

Faszination Forschung

TUM Research Highlights

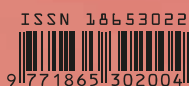
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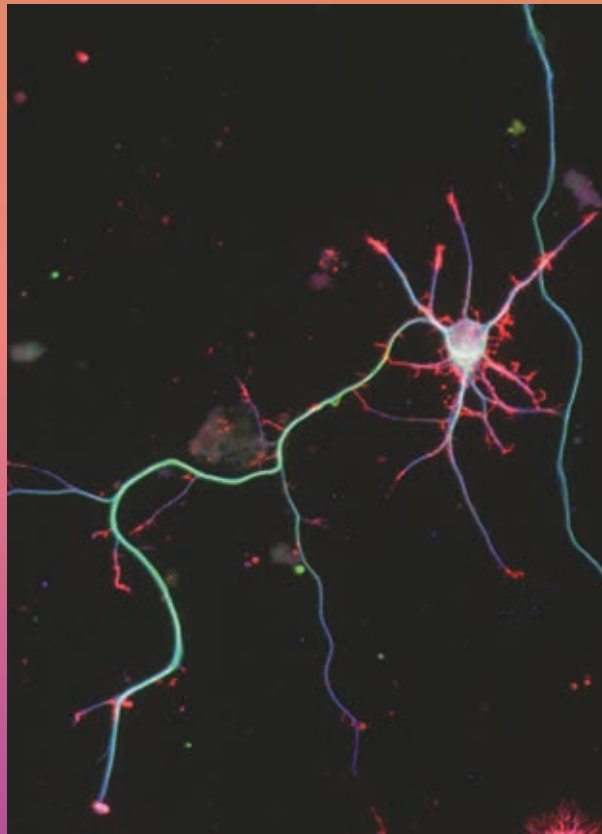


Special Issue: Neuroscience

Multiple Sclerosis Research: A New Collaboration Hub for Clinicians and Basic Researchers
From Bench to Bedside and Back: Translational Medicine
On the Trail of Alzheimer's



Nominal charge
EUR 9.00



Microscope image of a neuron from a mouse brain. The long and thin colored structures are the neurites by which neurons communicate with each other.

Dear TUM friends and associates,

Neuroscience is a domain of excellence on our medical research agenda. At TUM, basic and clinical research are close companions rather than poles apart. As a technical university offering a highly differentiated range of subjects, we look to the future by networking neuroscience with other disciplines such as informatics and engineering, thus enabling a holistic approach to research. This concept also resonated with the international experts commissioned by the Klaus Tschira Foundation to consider funding for a multiple sclerosis research center: their decision was a clear vote in favor of TUM. As a result, we are now investing their donation of 25 million euros in a brand new building to house our research into this autoimmune disease, which has such a complex impact on the nervous system.

This edition of our magazine introduces four scientists who are each investigating different aspects of multiple sclerosis (MS). Mikael Simons is researching the molecular processes underlying formation and degeneration of the myelin sheath – the protective coating around our nerve fibers that plays a central role in MS. For Thomas Korn, the aim is to understand exactly what happens to the immune system of MS patients – why misdirected immune cells penetrate the brain and then target the body’s own tissue. The role of specific immune cells, B lymphocytes, and resulting therapeutic targets are the focus of Bernhard Hemmer, whose institute has been involved in demonstrating the efficacy of an innovative B cell therapy for MS. And Thomas Misgeld looks at the degeneration of nerve fibers, discovering that – contrary to previous assumptions – axons can also die off when the myelin sheath is intact. Since this degeneration process is reversible in the early stages, this finding also holds promise.

Arthur Konnerth developed pioneering techniques for observing individual nerve cells in living organisms. He and his team have succeeded in gaining valuable insights into brain activity, which have helped advance research into conditions such as Alzheimer’s disease.

This issue then takes you behind closed doors at TUM’s Neuroimaging Center. Here, scientists from a wide variety of fields work together to advance research and application of the latest imaging techniques in neurology.

In partnership with colleagues in the US, leading international robotics expert Gordon Cheng has successfully demonstrated that people with paraplegia can regain conscious control of their legs by training with an exoskeleton. He is now working



with neurologists at TUM to explore how MS patients can benefit from this approach. Turning to medical informatics, specialist Klaus A. Kuhn explains what neuroscience stands to gain from big data analytics and outlines the technical hurdles that are yet to be overcome.

Close collaboration between basic researchers and clinicians is vital to accelerate the development of new drugs and therapies. Taking four doctors as our case studies, we zoom in for a closer look at this translational approach. Keeping the spotlight on neuroscience, we also examine TUM’s efforts to counter the shortage of upcoming medical researchers, which is a topic of widespread concern.

In short, this issue of Faszination Forschung transports you to the cutting edge of world-class research – on each and every page. When reading these articles, you will quickly see how TUM spares no effort to secure its leadership in neuroscience – ensuring we are equal to even the most formidable challenge. I trust the enthusiasm of our neuroscientists will prove infectious, and their vigor in tackling the major neurological issues of our time will make for a truly compelling read.

Wolfgang A. Herrmann

Prof. Wolfgang A. Herrmann

Multiple Sclerosis Research

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Clinicians and Basic Researchers Collaborate to Advance MS Research

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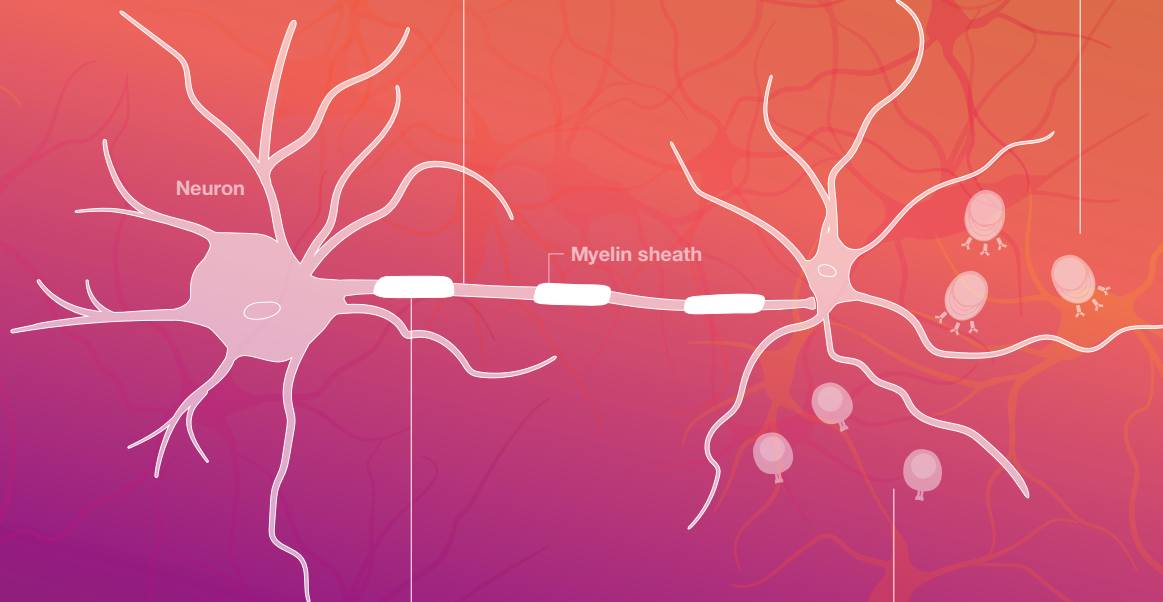
Discovered that nerve fibers can degenerate despite an intact myelin sheath:

Thomas Misgeld

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Investigates particular immune cells as potential targets for MS therapies:

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Further Insights while Healing Patients



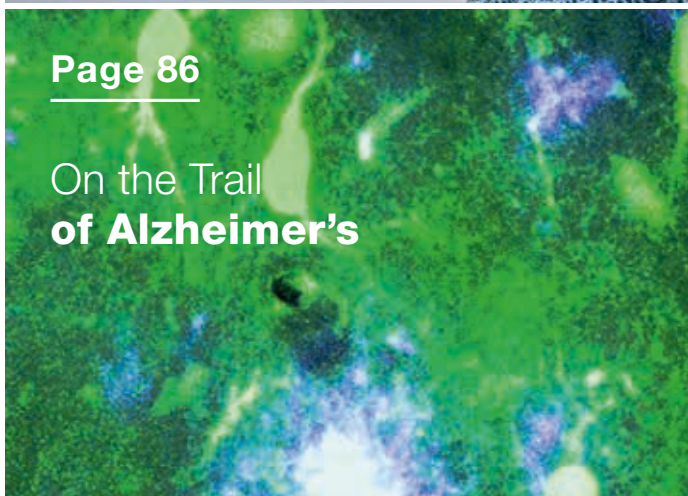
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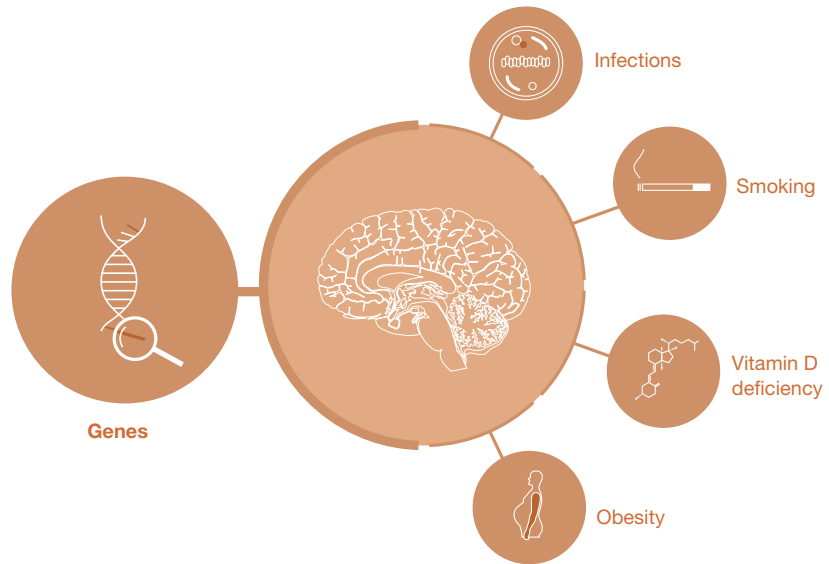
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Science communication – a fundamental part of research

Multiple Sclerosis at a Glance

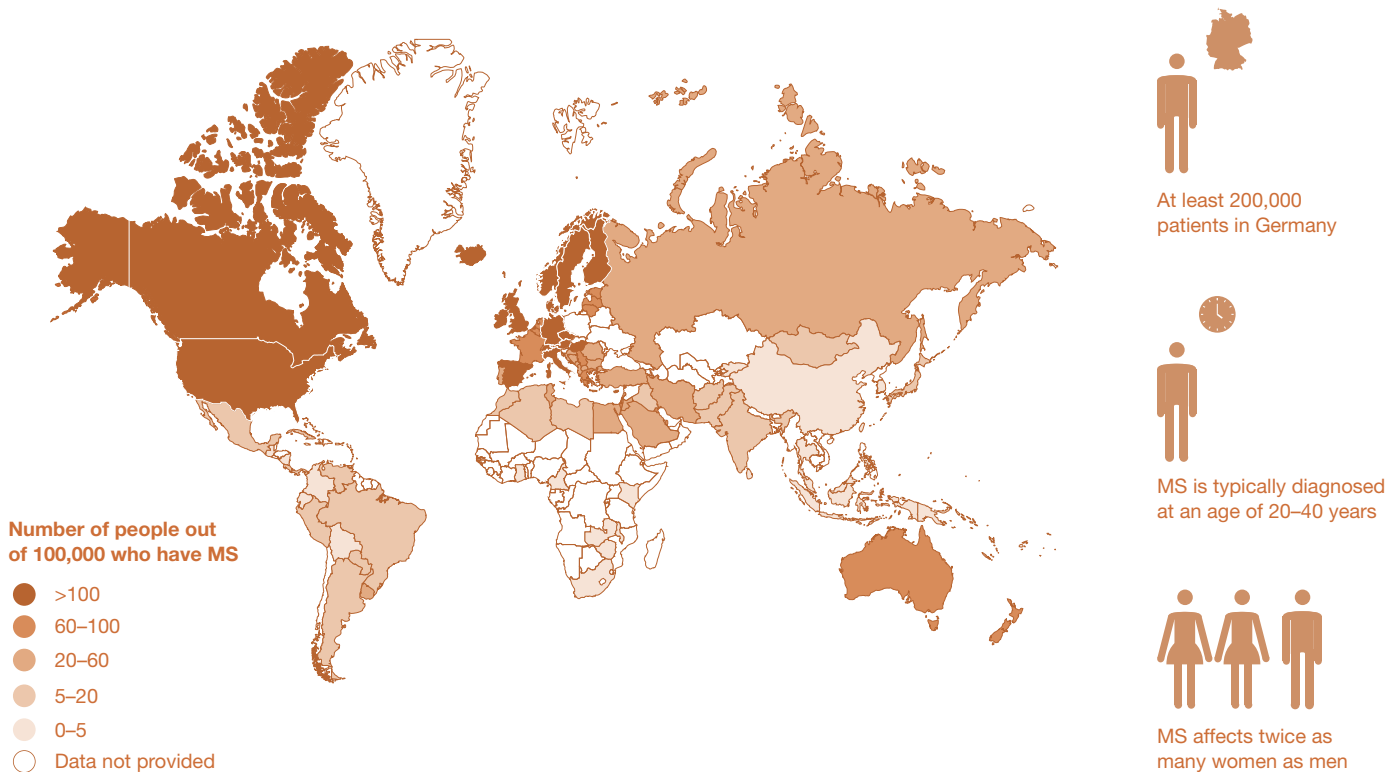
Risk factors for MS

Today, about 200 risk genes associated with MS are known. Various environmental influences are suspected to play a role in MS.



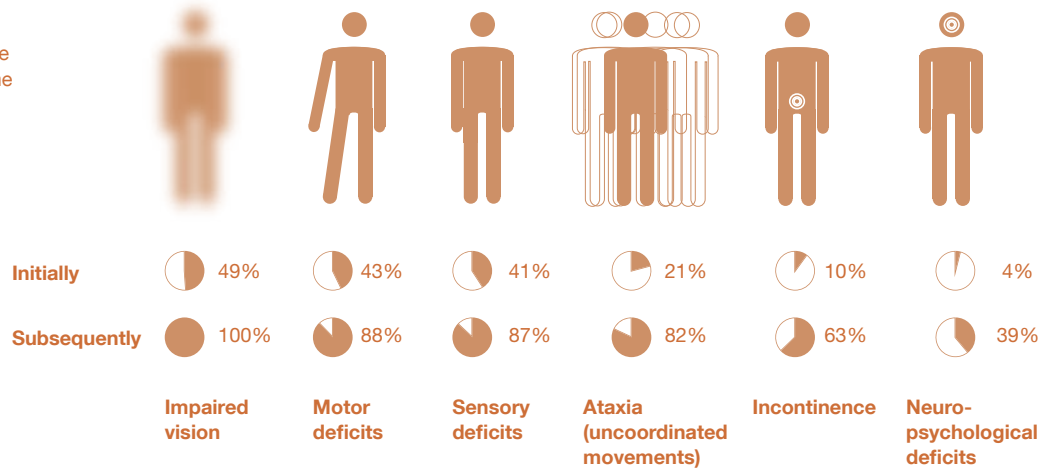
Worldwide

about 2.3 million people have MS



MS symptoms

Percentage of patients who experience the listed symptoms initially (at the time of diagnosis) and during the course of the disease.



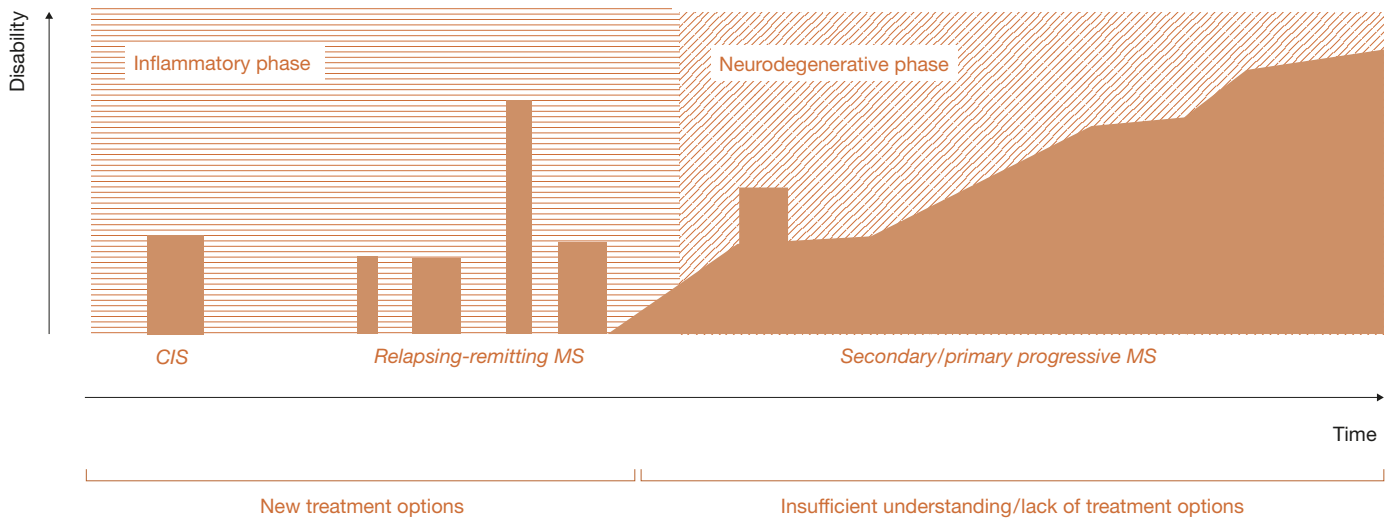
“Multiple sclerosis (MS) is one of the world’s most common neurological disorders. In many countries, it is the leading cause of non-traumatic disability in young adults.

While some people with MS experience little disability during their lifetime, as many as 60% may be unable to walk without assistance 20 years after onset.” *Atlas of MS 2013*

Course of MS

In about 90% of patients, MS starts a relapsing-remitting course with neurological symptoms that occur and fully or partly fade away. The majority of the patients will enter a secondary progressive course after 15 to 25 years with progression of

disability in the absence of relapse activity. In 10% of patients, usually when the disease starts at an older age, a primary progressive disease course is observed. In these patients disability progression occurs in the absence of any relapse activity.



Collaboration Hub for Clinicians and Basic Researchers

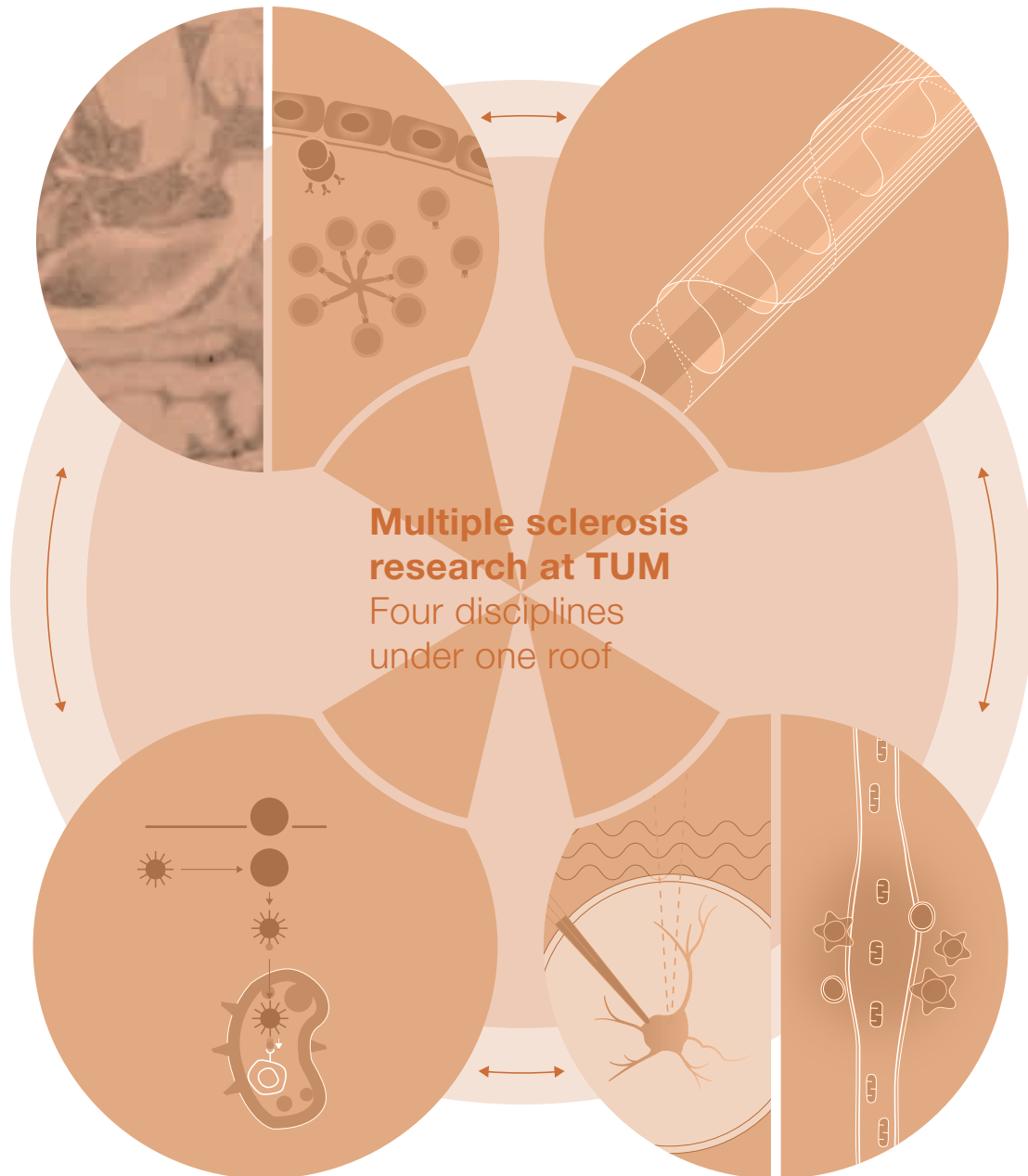
TUM is building a new research and treatment center for multiple sclerosis (TUM-MS) – at a cost of 35 million euros. The center will bring together the numerous research groups at TUM dedicated to this – as yet incurable – disease. Clinicians and basic researchers will work in close collaboration under one roof to ensure new findings are quickly translated into clinical trials. At present, TUM's university hospital, Klinikum rechts der Isar, already cares for 1,000 MS patients each year. This major project is made possible by a donation of 25 million euros from the Klaus Tschira Foundation, a German charity established by physicist Klaus Tschira, and by additional support from the Bavarian state.

Neurology

Prof. Mühlau Prof. Hemmer
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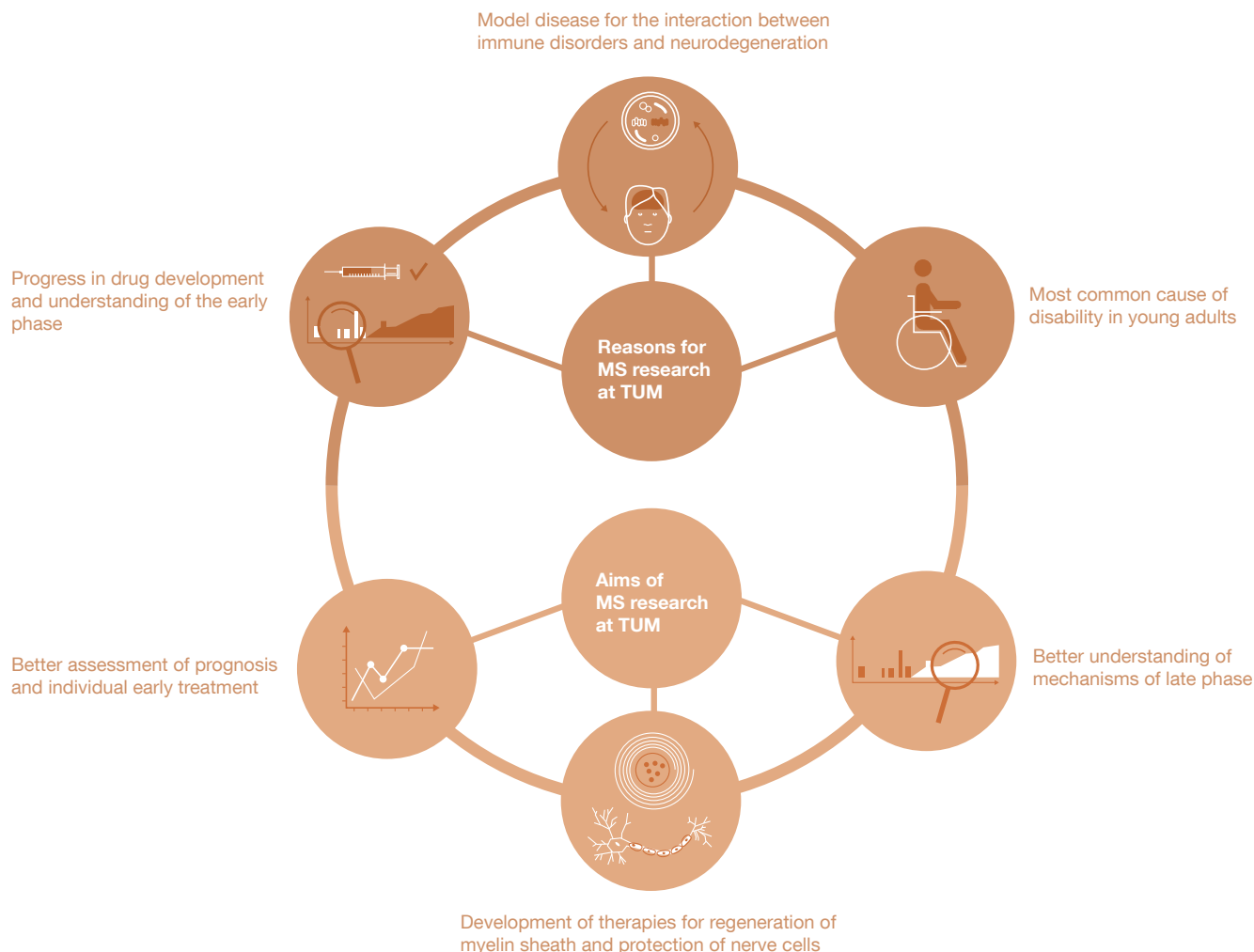


Neuroimmunology

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“Our aim is to build bridges between clinical research, patient care and basic research. Technologies such as the latest in vivo imaging methods, which are not normally available at hospitals, now play a decisive role in major research breakthroughs,” is how Prof. Bernhard Hemmer, Director of the Department of Neurology at Klinikum rechts der Isar hospital, explains the need for the new MS center.

However, technology is not the only consideration for Hemmer and the other scientists. Their top priority is to bring basic research staff together with research physicians and specifically enable and promote “communication and interaction between the various disciplines and working groups.” The neurologist refers to translational medicine in this context, meaning that “the issues facing clinicians feed into basic research and, vice-versa, research findings are channeled into clinical practice.”

There is also another reason for establishing a research and treatment center for MS: Over the past few years, the TUM School of Medicine has stepped up its research in the fields of neuroscience and neuroinflammation, with the pathology

of multiple sclerosis becoming a central focus. This autoimmune disease affects the nervous system, with misdirected immune cells attacking brain and spinal cord. This research trajectory began with the establishment of TUM’s dedicated MS clinic, which participates in numerous therapeutic studies, both German and international.

Since then, this expertise at TUM’s university hospital has expanded to encompass MS-related areas such as molecular neuroimmunology, genetics, magnetic resonance imaging and biomarker research. TUM’s research in the field of neuroinflammation tackles the question of how autoimmune reactions occur and how these cause damage in the brain. This is flanked by outstanding basic neuroscience research at the Biederstein campus, also focusing on topics surrounding MS. Here the research focuses on the areas of neurotransmission (signal transfer between nerve cells), axonal degeneration (destruction of nerve fibers), and neuron-glia interaction (communication between nerve cells and the glial cells that form the protective tissue surrounding them). “With Professors Misgeld, Simons, Korn and Mühlau, plus their working groups, we believe we have put together the right team ▶



Bernhard Hemmer



Thomas Misgeld



Thomas Korn



Arthur Konnerth

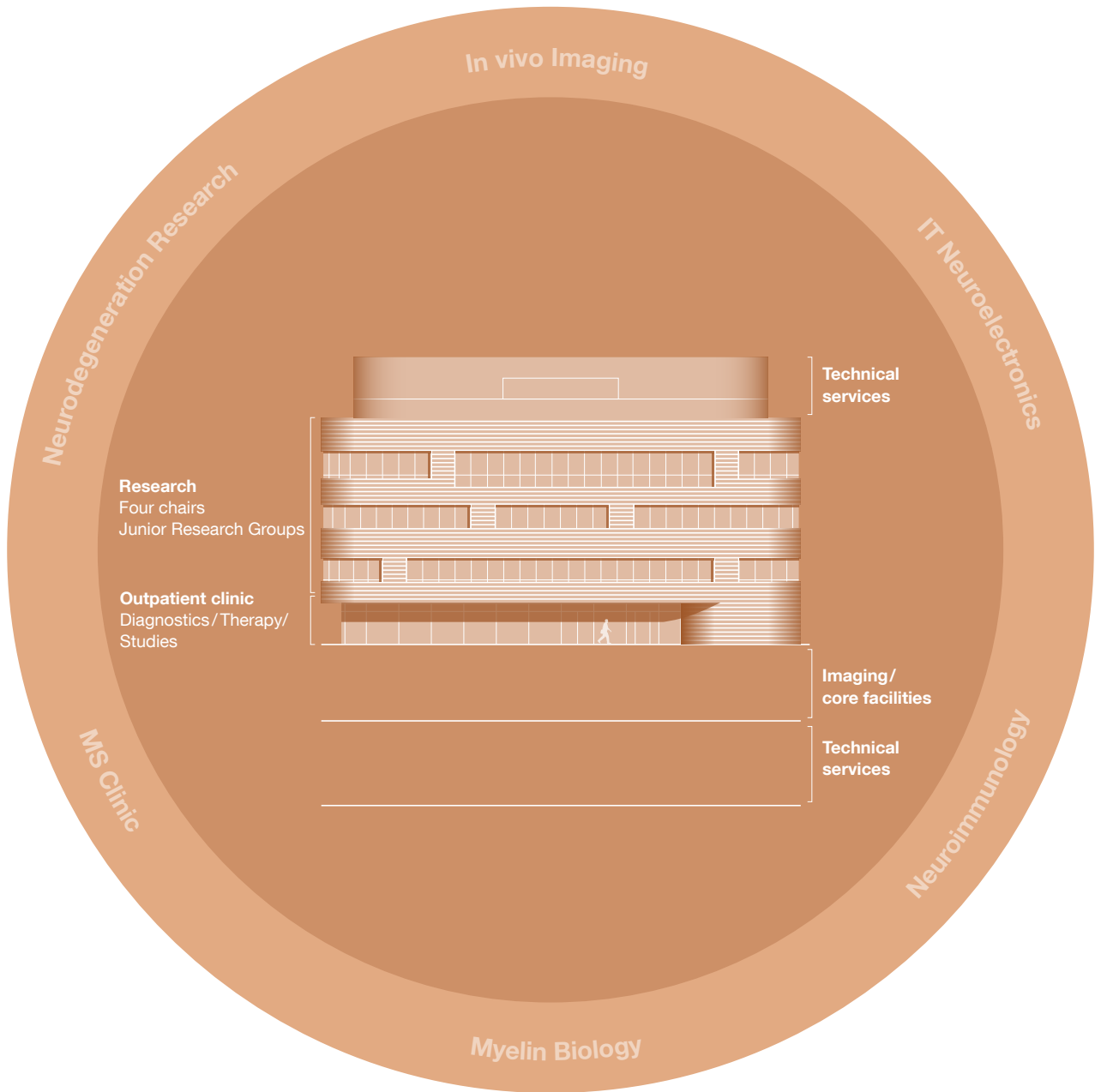


Mikael Simons



Mark Mühlau

Layout and concept of the new MS center



TUM's upcoming MS center will be located within the grounds of the university hospital, Klinikum rechts der Isar, and is set to open its doors in 2020. The architecture of the new building has been designed to accommodate an MS clinic housing the full range of diagnostic and treatment options along with research laboratories across the four floors above ground

level. The basements are reserved for medical imaging as well as infrastructure and technical services. The square building with its rounded corners will boast a total area of 4,600 square meters (sqm) and usable space of almost 2,700 sqm, ensuring room for six working groups of over 100 researchers and clinicians.

to advance our understanding and eventually the treatment of this disease at our upcoming MS center,” declares Hemmer with conviction.

Improved understanding of disease mechanisms

Driving all those involved is the determination to finally gain a better understanding of why the immune system attacks the body’s own nervous system, what mechanisms lie behind neurodegeneration, and how the disease can be predicted – or ideally even prevented.

Another question is how to halt or treat the condition in its chronic phase, when the nerves are already damaged. “Visualizing chronic disease progression is especially challenging. To date, systematically tracking neuronal atrophy also remains difficult beyond what we can directly examine in our patients. We need imaging techniques that allow us to view the degeneration process, or myelin destruction, as well as regeneration in its turn. And then we also need to get to grips with the factors that influence the process,” emphasizes Hemmer, who himself specializes in neuroimmunology.

What sets the research concept for TUM-MS apart is the fact that it brings together the full range of experts devoted to MS – extending from basic research right through to clinical practice. “Here we can develop therapies from bench to bedside – so if we discover a new pathomechanism, we can develop substances to target it, proof their effects in vitro and in vivo models and eventually test them in patients. As an academic center we are looking to develop new treatment strategies to the stage where they are attractive to pharma companies, which then initiate the necessary approval trials, since these are beyond our budget,” outlines Hemmer.

Flat hierarchies

The professors involved see it as their task to network their working groups, harness synergy effects and, above all, work

together to set and advance the research agenda. Maintaining flat hierarchies is particularly important to Hemmer, and he and his colleagues thus favor the department concept, with TUM-MS run by a committee rather than a single person. A team of clinical and basic researchers will be at the center’s helm, all on an equal footing and joining forces to move the field forward. This is intended to bridge the remaining divide between clinical practice and basic research. According to Hemmer, one reason why these two fields often do not interact as much as would be ideal, is that researchers and clinicians are often based in different locations and focus on different areas. Another is that communication between both communities on research is often suboptimal. “Our center will be striving to overcome that.”


TUM-MS will be one of several research centers devoted to MS research across Europe – so how will it position itself? “The integration of clinical and neurological research, along with the expertise TUM features on these areas, is unique in Germany or even Europe,” says Bernhard Hemmer. “Scientifically, our focus is clear: we will be tackling the role of inflammation in neurodegeneration and the consequences for neurons and glial cells. This means working hand in hand with the SyNergy excellence cluster (Munich Cluster for Systems Neurology), established in partnership with Munich’s LMU university,” explains Hemmer. The neuroimmunologist is convinced that the new MS center will become an attractive institution for young researchers and junior physicians: “Our center will bring together a critical mass of researchers and physicians, which will be well integrated into the Cluster of Excellence, as well as into other research networks within and across TUM and its faculties. The basic researchers will have direct access to key issues arising in clinical practice, as well as to biological material. And physicians can make MS the focus of their training, gaining contact to top basic researchers with a huge amount of expertise.”

Evdoxia Tsakiridou

“The integration of clinical and neurological research, along with the expertise TUM features on these areas, is unique in Germany or even Europe.”

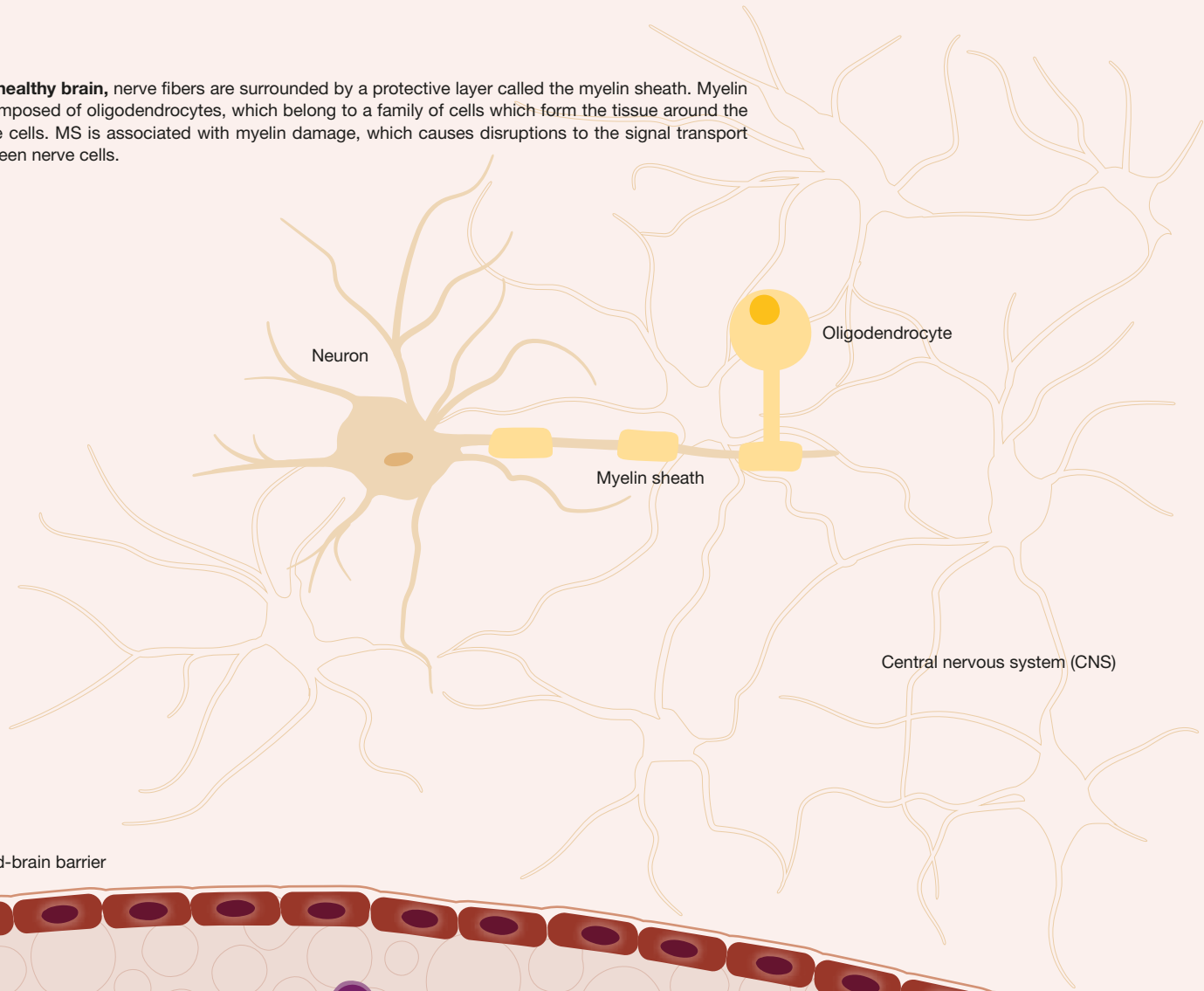
Bernhard Hemmer

New Treatment Options for MS Patients

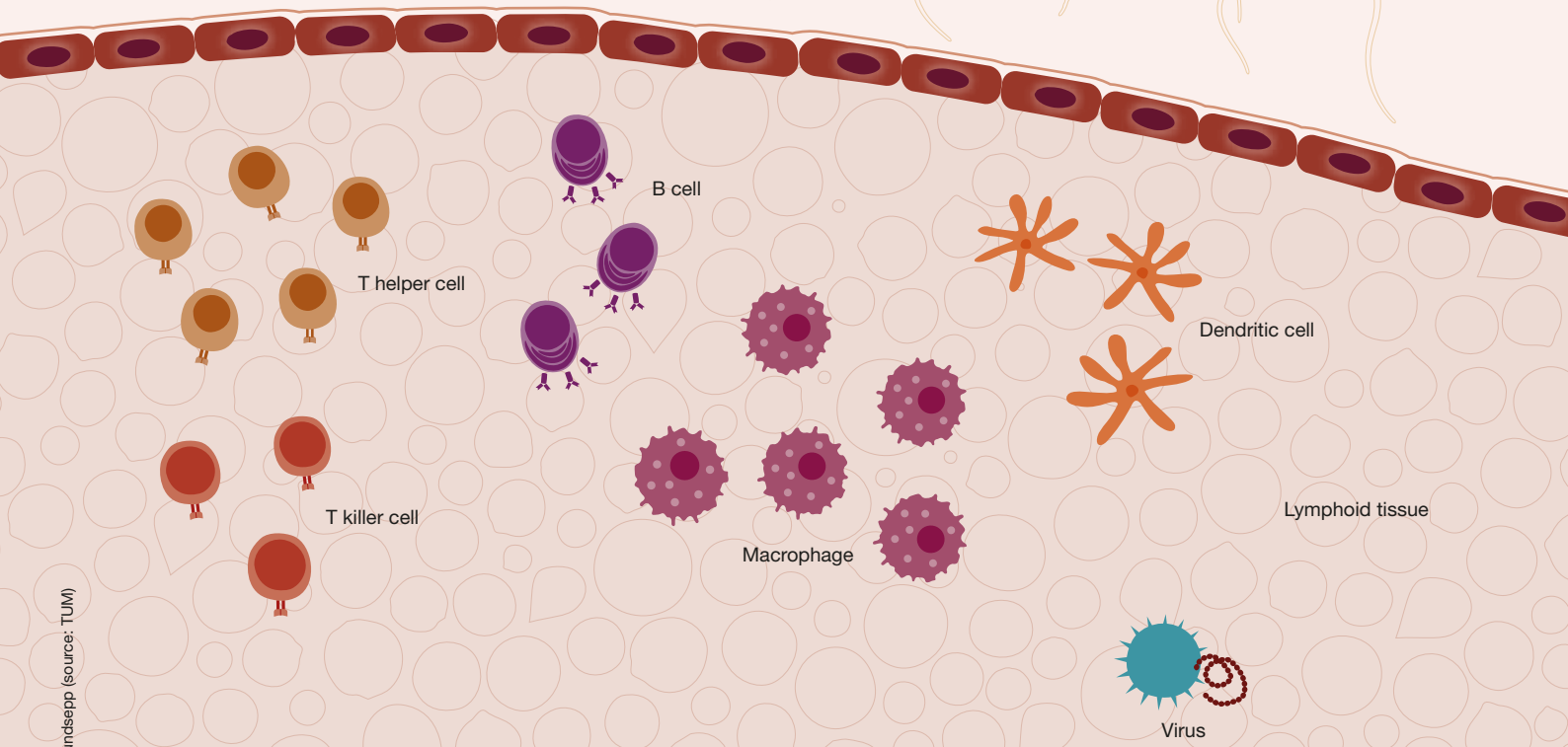


In multiple sclerosis (MS), B cells play a decisive role in the onset of disease. An international study – involving researchers from TUM – has demonstrated that a newly developed drug targeting these immune cells is effective in various forms of MS. This treatment is set to be available from 2017.

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.



Blood-brain barrier



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.

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 Ner-

venimpulse 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.

“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.”

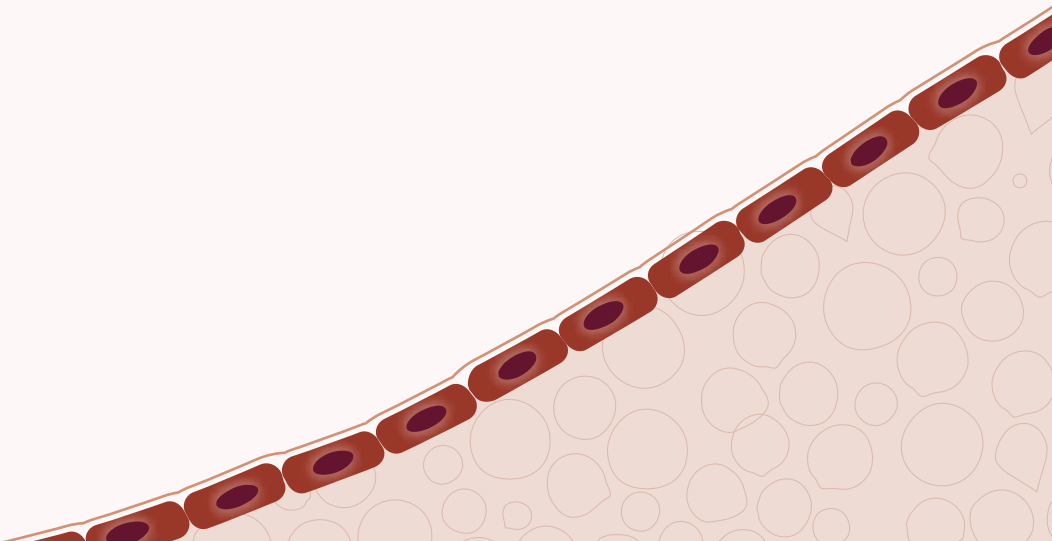
Bernhard Hemmer

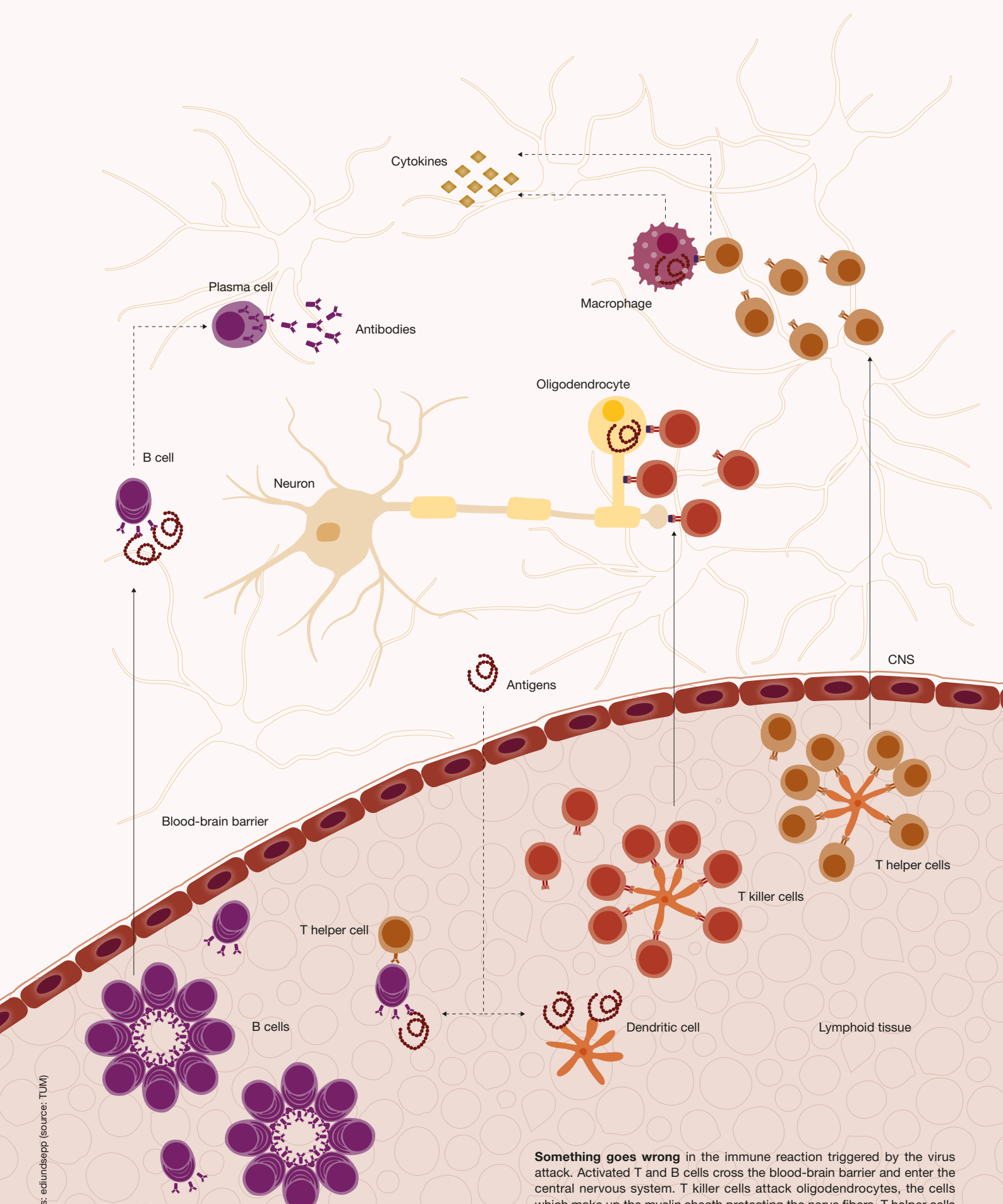
At some point, however, it can also happen that the good guys turn bad. “Genetic and environmental factors lead our immune system to make mistakes, with B and T lymphocytes identifying the brain and spinal cord as foreign and going into attack mode,” explains Prof. Hemmer. “In the initial phase of the 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: edlundsepp (source: TUM)

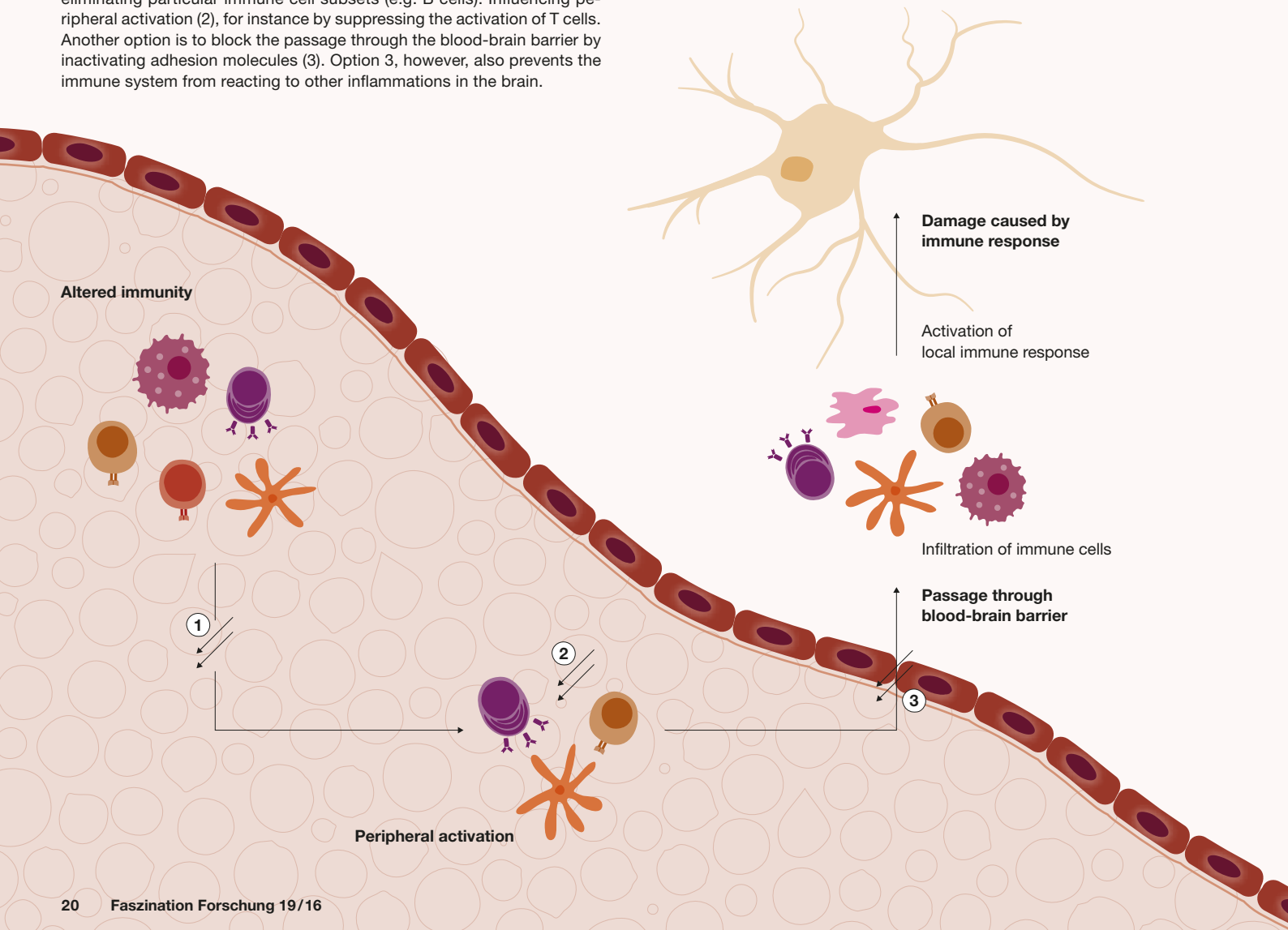
Something goes wrong in the immune reaction triggered by the virus attack. Activated T and B cells cross the blood-brain barrier and enter the central nervous system. T killer cells attack oligodendrocytes, the cells which make up the myelin sheath protecting the nerve fibers. T helper cells produce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

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

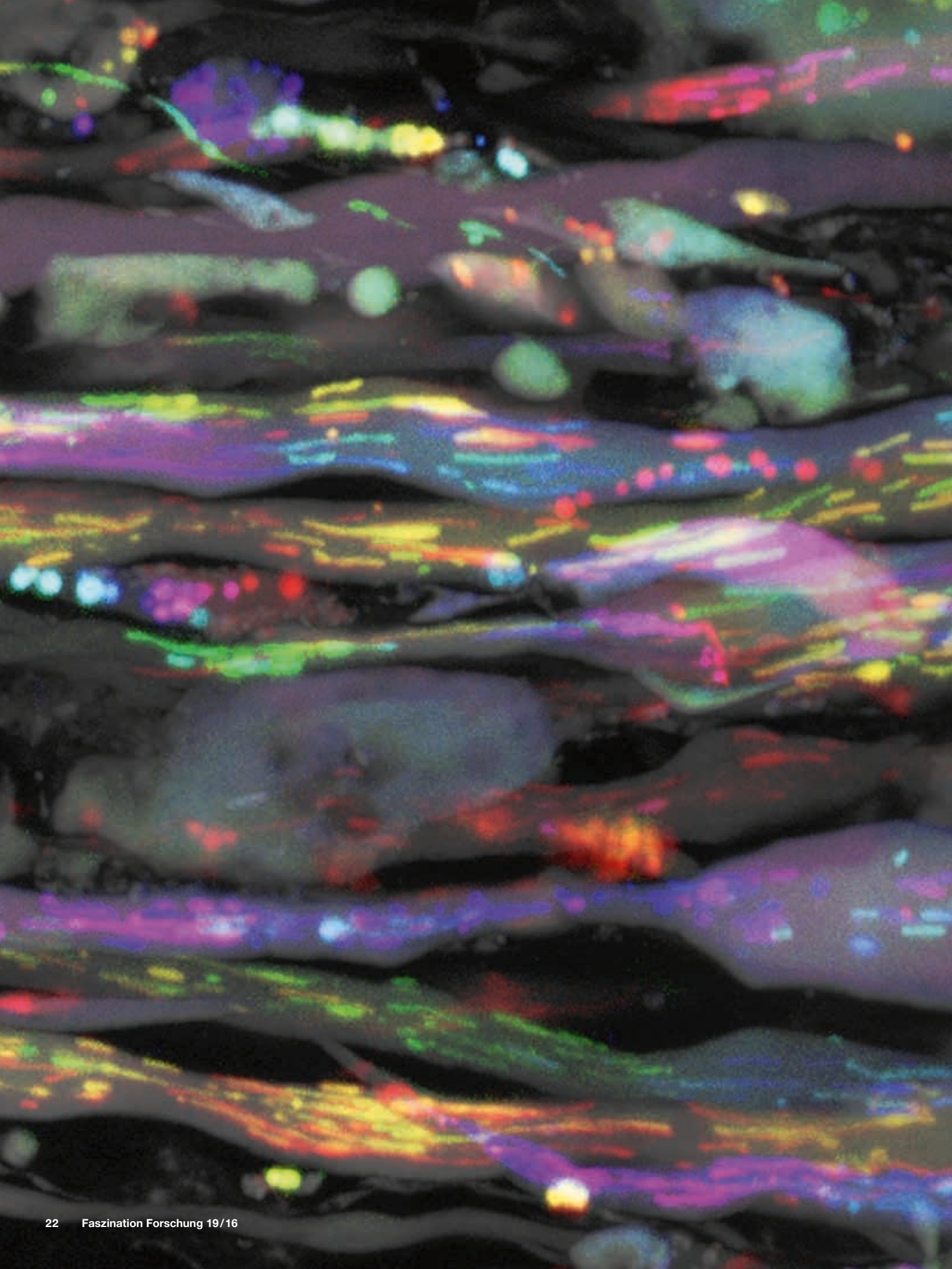
For Hemmer, though, the battle against MS is far from over. The outlook for patients in the chronic phase, when the neurons and axons have already degenerated, remains bleak. The B cell therapy cannot help them then, since – as Hemmer explains – the peripheral immune system only plays a minor role at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

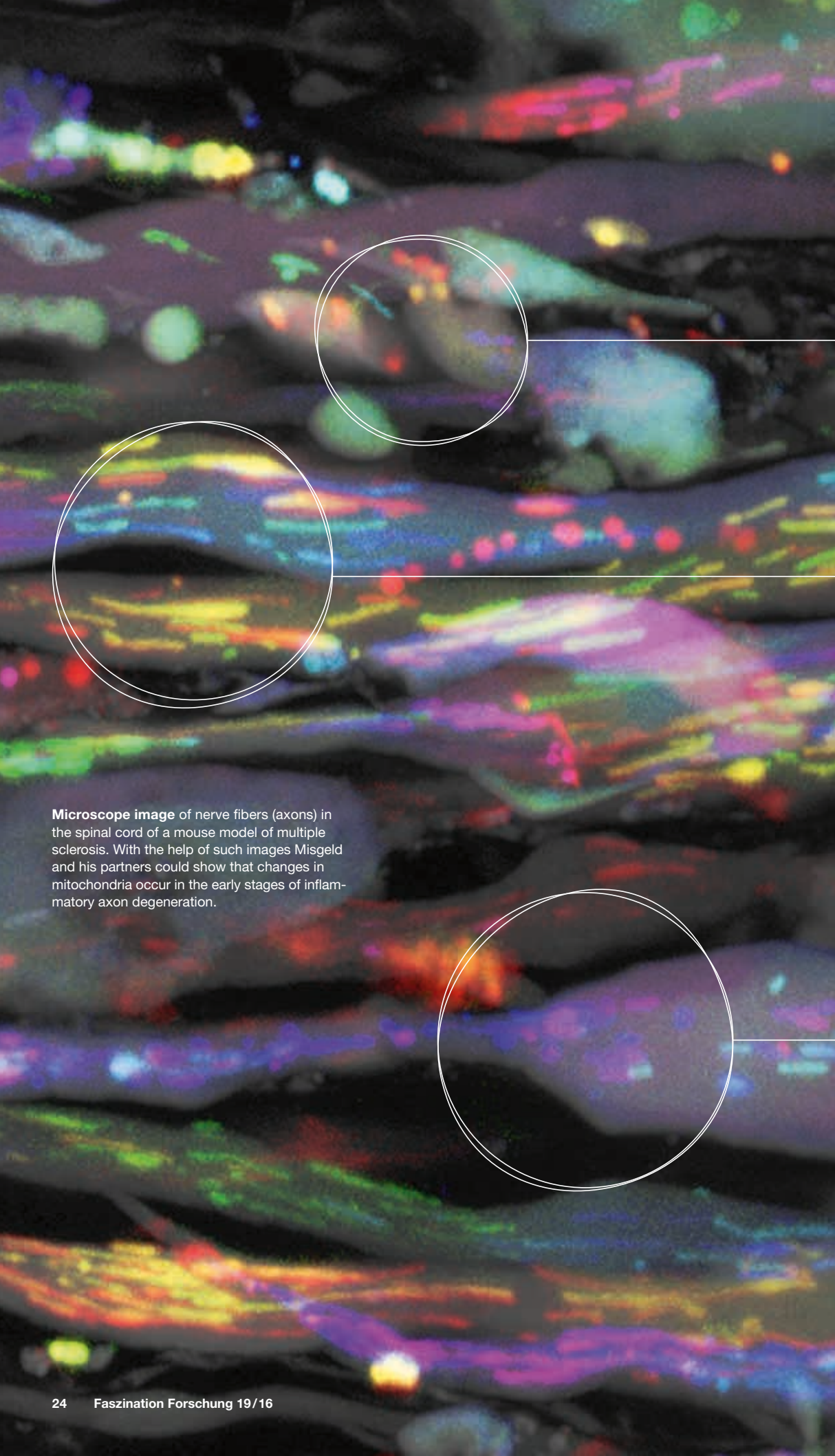
“How can we prevent neuronal damage, reverse defects and repair the myelin sheath? Treating the late effects is the major challenge facing us in the coming years,” sums up Hemmer, who is confident that the new MS center will help find answers to these questions.

Evdoxia Tsakiridou



Damaged Nerve Fibers Have the Ability to Recover

Researchers in Munich are using the latest microscopy techniques to investigate the mechanisms behind neural damage in multiple sclerosis. Using animal models, they have been able to demonstrate that aggressive free radicals cause damage to the fibers extending from nerve cells, but these go on to repair themselves once the renegade molecules have been neutralized.



Microscope image of nerve fibers (axons) in the spinal cord of a mouse model of multiple sclerosis. With the help of such images Misgeld and his partners could show that changes in mitochondria occur in the early stages of inflammatory axon degeneration.

Linkwww.neuroscience.med.tum.de*Evdoxia Tsakiridou*

Geschädigte Nervenzellen erholen sich

Der Krankheitsmechanismus der Multiplen Sklerose (MS) ist komplex und immer noch nicht restlos aufgeklärt. Bekannt ist, dass die eigenen Immunzellen das zentrale Nervensystem angreifen. Es bilden sich lokale Entzündungsherde im Gehirn und Rückenmark und die Signalverarbeitung in den Nervenzellen (Neurone) ist gestört. Es folgen Schäden an den Schutzschichten (Myelinscheide) von Neuronen und ihren Fortsätzen (Axone). Im weiteren Krankheitsverlauf degenerieren die Axone mit der Folge, dass die Nervenzellen ihre Funktion einbüßen.

Bislang glaubten Forscher, dass der Abbau der Myelinschichten zum Absterben der Nervenzellen führt. Thomas Misgeld, Lehrstuhlleiter für Zellbiologie des Nervensystems an der TUM, und sein LMU-Kollege Martin Kerschensteiner fanden jedoch bei Studien am Maus-Modell heraus, dass auch Axone mit intakt erscheinender Myelinscheide untergehen. Diese sogenannte fokale axonale Degeneration (FAD) läuft in mehreren Phasen ab: Zuerst schwellen an bestimmten Stellen die Nervenzellen an, später zerfallen sie in Einzelteile. Das geschieht nicht sofort. Zahlreiche Axone verharren für einige Zeit in geschwollenem Zustand, bevor der Zerfallsprozess einsetzt – und manche erholen sich spontan. Die beiden Forscher gehen deshalb davon aus, dass der Abbau der Myelinscheide nicht die einzige Ursache für die Axondegeneration sein kann. Zwischenstufen des FAD-Prozesses fanden die Wissenschaftler auch in Proben, die aus dem Gehirn von MS-Patienten stammen.

Charakteristisch für die FAD ist auch, dass die Mitochondrien, die Energielieferanten der Neuronen, deformiert sind. Diese Schäden werden vermutlich von Immunzellen verursacht, die Sauerstoff- und Stickstoffradikale produzieren. Mithilfe molekularer Bildgebung konnten Misgeld und Kerschensteiner in pharmakologischen Experimenten mit Mäusen zeigen, dass solche Molekülradikale die Mitochondrien schädigen und FAD auslösen können. Neutralisierten sie die aggressiven Moleküle mit entsprechenden Substanzen, konnten sich die betroffenen Axone wieder erholen. Die Forscher gehen deshalb davon aus, dass die FAD auch bei der MS umkehrbar sein könnte.

Nun lautet die Frage: Löst die Schädigung der Mitochondrien die FAD-Kaskade aus? Es gilt auch, die intrazellulären Signalwege aufzuklären, die die Radikale aktivieren. Die Wissenschaftler hoffen auf der Grundlage eines besseren Verständnisses, eines Tages mit entsprechenden Medikamenten auf diesen molekularen Prozess einwirken zu können. □

Degenerated axon

Mitochondria (colored dots) are damaged and round shaped

Intact axon

Mitochondria (colored lines) are intact and elongated

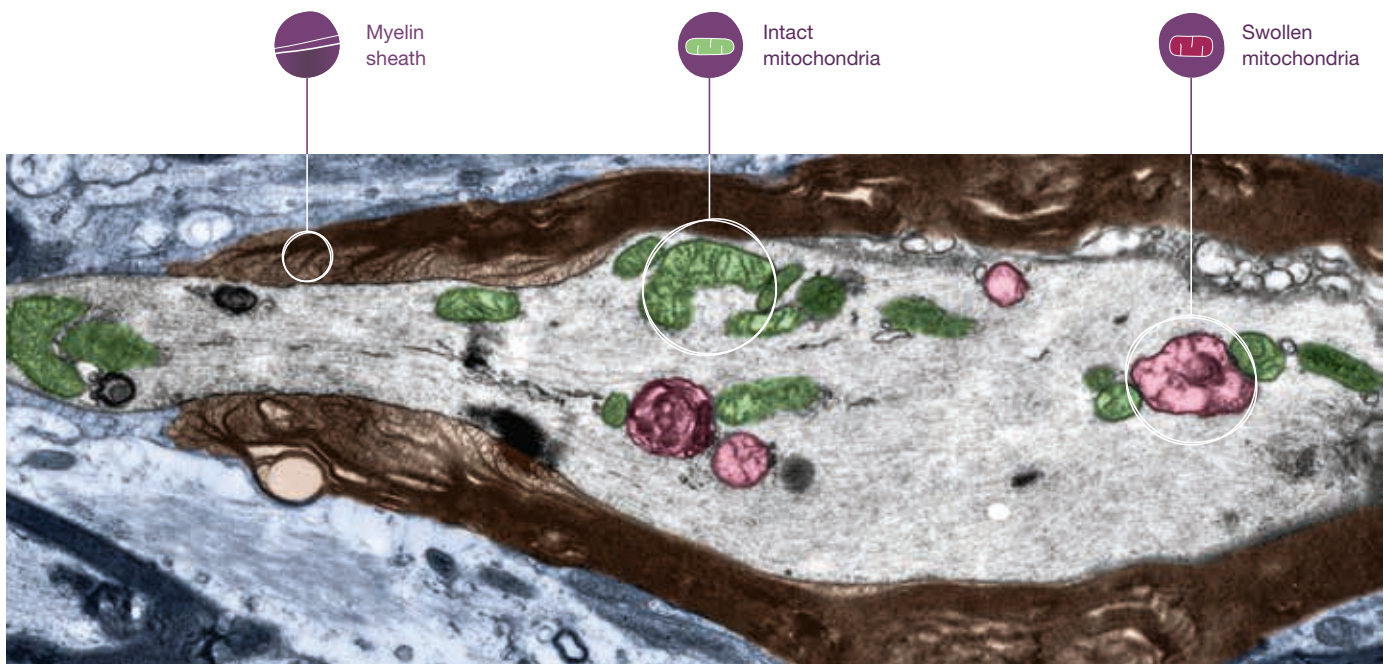
Swollen axon

Mitochondria swell and begin deforming into round shapes

We still don't know enough about the molecular processes involved in multiple sclerosis, and about axonal degeneration mechanisms in this disease in particular," acknowledges Prof. Thomas Misgeld, director of TUM's Institute of Neuronal Cell Biology. Although researchers around the world have been focusing intensively on multiple sclerosis (MS) for many decades now, they still have not fully unraveled the complexities of this disease. Through painstaking research, they continue to piece the MS puzzle together.

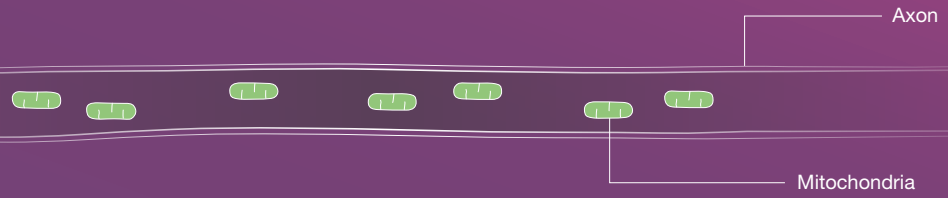
This autoimmune disease is characterized by local inflammation sites in the brain and spinal cord at its onset, as well as by episodic disruption of signal (action potential) conduction in the nerve cells, or neurons. The resulting symptoms include visual impairment, numbness or paralysis. A particularly striking aspect is damage to the myelin sheath – the fatty protective layers that surround and electrically insulate the long projection fibers of neurons, known as axons. Numerous axons also degenerate over the course of the disease – a process that can lead to irreversible loss of neuronal function. "There is a clear correlation between permanent neurological problems in MS patients and the extent of axonal damage," stresses Misgeld.

Until recently, many in the research community believed that destruction of the myelin sheath was the cause of subsequent axonal degeneration and neuronal atrophy. Now, however, there is a new take on this. Using a mouse model, research teams working with Misgeld and his colleague Martin Kerscheneiner (LMU Munich) were able to demonstrate that axons with intact protective coating also die off. The two researchers thus now consider it unlikely that myelin sheath destruction could be the sole cause of axonal degeneration. As yet poorly understood, this mechanism – known as focal axonal degeneration (FAD) – involves several steps. First, the axons swell up at certain points, before later disintegrating into individual pieces. To picture this, imagine pearls forming on a string, detaching themselves and then dropping off. However, the breaking-away stage does not happen immediately. Many axons hang on in a swollen condition for a few days before the disintegration process takes hold – and some spontaneously repair themselves. "Interestingly, such interim stages of the FAD process are also found in brain biopsies from MS patients," comments Misgeld. ▶

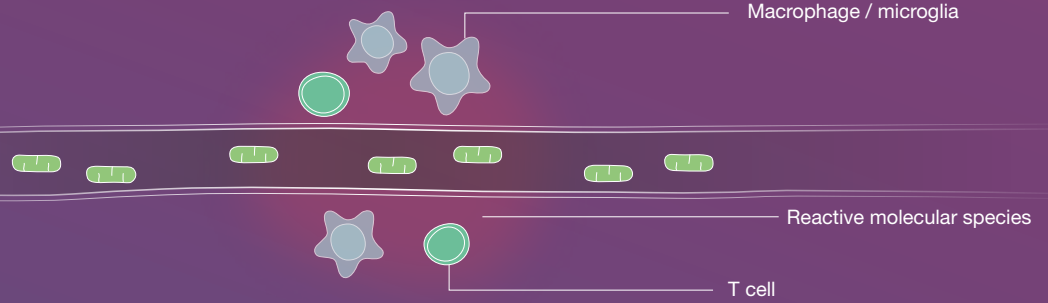


Electron micrograph of an axon located in the spinal cord of a mouse model with multiple sclerosis. The axon is the first stage of degeneration which is characterized by swelling mitochondria. It contains intact looking mitochondria (green) and swollen ones (red). The myelin around the axon (colored brown) is intact.

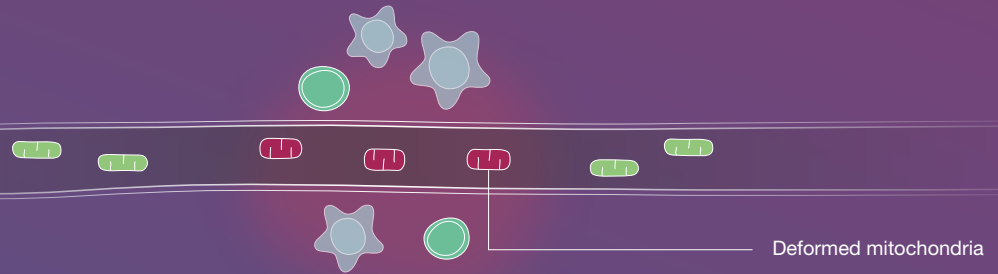
Normal



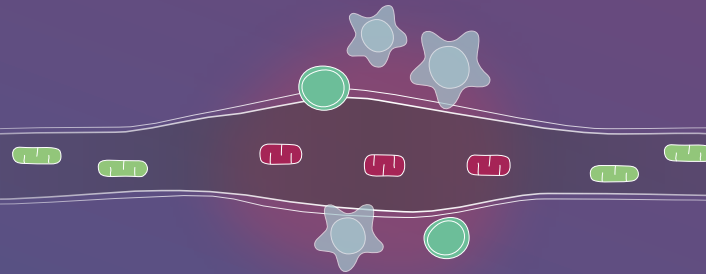
Neuroinflammation



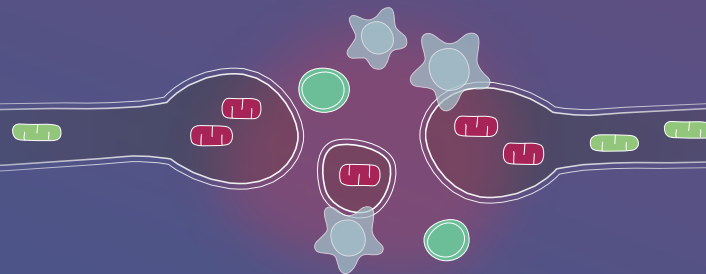
Mitochondrial damage



Axonal swelling



Degeneration



Picture credit: Nikke et al., Nature Medicine 2011. Graphics: eciundisepp (source: TUM)

Focal axonal degeneration is a process which can lead to axon degeneration in inflammatory lesions in the spinal cord. A normal nerve fiber – characterized by elongated mitochondria – swells and fragments, often despite an intact myelin sheath. Even before a nerve fiber swells, its mitochondria show local damage. It is notable that in the early stages of this process some axons recover spontaneously.

“There is a clear correlation between permanent neurological problems in MS patients and the extent of axonal damage.”

Thomas Misgeld

Prof. Thomas Misgeld

Homing in on the brain

Following medical training in Munich, at TUM and the Max Planck Institute for Neurobiology, Thomas Misgeld did postdoctoral research in the United States. At Washington University in St. Louis and at Harvard, he acquired expertise in cutting-edge microscopy techniques for in vivo imaging that continue to shed new light on the life of individual nerve cells.

Returning to TUM in 2006 as a Kovalevskaja group leader within the Institute of Neuroscience, he became a fellow of the TUM Institute for Advanced Study and one of the university's first tenure track professors, as well as a principal investigator in the Excellence Cluster CIPS-M (Center for Integrated Protein Science Munich).

Now a full professor, he is director at the TUM Institute of Neuronal Cell Biology and an associate member of the German Center for Neurodegenerative Diseases (DZNE). In 2012, Misgeld and a number of collaborators at TUM, DZNE and LMU established the Munich Cluster for Systems Neurology (SyNergy), an Excellence Cluster dedicated to investigating the mechanistic basis of neurological diseases. Misgeld and Prof. Christian Haass, a renowned Alzheimer's researcher at DZNE and LMU, are co-spokespersons of SyNergy.



Misgeld's team uses confocal and two-photon microscopy to carry out in vivo measurements on nerve fibers in model organisms. The image on page 26 was recorded in this way.



And that is not the only peculiarity. FAD typically also involves deformation of the mitochondria. These act as a cell's power houses, moving back and forth along the axons and supplying the neurons with energy – and have also been found to swell up in FAD. Thus, mitochondria are damaged very early on in MS, and Misgeld and his colleagues are also aware that: "Oxygen and nitrogen radicals produced by the immune cells play a major role here." Using molecular imaging as a read-out, the researchers were able to conduct pharmacological experiments in mice that demonstrate that these two free radical types can damage the mitochondria and trigger FAD. If the aggressive molecules were neutralized by appropriate substances, the affected axons were able to recover. So the researchers have reason to believe that FAD could also be reversible in MS.

According to Misgeld, whether patients stand to benefit from these findings also depends on resolving a series of questions: What exactly happens inside the mitochondria? Is their damage a trigger in the FAD cascade? Which intracellular signaling pathways are activated by the radicals? What is the role of the spike in axonal calcium levels observed in the early stages of FAD?

There is a chance that it might become possible to influence this molecular process with the right medication – always assuming that it can be completely decoded at some point. FAD could then be a potential treatment target. However, as Misgeld cautions: What works in a mouse model is by no means guaranteed to work in patients. And it is not yet known whether structural recovery of axons goes hand in hand with full recovery of their function. Similarly, it is still unclear whether FAD is the sole mechanism behind axonal degeneration in MS.

Other questions preoccupying the neurobiology specialist include: Are the mechanisms of axonal degeneration in MS unique to that condition, or do similar processes also play a role in other neurological disorders, for instance in dementia or following trauma? And are the disease-induced mechanisms related to the physiological processes involved in the development of the nervous system, during which numerous axons are dismantled and remodeled?

As it stands, nobody knows the answers – since, according to Misgeld, there are still huge gaps in our basic understanding of the nervous system. "We must now focus intensively on the structural and developmental dynamics of the brain."

Evdoxia Tsakiridou



Cluster for Systems Neurology (SyNergy): Investigating the Mechanisms Underlying Neurological Disease

“It is becoming increasingly clear that, in all neurological disorders, the main pathomechanism is always accompanied by other pathological processes that influence the course of disease. In stroke patients, for instance, blockage of a blood vessel triggers inflammation. And in multiple sclerosis, which is primarily an immune system disease, inflammation leads to degeneration of the axons. Certain immune cells play a central role in Alzheimer’s too,” underscores Thomas Misgeld, Professor at TUM’s Institute of Neuronal Cell Biology and a researcher at the German Center for Neurodegenerative Diseases (DZNE).

So the progression of many neurological disorders might be determined by mechanisms common to multiple conditions – an analytical level that has not played a central role in research efforts to date, since scientists have typically considered each pathology within its own limited context. However, for some time now, researchers and clinicians have been striving to link up traditionally separate specializations within neurology (inflammation, degeneration, vascular disorders and glial cell dysfunction) and develop Munich into the European center for systems neurology – still a young scientific field.

To achieve this, Munich’s two universities joined forces with the German Center for Neurodegenerative Diseases (DZNE), the Max Planck Institutes of Biochemistry, Neurobiology and Psychiatry, and the research center Helmholtz Zentrum München to establish the SyNergy excellence cluster. This research alliance has received around 30 million euros in funding from Germany’s Excellence Initiative since 2012 and is coordinated by Alzheimer’s researcher Christian Haass (LMU) and Thomas Misgeld (TUM) as co-spokespersons.

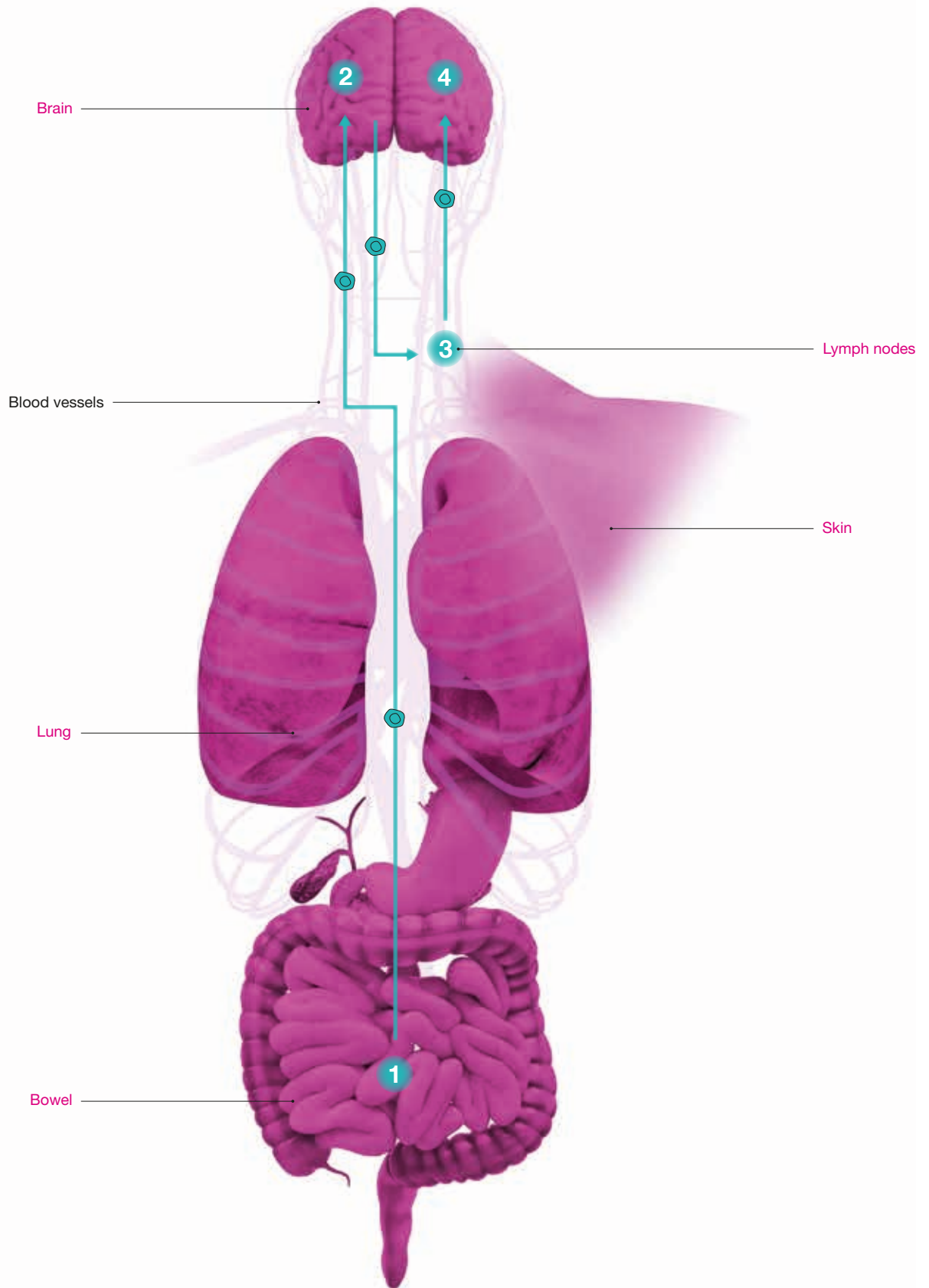
Around fifty scientists and their teams are investigating the joint mechanisms of inflammatory, degenerative and vascular diseases of the nervous system within the SyNergy cluster. This is accomplished through so-called “Tandem Projects”, which involve collaboration between at least two SyNergy researchers from different fields within the areas mentioned. “The idea is to explore the overlaps between the various areas

of specialization – for instance between neuroinflammation and the glio-vascular system,” specifies Misgeld. This broader focus across traditional boundaries is what sets the cluster apart. The initiators are looking to gain more comprehensive insights into neurological pathomechanisms with an eye on the bigger picture. They also want to give the members of the cluster the opportunity to enter new areas of research and collaborate across disciplines.

However, it is not just a question of joint research, but also of intensive collaboration between institutions. “We have the Institute for Stroke and Dementia Research under the same roof as DZNE – and soon also the MS research center at TUM as a similarly collaborative institute. The interplay and collaboration between these areas is what we are striving to reinforce. We have already cleared the first hurdle by establishing the cluster as a joint initiative. The partnership between the two Munich universities, and especially with Prof. Haass and the other colleagues at DZNE, is the cluster’s major strength. And now we intend to tighten the cooperation still further,” reports Misgeld.

Applications for the next round of the Excellence Initiative are now in the preparation stage, with participants seeking to secure funding of 20 to 50 million euros for the next seven-year period. “It has a huge lever effect. Because it also motivates other faculties and institutions to join forces and invest in this area,” Misgeld concludes. “In the coming years, we hope to build the necessary infrastructure to totally transcend the boundaries between institutions and research topics – as we have already started to achieve at DZNE. The MS center is another good example of this. On the one hand, its outpatient department will treat MS patients and pursue clinical research. And on the other, the floors above will house research labs – not just for clinicians, neurologists and immunologists, but also for neuro- and developmental biologists tackling the basic issues underlying MS. We believe that integrating basic research is absolutely essential to gaining a better understanding of the pathomechanism of neurological disorders.”

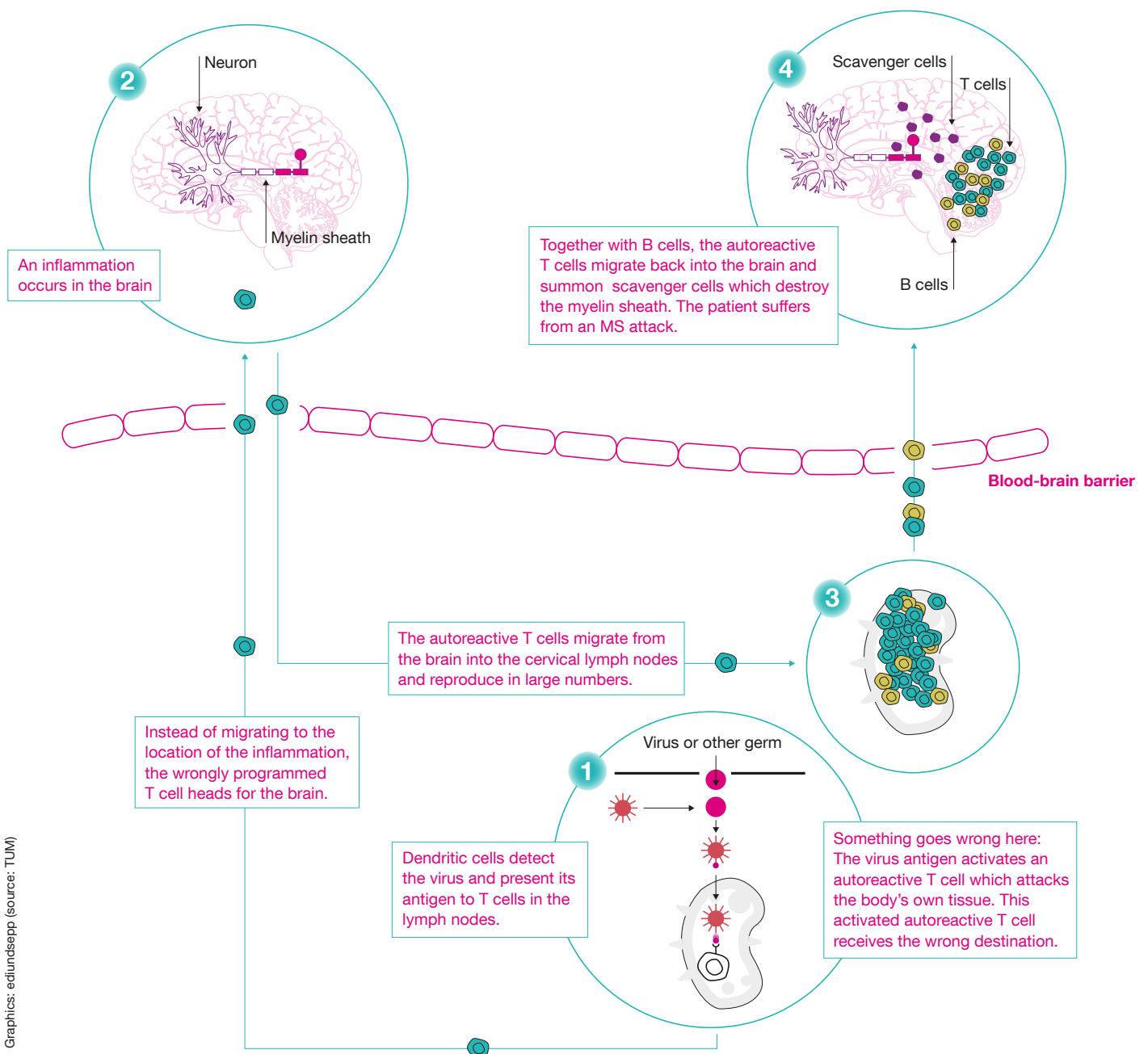
Evdoxia Tsakiridou



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.

Around 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

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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

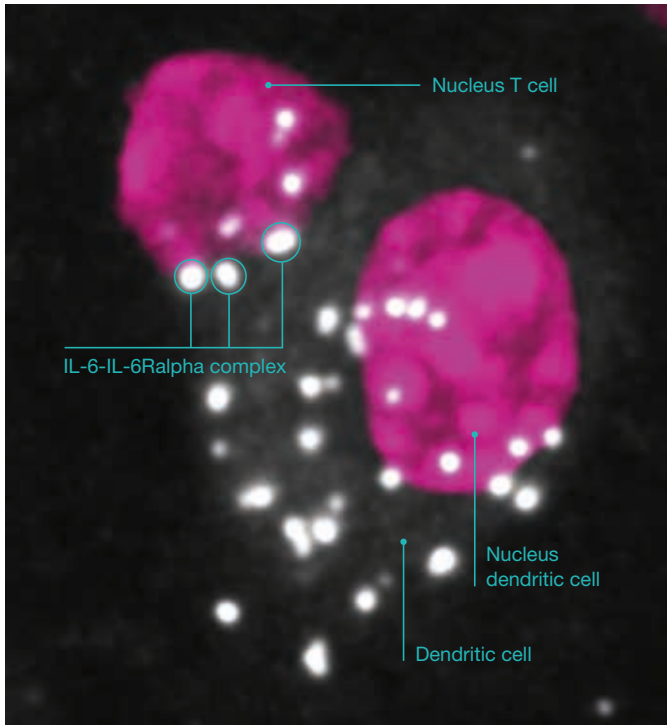
Strictly speaking, the sensitive brain is off-limits to all but certain types of T cell – the ones that carry out immune surveillance on its behalf. The blood-brain barrier prevents ▶



Prof. Thomas Korn

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



Much more than Glue

To function properly, our nervous system needs a substance called myelin, which surrounds and protects nerve fibers. If this myelin sheath is destroyed, as in multiple sclerosis (MS), the consequences are severe. Prof. Mikael Simons is researching how this protective insulating layer is formed – with the aim of improving treatment for MS patients.

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Claudia Doyle

Mehr als nur Leim

Die meisten Neurologen erforschen Nervenzellen, Neuronen genannt. Nur wenige Wissenschaftler widmen sich dem anderen Zelltyp im Gehirn, den sogenannten Gliazellen. „Früher war man als Neurologe, der an Gliazellen forscht, schon ein Exot“, sagt Mikael Simons, Professor für Molekulare Neurobiologie an der TUM und Wissenschaftler am Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE). „Aber das ist längst nicht mehr so.“

Simons hat eher als andere damit angefangen, sich für eine ganz bestimmte Art von Gliazellen zu interessieren. Er untersucht sogenannte Oligodendrozyten, die aus ihrer Zellmembran eine isolierende Myelinscheide um Nervenfasern herum ausbilden. Die Myelinscheide beschleunigt die Signalweiterleitung, sie schützt die Axone und versorgt sie mit Energie.

Die Myelinisierung des Gehirns beginnt kurz nach der Geburt, findet aber auch im Erwachsenenalter noch statt. Damit hat Myelin auch einen Anteil an der Plastizität unseres Gehirns.

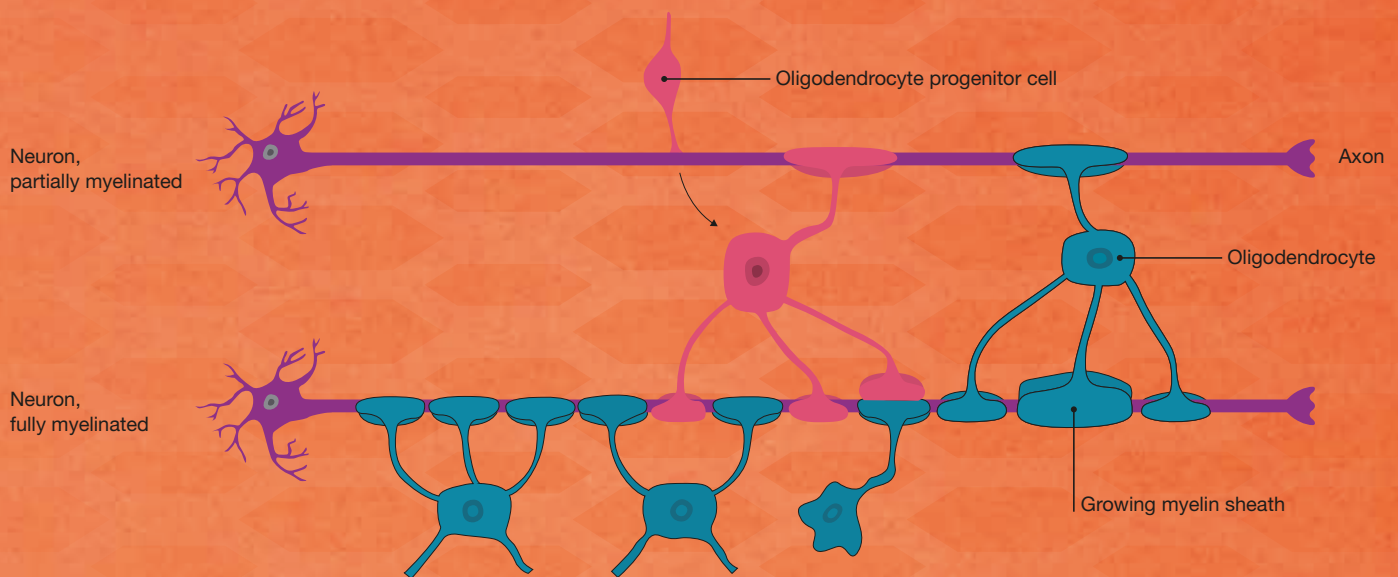
Dass unser Gehirn plastisch ist, sich also je nach Gebrauch in seiner Anatomie verändert, das weiß man schon seit fast 20 Jahren. Je nachdem, welchen Umwelteinflüssen wir ausgesetzt sind, welchen Sport wir treiben oder welches Musikinstrument wir üben, verändert sich die Struktur unseres Denkapparats. Gehirnareale wachsen oder übernehmen neue Aufgaben.

Bisher dachte man jedoch, dass einzig die Neuronen dafür verantwortlich sind. Dass sie in viel benutzten Bereichen neue Synapsen ausbilden und Datenautobahnen bauen. Doch das ist nur die halbe Wahrheit. Das Myelin ist ebenfalls beteiligt, es übernimmt die Feinabstimmung.

Das konnte schon in zahlreichen Experimenten gezeigt werden. Trainierten Probanden einen komplexen Bewegungsablauf oder lernten sie eine neue Sprache, dann sahen die Forscher im Magnetresonanztomographen, dass sich in bestimmten Gehirnarealen mehr Myelin gebildet hatte.

Simons hat mithilfe von modernsten Mikroskopiemethoden herausgefunden, dass für die korrekte Ausbildung der Myelinscheide ein Protein ganz entscheidend ist: das Myelin-Basische Protein (MBP). Fehlt MBP, dann degeneriert die Myelinscheide. Sie verliert ihre Stabilität und wird schließlich von Fresszellen abgebaut.

Solche grundlegenden Erkenntnisse über den Auf- und Abbau von Myelin sind essentiell für die Entwicklung neuer Therapien, zum Beispiel für Multiple Sklerose (MS). Bei MS-Patienten wird die Myelinscheide während eines Schubs zerstört. Dann wächst sie nach, jedoch selten vollständig. Einige Schäden bleiben, die Krankheit schreitet voran. Im Mausmodell hat Simons vor kurzem einen Stoff identifiziert, der bei der Regeneration der Myelinscheide hilft. Wenn zukünftige klinische Studien diesen Erfolg beim Menschen bestätigen können, wäre das ein großer Schritt hin zu einer besseren Therapie von MS. □



A cell cautiously feels its way along a nerve fiber. Luckily, it is the first one to make it to its chosen spot, with no other oligodendrocytes in sight. And so it gets going, slowly winding its membrane around the nerve fiber, or axon. Once, twice, again and again – it only stops when the axon is surrounded by dozens of membrane layers. This is known as the myelin sheath, and is itself still shrouded in mystery. Physicians are only now starting to understand how many different functions it fulfills in a healthy brain – and the role played by damaged myelin in neural disorders.

Most neurologists conduct their research into nerve cells, known as neurons. Only a few scientists devote themselves to the other type of cell in the brain, called glial cells or neuroglia. The word “glia” comes from the Greek for “glue”. And for a long time, this was the way most scientists viewed these cells – as a type of adhesive, connecting and supporting the neurons. Now, though, this definition is obsolete; as every neurologist knows, the glia cells do far more than that. In fact, without them, the neurons would not be able to function. “In the past, a neurologist researching glial cells was certainly a rarity,” agrees Mikael Simons, “but that has long since changed.” Simons is Professor of Molecular Neurobiology at TUM and an associate member of the German Center for Neurodegenerative Diseases (DZNE). He is interested in a par-

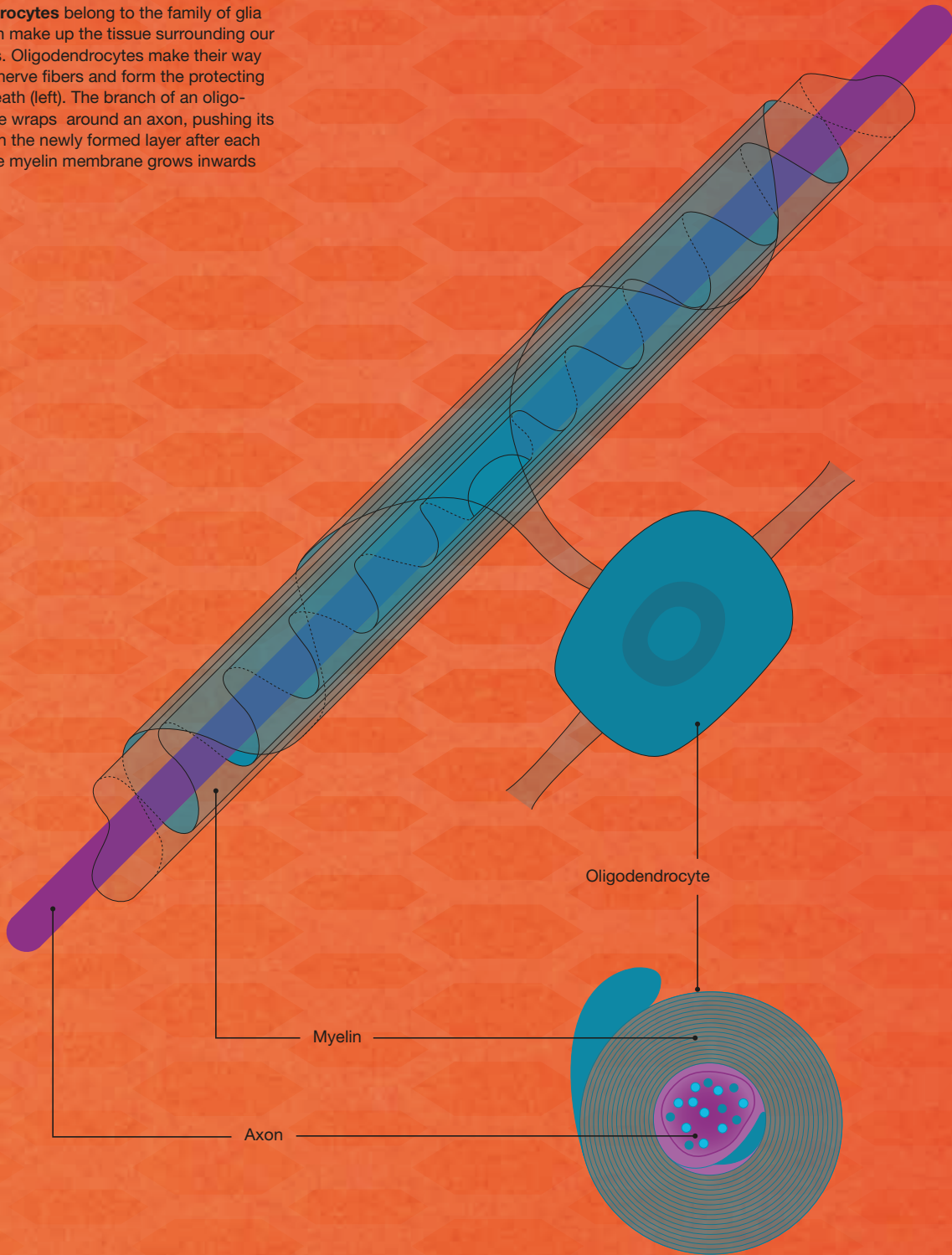
ticular type of glial cell – the oligodendrocytes, which coat the nerve fibers with an insulating myelin layer formed from their cell membranes. This myelin sheath accelerates nerve impulse conduction, protects the axons and supplies them with metabolites, which it transports from the blood vessels.

Immature brains at birth

When we are born, our brains are not yet mature. The neural pathways lie bare, and signals from one cell to another are relatively slow. Then myelination begins around birth in earnest. Oligodendrocytes make their way along the nerve fibers and set about forming a myelin sheath. This process also occurs in the peripheral nervous system, outside the brain. Here, the myelin is supplied by Schwann cells instead of oligodendrocytes. The principle, however, remains the same.

The myelin membrane grows inwards in the immediate vicinity of the axon. After each circuit of the axon, the tip of the oligodendrocyte pushes beneath the newly formed myelin layer and wraps itself around the axon again. “So possibly the opposite of what you might expect,” acknowledges Simons. Some neural pathways are fully myelinated, while others receive little to no myelin. There does appear to be an underlying system at work, but no scientist has yet succeeded in decoding it.

Oligodendrocytes belong to the family of glia cells which make up the tissue surrounding our nerve cells. Oligodendrocytes make their way along the nerve fibers and form the protecting myelin sheath (left). The branch of an oligodendrocyte wraps around an axon, pushing its tip beneath the newly formed layer after each circuit: The myelin membrane grows inwards (right).



“Here at TUM, basic and clinical research are already interwoven at the highest level. This really is a dream come true.”

Mikael Simons

What we do know is that the process follows some sort of hierarchical order. The very first neural pathways to be myelinated help conduct signals for vital functions, such as breathing. Then come neurons involved in more complex tasks such as coordinating movement. Finally, myelin is applied to axons in the cerebral cortex: the seat of our higher, intellectual functions.

Myelin promotes brain plasticity

Rather than taking place once and for all as part of childhood development, myelination also continues into adulthood. So the brain's plasticity also extends to myelin production.

We have long since known that the brain is plastic – that is, its anatomy changes according to use. The structure of our thinking apparatus is capable of adapting in line with our exposure to environmental factors, what sport we play or what musical instrument we practice, for instance. Brain areas grow or perform new roles. And if an area is no longer in use, it can be freed up to take on other tasks.

Previously, though, it was thought that the neurons were solely responsible for this, forming new synapses and building information highways in heavily used areas. It now turns out that this is only half the story. Myelin also has its role to play in brain plasticity, taking care of the fine-tuning.

This has already been demonstrated in numerous experiments. When test subjects practiced a complex sequence of movements or learned a new language, researchers were

Prof. Mikael Simons

Mikael Simons studied medicine at Heidelberg University, pursuing his doctorate in the laboratory of Konrad Beyreuther, a distinguished Alzheimer's researcher. However, this field was already very popular with scientists, and Simons wanted to explore completely unknown territory – such as the myelin sheath.

After periods of study abroad in Yale and Harvard, Simons then returned to Germany. He initially worked at Tübingen and Heidelberg universities, before taking up the position of Junior Group Leader at the University of Göttingen's Center for Biochemistry and Molecular Cell Biology in 2004. In 2007, he was then also appointed head of the Neurology department in Tübingen.

In 2008, Simons received a grant from the European Research Council, enabling him to set up a working group at the Max Planck Institute for Experimental Medicine. He was then made Full Professor of Molecular Neurobiology at the University of Göttingen in 2009, transferring to TUM at the start of 2016.

Simons is now engaged in basic research, but clinical issues remain of interest. His hope is that patients will eventually benefit from his research findings. TUM and its new MS center, currently in the planning stages, offer the ideal environment for him to achieve this. Awarded 25 million euros in funding from the Klaus Tschira Foundation (KTS), the MS center will open in 2020 and focus entirely on multiple sclerosis research. “Here at TUM, basic and clinical research are already interwoven at the highest level,” reports Simons, adding that such close collaboration is a rarity in Germany. “This really is a dream come true.”

then able to see increased myelin formation in specific brain areas on MRI scans.

Oligodendrocytes appear to increase myelination of axons that are particularly active and conduct a lot of signals. However, as yet we have no idea how the oligodendrocytes can actually determine what is happening inside the axons. “The two cell types seem to communicate in some way, but we don't know how,” Simons confirms.

In the central nervous system, at least, myelin is thus subject to constant changes. But researchers are still puzzled as to how this functions in such an inert, inaccessible membrane. How is it constructed? And can it disappear again too?

How is myelin depleted by disease?

To get to the bottom of this question, we must first take a closer look at the construction of the myelin sheath.

When the branch of an oligodendrocyte first wraps itself around an axon, there is still plenty of room between the superimposed cell membranes. As is customary in other cells, this space teems with protein factories, cellular powerhouses and all sorts of other vital molecules. But then the contraction process begins. The individual layers constrict and together form thick membrane stacks. Recently, Simons and his team were able to demonstrate the essential role of a specific protein in this process. Using various microscope imaging techniques, such as electron microscopy, they were able to ▷



Simons and his team use this large illustration of the brain for discussions and for planning experiments.



Mikael Simons and two postdocs, Ioannis Alexopoulos and Minou Djannatian, discuss and analyze data generated by convocal microscopy experiments.



Maria Cunha, a Ph.D. student in Simons' laboratory, uses a confocal microscope to observe myelination in a living but sedated zebrafish (inside the petri dish in the lower image).



observe how loss of myelin basic protein (MBP) in the mouse brain goes hand in hand with destruction of the myelin sheath. MBP can best be pictured as long, untidy strands of protein, swimming in the cytoplasm of oligodendrocytes. Once both ends of one of these protein fibers come into contact with superimposed areas of cell membrane, the protein folds itself tightly, pulling the membranes towards each other.

Like a zipper mechanism, this process continues until the entire myelin sheath has contracted into an extremely compact stack of cell membranes. Only the innermost and outermost layers of the membrane stack are exempt from this activity. Without MBP, the myelin sheath loses its stability, and is eventually destroyed by scavenger cells. This appears to be the case in many myelin diseases.

Improving regeneration in MS

What happens when the myelin sheath is damaged – however this occurs – can be seen in numerous diseases. Psychiatric disorders such as schizophrenia and depression are associated with changes in the myelin sheath. What has not yet been established is how these changes are triggered.

In multiple sclerosis, the situation is clearer. An inflammatory response in the brain leads the patient's own immune system to attack and destroy the myelin sheath. This causes various symptoms, including weakness and loss of sensation. The

disease usually occurs in episodes, with demyelination attacks followed by periods in which the myelin sheath partly regenerates.

However, this regeneration in MS patients is not complete. In the early stages of the disease, it still seems to work well, but as the disease progresses, the capacity for regeneration steadily declines.

“The most promising window for myelin regeneration is probably when inflammation is still active,” explains Simons. Once the inflammation has completely subsided, scar tissue (sclerosis) forms at the edges of the damaged myelin sheaths. While Simons does not rule out new myelin growing at these sites, he considers it a great deal more difficult.

Against this backdrop, he is searching for a drug to actively support patients in myelin sheath regeneration – and has already identified a promising candidate. “The good thing is that the molecule in question is already known,” he reveals. “Which might mean we can go straight into clinical trials.”

This entire field of research seems to hold many more questions than answers to date. But Mikael Simons relishes that – in fact, it is why he chose it. “In many branches of neurology, you have so many people on the case, at some point you might run out of questions entirely,” he muses. As far as the myelin sheath is concerned, that certainly does not look likely to happen any time soon.

Claudia Doyle

Physicians are only now starting to understand how many different functions the myelin sheath fulfills in the brain – and the role played by damaged myelin in neural disorders.



From Bench to Bedside

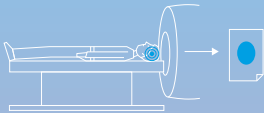
Translational medicine – the close interaction of basic researchers and clinician scientists – is the key to rapid and efficient development of new diagnostics and therapies.

and Back

Clinical research
focused on
the patient



Environmental factors
Genetic analysis



New diagnostic methods



Definition of
disease entity



Molecular mechanisms
underlying development
of the disease



Modeling

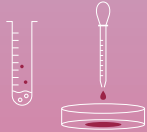
Definition
of targets

Targets for drugs

Modulation
of targets



Genetic analysis



Biochemical studies

Basic science
in the laboratory

Gerlinde Felix

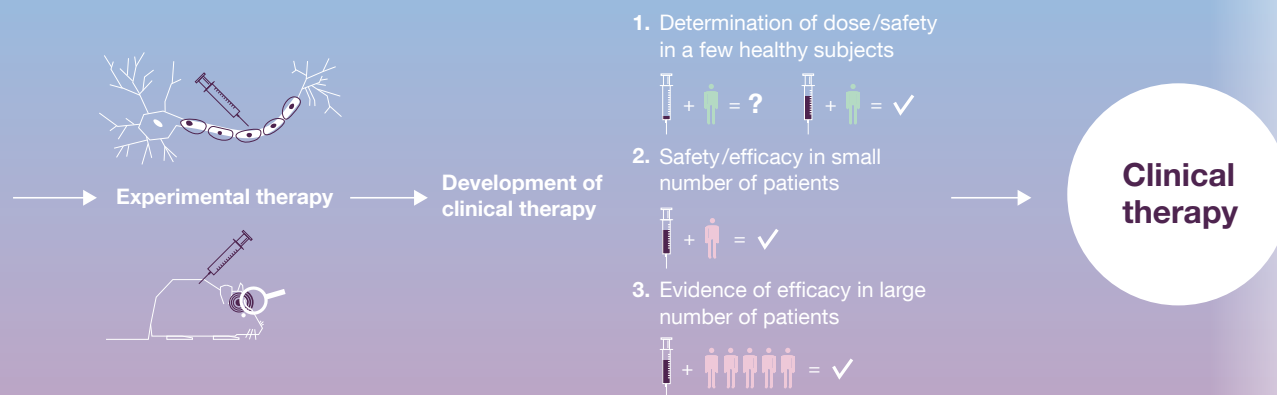
Vom Patienten zum Labor und zurück zum Patienten

Neurodegenerative Erkrankungen wie Alzheimer, die Frontotemporale Lobärdegeneration und das Parkinson-Syndrom sowie die neurologische Erkrankung Restless Legs Syndrom rauben extrem viel Lebensqualität. Manche erhöhen auch das Risiko für einen verfrühten Tod. Ursächliche Therapien gibt es noch nicht, lediglich symptomatische Verbesserungen, oder sie helfen nicht allen und eine frühe Diagnose ist insbesondere bei den Demenzerkrankungen noch nicht möglich. Es gibt genug zu tun für vier Wissenschaftler, Grundlagenforscher

Translational medicine involves close interaction between basic researchers from different fields (e.g. genetics, biochemistry, molecular biology) and clinician scientists. While clinicians place the patient at the center of their work and studies, basic researchers study the molecular processes underlying the disease. Together, they define modern disease entities and search for molecular targets as a starting point for therapeutic developments. Safety and efficacy studies in animals pave the way for clinical trials, which ultimately lead to new therapies for human patients.

und/oder Kliniker, die an der TUM beim Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE) oder am Helmholtz Zentrum München arbeiten und deren Arbeit und translatorischen Leistungen nachfolgend dargestellt sind. Dafür setzen sie auf Translation, also auf eine enge Kooperation zwischen Grundlagenforschung und Klinik sowie zwischen verschiedenen Fachrichtungen. Dazu gehören auch die Identifizierung von genetischen Faktoren mittels der Next Generation Sequencing-Methode, die es ermöglicht, das komplette Genom in kurzer Zeit zu lesen und genetische Auffälligkeiten

festzustellen, sowie das Verknüpfen mit klinischem Wissen und die Entwicklung von geeigneten Krankheitsmodellen an Zellen oder Tieren und deren Überprüfung beim Patienten. Auch die Zusammenstellung von bestens charakterisierten Patientenkollektiven, beispielsweise für Medikamenten-Studien, sowie Untersuchungen, die auch dem Wohlbefinden der Angehörigen dienen, sind Teil der Translation. Die Arbeit der Forscher trägt Früchte: Insbesondere bei der Alzheimer-Krankheit und beim Parkinson-Syndrom könnten schon bald Therapiefortschritte möglich sein.



The brain controls almost all of the body's functions. It is our brains that make us who we are. We each have billions of brain cells at the time we are born and lose up to 100,000 of them every day. This is entirely normal and humans are able to compensate for it. However, if this cell death spirals out of control, it results in debilitating neurodegenerative diseases. It is highly important to develop tools to diagnose a neurodegenerative condition at a very early stage and to stop it early in its course. But also in the case of other types of neurological disorders such as restless legs syndrome, care professionals would welcome more individualized – and therefore more effective – treatment options.

An interdisciplinary approach is essential to support rapid and efficient development of new medications and therapies, as well as improvements in prevention and diagnostics. This involves actively exchanging ideas between different fields and regular feedback between basic researchers and clinicians – a process known as translational medicine. In simple terms, it works as follows: Basic researchers detect a genetic variant,

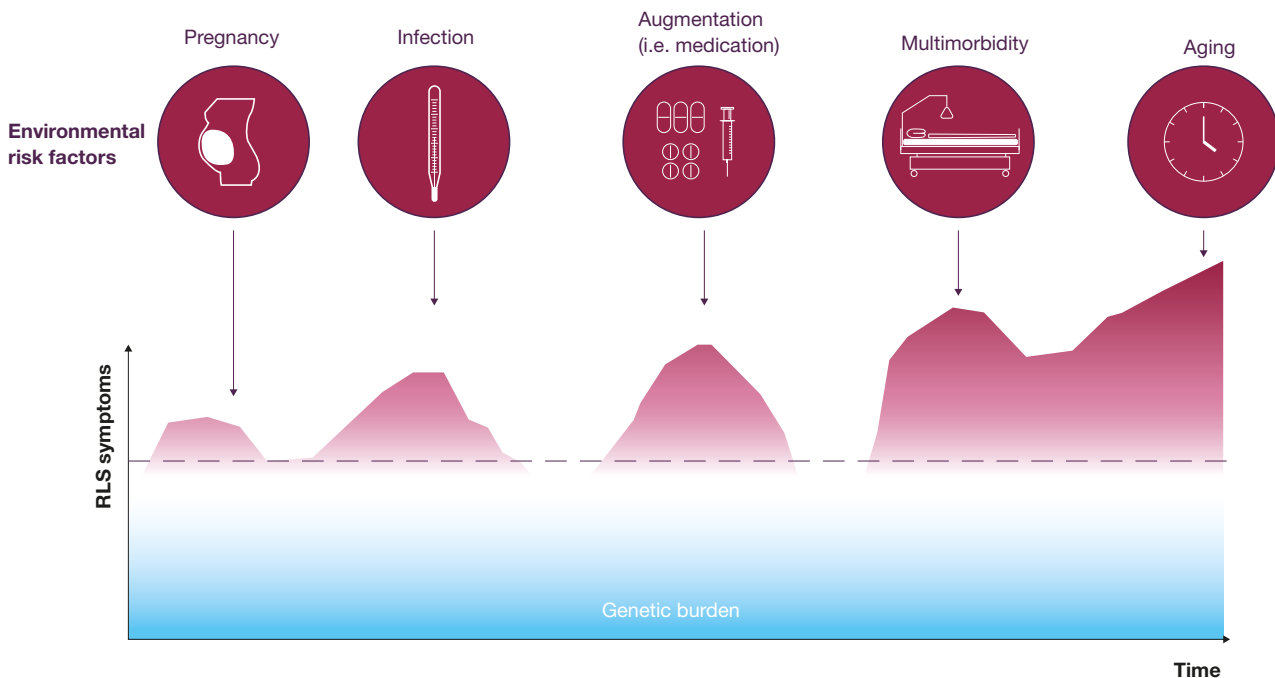
for example, which they initially investigate in animal models to gain insight into its role in the disease mechanisms. The team then seeks to identify suitable targets for therapeutic intervention. Initial animal studies are conducted to clarify the required dosage, check whether the active compound actually reaches the right part of the brain, is efficacious and has potential side effects. Clinicians can then investigate the therapeutic intervention in patients. If the drug appears safe enough, the first clinical trials (phase I) with small groups of healthy subjects go ahead to test for pharmacodynamics, pharmacokinetics, safety and tolerability. The active compound and its dosage, safety, tolerability and efficacy are then gradually tested on patient groups of increasing size in phase II and III trials. The following four examples give an impression of translational medicine in practice.

Restless legs syndrome:
coaxing secrets from the genes

“Up to ten 10 percent of the older population are affected by restless legs syndrome (RLS), a heterogeneous neurodevelopmental disorder that causes unpleasant sensations in the legs, disrupting sleep,” explains Prof. Juliane Winkelmann, head of a specialized outpatient clinic at TUM’s university hospital, Klinikum rechts der Isar. In one to two percent of the population, the condition requires treatment. Patients can be woken every night by involuntary movements, find themselves forced to walk around all night, and suffer extreme sleep disturbances. As Chair of Neurogenetics at TUM and Director of the Institute of Neurogenomics at research center Helmholtz Zentrum München, Winkelmann is investigating the role of genetics in this disorder. RLS is genetically determined, but for each individual to a different extent. Next-generation sequencing (NGS) is a promising new neurodiagnostics method that allows the entire genome or an exome (the protein-coding sequences that contain almost all disease-causing mutations) to be fully and rapidly sequenced at reasonable cost. Winkelmann is using NGS to identify genetic causes of neurological diseases and enable precise diagnosis. Thanks to international collaboration, she receives DNA samples from patients all over the world. “Comparing the sequenced genomes and exomes with reference genomes and exomes allows us to

identify rare genetic variants and establish whether they cause disease.” As she goes on to explain, this knowledge about genes and their functions enables researchers to form hypotheses about pathogenic (disease-causing) processes. These are then tested in animal models, such as mice or zebrafish. Equipped with new ideas, for instance about how to reduce symptoms with new drugs or a disease-specific diet, the researcher then returns to the patient. “We know that some genetic risk variants also have other functions in parallel, for example in glucose metabolism. So we then also try to identify phenotype-genotype correlations.” From the patient, the researcher goes back to the lab once more. “The more precisely we can categorize patients into groups by their genetic make-up, the better and more individualized the treatment,” enthuses Winkelmann. With RLS, for instance, some patients respond to iron therapy but others do not – again, it all depends on their genes.

Link
www.neurokopfzentrum.med.tum.de/neurologie www.helmholtz-muenchen.de/ing



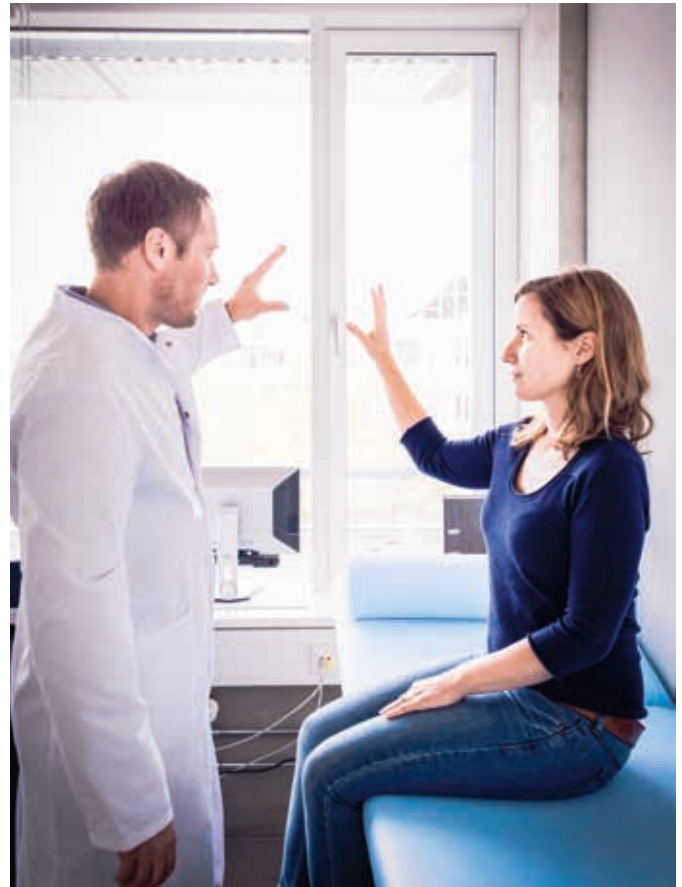
Restless legs syndrome is genetically determined, but the genetic burden affects individuals to a different extent. On top of the genetic susceptibility, environmental factors such as infections or multimorbidity can trigger or worsen the symptoms.



Parkinson's disease:
new treatment with old medication?

“Every day, in clinical practice, we are faced with the limits of our current options and see where research needs to forge ahead. That certainly motivates our quest for new therapies,” relates Prof. Günter Höglinger, Senior Consultant at TUM's Department of Neurology and Chair of the Department of Translational Neurodegeneration at the German Center for Neurodegenerative Diseases (DZNE). In the case of Parkinson syndromes, dopamine-producing neurons gradually die off in the midbrain. This cell death is caused by misfolded forms of the proteins alpha-synuclein or tau, which clump together to form larger aggregates. These aggregates spread like an infection from one neuron to the next, leaving the brain increasingly deprived of the neurotransmitter dopamine. This results

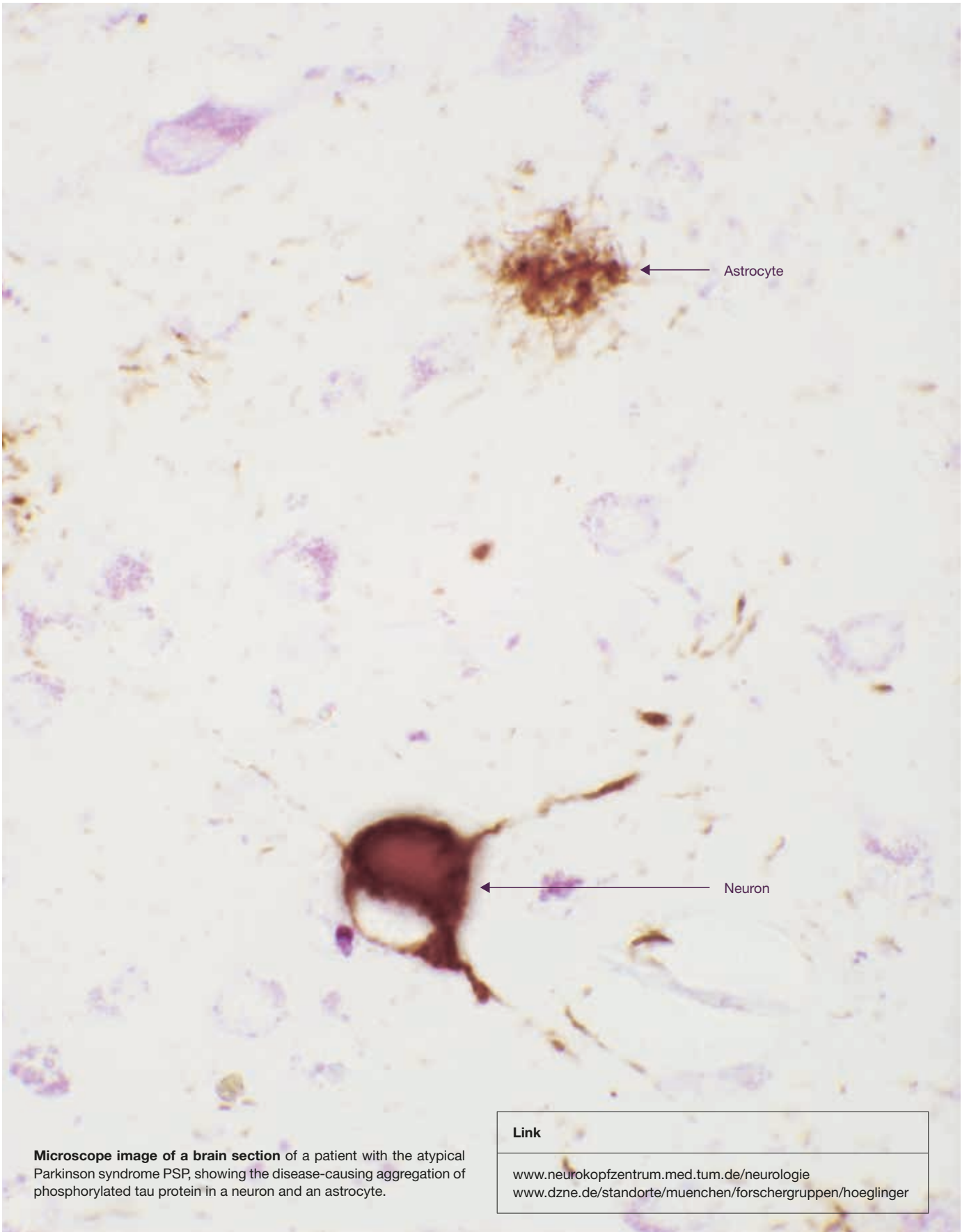
ing neurons. Research is also under way with colleagues in nuclear medicine to determine how tau deposits in the brains of living patients can be detected by positron emission tomography (PET). “We need to improve therapy and diagnostics simultaneously to yield the greatest benefit for patients,” underscores Höglinger. A systematic literature analysis he conducted, reviewing 6,000 articles spanning 20 years, is now improving diagnostic criteria for a specific form of Parkinson's around the world. Research into causes is also forging ahead. The first genetic risk variants have already been identified and the search is now on for more, using next-generation sequencing to read entire genomes from thousands of Parkinson's patients. In those carrying a risk variant, specific en-



in symptoms such as muscular rigidity, postural instability, shaking and slowness of movement. Dementia, pain, depression, psychosis, hallucinations and sleep disturbances follow later in the course of the disease.

However, the latest developments aim to protect the neurons from destruction through medication. Höglinger is helping plan and coordinate international phase II and III trials, starting in March 2017, to establish whether antibodies to tau protein can stop it clumping and thus prevent infection of surround-

ing environmental factors can cause alpha-synuclein or tau molecules to clump. Höglinger finishes by enthusiastically reporting on another project: in a high-throughput screening of 1,600 previously approved drugs in a cell culture model, he and his colleagues succeeded in identifying a substance that can dissolve alpha-synuclein aggregates and thus prevent neuron death. A clinical trial should be able to go ahead soon. “If that is successful, we would be able to use this drug directly to treat patients.”



Microscope image of a brain section of a patient with the atypical Parkinson syndrome PSP, showing the disease-causing aggregation of phosphorylated tau protein in a neuron and an astrocyte.

Link
www.neurokopfzentrum.med.tum.de/neurologie www.dzne.de/standorte/muenchen/forschergruppen/hoeglinger

Frontotemporal dementia: a rare disease

“Rare, but particularly tough on family members,” is clinical neuroscientist Prof. Janine Diehl-Schmid’s verdict on frontotemporal lobar degeneration (FTLD). A subgroup, frontotemporal dementia (FTD) is the particular interest of the professor from TUM’s Center for Cognitive Disorders and Cognitive Rehabilitation, based at the TUM’s university hospital, Klinikum rechts der Isar. FTD begins with behavioral disorders before sixty years of age – and sometimes significantly younger. Those affected lose inhibitions, social awareness and empathy, behaving inappropriately and becoming emotionally blunted and lethargic. As the disease progresses, memory, language, and orientation and practical skills are also impaired. Neurons die off in the frontal and/or temporal lobes, likely due to the accumulation of various proteins such as tau. The cause is unknown in 90 percent of cases, but in 10 percent FTD is genetic.

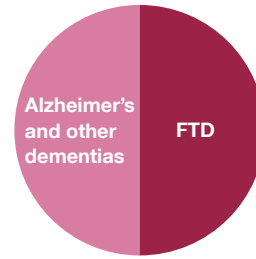
Diehl-Schmid established the first relatives group for frontotemporal degeneration in Germany back in 2002. More recently, she collaborated with a European research group to develop Internet-based expert information for patients and their relatives and carers (RHAPSODY). The researcher also builds patient populations for studies. Since 2002, she has compiled a bank of over 400 FTLD patients, incorporating DNA, blood and cerebrospinal fluid, as well as key clinical data such as behavioral symptoms, language impairments and neuropsychological test results. Diehl-Schmid is working to improve early diagnosis of FTLD and other neurodegenerative dementias using biomarkers and imaging procedures. She is also investigating gender differences in these diseases, as well as researching their underlying genetics in collaboration with Juliane Winkelmann. Recently, the Munich center – Germany’s center of FTLD expertise – participated in an international phase III clinical drug trial run by the company TauRX, although unfortunately without a successful outcome. “The aim of translational research has to be effective treatment. Sadly, we still have a long way to go,” reports Diehl-Schmid. She also mentions some reasons: There are too few known patients to compile large groups for rare diseases – so, she says, good research depends on a multi-centric approach. At the same time, she would like to see patients and their relatives offered greater incentives to participate in research projects, such as intensive psychological and sociomedical care and support over the course of the disease. “But that means spending money,” she concludes – pointing out that this concept has long since been implemented in the US.



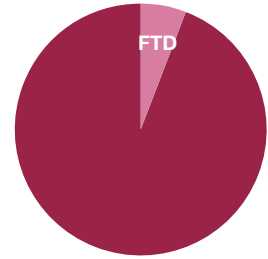
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www.psykl.mri.tum.de/zentrum-fuer-kognitive-stoerungen

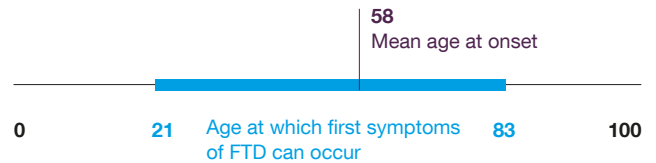
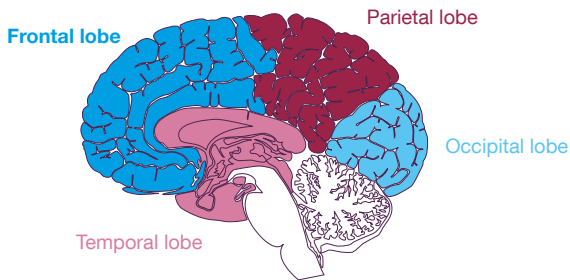
Frontotemporal dementia (FTD)



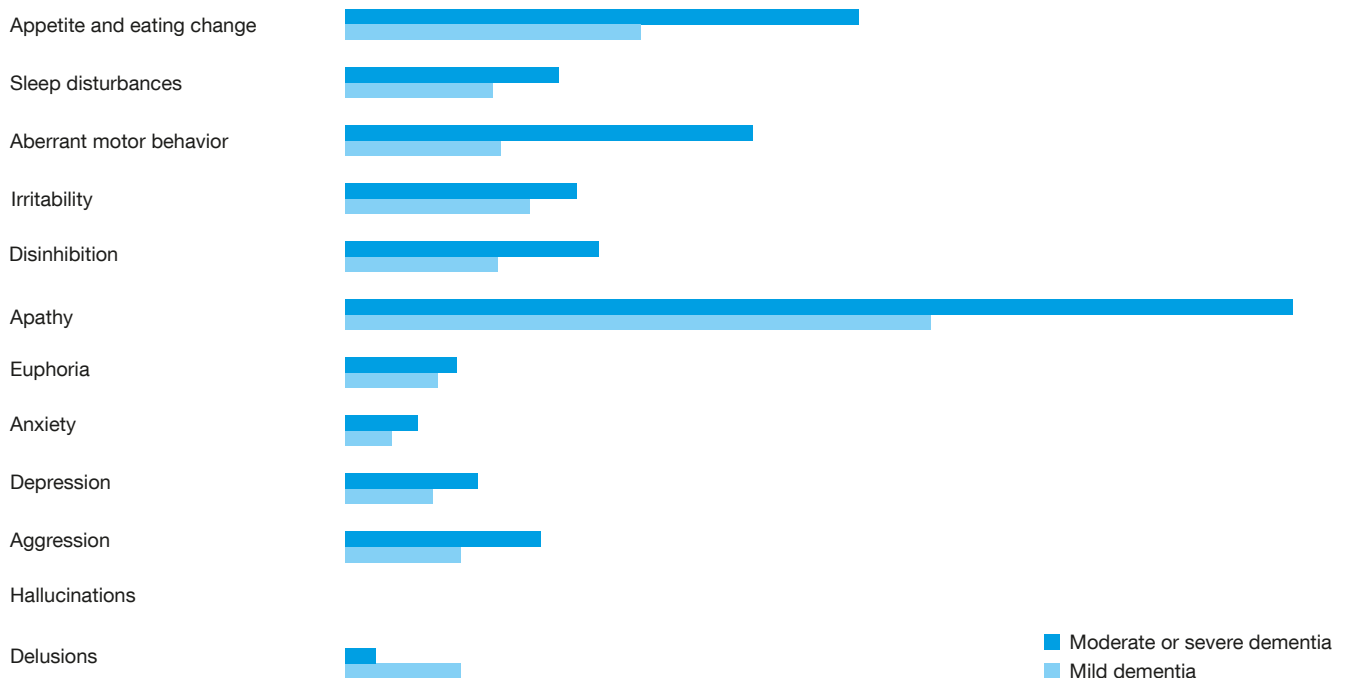
... accounts for half of the dementia cases of patients younger than 65 years

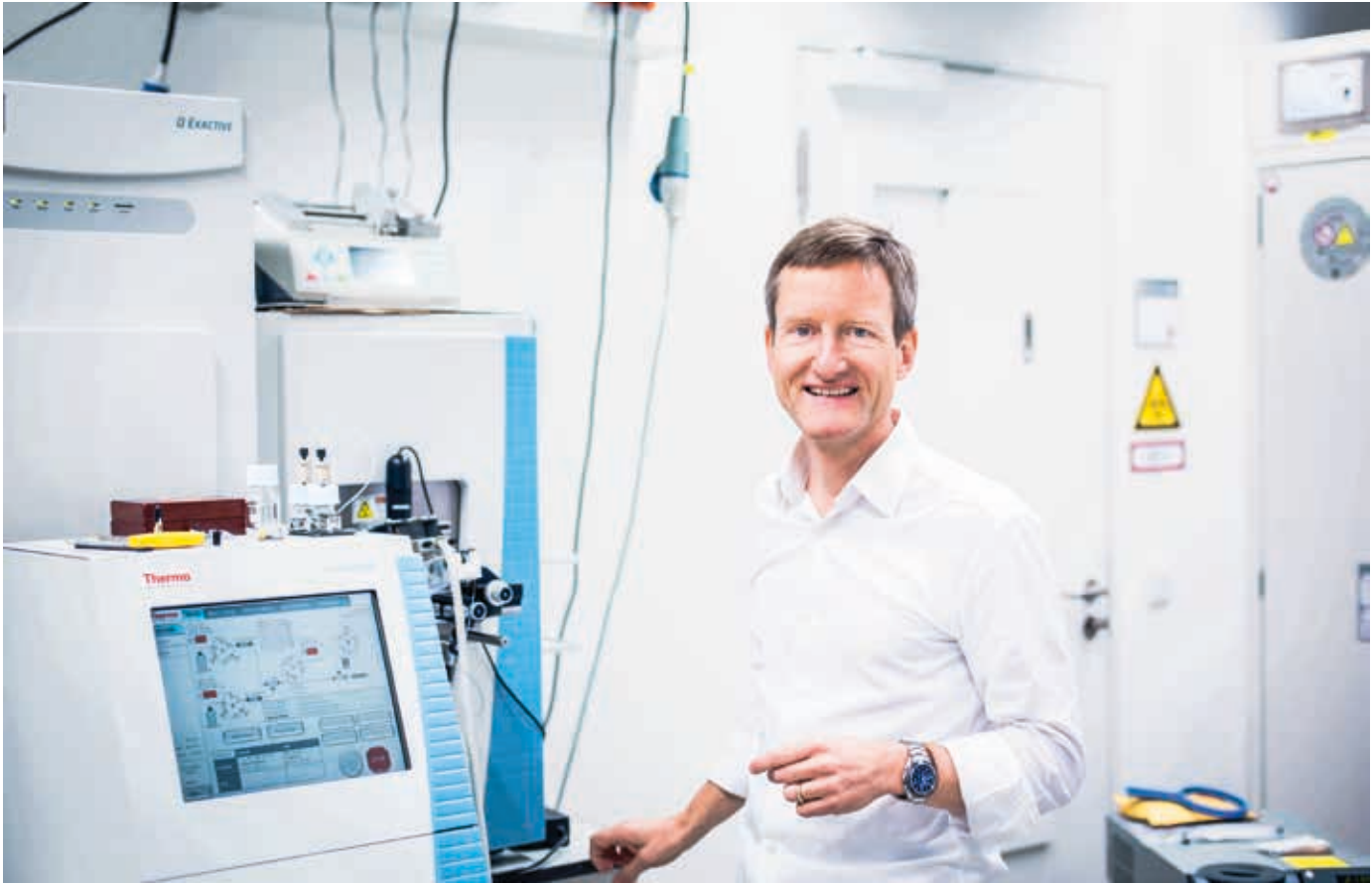


... accounts for less than 10% of all dementia cases



Extent of behavioral disturbances in different disease stages of FTD:



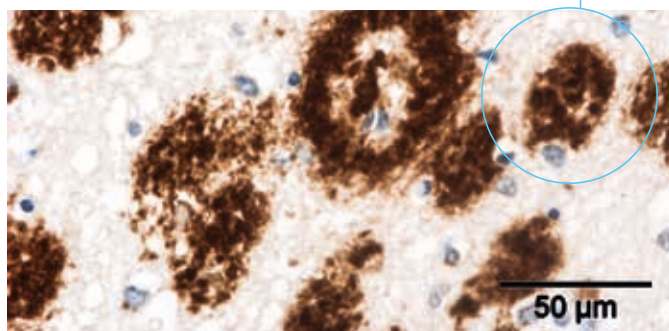
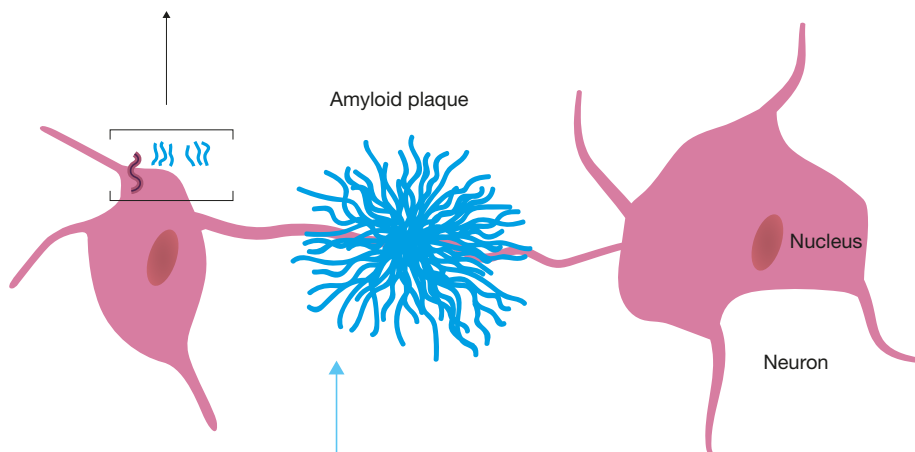
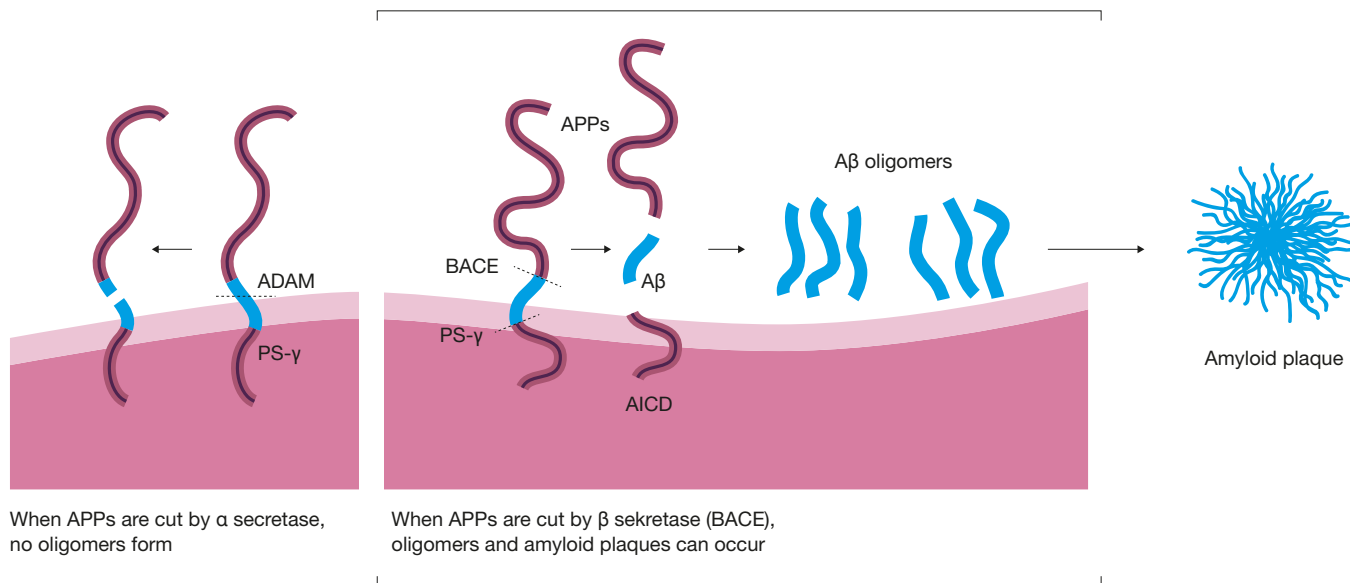


Alzheimer's: putting a stop to memory loss

“Advancing age is the biggest risk factor in 99 percent of Alzheimer’s cases, which, incidentally, now ranks among the top ten causes of death,” declares Prof. Stefan Lichtenthaler, Head of Neuroproteomics at TUM’s university hospital, Klinikum rechts der Isar, and the German Center for Neurodegenerative Diseases (DZNE). Where do things go wrong when Alzheimer’s strikes? The main focus is on a type of molecular scissors (enzymes known as proteases) occurring in the membrane of every brain cell. These snip large amyloid precursor proteins (APP) at specific points as they protrude through the cell membrane, altering the “small talk” with neighboring cells. In fact this process of cleaving or severing connections also takes place when individual tumor cells detach from a tumor – so cancer research also stands to gain from Lichtenthaler’s endeavors. If APP is cleaved by a beta-secretase (BACE1) enzyme, the result is sticky fragments known as amyloids. This amyloid formation occurs in every human, but the brain’s own waste disposal system normally removes most of them. However, with increasing age and the presence of risk factors such as type 2 diabetes, amyloid removal becomes progressively less effective. The first symptoms occur after around 20 to 25 years. The sticky amyloids clump together to form neurotoxic oligomers or aggregates,

which in turn cause tau protein to tangle. This results in inflammation and disruption of many processes vital to the life of the cell. As soon as enough tau tangles are present, the subsequent cell-destroying processes are thought to be unrelated to the presence of amyloid. “If we could block beta-secretase, that would prevent amyloid oligomers from forming in the first place,” explains Lichtenthaler. This type of medication would probably have to be administered in the pre-symptom stage to be effective. However, that only makes sense if early diagnosis using biomarkers becomes possible. Inhibitors for these molecular scissors are now undergoing clinical trials.

Another research focus is alpha-secretase (ADAM10), which cleaves APP in such a way that no oligomers form. Is ADAM10 also a drug target? Does activating it reduce aggregate formation? “Sticky amyloid formation declines by 30 to 40 percent,” Lichtenthaler confirms. One of the first steps here was to identify the secretase enzyme in collaboration with experts from other disciplines. Next, colleagues in the German city of Mainz will run a clinical trial to establish whether alpha-secretase activation might be suitable for use in Alzheimer’s therapy. There is already one hurdle: alpha- and beta-secretase also cleave numerous other proteins apart from APP. “If we



Molecular scissors (proteases) called ADAM10 and BACE1 can provide a lead for future Alzheimer’s treatments. When BACE1 cuts the APP proteins that protrude from the brain cells, amyloid plaques can develop, which are so characteristic of Alzheimer’s disease. If ADAM10 cuts the same protein, no plaque develops. However, both ADAM10 and BACE1 also act on other proteins in the brain cell, so the path to new medications is not straightforward.

Microscope image of brain tissue with amyloid plaque

block or activate these two secretases, there will be consequences for other proteins and their functions,” underscores Lichtenthaler. He thus devised a special method based on mass spectrometry to allow experts to determine directly in the neurons which proteins are being cleaved. Another detection test he developed is intended to monitor drug effects on the brain. “With this knowledge, pharma companies can decide early on whether an active substance appears promising and develop effective drugs more quickly.” Emphasizing that

there is also room for improvement in diagnostics, he shares an advance on that front too: “Thanks to PET imaging, amyloid deposits in the brain can now be visualized and quantified at an early stage.”

Gerlinde Felix

Link
www.dzne.de/standorte/muenchen/forschergruppen/lichtenthaler



How the Next Generation Furthers Insights while Healing Patients

Clinician scientists work with patients as practicing physicians, while also pursuing scientific research in the lab. The huge time commitment this requires means fewer and fewer physicians are choosing this route. At the same time, it is becoming increasingly important for researching physicians to work in close collaboration with scientists – and for scientists to connect their research to diseases. Here, we take a look at TUM's up-and-coming scientists engaged in multiple sclerosis research.

For years now, university hospitals and the German Research Foundation (DFG) have been bemoaning the lack of fresh talent in medical research. The DFG highlighted this as far back as 2008, while physicians from several universities, including TUM, address the issue in a recent article on higher education research¹.

The research career path poses a formidable challenge for young physicians. Following their doctoral thesis and graduation, physicians generally spend several more years training as a specialist. If they are aiming for a parallel path in research, they also need to simultaneously engage in noteworthy research, establish a reputation in their field and network with peers. A 2006 survey by the German Society for Internal Medicine (DGIM) discovered that resident physicians spend around ten hours a day treating patients in the hospital. Most of them only have evenings and weekends available for research, making it almost impossible to pursue their projects at an internationally competitive level and build the necessary networks.

Taking multiple sclerosis (MS) research as a case in point, this article shows how TUM is creating room to maneuver within clinical training, promoting networking and thus bringing more researchers into medicine again. This also means supporting young families, which is why SyNergy, the Munich Cluster for Systems Neurology (p. 31), provides funding to help young academics pay for childcare, for example. ▷

¹ Epstein et al., Beiträge zur Hochschulforschung 38, 1-2/2016
DFG, duz Special: „Karrierewege in der Hochschulmedizin“, 2008

Rotation system: half doctor, half researcher

Dr. Benjamin Knier has been training to become a neurologist since July 2011 and is working as a resident in the neurological center (Neuro-Kopf-Zentrum) at TUM's university hospital, Klinikum rechts der Isar. His focus lies on changes to the optic nerve and retina as a result of neuroimmunological disorders – both in mouse models and in human patients. Knier is researching immunological processes accompanying optic neuritis (inflammation of the optic nerve), with a view to opening the door for new therapeutic approaches. At the same time, he is exploring the extent to which retinal changes in MS patients might serve as a prognostic factor for the subsequent course of the disease and its response to various treatment methods.



The young researcher is a member of Prof. Thomas Korn's working group. To date, he has invested over two years in "off-the-clock" research, pursuing his scientific endeavors after hours and on days off. But TUM has also given him room to maneuver – in several different ways. The specialized outpatient clinic for MS at TUM's Klinikum rechts der Isar hospital operates a rotation system, with two residents sharing a position alongside the specialists there. This means that each resident can spend half of their time with patients and the other half on research. Knier also used one and a half years in this clinic to advance his project, procure funding and apply for grants. Now, a faculty grant awarded by TUM's Commission for Clinical Research (KKF) is enabling him to devote 80 percent of his time to research. He reflects: "If you want to pursue an academic route as a physician, you have to make that decision early on. The field is becoming more and more competitive and the professors ever younger." In Knier's view, upcoming researchers have a window of seven to eight years to establish themselves in their chosen area. "If you're looking to conduct research and train as a specialist physician, there are few university hospitals in Germany with conditions to match those at Klinikum rechts der Isar. In neurology, we enjoy a supportive environment and excellent infrastructure."

Faculty grant: a year devoted to research

Dr. Viola Biberacher is currently training as a neurology specialist and working as a resident in the Department of Neurology at TUM's Klinikum rechts der Isar hospital. A member of Prof. Mark Mühlau's working group, she is developing her expertise in magnetic resonance imaging (MRI) changes in MS and thus acts as a link to clinical neuroimmunology. Biberacher is researching various parameters derived from MRI analysis, for instance of the spinal cord, as well as from blood and cerebrospinal fluid testing. The objective is to identify correlations between these parameters – on the one hand, to gain a better understanding of the disease, and on the other, to enable more accurate predictions about its progression. Alongside this research, her work in the MS outpatient clinic has given her a chance to experience patient care. A faculty grant from TUM's KKF research commission is now freeing up a year for Biberacher to focus on her research endeavors.



Doctor and geneticist

PD Dr. Dorothea Buck is the senior physician in the outpatient clinic for neuroimmunology at TUM's Klinikum rechts der Isar hospital – a role that involves caring for patients with MS and other neuroimmunological diseases. She also belongs to a working group led by Prof. Bernhard Hemmer and is researching the genetics of the immune response in MS. In her clinical studies, she is focusing on genetic factors that contribute to the onset of MS and influence disease progression and therapeutic response. Discussing her research, Buck explains: "It dovetails very well with my practice as a doctor, creating synergies that benefit everyone involved." Her view is that working with patients equips clinical researchers with a deeper understanding of disease patterns and direct contact with those affected, which in turn can inspire research topics relevant to patient care. ▶





Three years of research in the US

After six years of neurological residency, Dr. Veit Rothhammer began working in the MS outpatient clinic at TUM's Klinikum rechts der Isar hospital. Funded by a grant from the German Research Foundation (DFG), he is now spending three and a half years conducting research in the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital, a teaching affiliate of Harvard Medical School in Boston. Rothhammer's research is focused on astrocytes – brain cells that exert local influence on inflammatory processes in the central nervous system of MS patients. Astrocytes govern the pathogenic potential of peripheral immune system cells that migrate to the brain in the course of disease, for instance. Moreover, they regulate repair processes in the brain which are relevant for the survival and functionality of neurons during chronic stages of MS.

In Munich, Rothhammer was a member of research groups led by Prof. Thomas Korn and Prof. Bernhard Hemmer. In Boston, he is part of the group of Prof. Francisco Quintana in multidisciplinary teams comprising physicians, biologists, biostatisticians, engineers and chemists. As he puts it: "You have to think outside the box and approach an issue from several different angles. That is the only way to gain insight of truly valuable nature." At Harvard University, his experience is one of close

interaction with researchers from a wide range of educational and cultural backgrounds. Rothhammer emphasizes the key role of mentors in both the professional and personal development of researching physicians, providing guidance, support and tuition, and engaging them in dialog. "My mentors have shown me the value of training as a clinician scientist through their own example," he confirms. Following his return from Boston to Munich in 2018, Rothhammer hopes to set up a research group at TUM to continue his research. In addition, clinical practice remains an equally important career goal for him. In his view, the clinical facilities and scientific research groups are exceptionally well networked at TUM – and particularly in neurology, which boasts fruitful collaborations with the biological and immunological institutes of TUM and LMU, as well as with the Helmholtz centers.

Combining clinical and biological research

As part of her training, Dr. Marina Herwerth is working as a resident in the neurological center (Neuro-Kopf-Zentrum) at TUM's Klinikum rechts der Isar hospital. She is using an experimental mouse model to investigate the mechanisms underlying the onset of MS and related autoimmune disorders. Two-photon microscopy (p. 92) enables her to examine new disease sites occurring in the spinal cord and explore ways to prevent this. Herwerth played a key role in setting up a cooperation between two MS research groups at TUM – one focusing on clinical immunology (Prof. Bernhard Hemmer) and the other on basic research in neurobiology (Prof. Thomas Misgeld). A faculty grant from TUM's KKF research commission enabled her to conduct research alongside her role in the clinic. However, like all her colleagues, she also relies on obtaining external funding. The Hertie Foundation

is currently providing funds for her MS project, which she is using to finance her position for two years. Summarizing the most important requirements of a clinician scientist, Herwerth pinpoints a high degree of motivation and an environment with solid support structures. She also emphasizes the important role of mentors, whose contacts prove valuable in building networks within the research community, for instance.



Junior research groups for basic science

An essential feature of multiple sclerosis research at TUM is the close collaboration between scientists and physicians. This enables investigation of underlying disease mechanisms such as molecular links, which can then be directly translated into new therapeutic strategies. The SyNergy excellence cluster (p. 31) specifically fosters this approach by networking basic and clinical research.



Gaining early independence

As a TUM Junior Fellow at the Institute of Neuronal Cell Biology, Dr. Tim Czopka is head of an independent Emmy Noether Independent Junior Research Group, financed by the German Research Foundation (DFG) and currently comprising four doctoral students. Using young zebrafish as an animal model, he is researching the mechanisms of myelination. Myelin forms a protective coating around nerve fibers, and the state of >

this myelin sheath is crucial to signal transmission between neurons. In MS, this protective layer comes under attack – and also undergoes partial repair. Czopka was one of the first to successfully visualize the cellular mechanisms of myelination in a living animal using high-resolution optical imaging techniques. Gaining a conceptual understanding of the way our nervous system functions and identifying specific molecular switches is of vital importance to understanding diseases and developing therapeutic approaches. And for Czopka, that is the very essence of his work as a biologist. In basic biomedical and neuroscience research, the lines between biology and medicine tend to be fluid. Very often, neuroscientific questions regarding brain function also have a medical component, since disordered brain development or function often manifests in human disease patterns. Czopka was recently awarded a prestigious European Research Council (ERC) Starting Grant for his project examining the heterogeneity of myelinating cells and researching the influence of aging on cellular behavior.

Combining biology and medical research

Dr. Leanne Godinho leads a research group at TUM's Institute of Neuronal Cell Biology. Godinho's training is in developmental biology and neuroscience and she is interested in the basic principles that underlie the assembly of the nervous system during embryonic and postnatal development. Her group uses the zebrafish retina as a model system. Zebrafish are vertebrates and their retina is remarkably similar to that of humans. Visual disturbances are common in many neurological diseases, including MS, with retinal ganglion cells a prime target. Through her work, Godinho hopes to provide insights into possible mechanisms of repair when neural circuits and the cells that form them are damaged by disease. As part of a Collaborative Research Center (CRC) consortium, she currently holds a grant funded by the German Research Foundation (DFG) to enable her



work. “The added benefit of receiving such a grant is the network of people that you come into contact with,” she explains, stressing that complementary expertise and resources are extremely valuable. “Collaborations and networks are driven by the people doing the work. TUM's strength lies in fostering both basic and clinical or disease-related research, permitting synergistic interactions between scientists to occur naturally.” Godinho works in close contact with the groups in her institute, with weekly joint meetings that allow for free exchange of ideas and provide opportunities to collaborate on projects of mutual interest. Some of these groups have a more medical bent to their work, for instance using mouse models of human diseases such as multiple sclerosis, and she has collaborated with them on a number of occasions to provide an efficient pipeline for testing tools in the zebrafish model prior to their use in mice.

Karsten Werth



STRETCHING
THE LIMITS

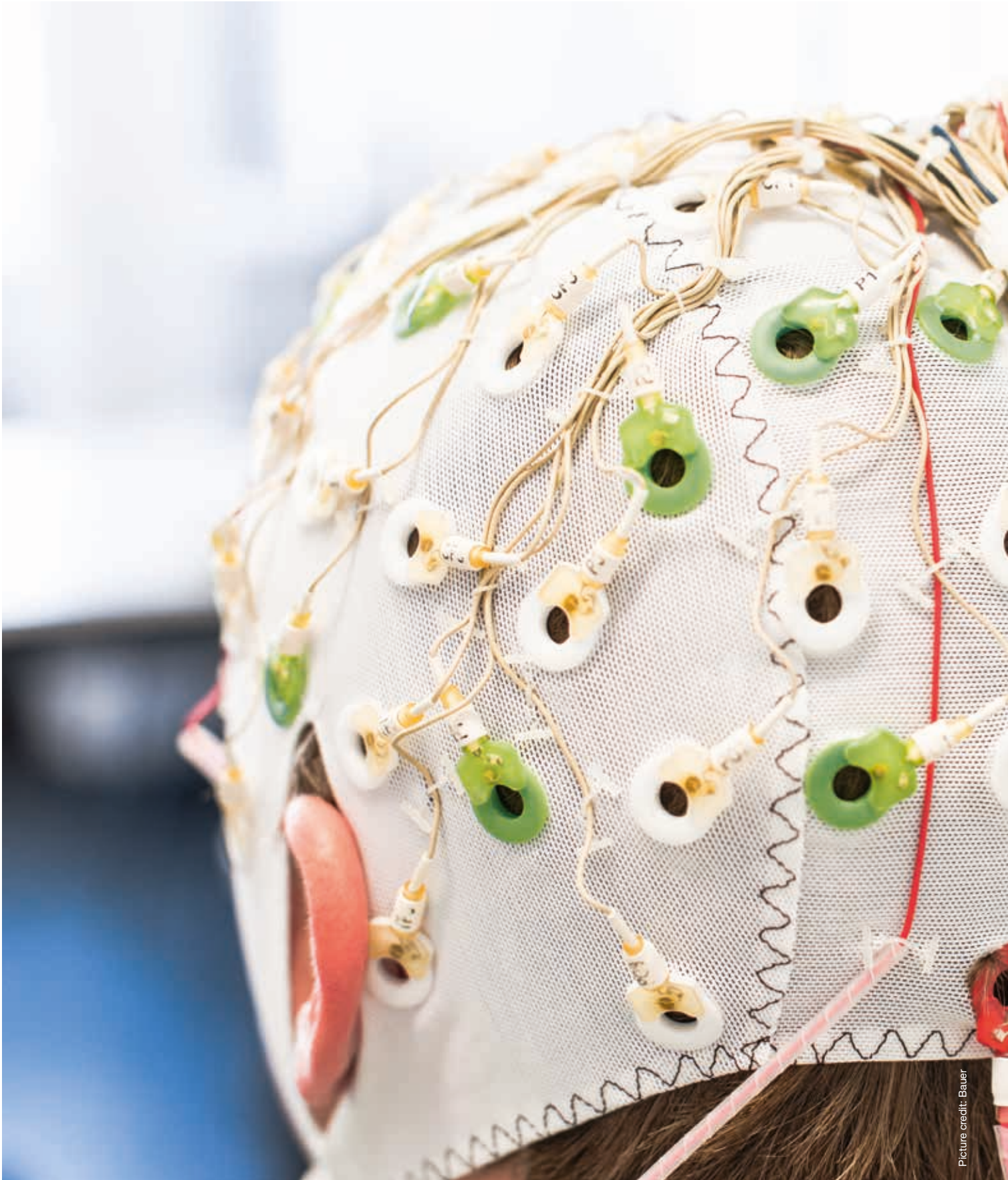
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Picture credit: Bauer



A Network View of the Brain

The TUM-Neuroimaging Center is an interdisciplinary platform, bringing scientists together from a range of fields to advance neuroimaging research.

Karoline Stürmer

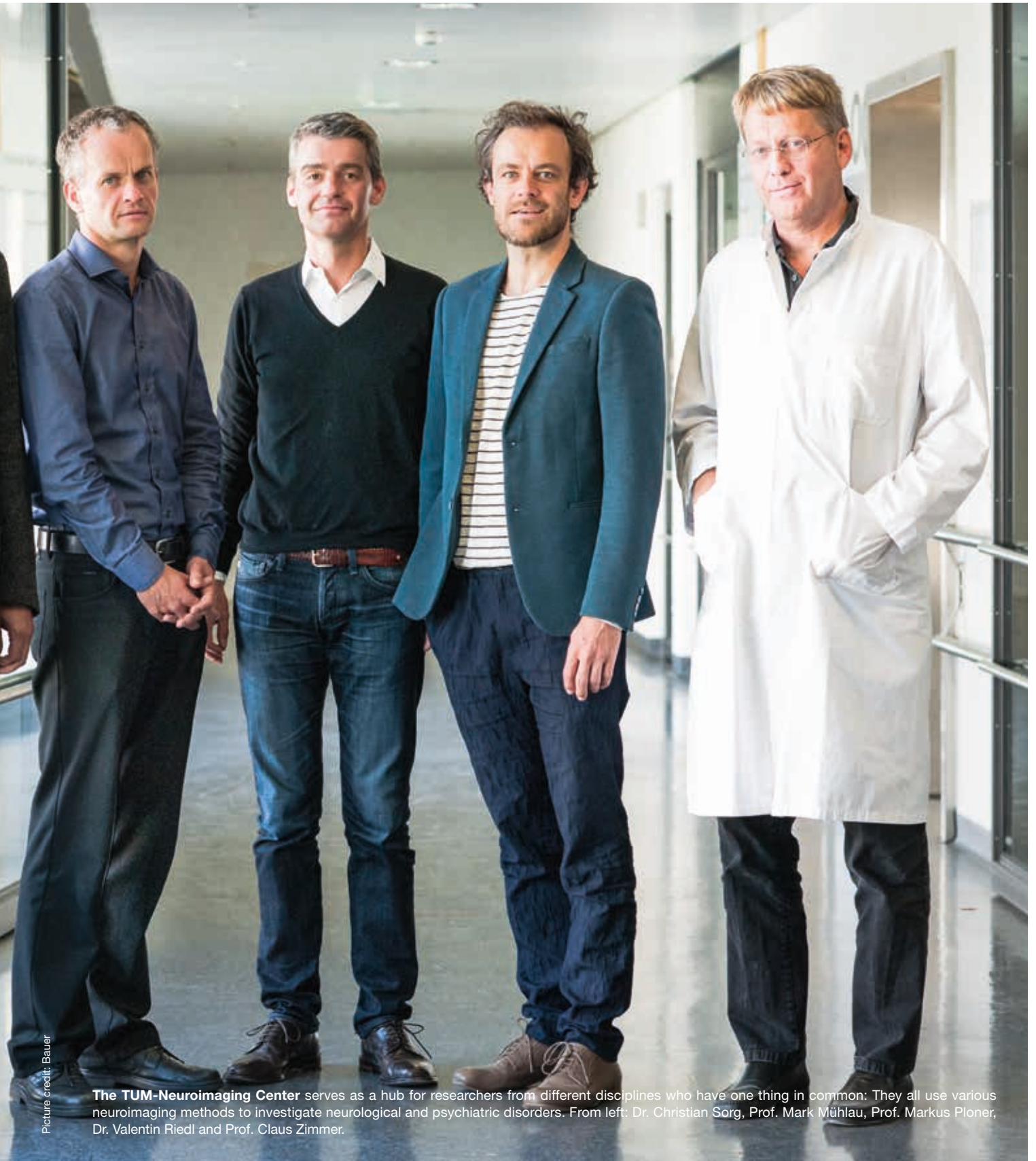
Eine Netzwerkperspektive auf das Gehirn

Das Neuroimaging Center (TUM-NIC) der TUM ist eine interdisziplinäre Plattform. Hier arbeiten Forscher aus unterschiedlichen Disziplinen wie beispielsweise der Neurologie, Neuroradiologie und Psychiatrie zusammen, um die Forschung im Bereich des Neuroimaging voranzutreiben. Der Brückenschlag, wie er hier mit gebündelter Kompetenz über viele neurologische und psychiatrische Erkrankungen möglich ist, eröffnet dabei völlig neue Perspektiven. Die Forscher untersuchen dazu beispielsweise mit Methoden wie der Diffusions-Tensor-Bildgebung (DTI), der funktionellen Magnetresonanztomographie (fMRT), der Elektroenzephalographie (EEG) und der Positronen-Emissions-Tomographie (PET), wie sich Netzwerke des menschlichen Gehirns bei bestimmten Krankheiten verändern, etwa beim chronischen Schmerz. Millionen von Menschen leiden in Deutschland an dieser Störung, für die sich oft keine Ursache finden lässt. Die Erkenntnis, dass solche Schmerzempfindungen auf Veränderungen von Netzwerken im Gehirn basieren, ist noch wenig verbreitet. Die Forscher am TUM-NIC konnten zeigen, dass dauerhafter Schmerz mit Veränderungen der Hirnaktivität in Teilen des „Motivations- und Evaluations-Netzwerks“ einhergeht. Dieses Netzwerk bewertet Reize und übersetzt sie in Verhalten. Dabei geht es um grundlegende Gefühle von Angst. Bei einer Fehlfunktion kann es zu Fehl- und Überbewertungen von Situationen und Sinnesreizen kommen, die dann als bedrohlicher und schmerzhafter eingeschätzt werden, als sie eigentlich sind. Das könnte nicht nur chronische Schmerzen, sondern auch Depression fördern. Demnächst wollen die Forscher nun untersuchen, ob Patienten mit Depressionen ähnliche Veränderungen dieses Netzwerkes zeigen wie Patienten mit chronischen Schmerzen. Von der Beobachtung des Zusammenspiels der unterschiedlichen Gehirnareale erhoffen sich die Forscher, das Gehirn und seine Erkrankungen besser zu verstehen, um Ansätze für neue Therapiemöglichkeiten zu entwickeln. Daneben geht es auch um die Weiterentwicklung diagnostischer Möglichkeiten. □

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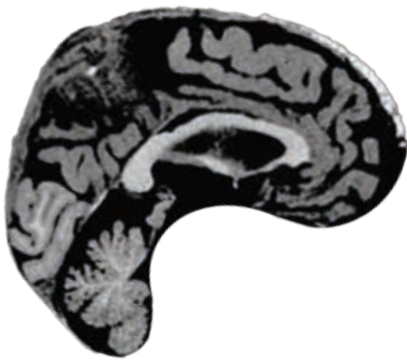
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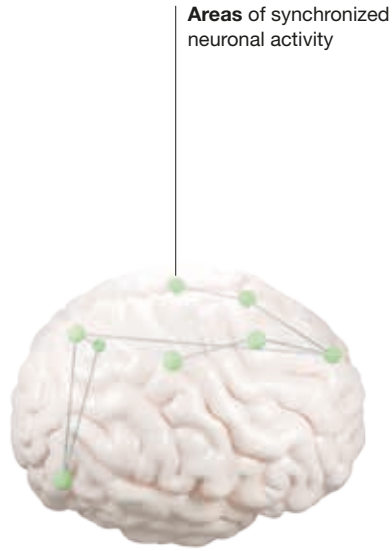
Picture credit: Bauer

The TUM-Neuroimaging Center serves as a hub for researchers from different disciplines who have one thing in common: They all use various neuroimaging methods to investigate neurological and psychiatric disorders. From left: Dr. Christian Sorg, Prof. Mark Mühlau, Prof. Markus Ploner, Dr. Valentin Riedl and Prof. Claus Zimmer.



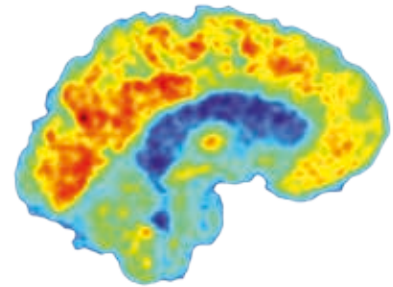
MRI
Magnetic resonance imaging

A strong magnetic field and additional radio waves are used to visualize the distribution of hydrogen atoms. Since hydrogen atoms occur most frequently in both blood and tissue, radio waves in different frequency bands can be used to reveal a range of information about the brain.



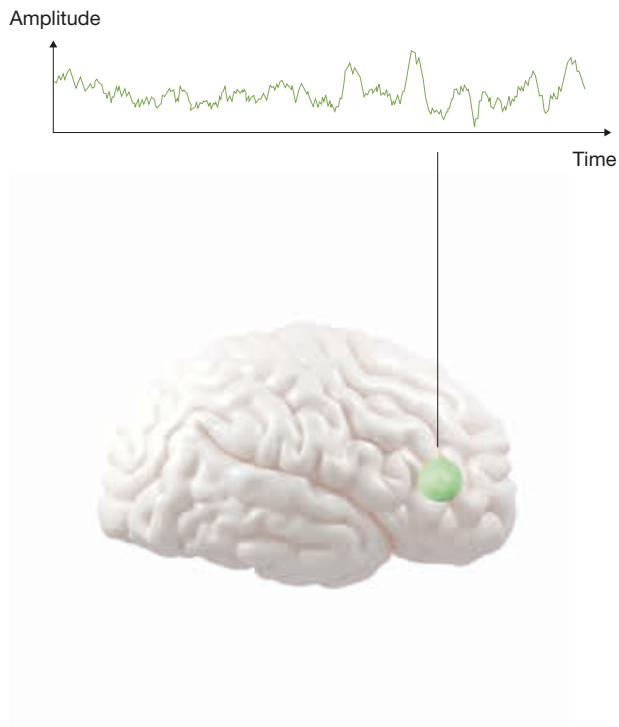
fMRI
Functional magnetic resonance imaging

fMRI provides an indirect way of visualizing the neuronal activity of nerve cell clusters in gray matter. Oxygen and glucose are the main sources of energy for neuronal activity. fMRI measures changes in blood oxygen levels and so detects local changes in brain activity.



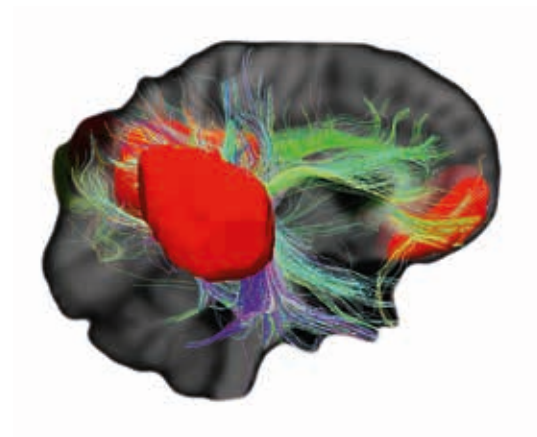
PET
Positron emission tomography

PET measures metabolic processes. A radioactive tracer is attached to a molecule which is processed by the body. Here, glucose labeled with fluorine makes the local neuronal activity visible.

**EEG**

Electroencephalography

EEG measures brain activity by means of electrodes placed on the head of patients or healthy subjects. EEG directly measures the currents resulting from the activity of nerve cells in the brain. This method of measuring brain activity has a high temporal resolution in the millisecond range.

**DTI**

Diffusion tensor imaging

DTI is used to map the large bundles of fibers in the white matter of the brain. DTI is an MRI process that detects the diffusion patterns of water molecules along the white matter fiber tracts.

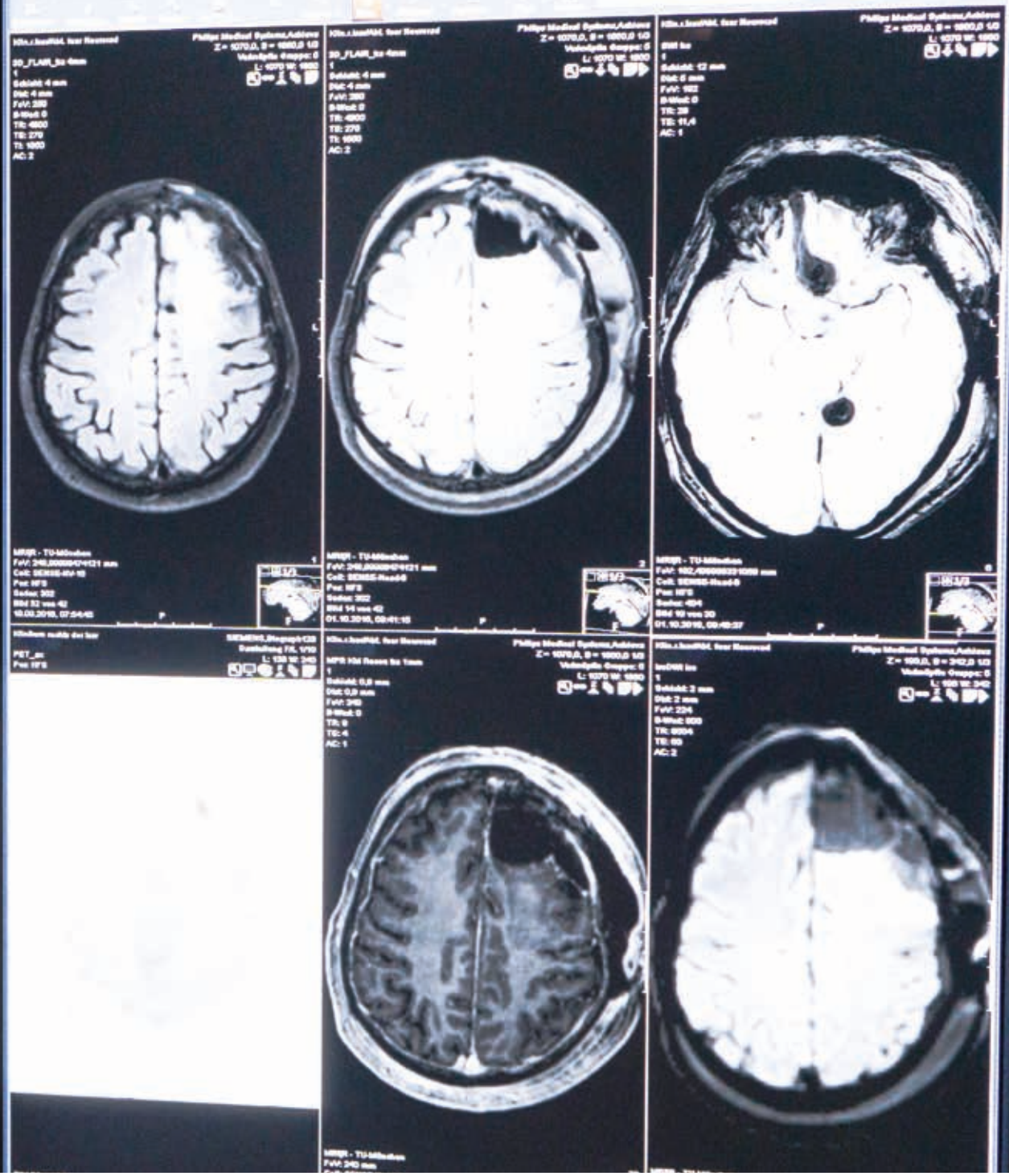
Preparation of MRI assessment to generate images of brain structures (structural MRI), of brain activity (fMRI) or of white matter fiber tracts (DTI).





View of the brain of one patient based on distinct MRI assessment techniques, which visualize different aspects of brain tissue.





Picture credit: Bauer



Markus Ploner and a colleague prepare an EEG recording. They use EEG to investigate how pain is processed in the human brain.

Researchers at the TUM-Neuroimaging Center (TUM-NIC) come from a variety of research groups and departments and specialize in very different areas. But they all have one thing in common: they use neuroimaging methods to investigate the structure and function of the brain in neurological and psychiatric disorders. These conditions include chronic pain, Alzheimer's disease, depression, obsessive-compulsive disorder, schizophrenia and multiple sclerosis. The researchers' aim is to learn from one another and put their bundled expertise to the best possible use, both within their research projects and in clinical practice. TUM-NIC was founded four years ago as an interdisciplinary platform to facilitate this aim.

The roughly 100 billion neurons of the human brain form complex, interconnected networks. Researchers at TUM-NIC are seeking to understand how these networks change in certain disorders. While chronic pain and depression might have quite different causes, for instance, various mechanisms at brain network level are similar. "With experts in neurology, neuroradiology and psychiatry, TUM-NIC is able to bridge many different neurological conditions and explore entirely new horizons in this area," states Prof. Mark Mühlau from

TUM's Department of Neurology. The researchers hope that this will enable them to gain a better understanding of the causes and mechanisms of disease, as well as of the hugely complex workings of the brain.

Neuroradiology lies at the core of TUM-NIC. In addition to powerful equipment used to examine patients, "Our physicists are continually refining and developing new methods to further advance clinical diagnostic and treatment options, as well as basic research endeavors," outlines Prof. Claus Zimmer, Director of TUM's Department of Diagnostic and Interventional Neuroradiology. Scientists from various departments process the data collected in this area and perform statistical analyses. With the aid of special tests, doctors and psychologists are then able to link the imaging results to cognitive changes in patients.

Take chronic pain, for instance. Millions of people in Germany are affected by this condition, with patients frequently experiencing sensations for years without any evident physical cause. "Recognition that these pain sensations stem from changes in the brain networks is not yet widespread," explains Markus Ploner, Heisenberg Professor of Human Pain Research at TUM's Department of Neurology. However, increasing



EEG recordings show brain activity with high temporal resolution. The traces show brain activity recorded at different EEG electrodes (FP1, Fp2, F3, ...) over a period of 5 seconds.

awareness of the causes of this type of pain changes the general perception of these patients, who are not always taken seriously. Together with his colleagues at TUM-NIC, Ploner conducted a more rigorous examination of the brain during ongoing pain and made a surprising discovery: chronic pain is associated with rhythmic nerve cell activity, known as gamma oscillations, in the prefrontal cortex. Nerve fibers closely link this brain area to the nucleus accumbens, with the two regions forming what can be referred to as the valuation or motivation network.

Strictly speaking, the brain is a huge network, which is divided into numerous subnetworks. Each network or subnetwork

comprises several interconnected areas. Networks can be observed both in active and resting states – our brains are always on. One of the best known resting state networks is the default mode network, which is active when the brain is mainly occupied with itself and the mind is wandering.

The valuation or motivation network is a resting state network that exhibits changes not only during chronic pain but also in other neurological and psychiatric disorders, as well as warning us of danger. The TUM-NIC researchers are investigating the interaction between nerve cells in this and other networks on three levels: ▶



The neurons of the human brain form complex, interconnected networks. Researchers at TUM-NIC are seeking to understand how these networks change in certain disorders.

1. How are the different areas of brain network structurally connected to each other?
2. Do the areas communicate with one another?
3. Is the communication on an equal footing or does one of them dominate?

The first question can be tackled with the aid of diffusion tensor imaging (DTI). The connections between the brain areas involved in the valuation or motivation network are made up of nerve fibers – the threadlike extensions of nerve cells, also termed the brain’s white matter. DTI uses magnetic resonance imaging (MRI) to measure and map the diffusion patterns of water molecules in body tissue. Since water molecules diffuse better along the nerve fibers than in other directions, large bundles of fibers can be identified particularly well with this method. “Patients with chronic pain do indeed exhibit reduced integrity of nerve fiber bundles in comparison with healthy subjects,” Ploner confirms. However, the mere presence of nerve fiber bundles between different areas is not sufficient to answer the second question – whether and how intensively the areas communicate with one another. The degree to which their activity is synchronized reflects the extent of their collaboration – the more closely they work together, the more frequently they are active at the same time. Alongside his colleagues, Dr. Christian Sorg, psychiatrist at TUM’s Depart-

ment of Diagnostic and Interventional Neuroradiology, investigated this aspect of the valuation or motivation network by using functional magnetic resonance imaging (fMRI). This imaging method visualizes changes associated with blood flow in active brain areas. It is based on differences between oxygen-rich and oxygen-poor blood and allows high spatial resolution. To increase the temporal resolution, researchers also monitored the changes using electroencephalography (EEG). This records the brain’s electrical activity by measuring voltage fluctuations on the surface of the scalp. “In both methods, synchronized activity in the monitored area was altered in chronic pain patients as opposed to healthy volunteers,” reports Ploner.

The valuation or motivation network is a network of brain regions found in many species that evaluates stimuli and translates them into behavioral responses. This process involves basic feelings: am I safe or in danger; should I be afraid; should I run away? “A malfunction here can result in erroneous or exaggerated assessment of situations and sensory input, which are then deemed more threatening or painful than they actually are,” explains Sorg. This might lead not only to chronic pain, but also to depression. So in a subsequent step, the researchers intend to investigate whether patients with depressive disorders also show similar changes in this network to those with chronic pain. ▷

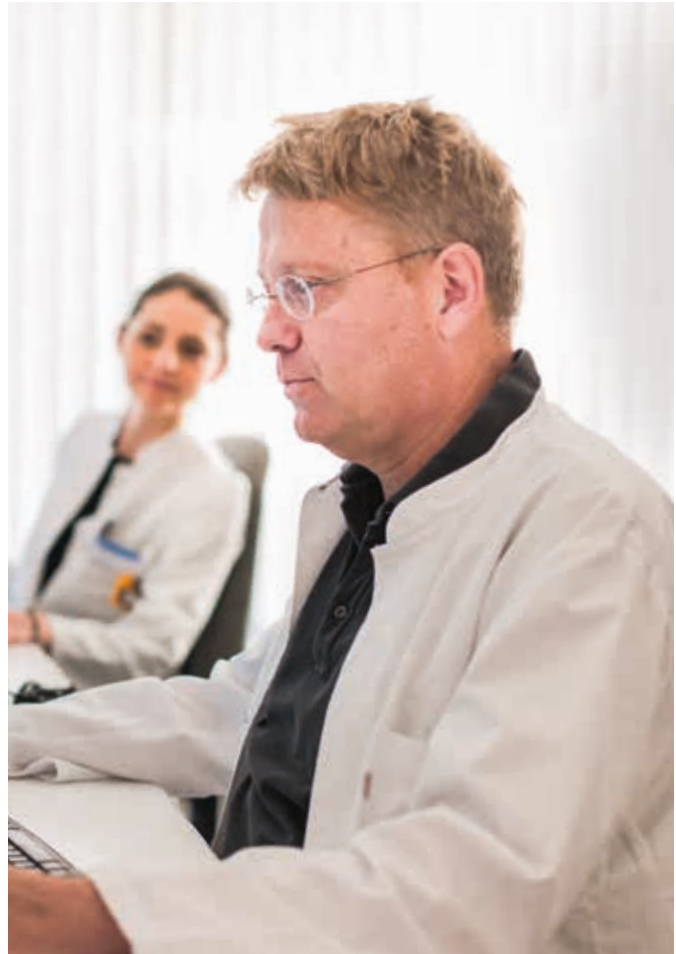
“The last few years in neuroscience have seen an increasing tendency to consider malfunctions across multiple diseases.”

Markus Ploner

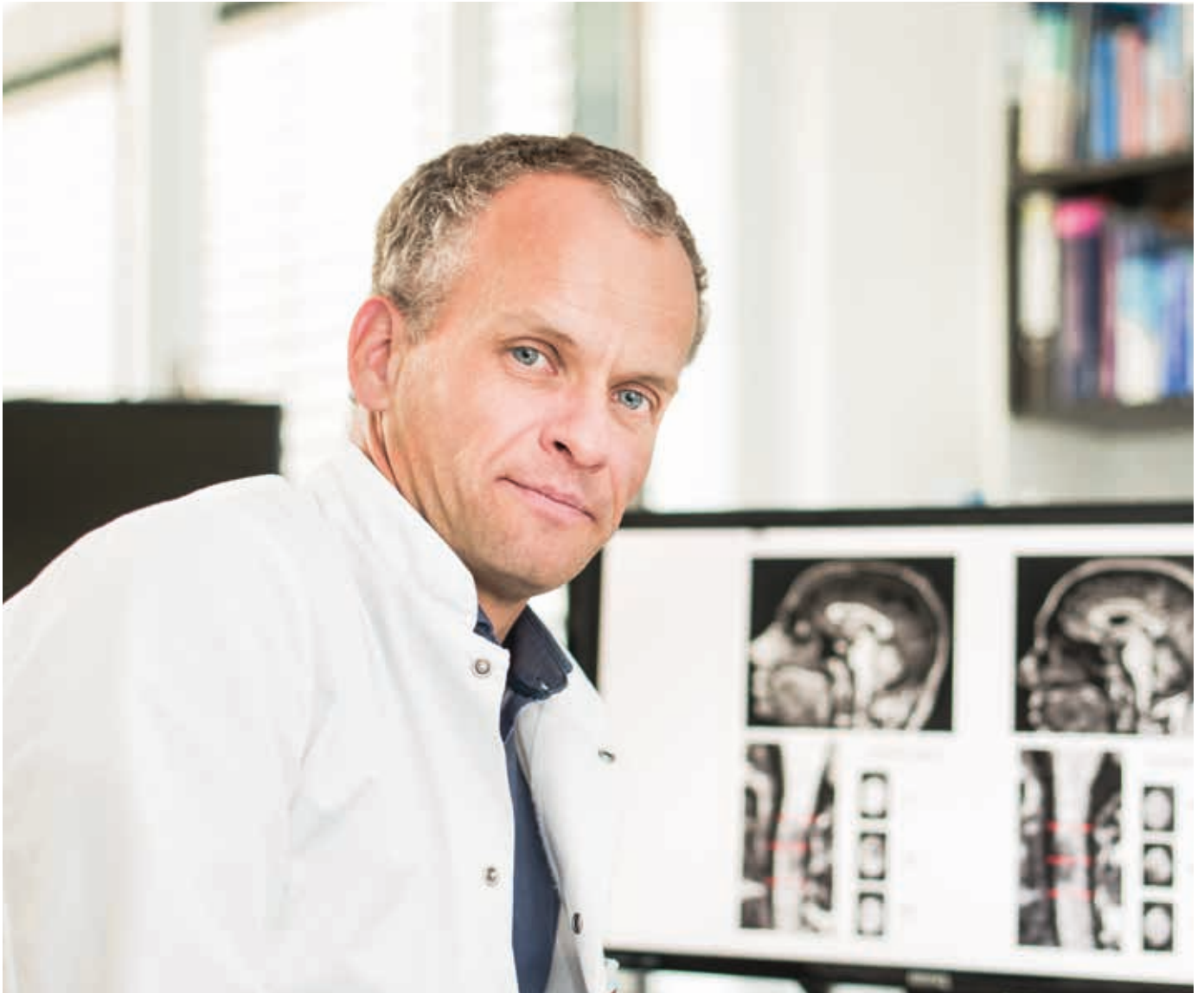


That leaves us with the third question: in which direction does the information flow within the network? This is next on the researchers' agenda. Dr. Valentin Riedl, doctor and neuroscientist at TUM's Department of Diagnostic and Interventional Neuroradiology, has developed a completely new method to this end, which he has already tested on healthy subjects. It involves a combination of fMRI and positron emission tomography (PET) – a technique used to visualize the distribution of a mildly radioactive tracer substance. Patients are injected with radioactively tagged glucose for this purpose. However, simultaneous use of fMRI and PET is only possible at a few locations worldwide – TUM's Department of Nuclear Medicine being one of them. Summarizing his method, Riedl explains: "Since active brain areas require substantial energy, which the body provides in the form of glucose, we can indirectly detect their activity in this way." Use of fMRI enables significantly greater spatial resolution than PET, thus also allowing focused imaging of the processes between the brain areas. "We know that the most energy is consumed at the synapses – the contact structures between the neurons – by the receptors," describes Riedl. The researchers are applying this cellular model of energy consumption at the macroscopic scale here, using fMRI and PET scans to observe not single cells but millions of neurons simultaneously. "Based on the distribution pattern of energy consumption within a network, we can thus determine the direction of information flow in the human brain," Riedl concludes.

By studying interaction between the various brain areas, the researchers hope to gain new insights. Ultimately, their aim is to improve their understanding of the brain and its disorders in order to develop new therapeutic strategies. Alzheimer's disease is a case in point. The TUM-NIC researchers now know how the amyloid and tau protein deposits typical of Alzheimer's spread out along different networks. "We are currently investigating how this type of pathological deposit modifies the activity and structure of the network areas affected," reveals Sorg. "Our expectation is that this focus on brain network changes will greatly improve our therapeutic options, for instance by enabling us to identify disease mechanisms more precisely and target treatment accordingly."



Improving diagnostic capabilities and quantifying structural changes in the brain are also key focus areas for the researchers. Prof. Mühlau, for instance, has succeeded in automating – and thus greatly simplifying – evaluation of MRI scans of diseased brain areas in patients with multiple sclerosis (MS). These images display areas of damage, or lesions, which previously had to be measured by hand to track their growth. The algorithm developed by Mühlau and his team is particularly well suited to analyzing large volumes of data. This enables large-scale comparison of MRI scan measurements with



“With experts in neurology, neuroradiology and psychiatry, TUM-NIC is able to bridge many different neurological conditions and explore entirely new horizons in this area.”

Mark Mühlau

values from other scientific fields such as genetics or immunology, thus yielding new insights into MS. For instance, use of this technique clarified that MS susceptibility genes – the genes associated with increased risk of developing the condition – have only a minor impact on disease progression, meaning that this is likely to be determined by other factors. Mühlau’s group also developed software for reliable measurement of grey matter. This tissue compartment of the brain contains neuronal cell bodies and is also damaged in MS. Prior to this, the white matter lesions typical of MS would interfere with evaluation. Although originally developed for MS, the researchers are now also using the software for Alzheimer’s patients. “The last few years in neuroscience have seen an increasing tendency to consider malfunctions across multiple diseases,” Ploner confirms. And TUM-NIC’s interdisciplinary research approach excels precisely in this area.

Karoline Stürmer

Authors

Claudia Doyle studied biochemistry in Leipzig, Germany. Between 2010 and 2013 she worked in the press office of several institutes of the Max Planck Society. In 2013 she started freelancing as a science journalist. She is currently studying journalism at the Deutsche Journalistenschule (German School of Journalism) in Munich. Her articles focus mainly on ecology and health.

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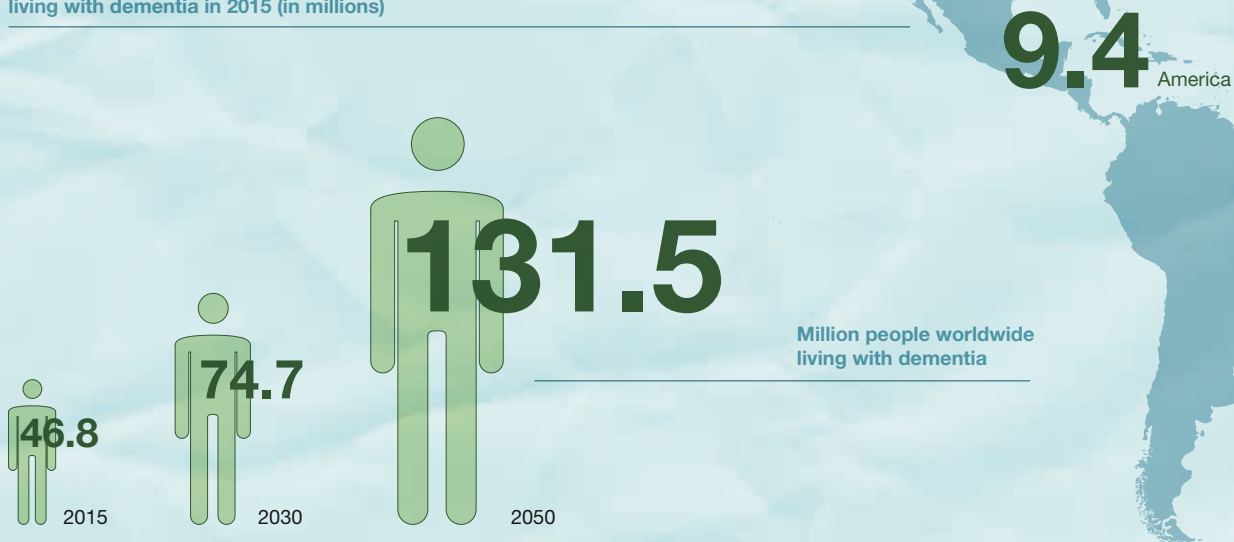
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On the Trail of Alzheimer's

Watching the brain's neurons directly as they fire is a neuroscientist's dream. And for several years now, TUM researchers have been able to do just that. What's more, they are incorporating their methods into work relevant for patients, for instance in the field of Alzheimer's research – with findings that may hold the key to improving treatment.

Estimated number of people living with dementia in 2015 (in millions)



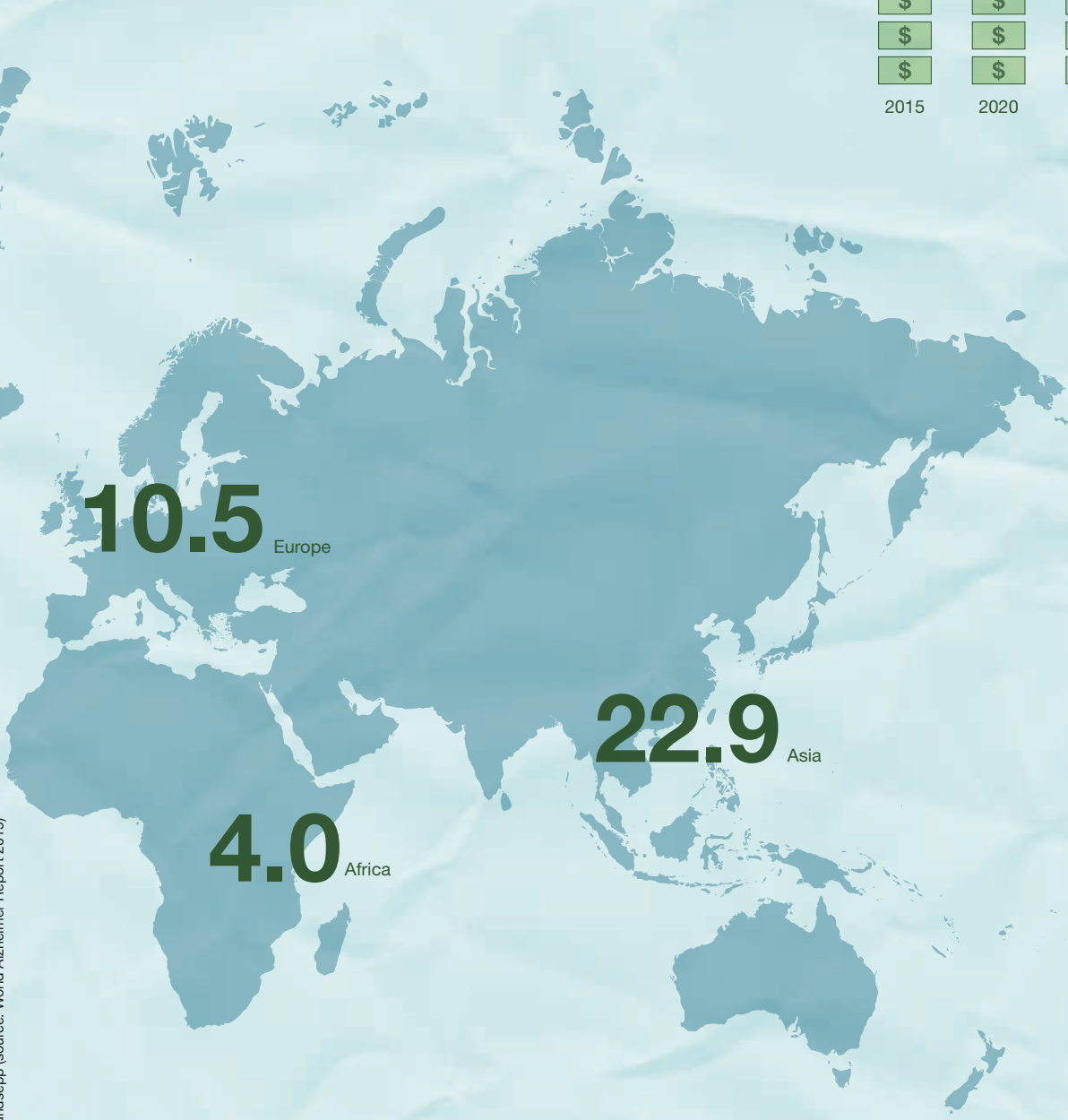
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3 sec

a person is diagnosed with dementia

Forecasted global costs of dementia (US\$ billions)



Graphics: edlundsepp (source: World Alzheimer Report 2015)

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Brigitte Röhlein

Fortschritte in der Alzheimer-Forschung

Neue Verfahren zur Beobachtung einzelner Nervenzellen im lebenden Tier, die Prof. Arthur Konnerth und seine Mitarbeiter am Institut für Neurowissenschaften der TUM entwickelt haben, ermöglichten es in den vergangenen Jahren, zusätzliche Erkenntnisse über die Arbeit des Gehirns zu gewinnen. Im Vordergrund steht dabei die Zwei-Photonen-Mikroskopie in Kombination mit der sogenannten Patch-Clamp-Technik. Erstere erlaubt es, mit roten und infraroten Laserimpulsen bis zu einem Millimeter tief ins Gewebe hineinzuschauen und dort dreidimensionale mikroskopische Aufnahmen zu machen, ohne dass die Zellen geschädigt werden. Man setzt dabei unterschiedliche Fluoreszenzfarbstoffe ein. Beim zweiten Verfahren benutzt man eine nur wenige Mikrometer dünne Glaspipette, die sich an einzelnen Zellen festsaugen kann. So kann man die Ionenkanäle untersuchen, die sich in der Membran der Zelle befinden und dafür sorgen, dass Ionen hinein- und herausfließen. Sticht man die Zelle mit der Pipette an, kann man auch gezielt Farbstoffe oder Pharmaka in sie einbringen.

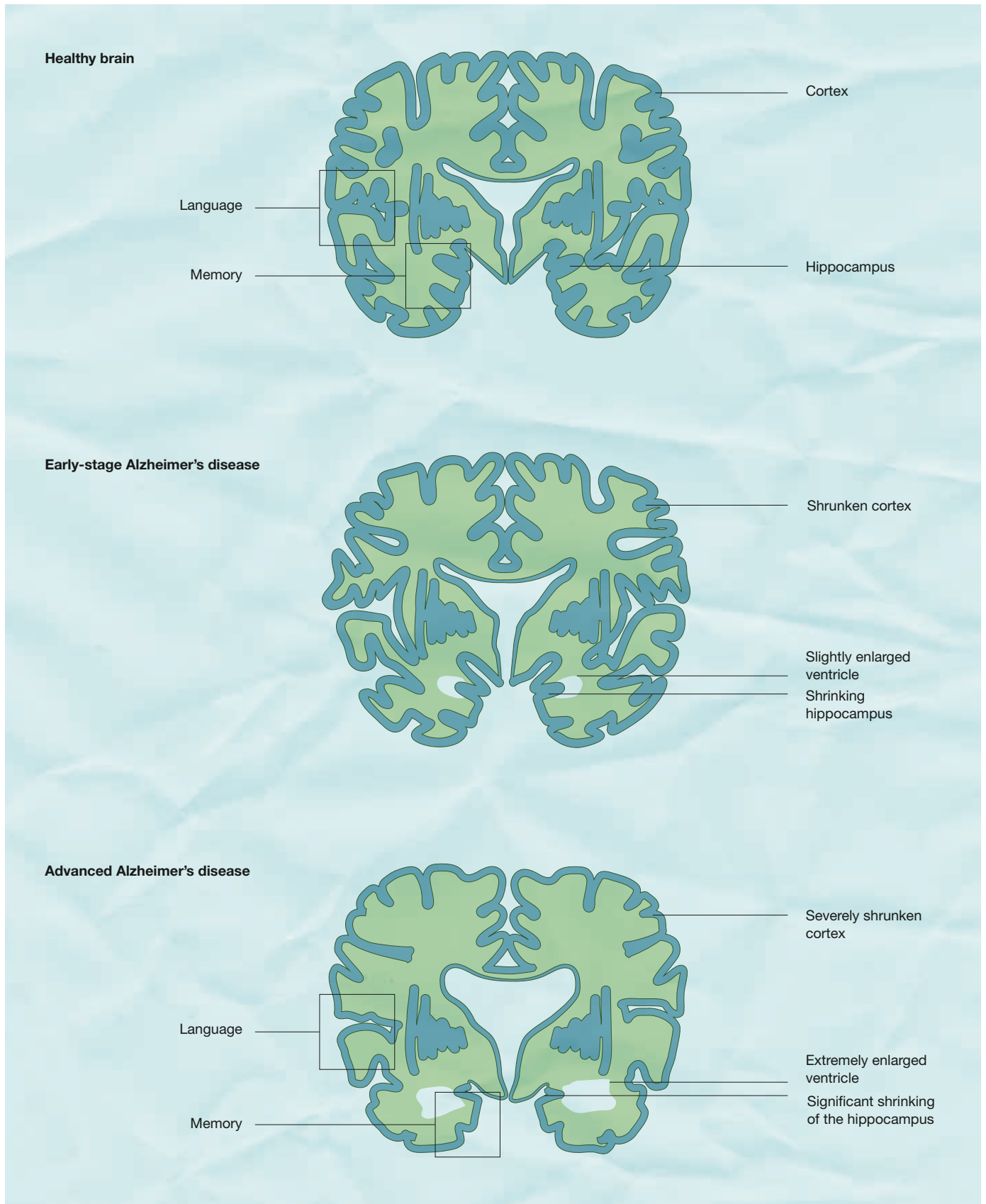
Die Verfahren werden unter anderem bei der Alzheimer-Forschung angewandt und haben bereits zu unerwarteten Einblicken geführt. So gelang es beispielsweise Dr. Marc Aurel Busche, mit der Zwei-Photonen-Mikroskopie zu zeigen, dass es bei Alzheimer-Mäusen einen großen Anteil von Nervenzellen gibt, die besonders aktiv sind. Diese Hyperaktivität findet man zunächst im Hippocampus, also der Region tief im Gehirn, die für Lernen und Gedächtnis zuständig ist, und zwar in einem ganz frühen Stadium der Erkrankung, wenn sich die Alzheimer-Plaques noch gar nicht nachweisen lassen.

Ein weiteres wichtiges Ergebnis war die Erkenntnis, dass sich die krankmachenden Veränderungen im Gehirn auch auf die Vorgänge der Informationsspeicherung im Schlaf auswirken. Vor allem die langsamen Schlafwellen, die unser Gehirn nachts erzeugt, dienen dazu, Gelerntes zu verfestigen und Erinnerungen in den Langzeitspeicher zu verschieben. Die Wellen werden über ein Netzwerk an Nervenzellen in der Hirnrinde gebildet und breiten sich dann in andere Hirnareale wie den Hippocampus aus. Dieser Vorgang ist bei Alzheimer-Mäusen gestört. Derartige Befunde könnten dazu führen, dass man in der klinischen Forschung neue Therapien entwickeln kann. □

What's going on inside your head? Something we often wonder as we struggle to understand each other. And all the more so when we encounter someone with a mental illness such as Alzheimer's, causing them to gradually lose their memory, become disoriented and no longer recognize their own family. Wouldn't it be great if we could take a look at the brain's inner workings and see where the problem lies? Needless to say, researchers would also jump at the opportunity, since you can only cure a disease once you understand its cause. In the past few decades, they have certainly made significant progress, developing imaging techniques such as MRI (magnetic resonance imaging) and PET (positron emission tomography), which enable us to monitor brain activity to varying degrees of clarity. These have taken us a very long way – yet still leave the question open of what is actually happening in the individual brain cells. ▷

“The major problem with treating psychiatric disorders, in particular, is that we don't have a detailed picture of the way the brain works under normal conditions.”

Arthur Konnerth



Graphics: edlundsepp (source: Alzheimer Forschung Initiative e.V.)

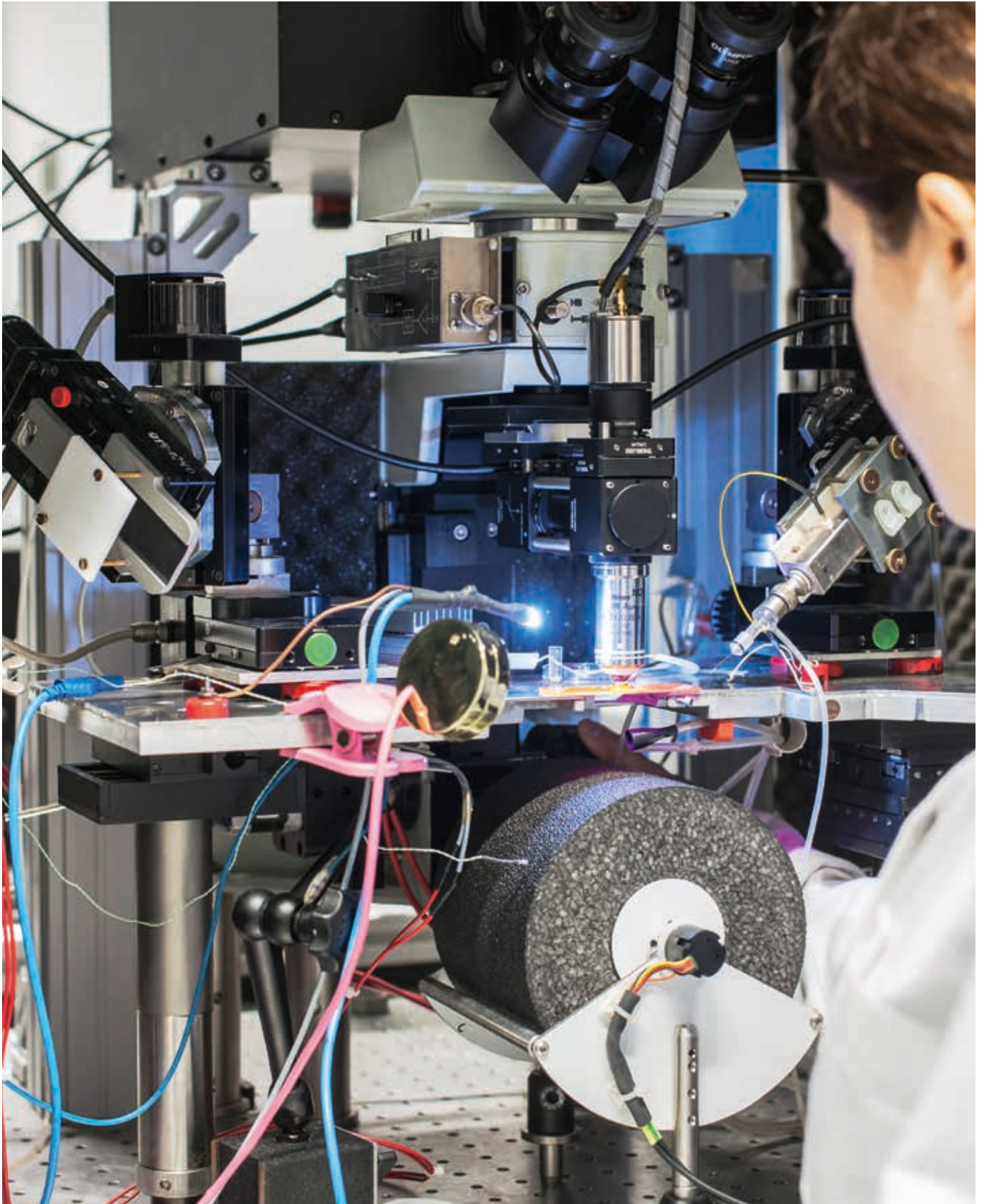
Alzheimer's is an incurable brain disease and the main cause of dementia – around two thirds of all dementia patients have Alzheimer's disease. It is characterized by the cells in certain brain regions ceasing to function and eventually dying.



Konnerth's working group combines patch clamp measurements, which involve attaching a pipette onto the nerve cell by suction, with two-photon microscopy. The micropipettes are fabricated internally by the group.

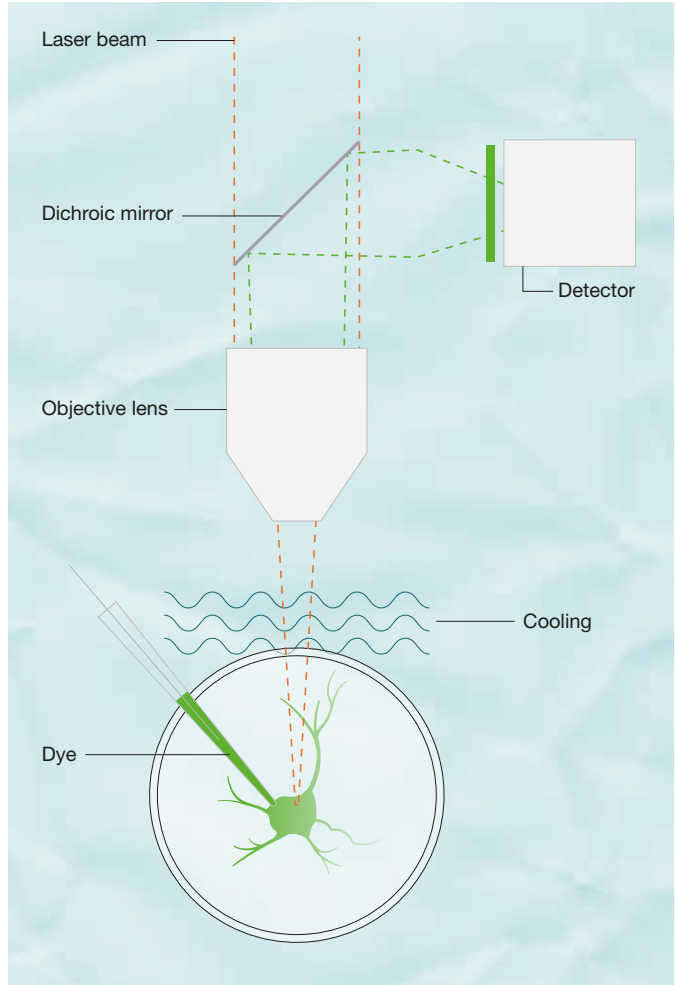
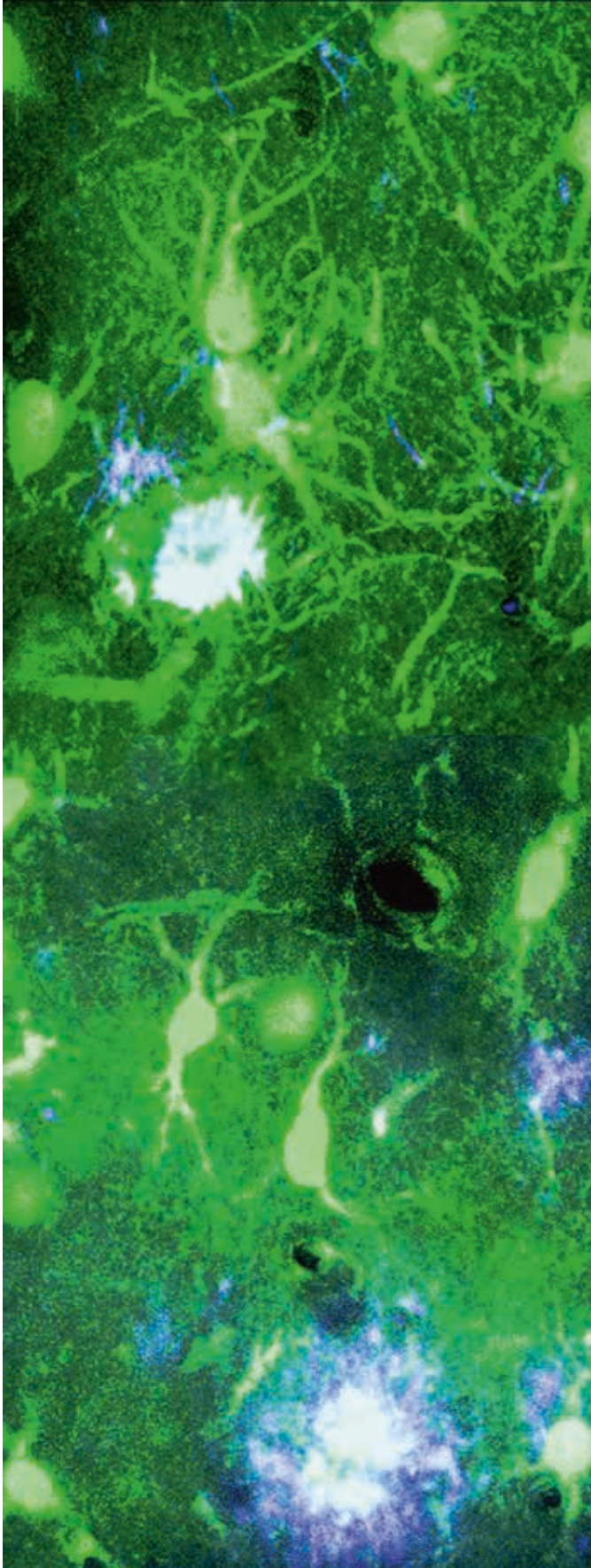
Scientists are however on the case, following every lead like detectives. Their most important equipment was previously the light microscope, enabling them to examine and analyze thin sections of the brain. They also inserted fine electrodes into the intact brains of living organisms to measure electrical activity. But it was in 2003 that research took a major leap forward, when Prof. Arthur Konnerth and his team at TUM's Institute of Neuroscience succeeded in developing a method to monitor the activity of individual nerve cells in a living brain. Today, the team's methods are used in many laboratories worldwide, for instance to improve our understanding of how the brain controls behavior and how disorders arise. "An effective treatment of diseases benefits enormously from a good understanding of the basic mechanisms of the normal function," declares the award-winning professor, now aged 63. "The major problem with treating psychiatric disorders, in particular, is that we don't have a detailed picture of the way the brain works under normal conditions. So we are trying to repair a system we don't fully understand in the first place. That is why therapies to date are often not sufficiently effective and have too many side effects."

This also applies to Alzheimer's disease. As far back as the nineteenth century, specific deposits known as plaques were found in the brains of dead dementia patients. The condition was named after Alois Alzheimer who had first observed these plaques in the brain of a presenile patient in 1906. Many studies since have shown that the plaques consist of beta-amyloid clumps and are typical of the disease. But whether they are its cause or simply a side effect is something researchers still cannot say for certain. Alongside plaques, scientists have identified other changes in the brain that are also highly likely to play a role. These include smaller, still flexible clusters of beta-amyloid, the presence of neurofibrillary tangles (NFTs) formed by tau protein inside the nerve cells, and signs of inflammation. In the end, though, reliably identifying the brain processes associated with Alzheimer's disease means watching the cells in action. ▷



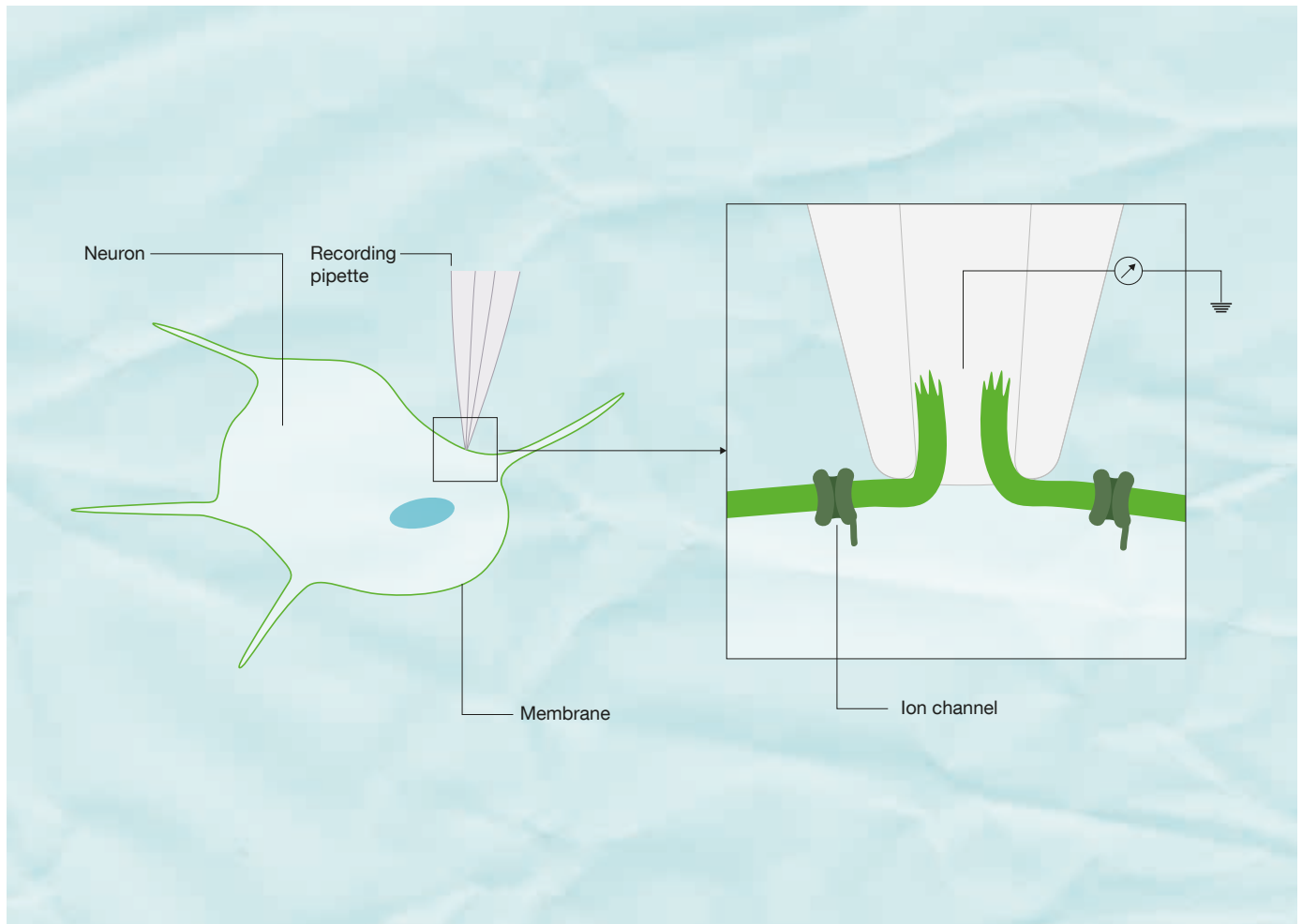
Picture credits: Bauer

A two-photon microscope allows the researchers to observe the nerve cells in the brain of live animals. The pipette for the patch clamp measurement can be seen on the right.



Left: Two-photon microscopy image of nerve cells (green) and beta-amyloid plaques (blue) in the brain of a mouse with Alzheimer's.

Above: In two-photon microscopy, a red laser beam penetrates the brain. A glass micropipette is used to inject dye into the nerve cells at the same time. The red laser beam causes the dye to emit a fluorescent green light under very specific circumstances, and this is registered by the detector. Since the dye binds to calcium, a molecule that always flows if the nerve cell is active, neuronal activity will be indicated by an increased brightness of that cell.



The patch clamp technique is used to measure the ion currents in the nerve cell or the cell membrane. It involves attaching a pipette to the cell membrane by suction. In order to measure the current throughout the cell, the cell membrane is perforated by strong negative pressure. Konnerth's group combines this technique with two-photon measurements, whereby fluorescent calcium indicator dyes are injected into the cells to allow the monitoring of neuronal activity.

Shedding light on the living brain

Inside the labs at Konnerth's Friedrich Schiedel Chair of Neuroscience, researchers can look directly into the brains of living mice. Here, they have a raft of highly refined methods at their disposal, which they can also combine – for instance two-photon microscopy and the patch clamp technique. Two-photon microscopy uses red and infrared laser beams to penetrate the living brain tissue at depths of up to one millimeter and obtain highly detailed microscope images without damage to the cells. To achieve this, various fluorescent indicator dyes are injected into the cells. For the precise recording of electrical activity they use the patch clamp technique which involves a glass pipette of just a few micrometers in diameter that can attach to individual cells. This enables scientists to examine ion channels in the cell membrane through

which ions flow in and out of the cell. If the membrane under the tip of the micropipette is perforated, dye or pharmaceuticals can also be introduced into the cell.

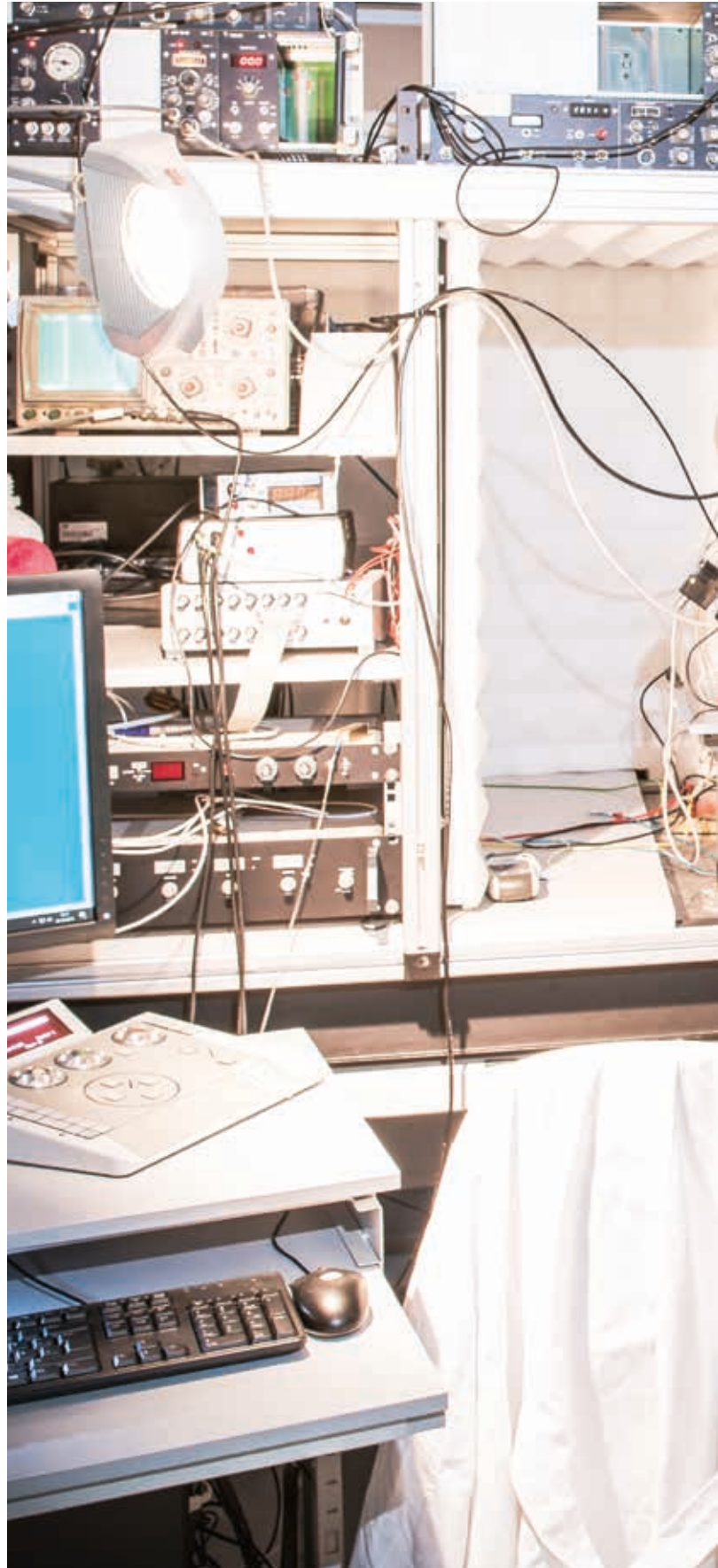
In addition to these fundamental procedures, the researchers have also honed several other methods of investigating and influencing live neurons, right down to observing single synapses. These are the junctions between cells that enable the transmission of impulses. "We have a whole arsenal of tools at our disposal," confirms Konnerth, who was awarded the Brain Prize in 2015 for his pioneering work. "It's actually more physics than medicine." To further advance interdisciplinary competence, he and his colleagues at the TUM Medical School established a new study program for medical students to learn and apply these advanced methods. ▶

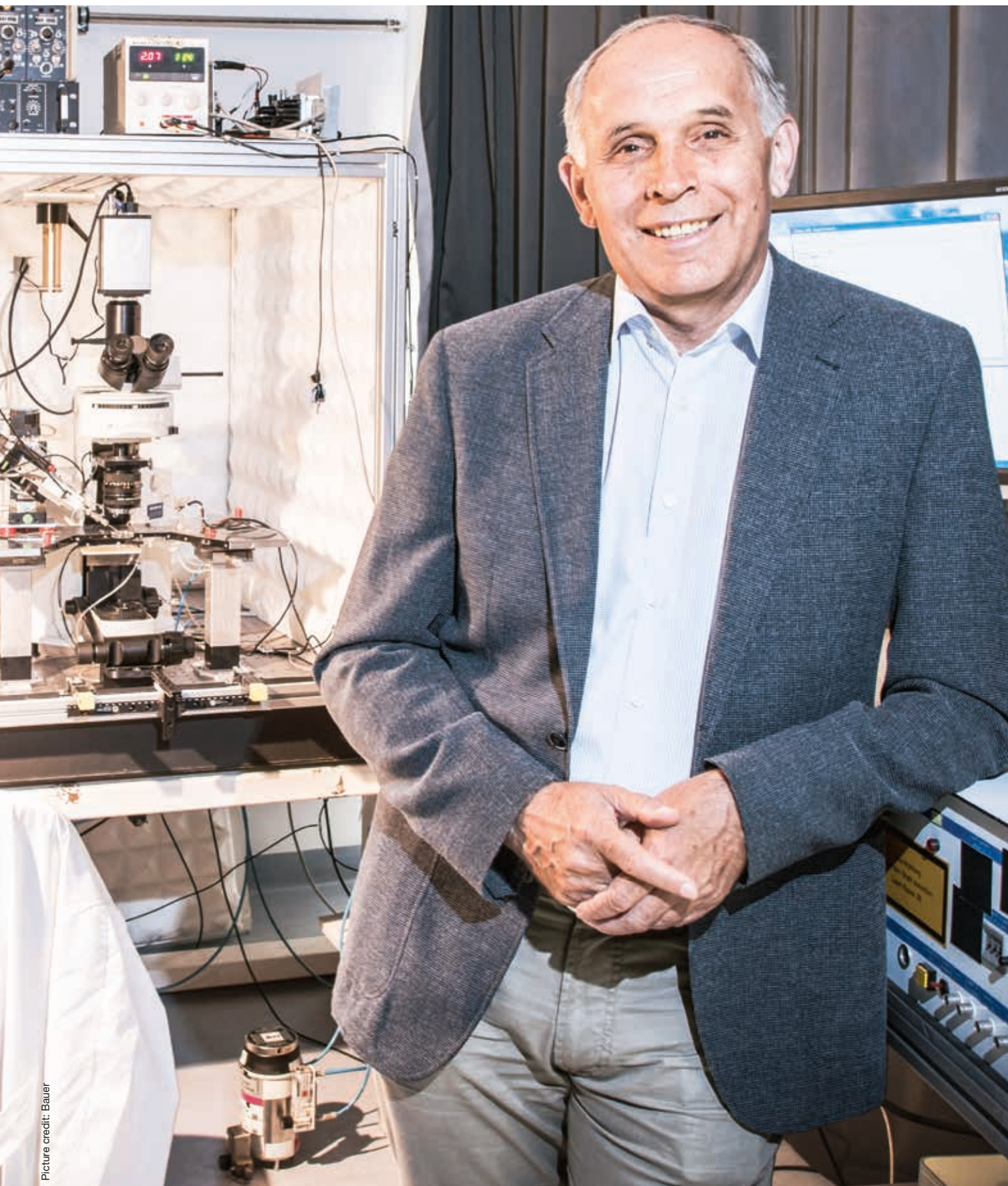
An international family

The latest breakthroughs in brain research were made possible in particular by interdisciplinary collaboration. Prof. Arthur Konnerth himself unites several of the disciplines in question, which is probably the secret of his phenomenal success – combining indepth physics and engineering knowledge with a thorough grounding in medicine. And he is quite determined not to limit himself to a single specialty, preferring to see himself as a “basic researcher and academic mentor.”

Born in a German speaking region of Romania, Konnerth immigrated to Germany with his parents in 1974 and started his medical studies soon after his arrival. Even back then, he was determined to pursue basic research, hoping to be able to combine research with clinical practice. However, when he came to the end of his medical education, “Germany just didn’t have the necessary structures in place,” he recalls with regret. “It wasn’t possible to combine the research and clinical work in an effective way at the time.” Undaunted, he began his lab work already during his undergraduate studies, being especially interested in the development of new methods for his research. This was made possible in part because he was “lucky enough to be working alongside outstanding academic teachers from early on.” He studied medicine in Munich and attended the city’s Max Planck Institute of Psychiatry. After a period in the US, Konnerth moved to Göttingen in 1985 to work with Bert Sakmann, who received the Nobel Prize together with Erwin Neher in 1991 for development of the patch clamp technique. Konnerth later went on to lead the Cellular Neurophysiology working group in Neher’s lab, before taking up appointments at various German universities.

The versatile researcher rapidly rose to success in all his various endeavors. As a result, he has already been distinguished with almost every award in the field. The latest in a long list is the million euro Brain Prize, which he received alongside three other researchers in 2015. Looking back over his career, Konnerth now says: “It wasn’t always a dream come true, but things have certainly gone well. This field offers plenty of freedom to go after the things you think are important and I really appreciated that. But of course good health and good fortune play an important role too.”





Picture credit: Bauer



Konnerth's institute produces two-photon microscopes itself and uses its own workshop for this purpose. Shown here is the construction of one component of the microscope, the so-called scan box. This is where the team makes fine opto-mechanical components for a two-photon microscope.



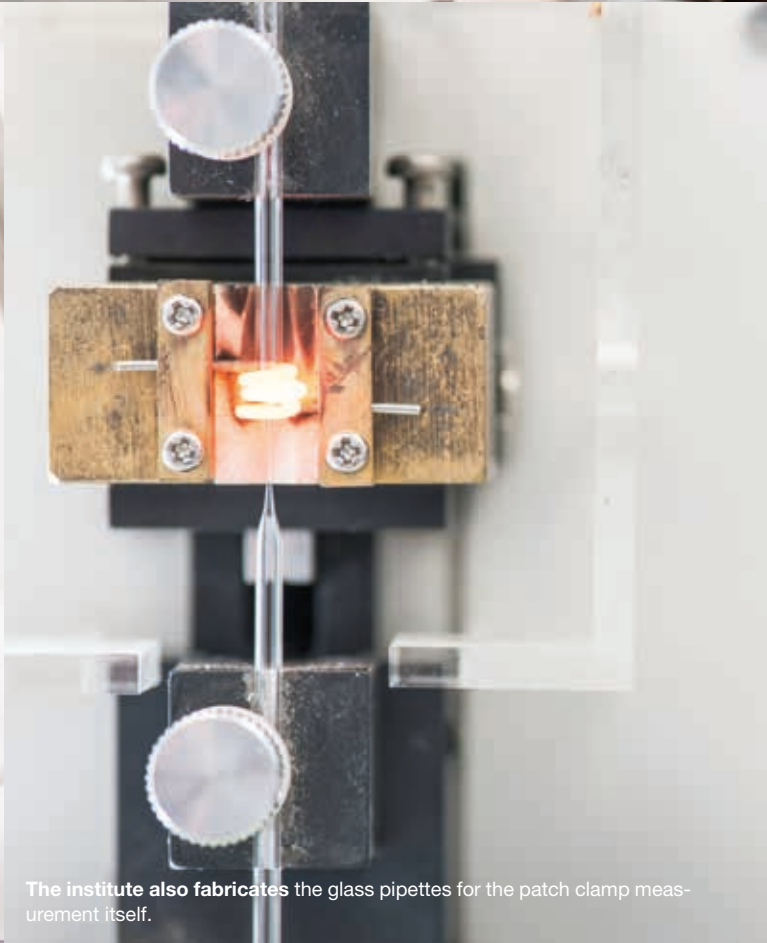
Construction of a tissue holding device.



Alignment of the two-photon microscope's red laser beam.



Embedded brain tissue is finely sliced and then stained to make even the tiniest protrusions from the nerve cells visible.



The institute also fabricates the glass pipettes for the patch clamp measurement itself.

Picture credits: Bauer

“I was especially drawn to Alzheimer's as a research topic. Psychiatric conditions are particularly fascinating, since they have an impact on us as people. And yet we know so little about them.”

Marc Aurel Busche

Dr. Marc Aurel Busche, 33, took advantage of this opportunity and went on to complete his Ph.D. in parallel to his medical studies. He is one of the scientists bridging the gap to clinical research. In his case, this entailed specializing in psychiatry and psychotherapy at TUM's university hospital, Klinikum rechts der Isar, with a particular interest in Alzheimer's disease. “I'm basically a hybrid,” he grins. “I was especially drawn to Alzheimer's as a research topic. Psychiatric conditions are particularly fascinating, since they have an impact on us as people. And yet we know so little about them. Now that we have these methods, there's a huge opportunity to take our research to a whole new playing field – both with animal models and in our work with humans.”

Challenging and developing established concepts

Busche and his colleagues have indeed been successful in gaining new insights into Alzheimer's disease over the past few years. “For instance, we were the first group able to use two-photon microscopy on a living brain to reveal that mice with Alzheimer's have large numbers of particularly active neurons. This hyperactivity initially occurs in the hippocampus – a region deep in the brain responsible for learning and memory – and at a very early stage of the disease, before the Alzheimer's plaques are even present.”

These findings came as a surprise to his doctoral advisor, Arthur Konnerth: “It had long been suspected that neurons surrounding the plaques were less functional than elsewhere – because of earlier evidence that beta-amyloid from plaques interferes with synaptic transmission. At the outset, we were actually looking to interrupt this slowdown. And then came the major surprise that, contrary to our expectations, some of the cells were in fact hyperactive.” This outcome fits in well with independent findings of US researcher Lennart Mucke in San Francisco. Through studies both in mice and Alzheimer's patients, he was able to observe brain impairments that were similar to those occurring in epilepsy. “This overexcitation is what Marc Aurel Busche can see through the two-photon microscope,” as Professor Hans Förstl puts it. The Director of the Department of Psychiatry and Psychotherapy at Klinikum rechts der Isar goes on to explain: “The body is not equipped to downregulate that level of hyperactivity. You could say the brain is overheating.” This finding thus suggests the use of antiepileptic drugs to treat some aspects of Alzheimer's, although additional treatment is still needed. Various promising studies have now been conducted on mice, and clinical trials have recently gone ahead with patients in Munich and the US.



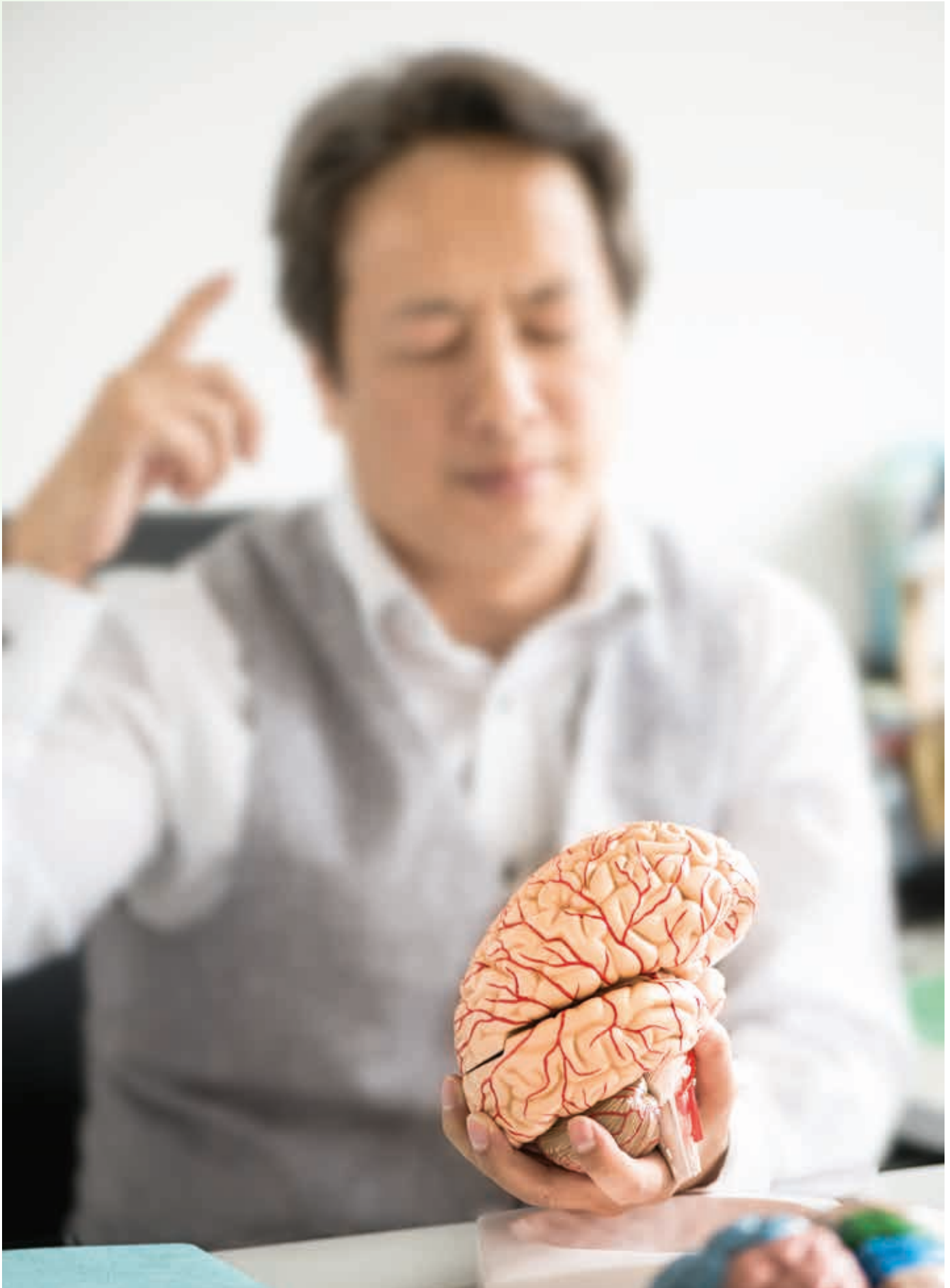
Marc Aurel Busche is a physician at TUM's university hospital and also conducts research into Alzheimer's at Konnerth's laboratory. With the assistance of two-photon microscopy, he discovered an unusually high number of very active nerve cells in the brains of mice with Alzheimer's. This is consistent with the hyperactive behavior which many physicians observe in Alzheimer's patients.

Busche and his team gained another fundamental insight into brain abnormalities accompanying Alzheimer's disease by monitoring neuronal activity during sleep. Sleep plays an important role in memory formation. In particular, the slow oscillations our brains generate at night are key to consolidating what we have learned and to shifting memories into long-term storage. These waves of activity are formed throughout a network of nerve cells in the brain's cortex and then spread out into other parts of the brain, such as the hippocampus. "There is a high degree of coherence between distant neural networks while we are asleep. But this is disrupted in mice with Alzheimer's," explains the researcher. "You could liken it to a heart flutter, where the chambers beat out of sync. In our case, wave activity still occurs locally in various regions of the brain's cortex, but the waves are no longer able to spread and synchronize properly." The original observation of neuronal hyperactivity may offer an explanation here too, particularly since Alzheimer's patients often have difficulties sleeping – and usually long before they become forgetful.

Busche and Konnerth published their findings in the October and November 2015 editions of "Nature Neuroscience". "The concept offers a completely new approach to understanding this condition – the great thing being that clinical interests align here with the cellular techniques that Marc Aurel Busche masters so well," concludes Hans Förstl.

Arthur Konnerth shares this opinion and has great expectations that the latest methods will take us further still: "Our hope is that we will one day gain a full understanding of the way cells actually work. What we need to accomplish now towards this goal with the highest priority is to gain an understanding of how single cells deal with incoming signals." This is still a source of major controversy among scientists. But if we could achieve clarity here, it would be a fundamental advance in understanding how the brain works.

Brigitte Röthlein



Picture credit: Eckert

From Aid to Empowerment

Patients with paraplegia have partially regained feeling in their legs after a year's mobility training with an exoskeleton as part of the Walk Again Project. An artificial skin developed by Prof. Gordon Cheng played a key role here, enabling sensory feedback from the exoskeleton to the patient. Now, Cheng is teaming up with neurologists at TUM to explore how this type of training could help people with multiple sclerosis.

Link

www.ics.ei.tum.de

Birgit Fenzel

Vom Hilfsmittel zum Heilmittel

Robotik und Neurologie können viel voneinander lernen. Davon ist Prof. Gordon Cheng fest überzeugt. Am Lehrstuhl für Kognitive Systeme an der TUM entwickelt er humanoide Roboter, die sich wie Menschen auf zwei Beinen fortbewegen. Ein Schwerpunkt seiner Arbeit ist dabei die Entwicklung einer mit Sensoren und Mikroprozessoren bestückten künstlichen Haut, die über sensorische Rückmeldung die Sicherheit der Maschinen verbessert. Sie kam auch zum Einsatz bei einer Studie, bei der querschnittgelähmte Menschen in einem dreistufigen Trainingsprogramm das Gehen mit einem Exoskelett lernten, und die überraschende Nebeneffekte zeigte. Nach einem Jahr des Trainings, das aus einer Kombination aus Neuro-Feedback und robotischen Hilfsmitteln bestand, hatten alle acht Teilnehmer nicht nur die bewusste Kontrolle über ihre Beine wiedergewonnen, sondern auch Teile ihres mit der Rückenmarksverletzung verlorenen Gefühls in den unteren Extremitäten. Anknüpfend an dieses Ergebnis richtet der Roboteriker seine Forschung gemeinsam mit Prof. Bernhard Hemmer, dem Leiter der Neurologie am Klinikum rechts der Isar, künftig auch stärker auf die Erforschung von entzündlichen Erkrankungen des zentralen Nervensystems aus. „In den vergangenen acht Jahren war ich Teil eines internationalen Forschungsteams. Im Rahmen des „Walk Again Projects“ haben wir uns auf Wirbelsäulenverletzungen fokussiert und dabei festgestellt, dass das Gehirn genügend Plastizität hat, um bei entsprechendem Training Schädigungen des neuronalen Gewebes, auch bei Multipler Sklerose und anderen Erkrankungen, zu kompensieren“, ist Cheng überzeugt. Erste Tests mit Patienten bestätigen seine Vermutung. □

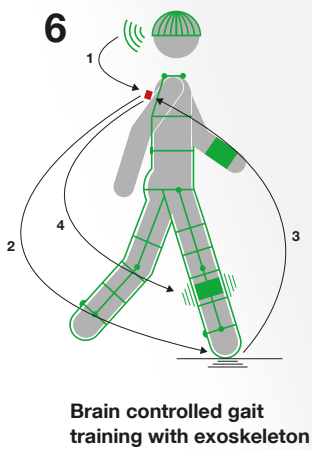
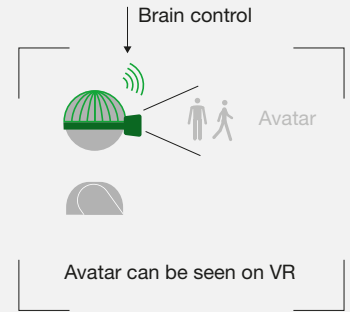
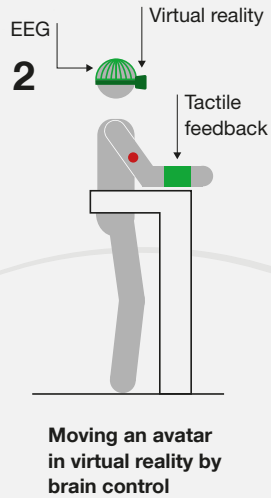
Training based on a combination of neurofeedback and robotic aids could benefit not only paraplegic patients but also those with other neurological conditions such as multiple sclerosis (MS). This technology was developed within the Walk Again Project, which made headlines in 2014 when paralyzed participant Juliano Pinto kicked off the soccer World Cup in Brazil at the opening ceremony. The 29-year-old was wearing a robotic body suit, controlling its leg movements with his thoughts.

“When we started work, our aim was to develop equipment that would enable people with paraplegia to regain mobility by controlling prosthetic limbs or exoskeletons with their brains. We did not expect that training in this way over an extended period might itself have a therapeutic effect,” reveals Gordon Cheng, Director of TUM’s Institute for Cognitive Systems. His laboratory is responsible for the artificial skin fitted to the mind-controlled exoskeleton used in Juliano Pinto’s big debut in Rio two years ago. This robotic skin also played a decisive role in a clinical trial conducted within the Walk Again Project, the outcome of which was recently published. The electronic artificial skin uses sensors to detect pressure or touch, for instance, relaying these signals back to the person wearing the exoskeleton. Like the extraordinary World Cup participant, all of the eight people on what researchers refer to as the Walk Again Neurorehabilitation protocol were paralyzed from the hip down due to spinal cord injuries. “None of them could move or feel their legs,” confirms Cheng, describing their initial condition, which, in fact, improved dramatically over the course of the trial.

After six months of intensive training, the first signs of success were already clear. During this period, the participants not only learned to move the exoskeleton forward through brain activity, but also assimilated the robot’s legs and feet into their own body schema. “We were very surprised when they told us that they were actually experiencing the exo’s movements as their own steps,” Cheng recalls. Interpreting this man/machine merger, he explains: “Evidently, with the right training, we can trigger new connections in the brain, allowing us to reorganize our body schema to integrate new elements such as the exoskeleton.”

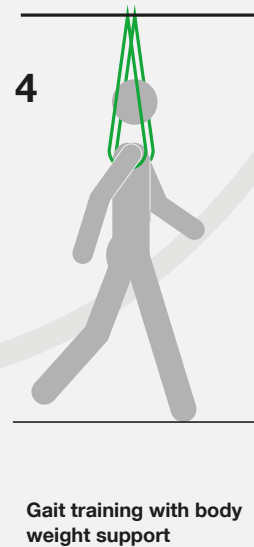
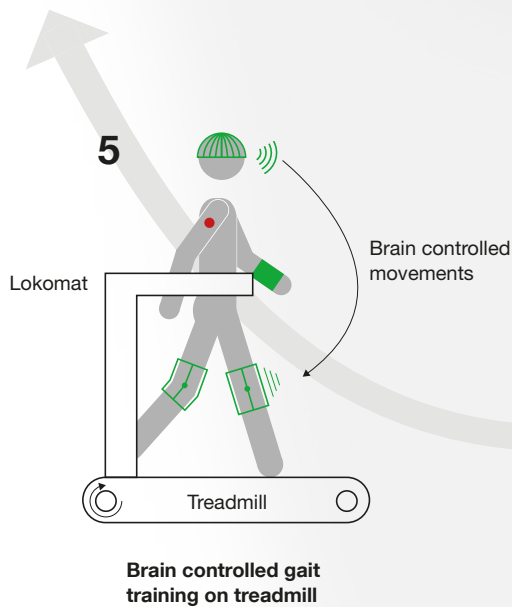
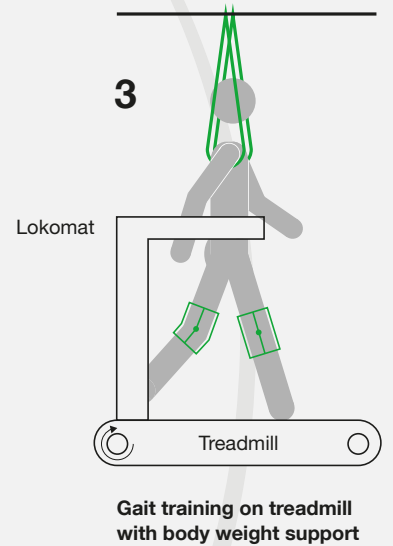
A year’s training to regain feeling in the legs

An even greater surprise for Cheng and his colleagues was that the participants’ medical condition also improved significantly – another side effect of training that emerged in subsequent months. “After one year, they were all able to feel contact and pain in areas of the body that had been without sensation for years – and regained at least some ability to voluntarily move their legs,” he reports, describing changes that astonished and delighted researchers and participants alike. “While training with the exoskeleton, one woman suddenly felt a burning sensation in her legs,” he recalls. “She started crying – not due to pain, but because she was so happy to be walking again after such a long time.” ▷



“After one year of training, all patients were able to feel contact and pain in areas of the body that had been without sensation for years – and regained at least some ability to voluntarily move their legs.”

Gordon Cheng





Gordon Cheng developed the artificial skin in order to provide robots with tactile feedback.

Prof. Gordon Cheng

Gordon Cheng is a passionate robotic engineer who believes that in the future, robots and smart machines will better assist especially older and handicapped people in their daily lives.

Cheng studied information sciences at Wollongong University (Australia) and was awarded a doctorate in systems engineering in 2001 from the department of systems engineering of the Australian National University. He founded the department of humanoid robotics and computational neuroscience at the Institute for Advanced Telecommunications Research in Kyoto (Japan), where he was Department Head from 2003 to 2008. In addition, from 2007 to 2008 he was a project manager at the National Institute of Information and Communications Technology (Japan) and the Japan Science and Technology Agency, where he was responsible for the Computational Brain project (2004-2008). In 2010, Cheng founded the Chair for Cognitive Systems at TUM.

As far as Cheng and the team are concerned, there is just one plausible explanation: the training triggered plasticity in the brain. This refers to the brain's capacity to transfer specific tasks from a damaged region to a healthy one. "But I also think it rekindled neurons in the spinal cord. It's got to be both," is Cheng's interpretation of this unexpected therapeutic progress after just twelve months of training. "The combination of visual and tactile feedback is the key to the training's success," he states with conviction.

In the first stage of the program, the eight men and women learned to make an avatar walk by means of their own thoughts. To achieve this, they wore an electrode cap, which recorded their brain activity and conveyed it to a computer. Whenever it received the appropriate brain signals, this computer then set the virtual person in motion, with participants viewing it through virtual reality goggles. In stages two and three, the participants worked with the exoskeleton, taking their first steps on a treadmill before continuing their training on normal surfaces. In all three stages of training, they received sensory feedback from small motorized components in the sleeves of their clothing, which vibrated when the feet of the avatar or exoskeleton touched the ground. During training with the exoskeleton, this tactile feedback came from the artificial robot skin developed by Gordon Cheng and his team at TUM. This artificial skin was applied to the soles of the robotic exoskeleton's feet.

Could MS patients benefit from robotics?

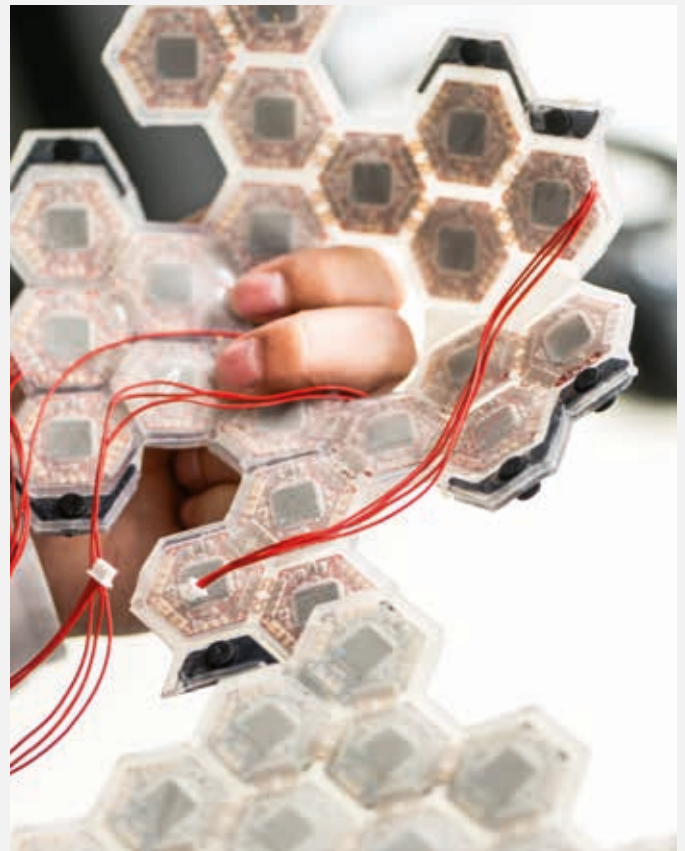
Building on these promising trial outcomes, Gordon Cheng now intends to apply his research to new treatment scenarios. “We have spent the last eight years focusing on spinal injuries and established that the brain has enough plasticity to compensate for neural tissue damage, given the right training. That could also apply to other conditions,” he explains. With this in mind, he has already been in touch with Prof. Bernhard Hemmer, Director of the Department of Neurology at TUM’s university hospital, Klinikum rechts der Isar. Hemmer specializes in neuroimmunology. His research focuses on inflammatory diseases of the central nervous system – in particular multiple sclerosis. This condition damages the protective sheath around nerves in the central nervous system and can trigger almost any kind of neurological symptom. “I learned a lot about this disease from him – and identified many similarities to paraplegia in the process,” recounts Cheng. Symptoms such as sensory disturbances or impairment, muscle weakness and paralysis are all typical of MS. As Cheng discovered in his discussions with Prof. Hemmer’s patients, “Many of those affected lose their sense of touch and can no longer feel their feet hitting the ground.” As he also found out, they use their vision to compensate for this loss of

sensation. “Assuming they are able to control their legs in the first place, these patients tend to move unsteadily and often stumble. When they close their eyes, many of them can no longer move at all.” Cheng is familiar with this problem from developing humanoid robots. Without tactile perception, these machines also struggle to stay steady on their feet. With artificial skin, though, they can even accomplish this on uneven terrain. “The issues facing robotics are also of interest to neurologists,” he is sure. He now believes that a combination of neurofeedback and assistive robotics could also have the potential to help restore MS-related impairments altogether. At the same time, Cheng has continued optimizing his humanoid robots and fine-tuning the exoskeleton – the aim being to make it faster, lighter and, above all, less expensive. He has also made further advances with the artificial robot skin, maintaining the system’s sensitivity while shrinking its components and attaching it to a rubbery surface. This is flexible enough to cling to whatever it is applied to – whether a robot’s hand or foot or a human body, it adapts to ensure a perfect fit. This brings Gordon Cheng another step closer to the goal he has clearly in his sights: “I want to develop a body suit made of artificial skin to help people with neurological disorders get their life back to normal.”

Birgit Fenzel



Cheng’s group developed this new EEG (electroencephalogram) device for measuring brain activity.



The artificial skin is made up of several hexagonally shaped unit cells, each featuring multiple sensor modalities.

Big Data Improves our Understanding of Diseases

What causes a disease? Why do some patients respond to a particular drug while others do not? What would the optimum therapy be for each individual patient? At TUM's Chair of Medical Informatics, Prof. Klaus A. Kuhn and his team are working to answer these questions with the help of big data.

Link

www.imse.med.tum.de

Birgit Fenzel

Mit Big Data Krankheiten besser verstehen

Viele der häufigen und gefährlichen Krankheiten wie Krebs, Herzinfarkt, aber auch Schlaganfall und andere neurologische Erkrankungen werden durch zahlreiche Faktoren beeinflusst. Entsprechend schwierig sind Ursachenforschung, Diagnose und Therapie. Big Data könnte bei der Lösung des Problems eine große Rolle spielen. Davon ist der Medizininformatiker Prof. Klaus A. Kuhn von der TUM überzeugt. „Wenn wir über eine breite Basis von heterogenen, nach Art und Herkunft vielfältigen Daten verfügen, besteht eine gute Chance, Krankheitsverläufe, Krankheitsprävention, Diagnostik und Therapie besser zu verstehen“, betont er. Während der Behandlungen werden immer mehr technische

Geräte angewendet, die Daten produzieren. Untersuchungen wie Röntgen, CT oder MRT erzeugen eine große Menge an heterogenen Daten. Zusammen mit ärztlichen Berichten, den persönlichen Patientendaten sowie den Analyseergebnissen aus den neuen Laborverfahren, die sich als sogenannte Omics-Technologien nach der Entschlüsselung des menschlichen Genoms rasant entwickelt haben, ist das Datenvolumen seit einigen Jahren explosionsartig angewachsen.

Am Institut für Medizinische Statistik und Epidemiologie arbeitet Kuhn mit seinem Team an Konzepten und Lösungen, diese umfangreichen und heterogenen Daten aus Klinik, Forschung und Labor zu integrieren und zugänglich zu machen. Die Idee ist es, mithilfe von Informationstechnologie und analytischen Verfahren auch Vorhersagemodellen den Weg zur personalisierten Medizin zu bereiten. □

Prof. Kuhn, do you hope medicine can benefit from big data and data mining technologies, where algorithms and statistics are used to analyze huge data volumes?

One major benefit would be new research findings enabling medical professionals to tailor treatment precisely to individual patients. Gaining a better understanding of the way diseases develop and progress is also a key aim. To find biomarkers to predict the course of disease is also important.

Are there specific neurological conditions that are particularly well suited to these big data analyses, and why?

In many cases, diseases have no single cause – there are a number of contributing factors. In neurology, this would apply to strokes, for instance, and also to multiple sclerosis, where a number of risk factors have been identified. The interplay between these various factors and their influence on the disease is complex and, to a large extent, not yet understood. But if we have access to large collections of heterogeneous data – comprising different types of data from different sources – we have a good chance of gaining a better understanding of disease progression, prevention, diagnosis

and treatment. With information technology and subsequent analyses, including predictive modeling, big data can help to pave the way for personalized medicine.

At your institute, you are developing innovative IT concepts and solutions for translational medicine – a bench-to-bedside approach that links the lab to clinical practice and bundles knowledge, resources, expertise and techniques across disciplines. How do you get a handle on the information chaos that arises when you capture all kinds of data from the most varied of sources?

We use various integration methods. The data warehouse concept is an important example – a warehouse in this context being a large database. It duplicates data from the various systems we work with – in IT we call this replication. This replicated data can then be queried and reorganized without touching the original sources. This type of database gives data scientists and analysts a collective view of all factors that might be relevant based on our knowledge to date. There are also other methods that do not involve data replication.



Big Data in Medical Research

Big data describes the integration and analysis of large data volumes of high variety from different sources. An important aim is to detect patterns that are not evident in smaller or homogeneous data sets. In medicine, large data volumes are generated by “omics” technologies – that is, genomics, proteomics and metabolomics, or the study of genes, proteins and metabolites, and by imaging procedures. Sensor data from wearable devices are playing an increasingly important role for “big data”.

Neurologists and neuroscientists at TUM are exploring the potential of big data as an approach for predicting the course of disease and therapeutic outcomes. Patients respond very differently to medical treatments and physicians can lose valuable time trying to find the most effective therapy for each individual patient. As a step towards improved prediction, a database can play an important role: the basic idea is to integrate medical reports, descriptions of clinical findings, therapies, data on disease progression with imaging data (MRI, CT, etc.) and genetic information for large numbers of patients. Researchers see huge potential in this approach to gain new insights and to enable physicians to select the therapy most likely to be effective for a new patient based on the specifics (clinical findings, imaging data, genetics, etc.) of their individual case.

“One major benefit would be new research findings enabling medical professionals to tailor treatment precisely to individual patients.”

Klaus A. Kuhn

How does your database work?

Well, the aim is to mine the relevant information from these large data volumes and detect relationships and patterns by analytical methods. Data documenting the course of a disease and the possible side effects of a therapy in a specific age group may be combined with information about other factors such as information on genetics. One of the ultimate goals is to support decisions with data and knowledge at the point of care. There are successful examples, such as in the prediction of drug effects based on genetic testing. The issue then was why some patients respond to a particular drug while others do not.

Your analytics and computational models call for a database that is as large and wide-ranging as possible. Why does quantity not mean quality in this case?

We face challenges with harmonization and standardization in this area. More and more technical devices are being used in medical care that produce high volumes of data. In particular, imaging techniques such as X-ray, CT and MRI scans generate large amounts of heterogeneous data. Together with medical reports, personal patient information and analysis results from new lab techniques – omics technologies have evolved at high speed since sequencing the human genome – the last few years have seen an explosion in data volumes. In this area, as in today’s imaging procedures, standardization is a core challenge, since different devices and imaging techniques can lead to different findings, for instance.

So what are the next steps, in your view?

The main focus will be on data integration both within and across institutions, spanning high variety and heterogeneity. This requires us to harmonize and standardize both data and processes. Ethical, legal and social questions we face in today’s medical research play a key role here, especially in dealing with sensitive patient information. Data protection concepts thus are increasingly important – bringing us back to technical challenges in which we are very well positioned.

Interview by Birgit Fenzel



Prof. Klaus A. Kuhn

Klaus Kuhn holds degrees in computer science, mathematics and medicine (Dipl. Inform., Dipl. Math., Dr. med., Dr. med. habil.) from the Universities of Stuttgart, Freiburg, Tübingen and Ulm. He worked at the University Hospitals of Heidelberg and Ulm. From 1996 to 2004 he held the Chair of the Department of Medical Informatics at the University of Marburg (Philipps-Universität Marburg). In parallel to this he was Chief Information Officer at the University Hospital of Marburg. At TUM, he is a full Professor of Medical Informatics. Between 2007 and 2011 he was President and Vice-President of the German Association for Medical Informatics, Biometry and Epidemiology. Kuhn was elected a Fellow of the American College of Medical Informatics (AMIA) in 2008.



Beate Spiegel

In 1995, Klaus Tschira established the Klaus Tschira Foundation, a charity which was built on his vision to foster the natural sciences, mathematics and computer science, as well as the appreciation of these fields. In 1997, Beate Spiegel joined in and began building up the foundation together with Klaus Tschira. Since 2011, she has been the managing director of the Klaus Tschira Foundation. She worked side by side with Klaus Tschira until his passing in 2015, and now shares the managing responsibilities with his sons Udo Tschira and Harald Tschira.

Beate Spiegel studied law at the University of Heidelberg (1981-1983), and obtained her degree as a state certified foreign language and management assistant in 1986 from the Commercial Technical College Bensheim. For over a decade she worked at the European Center for Network Research of IBM Germany, Heidelberg. Due to her knowledge in the area of computer science development and her strong organizational competence, Klaus Tschira felt she was the right person to coordinate his foundation.

Science Communication – A Fundamental Part of Research

Germany's Klaus Tschira Foundation promotes dialog between researchers and the general public

Science thrives on communication. Not only does it play an essential role in promoting cross-disciplinary exchange among scientists; it is also hugely beneficial to each and every one of us. Scientific findings that are communicated to wider society – in a clear and comprehensible way – help us to make the decisions that shape our daily lives. The latest knowledge and insights are the most valuable tools we have, for instance, when it comes to weighing up one medical treatment against another.

The Klaus Tschira Foundation (KTS) is thus committed to strengthening science communication. A pioneering influence in Germany, the foundation encourages scientists to give clear accounts of their research – for instance through the Klaus Tschira Award for achievements in the public understanding of science. This is awarded to up-and-coming scientists who distill the substance of their doctoral thesis into an article that can be widely understood. The foundation also strives to improve the communication skills of scientists. On the one hand, it offers all prize entrants the opportunity to take part in a writing seminar free of charge. On the other, it

has joined forces with the Karlsruhe Institute of Technology (KIT) to open the National Institute for Science Communication (NaWik) in the German city of Karlsruhe. NaWik provides training for scientists in presentation skills, accessible writing and tweeting. That's right, tweeting – because the evolving media landscape is opening up new opportunities and giving scientists a direct line to other interested parties, whether via online forums, science blogs, open access journals or tweets from various conferences.

Simultaneously, the fast pace of media reporting also means that breaking news from the science community that reaches the broadest audience runs the risk of being incorrectly presented or interpreted. To support science reporting, the Klaus Tschira Foundation established the Science Media Center (SMC) Germany in Cologne. Run in partnership with the German Association of Science Journalists (WPK), SMC provides journalists with well-researched and contextual knowledge, as well as expert statements on hot topics – thus acting as an independent, neutral and rapid source of information.

However, researchers need to look beyond their obligation to “push” their findings or expert opinions into the public arena. Countless times, scientists have told me that it was questions from schoolchildren that pointed them in new directions or gave them fresh ideas. It would be a mistake to underestimate how valuable science communication can be to science itself. The time has come, then, for the efforts of scientists committed to furthering this communication to be also acknowledged by the scientific community and to play a role in the advancement of career prospects. □



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