

From Bench to Bedside

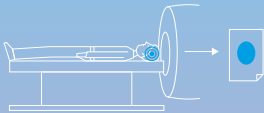
Translational medicine – the close interaction of basic researchers and clinician scientists – is the key to rapid and efficient development of new diagnostics and therapies.

and Back

Clinical research
focused on
the patient



Environmental factors
Genetic analysis



New diagnostic methods



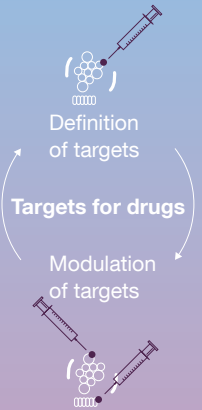
Definition of disease entity



Molecular mechanisms
underlying development
of the disease



Modeling

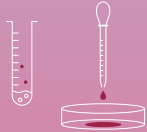


Definition of targets

Targets for drugs

Modulation of targets

Genetic analysis



Biochemical studies

Basic science
in the laboratory

Gerlinde Felix

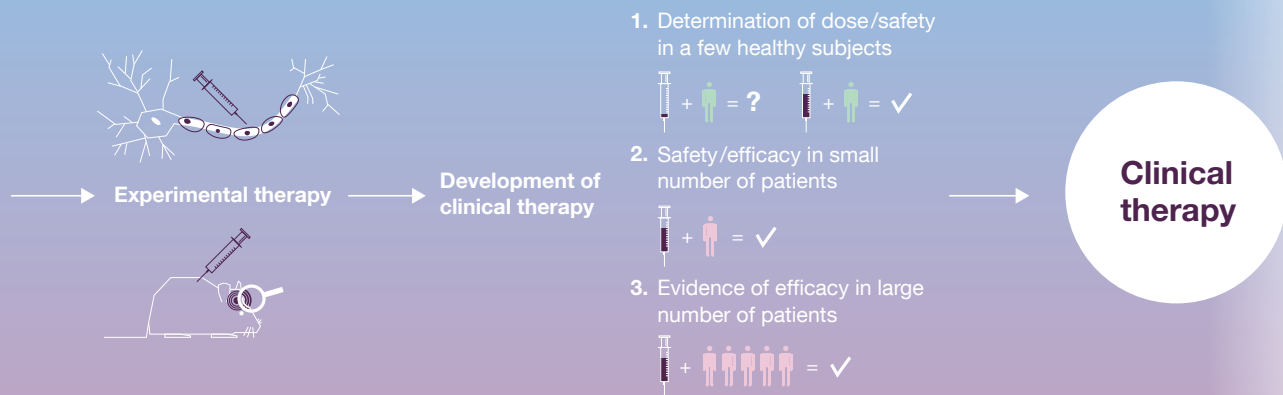
Vom Patienten zum Labor und zurück zum Patienten

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,

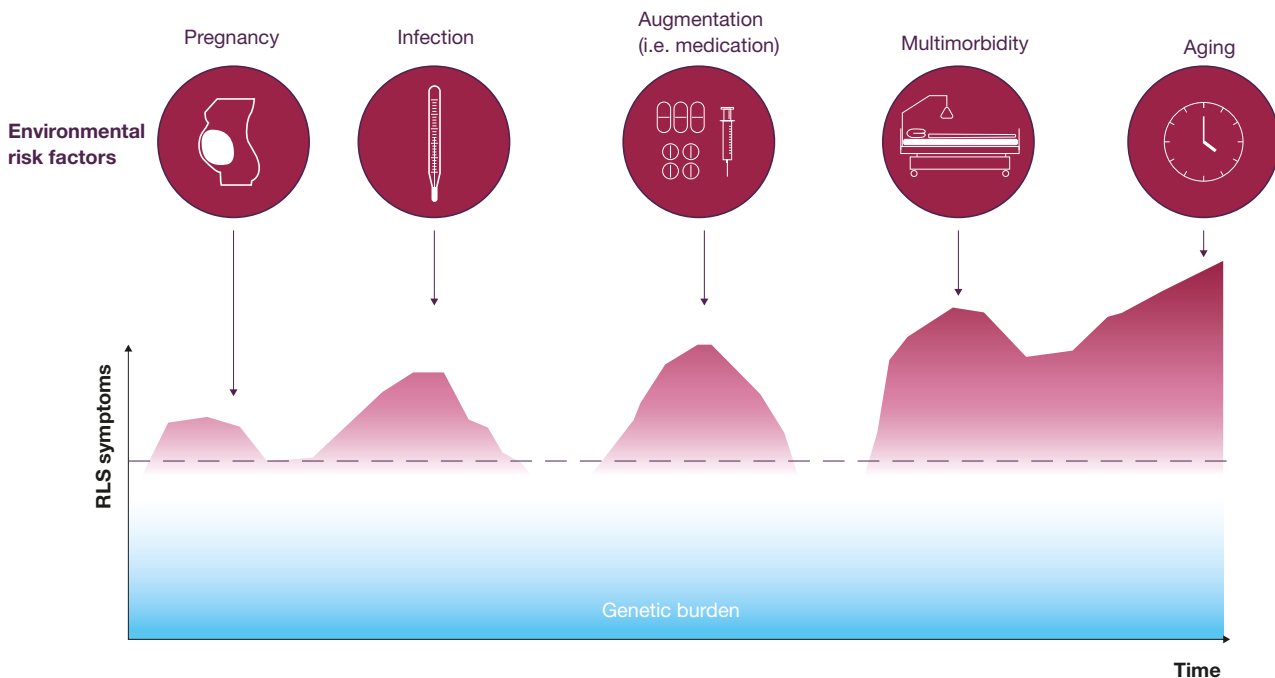
for example, which they initially investigate in animal models to gain insight into its role in the disease mechanisms. The team then seeks to identify suitable targets for therapeutic intervention. Initial animal studies are conducted to clarify the required dosage, check whether the active compound 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.

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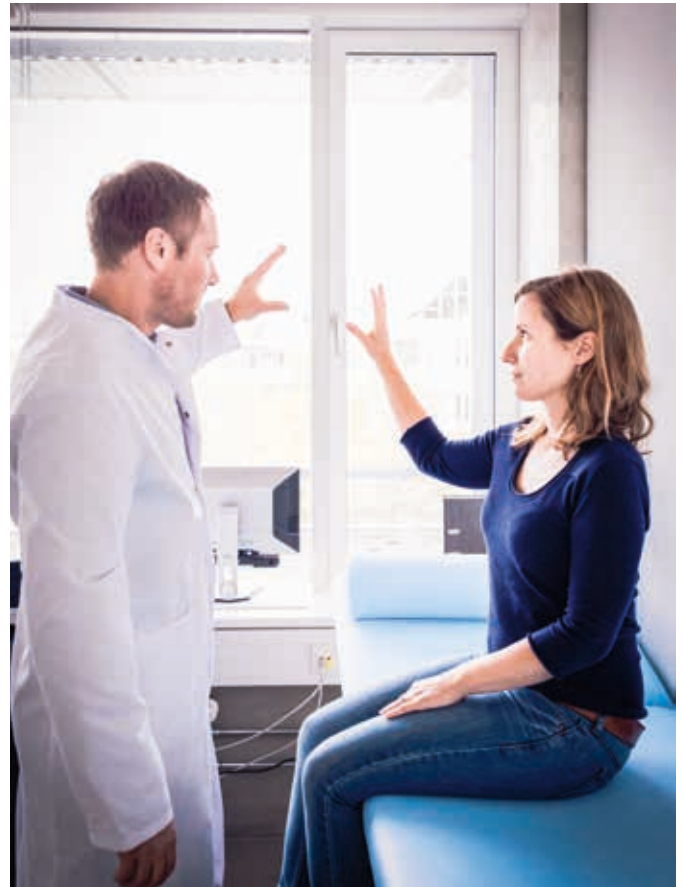
Restless legs syndrome is genetically determined, but the genetic burden affects individuals to a different extent. On top of the genetic susceptibility, environmental factors such as infections or multimorbidity can trigger or worsen the symptoms.



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

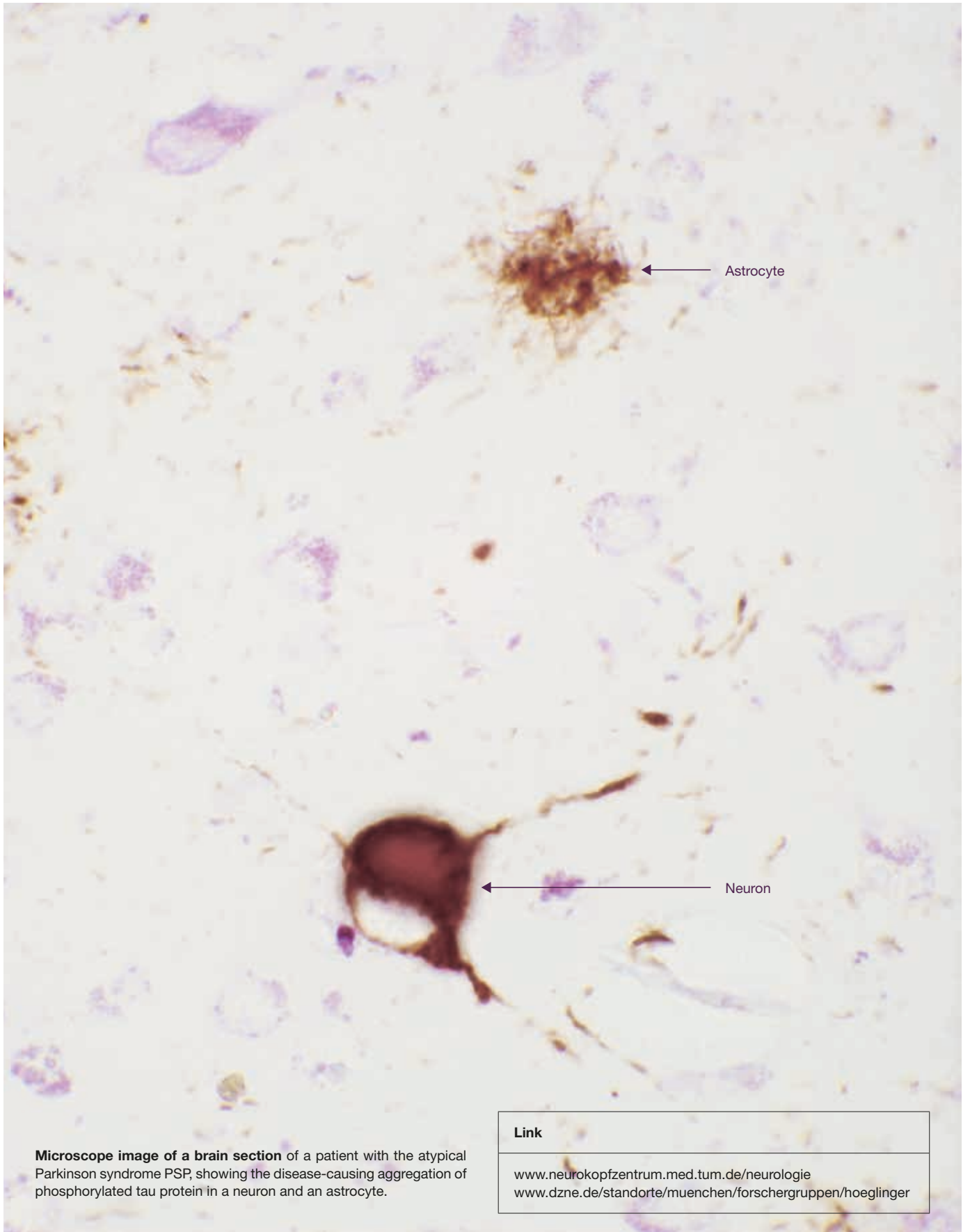
ing neurons. Research is also under way with colleagues in nuclear medicine to determine how tau deposits in the brains of living patients can be detected by positron emission tomography (PET). “We need to improve therapy and diagnostics simultaneously to yield the greatest benefit for patients,” underscores 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.

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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.

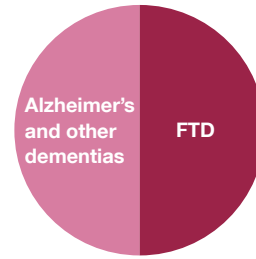
Diehl-Schmid established the first relatives group for frontotemporal degeneration in Germany back in 2002. More recently, she collaborated with a European research group to develop Internet-based expert information for patients and their relatives and carers (RHAPSODY). The researcher also builds patient 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.



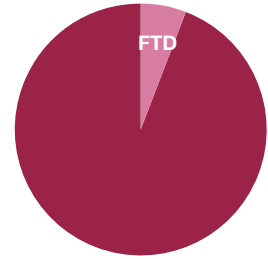
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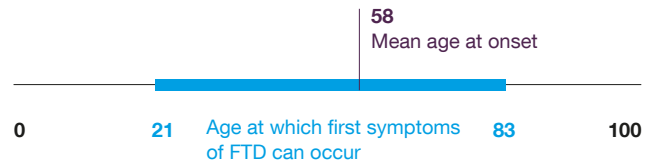
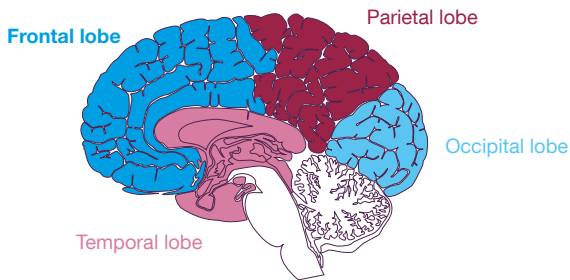
Frontotemporal dementia (FTD)



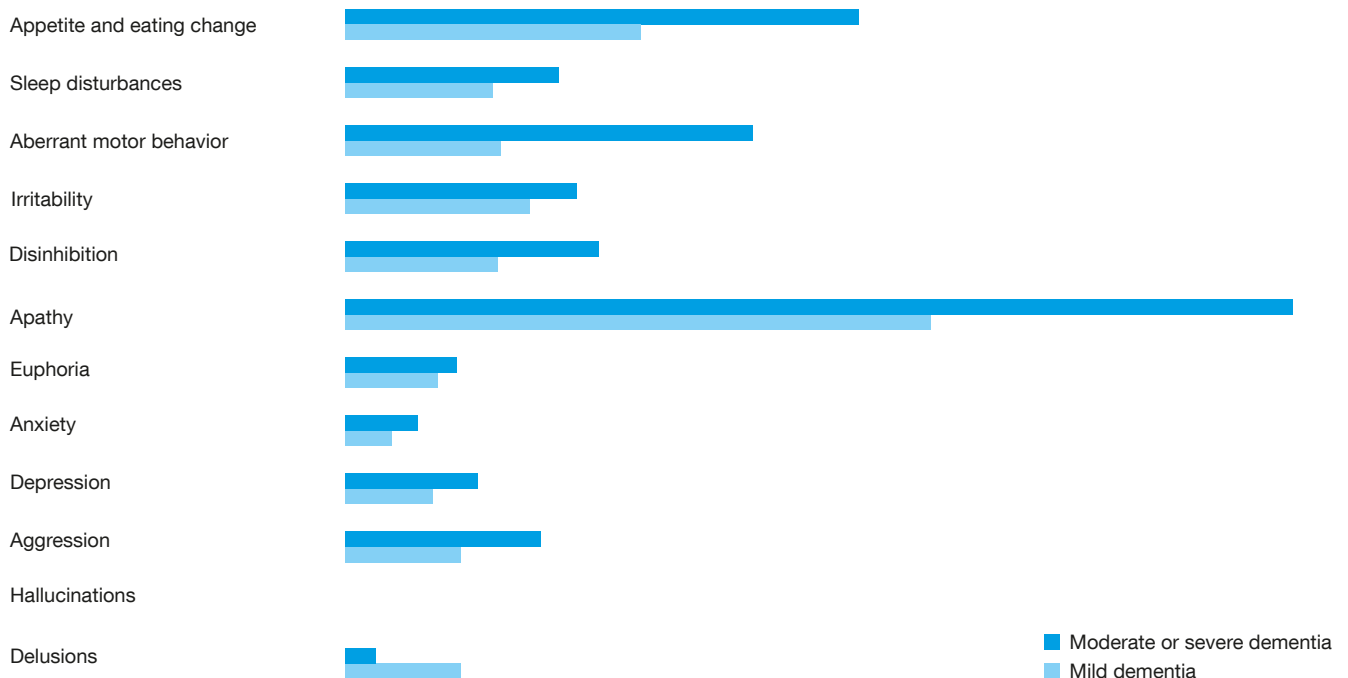
... accounts for half of the dementia cases of patients younger than 65 years

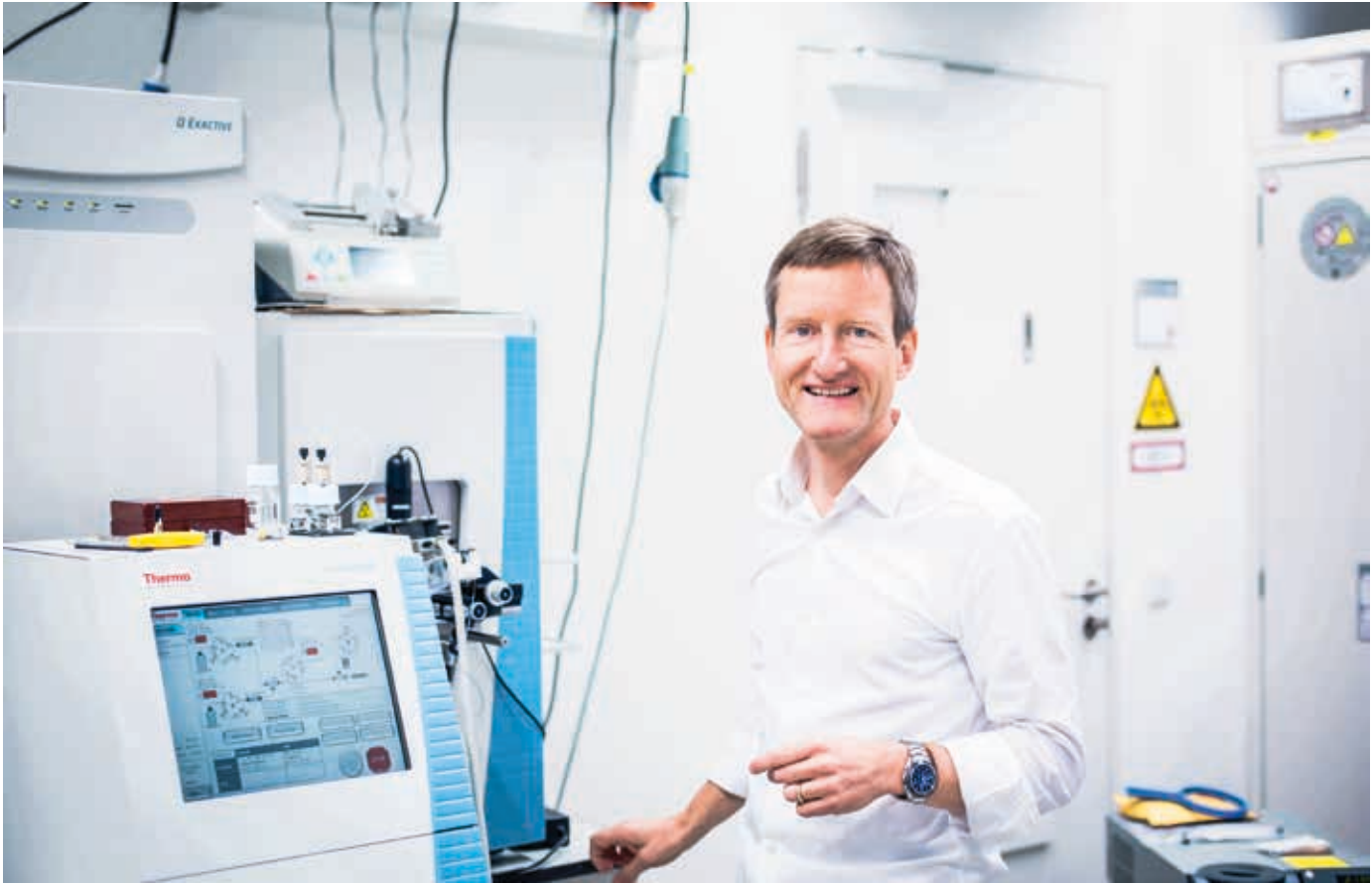


... accounts for less than 10% of all dementia cases



Extent of behavioral disturbances in different disease stages of FTD:



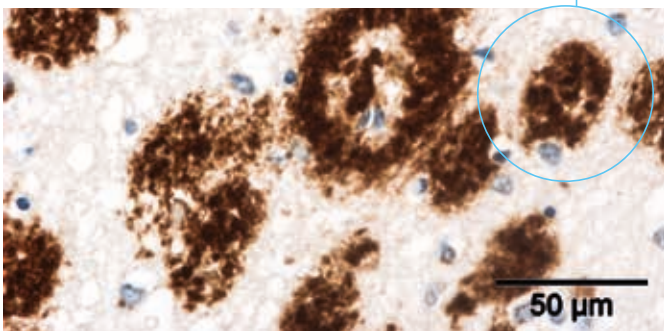
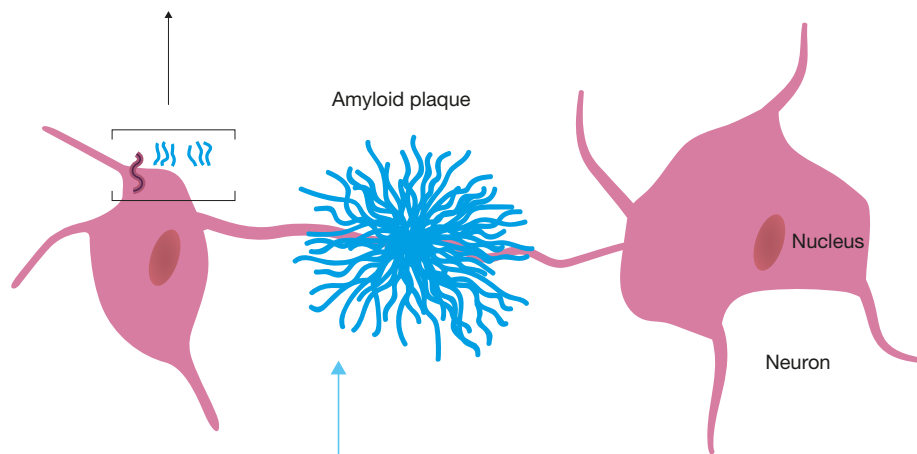
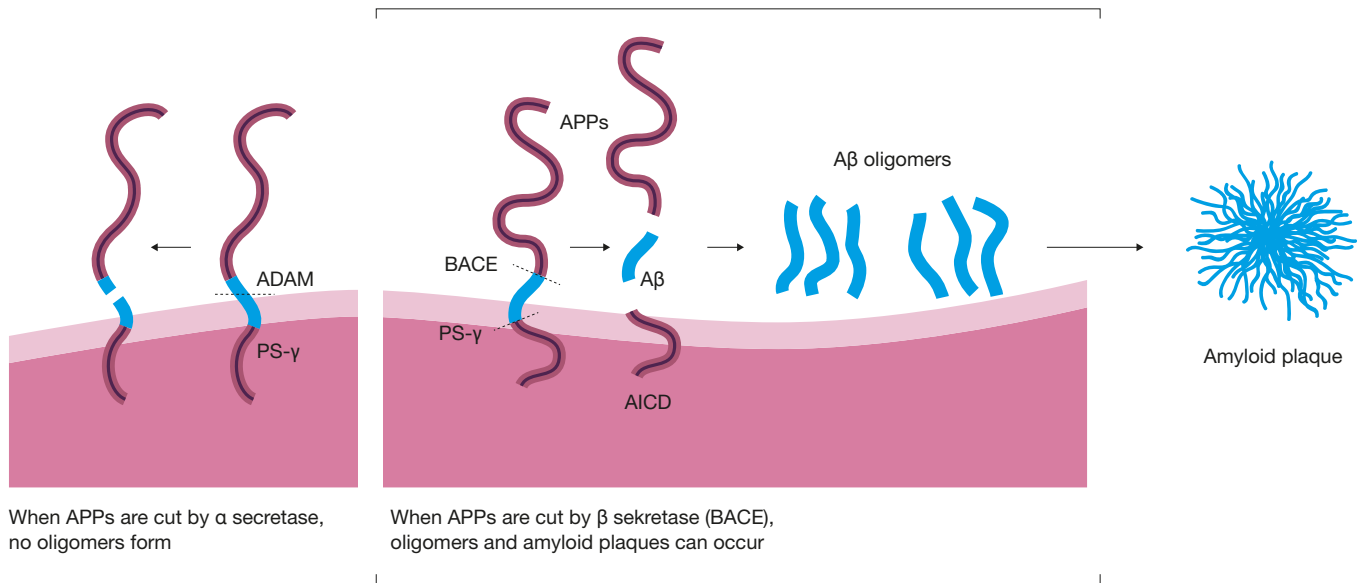


Alzheimer's: putting a stop to memory loss

“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

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