BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

Number **49**
1st Semester 2021

NEWSLETTER

Towards an MS vaccine?

In 2020, Belgians donated more than half a million euros to research on multiple sclerosis, thus confirming their confidence in research and progress. Basic research requires proactive support and time to get results. For a currently incurable disease such as multiple sclerosis, this is the only way to find solutions.

Once again this year, the Charcot Foundation is translating its promise into concrete actions. Ten Belgian university teams will be financed in 2021 by the Charcot Fund for first-rate, innovative and very concrete projects.

The research themes concern:

- The subjects covered by this research include:
- The interactions between the immune and nervous-system cells, including those in the brain's blood vessels,
- The impact of some MS treatments on the immune system,
- The impact of gut microbes (microbiome) on susceptibility to the disease,
- The use of immune cells to repair demyelination lesions,
- The biochemistry of the fats released by myelin destruction,
- The use of an extra-powerful MRI machine to improve analysis of the micro-damage caused by the disease to nerve cells (neurons).

Discover our winners and their projects in this newsletter and their videos on our website. You will also find the most recent information and recommendations regarding COVID-19 and MS: www.fondation-charcot.org.

Finally, this newsletter asks the key question: will a multiple sclerosis vaccine ever be possible? This simple but relevant question requires a nuanced answer. Because MS is a very complex neurological disease. However, a recent article in the journal *Science* suggests that this may not be a vain hope ...

Good reading. Stay safe !

Prof. Dr **Christian Sindic**
President

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Responsible publisher: I.Bloem
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2020
Ensuring the continuity of research

2021
Opening the door to the future

The Charcot Fund 2020

A turbulent year, to be sure, but nothing has changed for our researchers. On the contrary, the first research results have already been obtained thanks to grants from the Charcot 2020 Fund.

One of the laureates, Prof. Peter Feys, is happy to present on our Vimeo channel the work made possible by our donors.

"This project studies how people with cognitive and motor impairments caused by MS can learn complex steps. People take these steps in a specific order and receive different instructions or feedback (eg noise or music). During the movements, with and without duplication, we will measure brain activity in the regions responsible for programming the movements by means of electrodes placed on the skull. The information provided by this research will help improve rehabilitation programs for people with cognitive disabilities."

The Charcot Fund 2021

The Charcot Fund 2021 is once again allocating €500,000 this year to research projects focused on therapeutic innovations. **Stimulating fundamental research is the essential first step to better understand the disease and to develop techniques to find or optimize therapies.**

Ten Belgian university research teams will receive support from the Belgian Charcot Foundation in 2021. Their projects may seem abstract, highly technical and far removed from the patients' reality. This is not the case because they all pursue the same objective: to improve the quality of life of patients through improved treatment.

The references of all the studies cited are available on request from the Belgian Charcot Foundation.

With the support of

Degroof Petercam

Jury of the Charcot Fund 2021

Prof. Dr. Christian Sindic (President), Professor Emeritus, UCLouvain
Prof. Dr Bernard Dachy, Head of Department of Neurology and Revalidation, CHU Brugmann.
Prof. Dr. Alain Maertens de Noordhout, Head of Department of Neurology, CHR Citadelle, Liège.
Prof. Dr Alex Michotte, Head of Department of Neurology, UZ Brussels.
Dr Pierrette Seeldrayers, Neurologist.
International MS expert: Prof. Dr. Jérôme de Sèze, Head of Department of Neurology of CHU Strasbourg, France

Fundamental research: more than € 500,000 for therapeutic innovations

Dr. Solène Dauby, Prof. Pierre Maquet and Dr. Emilie Lommers
ULiège - Cyclotron Research center
€ 76.350 / 2 years

"Multiple sclerosis is a major cause of disability in young people. This inflammatory disease affects both components of the brain and spinal cord: gray matter (body of neurons) and white matter (their extensions). Mechanisms affecting white matter in the form of «plaques» are relatively well known and observed by standard imaging. On the other hand, grey matter and "normal appearing brain tissue" damage, which is responsible for a significant part of the disability, is less accessible to conventional imaging approaches. We will study those areas by using new and highly precise imaging techniques. Hopefully, we will demonstrate a correlation between certain radiological physical parameters and the course of the disease. Our results could be used to better guide our future therapeutic strategies."

Prof. Stanislas Goriely, Prof. Muriel Moser and Dr. Isabel Vogel
Université Libre de Bruxelles
€ 27.042 / 2 years

"In autoimmune diseases such as multiple sclerosis (MS), the balance between regulatory mechanisms and misguided immune cells attacking the body is often shifted in favour of auto-reactive cells. Manipulating the immune response to restore this balance and enhance regulatory functions is therefore a central paradigm in the search for MS therapies. We identified a specific signalling pathway, triggered by a receptor named CD27 that could be a target for such manipulation. By stimulating this receptor, we were able to reduce the activity of harmful auto-reactive cells and enhance the function of protective regulatory cells. In our current research we therefore explore the effect of stimulatory antibodies in an animal model of autoimmunity. This could be a first step towards a novel treatment approach for MS."

Prof. Veerle Somers, Dr. Judith Fraussen, Dr. Bieke Broux and en Prof. Markus Kleinewietfeld
UHasselt – BIOMED
€ 50.000 / 1 year

"Understanding how B cell destruction with ocrelizumab affects the immune system in the treatment of MS. The destruction of B cells, a subset of immune cells, shows high efficacy in MS treatment. The B cell depleting agent ocrelizumab has been approved for the treatment of both relapsing-remitting and primary progressive MS. However, its effects on the immune system remain largely unknown. Therefore, we aim to identify immunological changes after ocrelizumab treatment in individuals with MS and its implications for COVID-19 management. To do this, we will analyse blood samples of individuals with MS before, after 6 and 12 months of ocrelizumab treatment and after treatment interruption related to COVID-19. This project will increase insight into the working mechanism of ocrelizumab and will be crucial in designing anti-SARS-CoV-2 vaccination strategies for ocrelizumab-treated individuals with MS."

Prof. Laurence Ris
UMons
€ 40.000 / 2 years

"Nearly half of Multiple Sclerosis (MS) patients suffer from impaired cognitive function. These cognitive problems concern several aspects such as long-term memory, attention, efficiency and speed of information processing. Combined with fatigue, these symptoms have a significant negative impact on the quality of life of patients. The mechanisms underlying these symptoms are not yet well known, but scientific findings point to a role for inflammatory processes taking place in the brain. Using an animal model, this project will enable us to better understand these mechanisms but also to propose new therapeutic targets for the treatment of cognitive disorders."

Dr. Jennifer Vandooren and Prof. Ghislain Opdenakker

KU Leuven - Rega Institute for Medical Reserach

€ 47.385 / 2 years

"Proteases, enzymes that cleave amino acid bonds within proteins, are crucial molecules in health and disease. Previous studies have implicated proteases in multiple sclerosis pathogenesis, for example by helping immune cells to travel from the blood into brain tissue or by removing the protective sheath (myelin) that covers nerve fibers. With support from the Charcot Foundation, we will study the interactions between proteases derived from immune cells, interleukins (molecules that regulate the actions of immune cells) and systems that regulate protease activity during the different phases of MS. Consequently, we may discover key elements to direct new approaches for MS therapy and explain why some approaches do not work.".

Dr. Bieke Broux and Dr. Baharak Hosseinkhani

UHasselt – BIOMED

€ 48.650 / 2 years

"In multiple sclerosis (MS), several questions about why the vessels in the protective blood-brain barrier (BBB) become leaky and why immune cells invade the brain are still unanswered. Scientists have recently shown that stressed cells communicate with each other by releasing tiny bubbles, known as extracellular vesicles (EVs), packed with important biological information. These EVs can cross the BBB, suggesting their potential role in the pathological progression of MS. We have recently shown that EVs are actively involved in the disruption of the BBB. In this project, we will investigate whether EVs are the key mediators of intercellular interactions in the MS brain and whether they contribute to brain damage. Results obtained from this study will lead to better knowledge of the disease, which might help to identify new biomarkers, as well as novel therapeutic targets."

Prof. Marie D'hooghe, Prof. Jeroen Raes and Prof. Marie Bjerke

Nationaal MS Centrum Melsbroek - Center for Neurosciences

€ 71.562 / 1 years

"While first degree relatives (FDRs) of persons with multiple sclerosis (MS) in Belgium are 10-12 times more likely to be diagnosed with MS, their risk is currently not predictable. Mounting evidence suggests that the human gut flora, a complex ecosystem composed of billions of microorganisms, might be involved in MS and other chronic inflammatory diseases. Our project investigates the gut flora in families with 2 or more FDRs with MS. We compare shared and unshared characteristics among pairs of FDRs who both have MS and among mixed pairs (one has MS, the other does not have MS). Finding differences in the shared characteristics between these pairs contributes to unravel the complexity of interactions which influence the risk of getting MS."

Dr. Jeroen Bogie and Dr. Noam Zelcer

UHasselt - BIOMED and Department of Medical Biochemistry - Amsterdam University Medical Center

€ 60.000 / 2 years

"Instead of protecting us, the immune system sometimes goes awry, as in the case of the autoimmune disease multiple sclerosis. Previously, we demonstrated that lipids such as fatty acids are essential in driving the disease-promoting and –resolving properties of immune cells in multiple sclerosis. However, the molecular mechanisms involved remain poorly understood. In this study, we aim to unravel if binding of fats to proteins controls faulty immune cell function in multiple sclerosis, and explore whether that knowledge can be utilized for therapeutic purposes."

Read more ▶

Fonds Charcot 2021

Dr. Inez Wens and Prof. Nathalie Cools
UAntwerpen - Laboratory of Experimental Hematology
€ 38.715 / 2 years

"Progressive MS is characterized by neurodegeneration. While most of the currently available MS therapies act on the inflammatory response and thereby slow down the progression of the disease, only a limited amount of treatment options focus on regeneration and nerve cell repair. Therefore, there is a unmet clinical need for regenerative treatment strategies, especially for progressive MS patients. This project will focus on a protein, brain-derived neurotrophic factor (BDNF), that has the ability to repair neurological damage, due to its stimulating role during myelin sheath repair. In addition, recent research showed that specialized immune cells, regulatory T cells (Tregs), also play an important role in the repair process of the myelin sheath. These observations offer the opportunity to develop designer Tregs that are engineered to express BDNF, aiming to induce regeneration, and to exploit its potent effects. Our findings will contribute to the development of novel regenerative MS-therapies."

Prof. Sofie Struyf and Prof. Niels Hellings
KULeuven and UHasselt
€ 43.000 / 2 years

"Neutrophils have been identified in several autoimmune diseases to be part of the changed immune landscape. Recent evidence also points toward a possible involvement of neutrophils in the pathology of MS. We will phenotypically characterize neutrophils from MS patients and identify disease-associated neutrophilic pathways and cellular subsets. We will uncover the impact of current MS treatments on neutrophil phenotype and function. Top ranked genes identified will subsequently be studied in vivo to reveal their contribution to MS pathology. We will focus on genes involved in neutrophil migration, activation and effector functions to reveal new therapeutic targets."

More information on :
www.fondation-charcot.org

YOUR WILL CAN MAKE A DIFFERENCE

Has the Belgian Charcot Foundation ground to a halt this year? Far from it. Research into multiple sclerosis has continued unchanged. After all, our researchers know how many MS patients are counting on them to find a solution to a disorder that is still incurable. Their research was made possible by the money raised by the Belgian Charcot Foundation from its donors and testators. That is why we are counting on your help.

"My husband was a roofer and I used to be a hospital nurse. Our children are now married and I have three fantastic granddaughters. When my husband fell ill a few years ago and he put his affairs in order, he suggested including the Belgian Charcot Foundation in his will. He told me he was happy that his children and grandchildren had all they needed and that he thought it was important to do something that would live on after him. "Darling, I always enjoyed mending people's roofs when they needed it, and you've always helped people, too. Research is like mending a roof so it doesn't leak into the living room." The Belgian Charcot Foundation seemed a natural choice as we have an aunt with multiple sclerosis in the family. We saw how she kept hoping for a solution, and that really does get to you. My husband's bequest has helped support research. I'm now 82 years old and our children are proud of our decision."

Thérèse F., Brussels

"I would like to help overcome Multiple Sclerosis and I would like to make a gift in my will or living trust to the Belgian Charcot Foundation"

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Messenger RNA vaccines, a new weapon against infectious diseases and a source of hope for multiple sclerosis?

The current Covid-19 pandemic has triggered intensive research into new vaccines, particularly mRNA (messenger RNA) vaccines such as those produced by Pfizer/BioNTech and Moderna, the purpose of which is to stimulate the immune system against one of the virus's surface proteins. They contain the mRNA that enables the viral protein to be synthesised and which is incorporated into nanoparticles made of pro-inflammatory lipids (liposomes). Further to IM injection, the mRNA is absorbed by antigen-presenting cells that are activated by the lipids in the vaccine. The viral protein is then synthesised and "presented" to lymphocytes, either able to synthesise specific antibodies or turning into "killer" cells which then target the cells containing the virus.

However, this type of vaccine can be adapted for a totally opposite, non-inflammatory purpose, to generate tolerance of potentially autoantigenic molecules. This has just been shown in a paper published in *Science* on 8 January 2021, "A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis". Its lead author is Christina Krienke, and the other two are now world-famous: Ugur Sahin and his wife Ozlem Türeci, the founders of BioNTech and creators of the Pfizer/BioNTech Covid vaccine.

The model used in the paper of experimental autoimmune encephalitis (EAE) in mice is traditionally used to study the immune-related aspects of multiple sclerosis in humans.

For this purpose, the vaccine was altered by incorporating the messenger RNA into lipid nanoparticles which this time did not trigger an inflammatory response. The mRNA, one component of which is slightly changed, contains the synthesis code of a fragment (20 amino acids) of a protein known as myelin oligodendrocyte glycoprotein (MOG). As its name suggests, it is specific to myelin and to the cells – the oligodendrocytes – that manufacture it. When injected in mice with a lipid emulsion, MOG triggers autoimmune encephalitis by stimulating autoimmune lymphocytes. As the modified vaccine is non-inflammatory, the antigen-presenting cells no longer stimulate the autoimmune cells, but induce tolerance by blocking them. The vaccine proved capable of preventing the development of autoimmune encephalitis and also of stopping relapses when given after symptoms began to develop. It acts via the regulatory lymphocytes, the number of which increases. It also has the remarkable ability to induce cross-tolerance against other myelin autoantigens such as the proteolipid protein. However, the overall immune response does not change.

Obviously, these results require independent confirmation. It is equally obvious that positive results achieved using an experimental mouse model may not necessarily be directly transposable to humans. Some molecules, while effective against EAE, have proven ineffective or even harmful in the case of MS, for instance the anti-Tumour Necrosis Factor (TNF). Nevertheless, it remains true that this is a brand new avenue in the search for a specific treatment, i.e. the development of a specific tolerance to myelin antigens by the immune system without triggering immune suppression or altering the overall functioning of the immune system. The importance of these results and of the hopes they raise have been confirmed by the comments by Alexandra Flemming in the *Nature Reviews* Immunology issue of 12 January 2021, and by Roberto Furlan in the March 2021 issue of *Molecular Therapy*.

We can therefore still hope that the scientific research triggered by the Covid-19 pandemic may yield positive outcomes for other diseases, especially multiple sclerosis.

This, however, does not detract from the importance of ongoing research on the neuroprotection of nerve fibres when the myelin sheath has been destroyed and on the potential for remyelination.

Prof. Dr. Christian Sindic