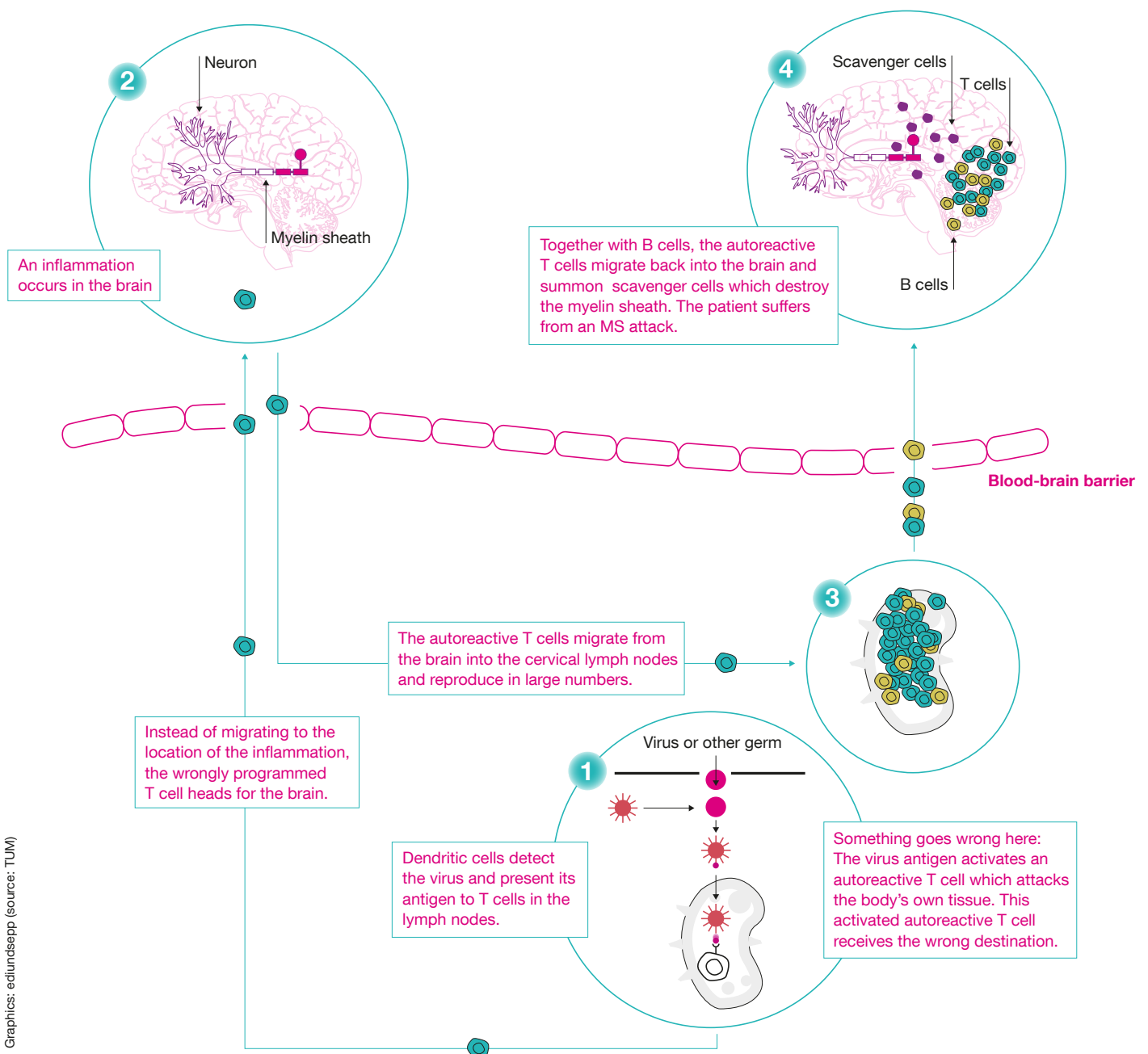


**The cause of MS** is still not fully understood. Most likely the disease starts where the body is in direct contact with the environment: at the skin, in the bowels or the lung. All humans suffer from occasional inflammations in these regions.

# A fine Line

The cells of our immune system protect us from disease by attacking and destroying pathogens. Sometimes, though, they get it wrong and target the body's own tissue. An autoimmune disease takes hold. Thomas Korn is researching ways to tame these misdirected immune cells, with a particular focus on multiple sclerosis.



## Ein fein austariertes System

Immunzellen schützen uns vor Krankheitserregern, indem sie diese angreifen und vernichten. Doch manchmal irren sie sich und attackieren körpereigenes Gewebe. Eine Autoimmunkrankheit entsteht. Prof. Thomas Korn erforscht, wie man diese fehlgeleiteten Immunzellen wieder besänftigen könnte. Im Fokus steht dabei Multiple Sklerose (MS).

Diese Krankheit spielt sich im Gehirn ab. Krank sind aber nicht die Nervenzellen, sondern das Immunsystem. Sogenannte autoreaktive T-Zellen des Immunsystems erkennen bei MS-Patienten nicht nur körperfremde Antigene (zum Beispiel Virus-Antigene) als Feind, wie es eigentlich sein sollte, sondern auch körpereigene Moleküle im Gehirn der Patienten. Das hat fatale Folgen. Die T-Zellen ordern Fresszellen ins Gehirn. Die nagen dann die Myelinscheide ab, die die Nervenfasern umhüllt und schützt. Korn will mit seiner Forschung herausfinden, wie die autoreaktiven T-Zellen es schaffen, sich ins Gehirn zu schmuggeln. Denn eigentlich dürften sie die Blut-Hirn-Schranke gar nicht passieren. Das gelingt ihnen nur im aktivierten Zustand. Korn vermutet, dass die Aktivierung der T-Zellen außerhalb des Gehirns stattfindet. Durch ein harmloses Schnupfenvirus oder ein Darmbakterium zum Beispiel.

**A**round 2.3 million people worldwide suffer from multiple sclerosis (MS). It is two to three times more common in women than it is in men. The further away from the equator people live, the greater the incidence of disease – although nobody is quite sure why.

MS is primarily diagnosed in young people and affects the central nervous system. “Yet the brain is actually healthy – it is the immune system that is dysfunctional,” explains Thomas Korn, Heisenberg Professor of Experimental Neuroimmunology at TUM’s hospital-based Department of Neurology.

Certain immune cells that are theoretically supposed to protect us from dangerous bacteria or viruses suddenly turn against the body’s own tissue. Instead of helping, they become destructive. This is because they not only detect viral antigens, but also cross-react with the body’s own molecules – that is, these cells become autoreactive.

Thomas Korn wants to get to the root of these misguided or autoreactive cells. He is seeking to establish where they are activated, why they are sending out the wrong signals, and how they can be stopped. Knowing all this would facilitate more effective treatment for MS and other autoimmune diseases.

### Immune cells destroy the myelin sheath

While MS rampages through a patient’s central nervous system, it does not actually target the nerve cells (neurons) themselves. Instead, its attacks are directed at cells with an

Um diese Theorie zu prüfen, will er den Weg der T-Zellen nachverfolgen. Er nutzt dazu Mausmodelle und verpasst T-Zellen, die sich in Lymphknoten oder in lymphatischem Gewebe aufhalten, eine farbige Markierung. Wochen später schaut er nach, wohin die markierten Zellen gewandert sind. Korn interessiert sich auch für die Kommunikation der Immunzellen untereinander. Die Zellen nutzen dafür spezielle Botenstoffe, Interleukine genannt. Interleukine können Immunzellen stimulieren, zur Teilung anregen oder abschalten. Sie können die Bildung von Antikörpern bewirken oder Fieber auslösen. Sie wären ein guter Angriffspunkt für neue Therapien.

Allein: Die Wirkung eines einzigen Interleukins unterscheidet sich je nachdem, in welchem Gewebe, von welcher Zelle und zu welchem Zeitpunkt es freigesetzt wird. Es ist ein fein austariertes System und gar nicht einfach, den komplexen Signalwegen auf die Spur zu kommen. □

Link

[www.neurokopfzentrum.med.tum.de/neurologie](http://www.neurokopfzentrum.med.tum.de/neurologie)

unwieldy name but extremely important function – the oligodendrocytes or oligodendroglia. They wrap themselves around the nerve fibers (axons) that protrude from the neurons and insulate them. The axon can be compared to an electrical wire, with the myelin sheath formed by the oligodendrocytes acting as the insulating plastic around it. This myelin sheath prevents short circuits in the brain.

In MS patients, immune cells in the brain eat away at this protective coating. But without the myelin sheath, the neurons can no longer communicate with one another properly. Electrical impulse conduction slows right down or ceases completely. Since this occurs in multiple areas of the brain at the same time, the result is a wide variety of neurological deficits – including speech disorders, visual impairment and numbness. One particular type of immune cell plays a key role in this: the T cell (T lymphocyte). If the immune system is a defense force, the T cells are the generals coordinating the attack. Once activated, they grab anything their T-cell receptors encounter and then call for assistance from scavenger cells, which destroy the intruder. Or, in the case of MS, gnaw the myelin sheath off the nerve fibers.

### Brain: no-go zone for T cells

Strictly speaking, the sensitive brain is off-limits to all but certain types of T cell – the ones that carry out immune surveillance on its behalf. The blood-brain barrier prevents ▶



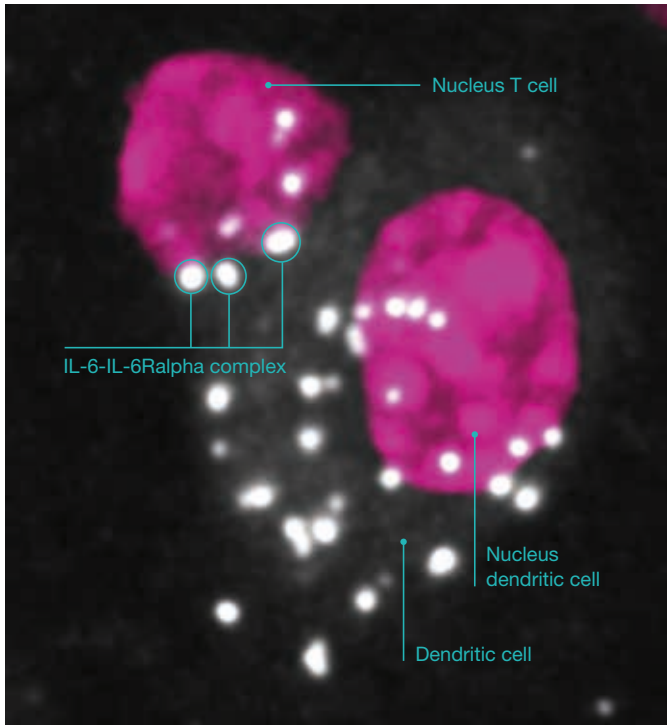
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**Prof. Thomas Korn**

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Thomas Korn studied human medicine in Würzburg and London and obtained his doctorate in cell biology at the University of Würzburg. During his specialist training in Würzburg and Homburg, he was already eager to discover how the immune system influences neurological disorders like multiple sclerosis. “In 2005, he received a grant from the German Research Foundation (DFG) to spend three years conducting research at the Harvard Medical School in Boston. On his return to Germany in 2008, he was

appointed senior physician at the University Neurology Clinic of TUM, praising Munich for “offering a very good research environment for immunologists”. Just two years later, he was appointed to the DFG-funded Heisenberg Professorship of Experimental Neuroimmunology, also at TUM. He has received numerous prizes for his research, including the 2008 Sobek Young Investigator Award and the 2010 Heinrich Pette Award from the German Neurological Society (DGN).



**Korn investigates** the role of messenger substances in autoimmune diseases. This microscope image of fixed cells shows how a dendritic cell presents the messenger substance interleukin 6 (IL-6) to a T cell.



**Immune cells** are isolated from inflamed tissues, for example the central nervous system, and functionally analyzed in culture plates ex vivo.

other T cells from migrating into the brain. However, when T cells outside the brain are activated, for instance by a harmless cold virus, they gain the ability to cross this barrier after all. Or at least, that is the theory.

To put this to the test, Korn is setting out to track the path of the T cells – and has received a European Research Council (ERC) grant for this purpose. To achieve this, he uses a mouse model, marking the T cells that reside in the lymph nodes or in lymphatic tissue at the mucosal surfaces, such as in the gastrointestinal tract. Later he then checks back to see where the marked cells have ended up.

### Track and trace

In mice with a condition similar to MS, Korn's hope is that he will also find these marked cells in the brain. This could be evidence that activated, autoreactive T cells do indeed migrate from the periphery into the brain. It would finally confirm the theory that relatively harmless infections can in fact trigger an episode of MS as a delayed effect.

If activated T cells make it to the brain from the gut, this could have major ramifications. It would indicate that our own intestinal bacteria could activate the T cells. And in that case, our individual microbiome – all the bacteria inhabiting our digestive system – could have a significant influence on whether or not we are susceptible to autoimmune diseases like multiple sclerosis. Korn's team has been researching this for around a year now. As it stands, the colored markers they assign to the T cells only last two to three days. Whether that is sufficient to track them all the way into the brain remains to be seen. In the long term, Korn's aim is to color-code the cells – offspring included – for an indefinite period of time.

In a subsequent step, Korn also intends to test this process in reverse – marking immune cells in the brain and then tracing their egress from the central nervous system. "If these cells do in fact leave the brain again, we could isolate them and analyze them more precisely," Korn explains. Perhaps they could even be manipulated in such a way as to avoid future attacks.





**In experimental models**, immune monitoring can be performed by extraction of immune cells out of tissues and assessment of their phenotypic and functional properties on the single cell level, for example by flow cytometry and single cell sorting.

### One molecule, many messages

Thomas Korn is also interested in communication between the various cells of the immune system. They use special messenger substances for this purpose, called interleukins. These can stimulate the immune cells, cause them to multiply or turn them off. They can trigger the formation of antibodies or cause a fever. “The function of an interleukin is always linked to its anatomical and cellular context,” specifies Korn. There are over thirty different interleukins. But that is not all – an interleukin’s effect will be quite different depending on the tissue it is released in, the cell secreting it, and when this process occurs.

Interleukin 6 (IL-6) holds particular significance for the T cells. It acts as a stimulator, triggering chronic inflammatory responses – including autoimmune diseases. While many different cells can produce Interleukin 6, the T cells react primarily to IL-6 released by specialized immune cells known as dendritic cells. Even when plenty of IL-6 from other sources is circulating in the blood, the T cells appear to take no notice

and hardly change their behavior. For a long time, researchers had no idea why that was the case.

Korn turned his attention to this question, developing dedicated mouse models to allow him to examine the influence of IL-6 produced specifically by dendritic cells. He believes he has gained a better understanding of a fundamental mechanism underlying communication between dendritic cells and T cells via the messenger substance IL-6. The results of this work have been published in the journal “Nature Immunology” just before this magazine was printed.

Meanwhile, Korn’s research into multiple sclerosis – and particularly the T cells – continues. After all, there are still plenty of issues to resolve in understanding how our immune system, which is supposed to protect and defend us, can turn into our own worst enemy.

*Claudia Doyle*