



BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

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NEWSLETTER

Belgian Charcot Foundation
Public interest foundation

Under the Patronage of Her
Majesty The Queen

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2020 - a year like no other

2020 will be remembered as a dark year due to the health crisis triggered by the Covid-19 pandemic and to its looming medium- and long-term economic consequences. Fortunately, the great majority of MS patients have escaped the severest forms of this viral infection. As we explain elsewhere, MS does not alter the immune system's defences against viruses and most MS treatments preserve a good antiviral immune response. Only the most powerful treatments have had to be postponed in some cases. Comorbidities such as heart disease, diabetes, excess weight and high blood pressure play a greater part than MS in the severity of Covid infections.

Researchers, virologists and the vaccine industry are all racing to develop a treatment for Covid and its more serious complications (pneumonia, blood clotting) as well as effective vaccines. This is understandable and indeed necessary. However, there is a risk that it may deprive other, equally important research projects of resources, and specifically projects relating to MS, its mechanisms and potential new treatments.

In these difficult circumstances, the Belgian Charcot Foundation has endeavoured to maintain the goals it set for itself several years ago, and selected a third fellow in July 2020, Jasper Van den Bos, who will spend the next four years researching the possibility of remyelination induced by the immune system at the laboratory of Professor Nathalie Cools (University of Antwerp).

The Foundation also decided to continue financially supporting research projects in 2021 to the same level as in previous years, i.e. with grants of €500,000. The applications for these grants will be reviewed at the end of this year by an independent jury. The winners will receive this grant for their research in January 2021. The continuation of these exceptionally generous research grants has been enabled only by the generosity and loyalty of our donors and sponsors. The Foundation mainly supports translational research as described in this issue. In the past, it has supported Phase 1 and Phase 2 clinical trials, one of Inosine® and the other of Pixantrone®, which have been described in detail in the Multiple Sclerosis Journal. It also remains willing to support the preliminary experimentation of new treatments in the future despite the complexity of these therapeutic trials and their very strict regulation.

In this way, and despite these difficult conditions, we hope to preserve Belgium's potential for MS research, which relies on both experienced teams and young researchers.

Prof. Dr. **Christian Sindic**
President



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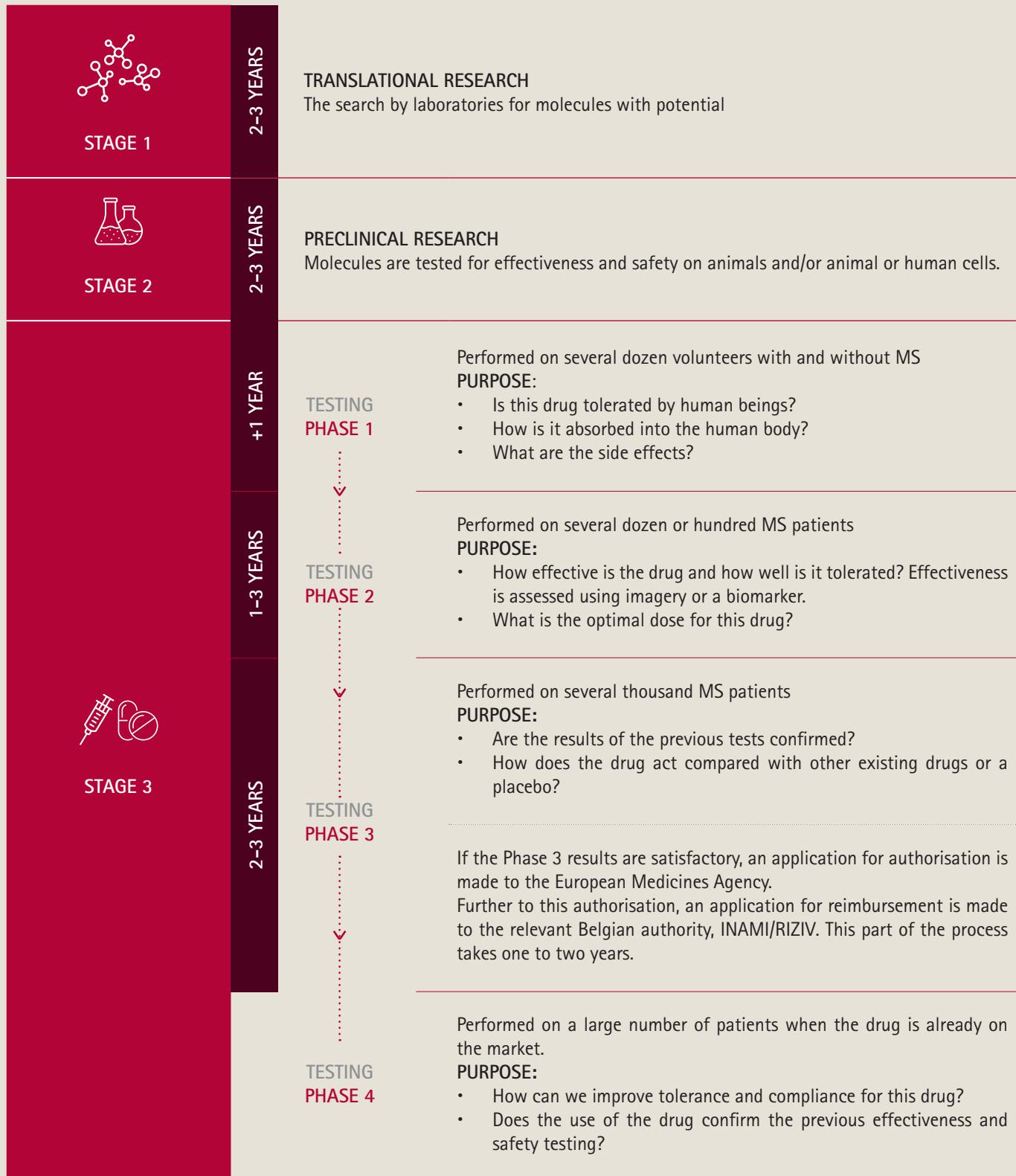
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THE RESEARCH. HOW DOES IT WORK?

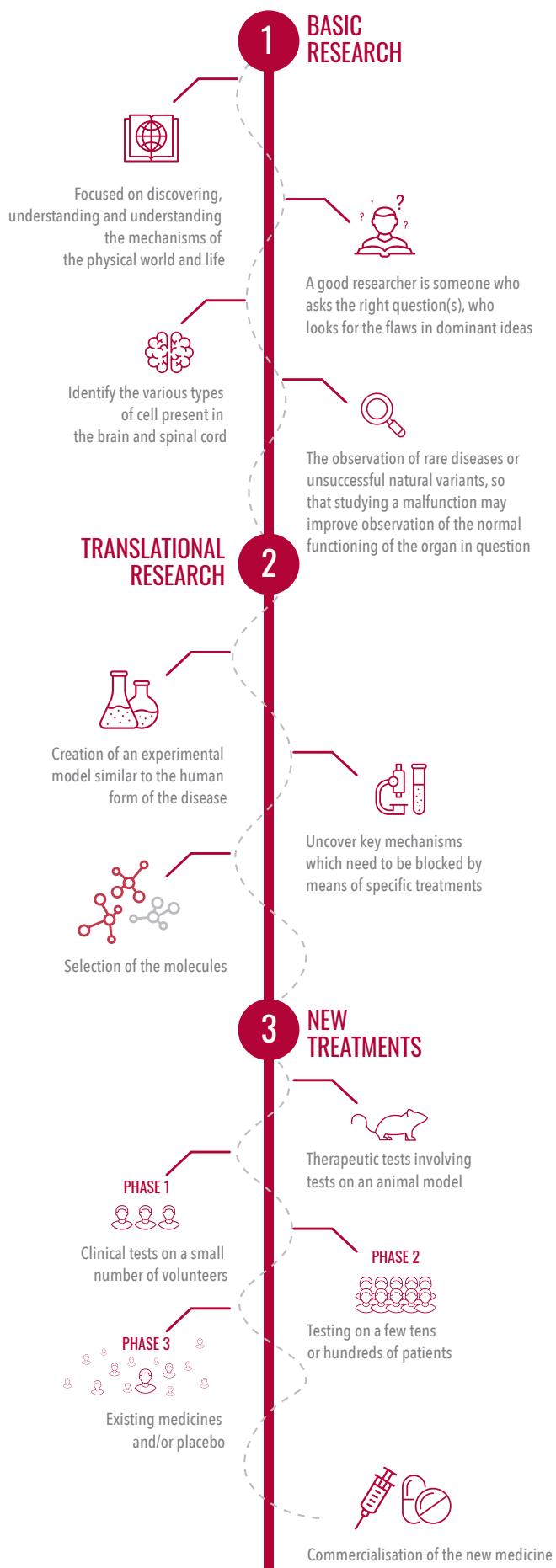
In 2020, you were bombarded with scientific terms.

Medical research is a necessary stage in understanding and beating a disease such as MS, but how does it work?

HERE ARE ITS VARIOUS STAGES:



PROGRESS IN MS RESEARCH



The driving force behind *basic research* is the desire to know and explore the mechanisms of the physical and living world in order to increase the sum of human knowledge and better respond to philosophical questions: where do we come from, who are we, where are we heading?

Such research is carried out – for instance – on the functioning of the normal brain, its cells and the connections and communication between those cells. The same applies to the immune system, its various components and the various populations of billions of cells that communicate with each other, interact and respond to positive and negative feedback. In basic research, there are no recipe-like methods, only observations that need to be measured, confirmed and integrated into a hypothesis that then has to be validated or invalidated. A good researcher is someone who asks the right question(s), who looks for the flaws in dominant ideas and wants to push back the limits of our knowledge. However, researchers are dependent on their measuring instruments. Their ultimate reward is to uncover "things hidden since the foundation of the world" (René Girard).

In the area of immunology, basic research has made great strides over the past 50 years: the discovery of the two major lymphocyte populations, B and T; the discovery of sub-populations within these categories; the discovery of histocompatibility, which plays a major part in the acceptance or rejection of transplants; the discovery of cytokines, which are molecules released by lymphocytes that affect other lymphocytes; the discovery of lymphocyte maturation from naive cells to memory cells; the discovery of the various types of antibodies, monoclonal antibodies and cytotoxic "killer" lymphocytes.

Basic neuroscientific research has enabled us to identify the various types of cell present in the brain and spinal cord, uncover neuronal circuits, define the function of various areas of the brain, measure nerve conduction velocities and identify all these connections as the "connectome".

The purpose of basic research is not to be applied to a specific health problem. However, it benefits from the observation of rare diseases or unsuccessful natural variants, so that studying a malfunction may improve observation of the normal functioning of the organ in question. On the other hand, the purpose of translational research is to apply new knowledge acquired through basic research to specific diseases so as to understand them better. Multiple sclerosis has benefited greatly from the remarkable progress made in immunology and also in chemistry and physics, which has underpinned the development of MRI and the visual detection of MS lesions.

One major problem in translational research on MS is the lack of a spontaneous animal model for the disease. No animals spontaneously develop an MS-like disease and it has been necessary to develop an experimental model comparable to another human disease, experimental autoimmune encephalitis. This model, which mainly involves T lymphocytes, has made it possible to uncover essential mechanisms applicable to MS, but for years also concealed the importance of the part played by B lymphocytes in the

human disease. Also, this model most often involves a single attack, which is very different from the multiple attacks observed in MS patients.

Translational research has enabled us to uncover key mechanisms which need to be blocked by means of specific treatments, such as the breakdown of the blood-brain barrier and the abnormal penetration from the blood into the brain of activated self-attacking lymphocytes. This mechanism is best blocked by using Tysabri® in the treatment of MS.

“ A good researcher is someone who asks the right question(s)

On the basis of the anomalies observed at molecular level which are responsible for the malfunctions of the immune and nervous systems, molecules can be selected in the hope that they can affect the progress of the disease. The lengthy process of therapeutic testing on an animal model if possible, either in vitro in a laboratory (cell cultures) or in vivo on live animals, then begins; it is followed by Phase 1 clinical testing, the main purpose of which is to check for harmful side effects on a small number of healthy volunteers; then by Phase 2 tests on a few dozen patients to determine the most appropriate dosage and check for paradoxical responses; if the results are encouraging, Phase 3 testing then proceeds on several hundreds or thousands of patients. Such clinical testing is strictly regulated, must be declared nationally and internationally, monitored by a committee of independent experts and regularly assessed. In some cases, it is halted early in the event of failure or serious side effects. The latter may even appear after the new drug goes on sale and may cause it to be permanently withdrawn (e.g. daclizumab in the treatment of MS).

However, both basic and translational research can yield surprises and unexpected results. In the case of MS, an interferon gamma treatment was tested and was found to trigger more attacks than the natural course of the disease (Panitch et al., *The Lancet*, 18 April 1987). For this reason, interferon gamma antagonists, in particular interferon betas, were tested with great success (Bétaferon®, Avonex®, Rebif®, Plegridy®). In the 1970s, researchers at the Weizmann Institute in Tel-Aviv synthesised a small peptide, glatiramer acetate, with a view to inducing experimental autoimmune encephalitis, and observed that in fact it had a protective effect against encephalitis. It was then tested on MS patients and now goes by the name of Copaxone®.

Researchers need to be born opportunists – in the best sense of the word – and especially analyse unexpected results.

Prof. Dr. Christian Sindic

► *The references of all studies mentioned are available from the Belgian Charcot Foundation on request.*

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CHARCOT FELLOWSHIP 2020-2024

Investing in the future of research

In 2016, the Belgian Charcot Foundation set up the Charcot Fellowship, a doctoral scholarship programme for young researchers (under 30 years of age). The aim of these fellowships is to strengthen the research potential of teams interested in multiple sclerosis in Belgium. By focusing on young researchers who wish to complete a PhD thesis on MS, the mandate aims to have long-term effects on research against this disease. The Fellows are always supervised by a team of experienced and renowned researchers.

2016-2020

The fellow is Elien GRAJCHEN (UHasselt). Promoter: Prof. Dr. Jerome Hendriks, Associate Professor of Immunology and Biochemistry, Institute for Biomedical Research, UHasselt.



Elien GRAJCHEN

In practical terms, what does the Charcot Fellowship mean to you?

The Charcot Fellowship has enabled me to spend four years studying the immunological mechanisms that underpin the progress of MS. Not only is this grant by the Belgian Charcot Foundation and its donors crucial to a better understanding of this autoimmune disease; it also helped me train as a researcher. Good researchers can't limit themselves to thinking analytically and complying with procedures, they also have to be open to the ideas around them. A good researcher is a team player and shares information. The Charcot Fellowship is quite right to insert young talent into experienced teams.

What stage have you reached in your work?

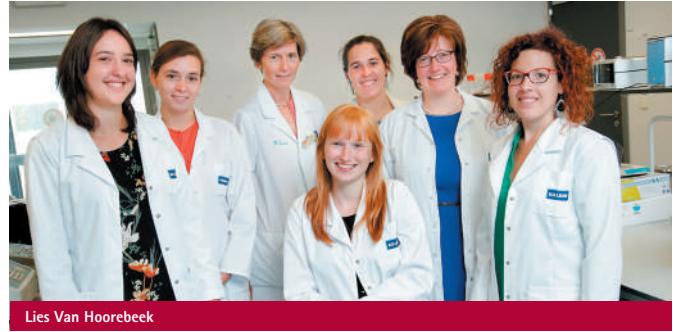
Last year, I published two peer-reviewed papers that clarify the role of fat metabolism in the function of the immune cells in MS. I'm currently finishing a third article and writing my doctoral thesis, which summarises my findings over the past four years. When you publish as a researcher, you're sharing your knowledge with other teams all over the world. These exchanges leverage research and speed up the discovery of solutions.

What are you aiming to achieve with your work?

My four years will be up in the spring of 2021. As the first fellow in this doctoral programme, I'll be defending my thesis then and officially gain my PhD. To secure Belgium's research potential, this programme is essential as it strengthens the existing teams. Biomedical research remains my great love, so I'll certainly continue with that. MS remains a mysterious condition and there'll be more than enough for me to do. The progress made by Belgian MS research over the past years is a strong incentive for me and for other young researchers.

2018-2022

The second fellow is Lies VAN HOOREBEEK (KU Leuven). Promoter: Prof. An Goris. Co-promoter: Prof. Dr. Bénédicte Dubois.



Lies Van Hoorebeek

In practical terms, what does the Charcot Fellowship mean to you?

The Charcot Fellowship has enabled me to spend four years researching the role of a specific type of variation in our genetic material – somatic variants – in the development and progress of MS. Our team uses issues that matter to MS patients as starting-points and tries to resolve them with research. Our aim is to improve knowledge of MS and subsequently its treatment. Each of us has their own project, but we all have different backgrounds: doctor, lab technician, bioinformatician, biomedical researcher... We help each other out according to our respective areas of expertise. The Charcot Fellowship has given me the opportunity to learn and develop as a scientist.

What stage have you reached in your work?

At this point, I'm half-way through. During these past months, we've also had to deal with the Covid-19 pandemic. We had to change our schedules and focus on what could be done from home. Luckily, my research includes a great deal of bioinformatic analysis, which can easily be done from home on a computer. In the meantime, we've drawn up a schedule that enables us to safely combine lab work and telework. We've managed to keep delays to a minimum and should be able to guarantee the continuity of our research over the next few months.

What are you aiming to achieve with your work?

According to the existing genetics textbooks, our genetic material remains unchanged throughout our lives. We now know that's not true and that genetic changes can occur during people's lifetimes. These changes are what I'm studying – they're known as somatic variants. The idea that they're very common and that they can have far-reaching effects is still a game-



Fighting multiple sclerosis

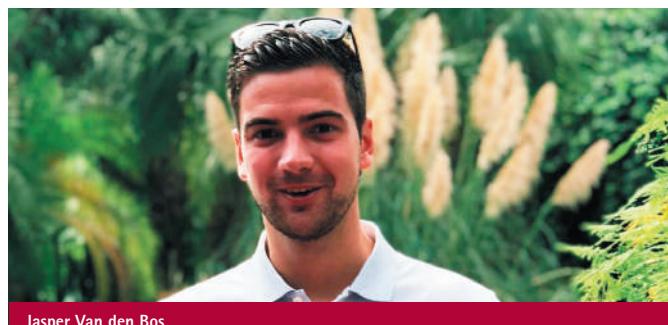
YOUR WILL CAN MAKE A DIFFERENCE

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.

changer. I hope to help make it possible to rewrite the textbooks in the very near future and that they can explain how somatic variants affect MS. Hopefully, this research can add a little more to the sum of our knowledge about MS and help patients in the long term.

2020-2024

In July 2020, the Belgian Charcot Foundation selected a 3rd Fellow, Jasper VAN DEN BOS, who will devote the next 4 years to a research project that will study the possible re-myelination caused by the immune system. The promoter is Prof. Dr. Nathalie COOLS and the co-supervisor is Dr. Ines WENZ, from the Laboratory of Experimental Haematology (UZA).



Jasper Van den Bos

For more information on MS and ongoing research projects, please visit www.fondation-charcot.org

“ 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

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