinson's or Alzheimer's, targeting mitochondrial dynamics and preventing the first stages of the degenerative process at the axonal level.

*Article: Interview with **Stéphane Hunot** of the team "Experimental therapeutics of neurodegeneration" directed by Dr. Etienne Hirsch – Szelechowski et al., Nature Communication, October 2014*



SPORTING AND CULTURAL EVENTS

- On Sunday, November 2, **Francis Joyon** embarked on the Route du Rhum on the trimaran IDEC flying the colours of the ICM.



- The 4th edition of the concert of the **Association Music Passion Parkinson** took place on November 15, 2014.
- The 1st edition of **Conf' & Sciences** on the theme of "Light in the sciences," organized by Indesciences in partnership with the ICM, the ENP, the Musée Lumière, the DIM Cerveau et Pensée, the Amicale Paris Sciences and Editions DUNOD, took place on Friday, November 28.
- On Thursday, December 4, the **Club INNER WHEEL Limoges – Haut-Limousin** received a delegation from the ICM in Limousin.
- The film "**Une merveilleuse histoire du temps**" (The Theory of Everything) was shown starting on January 21, 2015. The ICM was associated, for the occasion, with the operation "Le temps presse," to fight against ASL.
- During the 30th edition of the **Festival Int. Automobile**, which took place in Paris on January 27, Jean Todt, Vice-President and Founding Member of the Institute was awarded the Palme d'Or 2014.

OPERATION DECOUVREURS D'ESPOIR 2014: THANKS TO YOU, A GREAT SUCCESS!



You were **almost 3500** mobilized at the end of last year to accelerate research on the neurological diseases.

Thanks to your support and this admirable dedication alongside the researchers, patients and all the other donors, more and more numerous to join in the ICM adventure, you have given us the means to go ever further in the "conquest of the brain" and the development of new treatments.

For the patients, their families and all of us...

AGAIN, A BIG THANK YOU!

A PRIZE

On Wednesday, January 28, during the Cérémonie des Prix pour la Recherche of the Fondation de France, Anne Desmazières was awarded the Bouvet-Labruyère ICM 2014 prize for her project on the dynamics of assembly and reassembly of nodes of Ranvier during the process of myelination and remyelination.

AT THE HEART OF THE ICM

- On November 14, 2014, **Pr. Bertrand Fontaine**, Director General of the Institute of Translational Neuroscience of Paris – IHU-A-ICM was named President of the Comité de la Recherche en Matière Biomédicale and Santé Publique – CRMBSP. He succeeds Pr. Marc Humbert, designated in 2010.
- Prestigious guests, **Mathier LEHANNEUR, Jean D'ORMESSON, Jean GLAVANY, Guillaume LECOINTRE and Eric ORSENNA**, were received on the occasion the lectures "Sciences, Arts et Culture". Lectures that can be viewed on the site of the ICM.
- Results of the competition for the most beautiful photographs** based on research carried out at the Institute, organized by "Les Ajités," an association of young researchers in the ICM.



The winner of the exhibition, **Mariam Chammat**, with her photo "Brain Cloud".

THEY VISITED THE ICM

- On Thursday, November 6, **Mr. Yuichi Morii**, a scientific journalist for the famous Japanese newspaper Yomiuri, visited the ICM to learn how neuroscience research functions.
- On February 3, 2015, the **Club Féminin Pluriel**, an international network that brings together engaged, enterprising women, visited the ICM in the presence of Pr. Gérard Saillant.

AT THE IPEPS-ICM

- The ICM will install a new enterprise, **NeoVentures Biotechnology Inc.**, in the business incubator the iPEPS-ICM:
- BioSerenity** was the winner of the "International Innovation Awards" (iiAwards), organized at the end of 2014 by the City of Paris.
- GenosplICE technology** was 48th in the 2014 Deloitte In Extensio Technologie Fast 50 classification that rewards fast growing enterprises.

NEOVENTURES
CUSTOM APTAMERS



Geno
Splice

THEY ARE MOBILIZED

- On February 15, 2015, incited by **Jean-Baptiste Babinet and Guilhern Giraudet de Boudermange**, a team of marathonians ran for the ICM in the Barcelona semi-marathon.
- In March 2015, **Guillaume Zachello** will start a 750 km "solidarity walk" from Roncesvaux to Saint Jacques de Compostelle to collect funds for the ICM.

THE PLAN FOR THE NEURODEGENERATIVE DISEASES

During the launching of the plan for the neurodegenerative diseases 2014-2019, **Pr. Alexis Brice**, Director General of the ICM, participated as a scientific expert, notably in the Magazine de la Santé on France 5.

A WILD CAMPAIGN!

Thanks to the precious support of its historical partner Publicis, the Institute initiated its new publicity campaign on several media, television, print and web, both as a publicity film and a poster campaign sharing the same offbeat and humorous tone to underline the importance of saving our brain and helping researchers to protect it.



MAURICE LÉVY,

President of the Publicis group and Founding Member of the ICM, tells us about it:

What does the new campaign consist of?

We wanted this new campaign to reaffirm the very foundations of the ICM. One should not forget that this research institute is unique in the world. The patients need public administrations, enterprises and especially donors, holding hands, to help the researchers in their fight against the diseases of the brain and spinal cord. Private funds permit flexibility and reactivity, which are the strength of the Institute. This is why, with the Publicis teams, we wanted to create an original fundraising campaign aimed at the general public, which focused on medical research.

How does this campaign represent the values of the ICM?

The primary vocation of the ICM is to search in order to find the best treatments and ultimately to cure the patients. It's "with you" that the researchers and physicians will succeed in treating the diseases of the nervous system. Public administrations have less means and we have all kinds. Thus, the troubling question: "Is this what we must do to finance research on the diseases of the brain and the spinal cord?"

Why did the ICM, in partnership with Publicis, choose humour to transmit its message?

If a disease is sad and has devastating effects on the patient as well as his entourage, the action of the researchers is positive, almost joyful. But especially, there are too many sad, constrained, painful messages. To be visible and convince the donors, we dared to use humour. The researchers showed proof of theirs by accepting the idea.

What are the objectives behind this campaign?

The first objective is to support the work of the researchers. Everyone must understand the importance of contributing to the ICM. The poster and television campaigns, also visible on the web, aimed at increasing the visibility of the ICM, while retaining those who are already donors. The researchers need contributions to work. Money is also the indispensable fuel for research. We need everyone. Thank you in advance.



MY RECURRENT DONATION

Please fill out and return this form with your contribution and your bank identification details (RIB) to the following address:
Institut du Cerveau et de la Moelle épinière, Hôpital de la Salpêtrière - 47/83 bd de l'Hôpital 75013 PARIS

YES, in 2015, I will provide long term support for the ICM's researchers with a contribution of:

10 € 20 € 30 € 40 €

Other amount:€

Every month Quarterly

Starting on 05/...../2015*

*The date can be one month later, depending on when the first withdrawal is authorized.

IMPORTANT:

Don't forget to include your RIB (BIC-IBAN)

SEPA AUTHORIZATION OF WITHDRAWAL

Type of payment: Recurrent – Unique authorization reference⁽¹⁾ :

⁽¹⁾ You will receive the reference when the authorization is recorded

Beneficiary: INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE
N°ICS: FR25 ZZZ 535582

PERSONAL INFORMATION

Family name: First name:

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Post office code: City:

ACCOUNT (BIC-IBAN) TO BE DEBITED

IBAN (International Bank Account Number)

BIC (Bank Identifier Code)

Date⁽²⁾ :

Place⁽²⁾ :

⁽²⁾ Obligatory

Signature⁽²⁾

By signing this form, you authorize the ICM to instruct your bank to debit your account, and your bank to debit your account according to the instructions of the ICM. You can be reimbursed by your bank according to the conditions that you have established together. A request for reimbursement must be presented within 8 weeks of the date of an authorized withdrawal, and without delay or at the latest within 13 months of a non-authorized withdrawal. Your rights concerning the present authorization are explained in a document you can procure from your bank.

