



For a number of years now, I have been interested in the brain and its complex functioning.

When my friend Jean Todt spoke to me about creating a research institute that would be unique in the world, bringing together researchers, physicians and patients on the same site, I immediately thought it was an extraordinary project. I was privileged to meet Professors Gérard Saillant, Yves Agid and Olivier Lyon-Caen and to discuss with them. This is how I came to help them, to accompany them as best I could, with my means. Very rapidly, I committed myself to these professors, Founding Members and researchers.

Through these discussions and meetings with the scientists of the Institute the idea of my film LUCY came to me. They helped me to better understand the fantastic challenges of the exploration of the brain, which is one of the major challenges of the 21st century. Even if there are some "inaccuracies" in the script, Professors Saillant and Agid supported me, accompanying me throughout this course of this cinematographic project. I owe them in part its success.

The ICM is an eternal struggle that has value only if the research continues. It is not enough to be generous once, we must invest ourselves continuously. Each advance, each combat waged here concerns everyone. By helping the ICM, we help our children, our grandchildren. I am proud to fight each year for this Institute, very proud to participate in this exciting and important human adventure.

Luc Besson

Movie maker

And Founding Member of the ICM

TOWARDS A MORE TARGETED THERAPY FOR BRAIN TUMOURS



Cabanis, Emmanuel-Alain_ Sagittal section of the human brain

Today, in France, about **5000 new carriers** of malignant primary brain tumours are diagnosed each year. The symptoms depend on the localization of the tumour, its size and the rate at which it develops. Gliomas represent around 50-60% of all primary malignant tumours. Meningiomas, in contrast, are frequent but benign tumours.

Brain tumours (gliomas, medulloblastomas, derived from embryonic cells, and ependymomas) are the **2nd cause of cancer in children**. At present, treatments for brain tumours associate surgery, radiotherapy or chemotherapy, depending on the case, but often **do not lead to a cure**.

Both clinical and fundamental researchers develop the means and the tools to **identify** the different types of tumours and **apply the most effective treatment possible** for each type. At the ICM, two research teams work specifically on these two aspects.

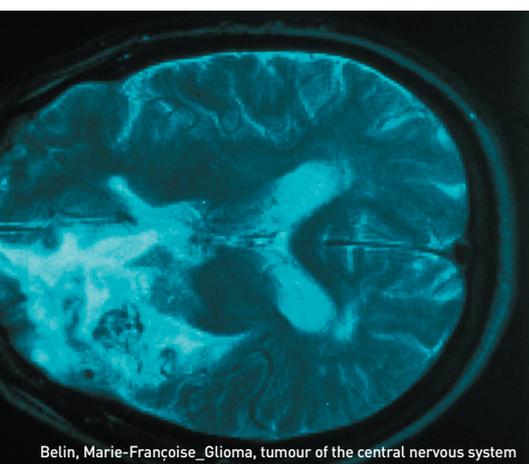
Progress in science has allowed us to increase our knowledge of the brain and better understand its functioning. We know that the brain consists of 100 billion neurons and ten times more glial cells. The role of neurons is to create and conduct the nerve impulse; the glial cells, for their part, provide multiple and important support functions (electrical insulation through formation of the myelin sheath, nutritional support, protection against aggressions). One speaks of a tumour when the abnormal proliferation of a cell leads to the formation of a cell mass.

What is a brain tumour?

Today, the reasons why a cell continues to multiply and becomes a tumour instead of disappearing in accordance with its "life cycle" are not well known. A brain tumour can develop in any region of the brain: **the hemispheres, the cerebellum, the brain stem and the pituitary.**

We should distinguish **primary brain tumours**, which develop directly in the brain, from **metastatic or secondary tumours** that arise from a primary tumour in the lung, colon, breast or skin. Cells from these tumours go and implant themselves in the brain.

There is a great variety of primary brain tumours. The most frequent are the **gliomas and meningiomas**. Malignant tumours are tumours that develop rapidly causing destruction of the brain region in which they are found, whereas benign tumours, called low-grade, evolve slowly without causing damage.



Belin, Marie-Françoise_Glioma, tumour of the central nervous system



Prof Marc Sanson,

Neuro-oncologist, clinician and head of the experimental neuro-oncology team of the ICM

“ The challenge for the coming years is to establish a real bridge between the advances of basic research and their real and significant consequences for the treatment of patients. ”

The most frequent primary tumours are the gliomas that derive from glial cells (astrocytomas and oligodendrogliomas). Low-grade tumours are not very aggressive, but in most cases they evolve towards a more malignant form called high-grade.

Tumours that develop from the meninges, meningiomas, are very frequent and most often benign. We can find lymphomas derived from the cells of the brain's immune system, *ependymomas* (tumours that form in the walls of the brain ventricles). The *neurinomas or schwannomas* come from Schwann cells (the glial cells responsible for formation of the myelin sheath around axons). Finally, we have observed adenomas that develop in the pituitary.

What advances have been made in research on brain tumours?

Today, two types of research that have different objectives can be distinguished, even if, in reality, they are closely related. Thanks to **basic, or translational, research**, we can better understand how tumours develop and identify their causes. In the past few years, high-throughput genomic research has made **important advances in this field**. We can now sequence all the genes and thus identify the molecular and gene alterations responsible for the formation of brain tumours. Researchers know better how to determine the properties of the cancer stem cells responsible for tumour proliferation. They have studied, in particular, cancer cells derived from glioblastomas, in order to identify the genes that are activated as well as the epigenetic mechanisms that control this activation. It has been shown that a group of genes (*transcription factors*), which are normally used by stem cells during brain development, are required for the activity of cancer stem cells. We have discovered that the tumours used for their growth genes involved into normal brain development.



Guichet, Pierre-Olivier_Glioblastoma

As for **clinical research**, its goal is to propose new treatments for patients, either to determine the optimal dose and the tolerance by patients of a new treatment (phase I) or, at a more advanced stage, to verify its therapeutic value (phase II and phase III). In addition, for several years now, powerful sequencing techniques have allowed us to better characterize the genetic alterations in gliomas, and notably glioblastomas. For oligodendrogliomas, the past few years have witnessed the identification of recurrent mutations in these tumours, such as the **mutations IDH1, CIC and FUBP1**. Researchers have distinguished sub-groups with different implications for prediction and prognosis. IDH1 mutations define a sub-group of gliomas with a more favourable outcome.

At the ICM, two research teams are mobilized in the fight against brain tumours, in association with neurologists and neurosurgeons in the Pitié-Salpêtrière Hospital. The team directed by Prof Marc Sanson works more particularly on the molecular biology and the gene mutations that are responsible for the appearance of tumours: oligodendrogliomas, low-grade gliomas, gliomas of the brain stem and meningiomas. They try to identify clinically applicable biomarkers, of diagnostic or prognostic value, but especially alterations that can be targeted by specific treatments. In this research group, the Gliotex team,



The tumour bank, a centre for biological resources specialized in samples of brain tumours.

directed by **Dr. Ahmed Idbaih**, grows cultures of glioblastoma stem cells in order to test targeted therapies (this project was supported by the Fondation ARC).

Dr. Emmanuelle Huillard and her team, created in 2012 and recipients of an ATIP/Avenir grant (Inserm and CNRS), try to understand the molecular and cellular mechanisms that intervene during the development of gliomas and, in particular, how the genes of normal development are "pirated" by the tumour cells. At present, the teams are collaborating on a project aimed at developing a model of oligodendroglioma by combining the gene mutations most frequently found in these tumours: IDH1 and CIC.

What are therapeutic prospects?

Today, it is still difficult to detect a brain tumour before it is visible by MRI (a technique of imaging by magnetic resonance). Nevertheless, the search for biomarkers, which constitutes a strategy for the **diagnosis**

of tumours, leads to development of the means to make the diagnosis earlier. Biomarkers are molecules present in blood, urine or cerebrospinal fluid (CSF), which indicate the presence of a tumour in the brain. Identification of biomarkers **allows direct diagnosis of the tumour and the choice of an effective treatment**. In order to determine how a tumour will evolve and its response to treatment, we apply the methods of molecular biology and immunohistochemistry on genes which are prognostic (evolution of the tumour) or predictive (response to treatment) markers. For example, during the diagnosis of an oligodendroglioma, we look for the presence of a chromosomal alteration or the co-deletion of chromosome regions 1p and 19q. This alteration is associated with a better prognosis and a better response to treatment. Finally, the mutation in the *IDH1* gene is an important factor in the prognosis of gliomas.

Currently, there are no cure for tumours. Clinical research tries, on the one hand, to improve the so-called classical treatments; for example, treat low-grade tumours by performing surgery in awake patients or better use radio- and chemotherapy to improve their efficacy and minimize their side effects, thus preserving the patients quality of life.

On the other hand, **targeted therapies** open new prospects. The genetic and molecular characterization of types and sub-types of tumours allows the development of **truly personalized therapies**. Some of these alterations, even if rare, constitute attractive targets if they are highly oncogenic; for example, the mutant form of the receptor EGFRIII and, especially, the fusion gene FGFR3-TACC3 or the mutant IDH1 enzyme, which can be neutralized with specific molecules, elicit **great hopes**.

The tumour bank, a technological platform at the service of basic research

Yannick Marie, director of operations, tells us about it.



What is the tumour bank?

"It's a biological resource centre specialized in samples from patients with brain tumours, created in 1996 by Prof Delattre. It contains the largest collection of brain tumours in Europe and includes 10 000 patients."

What does the platform do?

"We have a panel of samples of brain tumours that we try to make the most representative possible, in order to study, at the same time, what happens in the tumour, but also its environment (for example, changes in biomarkers in blood); the aim is to find biological markers that predict a response to a treatment or the evolution of the tumour. In addition, we perform research to characterize the different types and sub-types of tumours and identify the genomic alterations that are present."

How do you interact with the research units of the ICM?

"Our implantation in the Pitié-Salpêtrière Hospital has a great advantage for us, because we work in association with the Departments of Neurology, Neurosurgery and, Anatomopathology. Of course, we work closely with the teams of Prof Marc Sanson and Emmanuelle Huillard; we also provide biological samples to other research teams in the ICM that need them for their research (Eric LeGuern and Stéphanie Baulac who work on epilepsy)."

What is the future of the tumour bank?

"We have clearly made progress since our creation in 1996. Recently, we obtained certification in France (NFS96-900) thanks to Amithys Rahimian, responsible for tumour bank quality. She helped us unify our methodology. We house the samples of two national reference centres working on anaplastic oligodendriomas and primary brain lymphomas. In the future, we hope to develop our relations with academic and industrial partners in order to increase our visibility and improve our procedures."



Dr. Emmanuelle Huillard,
CNRS researcher and head of the team
"Molecular and Cellular Mechanisms of Glioma Genesis"
in the Unit UMR1127/ICM

“The proximity of the ICM to the Pitié-Salpêtrière Hospital is a major advantage and gives us access to a large number of tumour samples. In addition, interactions with other Institute researchers who are interested, notably, in normal brain development, are very enriching.”

UPDATE ON RESEARCH

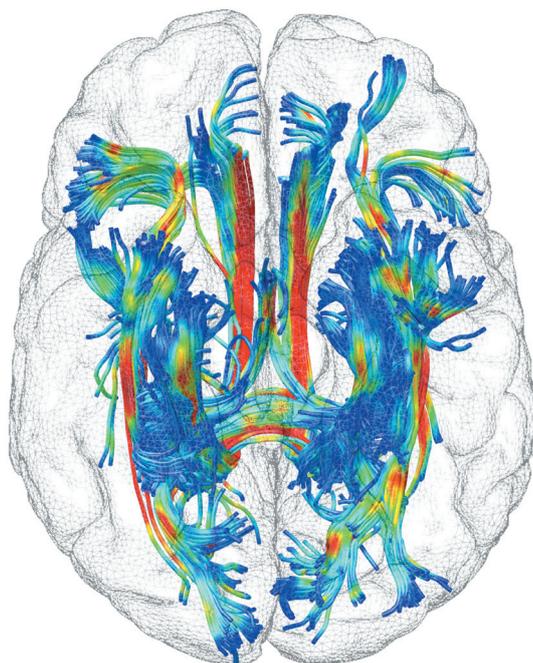
PROGRESS IN ALZHEIMER'S THROUGH CEREBRAL CONNECTIVITY

The research collaboration between Professor Harald Hampel (AXA Research Fund and UPMC Chair on Alzheimer's disease) and Dr. Michel Thiebaut de Schotten (CR2 CNRS - CRICM), both researchers at the Institut du Cerveau et de la Moelle épinière - ICM - Brain and Spine Institute, are very promising in terms of advancements in understanding Alzheimer's disease. This collaboration relies on Prof. Harald Hampel's international expertise and reputation in the field of Alzheimer's disease, particularly neuroimaging and biomarker research and that of Dr. Michel Thiebaut de Schotten in structural connectivity. Their current research breakthrough scientific projects involve early biomarkers of Alzheimer's disease, such as brain connectivity measures, as presented and highlighted on the cover of the September issue of the prestigious international journal *Alzheimer's & Dementia* (A & D - September 2014 - Volume 10, issue 5).

Teams of Prof. Hampel at the ICM and at the IM2A (Institut de la Mémoire et de la Maladie d'Alzheimer - Institute of Memory and Alzheimer's disease) and of Dr. Thiebaut de Schotten at the ICM, collaborating on the Pitié-Salpêtrière University hospital site, are using recent cutting edge neuroimaging methodologies to discover novel footprints as an indication of impaired anatomical neural networks at various stages of Alzheimer's disease (AD). They have the potential to model and predict the conversion from the silent stage of "cognitive normality" (prodromal asymptomatic stage of the disease) to the symptomatic stages of AD. Prof. Hampel, Dr. Thiebaut de Schotten and their teams put much hope in these advancing neuroimaging technologies. The neural network signature established by Prof. Hampel and Dr. Thiebaut de Schotten of a specific patient at a given disease time point, may provide breakthrough options to support early detection and effective AD therapy.

The illustration in cover of A&D's September issue, provided courtesy of Dr. Thiebaut de Schotten and Prof. Hampel, represents the white matter tracts emerging and ending in the hippocampus. The hippocampus is a brain region involved in memory and spatial navigation, functions that are affected in people with AD. The color code corresponds to the white matter integrity - density scale (e.g., red=very high, orange=high, yellow=medium ... violet=low). Such a marker - 3D architecture, layout and density of white matter tracts - may be key in the identification of early changes in neurodegenerative diseases such as AD.

Article : Rym Bouillé
Alzheimer & Dementia Revue - The Journal of Alzheimer's Association - Volume 10, Issue 5, Septembre 2014, Pr Harald Hampel (AXA research Fund and UPMC Chair - IM2A - ICM) & Dr **Michel Thiebaut de Schotten** (CR2 CNRS - CrICM)- "FRONTLAB" Team (B. Dubois & Richard Lévy), "Cognition, Emotion, Action" Axe



RESEARCH ON ALS AT THE ICM

One of the challenges facing the Brain and Spine Institute – ICM- is to better understand Amyotrophic Lateral Sclerosis – ALS – through basic and clinical research. This incurable and lethal disease is characterized by progressive and relatively rapid paralysis of the patients (1 to 5 years after the initial manifestation of the disease) and has no effective treatment. In this context, and in interaction with the technological platforms and clinicians of the Institute on the site of the Pitié-Salpêtrière Hospital (reference centre for ALS), the team directed by Dr. Séverine Boillée, at the ICM, tries to better understand ALS and identify new therapeutic targets in order to develop efficient treatments for this neurodegenerative disease.

ALS, also called "Charcot disease" after the neurologist of the Salpêtrière Hospital Jean-Martin Charcot (1825-1893), is sporadic in the majority of cases (limited to an individual), but about 10% of the cases are familial (several members of a family are affected), indicating a genetic origin for these hereditary forms.

ALS affects about 8000 persons in France, with a prevalence of approximately 5 cases in 100 000 individuals. However, these figures do not reflect the real impact of the disease, and its rapid evolution minimizes the number of cases. It is a very invalidating disease with a severe pathological, psychological and societal impact, which motivates the ICM to find preventive and therapeutic solutions as fast as possible.

ALS : why a progressive paralysis?

ALS affects the motoneurons – "motor" neurons located in the brain and the spinal cord, which are connected to skeletal muscles to send them contraction signals. When these motoneurons die, their connections with muscles are lost, consequently leading to progressive muscles atrophy and so to paralysis. This team's researches have shown that disease progression in ALS models, involves the participation of "macrophages" immune cells. The hypothesis is that these cells can influence the time course of neuronal death in ALS patients.

Research: understand the disease

The team of Dr. Séverine Boillée tries to identify and understand the biological mechanisms that are deregulated in ALS patients, causing abnormal toxicity of the immune cells, and leading to degeneration of the motoneurons.

A first research axis concerns the identification of genes involved in ALS (Dr. Millecamps). The participation of patients and their families is needed to discover these causes. This research is done in collaboration with clinicians of the site (Dr. Salachas/Pr. Meininger).

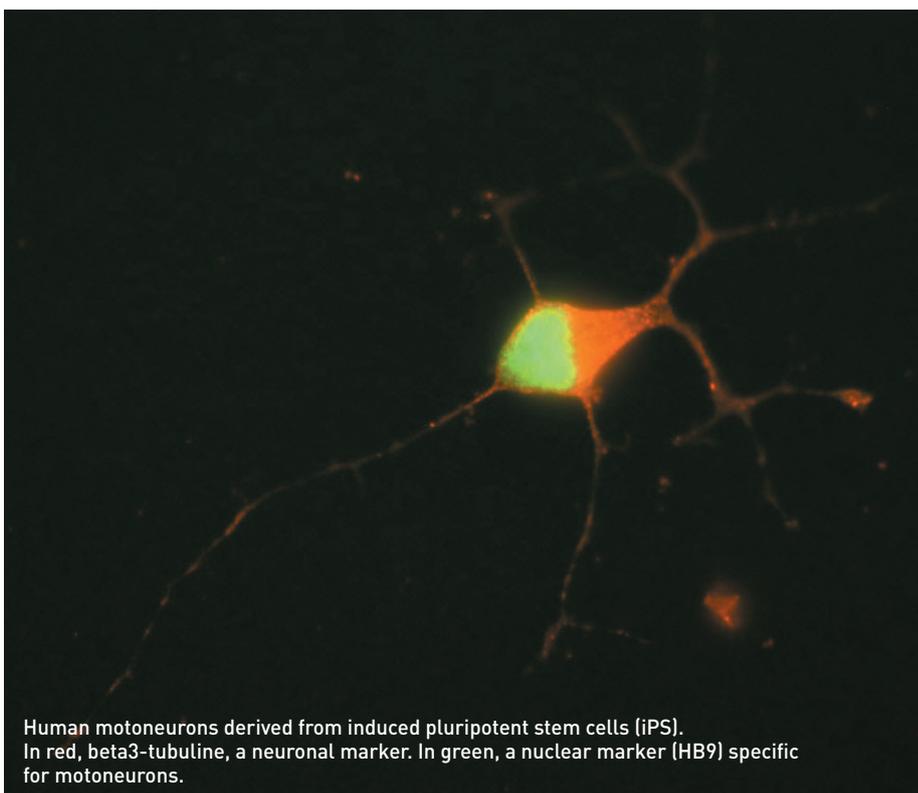
A second axis studies the balance between beneficial and toxic factors, released by macrophages and that affect motoneurons, in order to develop efficient therapies by targeting these factors. To study the early steps of ALS, the team uses experimental

models (Dr Lobsiger) including human motoneurons obtained through the iPS technology (stem cells, Dr. Bohl) from skin biopsies of ALS patients.

To confront the experimental results with the human disease and the affected nervous system, the team uses samples of spinal cord and brain obtained post-mortem from ALS patients, thanks to the Department of Anatomopathology (Prof Seilhan).

The research of Dr. Séverine Boillée and her team aims at identifying the factors related to this pathology and the molecular pathways in which to intervene, in order to develop new treatments to slow the progression of the disease.

Article: Rym Bouillé, interview with Dr. Séverine Boillée, Head of the team "Causes of ALS and Mechanisms of Motoneuron Degeneration"



Human motoneurons derived from induced pluripotent stem cells (iPS). In red, beta3-tubuline, a neuronal marker. In green, a nuclear marker (HB9) specific for motoneurons.

NEWS

SPORTING AND CULTURAL EVENTS

JULY/AUGUST 2014

- Operation *Sport4Change* of the entrepreneurs of **Loft 50 Partners**
- **A Chrono for a donation** – Gilles Lerideauw and GGCOX Racing

SEPTEMBER 2014

- Auction by the **Porsche Club Motorsport France**
- **Fée rarissime** – The Rotary Club Toulouse-Sud, The Rotary Club
- Balma, The Rotary Club
- **The Golf Trophy *les Echos***



On September 25, at the Chantilly Golf Club, the group *les Echos* supported the ICM and its fight against the neurological and neurodegenerative diseases.

OCTOBER 2014

- **The 24H of Grenoble** – Blandine Tissot
- **Auction of prestigious vehicles** – The Lions Club of Agen Val de Garonne
- **The grand meeting of "Classic Festival"** – Classic Days
- **The 20 kms of Paris**

THEY SUPPORT THE ICM



F.P. JOURNE 10 YEARS celebrated, last September 29th, its 10 years of support for the ICM in the presence of President Gérard Saillant, Jean Todt, Vice-President and sponsor of the *Centigraphe Souverain*, and Jean-Pierre Martel, Founding Member of the ICM.

Since 2008, 525 "*Centigraphe Souverain*" and "*Centigraphe Sport*" (creations of the master watchmaker) have been sold and have contributed to advance research in the Institute; 30% of the profits from each watch have been donated to the ICM.

On October 1, 2014, the sponsoring agreement between the **Fondation EDF** and the ICM was renewed in the presence of Hugues Renson, the executive director of the *Fondation EDF*, Bruno Crescent, sponsoring supervisor and director of purchasing of EDF, and Professor Gérard Saillant.



VISIT TO THE ICM

On Monday, September 8, Mr. Jean-Paul Delevoye, President of the *Conseil Economique, Social et Environnemental* (CESE) accompanied by Prof Gérard Saillant, Jean Todt, Prof Alexis Brice and Alexis Genin visited the ICM – a Carnot Institute – and BRAIN e-NOVATION, the first joint research laboratory in e-health.

IN THE HEART OF THE ICM

- On September 9, **Ms. Axelle LEMAIRE, State Secretary in charge of digital**, inaugurated the **first joint research laboratory in e-health and recipient of the ANR LabCom 2013 grant, Brain e-NOVATION**.



- On Monday, September 15, 2014, the donors and researchers of the ICM attended an **exceptional event with the projection of the film LUCY** in the presence of Luc Besson, Moviemaker, producer, scenarist and Founding Member of the ICM, and Prof Yves Agid.
- On October 1, 2014, **an exceptional lecture on Alzheimer Disease** was given at the ICM in the presence of Prof Gérard Saillant, Prof Alexis Brice, Prof Bruno Dubois and Dr. Marie-Claude Potier.
- October 15 was the **"ICM platforms day"**, which allowed discovery of the platforms and technological equipment of the Institute.

AT THE IPEPS-ICM

BRAIN e-Novation, BioSerenity and Dreem, three companies incubated in the ICM, were **winners of the World Innovation Challenge**.



DREEM

FIAC 2014

On October 22, 2014, a breakfast **"Creative Happening and fundraising event"** took place around a creation of Emmanuelle Antille in support of research in the ICM.



The "Grand Palais"

THEY ARE MOBILIZED

- **Séverine Boillée, team head in the ICM, and her group** doing research on Charcot disease (ALS) were mobilized for the Ice Bucket Challenge.



- On September 27, 2014, **Edor Kabashi, team head in the ICM, and all the members of his group** participated in the great solidarity march "*main dans la main*" organized by the Association "*s'investir pour la SLA*" in Paris.
- **Christel Chinour**, from the Limousin region, supported the ICM by participating in marathon.

YOUR QUESTIONS TO...

ALAIN MARIN,

President of the Association Music Passion Parkinson

The association Music Passion Parkinson wants to draw the attention of the public at large to Parkinson Disease through musical and cultural events, during a concert organized once a year for the benefit of the ICM.

What is the Association Music Passion Parkinson?

"The association consists of an office, ill and healthy volunteers, supporters, a guitarist sponsor Frank Texier and a Flamenco group LOS MOJITOS, amateurs who want to alert about the disease during festive moments of sharing; we try to improve the morale of patients who have lost their taste for life."

How long have you supported the ICM?

"In 2011, when I produced my first musical event, a relation of confidence and friendship was born between our association and the ICM. It's a wonderful human adventure."

Why did you choose to support research all this time?

"When "Miss Parkinson" came into my life, in 2010, and when I could no longer sleep, I discovered, by surfing on the internet, the birth of the Institute that represented the best in research: transversality, international coordination of all the necessary competencies on the same platform, visibility of the advances, etc."

What do you wish for the ICM in the coming years?

"I start from the principle that without solidarity no performances are long-lasting or honourable ... It's together that we can advance research and improve the daily life of persons affected by Parkinson disease, which is exhausting; and, in the end, all of the treatments have side effects that are handicapping. I want to see a synergy of all who have good will to help the researchers of the ICM find new possibilities as fast as possible, so that we, the patients, can keep up hope. From the bottom of my heart, a big thank you to the ICM."



MY RECURRENT DONATION

Please fill out and return this form with your contribution and your bank identification details (RIB) to the following address:
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YES, in 2014, I will provide long term support for the ICM's researchers with a contribution of:

10 € 20 € 30 € 40 €

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Every month Quarterly

Starting on 05/...../2014*

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

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

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⁽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.

SUPPORT THE ICM AND ITS INNOVATIVE RESEARCH PROJECTS WHILE REDUCING YOUR TAXES.

Income taxes

66% of the amount of your donation to the ICM is deductible from your income tax, up to 20% of your taxable revenue.

Tax on Solidarity Wealth - ISF

75% of the amount of your donation to the ICM are deductible from the ISF, up to 50 000 €.

Our advice: make a donation before December 31, 2014,

- to reduce you income tax for 2014
- to reduce the tax base of your ISF as of January 1st.

The temporary donation of usufruct (DTU): a two level fiscal advantage

As a Foundation of Recognized Public Utility, the ICM is authorized to receive temporary donations of usufruct. **The principle:** you give to the ICM, by a notarized act, the usufruct of a possession for a limited time of at least 3 years. Examples of usufruct: rent from real estate or dividends from an investment portfolio.

Your fiscal advantage:

- since the revenue from your possession benefits the ICM, it is no longer taxable as income
- if you are subject to the ISF, the value of the property is no longer included in the tax base of the ISF (for the duration of the donation).

Our advice: before making a decision, seek counsel from your notary or our dedicated contact (see below).

For more information, contact our Donor Relations Representative:
Ms. Carole Clement - 01 57 27 44 87 - carole.clement@icm-institute.org

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ONE-TIME DONATION FORM

Please fill out and return this form with your contribution to the following address:
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YES, I support the ICM's research programs
on brain diseases and spinal cord trauma

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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 .