12 MAJOR SCIENTIFIC ADVANCES

2010 – 2015

INSTITUT DU CERVEAU ET DE LA MOELLE ÉPINIÈRE – ICM

BRAIN & SPINE INSTITUTE, PARIS

SEARCH, FIND, CURE. FOR YOU & WITH YOU.

5 YEARS ICM Brain & Spine Institute

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LETTER FROM THE PRESIDENT

— When we decided to create an institute dedicated to treatment of the diseases of the brain and spinal cord nearly 12 years ago, the project seemed both ambitious and revolutionary to us. With the founding members, we decided to create this institute with 5 goals that we have kept in mind since then:

Scientific excellence:
The best researchers are involved.
The objective is to find.
"At the service of patients":
Bring together the sick, the doctors, and the researchers in one place to develop a virtuous cycle of scientific excellence starting and ending with the patient.
Flexibility:
To allow scientific creativity to blossom.
Openness:
Create a place for exchange, promote dialogue between civil society and industrial partners.
Transmission of knowledge:
At the national and international scales

I am proud to introduce this document that brings together the major research advances since the inauguration of the ICM, 5 years ago, September 24, 2010. This crucial period of the first five years has had some conceptual and financial difficulties, but we have completed this first step with success, a priceless foundation for the future and for the millions of diseased who count on us. You will find in this document that the objectives that we set were met, and that the major scientific discoveries significantly advanced three large domains:

– understanding of the brain and its functioning;
– diagnosis and prediction of neurological, particularly neurodegenerative, diseases;
– therapeutic solutions.

In parallel, researchers develop translational research, which constitutes a direct bridge between fundamental research and clinical research by stimulating the latter with therapeutic and methodological innovations and investigation tools originating from fundamental research. Reciprocally, clinical research provides new observations of the nature and progression of diseases for fundamental research.

Thanks to considerable technical and financial means established since 2010, 650 researchers, engineers, and technicians bring this institute to life, directed towards the future and towards new solutions for the diseases of the brain and spinal cord.

This formidable scientific and human adventure was made possible thanks to mobilization of many: public fund, private companies, individuals. Everyone without exception is included because this battle concerns all of us.

Before letting you discover in more detail the different steps that we made to advance the field of neuroscience, I would to thank everyone who brings to our sides the hope, in turn ambition, to prevent, cure, and one day repair the diseases of the brain and spinal cord.

Professor Gérard Saillant
President of the ICM

1

UNDERSTAND THE BRAIN

How does the brain learn to read? What are the different factors that determine our choices? How does the brain make new neurons? How can the body initiate movement without control from the brain? Researchers at the ICM have responded to these fundamental questions.

Perceive, act, think, reflect, memorize, decide, speak, smell, feel, read, write, learn, walk, dream. None of these are possible without the brain. The brain controls our social behavior and our movement. Thanks to the brain, we are conscious of the world that surrounds us and others.

In order to understand the mechanisms that underly mental functioning, whether motor, intellectual, or emotional, ICM researchers study how information is treated by neurons thanks to numerous tools, clinical analyses, or electrophysiological exams using brain imaging. Understanding the normal brain is critical in order to better treat its altered functioning in a sick patient.

ICM RESEARCHERS AND CLINICIANS WORK IN CLOSE COLLABORATION IN ORDER TO:

IDENTIFY
the mechanisms at the origin of our behaviors and the regions involved in language, writing, visual attention...

UNDERSTAND
the development of the nervous system,
its functioning,
its plasticity,
and most of all,
consciousness
creativity
the basis of motivation
the reasons for our choices
our social interactions
locomotor circuitry
the relationships between different regions of the brain

THE MAJOR ADVANCES OF THE ICM

MOTIVATION

DECRYPT THE MECHANISMS

FROM CHOICE OF A RESTAURANT TO THAT OF A PARTNER, THE MOTIVES FOR OUR BEHAVIORS SOMETIMES ESCAPE US. WHY DO WE DO WHAT WE DO? WHAT ARE THE FACTORS THAT ACT WHEN WE MAKE A CHOICE? AND WHAT REGIONS OF THE BRAIN ARE INVOLVED?

Explain the reasons for our choices and map the different regions of the brain involved in motivation, these are the objectives of the team of Mathias Pessiglione, Jean Daunizeau, and Sébastien Bouret.

Why do we resist temptation of an immediate pleasure (a piece of cake in the moment) to wait for long-term goals (lose 2 kilos)? Thanks to the hippocampus, these researchers respond! By allowing us to imagine future situations (being on the beach), this seat of memory keeps us from succumbing to the attraction of immediate pleasures and thus motivates our actions in the long-term.

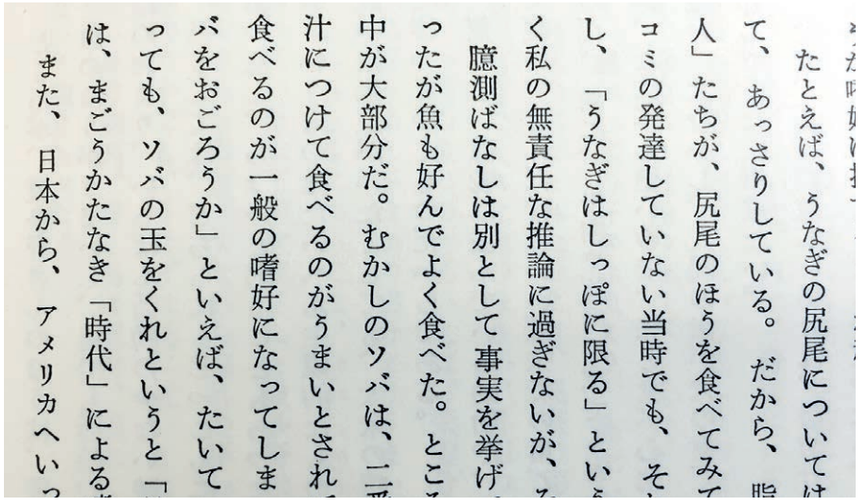
Why do we appreciate a person or a painting? Another small region of the brain, situated between the eyes, the medial prefrontal cortex, intervenes in our evaluations. It is responsible for attributing value: its activity increases when something pleases us. Our researchers recently showed that this activity is influenced by context. Its activity increases when ambient music is playing, which predisposes us to appreciate what we are in the middle of eating or the person who is facing us.

And that's not all! This region also integrates the degree of confidence that we have in our judgments. Thus, the more that we are sure of ourselves, the more we make clear cut judgments.

Motivation is not localized to one region of the brain. These researchers invented a mathematical model in order to describe the way the different regions of the brain coordinate in order to generate our behaviors. This method will allow us to understand how relevant information is treated and transformed across neuronal networks.

Decrypting the mechanisms of motivation allows better understanding of diseases in which they are altered, such as in depression, schizoprenia, and also Parkinson's and Alzheimer's diseases.

LEARNING



たとえば、うなぎの尻尾については
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バをおごろうか」といえば、たいて
っても、ソバの玉をくれというと「
は、まごうかたなき「時代」による
また、日本から、アメリカへいっ

HOW DOES THE BRAIN LEARN TO READ?

OUR BRAIN IS ADAPTED TO THE APPEARANCE OF WRITING AND READING THANKS TO A SMALL ZONE THAT IS SPECIALIZED IN RECOGNIZING LETTERS. BUT WHY THIS REGION?

At birth, there is nothing that distinguishes the brain of a baby born today from a baby born ten thousand years ago, well before the invention of writing. Therefore, our brain is not especially predisposed to learning how to read. Additionally, when a child today learns to read, this learning occurs thanks to the same brain regions, regardless of what language, alphabet, and culture in which he or she is raised.

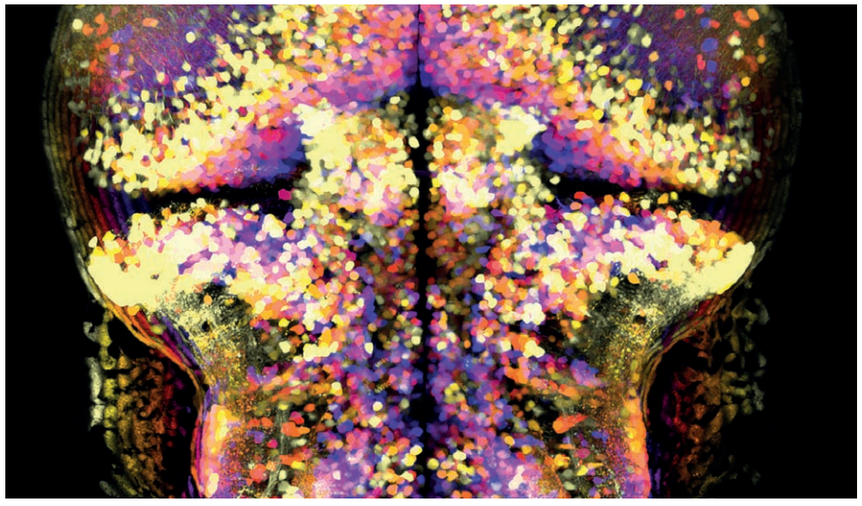
The same small region of the brain, within the visual cortex, allows us to identify the letters that we see. Why then, within the vast regions of the visual cortex that allow us to recognize our surroundings, is there a specific region that specializes in reading, while neighboring regions specialize in recognizing faces or places?

In order to respond to this question, researchers from the team of Laurent Cohen utilized diffusion magnetic resonance imaging. This technique allows following of white matter fibers that allow communication between different regions of the brain.

The zone involved in recognizing letters has particularly important connections with the language regions that are responsible for word comprehension and speech production. These connections provide access from vision to representations that are normally specific to spoken language. The face recognition region is connected to the system implicated in emotions and social relationships.

Learning to read leads to reorganization of the visual system and the emergence of a specialized zone for establishing new brain connections. This learning is possible at any age, which signifies that the circuits for reading can be established throughout life.

LOCOMOTION



LIGHT ON NEURONS

A TECHNIQUE THAT ALLOWS REMOTE CONTROL OF NEURONS ALLOWED IDENTIFICATION OF A CLASS OF NEURONS THAT INTEGRATES SENSORY CUES IN THE SPINAL CORD OF THE ZEBRAFISH.

330,000 people in Europe are affected by spinal cord injury. These injuries can lead to serious paralysis and currently do not respond to available treatment. The brain can no longer control voluntary movements in a paraplegic patient that has communication cut between the brain and the spinal cord.

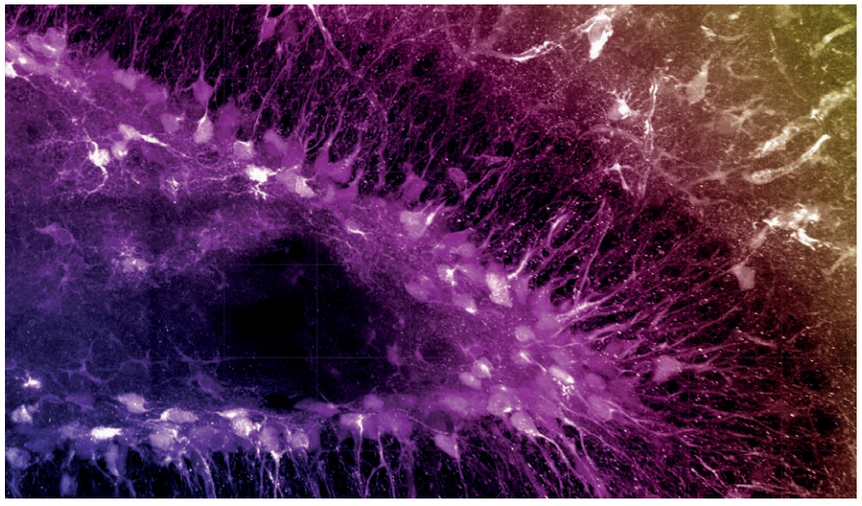
Reestablishing normal motor functioning in handicapped patients is thus a major target of neuroscience research. With this goal in mind, Claire Wyart's team studies the way in which networks of neurons in the spinal cord are recruited to set locomotor circuits in place. The locomotor network allows walking without thinking once the decision to move has taken place. This ability to continually generate movement without input from the brain is thanks to the ability of the spinal cord networks to generate oscillations.

In order to identify the necessary and sufficient classes of neurons to generate movement, researchers in Claire Wyart's team study zebrafish locomotion. This small transparent animal is particularly adapted to optogenetic techniques. This cutting edge technique allows activation of neurons at a distance using light. By both activating and inhibiting neurons, their role in controlling movement can be determined.

A new neuronal circuit involved in locomotion was identified using this technique. When stimulated, these mechanosensory neurons deep within the spinal cord can initiate movement in the zebrafish independently from the brain. These sensory neurons perceive muscle tension and transmit information directly to motor neurons responsible for muscle contraction.

This sensory system that had never before been described could be intact in patients that have experienced spinal cord injury. One hope to treat patients with spinal cord injury would be to activate this circuit in order to permit movement independently of control from the brain.

AGING



MAKING NEW NEURONS

IDENTIFICATION OF A GROWTH FACTOR CRITICAL FOR PRODUCTION OF NEW NEURONS REPRESENTS AN INCREDIBLE HOPE IN THE FIGHT AGAINST NEURODEGENERATIVE DISEASES.

Throughout an adult's life, new neurons are generated to maintain cognitive capabilities. However, age and certain brain pathologies can contribute to a decrease in birth of new neurons, which can contribute to serious cognitive decline, such as in Alzheimer's disease.

In humans, new neurons are produced in the hippocampus, a brain structure that plays a key role in memory. These new neurons are produced from specialized brain stem cells to produce neural stem cells. The majority of these neuronal stem cells are "dormant" and the factors that allow them to become "awake" in order to divide and transform themselves into neurons are poorly understood.

Boost the production of new neurons by awakening neuronal stem cells. This is the challenge that Jean-Léon Thomas and his collaborators are tackling. How? By stimulating with a vascular growth factor, the VEGF-C. Researchers showed that VEGF-C activates neuronal stem cells, stimulates their division and their transformation into neurons. VEGF-C acts by binding to its receptor that is expressed on the surface of cells, which is necessary to "awaken" and thus create new neurons.

Heightened anxiety was observed in mice that do not express the VEGF-C receptor at the surface of stem cells, suggesting that the vascular growth factors could also participate in control of emotional behavior. The regression of neuronal stem cell activity during aging could also be associated with the appearance of personality problems, such as anxiety and depression.

This work brings new hope in development of treatments: VEGF-C is a good candidate to activate the production of new neurons and compensate for the cognitive decline in patients with neurodegenerative pathologies, including Alzheimer's disease.

2

DIAGNOSE AND PREDICT

Six new risk factors identified for Parkinson's disease, an early and reliable diagnostic for Alzheimer's disease, a new gene implicated in epilepsies, a new revolutionary tool to determine the state of consciousness and to predict the evolution of patients in a vegetative state...Here are a few results from five years of intensive research led by the researchers and the clinicians of the ICM.

One person in eight will be affected by a nervous system disease over the course of their life. In order to better care for these patients, it is absolutely essential to detect diseases early or even to predict their onset.

850,000 patients suffer from Alzheimer's disease, more than more than 150,000 patients suffer from Parkinson's disease and more than 85,000 suffer from multiple sclerosis. The figures are alarming given the impact of these neurodegenerative diseases on the quality of life of patients and their families. A major challenge for clinicians is to identify risk factors, to diagnose these diseases as quickly as possible, and to distinguish between different diseases at early stages.

Of the 500,000 epileptic patients in France, only half receive adequate treatment, primarily because of the complexity to properly diagnose these patients. In certain cases, identifying genes responsible for epilepsies allows a better choice of treatment.

Finally, brain trauma can lead to difficult handicaps. When patients are incapable of communicating, having tools that can predict their state of consciousness is a major asset for both clinicians and patients.

ICM RESEARCHERS AND CLINICIANS WORK IN CLOSE COLLABORATION IN ORDER TO:

IDENTIFY
the genes responsible for diseases
risk factors
prognostic and diagnostic factors
biological markers to detect and follow the disease

DEVELOP
relevant diagnostic tools

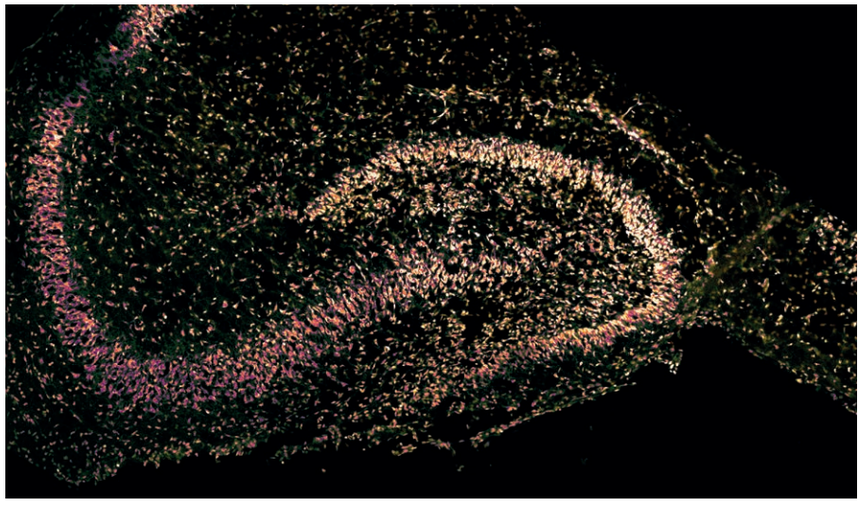
PREDICT
the evolution of pathologies

DIAGNOSE
to treat as early and as best as possible

DEVELOP
precise and personalized medicine

THE MAJOR ADVANCES OF THE ICM

ALZHEIMER'S DISEASE



A PRECISE AND EARLY DIAGNOSIS

MORE RELIABLE, QUICKER, MORE PRECISE AND SPECIFIC: THE DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE HAVE BEEN REDEFINED BY A NETWORK OF INTERNATIONAL EXPERTS.

With one-third of patients being incorrectly diagnosed for Alzheimer's, it was clear that the diagnostic criteria for Alzheimer's disease needed to be redefined. A team of international experts brought together by Bruno Dubois who have tacked the task to refine these criteria for ten years just developed a simplified and extremely reliable diagnosis for the disease.

Three criteria, or biomarkers, are now available to contribute to diagnosis of the disease.

Atrophy of the hippocampus, fundamental region of the brain for memory is affected early in the disease. This atrophy can be observed with an MRI of the brain.

Visualization of lesions of the disease using positron emission tomography (PET).

The presence of certain proteins in cerebrospinal fluid (liquid in which the brain bathes) shows changes that occur specifically because of the disease. A lumbar puncture is necessary for this exam.

The diagnosis is based on clinical observations associated with one or several of these biomarkers.

Detecting diseases as early as possible, is a major goal for clinicians in order to better treat patients, especially for young patients and atypical cases that make diagnosis difficult. These new markers will make this possible.

These new diagnostic criteria also benefit research they allow inclusion of patients who are actually suffering from Alzheimer's disease in therapeutic trials as well as development of new medicines and testing their efficiency.

PARKINSON'S DISEASE

SIX NEW GENETIC RISK FACTORS

SIX NEW GENETIC RISK FACTORS FOR PARKINSON'S DISEASE WERE RECENTLY IDENTIFIED. THIS MAJOR STEP FOR PARKINSON'S DISEASE WILL ALLOW IDENTIFICATION OF PEOPLE AT RISK AND TO BETTER UNDERSTAND THE CAUSES UNDERLYING THE PATHOLOGY.

4 million people in the world suffer from Parkinson's disease. Ranked second for causing motor handicaps, this disease is extremely crippling. Until the 2000s, the disease was thought to be purely a product of environmental causes (ex. exposure to toxic substances). However, it has become apparent in recent years that genetic factors play an important role in predicting the appearance of the disease.

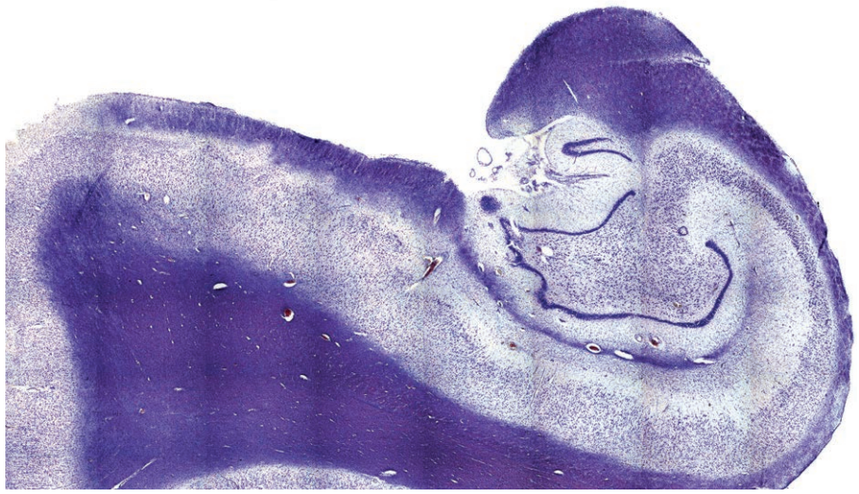
A major challenge for researchers is to define the complete genetic profile of the disease in order to have tools to diagnose and even predict its onset before the first symptoms appear.

Produce a DNA identity card of thousands of Parkinsonian patients, this is the major international project in which Alexis Brice's team participated. The goal is to identify modifications of genetic information or mutations that are associated with Parkinson's disease. By analyzing the ensemble of DNA from more than 100,000 people, including healthy people and those affected with Parkinson's, the researchers determined which genetic variations are implicated in the disease.

Six new genetic risk factors for Parkinson's disease were identified thanks to this study. Furthermore, the researchers confirmed the identification of 19 previously identified risk factors. More of these different genetic variations present in an individual increases the risk that the person will develop Parkinson's disease.

This discovery will allow development of diagnostic tools to identify people who have an elevated risk to develop the disease. Furthermore, understanding the causes of the disease opens the path to development of targeted therapies.

EPILEPSIES



ONE GENE, DIFFERENT PATHOLOGIES

THE DISCOVERY OF DEPDC5, A GENE IMPLICATED IN DIFFERENT TYPES OF HEREDITARY EPILEPSIES OPENS NEW AVENUES TO DIAGNOSE AND TREAT THESE EPILEPSIES THAT ARE THE MOST RESISTANT TO TREATMENT.

For the 500,000 people affected in France, epileptic seizures occur without warning or explanation. These seizures correspond to abnormal excessive activity that occurs briefly in a group of neurons. Symptoms which include stiffening, rhythmic tremors, absence seizures, and hallucinations are variable and closely linked to the localization of neurons that are abnormally activated. When these neurons are located in a precise region of the brain, for example, the frontal lobe or temporal lobe, these seizures are called focal seizures. These represent 70% of epilepsies.

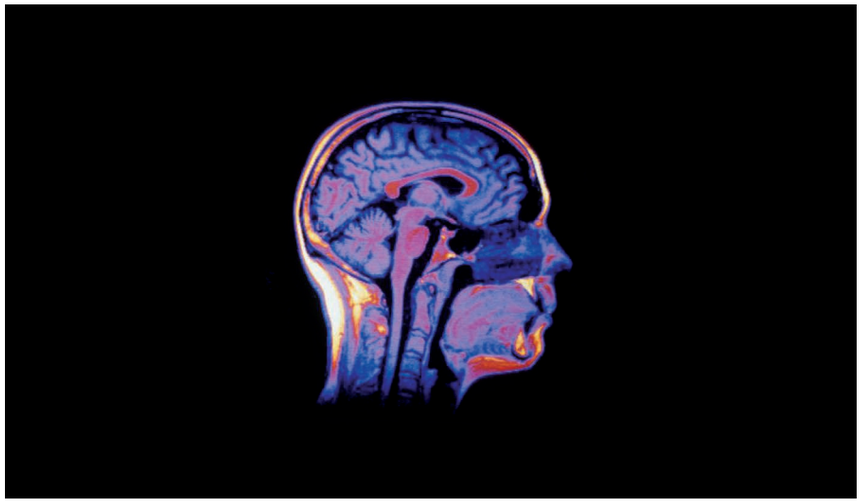
***DEPDC5*, a major gene that is implicated in several familial forms** of focal epilepsies, is located on chromosome 22 and was recently discovered by the team of Stéphanie Baulac and Eric Leguern. Surprisingly, this gene is implicated in forms of epilepsies considered up to now to be distinct because of their different symptoms and different localization in the brain. These results show for the first time that the alteration of a single gene can lead to distinct pathologies.

***DEPDC5* is also implicated in epilepsies that are resistant to treatment** that can be associated with malformations of the cerebral cortex. *DEPDC5* seems to intervene in transmission of messages from within neurons and its role is different from other genes already identified to be involved in epilepsies. For this reason, researchers are developing experimental models in which *DEPDC5* is altered in order to elucidate the mechanisms responsible for these focal epilepsies and to test new targeted anti-epileptic treatments.

Identify and classify the origin of different forms of epilepsy could allow prediction of how the epilepsy will evolve during the aging process of a patient, and possibly in the future, to offer new personalized treatments.

Thanks to this discovery, the diagnostic of DEPDC5 is offered to families, and will allow for a better choice of treatment. This discovery also opens new avenues for therapies to target focal epilepsies resistant to treatment.

UNCOMMUNICATIVE PATIENTS



DETERMINE CONSCIOUSNESS LEVELS

IT IS NOW POSSIBLE TO CHARACTERIZE CONSCIOUSNESS LEVELS OF UNCOMMUNICATIVE PATIENTS AND TO PREDICT THEIR EVOLUTION THANKS TO A CALCULATION OF NEARLY A HUNDRED CEREBRAL MEASUREMENTS FROM THE PATIENT'S ELECTROENCEPHALOGRAM.

How can we tell if a sick people are conscious of the world or a fortiori are conscious of themselves when they are unable to communicate? This question raises the considerable diagnostic, prognostic, and ethical stakes for patients, their close ones, and their caregivers.

A vegetative state, minimal state of consciousness, coma: facing an uncommunicative patient following brain injury, including traumatic brain injury, cardiac arrest, and intracranial hemorrhage, it is sometimes difficult to determine a patient's state of consciousness with only the help of clinical exams.

A new revolutionary tool that allows diagnosis but also prediction of the evolution of a person's status for the following six weeks was developed by teams of Lionel Naccache and Stanislas Dehaene. This tool is based on recording cerebral activity by electroencephalogram (EEG). Thanks to a consistent test for measuring brain responses in response to a series of sounds, the researchers identified around a hundred brain "signatures" that allow, for example, distinguishing a sick person in a vegetative state, from a sick person with minimal consciousness.

Diagnosis and prediction of a patient's neurologic future is new possible thanks to an algorithm (program) that integrates all of these brain signatures; this is the first time that such an algorithm has had such a prognostic value. This method is complementary to clinical observations (evaluation of muscle tonus, pupils, and their reactivity) in order to diagnose a patient's state of consciousness and predict the recovery of consciousness in sick patients.

An international trial is currently in progress, and a partnership with Mensia technologies SA seeks to develop an application to measure the level of wakefulness of minimally conscious subjects in real time and at the patient's bedside.

In the near future, simplified versions of these analyses will be available and will facilitate their use by all clinical departments that have readily available traditional EEG recording materials, which are frequently used, inexpensive, non-invasive, and reproducible.

3
FIND THERAPEUTIC SOLUTIONS

New treatments against multiple sclerosis and against Huntington's disease have been proven to be effective, a surprising discovery allows prevention of neuronal death in Parkinson's disease, and finally, deep brain stimulation abolishes the symptoms of obsessive compulsive disorder in the majority of patients.

The major challenge of the twenty-first century is to stop the evolution of neurologic diseases. By bringing together the sick, doctors, and researchers in one place, the ICM can rapidly develop treatments for nervous system lesions and apply them to patients rapidly, from the level of simple model organisms in the laboratory up to therapeutic trials in patients at the Clinical Investigation Center of the ICM.

The strength of the ICM is also its incubator, the iPEPS-ICM, which establishes a path between research and concrete applications that result from it. Promotion of this knowledge and know-how allow rapid creation of medical applications directly from fruits of the research.

Therapeutic solutions include medicines to combat disease and to slow its progression, but also medical measures, such as deep brain stimulation, to allow patients to live better in their daily lives or digital solutions that improve patients' autonomy, such as smartphone applications, connected objects, or even therapeutic games.

ICM RESEARCHERS AND CLINICIANS WORK IN CLOSE COLLABORATION IN ORDER TO:

REPAIR
damages

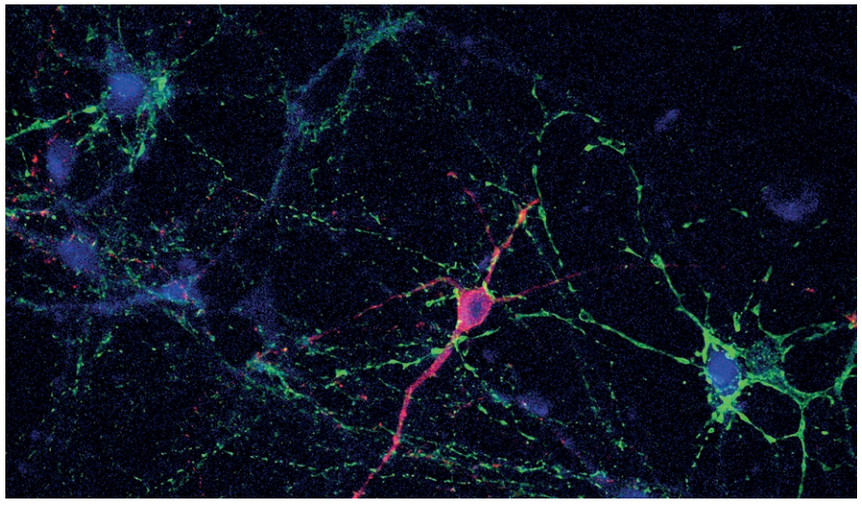
SLOW
disease progression

IDENTIFY
new therapeutic targets

TREAT
diseases

THE MAJOR ADVANCES OF THE ICM

PARKINSON'S DISEASE



PROTECT NEURONS

A VIRUS TO FIGHT AGAINST PARKINSON'S DISEASE? AN UNEXPECTED DISCOVERY LOOKS PROMISING FOR THE DEVELOPMENT OF NEW THERAPEUTIC APPLICATIONS.

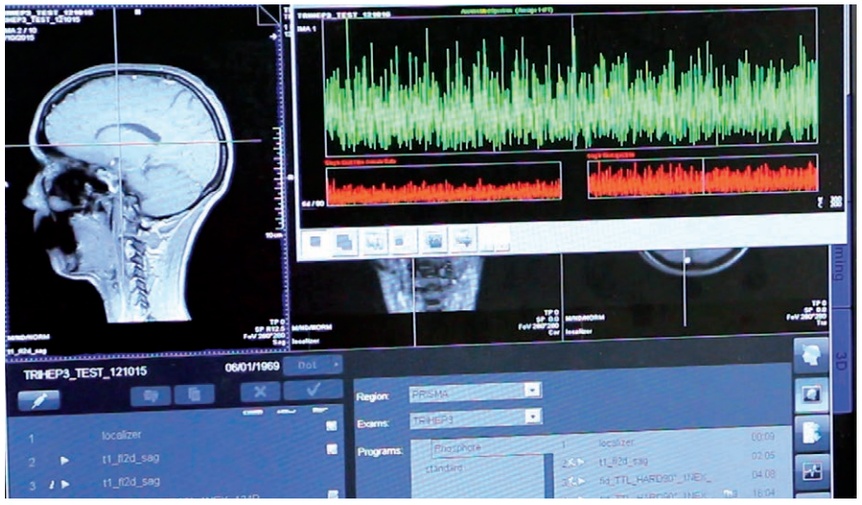
The progressive death of neurons of a deep region of the brain, the substantia nigra, is the principal cause of Parkinson's disease. Although doctors know how to partially treat the motor symptoms with medicine, they do not know how to block the neuronal death itself. Finding a way to protect the neurons is a major challenge for research.

An astounding discovery from the lab of Stéphane Hunot in the team of Etienne Hirsch and Daniel Gonzalez-Dunia at the University of Toulouse: a protein that forms part of a virus is capable of protecting neurons implicated in Parkinson's disease. The virus, the Bornavirus, infects cells of the nervous system. To ensure its survival, being able to multiply only inside a host cell, it produces the protein X, which prevents neurons from dying. Protein X acts by protecting mitochondria, the "energy centers" of the cell, which provide the energy necessary for the cell to function. In Parkinson's disease, mitochondrial dysfunction in part leads to the progressive loss of neuronal function. By protecting the mitochondria, protein X protects neurons from death.

The researchers went even further by showing in an experimental model that a fragment of the protein administered intranasally has a neuroprotective effect that is as effective as the entire protein. This result is quite important because these protein fragments, or peptides, are able to easily cross the sealed barrier that separates and protects our brain from the rest of the organism, which also prevents large proteins from penetrating it.

These very encouraging results open the path to new therapies for Parkinson's disease and also other neurodegenerative disorders.

HUNTINGTON'S DISEASE



A MEDICAL OIL

RESEARCHERS FOUND THAT A SYNTHETIC OIL, TRIHEPTANOIN, HAD THERAPEUTIC POTENTIAL IN PATIENTS WITH HUNTINGTON'S DISEASE. BY IMPROVING THE ENERGY EFFICIENCY OF THE BRAIN, THIS MEDICINE COULD SLOW DOWN THE EVOLUTION OF THE DISEASE.

Provide the brain the energy it lacks to treat Huntington's disease, this was the successful gamble taken on by Fanny Mochel and Alexandra Durr. This neurodegenerative affliction affects 5,000 people in France. The disease manifests between the ages of 30 and 50 years old with the appearance of progressive motor, behavioral, and psychiatric troubles alongside neuronal degeneration, notably in the brain regions implicated in the control of movement. Weight loss is also frequently observed at early stages of the disease.

The beginning and progression of symptoms of the patient could be caused by a defect in energy efficiency in a patient's brain. In order to correct this deficit, researchers tested the therapeutic potential of a synthetic oil, triheptanoin.

A therapeutic study involving ten patients with Huntington's disease showed the efficacy of this treatment. Thanks to magnetic resonance imaging, the researchers showed that after a month of treatment with patients taking the medicine alongside their meals, the brain metabolism improved in the abnormal brains of these patients.

This data represent a great hope for Huntington's disease by establishing the use of this oil as a possible molecular candidate for future therapeutics. An operating license was signed with the company ULTRAGENYX, which commercializes triheptanoin.

Based on these results, a year-long therapeutic trial, TRIHEP3, launched in France and in the Netherlands, which will use clinical and imaging parameters to gauge results.

OCD (OBSESSIVE-COMPULSIVE DISORDER)

TREAT WITH BRAIN STIMULATION

IN THE MAJORITY OF PATIENTS SUFFERING FROM OBSESSIVE-COMPULSIVE DISORDER RESISTANT TO CLASSICAL TREATMENTS, DEEP BRAIN STIMULATION OF A SPECIFIC REGION OF THE BRAIN CAN ABOLISH SYMPTOMS.

Compulsions, repetitive behaviors, verification rituals that a subject feels obliged to perform in order to appease distressing ideas (fears of contamination, fear of not having closed a door or the gas), obsessions in the form of recurrent thoughts, images with disagreeable content that impose themselves involuntarily without leaving the mind at rest: these symptoms of obsessive-compulsive disorder affect 2-3% of the population. This disorder is profoundly debilitating for both the affected person and their friends and family.

Currently, treatments with cognitive and behavioral psychotherapy and/or antidepressants allow improvement of symptoms in two-thirds of patients. However, certain severe forms are resistant to classical treatments and are the target of particular research to develop innovative therapies.

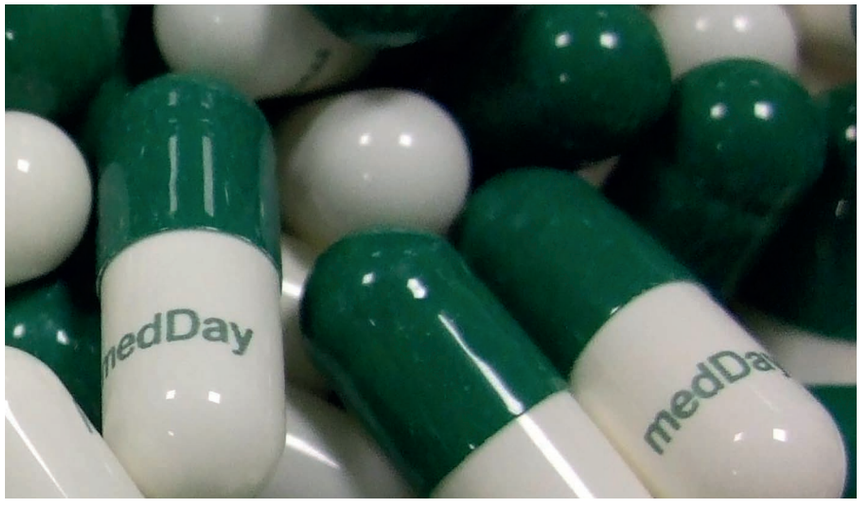
From clinical observations and from brain imaging data, researchers in the team of Luc Mallet identified a sub-cortical region, the subthalamic nucleus, as a region implicated in the emergence of the most prominent symptoms, including overwhelming doubt, which is probably at the origin of verification behaviors.

Deep brain stimulation of this region, which consists of delivering a continuous current on the targeted brain structures, allows attenuation or even abolishment of visible symptoms in 75% of patients. This treatment is tricky but allows a sustainable improvement in quality of life for patients.

Optogenetic stimulation techniques, set up by Eric Burguiere, allow specific modulation of the activity of neurons implicated in behaviors in experimental models. This approach is essential to better understand the compulsions, the mechanisms of action for brain stimulation, and to optimize its use in humans.

Deep brain stimulation of the subthalamic nucleus abolishes OCD symptoms in the majority of patients.

MULTIPLE SCLEROSIS



TOWARDS A NEW TREATMENT

FOR THE FIRST TIME, A MEDICATION, MD1003, SLOWS THE PROGRESSION OF THE DISEASE AND IMPROVES THE HEALTH OF PATIENTS WITH PROGRESSIVE MULTIPLE SCLEROSIS.

Number one cause of severe handicap without a traumatic origin for people in their thirties, multiple sclerosis (MS) can manifest in one of two forms. 10 to 15% of patients suffer from a progressive form that leads to vision and walking troubles, incontinence, cognitive changes, fatigue, and pain. The remitting form is characterized by spurts, at least partially reversible, with symptoms that can surge at any moment. The remitting form can transform into the progressive form (secondary progressive) after a number of years. Currently, there is no treatment to cure the disease other than those that seek to limit inflammation to decrease the symptoms.

The efficiency of a new treatment, MD1003, was recently demonstrated for primary and secondary progressive forms of MS by MedDay, a start up incubated within the ICM and directed by Frédéric Sedel. A clinical study on 154 patients that took place over a year at 16 reference centers for MS in France demonstrated a significant improvement of health status of patients and a slowed down time course for the disease. Moreover, the treatment was well tolerated by patients and safe for use.

MD1003 acted by favoring the repair myelin (the insulating sheath around axons that permits fast transmission of information) and by increasing energy production at the level of axons (an extension of neurons), which reinforces information transmission in the nervous system.

A second therapeutic trial is in progress in order to evaluate the effect of this treatment in MS patients who present a loss of vision. The results are expected for the end of 2015.

This is the first time that a treatment has had such positive effects for progressive MS. The medicine should be available in the short term, which is extremely encouraging both for clinicians and for patients.

PERSPECTIVES

"Our goal: become a research institute and a leader in neuroscience at the international scale and at the origin of new solutions for curing the diseases of the nervous system."

— "Search, find, cure, for you, and with you." These are the watchwords of the scientists, clinicians, and the support teams that have been working at the heart of the ICM for the last five years. And this is only the beginning of the important challenge that lies ahead: considerably reducing the delay that separates patents from a treatment for their disease. Creativity and discovery are attributes of science, submitted to surprise and to incertitude.

Faced with the public health challenge of neurodegenerative diseases, we would like to bring together all of these attributes in order to spur development of our knowledge, and guarantee that this knowledge bears fruit in the years to come. The support of our donors and partners has been considerable in order to concretize such a project and to make the ICM become a reality. Today, the institute has entered active phase of research and seeks to be a top-ranked international institute.

The objectives of our research program are to understand the functioning of the brain, find rapidly new therapeutic solutions to defeat nervous system diseases (Alzheimer's, Parkinsons, multiple sclerosis, ALS, spinal cord pathologies, and others), to diagnose these diseases at early stages, to preserve brain capacity or to repair it, and finally, to contribute to aging in good health.

The ecosystem of the ICM creates a favorable environment for discoveries and encourages risk-taking. Our strategy consists of regularly recruiting new teams, welcoming the best international scientists financed by research chairs, attract youth and new talents by giving out fellowships, developing new technologies, and to promote research to rapidly create medical applications.

The acceleration of discoveries also happens above all thanks to the richness of collaborations and exchanges. At the heart of the ICM, we are developing collaborative, innovative, and multidisciplinary research projects as well as welcoming industrial partners and incubating start-ups in order to transform research results into concrete applications. We are establishing these connections in Europe and in the world with foreign research center of international renown. Finally, exchange is synonymous with sharing, that is of knowledge with the public and with donors, which will constitute a major objective of scientific conferences and of "Science, Art, and Culture," open to all.

Thank you all, individuals, foundations, and businesses, for your support, your confidence, your loyalty, and belief in our involvement and our passion.

Professor Alexis Brice
General Director of the ICM

Today medicine relieves.
Tomorrow we want to prevent, cure, and repair.

These 12 advances were selected for their distinctive nature in the research centered on the diseases of the brain and the spinal cord at the ICM. However, these are not the only ones; you can find the numerous discoveries of the ICM since 2010 on the institute's site:
icm-institute.org/en/

Today, the ICM is:

25
research teams

650
researchers, engineers, technicians,
PhD students and post-doctoral fellows

22,000 sqm
of laboratories

1,200 sqm
for clinical research

More than 1,000
scientific publications since 2012

1,000 sqm
for incubating 20 startups

24
technical platforms at the forefront of technology

1 objective:
Search, find, cure. For you & with you.

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