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SPECIAL FOCUS
MULTIPLE SCLEROSIS

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EXEMPLARITY
AND EFFICACITY

During this summer’s heat wave, the ICM persists in its development. You will find in this edition the essentials of the annual accounts of the ICM, taken from the annual report and the report on the moral and financial situation of the year 2014. You will see that our situation is healthy and that the management of the Institute is rigorous.

In addition, you will surely be glad to learn that MedDay, a start-up in the ICM’s business incubator, has developed a new treatment for progressive multiple sclerosis. You will find, in this edition, all the information you wish about this good news, which is further proof that our model “from the patient to the treatment” via physicians and researchers is exemplary and efficacious.

Finally, Smuggler, a brand of men’s suits “Made in France” has become a partner of the ICM. There also, we have more proof that our “mixed economy” in which partnerships with you, our donor friends, and private enterprises is an exemplary and efficacious model that offers our researchers, many of whom belong to public organisations, supplementary means, even the recruitment of “private” teams.

You see that our Institute, in a tormented universe and a difficult environment in terms of public financing, demonstrates its dynamism daily.

Jean Glavany
Founding Member

NEWS

A PARTNERSHIP WITH THE CHU OF CLERMONT-FERRAND HAS BEEN ESTABLISHED

A first research project has been initiated with the team of Dr. Laurent Sakka at the Clermont-Ferrand Medical School and the team of Claire Wyart at the ICM. This first collaborative research project will address the question of motricity and the development of new regulatory pathways on which to act to improve post-traumatic repair of the spinal cord.

SMUGGLER

This French brand of men’s suits “Made in France” has established a partnership with the ICM in order to support research on the diseases of the brain and lesions of the spinal cord. For each suit or jacket sold, ten euros will be donated to the Institute.

AN ANTI-STRESS HEADSET

MyBrain Technologies is a young company, started by two young ICM researchers, that is incubated in the business incubator of the Institute the iPEPS-ICM. On the basis of their work on EEG (electroencephalographic) technology, the founders developed, in conjunction with the EEG platform of the ICM and the team of Nathalie George, a “neurofeedback” headset to fight against stress. Long term, this technology should also help fight against attentional disorders, hyperactivity or sleep problems.

PARTNERS: 20 KM DE PARIS

On October 11, 2015, the Brain and Spine Institute will be present at the “20 KM DE PARIS”. An 11-year partnership that contributes support equal to the challenge posed by the diseases of the brain and spinal cord.

The “20 KM de Paris” race is a personal and collective challenge. October 11, 2015, at 10 o’clock at the Iéna Bridge, will be another wonderful morning under the sign of the passion for sports and generosity. If you wish to support the Institute during this event, there are two possibilities:

- The first is to run wearing the colours of the ICM. The Institute will be present in the village during the distribution of numbers to alert the public to the challenges and propose tee-shirts with its colours.
- The second is to collect funds to help research. The runners can create a free personalized web page on the Alvarum platform calling for donations and invite their friends to support them during the race to finance research.

If you also wish to organize an event for the benefit of the ICM, please contact Agathe Gioli: agathe.gioli@icm-insitute.org

- icm-institute.org/fr/legs-donations-et-assurances-vie/
- You will find a special focus on bequests, donations, life-insurance
- icm-institute.org/fr/les-conferences-de-icm/
- You will find an exceptional lecture on multiple sclerosis
- View the lecture “Science, Art et Culture” with Jean-Didier Vincent
- Discover the video of the sessions of “connected health” on the impact of connected objects on clinical and epidemiological research

AGENDA

- September 12 and 13
  - At the Parc des Expositions of Toulouse, Fée-Rarissime will propose, as usual, baptisms behind the wheel of a Ferrari for the benefit of the Hôpital Sourire and the ICM.

- All information on “A circuit for the brain”, at http://ucplc.fr/

AGENDA

- September 24
  - The ICM will celebrate the 5th anniversary of its inauguration


MULTIPLE SCLEROSIS: DECIPHER, MEASURE AND TREAT

Multiple sclerosis (MS) is the first cause of severe handicap in persons in their thirties not due to trauma. It affects about 1 person in 1,000 in France and about 2.8 millions worldwide. It is an inflammatory disease of the central nervous system in which the immune system, normally implicated in the fight against viruses and bacteria, becomes activated and attacks elements normally present in the body.

In the case of MS, the inflammatory reaction destroys the myelin sheath that surrounds neuronal projections, the axons, which transmit the nervous influx (like the insulation that surrounds electrical wires to assure good conductance of current). The principal aim of this protection is to assure rapid transmission of the nervous influx in order that information originating in the brain can rapidly reaches the muscles. Repeated attacks of inflammation alter the transfer of information and lead to motor, sensory, balance and visual disorders. ICM researchers try to understand the mechanisms of destruction of the myelin sheath. By blocking their migration towards the nervous system, degradation of the myelin sheath is reduced, favouring its repair and the restoration of nerve functions. One of the gene networks identified by this analysis is of major importance for the identification of new therapeutic targets in MS.

The mechanisms of destruction

The team of Bertrand Fontaine and Sophie Nicole has discovered five new groups of genes associated with a predisposition to MS. These gene networks are implicated in the adhesion and migration of certain cells of the immune system, the T lymphocytes, into the brain. The entry of T lymphocytes into the brain is a crucial step in the development of MS, because they are responsible for the destruction of the myelin sheath. By blocking their migration towards the nervous system, degradation of the myelin sheath is reduced, favouring its repair and the restoration of nerve functions. One of the gene networks identified by this analysis is of major importance for the identification of new therapeutic targets in MS.

Factors implicated in repair

Brahim Nait Omesmar and Anne Baron-Van Evercooren have discovered the beneficial role of several molecules in myelin repair. Their latest advance was the identification of a “pro-myelinating” molecule, called Olig2. This discovery could play a major role in the development of treatments aimed at stimulating the repair of damage caused by MS.

The team of Catherine Lubetzki and Bruno Stankoff are also interested in the early mechanisms underlying the formation of Nodes of Ranvier, regions of the axon which are not myelinated and transmit the nervous influx. They have demonstrated that structures resembling Nodes of Ranvier, called pre-nodes, appear before myelination starts. These pre-nodes are important because they are not destroyed by the immune system in MS, and can thus play a major role in remyelination.

The mechanism of multiple sclerosis

The mechanism of destruction

The neurons of the brain and spinal cord send information to the rest of the body. Depending on the neurons affected by MS, the symptoms will be motor or sensory.

The disease destroys the myelin sheath

Myelin assures the rapid transmission of the nervous influx. Its destruction, in MS, interrupts transmission. If motor neurons are affected, the information cannot reach the muscle, causing motor disorders (gestures, gait, etc.).

The recruitment of reparative cells

The team of Catherine Lubetzki and Bruno Stankoff studies the cellular and molecular mechanisms of de/remyelination, notably those that control the migration and recruitment of the cells that produce myelin. These researchers have just shown that these cells are activated during demyelination, become more motile and express factors that increase their mobilization. In collaboration with other researchers of the ICM, this team demonstrated the role of a molecule [netrin] that prevents the recruitment of these reparative cells. Blocking this molecule accelerates myelination. This discovery is extremely important because accelerated recruitment of myelin-producing cells permits repair of the axon during a period in which the lesions are still reversible. The team of Brahim Nait Omesmar and Anne Baron-Van Evercooren have discovered the beneficial role of several molecules in myelin repair. Their latest advance was the identification of a “pro-myelinating” molecule, called Olig2. This discovery could play a major role in the development of treatments aimed at stimulating the repair of damage caused by MS.

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A closer look at the mechanisms of de/remyelination

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FOCUS

ALEXIS GENIN, Director of Research Applications

“The ambition of the ICM is not only to perform excellent research, but especially to use it as a basis for the development of new treatments, applying the knowledge obtained by research and the competencies of the researchers. The iPEPS-ICM incubator establishes a bridge that aims at valorising all work done in the ICM, help Institute researchers to create their “start-up” and rapidly develop medical applications. The adventure of Frédéric Sedel and MedDay is a fine example, and we are proud to have accompanied this start-up in the development of the new treatment. Examples of such a rapid success are extremely rare!”

3/ TREAT

After a surprising clinical observation, the founder of MedDay, Frédéric Sedel, followed-up on his idea and registered a patent. Once patented, his idea gave rise to the creation of a company to realize his project. The company, MedDay is incubated at the ICM.

In less than two years, this scientific adventure resulted in the development of a treatment for progressive multiple sclerosis, an achievement that many important pharmaceutical companies take more than 15 years to realize.

MedDay is today a private biotechnology company, incubated in the Brain and Spine Institute, which develops new treatments for nervous system disorders. The adventure of Frédéric Sedel and MedDay is a fine example, and we are proud to have accompanied this start-up in the development of the new treatment. Examples of such a rapid success are extremely rare!

ALZHEIMER DISEASE

A GENETIC FACTOR IDENTIFIED

About 860,000 persons have Alzheimer type dementia in France and 35 million worldwide. Alzheimer disease is thus, today, at the centre of our preoccupations. Alzheimer disease is characterized by the slow degeneration of neurons that begins in a specific region of the brain (the hippocampus) then extends to the rest of the brain.

Understanding the genetic bases of the disease is fundamental, on the one hand to make the diagnosis and on the other to understand the mechanisms responsible for neuronal death. In a study involving 2,600 Islanders, Harald Hampel (Pierre and Marie Curie University/IM2A/ICM) and his colleagues discovered a correlation between the presence of a mutation (modification of information) in the gene ABCA7 and the development of Alzheimer disease.

If the role played by the ABCA7 protein in Alzheimer disease is still unknown, these studies open the way for new methods of diagnosing Alzheimer disease as well as other neurodegenerative disorders.

AUTISM

WHAT IF IMITATION HAS A THERAPEUTIC EFFECT?

If they are imitated, the social behaviour of autistic patients improves via effects on strategic regions of the brain. This is suggested by a recent study conducted by ICM researchers using functional magnetic resonance imagery (fMRI). Autism affects 430,000 persons in France, 25% of which are children. This pathology is characterized by difficulties of communication with others and developing social relations. Several studies have shown that the administration of oxytocin to autistic patients in the form of a nasal spray improves their social interactions and cooperation with others. Recent studies by the teams of Jacqueline Nadel and Philippe Fossati, published in Brain show that the imitation of autistic patients has an action similar to that of oxytocin.

The study involved six autistic men and consisted, for the researchers, of imitating, or not, a movement of the hand made by the patients whose brain activity was measured by fMRI. The researchers observed an activation of the right side of the insula in autistic patients when they were imitated and a reduction in the activity of regions of the brain that are exaggeratedly active in the autistic subjects.

The region of the insula, also activated by oxytocin, plays a central role in social behaviour and the development of emotions. By suggesting that the imitation of autistic patients has a therapeutic effect via the modulation of specific brain regions, these results open new perspectives for the treatment of autism.

See the complete interview with Frédéric Seidel at http://icm-institute.org/fr/actualite/sclerose-en-plaques-progressive-un-succes-pour-medday/
THE ESSENTIALS OF THE ANNUAL ACCOUNTS OF THE ICM FOR 2014

Understand and treat the diseases and traumatisms of the nervous system are a major challenge worldwide for the 21st century. Today, medicine relieves... Tomorrow, it must prevent, cure and repair. These disorders affect about a billion persons throughout the world,* a number that will continue to increase as the population ages. In France, life expectancy has increased by 15 years during the last 50 years: 1 girl out of 2 who are born today will become a centenarian. In 2050, 1 French person out of 3 will be 60 or more (1 in 5 in 2005). Each year in the world, 50 million persons* are injured or become invalids following a cranial or spinal trauma. These numbers will increase considerably between now and 2020, particularly in developing countries.

FACED WITH THIS CHALLENGE, THE MISSIONS OF THE ICM ARE TO:
• Prevent, i.e. to prevent the disease from developing;
• Cure, i.e. to slow, even stop, the evolution of the pathological process;
• Repair, i.e. to reconstruct the neuronal circuits affected in the nervous system;
• Relieve, to attenuate or suppress symptoms such as memory loss, language disorders, pain, anxiety, depression...

THE AIM IS TO PRODUCE INTERNATIONAL LEVEL RESEARCH BY COMBINING SCIENTIFIC CREATIVITY WITH A THERAPEUTIC GOAL.

THE SCIENTIFIC PROGRAM IS FOUNDED ON THE FOLLOWING PRINCIPLES:
• Create a research “strike force”, which means recruiting the best French researchers classed by AERES (agency for the evaluation of research and higher education) and the best foreign researchers evaluated by the Institute’s International Scientific Advisory Board;
• Offer researchers the most advanced technological platforms and a very efficient Biological Resource Centre;
• Develop multidisciplinary “translational” research in association with industrial partners and the best French and international research centres;
• Define privileged research axes.

THE ICM: A NEW MODEL
For its investments and functioning, the ICM, a “Foundation of recognized public utility” since 2006, is accompanied by its institutional partners: Ile-de-France, Mairie de Paris, Caisse des Dépôts, Assistance Public-Hôpitaux de Paris, CNRS, Université Pierre et Marie Curie.

The generosity of its donors and partnerships with sponsoring enterprises provide support, notably to permit:
• Financing, on its own resources, of the teams or researchers recruited worldwide on criteria of excellence;
• The realization of innovative research programs;
• Investments in advanced equipment.

FINANCIAL REPORT

1-RESOURCES
Resources for 2014 reached 26.2 M€. They include 24 M€ for the fiscal year and 2.2 M€ of affected resources carried over from previous fiscal years.

The products of the fiscal year correspond essentially to funds collected (46%) either from the public at large (34%) or from businesses or private foundations (12%).

They also include:
• Revenues from the activities of the technological platforms (2.2 M€) and research collaborations with industrial partners (2.6 M€);
• Subsidies from public (3.3 M€) and private (1.8 M€) sources.

2-USES
Total of uses in 2014 reached 27.2 M€: 24.1 M€ used in 2014 and 3.1 M€ of already affected resources. Among uses in 2014, the amount dedicated to social missions was 19 M€, which represents 78.5% of total uses for the fiscal year. The social missions of the ICM include:

• The research projects (58%);
• The technological platforms (30%);
• Other scientific activities and the development of international alliances (9%);
• Incubation of innovative enterprises (3%).

The research projects financed mainly concern neurodegenerative diseases and traumatisms of the spinal cord. The technological platforms (neuroimaging, vectorology, sequencing/genotyping, cell culture and histology) added support for these projects. The costs of fundraising correspond to the expenses engaged to collect funds from private individuals (donations and bequests) and business and private foundations (sponsoring or patronage). They represent 14% of uses.

The costs of functioning correspond to the expenses of support teams (finance, human resources, informatics and logistics), which represent 7.5% of total uses for the fiscal year. Engaged affected resources (3.1 M€) correspond mainly to donations by enterprises and foundations received during the year that will be used for specific pluriannual research programs.

3-USES OF RESOURCES COLLECTED FROM THE PUBLIC
Resources collected from the public at large, used in 2014, reached 9.6 M€.

In brief, out of 100€ of resources collected from the general public, 71€ were used to finance the social missions and investments of the Institute, 27€ were used for fundraising and 2€ covered the costs of functioning of the ICM.

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

The brain and spine institute donors journal
THE ESSENTIALS, 2014

SIMPLIFIED BALANCE SHEET

<table>
<thead>
<tr>
<th>ASSETS (IN K€)</th>
<th>31.12.14</th>
<th>31.12.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>42,846</td>
<td>39,600</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LIABILITIES (IN K€)</th>
<th>31.12.14</th>
<th>31.12.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association funds</td>
<td>20,418</td>
<td>23,720</td>
</tr>
<tr>
<td>Results of the fiscal year</td>
<td>-992</td>
<td>-3,112</td>
</tr>
<tr>
<td>Dedicated funds</td>
<td>4,694</td>
<td>3,884</td>
</tr>
<tr>
<td>Debis</td>
<td>18,726</td>
<td>15,108</td>
</tr>
</tbody>
</table>

Commentaries

The total amount of investments by the ICM since its creation has reached nearly 21 M€, mainly dedicated to the technological platforms that support research.

- The ICM acquired a cryoprobe for imaging, completed its equipment for the functional experimentation platform and finished the installation of its business incubator. The net immobilized assets reached 10.1 M€. As of December 31, 2014, the treasury amounted to 18.4 M€.
- The equity of the ICM was 19.4 M€. It included 11.7 M€ of association funds plus 2.6 M€ of subsidies for investments and a carryover of 5.1 M€. The non-expendable endowment of the ICM is 1.2 M€.
- At the end of the fiscal year, dedicated funds (funds remaining to be used for specified programs) reached 4.7 M€.

Particularly attached to the maintenance of excellence, the ICM has set up internal and external control procedures in order to guarantee the rigor and efficacy of its management: adhesion to the Comité de charte du don en confiance (Committee of the charter for donating with confidence) and an independent auditor.

EXCERPT FROM THE 2014 REPORT OF THE CONTROLLER OF THE COMITÉ DE LA CHARTE POUR LE DON EN CONFIANCE

“The last three year period saw the rapid and courageous launching of the social missions of the Foundation, which installed high level teams and their equipment in a superb building. The foundation offered its researchers facilities to which they did not previously have access and reinforced, in different ways, perspectives for the internationalization of their work. The new period that is starting is characterized by the will to set up a stable organisation, based on a rational and concerted public/private partnership endowed with balanced financial bases, while maintaining the same ambitions for high level performance in the sphere of national and international scientific research.”

I am making a contribution of: ………………………….

□ By postal or bank check, to the order of the ICM
□ By credit card (except American Express)

N° of your credit card: ……………………………………….

Last 3 numbers on the back of the card: ……………………….

Expiration date: …/…/….

Date: …/…/….

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

You can make a donation online at: www.icm-institute.org

“Today, Madame A. is learning to play the X-Torp game.

“I succeeded in playing the game, and that made me happy. It’s easier to play than to do tests on paper with the doctor, when I was always afraid to make mistakes. I do exercises at home with cross-word puzzles, and I watch amusing television programs during which questions are asked that stimulate my memory, but I like the games better. With the caregiver who accompanies me, they provide a very good occasion for me to work on my memory.

I forget a lot of things in the course of a day and thanks to these games, I pay more attention to my memory and concentration.”

Developed by the GENIOUS Group in partnership with the CoBtek team of Nice Sophia Antipolis University and the association «Innovation Alzheimer» directed by Pr. Philippe Robert, X-TORP is a therapeutic game conceived in the context of the project Az@GAME, which aims to motivate patients to have cognitive and motor activities. X-TORP is an innovative therapeutic video game that:

- Measures the evolution of Alzheimer disease;
- Stimulates cognitive capacities;
- Fosters the patient’s physical activity;
- Maintains social relations.

The ICM and the GENIOUS Group have developed a joint laboratory, BRAIN e-NOVATION, incubated in the business incubator IPEPS-ICM. This laboratory aims to create health-related innovations for use by therapists and patients.

All the informations in this document comes from the Annual Report and the Report on the Moral and Financial Situation of the Year 2014. The Annual Report is available on the internet site of the Foundation (icm-institute.org) or by written request.
ALL YOU NEED TO KNOW ABOUT BEQUESTS

As a Foundation of recognized public utility, the ICM is authorized to receive bequests, donations and life-insurance policies totally exempted from inheritance or mutation taxes. All that you transmit to the ICM benefits research directly. A bequest lets you transmit part or all of your possessions. To be taken into account, your desire to make a bequest must be formally inscribed in a will, which can be modified at any time.

What possessions can I transmit to the ICM?
You can transmit all kinds of possessions: movable property (such as a sum of money or a portfolio of actions), real estate (a house, a commercial property, land,...), or even copyrights, jewellery, works of art...

Is there a minimal sum that I can bequeath to the ICM?
There is no minimal amount that can be bequeathed to the ICM. All property transmitted, whatever the amount, will permit us to advance research and develop new treatments.

We are at your entire disposal to listen to you and answer your questions, in complete confidentiality.

Don’t hesitate to contact our bequest and donations service at 01 57 27 44 87 or by email: contact@icm-institute.org.

THE DONATION DEPARTMENT
AT YOUR SERVICE
Maylis de Gironde
01 57 27 40 22
contact@icm-institute.org

MY RECURRENT DONATION
Please fill out and return this form with your contribution and your bank identification details to ICM – Hôpital Pitié-Salpêtrière 47 – 83 boulevard de l’Hôpital 75013 Paris

☐ Yes, I will provide long term support for the researchers of the ICM with a contribution:

☐ 10 € ☐ 20 € ☐ 30 € ☐ 40 € ☐ Other amount: €

☐ Every month ☐ Quarterly

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

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

IMPORTANT
Don’t forget to include your bank details (BIC-IBAN)

SEPA AUTHORIZATION OF WITHDRAWAL

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

Beneficiary: INSTITUT DU CERVEAU ET DE LA MOELLE EPINIERE

IBAN: FR25 ZZZ 335582

I authorize my bank to withdraw the sum indicated at the specified frequency. These withdrawals will be made on the 5th of each month or trimester following the date of the authorization.

MY COORDINATES

Family name: __________________________________________ First name: ___________________________

Address: ________________________________________________________________

Post office code: __________________ City: __________________________

THE COORDINATES OF MY ACCOUNT (BIC-IBAN)

International identification number of the account - IBAN

International code of your bank - BIC

Date:(2) __ __ / __ __ / 2015

Place:(3) __________________________ Signature:(3)

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

(2) Obligatory

(3) Unique authorization reference