SPECIAL ISSUE
ON NEURODEGENERATIVE DISEASES: THE IMMUNE SYSTEM TO THE RESCUE

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**REPAIRING THE BRAIN**

The nervous system diseases affect about one third of European population, i.e. 179 million people. This represents one third of Europe’s health budget. The consequences for the patients and their families are significant.

Understand and treat nervous system diseases and injuries constitute for the Brain & Spine Institute (ICM) a major issue worldwide.

Today medicine relieves. And tomorrow? Tomorrow’s medicine is said to be that of “4p”: “Predict” the disease, so to cure it before it starts; “prevent”, to identify patients at risk and stop the disease course before it appears; “personalise” medicine, so that each patient gets individualised care; make patients “participate”, because progress involves share and co-construction.

I am pleased to introduce this new edition of the Donors newsletter, devoted to the work carried out within the ICM in neuro-immunology. This discipline aims to identify the mechanisms that shall help the brain to defend and repair itself. Thank you for your support and your commitment with us.

You are our reason for working, so that, together, we can overcome brain and spine diseases.

Prof. Yves Agid
Founding member of the ICM

**THE PRESIDENT OF THE REPUBLIC AT THE ICM**

The President François Hollande went to the ICM on the 6th April 2016 to meet the Institute’s researchers and founders. He attended several presentations, of the ICM by its leaders, and of their work by three researcher-clinicians: Claire Wyatt, Prof. Lionel Naccache and Dr. Carine Karachi. He also visited the Magnetoencephalography platform (MEG) with Nathalie George (ICM researcher). His visit was part of the day dedicated to University Hospital and research Institutes (IHU), taking place at the ICM. Six IHU were created in 2012 thanks to the Future Investment Program (PIA). These associate world-renowned medical and scientific teams around a project combining research, care, training and application, in a dedicated therapeutic field. Among these six institutes, the IHU-A-ICM aims to carry out a project of excellence in the field of research on nervous system diseases. The International Day of IHU, with François Hollande, Marisol Touraine, Minister of Social Affairs, Health and Women Rights, and Thierry Mandon, Secretary of State for Higher Education and Research, was an opportunity for each Institute to present projects and consider future perspectives.

**MENTAL DISORDER**

The Cité of Science and Industry opened the exhibition “Mental Disorder” on the 4th April, in partnership with the ICM, Philippe et Maria Halphen Foundation and Meeting For Minds. The exhibition “Mental Disorder” wants to provide knowledge about mental health, raise public awareness of mental disorders and dispel prejudices. This was adapted in France by several researchers: Luc Mallet (ICM), Xavier Briffault (CERMES3) and Margot Morgiève (ICM and CERMES3).

**PARTNERS:**

FERBLANC FUNDRAISING RIDES FOR THE ICM

Henry Racker, British Association Ferblanc Fundraising’s chairman, aims to perform the Tour de France by 2021 for the benefit of the Brain and Spine Institute-ICM. Committed alongside researchers for years to fight against brain and spine diseases, 18 cyclists have ridden from Béziers to Nice, for their 5th step, cycling 500 km in only 4 days.

Beyond the athletic feat, the strong mobilization of Ferblanc Fundraising, cyclists, partners and sponsors, have raised, this year again, significant funds for research on nervous system diseases.

Their next challenge? Ride from Nice to Geneva in September 2017! Many thanks to Henry Raker and Ferblanc Fundraising for this continued support.

If you also want to organise an event for the benefit of the ICM please contact Agathe Giot-Viot: agathe.giot@icm-institute.org

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**EVENTS**

- **8th June 2016**
  - ICM Gala evening

- **12th June 2016**
  - The "teufs teufs du Coeur en goguette", car event, les Essarts le Roi (78)

- **19th June 2016**
  - The Marathon of Vassivière (87)

- **26th June 2016**
  - The Marathon of Vassivière (87)

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**NEWS**

icm-institute.org/fr/videos

- Conference of Christophe André on meditation
- Bassem Hassan exceptional researcher
- Visit of Francois Hollande
- icm-institute.org/fr/actualités
- BRAIN’Us: Your kids play, science progresses
- World Autism Awareness Day
- World Day of MS
Through a collaborative approach gathering researchers, clinicians and mathematicians, the ICM neuro-immunology group aims to understand the role of the immune system in the development of several neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). This knowledge will ultimately provide new therapeutic approaches against these diseases.

**THE NEURO-IMMUNOLOGY GROUP: A CROSS-DISCIPLINARY APPROACH**

**IMMUNE SYSTEM AND NEURODEGENERATIVE DISEASES**

In the central nervous system, the immune system’s cells, more specifically the macrophages (those called microglial cells in the brain) organise the most appropriate response to get rid of pathogens (such as protein accumulation in the brain of patients suffering from Alzheimer or Parkinson) and protect neurons. But sometimes, excessive inflammatory reaction can be harmful and have destructive effects on neurons. Thus the brain’s immune response can either help fighting against the disease or accelerate neurons degeneration.

**OBJECTIVES**

Objectives are twofold. On the one hand, understand why, in which cases and through what mechanisms the immune response is rather destructive or protective, in order to try and modulate it. On the other hand, “model” the role of the immune system in the course of each disease, in order to develop personalized medicine.

**THE BET**

Study these four diseases in parallel and ease the transfer of knowledge from one to another. Understand how the protective immune response starts would help shifting it when it becomes destructive.

**MODELLING**

Collaborating with Olivier Colliot and Stanley Durrleman, researchers will create digital models of the evolution of immune response in the disease course. This modelling will provide a better understanding of the effects of certain biological mechanisms, it will also help identify blocked signalling pathways and ways to get round them by simulating the ‘pathological environment’ of each disease.

**PERSPECTIVES**

- Highlight markers, i.e. measurable biological characteristics, of the different diseases’ course
- Identify new therapeutic targets to develop treatments and modulate inflammatory response
- Evaluate the effectiveness of treatments and potential side effects, in order to select quickly and efficiently the molecules to be tested in clinical trials
- Reinvent existing molecules, i.e. identify new therapeutic uses associated with molecules already available or under advanced development
- Implement therapeutic strategies by boosting immune system protective ability

**INSUFFICIENT ACTIVATION**

**TOO MUCH ACTIVATION**

**RESEARCH**

**REPORT**

**THE CREDO**

Understand one disease will open new paths to cure the others.
**FOCUS ON RESEARCHERS’ PROJECTS**

**AMYOTROPHIC LATERAL SCLEROSIS (ALS)**

Séverine Boillée and Christian Lobsiger

ALS affects around 8,000 patients in France. This neurodegenerative disease breaks out at adulthood (40–80 years) and will evolve, in 3 to 5 years, towards complete paralysis. It is caused by the death of motoneurons, specific neurons that carry information from the brain to muscles. Due to the destruction of these motoneurons, muscles will gradually weaken and atrophy.

The team of Séverine Boillée showed that microglial cells, which carry a mutation causing ALS, release toxic factors on motoneurons. By preventing the “sick” gene to express, researchers can slow down the progression of ALS within an experimental model. Researchers are now trying to obtain microglial cells and macrophages from patients’ pluripotent stem cells (IPS technology, see box below) to check whether these affect motoneurons degeneration and identify factors involved in the disease course.

**MULTIPLE SCLEROSIS (MS)**

Violetta Zujovic

In France MS affects about 1 in 1,000 people, a total of about 70,000 people. And every year, there are 2,000 to 3,000 additional people affected by this disease. This disease affects the central nervous system: the immune system, which usually fights against viruses and bacteria, attacks the individual’s own elements. The MS inflammatory reaction destroys the protective myelin sheath that wraps the neurons’ extensions, called axons.

In multiple sclerosis, microglial cells are involved in the destruction of myelin; however these are also able to create an environment conducive to recruiting new cells to repair myelin. For this reason, Violetta Zujovic in collaboration with the team of Professor Bertrand Fontaine, combines genetics, immunology and neurobiology to establish how the immune process can promote remyelination. This innovative and multidisciplinary approach aims to identify new treatments to modulate inflammation and support the nervous system’s autonomous repairing.

**ALZHEIMER**

Cécile Delarasse

With nearly 860,000 people with Alzheimer-type dementia in France and 35 million patients worldwide, Alzheimer’s disease is now a major issue. Alzheimer is characterized by a slow degeneration of neurons, starting from one region of the brain (hippocampus), it then extends to the rest of the brain. This degeneration is the result of simultaneous increase of two types of lesions: firstly abnormal accumulation of β-amyloid peptide protein outside the nerve cells, which leads to the formation of “senile plaques”; secondly abnormal accumulation of tau protein in neurons leading to their degeneration. The progressive accumulation of these lesions results in the disease’s symptoms.

In Alzheimer, microglial cells destroy senile plaques. When the immune system is stuck, accumulations are formed, causing the death of neurons. Cécile Delarasse showed (in experimental models) a potential direct link between an immune system malfunction, independent of aging, and the formation of amyloid lesions. This is the assumption she wants to check through collaborating with Dr. Stephen Epelbaum: a clinical research protocol will measure and compare immune system responses in healthy subjects and patients with Alzheimer.

**PARKINSON**

Stéphane Hunot

Parkinson’s disease is the most common neurodegenerative disease after Alzheimer. It affects 150,000 people in France and 8,000 new cases each year. Very rare before 50 years old, occurrences increase after 60. This is a chronic neurodegenerative disorder, with a slow course, characterized by the death of a population of neurons called dopaminergic. These neurons produce a substance called dopamine, involved in the transmission of information between neurons and essential to smooth movement control.

Stéphane Hunot studies the involvement of another immune system key element in Parkinson’s disease: CD4 T lymphocytes. He showed that these lymphocytes (a type of white blood cell) infiltrate the brain and could be responsible for the death of neurons. While these have a protective role in the ALS, they are rather proinflammatory in Parkinson. Controlling this inflammation in the brain would help slow the disease course.

He also looks into the role of chronic stress in the evolution of the disease and its impact on the immune response. Working with Jean-Christophe Corvol from the Clinical Investigation Centre (CIC), he wants to study the immune response of PD patients according to their level of depression or anxiety. The objective is to identify blood markers for the disease progression in order to better tailor treatment.

**What if researchers could help the brain repair itself?**
Neurallys company develops medical devices for neurology and neurosurgery, especially to improve diagnosis and monitoring of patients with intracranial hypertension.

There are a lot of pathologies causing intracranial hypertension. Among the most famous, head injuries (120,000 per year in France), brain tumours (2nd leading cause of cancer in children), bruises, disruption of cerebrospinal fluid regulation (hydrocephalus). Trauma is estimated at 180,000 in France, 1.5 million in USA. More specifically, hydrocephalus affects 3 children per 1,000 live births.

The proposed treatment is neurosurgical: this consists in posing an internal ventriculo-peritoneal shunt (DVP) between ventricular system and peritoneum (or, more rarely, the heart) to drain an excess of cerebrospinal fluid in which bathes the brain. An operation is carried out every 15 minutes.

Considering the percentage of hydrocephalus in adults and the number of valves required for re-interventions (i.e. replacement or addition of an existing valve), the number of new paediatric patients treated each year is between 600 and 800; and 1,000 new cases occur each year in France. These figures should also include patients (of adults) who develop hydrocephalus during their life caused by tumour, head trauma, meningitis…

In these multiple configurations, medical professionals must know patients’ intracranial pressure in order to make the best clinical decision; at birth or later every day, to ensure that the proposed surgical solutions are suitable. This indicator is essential, but the devices currently available are invasive, expensive, require mandatory hospitalisation, some surgical risky move, a significant cost to society, and the data often lack accuracy (calibration problem and sensor drift after some time). It thus seems impossible right now to measure patients’ intracranial pressure for regular or preventive monitoring of chronic diseases or for patients at risk. The available offer varies between approximate and invasive one-shot methods.

Alone side ICM researchers and the team of Professor Cornu, Head of Pitié-Salpêtrie neurosurgery department, Neurallys company wished to invest in developing a major innovation to measure, monitor and better treat millions of patients, as well as provide medical professionals with appropriate tools to facilitate personalized and contemporary neuro-medicine.

The diagnostic criteria for Alzheimer’s disease evolve. Professor Bruno Dubois and Professor Harald Hampel, researchers at Pierre et Marie Curie University (UPMC), Brain and Spine Institute (ICM), and Institute of Memory and Alzheimer’s Disease (IM2A), launch a international programme to challenge the conceptions of this disease. Physiological processes leading to the disease start years or even decades before the first symptoms appear, which are, once installed, are irreversible. Therefore, to be fully effective, therapeutic interventions should be set up as soon as possible, before damage is permanent. It has thus become essential and urgent to clearly define the preclinical stage of Alzheimer. Research is progressing; it is now realistic to diagnose Alzheimer at preclinical stage through a multimodal approach, by combining imaging and biochemical methods. Researchers’ priority is now to identify and validate biomarkers of this asymptomatic phase, such as morphological and metabolic changes in the brain or the presence of particular proteins in the cerebrospinal fluid. This research axis appears today as a way toward therapeutic success.

Even though the importance of Alzheimer’s “silent” stage for preventive approaches was proven, we still know very little about it. It remains crucial to explore this stage’s natural history, including physiological disturbances and structural changes that it involves in the brain. It is also necessary to understand the factors leading to symptomatic disease. Besides, we cannot avoid thinking ahead ethical issues involved in early detection of Alzheimer’s disease. The article published when the programme was launched provides an updated review of scientific literature for each of these aspects, but also suggests practical recommendations for future research activities.

In the field, this conceptual upheaval around Alzheimer takes the form of an ambitious and innovative translational research project, the INSIGHT study, led by Professor Bruno Dubois and Professor Harald Hampel. Launched at the Institute of Memory and Alzheimer’s Disease (IM2A), INSIGHT’s main objective is to understand why and how Alzheimer’s disease occurs in some people and not others. To do so, researchers need to identify biomarkers of progression toward the symptomatic phase over time in an asymptomatic population of subjects at risk. A multimodal approach helps checking whether combined biomarkers provide greater predictive power. First results are expected this year.
AN EFFECTIVE DRUG AGAINST MYOCLONIC DYSTONIA, A RARE DISEASE OF THE NERVOUS SYSTEM

A team coordinated by Prof. Emmanuel Flamand-Roze of the Pitié-Salpêtrière hospital, AP-HP, and researcher at Brain and Spine Institute, has tested at the ICM Clinical Investigation Centre the effectiveness of zonisamide. This drug, currently used to treat some forms of epilepsy, was tested in 23 patients with a rare disease of the nervous system, myoclonic dystonia. The promising results of this study, funded by the AP-HP, were published in the journal Neurology (6th April 2016).

The myoclonic dystonia is a rare disease reflecting poor movement control in the brain, resulting in abnormal contractions of muscles. This entails two types of symptoms: muscle twitching (myoclonus), and abnormal posture of some parts of the body (dystonia). Unpredictable muscle twitching in each movement is the most disabling symptom. They usually prevail in the upper limbs and neck. Motor difficulties due to this disease can be very uncomfortable in everyday life. Often these obvious disorders entail stigmatisation, loss of self-esteem and social withdrawal of patients. Currently there is no effective drug against this disease. However there is a neurosurgical treatment with good results, but it is invasive and reserved for the severe forms of this disease.

The scientific team, including doctors and researchers, has carried out a double-blind placebo-controlled randomised study in order to test the efficiency of zonisamide in 23 patients with myoclonic dystonia. Zonisamide has been used in Europe for a decade to treat some forms of epilepsy. It is well tolerated in most patients who use it in this context.

The results of this study show that zonisamide reduces very significantly myoclonus and related disability. Patients’ dystonia is also improved by this treatment.

The results of this study entail stigmatisation, loss of self-esteem and social withdrawal of patients. Currently there is no effective drug against this disease. However there is a neurosurgical treatment with good results, but it is invasive and reserved for the severe forms of this disease.

I support the ICM research projects because for me brain and spine diseases are the 21st century’s major challenge. Unfortunately my work does not leave me the time to volunteer, so I looked for a way to get involved differently and help researchers. Passionate about running, I found on the ICM website that we can, through Alvarum platform, participate in sport competitions or races and mobilise people around us to make these moments opportunities for generosity. I am about to run 20 km in Paris for the ICM next October; and I intend to beat my last year raising record. I have more fun running now, trying to go faster than brain and spine diseases!

Laurent, 34 years old.

"Run faster than brain and spine diseases.”

AN EFFECTIVE DRUG AGAINST MYOCLONIC DYSTONIA, A RARE DISEASE OF THE NERVOUS SYSTEM
THE DONOR SERVICE
AT YOUR SERVICE
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