BELGIAN CHARCOT FOUNDATION

FIGHTING MULTIPLE SCLEROSIS

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NEWSLETTER

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Live from the research front

In this new issue of the Foundation's newsletter, you will find two articles by two scientists who have been financed several times by the Charcot fund: Professor Bieke Broux and Professor Anne des Rieux.

Bieke Broux describes the complexity of the immune system and of the disruptions that cause MS to develop and progress. Although immune cells can be roughly divided into three categories – T cells, B cells and myeloid cells – it has become apparent that each of these categories includes multiple sub-populations, some of which are pro-inflammatory while others reduce and control inflammation. In this "jungle" of cells, it can be very difficult to precisely determine the activity of each subgroup of immune cells and investigate their positive or auto-immune (negative) effects. The discovery of regulating T cells, however, has raised hopes. Not only are they able to regulate the entire immune system; they can also have a reparative effect on established demyelinated lesions. This could be a starting point for a form of cell therapy in which a patient's T cells were collected and selected, then made to proliferate and activated before being reinjected into the same patient. Although there is still a long way to go before this can happen, it represents a genuine source of hope.

Moreover, most of the current MS treatments do not penetrate the brain and do not have any direct effect on the immune cells that are already present there. Lemtrada, Tecfidera, Copaxone, Aubagio, beta interferons, Tysabri, Ocrevus, Kesimpta and others have no proven significant activity inside the brain. Only Mavenclad and the sphingosine 1-phosphate receptor modulators (Gilenya, Zeposia, Ponvory, Mayzent) are able to penetrate the nervous system and directly play a beneficial role. It is therefore especially important that we try to improve the transfer of drugs to the brain. One potential method may be the use of nanodrugs and of the nasal route, i.e., the olfactory membrane, which is far more permeable than the blood-brain barrier. Anne de Rieux discusses her current research in this area.

Both articles provide direct insight into the state-of-the-art research performed in Belgium thanks to your support and loyalty. Happy reading!

Prof. Christian Sindic

President

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The immune cell jungle in MS: could regulatory T cells show the way out?

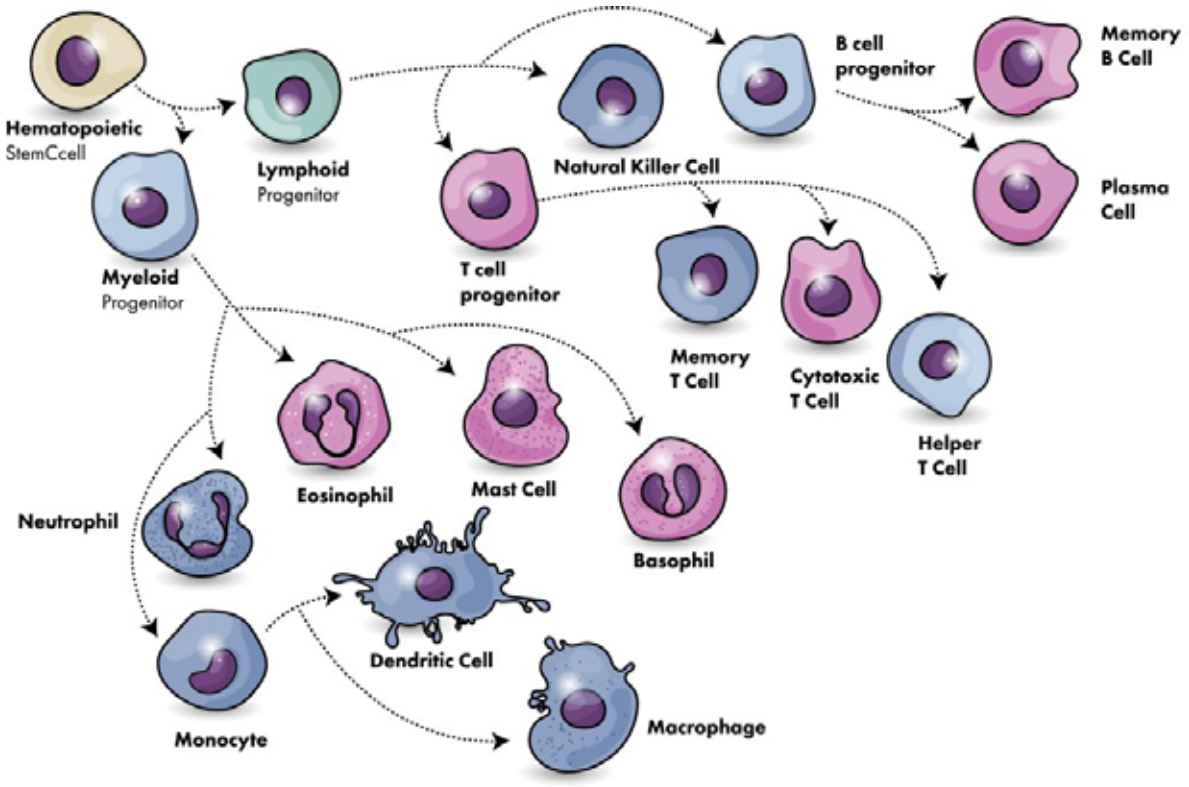
Multiple sclerosis – a brain scattered with lesions that are caused by an aberrant immune response against brain tissue, myelin to be exact. This has been known for decades, so why have we not found a cure yet?

Recent technological advances have taught us that the immune system is even more complicated than we ever conceived it to be. Fifteen years ago, at the start of my career, we believed that T cells (a type of white blood cell) were the main culprit in MS, and that they were either pro-inflammatory or anti-inflammatory. Now, we understand that even within the T cell population, tens if not hundreds of subsets and states exist. We now also know that one T cell can produce both pro- and anti-inflammatory molecules, making it even more complex. If you now also take into consideration that other immune cell types (e.g. B cells, NK cells, neutrophils, macrophages, dendritic cells, ...) have all been shown to be involved in MS, it almost becomes an inaccessible jungle.

Luckily, our scientific and therapeutic tools have evolved as well. At this moment, we can look in unprecedented depth at one person's immune system, even at the level of a single cell. In addition, we can look at interactions between all those different immune cells, and begin to understand their ways of communication. Also, recent successes in cell-targeting therapies, such as B-cell depleting antibodies, have taught us a lot about the immunology of MS. However, despite the success of current therapies, most of them do not work in all persons with MS, and they are still unable to prevent progression of the disease. This could have several reasons. First, the currently approved therapies do not induce repair of the damaged brain, and as people age, the brain's inherent capacity to repair itself becomes impaired. Therefore, the damage that has been done to the brain cannot be restored anymore. Second, researchers have identified "silent progression", also termed "progression independent of relapse activity" (PIRA), which appears to be driven by ongoing damage to brain cells in the gray matter. Finally, the existing therapies do not restore immune tolerance, meaning that the triggering event is not dealt with.

In recent years, cell therapy has gained increased attention in the medical field. For example, CAR-T cell therapy makes use of a patient's own T cells, which are genetically modified in the lab and then given back to the patient. This type of therapy is now approved for B-cell lymphoma and is under investigation for several other types of cancer. In the field of autoimmunity, researchers have been looking at so-called "regulatory T cells" (Tregs) as a potential way out of the immunological jungle.

Tregs are inherently equipped to dampen immune responses, but they are less functional in people with MS. In recent years, researchers have discovered a novel function of Tregs. Excitingly, these cells are also able to induce tissue repair, and more importantly, repair of myelin in the brain! This finding has sparked a renewed interest in these cells, and more specifically, in the idea of using them as a cell therapy. In theory, giving functional Tregs to a person with MS would restore their immune tolerance, thereby stopping attacks to the brain, and it would support repair



Immune Cells

Tregs are also able to induce tissue repair, and more importantly, repair of myelin in the brain

of damaged brain tissue. Of course, there is still a long way to go between this theoretical cure and an actual therapy. First, we need to make sure that the Tregs we give back to a patient are functional and remain so when in the body.

For example our lab has recently discovered that Tregs change and become, dysfunctional when they cross the blood-brain barrier, which is the gateway to the brain. In addition, we need to consider safety, specificity and other issues. Many researchers around the world are currently investigating whether genetic modification of Tregs is feasible to tackle these issues.

In summary, recent technological and therapeutic advances have uncovered the highly complex nature of the immune system, and we are still learning about what goes wrong in people with MS. Given their inherent capacity to restore immune tolerance, and to induce tissue repair in the brain, Tregs hold great potential of providing a next-generation therapy for MS.

Prof. Bieke Broux, Hasselt University

With the support of Degroof Petercam

Attention: new regulation for the deductibility of donations made in 2024

Since December 2023, a new tax regulation has made it compulsory to add the National Register identification number (NN, which can be found on the back of the Belgian identity card) of donors when making an electronic declaration via Belcotax using forms 281,71, from the 2025 tax year onwards, i.e. **for donations received in 2024**.

- If you make an online donation, you can provide us with your NN via the field provided on the form.
- If you are making a standard bank transfer and would like to receive a tax certificate, please send us your NN by e-mail to info@fondation-charcot.org.

Thank you in advance for your cooperation.

TRUST AND BELIEVE IN THE FUTURE

Support MS-research and include a bequest to the Belgian Charcot Foundation in your will You will enable researchers to go further and faster.

And **you will have a considerable positive impact** on the lives of thousands of people suffering from MS.

The Charcot Foundation is the only independent organisation in Belgium that exclusively supports **fundamental research into multiple sclerosis.**

We have the expertise of researchers. Let's have confidence in the future so that research can beat MS.

Why choose to make a donation in your will to the Belgian Charcot Foundation?

- because multiple sclerosis is still incurable and very often evolves into a disability and disrupts the lives of thousands of people
- 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
- because we commit ourselves to invest your donation completely in MS research.

Do you have any questions?
We will answer you in complete discretion.

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FONDATION CHARCOT STICHTING

How to ensure therapeutic molecules penetrate the blood-brain barrier?

One of the limitations to the development of drugs for the treatment of MS (or other neurological diseases) is the limited access of therapeutic molecules to the central nervous system.

The central nervous system is protected by what is known as the blood-brain barrier (BBB), which prevents toxic molecules from reaching the brain, but also limits the accumulation of drugs in therapeutic doses. The BBB is in fact a barrier around the blood vessels that supply the brain, preventing foreign molecules circulating in the blood from entering the central nervous system.

Of course, some molecules can cross the BBB, particularly if they are small, rather soluble in fats ("lipophilic") and not highly ionised, but in most cases the development and transfer to patients of molecules with high therapeutic potential are limited by their poor penetration of the BBB.

For this reason, many researchers are working on strategies to improve drug access to the brain.

Some of these strategies may be invasive (direct injection into the brain), but are ill-suited to chronic diseases such as MS. A more acceptable option is to temporarily open the BBB,

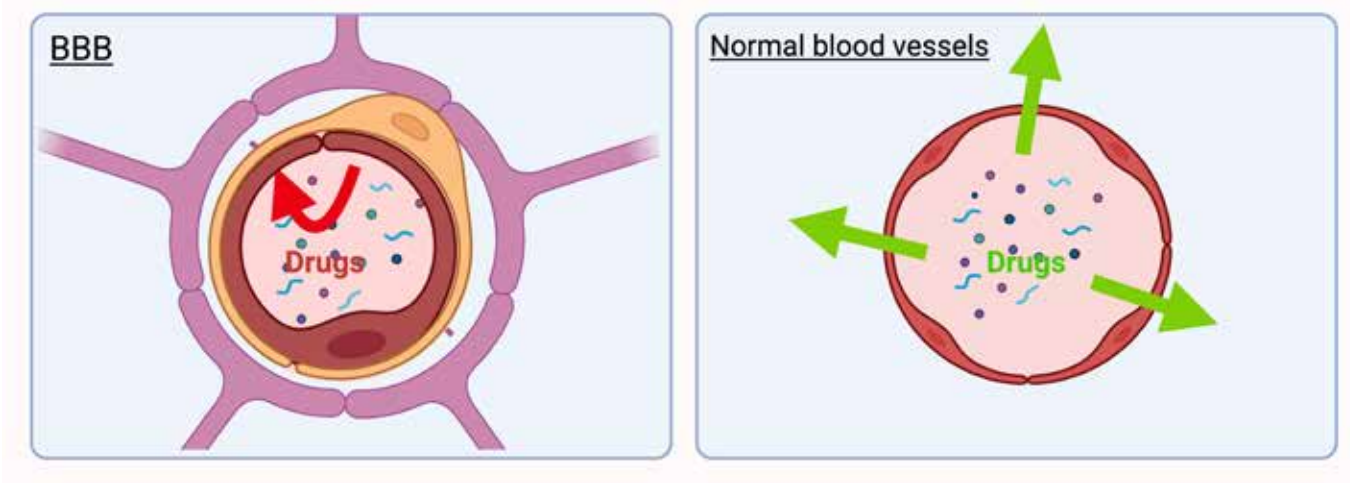

Figure 1: Difference between BBB blood vessels and normal blood vessels (the vessels in the rest of the body). Created with Biorender.

either with a hypertonic solution or physically, e.g., using focused ultrasound. However, such methods are not very specific, as they open up the BBB to all molecules present in the blood, including potentially toxic molecules.

Alternatively, researchers have developed strategies aimed at using the body's natural mechanisms to deliver essential substances that are needed by the brain, such as glucose, amino acids, or insulin. These are transferred from the blood to the brain via carriers or specific receptors on the surface of blood vessels in the BBB. It is therefore possible to alter a therapeutic molecule in such a way that the body considers it to be one of these elements and enables it to cross the BBB. This requires that the molecule be chemically modified without altering its therapeutic action, which is not always possible and needs to be optimised for each individual molecule.

Another option is to encapsulate the molecule in a vehicle known as a nanomedicine. These nanomedicines are small spherical particles of nanometric size (generally between 100 and 200 nm) that can carry a whole range of molecules. The surface of these nanomedicines can be modified so that they interact with the receptors or carriers in the blood vessels of the BBB. The advantage is that nanomedicines protect

fragile therapeutic molecules, solubilise them if they are not soluble in water, and enable their transport. Also, compared with direct modification of the molecule, a molecule cannot be inactivated by encapsulation in a nanoparticle, and once the nanomedicine or its surface has been modified, it can be used as a vehicle for virtually any molecule.

Finally, another possibility is to change the route of administration. Most drugs are administered either orally or intravenously. However, to avoid the molecule being blocked by the BBB, an alternative route is nasal administration targeting the olfactory mucosa: Nose-to-Brain or N2B. In this case, administration is non-invasive, and the molecule can pass through the olfactory mucosa and reach the brain directly.

Of course, there are limitations, since a drug passing through the nasal mucosa also enters the bloodstream. But more and more work is aiming to develop this route, either by offering nasal sprays that allow preferential delivery to the olfactory zone (Optinose™), or by adjusting the way in which drugs are formulated, including nanomedicines, so that they pass the olfactory barrier more easily.

Prof. Anne des Rieux,
Louvain Drug Research Institute, UCLouvain

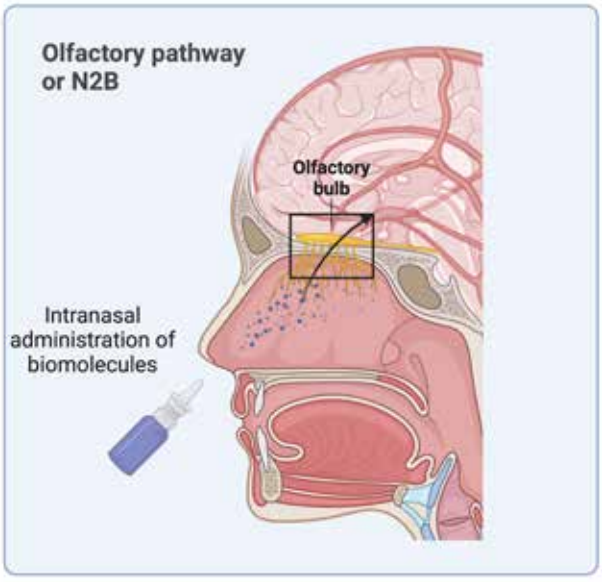

Figure 2: Administration of drugs by the non-invasive nasal route, which targets the olfactory mucosa. Molecules can cross this mucosa and reach the brain directly without having to cross the BBB. Created with Biorender.

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

PS: If you would like to find out more about this subject, we have just published a review of the new drug administration strategies to MS patients (https://doi.org/10.1016/j.jconrel.2023.10.052).