N° 27 – THIRD TRIMESTER 2014

THE ICM **NEWSLETTER**

Brain & Spine Institute - Paris

The Brain and Spine Institute brings to fruition a project initiated with my friend, Professor Gérard Saillant, and materialized by a "dream team" composed of our Founding Members. Today, our dream has become more than a reality; it embodies real hope for people suffering from diseases of the nervous system.

If we want research to advance, if we hope that each of us will live longer and in good health, it is necessary to provide the means for researchers. I am proud of the road we have travelled to this day, of the efforts made by the public and private sectors. Of course, all of the challenges can't be faced without the generosity and confidence of the tens of thousands of donors who have joined us since 2010.

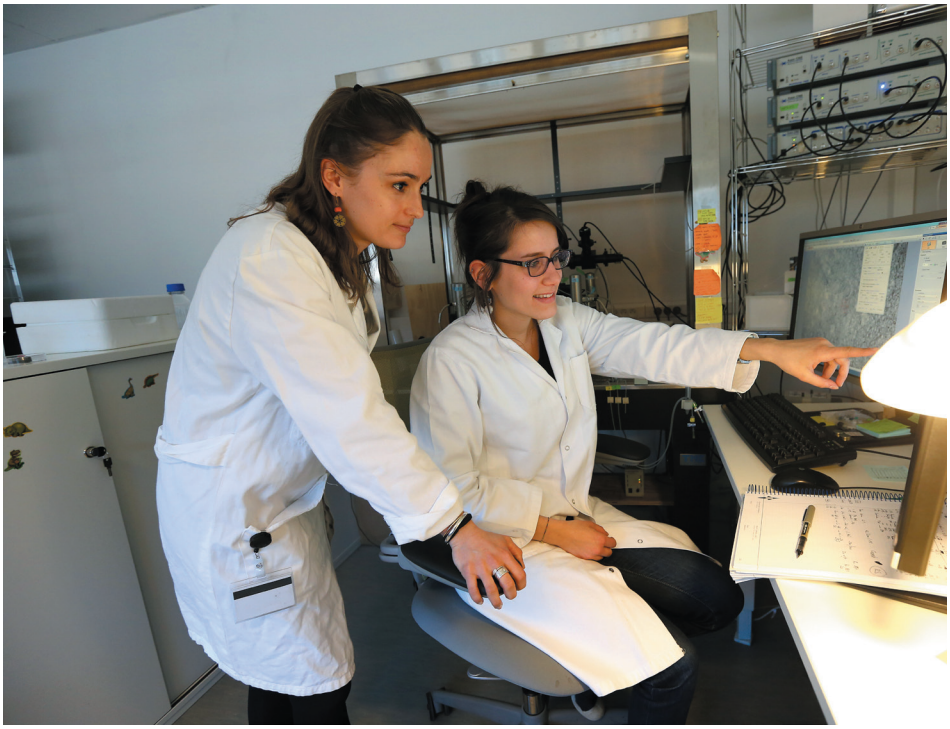
For them, the ICM has chosen to respect the charter of deontology of the Comité de la Charte du Don en Confiance (Committee for the protection of donors) and accepts its controls. In this issue, we wanted to account for the use of the resources you donated in 2013.

In addition, next September 21 will be World Alzheimer Day. Let us remember that 860 000 persons suffer from this disease in France, and this without counting the difficulties that face their families. We propose in this letter to summarize research in this field and inform you of new responses to the disease.

I sincerely thank you for your engagement at our side and at the side of our researchers, and wish to express to you our profound gratitude.

Jean Todt
Founding Member
and Vice-President of the ICM

ALZHEIMER DISEASE, RESEARCH IS ADVANCING



Many neurodegenerative diseases have a great number of features in common. Besides the destruction of nerve cells, Alzheimer disease, Parkinson disease, Creutzfeldt-Jakob disease and amyotrophic lateral sclerosis share the fact that they develop because of the accumulation of misfolded proteins. This is a major consequence of the disease, since these proteins, which lose their initial configuration, are no longer able to assure their primary function. They become inactive, even toxic, for neurons and cause their degeneration.

Alzheimer disease is a major source of preoccupation. A real issue for public health at a global scale, its socio-economic consequences are important. Synonym for cognitive deterioration, it is difficult to live with for the patient but also his entourage, which is often at a loss when faced by a parent's behaviour, to which it is not always easy to adapt. The ICM will review for you the recent advances made by medical research.

Alzheimer disease was described for the first time in 1906 by the German neurologist Alois Alzheimer (see the inset). It is a neurodegenerative disease the cause of which is still unknown and which frequently affects the elderly. The mean increase in life expectancy resulting from improved living conditions explains in part the increase in the number of persons affected by Alzheimer disease. And this number is going to increase considerably.

Today, it is estimated that **860 000 people in France and 35 million around the world suffer from dementias of the Alzheimer type.** Although its appearance before the age of 65 is rare (0.5%), its frequency is 2 to 4% beyond this age. It then increases proportionally with age, reaching 15% at age 80 years. The disease affects more and more women (1 woman out of 4 and 1 man out of 5, after the age of 85 years). **The number of patients in 2020 is estimated to reach two million within the French population alone.** Dependency appears 3 to 5 years after the first symptoms appear. It then becomes a medical, scientific, social, but also economic problem, which preoccupies all developed countries in which life expectancy has increased regularly for a century.

Alzheimer disease is characterized by a slow neurodegeneration that begins in the hippocampus then spreads to the rest of the brain. This degeneration is the result of the concomitant progression of two types of lesions: on the one hand, an abnormal accumulation outside nerve cells of a protein known as ß-amyloid peptide (also **A-beta** or **Aß peptide**) leads to the formation of **"amyloid plaques"** also called **"senile plaques";** on the other hand, an abnormal accumulation of the protein TAU inside the neurons causes them to degenerate. The progressive accumulation of these lesions is at the origin of the symptoms of the disease.

Memory loss is often the first symptom and orients the diagnosis. The disease then affects executive functions and spatial orientation. Disorders of language *(aphasia)* writing *(dysorthographia)*, movement *(apraxia)*, behaviour, mood *(anxiety, depression, irritability)* and sleep with insomnia then develop progressively.

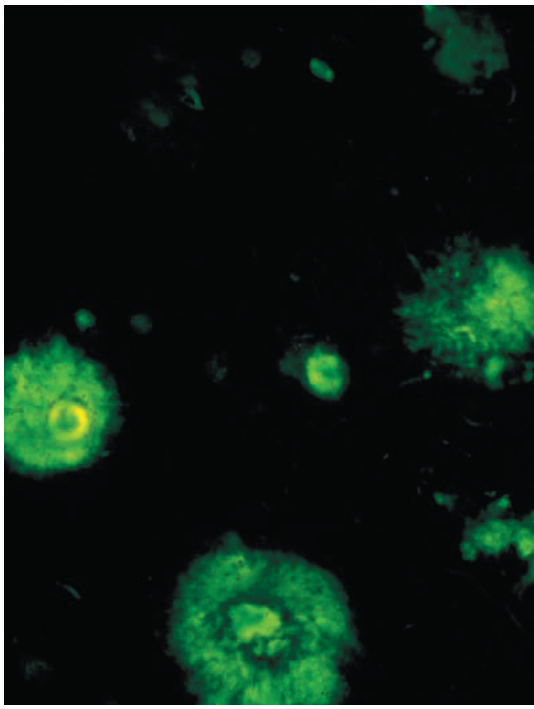
A bit of history:

In 1901, the German neurologist Alois Alzheimer examined for the first time a 51-year-old woman suffering from disorders of memory and language and other psychological signs. In 1906, after obtaining authorization from the family, the physician performed an autopsy and observed under the microscope two types of abnormal deposits inside and between the nerve cells. It was at this epoch that he evoked for the first time, during a lecture to his colleagues, "a particular disease of the cerebral cortex."

The name of the disease was attributed only in 1910, by Kraeplin who carried on the work of A. Alzheimer, in his 8th book on psychiatry in which he described the syndrome.

Joint studies of Alzheimer disease and prion diseases, why?

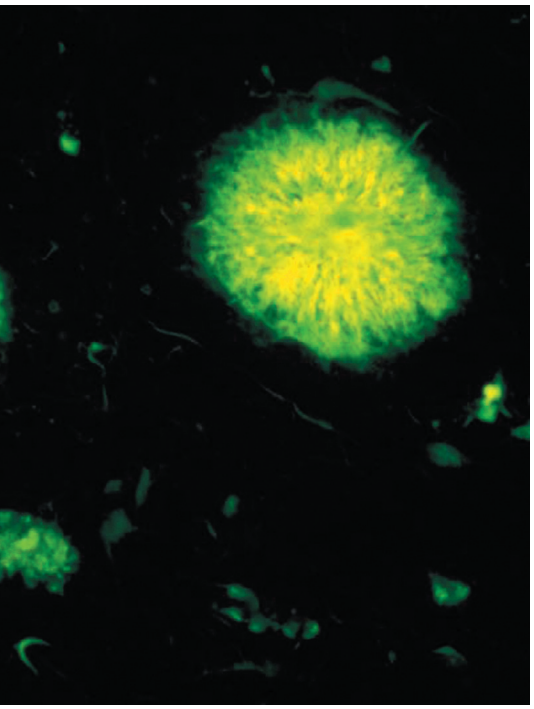
Alzheimer disease and the prion diseases are neurodegenerative diseases that have in common certain clinico-pathological signs, as well as the mechanisms by which the lesions spread and their neurotoxicity. Both groups of pathologies manifest themselves clinically by dementia, which is most often sporadic, without an apparent cause, but a small percentage has genetic causes. As concerns the lesions, both types of disease are characterized by the presence of amyloid plaques in the central nervous system formed by the accumulation of misfolded proteins. The plaques observed in Alzheimer disease are composed of Aß peptides, whereas those of prion diseases are principally composed of abnormally folded prion proteins called scrapie proteins or PrPsc. ß-amyloid and PrPsc are toxic to the brain and lead to the death of neurons, which is the origin of the principal clinical characteristics of these diseases.



Senile plaques or amyloid plaques observed by fluorescence in a case of Alzheimer disease. They derive from an accumulation of ß-amyloid peptide, consisting of 42 amino acids.

To better understand

- The **ß-amyloid peptide (A-beta peptide** or **Aß peptide)** is an insoluble protein fragment that cannot be degraded efficiently by the surrounding cells. It accumulates outside the cells, forming **"senile"** or "**amyloid"** plaques. The ß-amyloid peptide is neurotoxic.
- **TAU proteins** are normally present in our organism, in which they facilitate the polymerisation of microtubules (micro-fibrils that constitute the skeleton of cells and guide the transport of molecules in cells and their extensions). TAU proteins play a role in cell regulation and are necessary for stabilizing microtubules. In Alzheimer disease, modified TAU proteins form **neurofibrillary tangles,** which disorganize the microtubules and cause the death of the neurons.



And research?

At the ICM, the team of **Stéphane Haïk** and **Marie-Claude Potier** studies prion diseases and Alzheimer disease in parallel, because of the important biological analogies between them. The advances recently made on the prion diseases, the most frequent form of which is Creutzfeldt-Jakob disease, have contributed to a better understanding of the biological mechanisms underlying the development of Alzheimer disease.

This research team is particularly interested in the molecular mechanisms implicated in the dissemination of prions: a phenomenon of conversion of the normal protein into a toxic form that induces neuronal death. This phenomenon has also been evidenced in other neurodegenerative disorders like Alzheimer disease; **to understand it and try to block it by treatments adapted to these pathologies is a major challenge.** To this end, the team has developed cellular systems that facilitate observation of the process and elucidation of the mechanism of neuronal death. They also study the interactions between the prion protein and other major factors implicated in Alzheimer disease, the **ß-amyloid peptide** and TAU protein, the aggregation of which is responsible for neurodegeneration. By studying how these molecules accumulate outside and inside the neurons, respectively, the researchers try to find a way to reverse the phenomenon.

In Alzheimer disease, neurofibrillary TAU lesions are always present, but one can sometimes find them as well in certain prion diseases like the Gerstmann-Straussler-Scheinker disease, a syndrome of genetic origin. Certain mutations in the prion protein cause, indeed a neurofibrillary TAU pathology, which is also the most important lesion in the clinical expression of Alzheimer disease. The team of Stéphane Haïk and Marie-Claude Potier tries to understand how these abnormal proteins induce the neurofibrillary TAU pathology. The propagation of prions is explained by the fact that a misfolded prion protein, rich in ß-sheets, can aggregate, recruit the normal form of the protein, then convert it into the pathological form; the prions can then spread little by little, from neuron to neuron, from one brain region to another, and even from one person to another in the case of contamination or inoculation. In Alzheimer disease, how the Aß and TAU lesions could disseminate in time and space was long misunderstood. Researchers recently demonstrated that prion-type mechanisms also explain the dissemination of ß-amyloid peptide and aggregated TAU, both of which propagate little by little like a prion. A final question that interests researchers is the notion of **toxicity.** In prion diseases, one knows that toxicity depends on the expression of the prion protein on the surface of the neurons. It has also been shown that the toxicity of an oligomeric form of ß-amyloid peptide (several

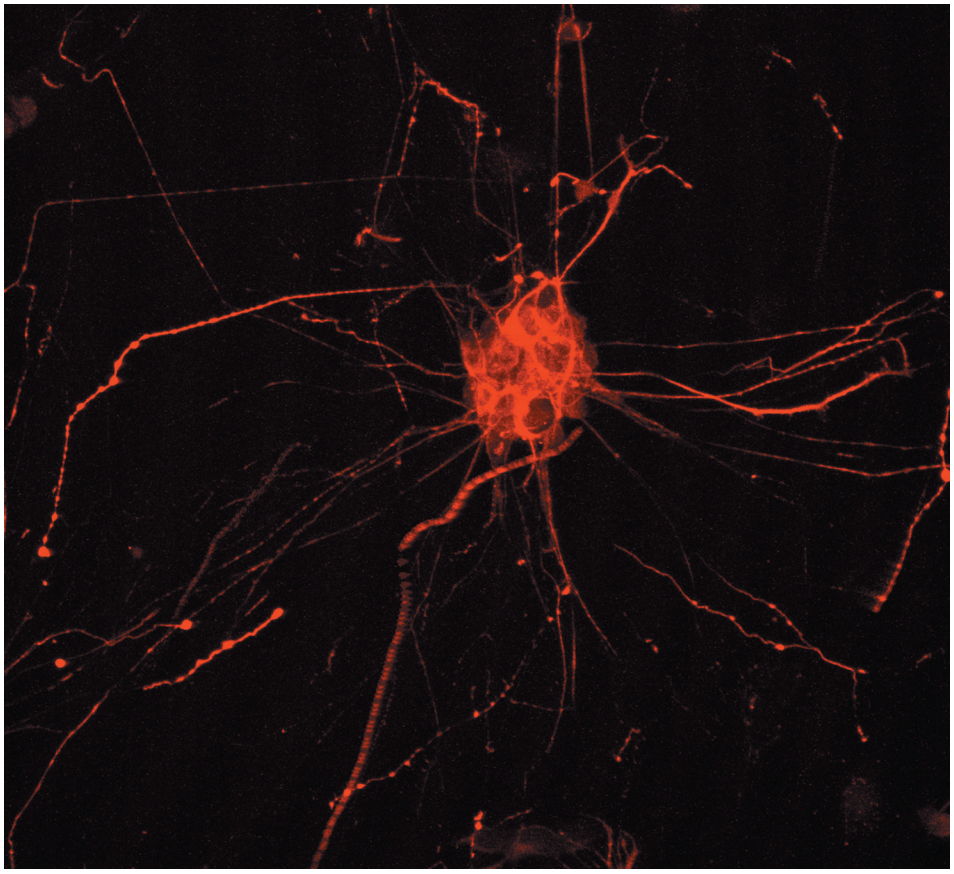
polypeptide chains) also depends on the presence of the prion protein on the surface of the neurons.

The team coordinates the **National reference centre for non-conventional transmissible agents,** also called prions, and pilots **the National network for the surveillance of prion diseases** in France. It is noteworthy that very few teams in the country are interested in human prion diseases. **As an extension of their studies at the ICM, the team also performs translational research aimed at exploiting the methods and results obtained by basic research to develop diagnostic and therapeutic approaches thanks to clinical research performed directly with patients.**

As in many neurodegenerative diseases, a solid research hypothesis implicates a disorder of lipid metabolism. For several years, the team has been interested in cholesterol. Here, it is a question of **brain cholesterol,** not to be confused with peripheral cholesterol that is part of the composition of cells and implicated in biochemical processes. An increase in the levels of brain cholesterol was observed in patients with Alzheimer disease. **This discovery oriented the work of the researchers towards a new direction:** in cell cultures developed by the team, they showed that an increase, even transitory, of cholesterol at the surface of the neuronal membrane leads notably to an increase in the production of amyloid peptide. The study of these mechanisms will permit them to go a little further and try to inhibit the effects of these lipids on the production of amyloid peptide.

In addition, **the team developed, in 2013, a system of cartography allowing for the co-localisation of different molecules in the brains of patients,** notably ß-amyloid peptide and brain cholesterol. With this technique, they demonstrated the existence of a high level of cholesterol in senile plaques, probably an indication of a relationship between cholesterol and neurodegeneration. **The researchers are now working on mutations in the precursor of amyloid peptides, which will help to better understand the underlying mechanisms.**

Finally, their studies on brain cholesterol led to the discovery of a modification of a cellular sub-compartment in Alzheimer disease, the so-called **endosomal compartment.** Endosomes are cell organelles that play a role in sorting and recycling. The endosomal compartment permits fragments of membrane to enter cells; it is at this level that amyloid peptides are produced. The studies conducted on endosomes have incited the teams to do research on **trisomy 21.** Indeed, people with trisomy 21 have a higher risk of developing Alzheimer disease. At age 60 years, about 45% of those with trisomy 21 have a dementia of the Alzheimer type, whereas in



Fluorescent labelling of the protein Tau in a human hNT cell

Stéphane Haïk,

Neurologist and Director of Research at INSERM, co-directs the team "Alzheimer disease and prion diseases" with Marie-Claude Potier

"Our ambition is to understand how the pathogenic agents in the two diseases act and develop effective diagnostic and therapeutic tools."

the general population the prevalence at the same age is less than 5%. This research will help understand why these people are more affected by Alzheimer disease.

What hope is offered by research at the ICM?

At present, **the teams that work in the ICM are particularly motivated to find a way to intervene as early as possible to stop the development of Alzheimer disease.** To reduce the time needed for applied research to find a treatment, it is necessary to increase collaborations between clinicians, researchers and patients. It is for this reason that the team of **Pr. Bruno Dubois studies subjects at the initial stage of their disease, even the prodromal stage,** a period during which a group of precursor symptoms announce the beginning of the disease. In collaboration with the team of Pr. Bruno Dubois, the **Clinical Investigation Centre – CIC directed by Dr. Jean-Christophe Corvol** (cf Newsletter n°26) performs **studies in presymptomatic carriers of genetic forms of the disease;** the objective is to be able to make **an early, even predictive, diagnosis and develop new strategies targeted to anti-B-amyloid and anti-TAU therapies**.

Advances in research at the ICM also concern the identification of new mutations in the gene encoding the prion protein, which cause either classical prion disease or a prion disease associated with neurofibrillary TAU pathology. **This new discovery will permit understanding of how amyloid lesions induce the well-known neurofibrillary tangles responsible for the disease.** Recently, the team of Stéphane Haïk and Marie-Claude Potier identified, in collaboration with researchers in other countries, a very particular form of Alzheimer disease characterized by an evolution that is so rapid that the diagnosis of Creutzfeldt-Jakob disease was evoked. They are trying at present to identify the factors that control the rapidity of its evolution.

The ambition of the team is to better understand how prions propagate in the nervous system, be they prion proteins or other proteins that aggregate in neurodegenerative diseases, like those implicated in Alzheimer disease. The researchers wish to understand how these misfolded proteins specifically target certain regions of the brain and induce neuronal death. Finally, they use concepts emerging from their studies on prions and techniques developed in their laboratory at the ICM to better understand how neurofibrillary TAU lesions develop in Alzheimer disease and cause dementia. Finally, they try to **apply the technologies they developed for research to applications that are useful for the diagnosis and treatment of brain diseases caused by misfolded proteins in humans.**

INSIGHT, an ambitious world-wide program

The teams of the Institute for Memory and Alzheimer Disease (IM2A) and the Brain and Spine Institute, associated with the IHU-A-ICM and in collaboration with Pfizer, are carrying out a unique study, world-wide, aimed at better understanding the factors that induce Alzheimer disease: the INSIGHT study. They will follow 400 healthy volunteers, aged 70 to 85 years, with memory disorders but not Alzheimer disease, with a battery of tests including PET imaging of amyloid. Because of their risk of developing Alzheimer disease, the aim of the study is to observe their evolution and describe the natural history of the disease.

Marie-Claude Potier,

Director of Research at the CNRS and molecular and cellular biologist, co-directs the team "Alzheimer disease and prion diseases" with Stéphane Haïk

"The ICM permits us to perform translational research in close collaboration with the clinicians of the Groupe Hospitalier Pitié-Salpêtrière where the ICM is located, and to accelerate our basic research thanks to its technological platforms for molecular biology and imaging."

UPDATE ON RESEARCH

TOWARDS THE DISCOVERY OF BRAIN SIGNATURES OF CONSCIOUSNESS AT THE PATIENT'S BEDSIDE

The teams of Lionel Naccache and Stanislas Dehaene were able to identify brain signatures of the state of consciousness of patients with severe brain lesions. These clinical signs will be a precious aid in diagnosing the state of consciousness of patients and predicting their capacity to recuperate.

Faced with a victim of a severe brain lesion (ex: cranial trauma, cardiac arrest, massive brain haemorrhage...), it is sometimes very difficult to determine his state of consciousness only on the basis of clinical examinations, even when performed by experts. How can one know whether a patient is conscious of the world around him, and particularly of himself, if he cannot communicate? This question touches on issues that are important for the patients and those close to them, as well as the medical personnel, concerning diagnostics, prognostics and ethics. During the past 15 years, several teams have developed new techniques to measure brain activity, which could offer objective and reliable elements of a response to this redoubtable question. The teams of **Lionel Naccache (ICM, CHU Pitié-Salpêtrière, Université Paris 6) and Stanislas Dehaene (NeuroSpin, Collège de France)** are working together in this direction.

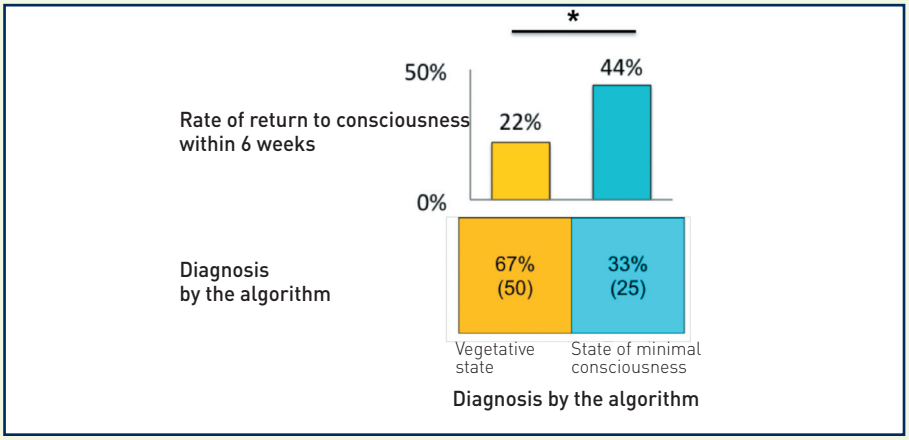
In 2009, they published a new test that consists of measuring the brain response to auditory novelty by recording the brain activity (EEG) of the patient with a helmet of electrodes. Later, these teams were able to validate the very great specificity of this test in a large number of patients that were vegetative, minimally conscious or conscious. In a study that appeared in June 2014 in the prestigious journal Brain, they went a step further in an extensive analysis of more than 200 EEG recordings of vegetative or minimally conscious patients. In each recording, they analyzed close to a hundred different EEG markers, in order to determine which was the most apt to predict not only the present clinical state of the patients, but also their prognosis for recovering consciousness in the 6 weeks to come. Some of these measures of brain activity were traditional (ex: evoked potentials, spectral analysis), whereas others were developed thanks to new methods of signal processing (measures of functional connectivity, complexity and entropy; measures of the variability of the response). As a result of this large-scale work, carried out by **Jacobo Sitt and Jean-Remy King,** certain brain signatures of the state of consciousness were identified and validated.

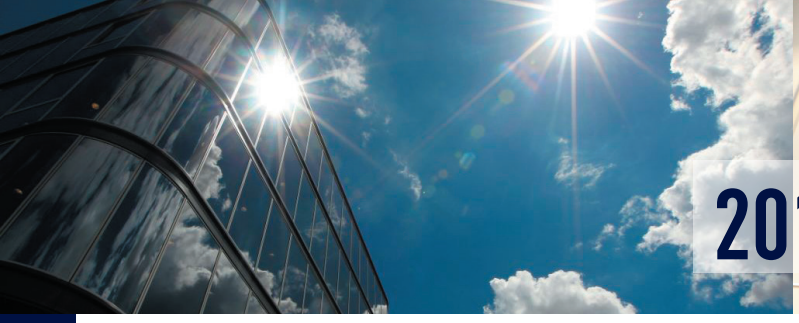
On the basis of these EEG measurements, the authors analysed the ability of an algorithm conceived to distinguish patients in a clinically vegetative state from those in a state of so-called minimal consciousness to make a diagnosis or prognosis. The majority of clinically vegetative patients were correctly identified by the mathematical classifier. However, other patients, judged clinically to be equally vegetative, were diagnosed as minimally conscious by the algorithm. To understand the "errors" of classification made by the algorithm, the authors of the study compared the evolution of the patients considered to be vegetative by the algorithm from that of those considered to be in a higher state of consciousness (see the figure). Surprisingly, twice as many clinically vegetative patients classified as minimally conscious by the algorithm (data in blue) regained consciousness compared to those the algorithm considered, like the clinicians, to be in a vegetative state (data in yellow).

This suggests that the EEG markers used contributed information that complemented the clinical data and improved the diagnosis of the state of consciousness of the patients and the prognosis of their capacity for recuperation.

In a near future, which the authors hope will be close at hand, simplified versions of these analyses should be available that will facilitate their use in all clinical departments with traditional systems for EEG recording. EEG is medical tool that is much used, inexpensive and non-invasive, which can be repeated as often as needed and can be used at the patient's bedside.

Article: Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state, Sitt JD, King JR, El Karoui I, Rohaut B, Faugeras F, Gramfort A, Cohen L, Sigman M, Dehaene S, Naccache L. Brain (First published online June 11th 2014)





2013 THE ESSENTIALS

THE ICM IN REVIEW

Understanding and treating diseases and trauma to the nervous system constitutes a major challenge for the 21st century world wide. Today, medicine relieves suffering... Tomorrow, it must prevent, cure, and repair.

The challenges

These disorders affect nearly a billion people throughout the world*. With the ageing of the population, this figure will continue to increase. For example, in France, life expectancy increased by more than 15 years over the course of the past 50 years: 1 out of 2 girls born today will live to be a hundred years old. In 2050, 1 Frenchman out of 3 will be over 60 years of age (1 out of 5 in 2005).

Each year throughout the world, 50 million people are hurt or become handicapped because of brain or spinal cord trauma. These figures will increase considerably from now to 2020, particularly in developing countries.

THE ICM

22 000 m² of laboratory space

1200 m² for clinical research
(77 studies, 1800 patients,
2000 consultations in 2013)

1000 m² for the incubation
of start-ups

25 research teams

600 researchers, technicians, doctoral students and post-doctoral fellows

15 enterprises currently
in the incubator
Technological platforms
(2 MRI 3T, MEG, EEG...)

PRINCIPLES AND VALUES OF THE ICM

SCIENTIFIC EXCELLENCE

The best researchers are involved, the objective is to discover

"AT THE SERVICE OF PATIENTS"

Associate patients, physicians and researchers

FLEXIBILITY

Encourage the expression of scientific creativity

OPENNESS

Create a centre for discussion; facilitate dialogue with civil society and industrial partners

TRANSMIT KNOWLEDGE

At the national and international levels

THE ICM, A MODEL AT THE HEART OF CARE

▶ AMBITIOUS

Treat and cure, one day, the disorders of the nervous system requires the existence of important research centres capable of working in networks

▶ INTERNATIONAL

At the ICM, an international scientific advisory board is in charge of recruiting high-level talent. The rigorous selection procedure constitutes one of the main guarantees of the Institute's scientific excellence

▶ UNIQUE

With the aim of shortening the interval between the discoveries of basic research and their application to therapeutics, the fact that they work in the same place facilitates the connection between patients, physicians and researchers

▶ ORIGINAL

The ICM is a private foundation of recognized public utility (decree of September 13, 2006) implanted at the very heart of the University Hospital of La Pitié-Salpêtrière; it benefits from both public and private financial support

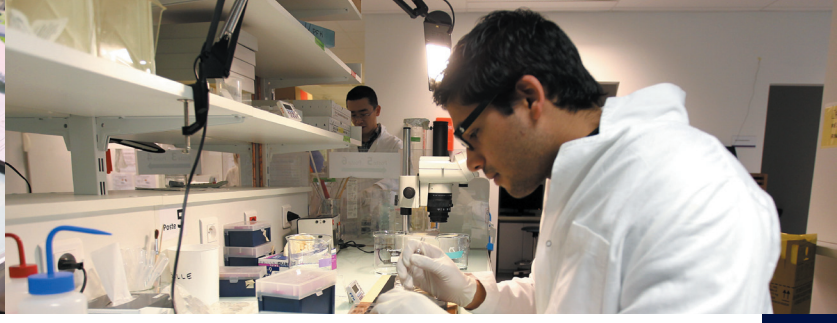
▶ MULTIDISCIPLINARY

At the ICM, this is the consequence of joint approaches accross different fields of research (molecular and cellular biology, neurophysiology, cognitive sciences, therapeutics)

▶ CAN BE CAPITALIZED ON

Indispensible for scientific research, partnerships with industry, notably pharmaceutical, truly accelerate research

**Sources : OMS, continentalnews, sante-medecine.creapharm.psymad*

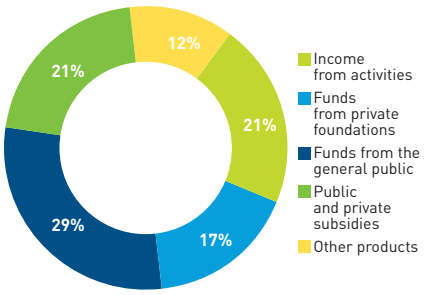


FINANCIAL REPORT

❶ RESOURCES 2013

Resources in 2013 reached 19.5 M€, and included 17 M€ of products of the financial year and 2.5 M€ of resources allocated but not used during previous financial years.
The products of the financial year were essentially revenue from fundraising (46%), either from the general public (29%) or from enterprises and private foundations (17%).
There was also:

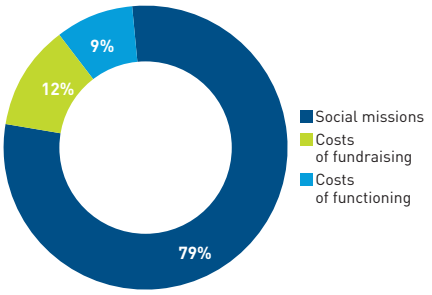
- revenue from the activity of the technological platforms (1.8 M€), research collaborations with industrial partners (1.8 M€)
- public subsidies (European Commission and Plan Alzheimer): 2.7 M€ and private subsidies: 0.9 M€
- other sources (rebilling of charges, rental fees from partners, financial products...): 2.0 M€.



❷ USES 2013

The total of uses, in 2013, was 22.6 M€: 19.8 M€ to be realized later from allocated resources. Among the uses 2013, the sum dedicated to social missions was 15.5 M€, and represents 79% of total uses for the fiscal year. The social missions of the ICM were:

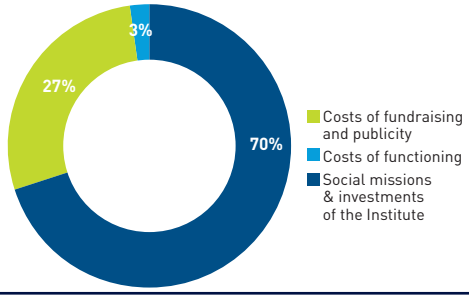
- research projects (53%)
- technological platforms (33%)
- scientific events and international partnerships (8%)
- research applications and industrial partnerships (6%)



The research projects financed concerned principally neurodegenerative diseases and trauma of the spinal cord. The technological platforms (neuroimagery, vectorology, sequencing/genotyping, cell culture and histology) contributed additional support for these projects. The costs of fundraising correspond to the costs of collecting funds from private individuals (contributions and bequests) and enterprises (patronage and sponsoring). They represent 12% of uses. The costs of functioning correspond to the costs of the teams-support (finances, personnel, informatics, logistics) and represent 9% of all uses for the fiscal year. Engagements to be realized from previously allocated resources (2.8 M€) correspond mainly to contributions received during the year from enterprises and foundations, which will be used later for specific pluriannual research programs.

❸ USE OF RESOURCES COLLECTED FROM THE GENERAL PUBLIC

Resources collected from the general public used in 2013 amounted to 6.6 M€. **In summary, out of 100 € of resources collected from the general public, 70 € were used to finance the social missions and investments of the Institute, 28 € were used for fundraising and 2 € contributed to the functioning of the organisation.**



The year 2013 also saw...

3 contracts for sponsorships signed with: the ***Fondation Cognacq-Jay*** to finance 2 post-doctoral researchers working on neurodegenerative diseases; ***Groupe Bolloré,*** to support research at the ICM; ***Arkea/Groupe Crédit Mutuel,*** which contributed part of the interests from its financial investments to the ICM.

In December, **the Circle of Friends of the ICM was created** and brought together the Major Donors (individuals, enterprises and foundations) to thank them for their mobilization since the beginning of this adventure.

In 2013, the ICM attracted 59 000 donors.

Many enterprises have given their support by contributing their know-how in their field of activity. Publicity agencies and websites have offered media space to the ICM free of charge. Artists and collectors have also offered works to the benefit of the Institute.

To develop its regional activities, two delegations were created, in 2013, with the following objectives:

- reinforce the visibility of the ICM.
- contribute to the development of the resources of the ICM.
- facilitate contacts between the ICM and neuroscience research partners in the regions.

This process will be extended progressively to other regions on a variety of themes related to diseases of the nervous system.

THANK YOU FOR YOUR GENEROSITY

SIMPLIFIED BALANCE SHEET

Assets (in K€)	31.12.13	31.12.12
Net fixed assets	11 778	14 441
Realizable and available assets	27 822	20 486
Total	**39 600**	**34 927**

Liabilities (in K€)	31.12.13	31.12.12
Associated funds	23 720	24 488
Results of the fiscal year	-3 112	-1 241
Dedicated funds	3 884	3 579
Debts	15 108	8 101
Total	**39 600**	**34 927**

COMMENTS

- 20 M€ invested since the ICM was created
- These investments were mainly dedicated to the technological platforms, indispensible for the advancement of research. During the year 2013, the ICM acquired a cryoprobe for imaging, completed the equipment of the functional experimentation platform and finished installing the business nursery.
- The working capital is 10.66 M€, a sum similar to that of the preceding fiscal year.
- The total equity amounts to 20.6 M€. It comprises the associated funds (11.7 M€) to which are added investment subsidies (2.8 M€) and 6.1 M€ carried forward.

Excerpt from the 2014 report of the auditor of the Committee for the protection of donors.

DON en CONFIANCE comitecharte.org

"During the preceding three-year period, the social missions of the Foundation were deployed rapidly and courageously in a superb building that houses high-level teams and their equipment. The foundation has offered the researchers facilities to which they previously had no access and reinforced in many ways the perspectives for internationalization of their work.

The new period that is beginning is characterized by the will to install a stable form of organization based on a concerted public/private partnership with balanced financial bases, while at the same time maintaining its ambitions for high-level performance in the sphere of national and international scientific research."

All the information in this document can be found in the Annual Report and the Report on the Moral and Financial Situation for the year 2013.

The annual report 2013 can be obtained on the ICM'S website (icm-institute.org) or by a simple writting request

Your confidence is our responsibility

NEWS

SPORTING AND CULTURAL EVENTS

- The 7th edition of **Classic Days,** which took place last May 3-4 on the Magny-Court Circuit, was a great success and greatly helped progress in research.
- On May 3- 4, the owners of Ferraris and enthusiasts of exceptional automobiles again came together for the road-trips of **Sogno di Cavallino** at Boiry-Sainte-Rictrude in support of the ICM.
- On May 14-16, the ICM organized several events for the 50th anniversary of the founding of INSERM.
- On May 17, a concert ***"Rappelle-toi Barbara"*** was organized, in the presence of our regional delegation, by the Lions Club of Aixe sur Vienne to pay homage to the artist Barbara and to benefit the ICM.
- On May 17-24 the ***Internationaux de Strasbourg*** took place, a women's tennis tournament that, thanks to its organizers, has continued to support the ICM.
- The 1st edition of the **Festival Pint of Science** took place on May 19-21, 3 evenings during which the public met with Pr. Yves Agid, Dr. Hartmann and Dr. Grabli to talk about the neurosciences.
- On May 27, 2014, the ICM sponsored the half-finals of the **French basketball championship** between Dijon and Limoges; the latter won.
- On June 6, Professor Gérard Saillant accompanied by Patrick Timsit were the honoured guests of the **Roland Garros** tournament, organized by the French Federation of Tennis.
- On June 22, 2014, the association ***"La tête c'est le pied"*** renewed its support for the Institute by participating in a sporting event, in Châtres, that combines running, walking...
- The ***Rallye des Teufs Teufs du Coeur*** drove again to support the ICM on June 22, 2014.

7th edition of the Rallye des Teufs Teufs du Coeur organized by the Lions Club of Essarts le Roi

CERCLE DES AMIS

On July 4, 2014, the *Cercle des Amis* was inaugurated at the Institute to bring together the Founding Members, the Members of the Comité des Amis and the Major Donors present since the beginning of the ICM's adventure.

AT THE HEART OF THE ICM

- ***Chercheurs en Herbe***

On June 4, 2014, a mini-congress took place with the distribution of diplomas to the *"chercheurs en herbe"*. On this occasion the students received diplomas for the work they accomplished during the school year.

- On June 12, 2014 the 1st edition of **Connected Health** took place; organized by the start-up Ad Scientiam incubated in the iPEPS-ICM, it was an occasion for clinicians, researchers and representatives of the digital industries to meet together.

THEY VISITED THE ICM

On Friday June 27, 2014, **Mr. Benoît Hamon,** *Ministre de l'Éducation nationale, de l'Enseignement supérieur et de la Recherche,* and **Ms. Geneviève Fioraso,** *Secrétaire d'État chargée de l'Enseignement supérieur et de la Recherche,* visited the Brain and Spine Institute – certified by the *Institut Carnot*

AT THE IPEPS-ICM

- **Iltoo Pharma, MedDay and inFine,** selected among 7 enterprises in the category "Start up Espoir", were in competition at the 11th business meeting of the AP-HP. MedDay was the winner.
- **Alexandre Carpentier, Carthera,** was awarded an official US patent for a probe for sEEG detection and photothermic laser treatment of pharmaco-resistant epilepsy under MRI.
- **Ad Scientiam** was selected in a call for demonstrations of connected products and **Benjamin Pitrat** represented Ad Scientiam at the Workshop "Connected Doctors and Pharmacists."

THEY ARE MOBILIZED

- **The "Bonk and Zumarka Team for the ICM"** will continue their exploits throughout the Hexagone until September 2014. On Sunday June 29, four members of the team participated in the triathlon "Ironman of Nice".
- **Blanding Tissot** will participate, in solo, in the 24 Heures de Genoble, an ultra-marathon, which will be held on October 4-5, 2014, and on the same occasion will support research at the ICM.

YOUR QUESTIONS TO...

CAROLE CLÉMENT,

In charge of gifts and relations with legators

ALL YOU NEED TO KNOW ABOUT BEQUESTS

A bequest allows you to transmit part or all of your possessions. To be taken into account, your desire to make a bequest must be included in a will, which you can modify or cancel at any moment.

What can I bequeath to the ICM?

You are free to bequeath anything you want. It suffices to mention it precisely in your will. You can decide to transmit the whole or part of your patrimony to the ICM: an apartment or a house, a sum of money, a life-insurance policy, a portfolio of stocks or a work of art...

Why is it recommended to make a will?

In the absence of a will, your possessions will automatically be divided among your heirs as prescribed by law. ***If you have no heirs or in the absence of a will your entire estate will go to the Government. A will allows you to designate the beneficiary (ies) of your estate when you will no longer be there.***

Why seek the counsel of a notary?

To make a bequest, the notary can give you advice specifically adapted to your situation. ***He can notably register your will in a file of last wishes that guarantees that it will be found and taken into account.***

Can I transmit property if I have children?

Yes, of course. Depending on the situation of your family, if you have direct heirs (spouse, children, grandchildren, great-grandchildren), the law stipulates that part of your so-called "reserved patrimony" is rightfully theirs. But ***you also have a "disposable portion" that you can bequeath to the ICM.*** *Don't hesitate to contact your notary.*

You have more questions? Don't hesitate to contact Ms Carole Clément at **01 57 27 44 87** or **carole.clement@icm-institute.org**

She is at your entire disposal and will accompany you personally through the process of making a bequest process without any commitment on your part.

Remember:

As a foundation of recognized public utility, the ICM is authorized to receive bequests, life-insurance policies and donations **that are totally exonerated from payment of inheritance taxes.** Your bequest will thus be integrally dedicated to the advancement of research.

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

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: .....

Address: .....

Post office code: ..... City: .....

ACCOUNT (BIC-IBAN) TO BE DEBITED

IBAN (International Bank Account Number)

BIC (Bank Identifier Code)

Date [2] : .....

Place [2] : .....

Signature [2]

[2] Obligatory

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.

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I'M LUCKY TO HAVE ALL MY FACULTIES

I am making a bequest to the ICM so that everyone can benefit longer from his brain

Brain and Spine Institute - ICM, is on the front line in the fight against diseases like Alzheimer, Parkinson, multiple sclerosis, stroke, tetraplegia caused by an accident...More than 600 internationally known researchers do battle daily for this cause. Their particularity? They work with patients and physicians in the heart of the Pitié-Salpêtrière Hospital in Paris. Thanks to them, one risks having all of ones faculties much longer.

YOUR CONTACT for all questions concerning bequests
Ms Carole Clément: 01 57 27 44 87
carole.clement@icm-institute.org

Crédits photos : INSERM / Jean-Philippe Parienté / ICM

More information on our website: icm-institute.org/menu/aidez/legsetdonations

ICM
Brain & Spine Institute

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 spinal cord trauma

I am making a contribution of:

..... €

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

❑ **By credit card** ❑ CB ❑ BLEUE VISA ❑ MasterCard

N° of your credit card

Last 3 numbers on the back of the card Expiration date

Date: ...../...../..... **Signature (obligatory)**

Surname: .....

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 ❑.

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