N°7 – THIRD QUARTER 2016

ICM
Brain & Spine Institute

FOR YOU & WITH YOU

The brain and spine institute donors journal

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SPECIAL REPORT ON BRAIN TUMORS

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TOWARDS PERSONALIZED MEDICINE

In a few weeks, holiday season will be upon us. This is a time to reflect upon the past year, as well as look towards the future with hope. Reading the Donors Newsletter is an opportunity to dream of new discoveries and peek at new horizons patients with neurological disorders will be able to benefit from - that is, one person out of eight of us.

Every quarter, we help you gain a deeper understanding of a complex neurological disorder. In this edition, we have decided to show you the world of brain tumors.

At the ICM, research in this field aims at better understanding the causes and mechanisms of these tumors to improve diagnosis, progress, and personalized therapy for patients based on each tumor and each patient's genetic profile. Hand in hand with the doctors and Nervous System Diseases Department of the Pitié-Salpêtrière Hospital, research is helping medicine advance towards "custom" treatment, adapted to each patient. It also makes discovering new technologies possible to tackle these tumors, such as the use of ultrasounds.

Your support is what has made this synergy possible: thank you for your continued commitment.

Jean Todt
ICM Founding Member and Vice President

12TH EDITION OF THE BCG PARTNERS CHARITY DAY

This global solidarity day was initially created to support

families of World Trade Center attack victims. Since 2004, Charity Day has expanded to include causes with a larger scope. To date, the event has supported over 250 charities. During this special day, various celebrities act as brokers to raise funds. This year, Jamel Debbouze, Michelle Yeoh, Jean Todt and Gérard Saillant were involved for the ICM. Other celebrities including Richard Berry, Elie Semoun, Patrick Bruel, Frédéric Chaud, and Elodie Fontan participated in the event.

L'ORÉAL-UNESCO AWARD FOR WOMEN IN SCIENCE

Christiane Schreiweis, from the "Behavior, emotion, and basal ganglia" team led by

Luc MALLET, was awarded the L'Oréal Foundation–UNESCO Award for Women in Science on October 12 2016. Her project? "When routine makes us lose control". Her research, supervised by Eric Burguière, aims at improving current knowledge on the origin of repetitive behavior to develop new treatments.

LES ÉCHOS GOLF TROPHY

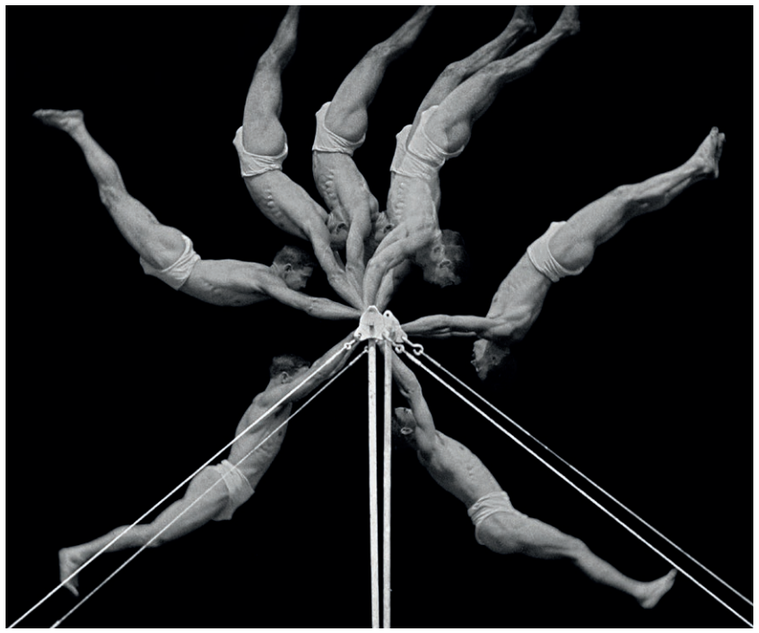
that supports the ICM during its annual event celebrated

its 25th anniversary this year. Mixing enjoyment and generosity, participants had the opportunity to play a second ball in exchange for a donation to the ICM, to increase their odds of winning the precision competition.

MUSIC PASSION PARKINSON

is hosting its 6th musical event in November 19 benefitting

the ICM. With Franky Texier reprising his role as ambassador, classical and latin musicians will play on the stage of Salle St Exupéry in Caissargues to benefit research done by the Institute.



PARTNERS:

ART AND SCIENCE AT THE FIAC FOR THE ICM

The International Contemporary Art Fair (FIAC) supports the ICM for the 6th consecutive year. On Wednesday, October 19, the ICM organized a fundraising event at MiniPalais in Paris with a performance blending Art and Science. This year's thematic, highlighting research, breakthroughs, hopes, research needs and to collect funding was "Understanding and treating movement disorders". The thematic put the spotlight on research conducted by Marie Vidailhet, Professor of Neurology at the Pitié-Salpêtrière Hospital and co-director of the "Abnormal movement and basal ganglia: pathophysiology and experimental therapy at the ICM" team. The goal of this year's performance was a living demonstration of "the close, almost intimate relationship between Art and Science (...) two fields in which we're constantly searching for a utopia, a better world, and looking to improve our life on this earth", underlined Jennifer Flay, FIAC Director in a past speech. The performance was created by the artist and poet Jean-Sébastien Leblond-Duniach.

For you & with you is the newsletter sent by the ICM to its donors. **No. 05 – June 2016**. Editor-in-chief: **Agathe Gioli-Viot**. Editorial board: **Jean-Louis Da Costa, Natacha Bitton, Carole Clément**. Design: EXCEL Production: **Louis**. Printer: **BB création** . Print run: **300 copies**. © Bgc – Harcourt – ICM – Inserm/Guichet, Pierre-Olivier – Les Echos – Music Passion Parkinson – J.P. Pariente – G. Demenÿ, INSEP – Louis – Fondation L'Oréal

Seen on the Web

NEW!

Get Institute news and research breakthroughs in your inbox with the ICM's new digital newsletter!

Sign up on icm-institute.org

WHAT'S ON THE WEBSITE?

Alzheimer's disease conference: read about research breakthroughs at the ICM

Vivatech: Presentation by Alexis Genin at Viva Technology 2016 on the topic of "health and technology"

Neurallys: Interview of Philippe Avray, Founder of Neurallys, a startup incubated at the ICM that is developing innovative hydrocephaly medical equipment

EVENTS

- November 17 2016 – World Epilepsy Day
- November 19 2016 – Music Passion Parkinson Organization's Musical Event, Caissargues
- December 8 2016 – Rare Diseases Conference at the ICM, Paris

BRAIN TUMORS: TOWARDS PERSONALIZED TREATMENT

In France, nearly 5,000 individuals with a primitive malignant brain tumor are currently diagnosed each year. To date, treatment includes radiation therapy, chemotherapy and surgery, but very rarely leads to full recovery. The teams at the ICM are working on improving their understanding of how these tumors develop in order to improve diagnosis and put innovative and personalized treatment strategies in place.

THE FIGHT AGAINST BRAIN TUMORS: ICM TEAMS

How do tumors develop? How can we diagnose them before it is too late? How can we better predict their aggressiveness? What kind of innovative therapeutic strategies would help target them specifically? Two research teams at the Institute, in close collaboration with the Neuro-Oncology Department at the Pitié-Salpêtrière Hospital, are involved daily in the fight against tumors.

EMMANUELLE HUILLARD'S TEAM

is focused on the mecanisms at work in the development of glioblastomas, a very aggressive tumor. Researchers are simultaneously studying normal brain development and tumor development.

The team's goals:
- Understand why cells keep multiplying and become a tumor instead of disappearing, according to their "life cycle";
- Identify new treatment targets to develop personalized therapy and preserve healthy cells.

"Our outlook is to increase understanding of how tumors function and develop innovative and ultra-targeted therapies to spare healthy cells and minimize side effects, and preserve the patient's quality of life as much as we can."
Emmanuelle Huillard

PROF MARC SANSON'S TEAM

is focused on primitive brain tumor biology in adults, notably gliomas, primitive central nervous system lymphomas, and meningiomas.

The team's goals:
- Identify biomarkers to improve tumor description, leading to better care;
- Understand cellular mechanisms and anomalies that lead to brain tumor development;
- Assess new anti-tumoral therapies with clinical trials.

"Patients are at the heart of our approach, (...) The advantage of being at the ICM is that everything is on-site, we are in a hospital, with patients and research teams we can partner with."
Marc Sanson

LATEST BREAKTHROUGHS

IDENTIFYING CAUSES AND UNDERSTANDING MECHANISMS

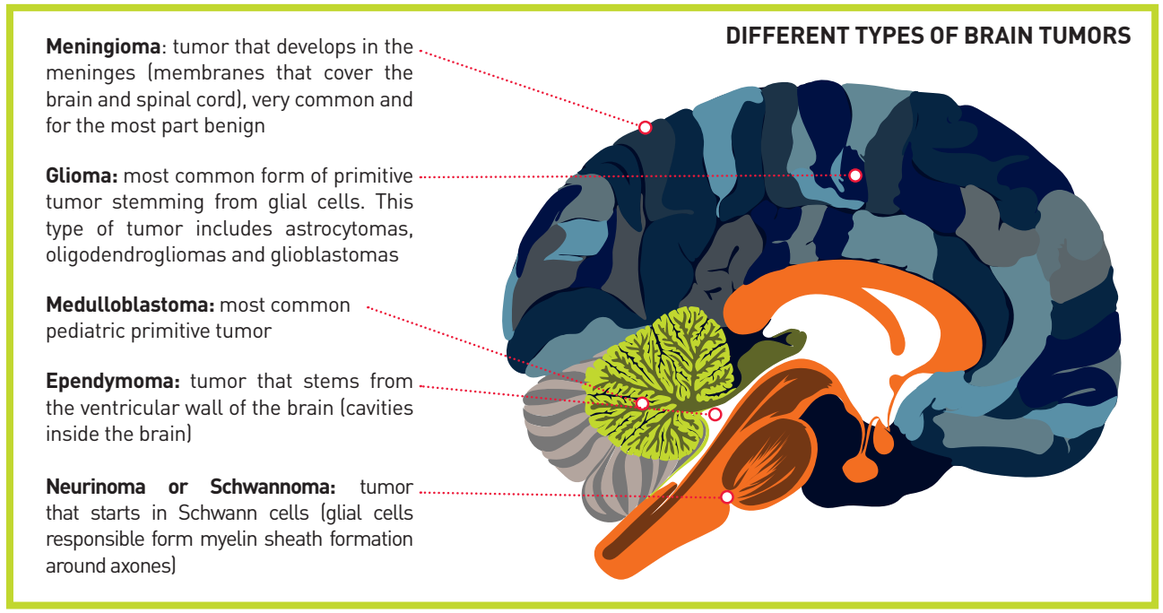
Teams at the ICM identified various genes involved in tumor development. These discoveries open up new opportunities towards understanding tumor development, identifying their causes and their mechanisms. This is a first step towards identifying potential therapeutic targets and give hope for personalized treatment on the long term.

• Two new genes identified

Thanks to international collaboration and the POLA network coordinated by Prof Jean-Yves Delattre at the ICM, Emmanuelle Huillard and Marc Sanson's teams characterized TCF12, a new gene involved in the development of anaplastic oligodendroglioma, an agressive form of skin cancer. Inactivation of this gene leads to loss of expression of tumor suppressor genes, which could in turn lead to a more aggressive tumor. This discovery paves the way for better understanding of how these tumors develop and identifying their causes. Vincent Gleize, a member of Marc Sanson's team, discovered the mode of action of gene CIC (a repressor for transcription, an essential step to go from DNA to protein) within tumor cells. 60% of oligodendrogliomas have a CIC mutation, and the gene's inactivation leads to an accumulation of proteins involved in cellular proliferation, in turn leading to tumor development. These discoveries bring long-term hope for personalized treatment based on genetic tumor profiles.

• Cells responsible for tumor relapse?

Franck Bielle from the experimental neuro-oncology team very recently found a very heterogenous set of tumor cells in anaplastic oligodendrogliomas (malignant primitive tumors) and identified a cell sub-population that could play a critical part in tumor relapse. These results give way to new therapeutic opportunities to circumvent resistance to current antitumor treatments.



DEVELOPING DIAGNOSTIC AND PROGNOSTIC TOOLS

It is currently complicated to detect a brain tumor before it becomes visible on an MRI (magnetic resonance imaging). However, biomarker research is a strategy that is used for early tumor diagnosis. Biomarkers are molecules present in blood, urine, or cerebrospinal fluid (CSF) that attest to the presence of a tumor inside the brain. Identifying biomarkers could help directly establish tumor diagnosis and allow successful treatment. To determine how the tumor is evolving and how it responds to treatment, we use molecular biology and immunohistochemistry methods to detect prognostic markers (of tumor progress) or predictive markers (of response to treatment). In oligodendrogliomas, for example, we look for chromosome alterations, in this case 1p/19q chromosomal co-deletion. This alteration is linked to a better prognostic and better response to treatment. Finally, IDH1 gene mutation is an important prognostic factor in gliomas.

• A non-invasive diagnosis method

The "IDASPE" trial, coordinated by Marc Sanson (for the APHP) and implemented in collaboration with the CENIR (Research neuroimaging platform) recently developed a technique for detecting a molecule that builds up in tumors following IDH1 gene mutation (found in 40% of gliomas). This opportunity for a non-invasive diagnostic tool will soon be used with patients. This diagnostic tool could also help monitor patient response to treatment and assess treatment efficacy.

• A new preclinical meningioma model

Michel Kalamarides and Matthie Peyre found a new meningioma model (most common primitive central nervous system tumors in adults over 35, benign in most cases yet can be aggressive and relapse) via inactivation of specific genes and growth factor activation. This unique model will allow them to test new and promising treatment protocols for patients.

• New diagnostic and therapeutic targets

Khe Hoang-Xuan identified specific and frequent mutations in primitive lymphomas in the central nervous system affecting genes MYD88 and CD79B. These mutations activate two signalling pathways that appear to play an important part in lymphomagenesis. They serve as diagnostic biomarkers, as well as opening up new opportunities for innovative targeted trials.

•••

DEVELOPING EFFECTIVE AND PERSONALIZED THERAPY

Brain tumor treatments currently available are mostly radiation, chemotherapy, and surgery. Some tumors are well delimited and non invasive: in these cases, surgery can lead to full recovery. However, in most cases, they are poorly delimited, invade parts of the brain, and require radiation and/or chemotherapy, that usually do not lead to full recovery... ICM researchers and clinicians are involved in developing new treatments and implementing clinical trials.

• Ultrasounds to treat brain tumors

Treatment of malignant primitive brain tumors currently leads to a variable remission timeframe in patients. However, the Blood-Brain Barrier (BBB), a hermetic vascular wall that limits neuron exposure to toxic agents, limits the crossing - and therefore the dissemination - of treatments in the brain.
Following this observation, teams led by Alexandre Carpentier and Ahmed Idbaih, and the neuro-oncology group at the Pitié-Salpêtrière Hospital, AP-HP, launched a Phase I/IIa clinical trial in July 2014 promoted by the AP-HP with patients with a relapsing malignant brain tumor. The goal is to render the Blood-Brain Barrier permeable, to increase penetration and dissemination of chemotherapy drugs into the brain. Thanks to the "SonoCloud®" ultra sound equipment designed by CarThera, the teams were able to temporarily make some blood vessels in the brain permeable in patients with a relapsing malignant brain tumor. Treatment, two minutes of ultrasound emissions, leads to permeation of the Blood-Brain Barrier for 6 hours and allows dissemination of the therapeutic drug in the brain that is 5 times greater than usual. This innovative method increases treatment dissemination, including chemotherapy, within the brain and gives hope for other cerebral diseases.

THE ICM AND THE NERVOUS SYSTEM DISEASES WING, HAND IN HAND TO FIGHT BRAIN TUMORS

The Nervous System Diseases (MSN) wing plays a part in developing new treatments against brain tumors and in implementing clinical trials, in partnership with the ICM.

Prof Jean-Yves Delattre:
"My main goal is that the MSN and ICM bring their shared expertise together to help clinical research and therapeutic innovation. This is a unique opportunity for both our patients and our country. To me this is an absolute priority."

Prof Jean-Yves Delattre is a neuro-oncologist and chief of the Pitié-Salpêtrière Nervous System Diseases wing (MSN wing) and Medical Director at the ICM. He also serves as co-director of the Gliotex experimental therapy platform and coordinator for the POLA network, a national anaplastic oligodendroglioma network. He is currently coordinating various multicentric trials on gliomas.

"We strive to develop innovative targeted molecular therapy that acts exclusively on tumor cells with a molecular anomaly, and respects normal cells in the body as much as possible. These smart treatments give hope for greater efficacy and fewer side effects in patients."

"This novel method gives new hope in treating brain cancer, as well as other brain pathologies, potentially Alzheimer's disease, for which existing therapeutic molecules have trouble entering the brain. This technique must be fully assessed in order to consider clinical use in a few years."
Alexandre Carpentier

• Hope for personalized treatment against glioblastoma

Thanks to the GlioTex experimental therapy platform, co-directed by Dr Ahmed Idbaih and Prof Jean-Yves Delattres, innovative treatment therapy based on tumor type is implemented. In this context, thanks to support from the ARC Foundation for Cancer Research and the Association for Research on Brain Tumors, a team led by Dr Ahmed Adbaih tested a drug that targets a gene responsible for cancer, oncogene MDM2, amplified in certain tumors. Results show a favorable therapeutic cell response, an encouraging result for development of future personalized therapy, specific to each tumor, and gives renewed hope for Phase I clinical trials in the near future based on laboratory experimental results.

• Specific and personalized therapy

Clinical trial "TARGET" aims to test specific and personalized therapy with patients affected by glioblastoma with a fusion gene, a highly oncogenic anomaly meaning that it is responsible for tumor development. This study, coordinated by Marc Sanson on a national and perhaps soon European level, is performed in partnership with Astra-Zeneca and the Assistance Publique - Hôpitaux de Paris.

Marc Sanson, team manager at the ICM

• Viruses to destroy tumors?

Phase I clinical trial "Oncovirac", directed by Ahmed Idbaih to test an oncolytic virus, a virus modified specifically to destroy cancerous cells in patients with glioblastoma, is set to launch soon. This trial comes from a partnership between Transgène, the company that developed the virus, and the Assistance Publique-Hôpitaux de Paris.

• Prolonged release of anti-cancerous molecules.

GECKO BIOMEDICAL, directed by Christophe Bancel, is developing technology that will allow prolonged release of anti-cancerous molecules during surgery for glioblastoma applications.

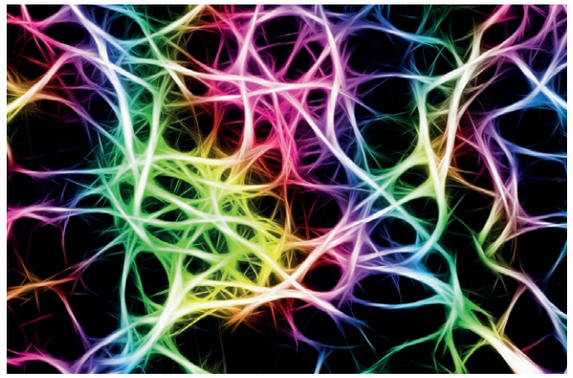
WHAT IS A TUMOR?

When a cell becomes cancerous, it multiplies indefinitely and in uncontrolled fashion, forming a tumor: a cluster of new cells within normal tissue.

A brain tumor can develop in any zone of the brain.
Two types of tumors exist:

- Primitive brain tumors, that develop directly inside the brain;
- Metastatic or secondary tumors, where the primitive tumor develops outside of the brain (in the lungs, colon, skin, or breast, for example) and where cancer cells will spread to the brain.

Malignant tumors are tumors that develop rapidly, destroying the area of the brain in which they are found.



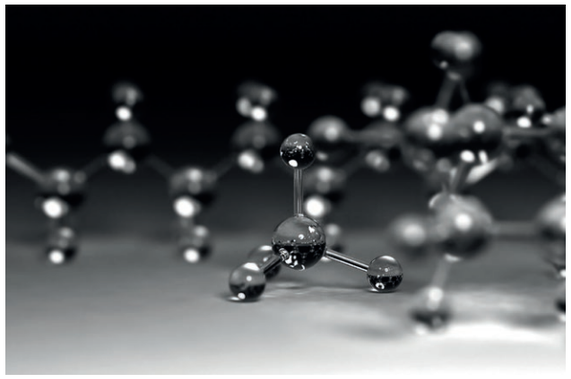
WHEN EPILEPSY SEIZURES INTERRUPT CONSCIOUS PROCESSES: ADVANCES IN NEURONAL MECHANISMS

Epilepsy is one of the most common neurological diseases, affecting nearly 1% of the general population. An epilepsy seizure is the result of excessive electric activity in a group of cortical neurons, which can alter their capacity to receive and send out information. In the case of generalized seizures, during which epileptic activity affects the whole cortex, patients undergo an interruption in their conscious processes and are incapable of treating sensory stimuli effectively. Those affected lose contact with the world around them and are metaphorically "absent". Using genetic modelling of absence seizures, generalized epilepsy in children causing cognitive task and conscious perception disruption, Stéphane Charpier's team found that these seizures continuously cancel cortical neuron ability to receive and process information from the outside. This is the first "real time" demonstration of a neuronal mechanism that plays a part in interrupting conscious perception mechanisms during generalized seizures. A complementary study in young epileptic patients will soon launch in partnership with the Rothschild Hospital.

OVERWORKED? SPENDING MORE!

Mathias Pessiglione's team at the ICM hypothesized that we have a limited daily supply of self-control, allowing us to act without impulse and make rational decisions. To test this idea, researchers gave three groups of volunteers exercises of varying difficulty. At regular intervals, researchers asked participants to choose between an immediate reward, a small amount of money right away, or a long-term reward, a larger amount of money later on. Those given the harder exercises opted for the small amount right away, meaning that they preferred an impulsive choice to a more profitable choice on the long term. Cognitive "fatigue" would therefore lead us to make more impulsive decisions. Whose fault? A small area of the brain located in the prefrontal cortex and solicited both in complex tasks and financial decisions. The area's activity decreases with fatigue, and as it decreases, impulsive decisions increase. This research shows how after a day of hard work, our impulsiveness increases when it comes to financial decisions, and results have an impact on the field of management: the amount and length of breaks in a work day should be adapted to avoid cognitive fatigue.

WITH YOU DISCOVER



NEW THERAPY CONSIDERED FOR PARKINSON'S DISEASE

Parkinson's Disease is the second most common neurological disease, after Alzheimer's disease. It affects between 100,000 and 120,000 individuals in France and over 6.3 million individuals globally. It involves the death of dopamine-producing neurons, essential to transmitting information between neurons and to harmonious movement control. Starting from research on natural substances that exist in very small proportion in tropical plants from the Annonaceae family, Etienne Hirsch's team at the ICM and Bruno Figadère's team from the Biomolecular Design, Isolation, and Development Laboratory (CNRS/Paris-Sud University) were able to characterize a new fully synthetic molecule, 3-phenyl-6-aminoquinoxaline (PAQ). It perfectly targets neuron cells to slow Parkinson's disease progress. This molecule can cross the blood-brain barrier (hermetic vascular wall that limits neuron exposure to toxic agents, as well as treatments) and could protect neurons that disappear in this disease. Parkinson's disease research on animal models also found that dopamine levels were partly restored to allow nerve influx. This breakthrough could eventually open a pathway towards curative treatment for Parkinson's disease. Research was partly funded by the Future Investments CARNOT program.

THE UNCONSCIOUS MIND UNDER CONSCIOUS INFLUENCE

A study led by Lionel Naccache proves than unconscious semantic treatment of a word is subject to strong conscious influence.
To do so, the authors studied the influence of context on understanding of words with various meanings, such as "glace", "avocat", "cruche", "bar" in French, on healthy volunteers and recorded their brain activity. Word triplets were shown to patients, who had to say whether the third word (target word) had a meaning or not. For example, in French, TRACTEUR-GRUE-CHANTIER or OISEAU-GRUE-CHANTIER. When the middle word is semantically linked to the target word, subjects replied faster. This is called a priming effect, experienced only when the first word's meaning is coherent with the context. For example, priming of the word "chantier" was present in the "tracteur-grue-chantier" triplet, but not in the "oiseau-grue-chantier" triplet. Surprisingly, identical results were obtained whether the 2nd word was shown in a subliminal manner or consciously visible. These results open up new opportunities to explore the patient's conscious state based on cerebral signatures linked to word analysis. With these new results, they hope to find more sensitive markers to explore the cognitive state of patients when their conscious state is difficult to assess.

"The tumor helped me envision another way of living"

Pierre Morel (right) and his co-pilot

You decided to participate in the 2016 Auto Tour, a French icon when it comes to vintage automobile races, in support of the ICM. What "drove" you to this?

I was diagnosed with a brain tumor in 2012, discovered by chance. When I got the results, I was 54 and running all over the place: I was at the head of my company and spent all my time working, so traveling and racing against time. Then, this! From one day to the next, everything changed. Following surgery (12 hours long, and 5 days to fully wake) and the obstacle course I went through, from a long stay in the hospital to chemotherapy and radiation, I decided to go back to work. It was at a slow pace, and my doctors were against it, but my life completely changed and I wanted to get involved and help research move forward.

How did you experience this hardship?

One day, disease hits unexpectedly, and your whole world turns upside down. The hospital, surgeries, care, and doctors' reservations when they say that a relapse is possible, and let us go home with a treatment, but not with a cure. Unfortunately, our specialists know what they're saying. In 2015, when the tumor came back, I felt ambivalent: as if once wasn't enough! I was going back in for a fight, and pretty much knew who my adversary was, and the almost identical path that was ahead. I felt defeated in advance, it seemed like everything I had endured the first time didn't do much good, and only confirmed that the road ahead would be very long.

How are you doing now?

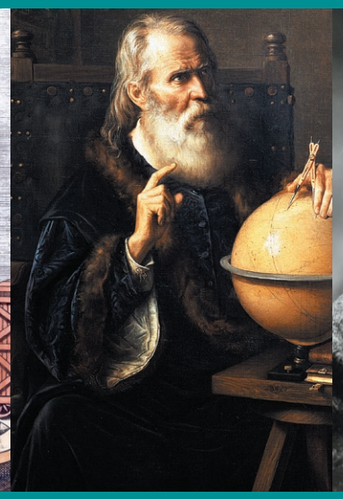
Better, since my last surgery. I adapted my everyday life...and my outlook on life. In my hospital bed, something indescribable happened, this feeling of being caught up by a need for spirituality. It was so clear to me: is (my) death for tomorrow? where do I come from? where am I going? what is the world about? and you see your whole life before your eyes... I realized what the fundamental principles of the world are, how important others are: I was a business owner, focused on profitability, and I slowed down because I realized the truth lies somewhere else. Getting involved to help research was an essential motivation that helps me maintain my fragile balance. I'm still alive, thanks to years and years of experience, and I want/need to give back to brain research. My next routine MRI is in November and I'm filled with courage and determination as it approaches: the fight isn't over!

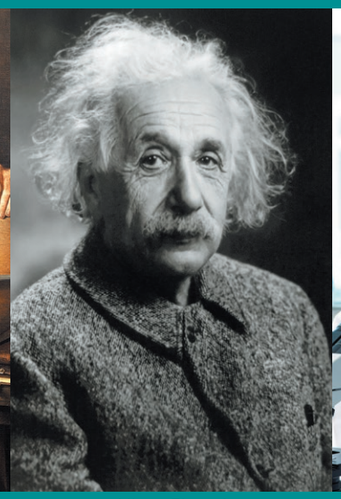
What are your plans for the future?

In my case, the best therapy is going from one new project to another. Always have a deadline, that I can count in months. The Automobile Tour was a fantastic road that allowed me, both literally and figuratively, to move forward in helping research and allowing others to avoid what I went through. I will continue racing and raising awareness for ICM research projects. My dream? One day have an ICM-sponsored car and drive around France, and perhaps the world, to tell my story and continue to support those who, every day, work for us. We are all involved in this fight!

YOUR BEQUEST TO THE ICM will change the course of History


Archimedes


Galileo


Albert Einstein


ICM Researchers

Alzheimer's, Parkinson's, Multiple Sclerosis, brain tumors, ALS…

With your support, these diseases will one day belong to the past.

Bequeathing your estate to the Brain and Spine Institute (ICM) is an invaluable way of helping advance nervous system diseases research. With a future bequest, you will help the 650 ICM researchers to discover new treatments that, tomorrow, will save thousands of patients. Essential breakthroughs in the History of Medicine will be thanks to you.

Please feel free to get in touch with your personal contact with any questions:

Mrs Carole Clément
+33 (0)1 5727 4141
carole.clement@icm-institute.org

In accordance with the Data Protection Act of January 6, 1978, you have the right to access, rectify or remove personal information that concerns you.

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☑ **Yes,** I will provide long-term support for ICM researchers with a contribution:

☐ 10 € ☐ 20 € ☐ 30 € ☐ 40 €

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*Date may be delayed to the month following depending on delay for the first withdrawal

IMPORTANT
Do not forget to attach your bank details (BIC-IBAN)

By signing this form, you authorize the ICM to instruct your bank to debit your account according the instructions of the ICM. You can be reimbursed by your bank according to the conditions 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 obtain from your bank.

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WITH YOU

YOUR SUPPORT HAS AN IMPACT ON YOUR TAXES

IS MY DONATION TO THE ICM TAX-DEDUCTIBLE?

Due to its status as a Public Interest Foundation, your donation to the ICM as an individual is partly deductible:
- Up to 66% of income tax (limited to 20% of your taxable income)
- Up to 75% for the solidarity tax on wealth (up to a limit of € 50,000 deducted)

Sponsorships allow companies to benefit from a business tax deduction equal to 60% of the amount donated, limited to 0.5% of their revenues.

WHEN SHOULD I DONATE TO BENEFIT FROM THE TAX BREAK?

For your donation to be tax-deductible, send in your support before December 31st! To do so, you may fill out the support form below and send it back to us, or donate online at **www.icm-institute.org**

A fiscal receipt will then be sent to you by mail or email if you select an online donation.

Every donation is an additional step towards new treatments against brain and spine diseases. Thank you for your support.

HOW CAN I MAKE A MONTHLY DONATION BY DIRECT DEBIT?

Simply fill out the back of the form below, sign and date, and send it back to us with your bank account details. A yearly fiscal receipt will be sent to you at the beginning of each year.

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No, you do not need to attach your fiscal receipt to your return. Simply keep it in case of an audit by the tax administration.

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☐ By check or postal order payable to ICM

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