BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

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NEWSLETTER

Disseminating knowledge to shed a light on future options

In June 2022, for the fourth time (after 2016, 2018 and 2020), the jury of the Belgian Charcot Foundation awarded a PhD fellowship to a young researcher to enable them to perform research in the field of multiple sclerosis and write a PhD thesis. This fellowship is intended to cover the successful applicant's salary for four years, and its amount is €200,000 (50,000/year).

Such a doctoral grant enables the laboratory that hosts this young researcher to increase its team's strength and hire a motivated staff member to develop new research and co-author new scientific papers. At the end of these four years, the researcher will be able to defend a doctoral thesis in biomedical sciences, and as a post-doctoral fellow they will be able to perform further research independently.

This year, for the first time, the Belgian Charcot Foundation has created a part-time two-year Clinical Fellowship of €25,000 per year. This fellowship is intended to free a young neurologist or clinician from the demands of day-to-day care and clinical routine to spend time analysing groups of patients and their medium and long-term progress in relation to their treatments, long-term changes in brain imaging, the effectiveness of new medications, etc. This fellowship thus allows for the analysis, with hindsight and in depth, of specifically clinical themes that are not followed up in the routine and often exhausting work performed in a hospital department.

Thanks to our donors and sponsors, we have been able to give young researchers an opportunity to train both scientifically and clinically, and contribute their vitality and enthusiasm to MS research and the long-term care of MS patients.

It is imperative that the results of both basic and clinical research be published to inform the medical and neurological scientific community. Even if some results are negative, it is important to make them known in order to shed light on future options and to trigger creative discussions on the reasons for any failure. This is both necessary and an ethical imperative in the dissemination of knowledge and in the long march towards increasing the effectiveness of treatments for a disease that remains incurable to this day.

Belgian Charcot Foundation
Public interest foundation

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YOUR LEGACY CAN MAKE THE DIFFERENCE

The Belgian Charcot Foundation is the only independent organisation that exclusively supports basic MS-research in Belgium. It is thanks to the generosity of its donors and the bequests received that the Foundation can ensure the continuity and excellence of this research

Why choose to help the Belgian Charcot Foundation?

- because multiple sclerosis is still incurable
- because it very often evolves into a disability and disrupts the lives of thousands of people
- because we absolutely must understand this disease in order to be able to fight it concretely
- because all the efforts we can make now bring us closer to the solutions: stopping the disease, repairing its damage and one day beating it completely

When you choose to make a donation or a bequest in your will to the Belgian Charcot Foundation, we commit ourselves to invest it completely in research.

Your bequest will enable researchers to go further and faster. Think about it.

Do you have any questions? We are here to answer them in complete discretion.

Isabelle Bloem.
Head of donations and legacies

"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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GENETICS
We are all genetic mosaics

Lies Van Horebeek, a researcher at the Laboratory of Neuroimmunology at KU Leuven, is the second Charcot PhD Fellow. This PhD fellowship is possible thanks to all donors of the Belgian Charcot Foundation. Lies has now successfully completed her fellowship, supervised by the renowned team of Professor An Goris and Professor Bénédicte Dubois. In this article, Lies and her promoters tell us about their work.

The importance of the Charcot PhD Fellowship

Lies : I studied biomedical sciences at KU Leuven as from high school I already knew that I found biology very interesting, especially the human body. During my training, I noticed that I was particularly interested in neurology and genetics. Then following an internship with Professor An Goris and Professor Bénédicte Dubois, I was completely sold on MS research. I was therefore very happy to be selected as the second Charcot PhD Fellow.

Prof. An Goris : I am extremely grateful to the Belgian Charcot Foundation for their continued support of our research group's research. The Charcot Fellowships are particularly important because they allow us to spend four years working with young researchers to investigate MS. In this way, we bring fresh new ideas to a renowned team. At the same time, we offer these young researchers the necessary framework to train in science, and in particular in good practices that ensure reliable and high-quality results.

Genetic risk factors for MS

Lies : If you imagine our genetic material as a book consisting of more than six billion letters, the genetic material of each of us is more than 99.9% identical. Only one in every thousand letters differs between you and me. It is these small differences or genetic variations that contribute to the many characteristics in which we differ from each other, such as height, colour of hair and eyes, aptitude for sports or music. This also determines a lower or higher susceptibility of developing a disease like MS.

Prof. An Goris : Our research group is a member, and I am currently coordinator, of the International MS Genetics Consortium (IMSGC), a collaboration of more than 25 research groups around

"The normal process towards developing a new treatment takes years. Reliable scientific insights, including those from genetic research, offer the opportunity to accelerate this process.

the world from Australia to the US. With this international group, we have identified more than 200 genetic risk variants that confer a higher susceptibility to MS. These risk variants are passed on from parents to their children. This also explains why about 15 in 100 people with MS also have a relative with MS.

Novel insights: we are all genetic mosaics

Lies : The title of my doctoral research is "Somatic mosaics in MS: detection and insights into the disease". Our body consists of thousands of billions of cells. Current school textbooks state that the exact same genetic material is present in each of those cells of our body. However, my research with the most recent, novel technologies sheds a different light on this. We note that there are not only variations between people, but that there are also variations between the cells of the same person. The number of genetic variations between cells of our body increases as we age. We did not get these variations from our parents. They can be caused by external factors, such as sunlight and smoking, and also by internal factors, such as during cell division when the genetic material is copied. This means that we are actually all mosaics of cells with slightly different genetic material. We were able to bring this to the attention of our international fellow scientists in a review article entitled "Somatic variants: new kids on the block in immunogenetics" in the scientific journal "Trends in Genetics". This allows other researchers to validate and build on our findings. However, we are by no means the only ones who have demonstrated the extent of genetic mosaics. For example,

Icelandic researchers at "deCODE genetics" found that even identical twins are not genetically identical as has been assumed up until now. The two halves of monozygotic twins show minor variations that begin just after fertilization, during embryonic development, and increase in number over the twins' lifetimes. Twins are easier to study, but the fact that we are genetic mosaics applies to everyone. Therefore, the school books have to be rewritten!

Genetic mosaics and MS

Prof. Bénédicte Dubois : What do those mosaics now mean for MS? We are only able to investigate this thanks to the many people with MS and their partners who are willing to participate in scientific research.

Lies : When someone agrees to participate in scientific research, a blood sample is taken and in the laboratory we use this blood sample to sort the different types of blood cells. In our study, we examined immune-system cells that play an important role in MS, more specifically the T cells and B cells. We extracted the genetic material, DNA, from these cells and were able to read it with new technologies. We then compared a large group of people with MS with a large group of healthy controls. Developing this method has been a major challenge in my research as we need to be able to reliably distinguish the real, biological variations from technical errors that occur because the DNA reading technologies are not yet perfect. This involved a big bioinformatics challenge!

Prof. An Goris : We are very grateful to the Belgian Charcot Foundation for making a such an innovative project possible. When we started this study, we hoped to find maybe one or at most a couple of these newly emerged genetic variations in some of the study participants. To our surprise, we found that the vast majority of individuals with MS carry such variations, and even healthy controls do. These results of Lies' research have meanwhile been confirmed by Finnish fellow researchers.

Lies: The newly emerging genetic variations can change proteins and change cells, e.g., by making them divide faster or making them more pro-inflammatory. By combining my results with the results of international colleagues, we see that there are "hotspots" where new variation occurs more often. We can now compare those "hotspots" in larger groups of people with MS and healthy controls. We expect that if these hotspots increase MS susceptibility, they will be more common in individuals with MS than in control subjects.

Prof. An Goris : The finding that we are all genetic mosaics, and the scale of this phenomenon, are very important. In addition to the genetic variations that are passed on from the parents to their children, we now also need to study further the newly emerged genetic variations between cells for their role in MS. We believe it is very important to include this in future genetic research, including in collaborations with the International MS Genetics Consortium. With even newer and better DNA reading technologies, we can continue this research on a larger scale in the future.

Importance of genetic research for MS

Prof. Bénédicte Dubois : Scientific research, in which different studies build on each other over a longer period of time, is important not only for a better knowledge of the disease, but also to achieve tangible results for the person with MS. The normal process towards developing a new treatment takes years. Reliable scientific insights, including those from genetic research, provide an opportunity to speed up this process.

Prof. An Goris : Many substances or molecules are suggested as possible new treatments. Only a small proportion of these successfully complete all the clinical studies required to develop an effective drug. Many molecules drop out along the way because they do not appear to be as effective or safe as hoped for. Genetic research can provide additional arguments for selecting the most promising molecules. If genetic variation in a molecule is associated with a disease, that molecule is a prime candidate for developing a potential treatment for that disease. It has now been repeatedly shown that support from genetic research for a molecule doubles that molecule's chance of passing all clinical studies and leading to an effective drug. Pharmaceutical companies have understood that importance very well: they are now extensively building on genetic research in the search for new treatments. The commitment of young, talented, and well-trained researchers such as the Charcot Fellows is therefore extremely important, at both universities and pharmaceutical companies!

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RESEARCH
The importance of papers in scientific and medical research

Conferences, workshops, congresses, webinars, posters... communication in the world of science takes many forms. However, even more than oral information, scientific papers published in international journals further to a critical re-reading by independent specialists remain the cornerstone of the broadcasting of scientific knowledge.

Scientific publications can take the form of reviews of a particular subject, which may in some cases be requested by the publisher of a scientific journal from a specialist, or spontaneously addressed to such a journal. The purpose of reviews is to summarise a new or 'hot' topic concerning which information is scattered in many publications. As they enable the current state of knowledge to be summarised, their impact can be strong. They are often based on an inventory of several hundred referenced papers that have been collected by the authors, and the results of which are viewed from a general perspective.

Meta-analyses are articles that group and add up the results of several clinical studies that are comparable but have been performed on limited groups of patients. By adding up the results of these studies, it is possible to extract information that is more reliable; however, it must be demonstrated that such an addition can be performed and that there are no confounding factors or recruitment biases. Such meta-analyses are particularly useful when comparing the efficacy of several drugs. Sophisticated statistical methods enable the summation of the results of each individual study to be validated – or not.

Traditionally, a scientific paper is a presentation of the results of experimentation which may be biochemical or performed on cell cultures or lab animals, most often mice. The samples analysed may therefore be animal or human.

The commonest approach is to test a working hypothesis using the most appropriate form of experimentation, by multiplying approach routes, by stimulating or inhibiting certain proteins, triggering cell differentiation in cultures, applying several technologies to detect the changes induced by various experimental conditions. Results must be reproducible from one experiment to the next, quantifiable, objective and hence independent of the observer, and compared with appropriate control groups. Other experiments are not based on prior hypotheses, but take the form of analysing all genetic factors (genomes), all proteins (proteomes), all microbes in an organ (microbiomes), all transcriptions of mRNA into proteins (transcriptomes), all lipids (lipidomes), etc. Differences are sought between what is observed in a specific disease with no reference to a prior hypothesis, and a mechanistic explanation is then sought for the differences observed.

Whatever the case, scientific papers must be written in a fairly standardised format, with an introduction that describes the current state of knowledge and the question(s) asked, a precise description of the equipment and methods used that enable the experiments to be reproduced as well as of the statistical analyses used, a 'Results' section with concise descriptions and illustrated with figures or photographs, and a discussion of the new data yielded by the experiment. A scientific paper always ends by referencing a number of papers and other publications published earlier on the same subject or a related topic. These are preceded by a summary, each word of which is carefully weighed. The authors must mention the financial support received for their experiment and any potential conflicts of interest.

Of course, scientific research relies heavily on technical progress, whether in imaging, protein and lipid analysis, or genetic analysis. It is therefore unsurprising that some discoveries are made almost simultaneously by different teams in different countries when a particular technology has increased analytic potential.

Scientific papers must then be submitted to a journal according to its subject and themes. They are reviewed critically and anonymously by a minimum of two independent reviewers, who usually request more or less substantial changes to the manuscript and give their opinion concerning the interpretation of the results achieved. This 'back-office' work is extremely important, as reviewers can detect inconsistencies or even major errors. The reviewed manuscript is finally accepted for publication if the authors' responses to the reviewers are satisfactory, if their methods are reliable and if their results contribute new or corroborating data.

These days, papers are often published online before they are printed. Some journals are even online-only. An increasing number of papers are open-access, i.e. anyone can read the paper in full without even having to subscribe to the journal. Members of an academic community may also be able to access them if their university library has taken out a subscription for all its members. It should be mentioned that a number of oral presentations are never published, the reason being that they are not sufficiently grounded. Some published papers may even be retracted if they are seen to contain errors. Such errors can occur in all research

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and be published in even the most reputable journals. Retraction of work should not be misjudged. On the contrary, it is a respectable and honest act. One instance is supplied by American professor Frances Arnold who, as an undergraduate, worked as a house cleaner, taxi driver and pizzeria waitress, and was awarded the Nobel Prize in Chemistry in 2018. She co-authored a paper in renowned journal Science in 2021, then requested its retraction because the results were not reproducible, thereby acknowledging a scientific error. One can only admire the greatness behind this approach.

It is therefore clear that innovative results must always be independently confirmed by a different team from the one that first published them.

Personally, I shall always be grateful to the anonymous reviewer of one of my first scientific papers for the many comments and criticisms they made on my manuscript, which helped me improve it and its successors! I have also had the satisfaction of being thanked by the authors of a paper for my anonymous comments, which they had found to be constructive and had enabled them to improve and consolidate their work. Like any other activity, scientific research is a human activity with its failures and successes, its difficulties and satisfactions, and a profession that is learned patiently over time.

Prof. Em. Christian SINDIC

- The references of all the studies cited are available on request from the Belgian Charcot Foundation.
- More information and videos at *www.fondation-charcot.org*
- This newsletter is also available in FR and NL on our website.