

THE ICM NEWSLETTER

Brain & Spine Institute - Paris



The ICM is an exceptional project put in place by individuals at the service of others. It is above all a magnificent human adventure, in which I am proud to participate. It began in 2003, with the challenge of bringing together, in one unique place, fundamental and clinical research.

With its international approach, the ICM attracts elite researchers and physicians specialized in the neurosciences. These professionals work to understand the functioning of the brain in order to apprehend its dysfunctions and to find new therapies to treat them.

The Institute's originality lies, notably, in the fact that it gathers, in the same centre, not only researchers and physicians but also patients, within an innovative structure: the Clinical Investigation Centre (CIC). The aim of the CIC is to place the patient at the heart of research, permitting the quasi-simultaneous application of technologies developed by industry actors researchers and health-oriented industry actors.

Today the ICM has become the reference centre in France for research on diseases of the brain and spinal cord. But to respond to the challenge and assure that research continues to advance, our engagement and mobilization must intensify. We must provide means for the researchers; they need us and we need them.

Jean-Pierre Martel
Founding Member

THE PATIENT AT THE HEART OF ADVANCES IN RESEARCH

The 100 000 patients with neurological or neurodegenerative disorders examined each year at the Pitié-Salpêtrière Hospital in Paris can, if they wish, participate in research projects at the Clinical Investigation Centre (CIC) of the ICM, under secure and reglemented conditions. This exceptional bridge between research and care saves precious time in the face of disease, and accelerates the rapid discovery of innovative treatment for millions of patients suffering from diseases of the brain and spinal cord.



Unlike ordinary laboratories, research at the CIC is carried out on healthy volunteers and patients, with a double objective: **understand the mechanisms** of diseases and **evaluate the efficacy** of new treatments early in their development. Such research cannot be carried out without the participation of the patients and volunteers who accept to take part in the centre's protocols. The CIC has, thus, been at the origin of **several scientific advances** that are improving our understanding and treatment of numerous diseases of the central nervous system (Parkinson's disease, multiple sclerosis, cerebellar ataxias, Alzheimer's disease, ...).

In this special issue, you will discover: the missions, legal framework and organization of the CIC as well as ongoing research, how you can participate, as either a patient or a healthy volunteer, and the results of the principal studies published over the past few years. Ongoing research and the way to take part in it, as a patient or a healthy volunteer; the results of the principal studies published these past years.

The CIC in figures

2 physicians

6 research nurses

3 nurse's aides

2 laboratory technicians

2 project leaders

1 pharmacy intern

6 hospital beds

8 wheelchairs for outpatients

4 examination rooms

1 laboratory for storing and
analyzing biological samples

**Daily contact with 600
researchers**

Salpêtrière hospital, showed that deep brain stimulation is effective in early onset forms of Parkinson's disease. The CIC also finished a proof-of-concept study on the **stimulation of a new brain target** (the pedunculopontine nucleus) in forms of **Parkinson's disease characterized by falls and gait disorders**; the results are now being analyzed (Dr Grablji). Late in 2013, a therapeutic trial was completed on a **neuroprotective agent derived from bee venom** (Dr. Hartmann): the definitive results will be obtained in 2014. The CIC is also participating in the evaluation of new treatments for non-motor symptoms of the disease: a study of hypersalivation, a frequent symptom in Parkinsonian patients, is underway (Pr. Vidailhet). A unique cohort of 400 Parkinsonian patients in France will be followed for 5 years to identify markers of response to treatment. **The first results of a study on symptoms that resist treatment** (sleep disorders, balance disorders) have been published (Pr. Vidhailet). Finally, a therapeutic trial on the **prevention of motor complications of the disease** has begun, and **partnerships have been established with two pharmaceutical laboratories** for research on biomarkers and the development of innovative treatments (Pr. Corvol, Dr. Lacomblez). The CIC has participated in one of the very **first international therapeutic trials** in progressive supranuclear palsy, a rare Parkinsonian syndrome.

• **Neurogenetics:** A new study on the genetic forms of Parkinson's disease has been initiated: new genetic risk factors have been identified thanks to a meta-analysis of more



than 100,000 subjects. The 21 new genetic factors will be published in 2014 by the international consortium of which the ICM is a part (Pr. Brice). Finally, the search for biomarkers of Parkinson's disease and the study of pre-symptomatic subjects continues, in collaboration with the Michael J. Fox Foundation in the US.

- **Multiple sclerosis:** This disease affects **2.3 million** people throughout the world. **3 new treatments** were tested at the CIC and are now available to patients: one to **improve gait disorders** (fampridine) and **2 new treatments for the inflammatory forms of the disease** (Pr. Lubetzki,

In 2013, **77 studies** were ongoing at the Clinical Investigation Centre – CIC ICM's, **20 of which were new studies** initiated during the year. The themes addressed were Parkinson's disease and abnormal movements, multiple sclerosis, dementias, neurogenetics, neuropsychiatry, amyotrophic lateral sclerosis, peripheral neuropathies, epilepsy and other neurological diseases. More than **400 patients** were included in these studies.

Which of these studies provided important information on neurological diseases?

• **Parkinson's disease:** The **second** cause of motor handicap, affecting **4 million people** throughout the world. In 2013, the Clinical Investigation Centre published the results of the EARLYSTIM study (Principal Investigator: Prof. Yves Agid) in the highly-respected **New England Journal of Medicine**. This study, which involved 17 centres in France and Germany and coordinated by the CIC of the Pitié-

The approach of MedDay, founded by Dr. Frédéric Sedel (CEO) and Guillaume Brion (COO) and incubated at the ICM, consists in treating neurological diseases by acting on brain metabolism. Very promising results have been obtained with the molecule MD1003 in 23 patients with progressive forms of multiple sclerosis, and two phase 3 studies involving 250 patients are in progress. MedDay benefits from support of the Clinical Investigation Centre and the Neuroimaging Centre, and by research at the ICM on 12 patients of Pitié-Salpêtrière Hospital. In addition, a trial with the same product will begin in the coming months at the CIC for a rare disease: adrenomyeloneuropathy.



Some people need help right now!



Dr. Papeix). Research on **progressive forms of the disease** is still ongoing. The CIC team hopes to **discover differential biomarkers** of inflammation, myelin and neurodegeneration (Pr. Stankoff) and to **develop treatments** to stop the progression of the disease (2 studies underway) and **promote myelination** (1 study underway). Finally, the CIC participated in **2 therapeutic trials of a symptomatic treatment for multiple sclerosis** developed by MedDay, a company incubated at the ICM (see below).

• **Dementias:** In order to begin treatment earlier for these disorders, the prevalence of which will increase considerably as the

population ages, the strategy of Pr. Bruno Dubois' team is to **study subjects at the initial stage** of the disease, or even during the **prodromal stage**, a period in which a series of precocious symptoms announce the onset of the disease. In collaboration with the team of Pr. Bruno Dubois, the CIC is also planning studies on pre-symptomatic carriers of genetic forms of the disease; the aim is to arrive at an **early, even predictive, diagnosis** and to **develop new strategies** based on anti-beta amyloid or anti-Tau therapies.

• **Amyotrophic lateral sclerosis:** A research program in conjunction with a pharmaceutical laboratory has yielded **very promising results** for this neurodegenerative disease. The Clinical Investigation Centre has also organized a study on the **associated symptoms** (balance disorders, emotions) and has collaborated in the development of a **tool enabling patients with severe motor disorders to write with their eyes**.

Therapeutic trials have also been conducted or are ongoing to advance our understanding of **epilepsy, which affects 50 million people**, and a special effort is being made for rare diseases: Pompe disease, Huntington's disease, cerebellar ataxias, channelopathies...

The Clinical Investigation Centre is promoting a dynamic, involving not only France but Europe as a whole, conducive to conducting common therapeutic trials and research programs. It cooperates closely with the most prestigious French and international research centres.

Recently, the CIC created a Centre for the Evaluation of Care and Therapeutics. Closer to the patients. This structure is dedicated to the pre-diffusion of new drugs, the study of patient cohorts and the evaluation of medical practices. It exists thanks to financing by the Pitié-Salpêtrière University Hospital, a partner of the ICM.



Anyone can participate in biomedical research, either as a healthy volunteer or as a patient, as long as he/she is affiliated with French Social Security. Special conditions exist for minors and persons under guardianship. To participate, one gives his "free, informed and expressed" consent, in writing, before the study begins, after receiving a written document containing clear and reliable information on the study's protocols.

One has the right to refuse to participate in a research project or to desist at any moment without consequences, notably in terms of the quality of treatment.

More information on [icm-institute.org/La recherche/](http://icm-institute.org/La_recherche/)
[Plateformes Technologiques /](http://Plateformes_Technologiques/)
[La plateforme de recherche clinique](http://La_plateforme_de_recherche_clinique)



Pr. Jean-Christophe CORVOL
Neurologist-pharmacologist at the Pitié-Salpêtrière Hospital, and Director of the Clinical Investigation Centre

“ The new advances made at the Clinical Investigation Centre of the ICM will, tomorrow, become treatments, new diagnostic tools, new means of prevention. The teams work every day to shorten the delay that separates discovery from the availability of a treatment for all patients. ”

UPDATE ON RESEARCH

A MAJOR ADVANCE IN OUR UNDERSTANDING OF SEVERE EPILEPSIES

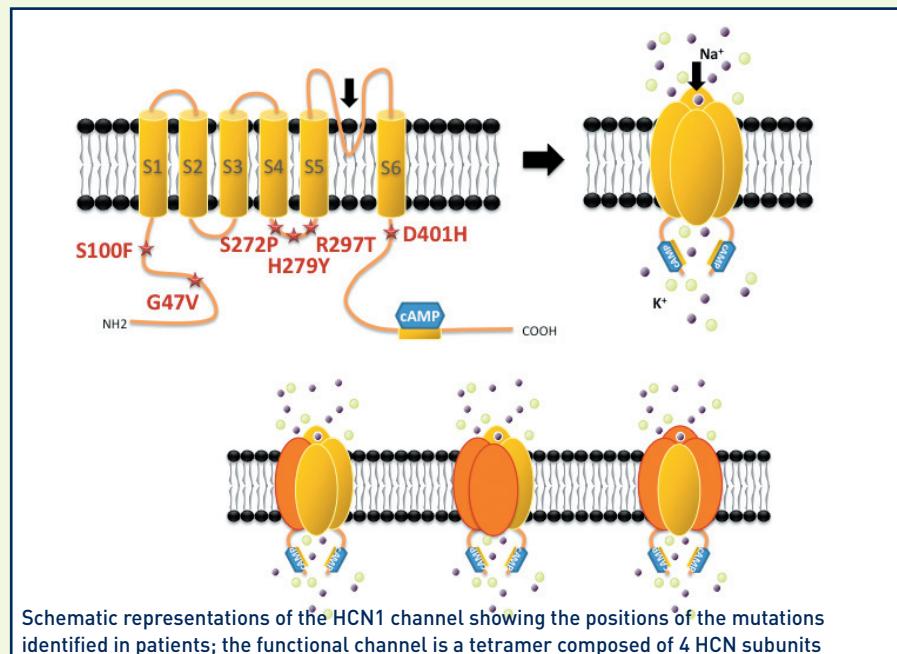
In collaboration with a German team from the Institute of Human Genetics in Würzburg and a European consortium (EuroEPINOMICS consortium), **Caroline Nava, Christel Depienne and Eric Leguern** (in the context of a collaboration between the team of Eric Leguern and Stéphanie Baulac and the team of Alexis Brice), and in relation with Carine Dalle, head of the electrophysiology platform (IHU-A-ICM), have just discovered that **a mutation in the gene HCN1** is responsible for severe infantile epilepsy.

Epileptic encephalopathies are severe epilepsies resembling Dravet syndrome, the best known form of genetic epileptic encephalopathy (EE). It is characterized by cognitive or motor degeneration.

The mutation in the gene HCN1 was identified by **sequencing the coding regions** of the genome in several children with Dravet syndrome. In the majority of cases, this syndrome is caused by a dominant mutation in the gene SCN1A that encodes a neural voltage-dependent sodium channel.

The gene HCN1, in neurons, directs the synthesis of the four subunits of channel responsible for a current with special properties called *ih*, which is important for the propagation of the nerve impulse.

The clinical symptoms of patients with the HCN1 gene mutation are similar to those observed in Dravet syndrome, but they evolve



differently: the oldest patients develop focal epilepsies, absences and severe behavioural disorders with autistic traits when they carry an HCN1 mutation.

The study was carried out **thanks to electrophysiological techniques associated with molecular biology** developed at the IHU-A-ICM, which enable us to approach the physiopathology of an increasing number of diseases that affect nerve transmission and lead to disabling disorders of the nervous system.

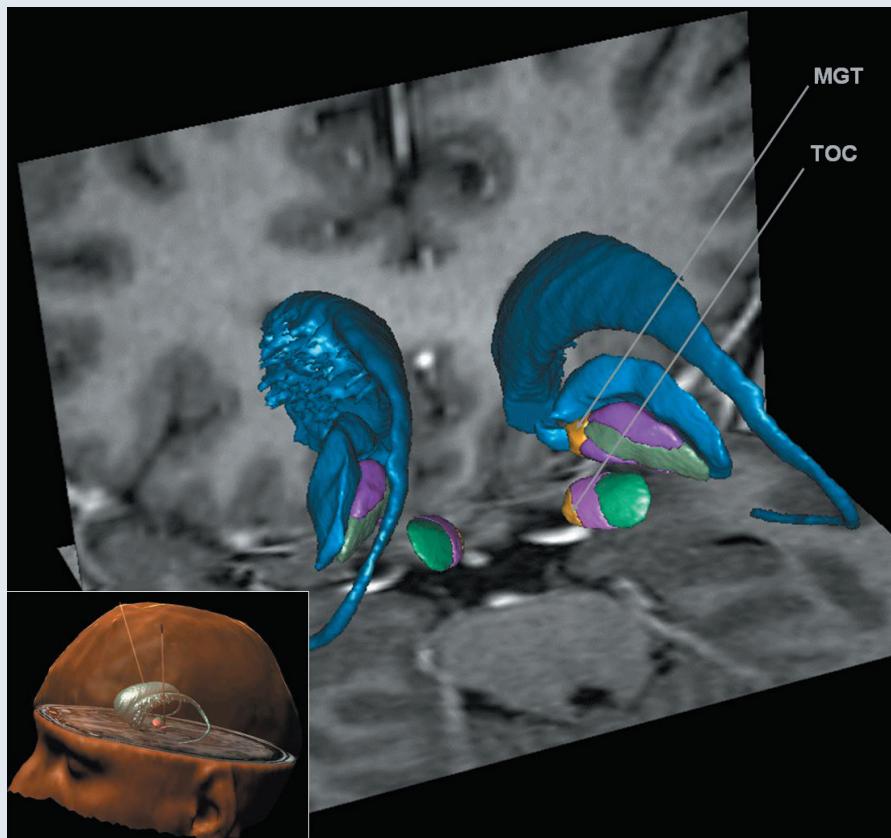
The identification of mutations in the HCN1 gene confirms the crucial role of HCN channels and the *ih* current in the mechanisms underlying epilepsy in humans. The discovery of a new genetic cause of a severe epileptic encephalopathy will allow us to offer a new diagnosis and an explanation of the disease to affected families.

References: Nava C, Dalle C, Rastetter A, Striano P, de Kovel C, Naboulsi R, Cancès C, Ville D, Brilstra EH, Gobbi G, Raffo E, Bouteiller D, Marie Y, Trouillard O, Robbiano A, Keren B, Agher D, Roze E, Lesage S, Nicolas A, Brice A, Baulac M, Vogt C, El Hajj N, Schneider E, Suls A, Weckhuysen S, Gormley P, Lehesjoki AE, De Jonghe P, Helbig I, Baulac S, Zara F, Koeleman B, EuroEPINOMICS consortium Haaf T, LeGuern E, and Depienne C. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. *Nature Genetics*.



Agnes Rastetter, Christel Depienne, Caroline Nava and Carine Dalle

OBSESSIVE COMPULSIVE DISORDERS



Intracerebral stimulation against OCD and Gilles de la Tourette syndrome



Dr Luc Mallet, psychiatrist and INSERM research director, heads the "Behaviour, emotion and basal ganglia" team of the ICM. Recently, he was awarded the 2013 Marcel Dassault Prize from the *Fondation Fondamentale*, in the category "Researcher of the year," mental disorders and, in particular, for his work on the role of deep brain structures in pathological repetitive behaviours, notably obsessive compulsive disorders (OCD).

Obsessive compulsive disorders (OCD) are a serious handicap for patients, who express both obsessive and anxiety producing thoughts and immensely exaggerated and repetitive behaviours. A major symptom is ritual verification; other common manifestations are hand washing or counting, etc. These compulsions are apparently performed by the patient in an attempt to calm his/her anxiety. OCD currently affects **2% to 3% of the population**.

"With my multidisciplinary team, we explore the brain mechanisms underlying compulsive verification to elucidate the neural bases of the dysfunctional processes which would explain the persistence of these repetitive behaviours. Our aim is to provide a personalized medical solution for each patient. We, therefore, work to

develop innovative treatments, particularly for resistant forms of the disease, with approaches ranging from experimental psychotherapies to the modulation of brain activity by sources external to or implanted in the brain," Dr. Luc Mallet stated.

One of the team's important discoveries is the attenuation or suppression of symptoms through deep brain stimulation (a non-destructive, adaptable and reversible neurosurgical technique that modulates the activity of brain circuits). Furthermore, by using optogenetic stimulation, a prominent researcher from MIT (Boston), who recently joined Luc Mallet's team, showed that it was possible to reestablish normal behaviour in mice engaged in compulsive grooming by restoring their capacity to control this behaviour.

Thanks to this technique, the team is refining their studies on basic processes at the origin of compulsions by determining the most specific targets and stimulation parameters involved in the process as a means to intervene more effectively in cases of this disorder. This program has been validated and was supported in 2013 by very competitive national and international programs (ARN and ERANET-NEURON).

In addition, Dr. Mallet, convinced of a future for connected tools, is developing collaborations with anthropologists and sociologists aimed at identifying to what degree household devices can provide personalized responses to compensate for the psychological handicap of patients in their daily lives.

NEWS

SPORTING AND CULTURAL EVENTS

- On February 28, 2014, the Lions Club of Essarts-le-Roi offered the ICM the benefits of their sporting event, "Teufs Teufs du Coeur."



The 53rd wine sale of the Hospices Nuits-Saint Georges took place on March 15-16, 2014. The benefits of the sale of the Charity lot, presided by Patrick Timsit, were donated to the ICM.

- On April 16, 2014, *Les Voiles St Barth* organized a gala to the benefit of the ICM.
- On Monday April 21, 2014, Francis Joyon crossed the finishing line in Rio de Janeiro, on his maxi-trimaran and, once again, emphasized his support of the ICM.
- On the week-end of May 3-4, 2014, **the association Sogno Di Cavallino** organized automobile shows to the benefit of the ICM, and **Classic days** marched in support of medical research.
- From April 6 to September 6, 2014, sporting buffs "**The Bonk and Zumarika Team for the ICM**", will push their limits and collect funds while participating in numerous competitions.

THEY VISITED THE ICM

On Thursday, February 27, 2014, Marisol Touraine, French Minister of Social Affairs, and Jeremy Hunt, UK Minister of Health, visited the ICM.

THE ICM, CO-ORGANISER OF RENCONTRES FRANCO-QUEBECOISE

More than 80 researchers from France and Quebec met together on March 20-21, 2014, at the Institute and Neurological Hospital of Montreal – Le Neuro in the framework of the second France-Quebec workshop on amyotrophic lateral sclerosis and fronto-temporal dementia (ALS/FTD).

AT THE HEART OF THE ICM

- The 7th edition of the **Matinées ICM** took place on February 18, 2014. As usual, donors met with researchers to discuss their scientific advances.



On February 20, 2014, the ICM had the privilege of welcoming Dominique Blanc, who moved spectators with her reading of the Marguerite Duras novel, "*La Douleur*".

- Brain Week** was a great success! From March 10 to 17, 2014, numerous events were held throughout France. The ICM, highly involved this year, had the honor of giving the inaugural address to open the festivities. Participants in "ICM afternoons," amusing and creative workshops organized by researchers of the ICM, discovered the world of research.

THEY ARE MOBILIZED

- The **2nd Diner caritatif de l'Assurance**, organized by the *Club des Assureurs*, took place on April 7, 2014. This year, the funds collected were donated to the ICM.
- The ICM informed and touched our British neighbors during a dinner in London on April 9, 2014.
- The Fondation AREVA** and the ICM have joined forces again, for 3 more years, to deepen our knowledge of brain dysfunction in brain dystonia.

THE IPEPS-ICM

At the 2014 Salon des Entrepreneurs, the *Ordre des experts-comptables* and the *Agence pour la création d'entreprises* (APCE) rewarded *Ad Scientiam*, a company incubated at the ICM, in the category of enterprises less than 6 months old.



BioSerenity, a young, innovative start-up, was just named winner of the 12th edition of the 2014 European Innovatec Awards, in the categories of "Creation" and "Start-up," for its project in finding intelligent health solutions for the follow-up and the diagnosis of epilepsy.



YOUR QUESTIONS FOR...

ANNE BELLOD,
Director of Administration

Why call the ICM a foundation of recognized public utility when it is in fact a research institute?

The ICM was created based on an original model. Original because it brings together patients, physicians and researchers in the same place to develop, at the same time, basic research and clinical research, and this, with the aim of shortening the time necessary to develop therapeutic applications.

But the ICM is also a private foundation, recognized to be of public utility by decree, of 2006, which gives it the right to receive gifts (donations, bequests, assignation as beneficiary of life insurance).

What resources are needed for the Institute to function? How are they allocated?

The ICM's 2014 budget amounts to 23M€ including its investments. 50% of the budget comes from private funds, such as those collected from the public at large, industrial sponsors and individual donors. The resources are supplemented by the financing of research projects by national or international, public or industrial contracts. In addition, the major research institutes (INSERM, CNRS, Pierre and Marie Curie University) contribute important means in terms of personnel and functioning to complement the financing. Seventy percent of the resources contributed by donors are used for the scientific missions of the Institute: research in Neuroscience and its applications.

Can one consult the Institute's accounts and how?

The accounts are approved each year by the ICM's Board of Directors. They are then published in an annual report that can be consulted directly online at icm-institute.org.

What are donations used for? Why should one give money for research?

The institute does not receive direct aid from the government. The donations are essential to assure its functioning each year and guarantee that pluri-annual research projects are completed.



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 2014, 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/...../2014*

*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

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

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

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

PERSONAL INFORMATION

Family name: First name:

Address:

Post office code: City:

ACCOUNT (BIC-IBAN) TO BE DEBITED

IBAN (International Bank Account Number)

BIC (Bank Identifier Code)

Date⁽²⁾ :

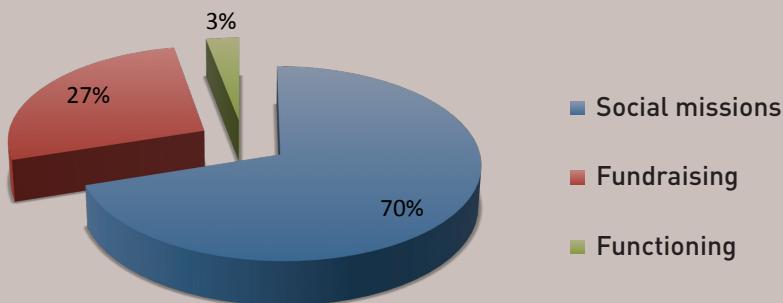
Place⁽²⁾ :

⁽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 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.

USE OF RESOURCES COLLECTED FROM THE PUBLIC AT LARGE IN 2013



The accounts of the ICM can be consulted on the Institute's website:
icm-institute.org/Communication/Publications officielles

In 2013, resources collected from the public at large totalled 4,926,000 €. They were used mainly to finance research. They financed 70% of the social missions of the Foundation. Fundraising represented 27%, a percentage similar to that of 2012 (26.5%). In addition, resources collected from the public at large contributed marginally to the functioning of the Institute (3%).

Your tax deductions

The ICM is a center of excellence and innovation in research and a foundation of recognized public utility. For this reason:

→ **75% (up to 50 000€) of the amount of your contribution is deductible from your ISF.**

- for departments 50 to 974/976, if you declare your income online, the final date for filing your declaration and your ISF contribution is June 10, 2014.
- if your taxable patrimony is equal to or greater than 2.57 million Euros, you have until June 16 to make your special ISF declaration and your contribution.

Simple and fast: make your ISF contribution with the help of a special form found
on our site www.icm-institute.org.

We will send you your tax receipt by email as soon as we have received your contribution.

→ **66% (up to 20% of your taxable income) of the amount of your contribution is deductible from your income tax.**

Your contact for any questions: **Ms Carole Clement – 01 57 22 44 87 – carole.clement@icm-institute.org.**



ONE-TIME DONATION FORM

Please fill out and return this form with your contribution to the following address:

Institut du Cerveau et de la Moelle épinière, Hôpital Pitié-Salpêtrière - 47 / 83, bd de l'hôpital 75013 PARIS

YES, I support the ICM's research programs

on brain diseases and trauma spinal cord

I am making a contribution of:

..... €

By postal or bank check, to the order of the ICM

By credit card

N° of your credit card

Last 3 numbers on the back of the card Expiration date

Date:/...../.....

Signature (obligatory)

Family name:

First name:

Address:

Post office code: City:

Email :

Your contribution to the ICM is deductible from your income tax up to 66% (within the limit of 20% of your taxable revenue) or 75% of your ISF (within the limit of 50 000 euros).

I would like to receive free information on bequests and donations.

Information concerning you is needed for us to obtain your donation and prepare your fiscal receipt. In conformity with the law "Informatique et Libertés" you can access, rectify and delete information simply by writing to the ICM, 47, boulevard de l'hôpital -75013 Paris. You can refuse the use of your address by third parties by checking the box .