FONDATION CHARCOT STICHTING

57

Fighting multiple sclerosis

Newsletter Number 57 1st semester 2025

TOGETHER, WE ARE OPENING UP NEW PROSPECTS

Each scientific advance in the fight against multiple sclerosis means further hope for patients and their families. The recent designation by the FDD of tolebrutinib as a "breakthrough therapy" for multiple sclerosis is a new source of hope for the secondary progressive forms of the disease. By targeting both innate and adaptive immunity, this treatment opens up new therapeutic possibilities and may well transform patient care in the future.

The understanding and control of the immune cells responsible for brain lesions is a key issue. Researchers are currently working on strategies to modulate inflammation and encourage myelin repair. These developing leads remind us that research is a lengthy process in which each discovery is a milestone on the way to a better future. May we thank Professor Jérôme Hendriks for his valuable presentation of these mechanisms and of potential future therapies.

That same spirit of perseverance and commitment is also to be found in the people who actively support research. Soon, dozens of runners will be taking part in the Brussels 20-km race and uniting their endeavours to advance science. You can encourage them by cheering them on, or contribute to their endeavour by sponsoring them. Every little counts and brings us closer to new victories against multiple sclerosis.

Finally, I would like to express my deep gratitude to the researchers whose hard work and determination have enabled such breakthroughs. We owe them the hope of an MS-free future, which is drawing closer each day.

Happy reading and thank you for your faithful support!

Professor Emeritus **Christian Sindic**
PRESIDENT

The references for all studies mentioned in this newsletter are available upon request from the Charcot Foundation.

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FINALLY, A STEP FORWARD IN THE TREATMENT OF THE SECONDARY PROGRESSIVE FORMS OF MULTIPLE SCLEROSIS!

On 13 December 2024, America's Food and Drug Administration (FDA) designated tolebrutinib a "breakthrough therapy" in the treatment of non-relapsing secondary progressive multiple sclerosis further to a successful Phase 3 clinical test.

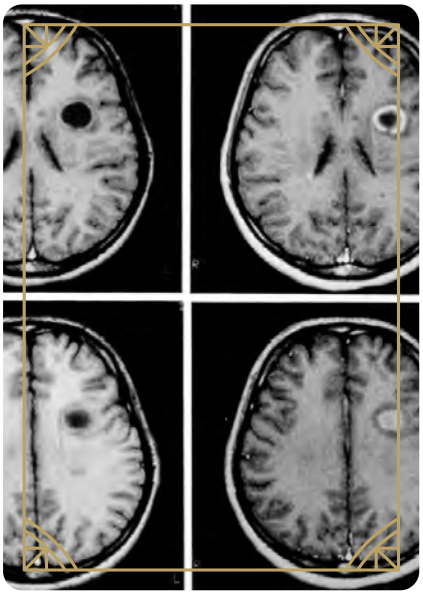
Tolebrutinib was developed by Sanofi and is a Bruton tyrosine kinase (BTK) inhibitor. These cells were discovered by Bruton in 1993 and are present in B lymphocytes, macrophages and brain microglia.

The latter are the macrophages specific to the brain. Tolebrutinib crosses the blood-brain barrier, and by blocking this enzyme prevents the activation of both B lymphocytes and macrophage cells. It so happens that the latter play a major part in lesion progression and therefore the symptoms of multiple sclerosis in the absence of a clinical relapse.

They are located on the periphery of chronically active plaques and are responsible for the continuous and insidious destruction of the myelin sheaths, which leads to the gradual expansion of demyelinating lesions (chronic expanding lesions). They are also activated by the degeneration of the nerve fibres (axons).

> The HERCULES Phase 3 study was performed on 1131 patients at the progressive stage of their disease, who had not suffered a relapse for at least 2 years prior to the beginning of the study.

In fact, on average, these patients had not relapsed for an average of 7 years and had an invalidity (EDSS) score of 3 (significant disability in one functional system) to 6.5 (requires 2 walking aids to walk about 20 m). 60% of the patients required walking aids, which indicated the high degree of disability among the population studied.



BRAIN MRI

revealing a large demyelinating lesion, with tissue destruction
at the center ("black hole") and contrast enhancement indicating
a breach of the blood-brain barrier and the acute nature of the inflammation

The chief result of this study was evidence that tolebrutinib increases the time prior to confirmed progression of the disability by 31% compared with the placebo group. Statistically, this is a highly significant difference. Moreover, the disability of 10% of the patients treated definitely improved, in fact in twice as many cases as in the patients taking the placebo.

This designation as a “breakthrough therapy” shows that tolebrutinib has the potential to slow down the development of disability and thus meet an essential medical requirement of progressive multiple-sclerosis patients.

OLIGODENDROCYTE–MYELIN–AXON COMPLEX

Main target of autoimmunity in multiple sclerosis

The main side effect was an increase in liver enzymes up to over three times the upper limit of normal in 4.1% of the participants (and 1.6% of the placebo group). All cases of liver-enzyme increase resolved without any particular medical intervention. A study of tolebrutinib in primary progressive MS (PERSEUS) is under way, with results expected during the second half of 2025.

What actually differentiates tolebrutinib from other current multiple-sclerosis treatments is that it targets not only adaptive immunity (B lymphocytes), but also the innate immunity conferred by the macrophages and brain microglia. Its other important characteristic is its ability to penetrate the central nervous system and act locally on demyelinating lesions.

The specific targeting of macrophages and microglia ensures that new therapies will become available to treat multiple sclerosis. The future may lie in an association of immunomodulators and anti-inflammatory medications, as well as medications that deactivate macrophages from the inception of the disease. This would enable progression independent of relapse activity (PIRA) to be prevented at a very early stage, and therefore the simultaneous blocking of the two major mechanisms responsible for demyelination: acute demyelination through the invasion of inflammatory blood cells and chronic demyelination through the local activation of macrophages.

Professor Emeritus **Christian Sindic**

TRUSTING AND BELIEVING IN THE FUTURE

Contribute to research by donating to the Charcot Foundation.

Speed up research on multiple sclerosis and make a difference to thousands of lives. The Charcot Foundation is Belgium's only independent organisation dedicated to basic research on this disease.

1 day of research= 7€ /month on 1 year

Remember us in your will

3 REASONS

- MS remains incurable and very often develops into a disability, shattering the lives of thousands.
- All our current endeavours are bringing us closer to solutions: slowing down the disease, repairing its damage and hopefully, one day, curing it completely.
- We undertake to invest the full amount of your legacy in multiple-sclerosis research.

DUAL LEGACY

If you have no close relatives, dual legacy reduces the inheritance-tax burden while supporting medical research. For further information, we advise you to contact your notary.

Any questions?

Please contact us for a confidential answer.

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COMING SOON

MACROPHAGES AND MICROGLIA

THE ENIGMA OF THESE DOUBLE-EDGED IMMUNE CELLS

In multiple sclerosis (MS), the immune system mistakenly attacks the nervous system, leading to damage in the brain and spinal cord.

Normally, the immune system protects the body from infections, but in people with MS, it becomes overactive. This abnormal response is triggered by a combination of genetic and environmental factors. As a result, immune cells migrate into the brain and spinal cord, causing inflammation and injury to nerve tissue.

This damage disrupts communication between nerve cells and leads to a variety of neurological symptoms, such as muscle weakness, balance problems, coordination difficulties, numbness, fatigue, and vision disturbances. These symptoms can appear in episodes (known as relapses) or progressively worsen over time.

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A key group of immune cells involved in MS are the phagocytes. These cells play a central role in the immune response and are abundant in active MS brain lesions.

Phagocytes include different subtypes, such as macrophages and microglia. Macrophages originate from blood monocytes and enter the central nervous system (CNS) during MS lesion formation. Microglia, on the other hand, are resident immune cells that are already present in the brain.

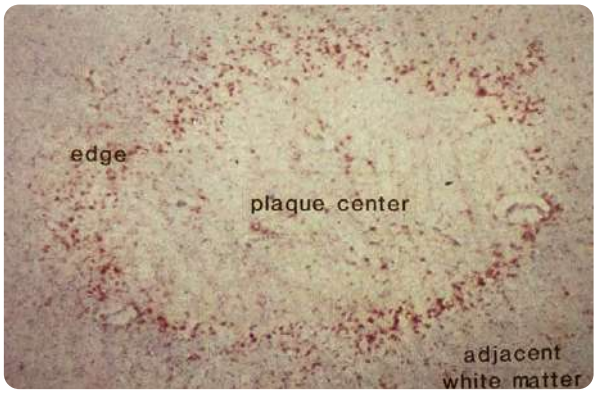
In MS, both macrophages and microglia become activated and contribute to nerve damage. They break down myelin, the fatty sheath that surrounds nerve fibers. Myelin is crucial for fast and efficient nerve signal transmission. When myelin is damaged, nerve communication is impaired, leading to the neurological problems seen in MS.

The brain has a natural ability to repair damaged myelin, a process called remyelination, which can restore nerve function. Because of this, researchers consider promoting remyelination an important treatment strategy for MS. For remyelination to take place, the brain must first establish an environment within the lesion that supports repair. While multiple cell types and processes are involved, phagocytes play a central role through two key steps.

In a healthy immune response, this shift helps resolve inflammation and supports the generation of new myelin-producing cells. However, in MS, this transition often fails, and phagocytes remain in a chronic inflammatory state. This prolonged activation leads to the formation of slowly expanding brain lesions that lack remyelination. The presence of these lesions is strongly linked to disease progression.

The reasons why phagocytes in MS lesions fail to switch to their repair-promoting state are not yet fully understood, but several factors contribute to the problem. One major factor is the persistent activation of the immune system due to the autoimmune nature of MS.

Additionally, phagocytes become overwhelmed by the large amount of myelin debris they must clear. The excessive accumulation of myelin-derived lipids disrupts their function and drives them into a harmful inflammatory state. Other factors, such as genetic predisposition, aging, gender, diet, and infections, may further contribute to the failure of lesion repair in MS.



CHRONIC ACTIVE LESION
WITH ACTIVATED PHAGOCYTES
AT THE PERIPHERY

Since unresolved inflammation plays a central role in MS, researchers are exploring therapies that promote its resolution to stimulate remyelination. Current treatments aim to suppress the infiltration and activity of phagocytes in the brain. For example, drugs such as Natalizumab and Fingolimod block molecules needed for immune cells to enter the CNS, while BTK inhibitors, and Dimethyl fumarate help reduce their inflammatory activity.

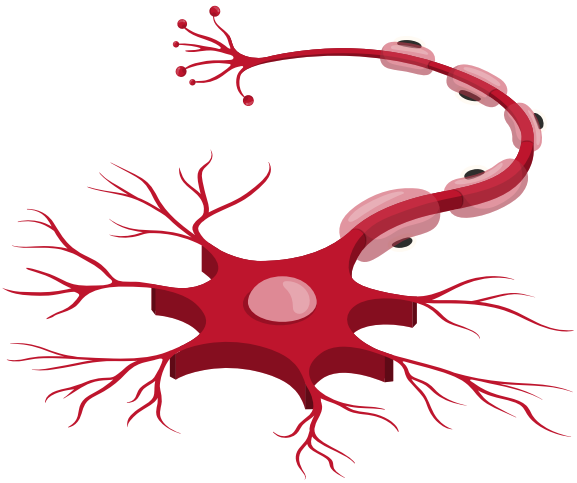
Experimental approaches are also being developed to target phagocytes more specifically in the CNS. These strategies include enhancing myelin debris clearance and improving lipid processing, reprogramming cell metabolism, increasing the production of inflammation resolving lipid mediators, and reducing oxidative stress.

> While many of these strategies have shown promise in preclinical models, further research is needed to confirm their effectiveness in clinical trials.

Because MS presents differently in each patient, developing personalized treatments is essential. The complexity of the disease means that a combination of approaches targeting different aspects of MS pathology will likely be necessary.

Despite the challenges, advances in research offer hope for future therapies that may slow disease progression and even promote recovery.

Prof. **Jerome Hendriks**
PROFESSOR IN NEUROIMMUNOLOGY
UNIVERSITY OF HASSELT



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