BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

Number 47

NEWSLETTER

Innovation and concrete results

Increasingly, we are able to effectively treat active inflammatory MS lesions, which have specific MRI characteristics as they capture an intravenously injected contrast agent - gadolinium - which enables the focal opening of the blood-brain barrier. We now have drugs which make it possible to prevent over 90% of such active lesions from occurring. However, we know that there are other, chronically active lesions, which do not capture the contrast agent and which extend slowly but surely, centrifugally, around formerly active lesions.

These chronic lesions, partly active at the edge and inactive at the centre, have a propensity to "creep" and are therefore partly responsible for the gradual increase in the severity of the disease. The periphery of these lesions contains macrophages that very gradually destroy the myelin sheaths. These macrophages are loaded with iron which is probably produced by the destruction of the oligodendrocytes that manufacture the myelin sheath. Recently, MRI technology has enabled this thin ring of iron to be detected around formerly active lesions. The work of Prof. Tom Vanden Berghe focuses particularly on the toxicity of iron, which can cause cell death, and on the ways in which this toxicity can be countered by the use of new molecules.

These slow-growing lesions, which are known as slow expanding lesions (SEL), develop inside brains when the blood-brain barrier has once more become impermeable. A basic issue, then, is delivering the requisite therapeutic molecules to the brain. Prof. Anne des Rieux is working on a new method of getting molecules to penetrate the brain via the nasal mucous membrane, the upper part of which is separated from the olfactory bulbs only by the cribriform plate, a thin bone with multiple holes. Nanomolecule sprays containing therapeutic substances could enable drugs to be introduced directly into the brain, bypassing the blood-brain barrier.

This research is periodically the focus of scientific meetings organized by the Belgian Charcot Foundation. Belgian teams that have benefited from Charcot funds will present their results with the participation of renowned overseas specialists. To obtain valid scientific advances, it is essential that researchers exchange and communicate with each other.

Prof. Dr. Christian Sindic
President

Belgian Charcot Foundation
Public interest foundation

Under the Patronage of Her Majesty The Queen

Huart Hamoir Avenue 48
B - 1030 Brussels
Phone: +32 2 426 49 30
info@fondation-charcot.org
NN 468 831 484

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Av. Huart Hamoir, 48 - 1030 Brussels

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FUNDAMENTAL RESEARCH

Laureates of the Charcot Fund 2020

In line with previous editions, the Scientific Jury of the Charcot Fund 2020 is continuing with its choices to guarantee the excellence and continuity of MS research in Belgium. Its objective is to rapidly make MS a controllable neurological disease. The avenues being followed are: prevention, personalised treatment and the possibility of remyelination.

The Jury's choice this year therefore has focused on projects that work on a better understanding of the mechanisms of the disease, on projects that explore the role of macrophages and intercellular communication in remyelination and finally on two research projects involving revalidation processes.

A budget of €500,000 has been allocated to 10 university teams:

The why and how

Neuroimmunology
and Immunology
Prof. Laurent Gillet
Université de Liège
and Prof. Niels Hellings
Hasselt University, Biomed
€50,000 / 2 years
"We are seeking to answer the questions: How do herpesviruses contribute to the development of multiple sclerosis and is preventive vaccination a possible solution to eliminate this risk factor?"

Immunotherapy
Prof. Veerle Somers
and Dr. Judith Fraussen
UHasselt, Biomed
€40,000 / 2 years
"We aim to find specific targets in pro-inflammatory age-associated B cells which could lead to a more specific and efficient new therapy for MS."

Neuroimmunology
Dr. Bieke Broux
UHasselt
€47,000 / 2 years
"We aim to identify a novel cellular mechanism that contributes to brain damage in MS, which in turn might lead to new therapeutic targets."

The role of macrophages

Immunology
and Neuroimmunology
Prof. Jerome Hendriks,
Dr. Mjaarour Haidar
and Prof. Noam Zelcer
UHasselt, Biomed
€60,000 / 2 years
"To find out whether impaired lipophagy in phagocytes promotes the accumulation of myelin-derived lipids, and whether inducing lipophagy enhances repair, suppresses neuroinflammation and presents a therapeutic target in MS."

Neurobiology
Dr. Elisabeth Piccart
and Dr. Tim Vanmierlo
UHasselt
€30,000
"We aim to show that we can effectively boost remyelination in human stem cell-derived oligodrendrocytes, which will be crucial to developing a new remyelinating therapy."

Immunology
and Neuroimmunology
Prof. Tom Vanden Berghe
UAntwerpen
€51,590
"Anti-rust therapeutics improve the clinical picture in experimental relapsing remitting MS."

Our mission:
Overcoming MS through research

- Prof. Dr. Christian Sindic

VIDEO > fondation-charcot.org

Intercellular communication

Neuroimmunology
Prof. Roosmarijn Vandenbroucke
UGent
€50,000 / 2 years
"We aim to find specific targets in pro-inflammatory age-associated B cells which could lead to a more specific and efficient new therapy for MS."

Immunology
and Neuroimmunology
Prof. Vincent van Pesch, Dr. M. Alhouayek, Prof. G. Muccioli and Dr. L. D'auria
UCLouvain
€60,000 / 2 years
"Our aim: to make a functional study of lipid mediators and microRNAs from the cerebrospinal fluid in the pathophysiology of multiple sclerosis in order to identify innovative therapeutic targets."

Rehabilitation process

Rehabilitation
Prof. Jeroen Van Schependom
Vrije Universiteit Brussel
€39,235
"We will investigate the possibility of transcranial electrical stimulation as alternative therapy for slowing down demyelination in multiple sclerosis patients."

Rehabilitation
Prof. Peter Feys
UHasselt
€62,013 / 2 years
"This research project, investigating the best instruction- and feedback methods in learning new movement tasks, aims ultimately to optimize the rehabilitation programs for persons with cognitive limitations due to MS."

Jury of the Charcot Fund 2020

Prof. Dr. Christian Sindic, President of the Belgian Charcot Foundation.
Prof. Dr. Bénédicte Dubois, President of the Belgian Multiple Sclerosis Study Group. Head of the Department of Neurology, UZLeuven. Head of the Laboratory of Neuroimmunology and the Research Group in Experimental Neurology, Department of Neurosciences KU Leuven.
Prof. Dr. Alain Maertens de Noordhout, Head of the Department of Neurology at the CHR Citadelle Liège.
Prof. Dr. André Goffinet, Professor Emeritus of the Faculty of Medicine, Institute of Neurosciences, UCLouvain.
Prof. Dr. Carlo Pozzilli, Department of Neurology and Psychiatry, La Sapienza University of Rome.
Professor of Clinical Neurology and Head of the Multiple Sclerosis Centre of the Ospedale Sant'Andrea, University of Rome "La Sapienza", Italy.

The successfull candidates received these grants at an academic session on 23 January at the University Foundation in Brussels.
More information on these research projects and/or on how you can support innovative research on :
www.fondation-charcot.org/en

WARNING!

Coronavirus

The Belgian Charcot Foundation adheres to the guidelines of our health authorities: https://www.info-coronavirus.be/nl/ or https://www.info-coronavirus.be/fr/, which are updated when necessary.

The Belgian Charcot Foundation follows the advice of the Belgian Study Group for MS regarding the treatment of MS patients.
Therefore, the following recommendations apply:

1. The preventive measures provided to the general population apply even more especially to patients with MS, especially when they are treated with disease-modifying drugs.
2. In patients with MS, treated with disease-modifying drugs it is recommended that:
   - Interferon-beta (Avonex®, Betaferon®, Rebif®), glatiramer acetate (Copaxone®), teriflunomide (Aubagio®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), natalizumab (Tysabri®): treatment is continued.
   - Ocrelizumab (Ocrevus®), cladribine (Mavenclad®), alemtuzumab (Lemtrada®), rituximab (Mabthera®): starting or redosing of treatment is postponed if the disease severity/activity of the patient allows.
3. Persons with MS who are treated with disease-modifying drugs and are infected with Covid-19: the ongoing treatment is stopped until recovery

Stem cell transplants

Various "firms" misleadingly appropriating the term "medical" or "scientific" are currently reaching out to MS patients to extol the effectiveness of **"stem cell" transplants** in treating their disease. These "transplants" are carried out abroad, in Russia, India, Israel, or in countries of Eastern Europe... They sometimes recommend "crowdfunding" among their family to raise the money needed...

It must be stressed that currently **there are no scientifically established applications or clinical results for this type of treatment.**

Hematopoietic stem cells are used clinically in treating leukaemia and lymphomas, successfully, and are used to regenerate blood cells after chemotherapy.

Intensive research is being carried out on other stem cells, particularly those called "mesenchymal", for example, to induce differentiation into nerve cells, but there is currently no recognised and established clinical application in human diseases.

The Charcot Foundation financially supports research of this kind into MS in Belgium. It could lead to protection of nerve fibres and remyelination, but this must be a rigorous process which assesses the risks and benefits and be validated in animal MS models.

€7 A MONTH FOR ONE YEAR = ONE DAY OF RESEARCH

Donating €7 a month by standing order really supports research into MS in Belgium.

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Gifts of €40 or more are tax deductible.

INNOVATION AND CONCRETE RESULTS

MS research, in part with the support of the Charcot Foundation, has already led to current treatments for some forms of the disease which are more effective, less invasive, and slow down the progression of multiple sclerosis.

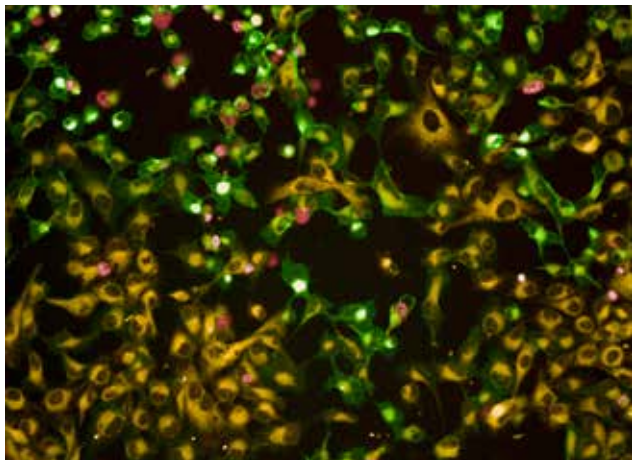
To carry on with such positive developments, basic research is indispensable. It is therefore with great pleasure that we present the first results of research projects funded by the Charcot Foundation thanks to its donors.

Rustproofing against MS?

One innovative, inter-university and multidisciplinary project has been implemented by Prof. Tom Vanden Berghe with Prof. Peter Vandenabeele and doctoral student Emily Van San, who together with VIB/UGent and UAntwerpen have been working on "ferroptosis".

Prof. Tom Vanden Berghe (VIB/UGent – UAntwerpen): "Yes. Our bodies contain a kind of biological rust which is basically similar to the rust that occurs on iron in nature. To grow and function properly, our bodies require iron, which needs to be well protected against rust. The formation of biological rust, known in scientific jargon as ferroptosis, can cause brain damage. At our lab, we study biological rust and inflammation within the context of multiple sclerosis (MS).

The effect of MS is similar to that of an electrician who strips off the protective insulation from electric wires and causes the system to break down. In the brain, the body's own immune cells attack the nerve insulation, myelin, meaning that the nerve fibres can no longer correctly dispatch signals to the rest of the body. Earlier research has shown that iron accumulates on the damaged areas of the brain (MS plaques) and that the structure of myelin is highly sensitive to iron.



Copyright: VIB Screening Core & UGent Expertise Centre for Bioassay Development and Screening (C-BIOS). The "rusting" cells turn from yellow to green, after which they die and turn red.

Certain proteins and vitamins have a "rustproofing" effect, for instance the Vitamin E that is found in sunflower seeds. Unfortunately, there are as yet no rustproofing drugs on the market, although some are being developed in both Europe and America. So, together with Prof. Koen Augustyns (@UAntwerpen), we have developed a new generation of rustproofing chemicals that are in many ways better than earlier drugs. To determine whether these new-generation drugs will have an effect on the clinical picture of MS, the lab has developed a mouse model for relapsing-remitting multiple sclerosis (RRMS). This form of MS affects 85-90% of patients and is characterised by inflammatory relapses, during which myelin is destroyed, followed by remissions during which myelin regenerates and symptoms decrease.

Primarily, we have noticed that slowing down biological rusting – ferroptosis – delays the onset of the next attack and generally improves the clinical picture. Of course, we have yet to determine whether this effect, and therefore the use of rustproofing therapy, has potential in the case of MS patients. **The existing therapies mainly slow down the immune system, and it may be that in the future it will be possible to add rustproofing and even regenerative drugs and more or less completely drive back the disease."**

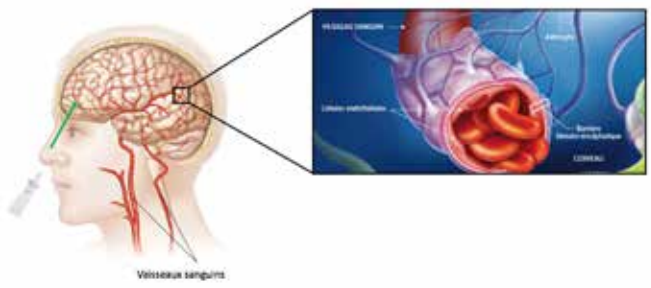
A nasally-administered drug

One instance of research with highly concrete results has been achieved by the team of Prof. Anne des Rieux (UCLouvain). With Viridiane Gratpain, Yasmine Labrak and Ariane Mwema, they searched for a way to administer MS drugs differently in order to improve patient quality of life and drug efficacy. Their solution was to replace oral or injected drugs with nasal sprays.

Prof. Anne des Rieux, (Louvain Drug Research Institute, UCLouvain): "To keep it short, MS is an inflammatory autoimmune disease that affects the central nervous system (CNS). This means that a person's immune defences attack the myelin sheath which isolates the brain and spinal cord nerves, and plays a major role in the transmission of nerve impulses. Ultimately, the destruction of this sheath causes the neurons to degenerate and many symptoms appear, such as fatigue, pain, eyesight deterioration

or urinary problems. At the more advanced stages, patients may suffer from paralysis of one or more limbs or even become completely disabled. Indeed, MS is the top cause of non-traumatic disability in young adults.

Although regeneration processes sometimes occur in the early stages of the disease, they are usually ineffective. For this reason, we need to find new drugs that can rebuild the myelin sheath.
Many teams and researchers are working to better understand MS, to develop treatments and therapies, but we still have a long way to go. One of the major limitations to treating MS is the very small percentage of drugs that can reach the CNS[1], which is protected from harmful substances by the physiological barrier known as the blood-brain barrier which also impedes the entry of drugs. It would seem that 98% of the new molecules currently being developed cannot pass this barrier and thus reach the brain.



Adapted from: https://www.saintlukeskc.org/health-library/understanding-cerebral-angiography and https://www.sciencesetavenir.fr/sante/alzheimer-un-probleme-d-etancheite-du-cerveau_28646

At the Louvain Drug Research Institute (LDRI), our team is focusing on new approaches to deliver drugs more efficiently to the CNS . Our goal is to reduce inflammation and repair the damaged myelin sheath.

Our strategy is to place a molecule of interest on a vehicle approximately one nanometre in size - this is known as nanomedecine - and to administer it nasally.

In the case of MS, vehicles are doubly useful, as they not only protect the molecule of interest as it is delivered to the damaged areas, but also target the cells responsible for the protection of the myelin sheath.

Moreover, nasal administration is particularly effective as it permits direct access to the brain and therefore avoids the blood-brain barrier.

The first papers containing the specific results of this research are expected in the coming months and may represent a genuine advance in the delivery of drugs to the brain. Of course, this research could also help patients with diseases other than MS. "

[1] https://uclouvain.be/en/research-institutes/ldri/addb.html

Further information, as well as a video in which researchers explain their projects in greater detail, is available on:
www.fondation-charcot.org/en
This research demonstrates the importance of work by universities on the disease. The teams actively include young researchers, thus ensuring the future of MS research and its innovative character.

The references of all the studies mentioned are available on request to the Belgian Charcot Foundation.

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