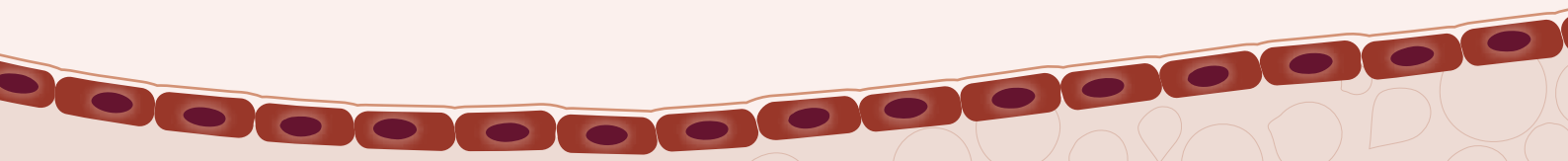
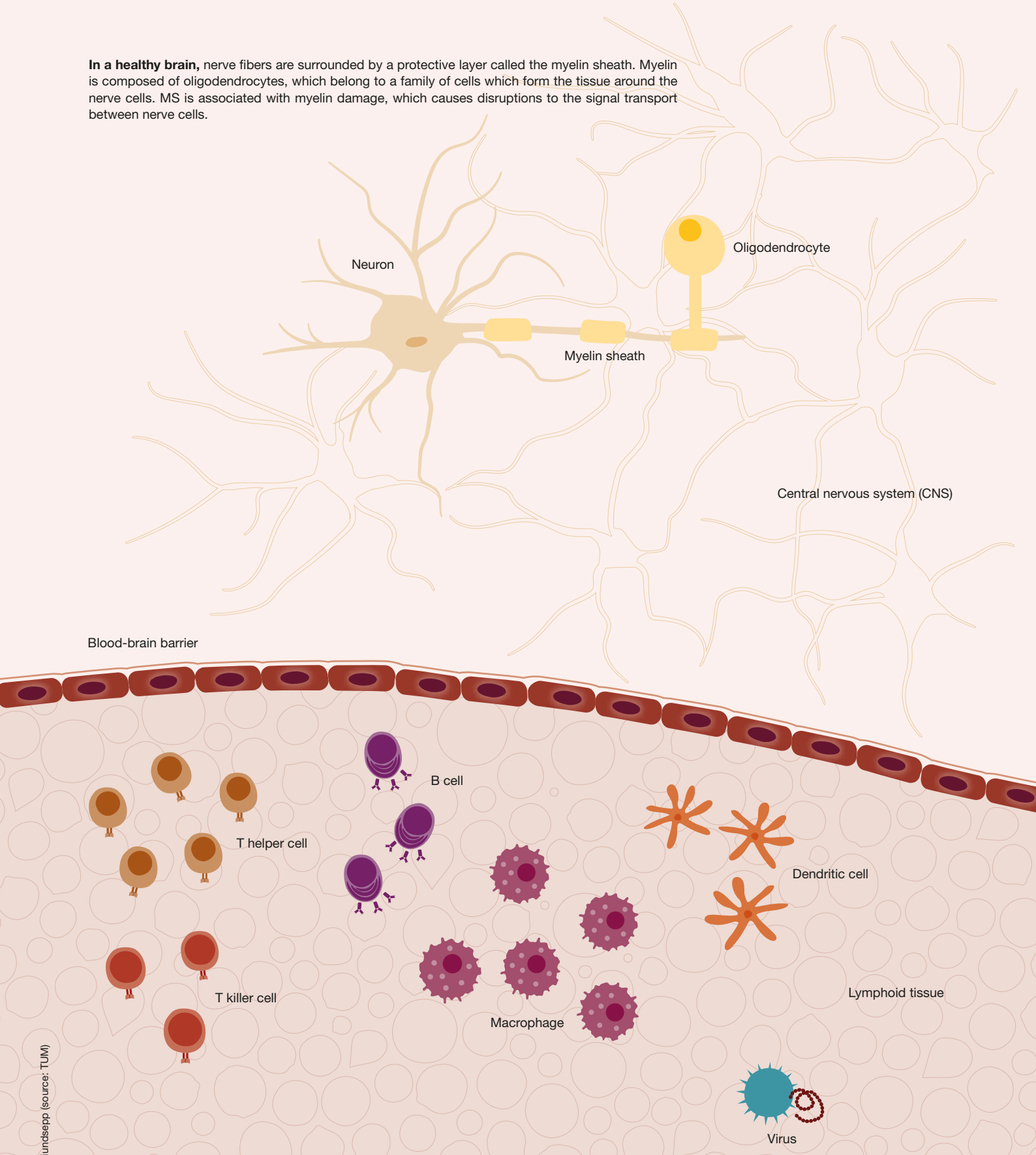
New Treatment Options for **MS Patients**



In multiple sclerosis (MS), B cells play a decisive role in the onset of disease. An international study – involving researchers from TUM – has demonstrated that a newly developed drug targeting these immune cells is effective in various forms of MS. This treatment is set to be available from 2017.

In a healthy brain, nerve fibers are surrounded by a protective layer called the myelin sheath. Myelin is composed of oligodendrocytes, which belong to a family of cells which form the tissue around the nerve cells. MS is associated with myelin damage, which causes disruptions to the signal transport between nerve cells.



Graphics: ediundsepp (source: TUM)

MS could start with an initially harmless infection. Viruses enter the body and disseminate antigens. Dendritic cells identify these antigens and call immune cells (T and B cells) into action. Scavenger cells (macrophages) are commanded to destroy the viruses.

Evdoxia Tsakiridou

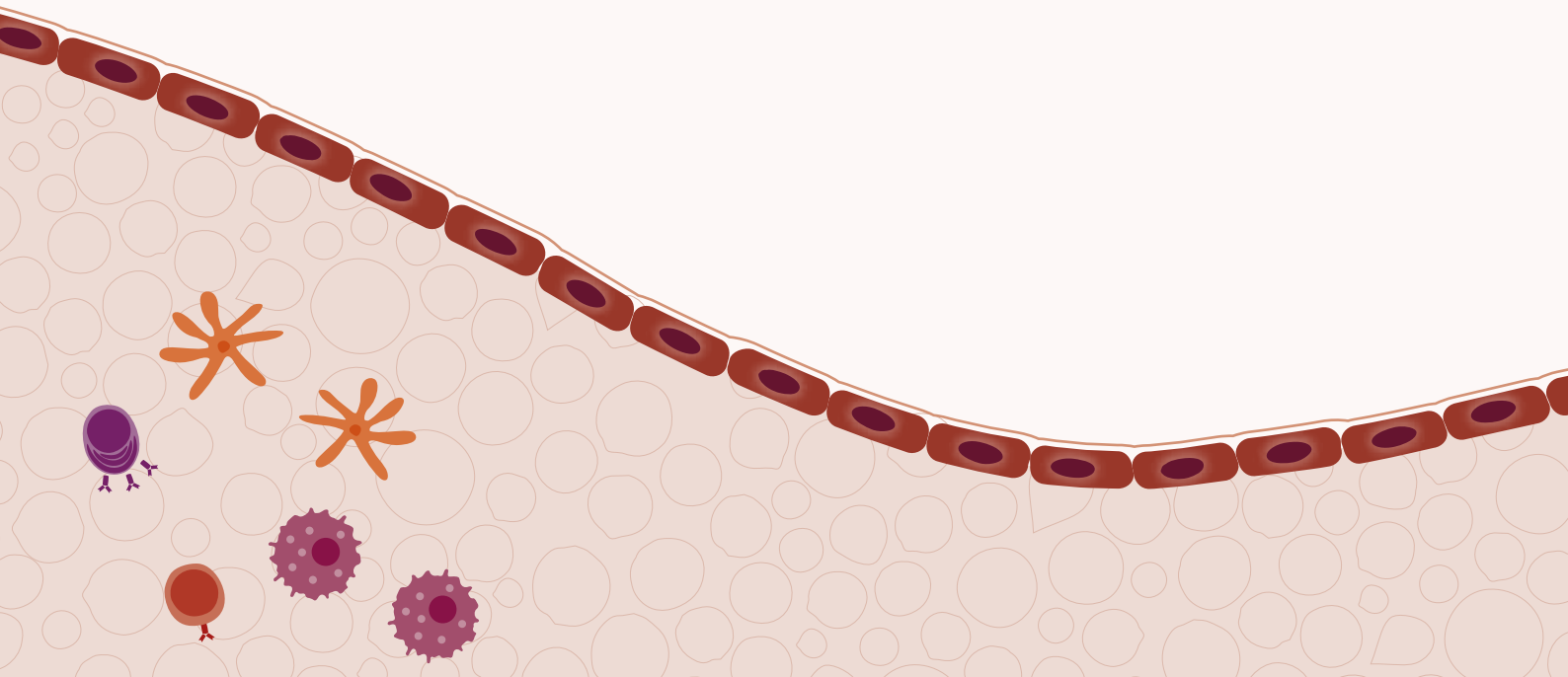
Neue Behandlungsmethode für MS-Patienten

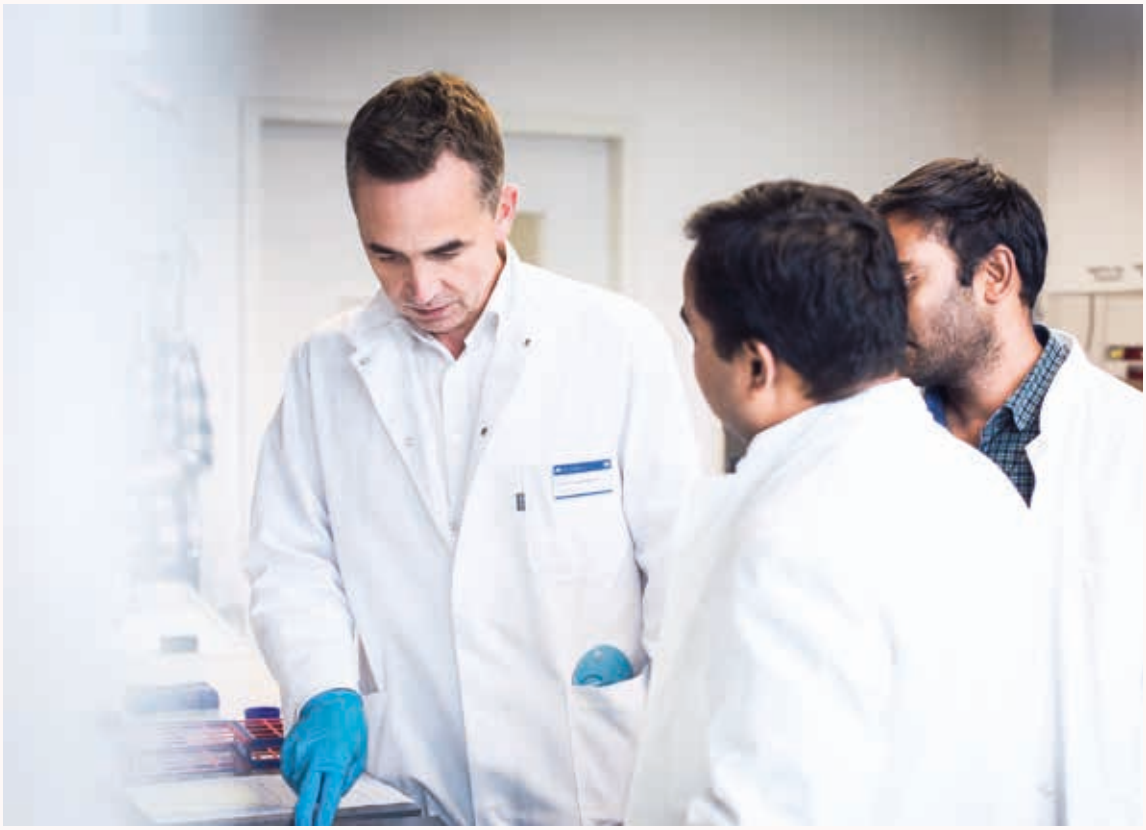
Nach wie vor ist unklar, warum sich bei der Multiplen Sklerose (MS) das Immunsystem so gezielt gegen Gehirn und Rückenmark richtet. Im Laufe der Zeit werden die Nervenzellen so geschädigt, dass sie ihre Funktion verlieren und die Patienten bleibende neurologische Ausfälle entwickeln. Bis vor zehn Jahren waren Experten der Meinung, dass die MS eine durch bestimmte Immunzellen, sogenannte T-Zellen, vermittelte Erkrankung ist. Untersuchungen, an denen der Neuroimmunologe und Direktor der Neurologischen Klinik der TUM, Bernhard Hemmer, beteiligt ist, zeigen, dass eine andere Gruppe von Immunzellen, die B-Lymphozyten, eine entscheidende Rolle spielt: Bei der MS sind sie an der akuten Entzündungsreaktion im Gehirn und Rückenmark beteiligt und möglicherweise spielen sie auch eine wichtige Rolle in der chronisch fortschreitenden Phase der Erkrankung.

Die Forscher gehen davon aus, dass sich bei MS-Patienten ein Teil der B-Zellen gegen bestimmte Eiweißstrukturen auf den Nervenzellen richtet. Diese B-Zellen unterhalten den Krankheitsprozess aller Wahrscheinlichkeit nach dadurch, dass sie autoaggressive T-Zellen aktivieren und Antikörper freisetzen, die die Schutzschichten der Nervenzellen angreifen. In der Folge werden letztere abgebaut, sodass die Nervenimpulse nicht mehr normal weitergeleitet werden. Welche spezifischen Eiweißstrukturen auf der Nervenhüllschicht von den Antikörpern der B-Zellen attackiert werden, wissen die Forscher noch nicht.

In der Zwischenzeit konzentrierten sich internationale Forscherteams und Pharmafirmen darauf, Medikamente zu entwickeln, die sich gezielt gegen B-Zellen richten. Sie nutzen den Umstand aus, dass die B-Lymphozyten bestimmte Oberflächenmerkmale tragen, die kein anderer Zelltyp aufweist. Die Wissenschaftler setzen sogenannte monoklonale Antikörper ein und entfernen auf diese Weise selektiv die B-Zellen aus dem Immunsystem der Patienten. Nach erfolgreichen Pilotstudien folgten große, weltweite Studien, an denen Hemmer beteiligt war, um die Wirksamkeit des Medikaments nachzuweisen. Das Ergebnis: Die B-Zell-Therapie gehört nicht nur zu den wirksamsten Behandlungsmethoden bei der schubförmig verlaufenden MS. Sie ist überhaupt die erste Therapie, die auch bei der primär fortschreitenden MS wirksam ist. Die erste B-Zell-Therapie weltweit wird aller Voraussicht nach im Jahr 2017 zur Behandlung der MS zugelassen werden. □

Link
www.neurokopfzentrum.med.tum.de/neurologie





Neuroimmunologist Bernhard Hemmer actually goes after the good guys: T and B cells. They belong to the immune system patrol unit – the lymphocytes. Like national park rangers, protecting animals and plants and pursuing poachers, these spherical cells are always on the lookout for intruders such as bacteria, viruses, tumors or other foreign bodies. Around the size of red blood cells, they circulate through the blood vessels and lymphatic system to attack foreign antigens. In the case of a viral infection or genetic mutation, the membranes of the body's own cells undergo changes. This is sufficient for the T cells to recognize them as foreign, hunt them down and destroy them – either directly or by recruiting so-called scavenger cells. B lymphocytes play an important role in T-cell activation, specifically processing the foreign proteins for the T cells and supplying them with the relevant messenger substances. In turn, some of the T cells convert into "helper" cells, which release substances that activate the B cells and lead them to the site of infection.

Once the B cells have been activated, they mobilize their own machinery and quickly divide and convert into plasma cells to produce suitable antibodies. They bind to the pathogens to inactivate them by either destroying their cell walls or aggregating them to large clumps which will be phagocytosed by macrophages.

Graphics: ediundsepp (source: TUM), Picture credit: Jooss

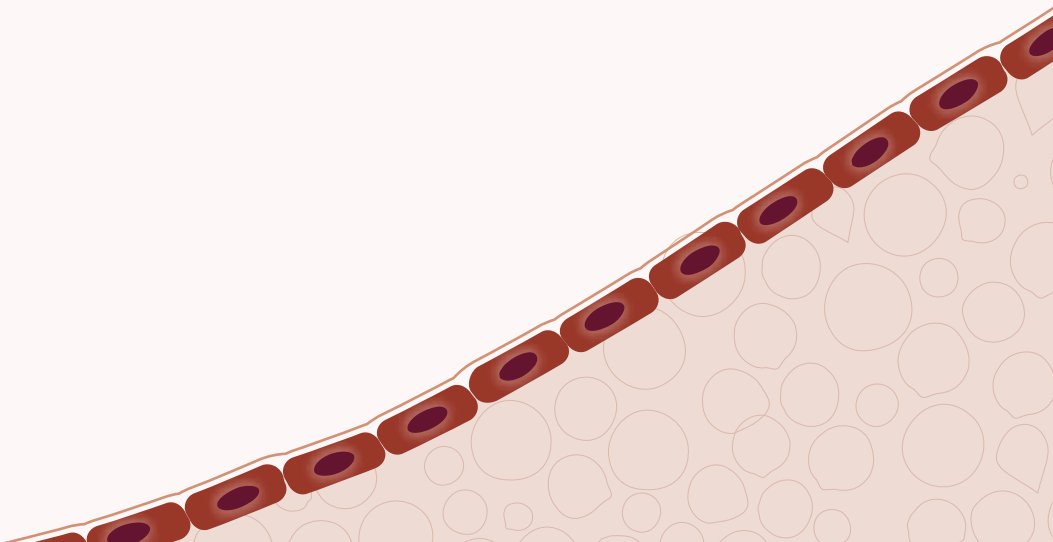
> *"Genetic and environmental factors lead our immune system to make mistakes, with B and T lymphocytes identifying the brain and spinal cord as foreign and going into attack mode."*
>
> *Bernhard Hemmer*

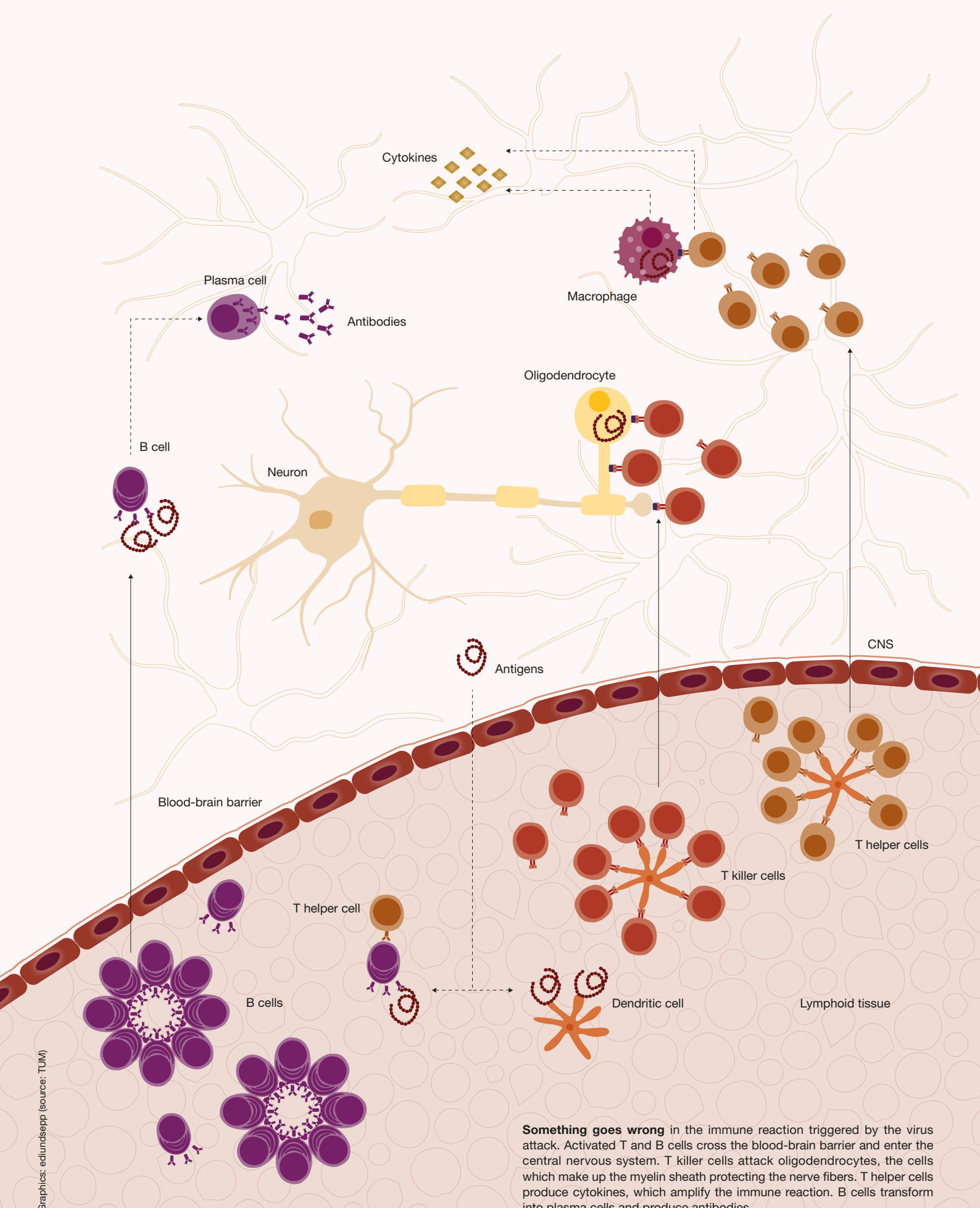
At some point, however, it can also happen that the good guys turn bad. "Genetic and environmental factors lead our immune system to make mistakes, with B and T lymphocytes identifying the brain and spinal cord as foreign and going into attack mode," explains Prof. Hemmer. "In the initial phase of the disease, there are strong indications that first activation occurs in the lymph nodes and spleen. The two cell types multiply there, migrate to the brain and trigger an inflammatory response. This results in damage to the oligodendrocytes, whose cellular extensions form the protective layer around nerve fibers, as well as to neurons."

It remains unclear why the immune system specifically targets the brain in this way and the resulting inflammation continues for decades. Until ten years ago, the conventional theory was that MS was a disease mediated solely by the T cells. This hypothesis was based on the observation that B cells played no role in the most common MS animal models (researchers can induce MS by injection with brain proteins). However, studies Hemmer was involved in then showed the opposite, with researchers finding mounting evidence that B lymphocytes occur in the brain and are linked to the onset of inflammation and possibly to progression of the disease. These studies marked a definitive break with the theory that T cells alone are responsible for the onset of MS.

"We now think that some of the B cells in MS patients target specific protein structures on the oligodendrocyte and myelin sheath. These B cells probably maintain the disease process by activating autoaggressive T cells and secreting antibodies. These attack the oligodendrocytes and the myelin sheath that protects the nerve cell extensions, or axons. This leads to destruction of the myelin sheath, impeding the transmission of nerve signals. But we don't yet know exactly which specific protein structures are attacked by the B cells and antibodies," clarifies the physician.

Looking for the B cells' target structures is like looking for a needle in a haystack. Researchers have been able to demonstrate which immune cells accumulate in the cerebrospinal fluid. They even know their molecular profile. And they have also detected various autoantibodies that could play a role in widespread and rarer variants of MS. But identifying the proteins remains problematic. "The methods used today to detect antibody reactions to protein structures do not work reliably. The main reason for this is that proteins in the brain exhibit many modifications that are not yet fully understood and thus cannot really be replicated in the test tube," Hemmer acknowledges.





Graphics: ediundsepp (source: TUM)

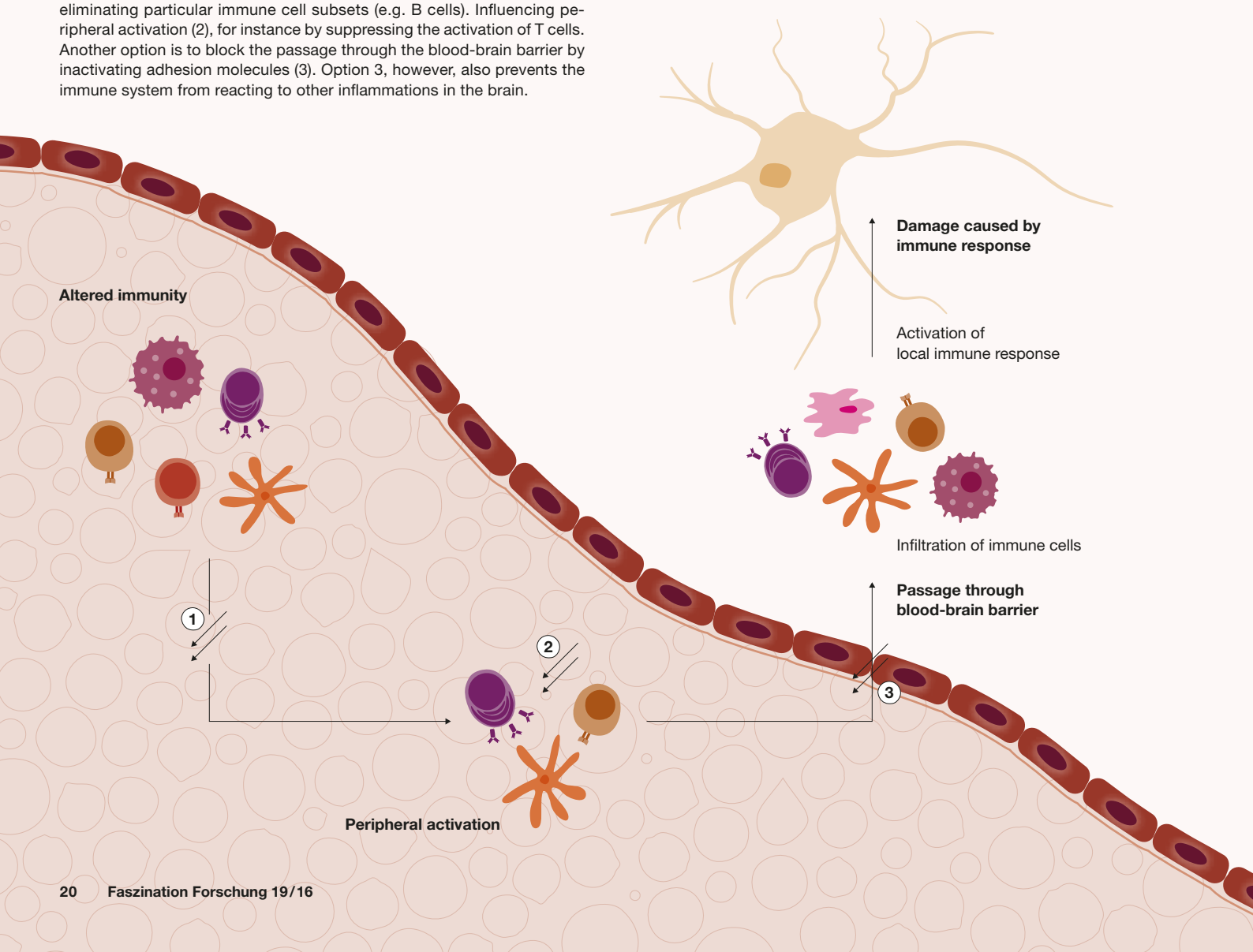
Something goes wrong in the immune reaction triggered by the virus attack. Activated T and B cells cross the blood-brain barrier and enter the central nervous system. T killer cells attack oligodendrocytes, the cells which make up the myelin sheath protecting the nerve fibers. T helper cells produce cytokines, which amplify the immune reaction. B cells transform into plasma cells and produce antibodies.

Researchers currently lack suitable methods to fully assess the complex protein spectrum of the human brain (proteome) that would enable proper examination of antibody reactions using screening techniques. They are trying to develop new methods to express the proteins they are seeking as they occur in the human brain. “Our major challenge lies in identifying the proteins of the brain that are attacked by the immune system in MS. The more technologies evolve for in vitro proteomics, allowing us to detect proteins and study immunoreactivity, the better our chances of understanding the entire MS-specific immune response and ultimately developing specific therapies,” outlines Hemmer.

In the meantime, physicians, international research groups and pharma companies are concentrating on developing B-cell-specific therapies. Drugs specifically targeting B lymphocytes were first administered over ten years ago, initially to individual patients and then within controlled pilot trials. Since B cells have certain surface characteristics that no other cell type exhibits, scientists were able to selectively remove B cells from the patient’s immune system using monoclonal antibodies.

The successful pilot studies were then followed by large, global trials in which Hemmer was involved, the aim being to systematically investigate and demonstrate the efficacy of the medication. The results are now in: not only is the B cell therapy one of the most effective treatment methods for relapsing-remitting MS, it is also the very first to be effective in the primary progressive form of the disease. According to Hemmer, the world’s first approved B cell therapy is likely to be used in everyday clinical practice in 2017. “This is a milestone in the history of MS. We finally have a highly effective treatment option at our disposal – and, as far as we can see to date, one with relatively few side effects.”

First treatments exist for the inflammatory phase of relapsing-remitting MS. They can act on three different targets: (1) Modifying immunity by eliminating particular immune cell subsets (e.g. B cells). Influencing peripheral activation (2), for instance by suppressing the activation of T cells. Another option is to block the passage through the blood-brain barrier by inactivating adhesion molecules (3). Option 3, however, also prevents the immune system from reacting to other inflammations in the brain.



Prof. Bernhard Hemmer

Eyes on the prize

"You need to be hungry, focused and resilient" – a motto Bernhard Hemmer has lived by from the very early days of his career. To begin with, the Director of the Department of Neurology at TUM's university hospital wondered if he might prefer to study computer science. However, community service (instead of military service) tipped the scales in favor of medicine, which he studied from 1984 to 1991 in the German city of Freiburg. He completed his residency at the University Neurological Clinic there, going on to qualify as professor at the Philipp University of Marburg. During this period, he also spent three and a half years at the National Institutes of Health in the US, investigating the immunology of multiple sclerosis.

In his clinical work, Hemmer specialized in treating inflammatory conditions of the nervous system. However, not content with that, he is determined to get to the bottom of the causes of MS. "I spent most of my training in an immunology lab. Neuroimmunology is my true passion," he reveals. His focus is thus on the molecular and immunological causes of these inflammatory diseases and the quest for new therapies.

"This type of work requires a lot of dedication. Success comes if you keep moving towards your goal, persevering even if you hit a hard patch and your legs start hurting," muses the enthusiastic sportsman, who enjoys hiking and jogging in his spare time. Fortunately, his wife and children are understanding of his passion for his work. Indeed, his 21-year-old daughter is now following in her father's footsteps and studying medicine, while his 17-year-old son is preparing to graduate from high school. Hemmer, a keen cook – especially of Mediterranean dishes – plans his schedule around dinners and weekends with his family.

Hemmer comes back to the plans for the new MS research and treatment center, set to open in 2020. This initiative is a dream come true for him: "We will be able to study every aspect of the disease and find out why our immune system attacks the body's own central nervous system and which molecular structures play a decisive role in this condition."

His attention is also captured by the potential for future therapies based on big data. The idea is to combine all the available information about genetics, biomarkers and environmental factors, as well as data from medical imaging and clinical practice, and use analytics tools to mine it. Someday it should then become possible to give each patient an individual prognosis for their condition and offer them tailor-made therapies.

For Hemmer, though, the battle against MS is far from over. The outlook for patients in the chronic phase, when the neurons and axons have already degenerated, remains bleak. The B cell therapy cannot help them then, since – as Hemmer explains – the peripheral immune system only plays a minor role at this late stage of the disease.

This is because the early phase of MS unfolds outside the blood-brain barrier. Hemmer and his team think it is likely that deactivating the B cells also has a profound impact on T-cell activation. This may have a profound and long-term effect on the cascade triggered by the misdirected immune response.

However, in the later stage the disease shifts to the nervous system, where diffuse inflammation in the tissue is observed. Unfortunately, the current therapies are not effective there. If the nerve cells are repeatedly exposed to inflammation, they ultimately degenerate irrespective of the inflammation. This typifies the chronic phase of the disease.

"How can we prevent neuronal damage, reverse defects and repair the myelin sheath? Treating the late effects is the major challenge facing us in the coming years," sums up Hemmer, who is confident that the new MS center will help find answers to these questions. *Evdoxía Tsakiridou*

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