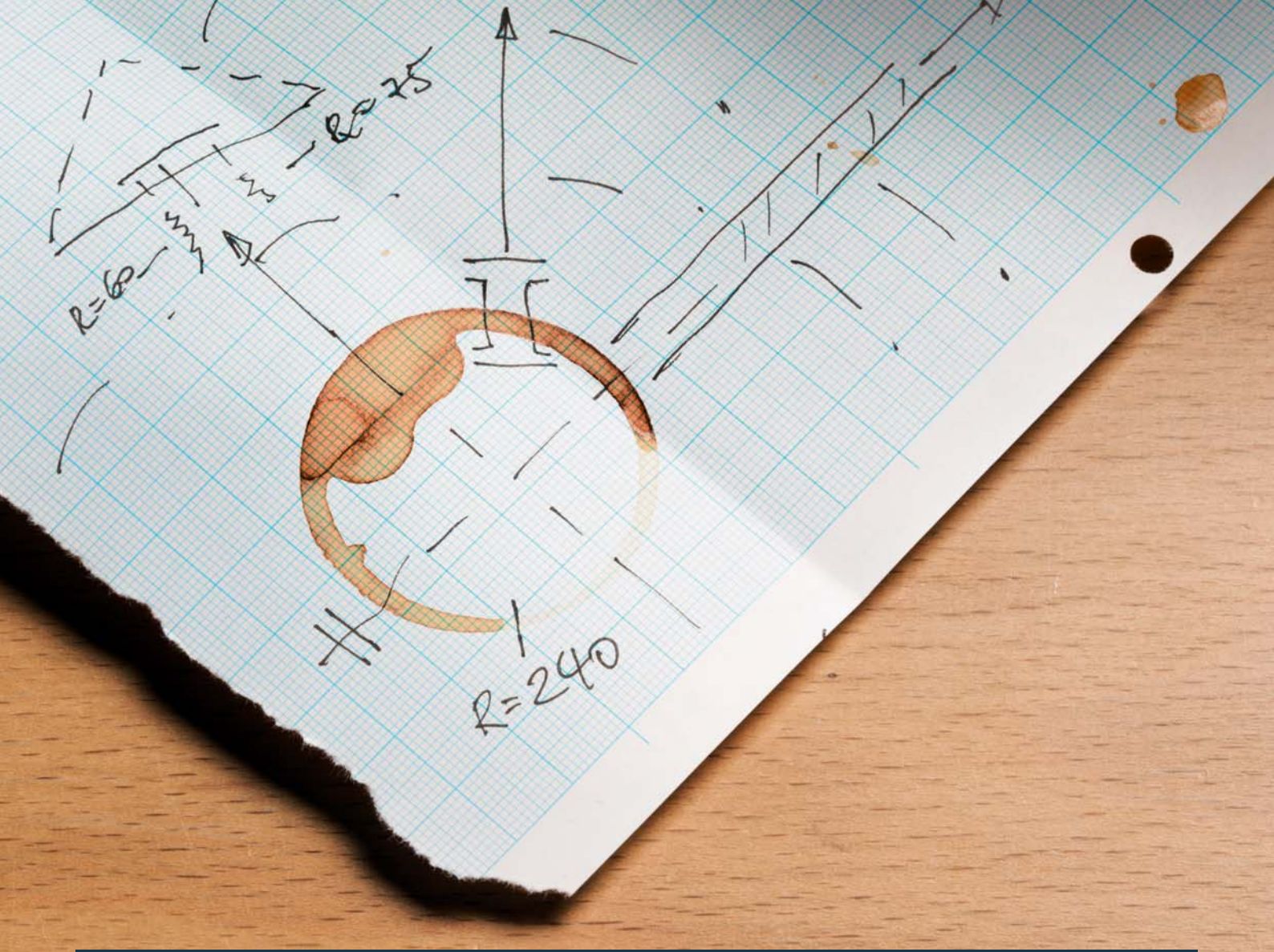
Faszination **Forschung**

TUM Research Highlights
Technische Universität München's Science Magazine
December 2015 | Edition 17

People
Behind Europe's Top Research

ISSN 18653022
9 771865 302004
Nominal charge
EUR **9.00**



Kann man mit ein paar Litern Kaffee Millionen Liter Sprit sparen? MAN kann.

Seit Rudolf Diesel 1897 bei MAN den ersten Dieselmotor entwickelt hat, arbeiten unsere Ingenieure ständig daran, ihn immer noch effizienter zu machen. Ihr Antrieb dabei sind Neugier, Forscherdrang – und jede Menge Kaffee. Das Ergebnis sind unzählige schlaflose Nächte, tonnenweise Skizzen – und geniale Innovationen, die den Dieselmotor immer sauberer und immer sparsamer machen. Wie wir mit Innovationen nicht nur Trucks und Busse, sondern auch Schiffe und sogar ganze Kraftwerke nachhaltig effizient machen, erfahren Sie auf **www.man.eu/mankann**

Engineering the Future – since 1758.

MAN

Dear TUM friends and associates,

Successful scientists share not only a passion for discovery, but also a willingness to compete at the highest level. The researchers we introduce in this edition have overcome stiff competition to convince the European Research Council (ERC) of the merits of their project proposals. The prestigious grants in question are awarded according to a single criterion – scientific excellence. These ERC grants also function as a seal of quality for the associated scientific institutions, since recipients can choose to carry out their research at any location in Europe. So we are extremely proud that TUM is one of the most attractive universities for ERC grant holders.

In Germany as a whole, TUM is the university with the second-highest number of ERC grants. Since the European Research Council was founded in 2007, 42 of our scientists have received funding across 45 projects. 2014 was a particularly strong year in this regard, with TUM gaining the most ERC Consolidator Grants of any German research organization and ranking fourth in Europe.

The international success of our scientists against this fierce competition – the success rate of ERC applications lies at around 11 percent – is also confirmation of our stringent recruitment policy. Many scientists supported by the ERC have also gained numerous other awards in their fields. And almost all ERC recipients at TUM have been granted this funding during their time with us and chosen to remain here. We view this as a great distinction, since these grants are transferable, allowing researchers to move freely between European locations. Scientists here receive support and personal advice from our TUM ForTe office to help with their applications for funding at both a national and EU level. Equally, gaining an ERC grant means scientists are eligible for our TUM Faculty Tenure Track program – a career planning and development path for young scientists that is currently unparalleled in Germany. This program gives leading researchers an additional incentive to bring their ERC grant to TUM or to stay on with us.

The European Research Council promotes basic research – based on the conviction that the resulting insights pave the way for new, application-oriented avenues of research. ERC projects often entail bold and challenging questions with open outcomes, which could nevertheless result in breakthrough findings at some stage. So it is all the more important that ERC grants fund researchers for up to five years, giving them the independence to focus exclusively on their chosen path. The wide reach of excellence in basic research at TUM is highlighted by the distribution of ERC projects across a total of eight departments – from Medicine and Physics through Informatics and Electrical, Electronic and Computer Engineering to Chemistry, Mathematics and Mechanical Engineering, as well as Nutrition and Food Sciences, Ecology and Ecosystem Management, and Agricultural Economics. Readers of Faszination Forschung will already be familiar with many of these projects from previous issues. The seven outstanding researchers to whom this edition is dedicated and of whom we are proud reflect anew this broad spectrum of excellent research.

“We are extremely proud that TUM is one of the most attractive universities for ERC grant holders.”

Wolfgang A. Herrmann

Thomas Korn is setting out to investigate the theory that, in the autoimmune disease multiple sclerosis, autoreactive immune cells are first activated elsewhere in the body and only then migrate to the brain, where they attack the nerve fibers. If he succeeds in proving this, it would explain how ▷

Picture credit: Eckert

harmless infections can trigger MS attacks – and, crucially, pave the way for research into ways of combating these misguided T cells outside the sensitive brain.

Dieter Saur is tackling a type of cancer that remains very difficult to treat: pancreatic carcinoma. Only a small part of a pancreatic tumor consists of malignant tumor cells. The rest is made up of other cells within the body that are manipulated by the tumor to aid its growth. Saur is seeking therapeutic approaches that both combat the tumor cells and remove the body's cells from the tumor's control.

Thomas Misgeld is researching the mechanisms behind the reduction of nerve fibers in the brain. At the beginning of life, this loss of axons is a completely normal process but it can lead to neurodegenerative diseases in old age. The neurologist intends to use his ERC grant for further research into the basic biological features of this process.

Shock waves and their potential for tailored generation is the particular interest of **Nikolaus Adams**. The engineer is using complex computer simulations to gain a fundamental understanding of this phenomenon with a view to possible applications, including in medicine.

Wilhelm H. Auwärter's research focuses on special molecules – metalloporphyrins – and the way they behave on an atomic scale. The physicist's insights could contribute to optimizing magnetic and optoelectronic material properties, for instance in organic solar cells or innovative catalysts.

Controlling robots in such a way that they can work safely with their human counterparts is the aim of control systems engineer **Sandra Hirche**. She is developing a human behavior model that can be embedded in a robot's control software.

How can we feed the world's population despite climate change? This is the question posed by **Pascal Falter-Braun**, who is examining protein networks in plants for properties associated with particular resistance to drought or disease. His findings could point to a strategy for breeding more robust crop varieties that could flourish in poor soil conditions and unfavorable climates by modifying these protein networks.

We hope you will enjoy reading this edition of Faszination Forschung – and that the featured highlights leave you all the more convinced that TUM is on the right track with its rigorous recruitment policy, designed to attract the very best.

Prof. Wolfgang A. Herrmann

"The wide reach of excellence in basic research at TUM is highlighted by the distribution of ERC projects across a total of eight departments." *Wolfgang A. Herrmann*

Promoting Research Pioneers

The European Research Council

The European Research Council (ERC) is a relatively new funding program for basic research in Europe. Set up in 2007 by the European Commission, the ERC supports individual scientists based on the sole criterion of scientific excellence. Its Scientific Council consists of internationally recognized researchers, with proposals evaluated for funding by independent peer review.

The ERC's concept is unique at EU level due to the absence of any additional selection criteria such as a scientist's country of origin and host institution or specific disciplinary focus. Its importance is reflected in its budget: the ERC has been allocated 13.1 billion euros under Horizon 2020, the current EU Framework Programme for Research and Innovation, amounting to 17 percent of European research spending.

Competition for ERC grants is fierce, with around 11 percent of all submitted proposals (for Starting, Consolidator and Advanced Grants) approved to date. This stiff competition and stringent quality criteria contribute to the prestige of the awards. And since researchers can take their ERC funding with them to the European location of their choice, the grants have also become an important yardstick for research quality in Europe's scientific institutions.

The ERC offers several funding schemes tailored to the typical phases of an academic career:

Starting Grants support promising researchers at the outset of an independent career. Awarded two to seven years after completion of a doctorate, they provide funding of up to 1.5 million euros for a maximum of five years.

Consolidator Grants are awarded to young scientists with seven to twelve years' experience since their doctorate who have already made their mark with promising results and are at the stage of consolidating their research team. They are endowed with up to 2 million euros over a maximum of five years.

Advanced Grants target established scientists with outstanding track records who are applying with ambitious, pioneering and unconventional research proposals. They entail funding of up to 2.5 million euros over a maximum of five years.

Available since 2011, Proof of Concept Grants provide existing ERC grant holders with up to 150,000 euros to explore the potential for marketable innovations developed from their research findings.

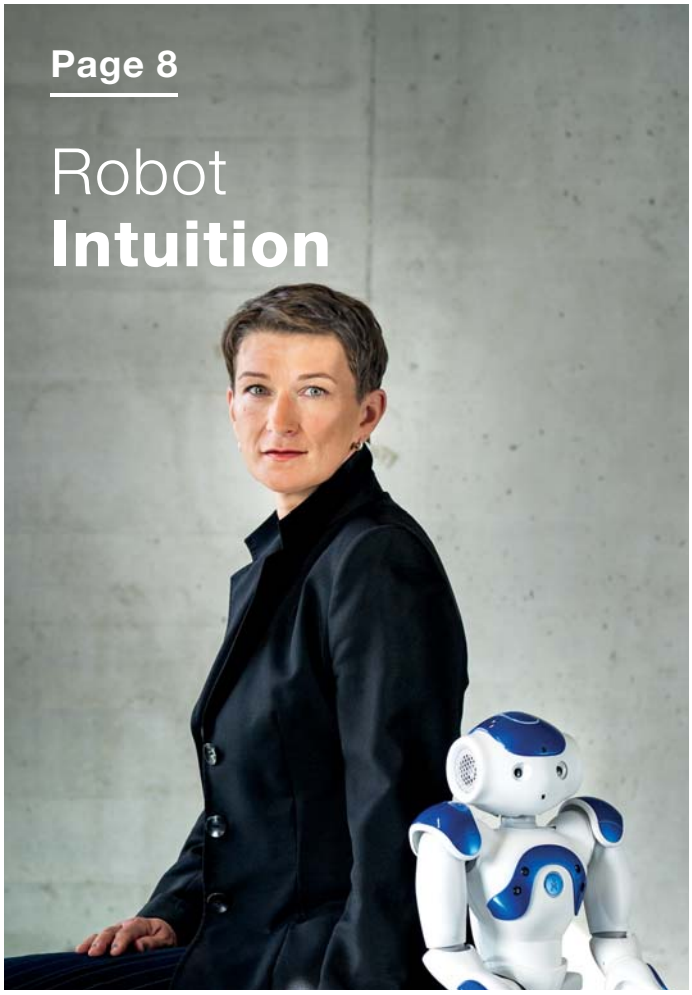
Since 2012, small teams of scientists can also apply for Synergy Grants, providing funding of up to 15 million euros over a maximum of six years.

Location Analytics – improved performance for your processes.

The multimodal transport of freight by road, rail, sea and air requires efficient management of the infrastructure and your processes. Esri Location Analytics makes you reduce volatility in the system and turn your logistics from a cost factor into a competitive advantage. With Location Analytics, you are able to record your traffic flows and analyse them in a geographical context. You recognise and exploit hidden assets and depict your geographically prepared logistics processes directly in your business systems. For the benefit of your operating efficiency and delivery performance and to the delight of your customers.

esri Deutschland

Esri Deutschland GmbH, Ringstr. 7, 85402 Kranzberg, phone +49 89 207 005 1200, info@esri.de, esri.de
A company of Esri Deutschland Group



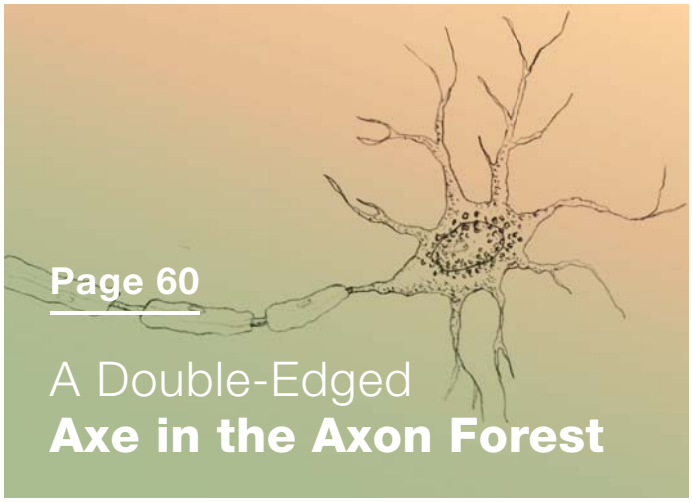


Table **of Contents**

8 **Robot Intuition**
Sandra Hirche is researching new control mechanisms that allow robots to work safely and intuitively with humans.

16 **Multiple Sclerosis:**
How Immune Cells Attack the Brain
Thomas Korn is tracking down how autoreactive immune cells access the brain, where they command killer cells to destroy the protective sheaths around nerve fibers.

26 **Thought for Food**
Pascal Falter-Braun is searching for ways to feed a growing world population in times of climate change. He investigates protein networks in plant cells in order to uncover how some plants can tolerate drought stress better than others.

36 **Pinning Molecules Down**
Wilhelm H. Auwärter has found a way to attach single molecules to tailored surfaces, which allows him to observe their behavior with a scanning tunneling microscope.

48 **Pancreatic Cancer:**
New Approaches to Neutralize a Deadly Threat
A pancreatic carcinoma comprises not only of tumor cells, but mostly of other body cells, which it manipulates. Dieter Saur is testing a new, two-fold strategy to act on both tumor and manipulated cells.

58 **New State-of-the-Art Compact X-Ray Source**
TUM installs the world's first mini particle accelerator for high-brilliance X-rays, which offer much better image quality.

Page 36

Pinning **Molecules Down**

Page 16

How Immune Cells **Attack the Brain**

"Without funding from the ERC, I would not have been able to carry out this research."

Thomas Korn

60 **A Double-Edged Axe in the Axon Forest**
Thomas Misgeld investigates the processes behind axon loss, a phenomenon that is a natural process at a young age. If it resumes in old age, however, it could contribute to diseases such as Alzheimer's disease or multiple sclerosis.

74 **Spotlight on Shock Waves**
Nikolaus Adams uses numerical simulations to investigate shock waves and their possible technical applications, for instance in biomedicine or nanotechnology.

In every Issue

3 **Editorial**

73 **Authors**

73 **Imprint**

82 **Point of View:** *Prof. Jean-Pierre Bourguignon*
President of the European Research Council
Secure Funding for Frontier Research

Robot Intuition

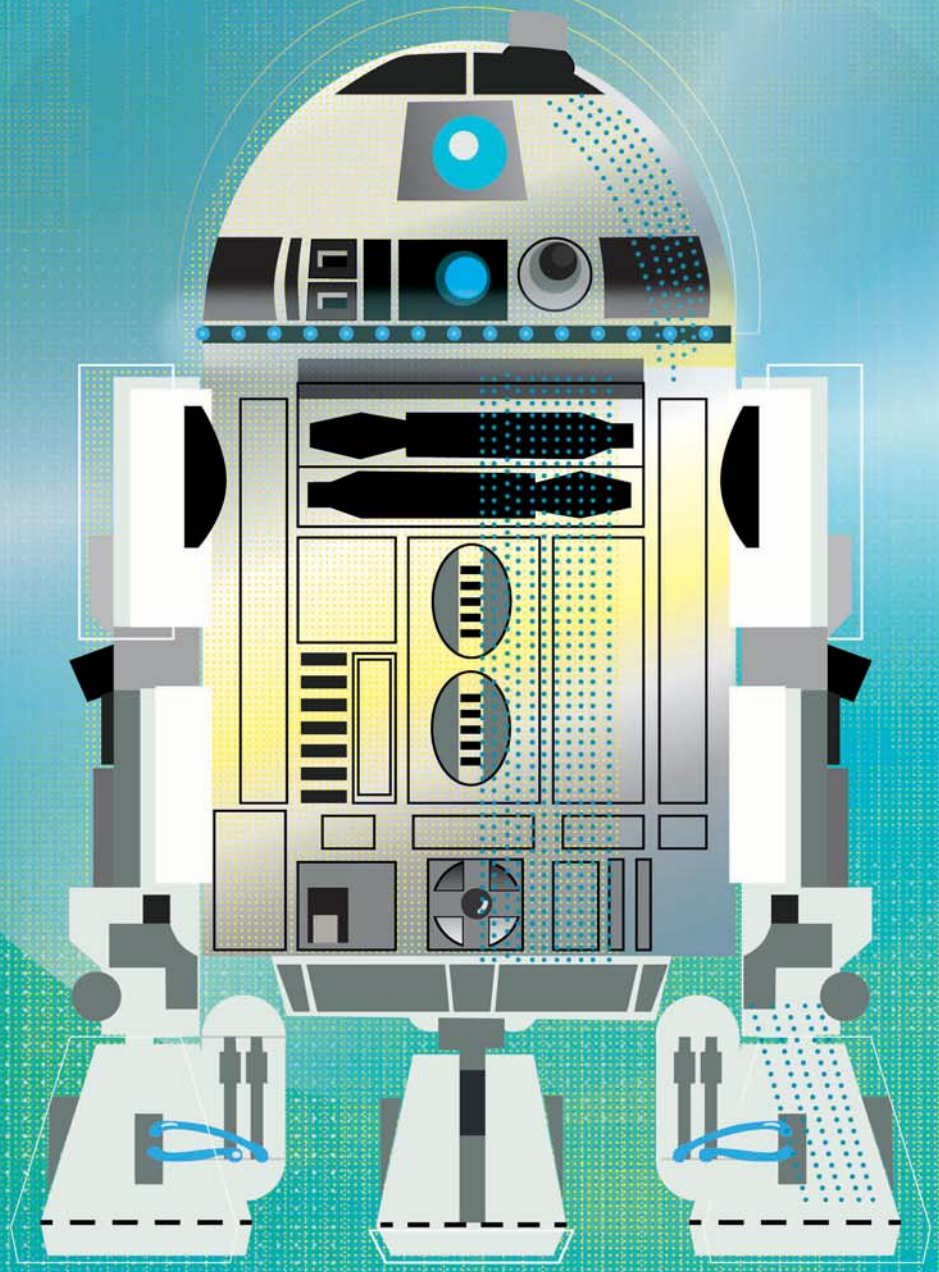
To ensure that robots can work with humans safely and intuitively in the future, control systems engineer Sandra Hirche and her team are researching new control mechanisms based on mathematical models of human behavior. Their work should enable a robot to accurately predict the movements of its human counterpart and adjust its own reactions accordingly. The aim is to have robots learn from their own experience and continuously improve their own control functionality. Prof. Hirche's project has been funded by the European Research Council (ERC) since 2014.

Evdoxía Tsakiridou

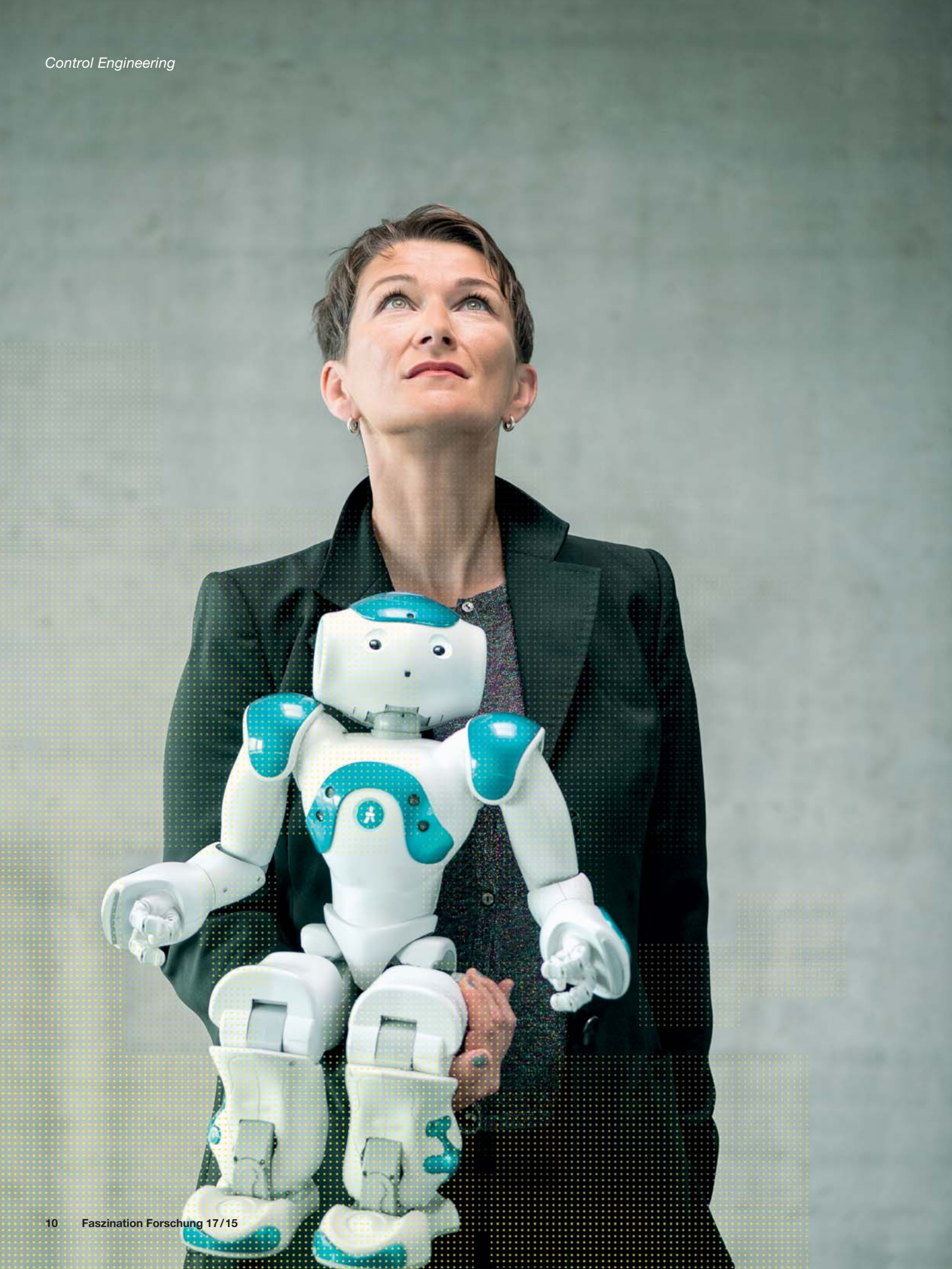
Roboter mit Intuition

Ohne Regelungstechnik wären technische Systeme wie Heizungen, Autos, Flugzeuge oder Fabrikanlagen nutzlos. Erst mit einem Regelungsvorgang lassen sich gezielt physikalische, chemische oder andere abstrakte Größen beeinflussen. „Wenn Sie mich fragen, wo sitzt das, was ihr baut? Die Regelungstechnik sitzt in der Software", sagt Sandra Hirche. Die 41-jährige leitet den TUM Lehrstuhl für Informationstechnische Regelung und erhält seit 2014 vom Europäischen Forschungsrat (ERC) eine Förderung für das Projekt „Control based on Human Models" (CON-HUMO): „Wir möchten intelligente Steuerungsmechanismen für assistierende Roboter entwickeln, die auf den Menschen adaptiv reagieren und intuitiv mit ihm zusammenarbeiten."
Jedem Regelungsentwurf liegt ein mathematisches Modell zugrunde, das reale Vorgänge abstrakt beschreibt. In strukturierten Umgebungen, wie Produktionsanlagen mit bekannten Rahmenbedingungen, ist die Steuerung kein Problem, denn es gibt wenig Unvorhergesehenes, das die Experten beim Regelungsentwurf vorab beachten müssen. Wie sieht es aber aus, wenn ein Roboter mit einem Menschen zusammenarbeitet und sich ihm intuitiv anpassen muss? „Die Schwierigkeit liegt im komplexen menschlichen Verhalten. Deshalb müssen wir antizipierende Steuerungen kreieren, sodass der Roboter vorhersehen kann, wie sich sein menschlicher Partner in den nächsten Sekunden bewegen möchte und geeignet darauf reagieren kann", erläutert Hirche.

Dazu will die Regelungstechnikerin auf Methoden des sogenannten maschinellen Lernens zurückgreifen. Dieses Verfahren stammt aus der Informatik und erlaubt die automatisierte Abbildung des Menschen in statistische Modelle, die auf der Wahrscheinlichkeitstheorie beruhen. Der Roboter soll, so die Idee, ein strukturelles Grundmodell des Menschen erhalten und aus eigenen Beobachtungen lernen und inkrementell sein mathematisches Modell immer weiter verbessern. Basierend auf solchen Modellen sollen seine Verhaltensregeln abgeleitet werden. Die lernende Steuerung zu entwickeln ist für Hirche nur ein Teil des Projekts. „Wir wollen auch explizit die Unsicherheit über die Prädiktion in der Steuerung mit abbilden. Letztendlich geht es darum, die Sicherheit von Vorhersagen zu bewerten und dem Roboter die angemessenen Entscheidungsfähigkeiten bereitzustellen." □



Picture credit: edlundsepp



Prof. Hirche, what does the ERC grant mean for you personally?

Receiving an ERC grant is like being awarded a highly prestigious prize. It will certainly help my work by enabling me to engage in high-risk research over a timeframe stretching from ten to twenty years.

What do you mean by high-risk research?

By that, I mean heading into uncharted territory to explore areas that are going to be important for society in the future.

What are your core areas of research?

We are interested in developing intelligent controls for robots that assist humans. There are many areas of application here, ranging from age-appropriate production environments to smart assistive robots and mobility aids to robot-based rehabilitation training. This also includes robots in the construction and logistics sectors, where heavy loads have to be carried.

How did you get interested in this area of research?

I came across the subject of haptic human-robot interaction, in particular telerobotics, during my dissertation. I was especially fascinated by the combination of humans and machines and how this interplay can be expressed in mathematical models. This is relevant in every situation where humans come into contact with robots, for example on a production line or through a robotic prosthetic limb. ▷

Prof. Sandra Hirche

Changing the world in pioneering spirit

For Sandra Hirche, research means understanding things that no one has understood before. In her own words, she loves the pioneering aspect of her work and the lifelong learning opportunity created by the constant evolution of her research topic. Growing up in Berlin, she started studying physics at the Humboldt University but later switched to engineering. Physics is primarily about observing, creating models and trying to explain the world. “But I also wanted to change the world. In engineering, you actually create something that can be of use to people,” explains the 41-year-old engineer. During her studies, Sandra Hirche completed a nine-month work placement at Boeing in Seattle (USA). At the end of her time in the States, she realized that although it was a “fantastic experience”, her future did not lie in industrial research for military applications.

She preferred the academic world. After completing her Ph.D. in 2005, she went to the Tokyo Institute of Technology. The control engineer with a passion for travel relished the cultural challenges of living in a country like Japan and the opportunity to expand her knowledge in the field of robotics. During this time, she was given a lot of freedom to conduct her own research and also had the opportunity to discuss actual technical problems with interesting researchers. On her return, she was appointed Associate Professor at TUM in 2008. She has been Chair of Information-Oriented Control in TUM’s Department of Electrical and Computer Engineering since 2013.

Link
www.ei.tum.de

Picture credit: Eckert

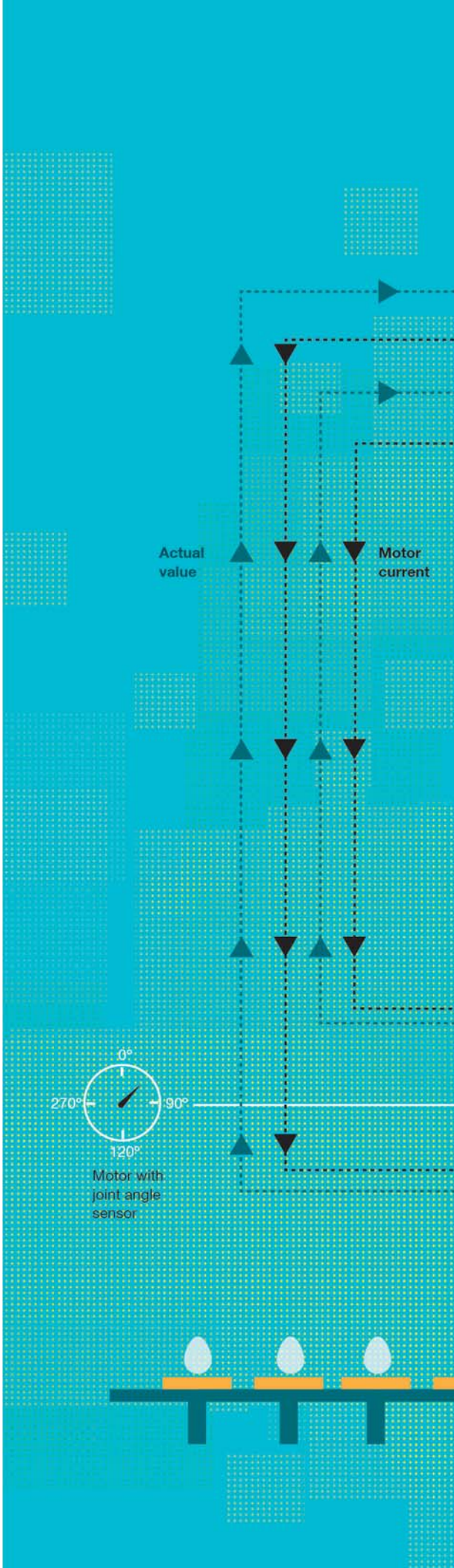
What is the main focus of your ERC grant project?

The aim of our project “Control based on Human Models” (CON-HUMO) is to develop intelligent control mechanisms for collaborative robots that respond adaptively to humans and interact with them intuitively. The difficulty here lies in the complex nature of human behavior. We have to create anticipatory controls so that the robots can predict how a human is going to behave and react accordingly.

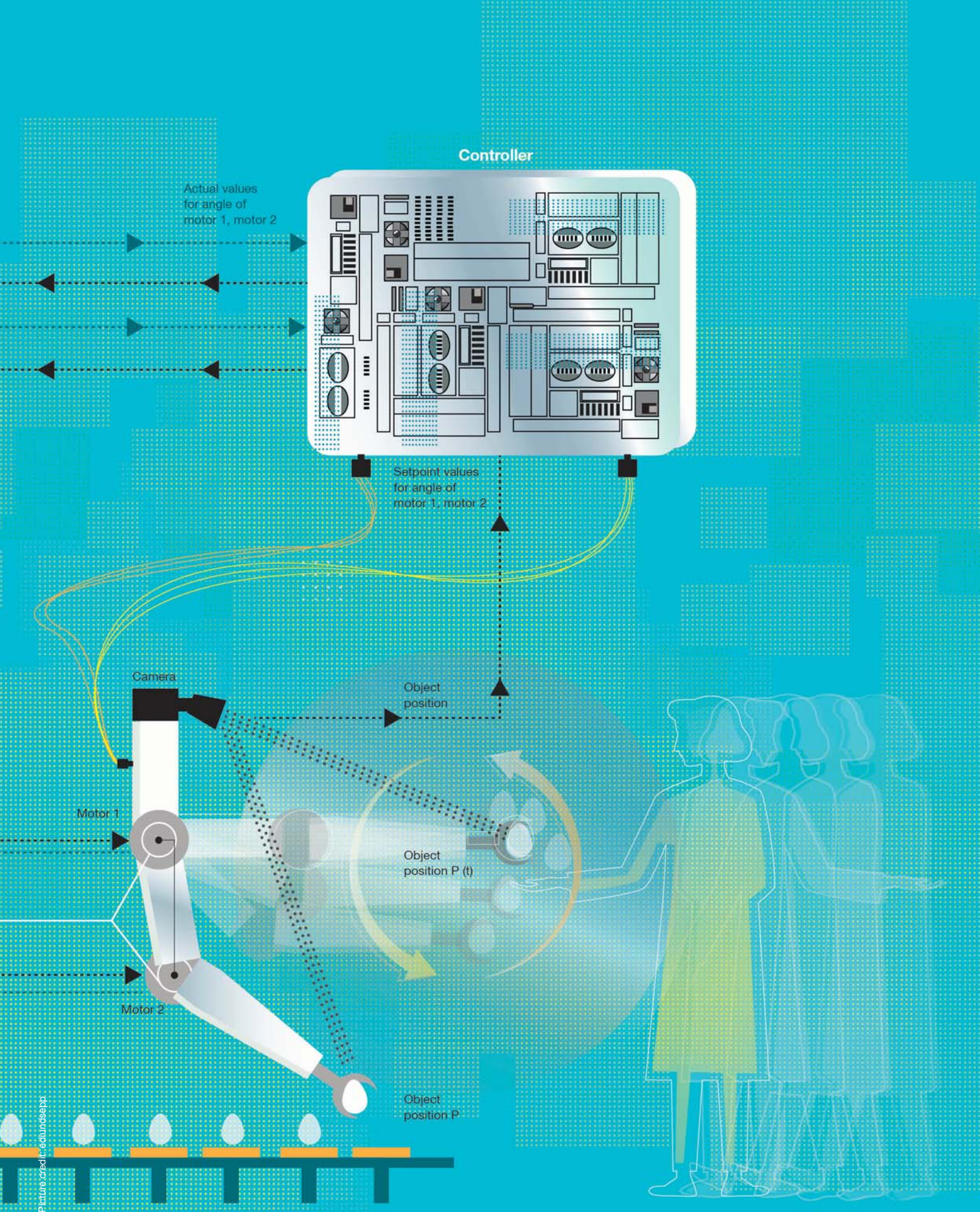
How is this different to conventional control engineering?

In conventional control engineering, for example in the case of a factory robot that does not interact directly with humans, we have a physical process: The robot lifts an object from point A to point B. The model of the robot dynamics can be described with mathematical equations, including how the joints and links are connected, how the mass is distributed and what frictional forces apply. This model forms the basis of the control blueprint, defining the motor current required to move the robot arm from A to B. For this to work, we use sensors located for example in the robot’s joints to ensure that the robot can respond to changes in its environment. Mathematical models are key to developing these kinds of controls. Now, we want to do the same but in the context of humans. In other words, we want to map human behavior in mathematical models. That is also what makes this project so challenging. ▷

“In engineering, you actually create something that is useful to people.” *Sandra Hirche*



In conventional control engineering, a robot would take an object from a defined location P. Algorithms in the robot controls convert this location into angular values for the electromotors inside the robot arm’s joints. The engines are driven until the actual values of these angles are equal to the setpoint values given by the object location. If a human hands over an object for the robot to pick up, the object location is not as exactly defined. The robot has to predict how the human will move and where this handover point will be.



Picture credit: edlundsepp

"We have to be able to guarantee that a robot can interact safely with people. But we also have to guarantee that it can act intuitively with humans – and this is something that we still don't know how to formalize." *Sandra Hirche*

Picture credit: Eckert

Where do you see these challenges?

Computer science provides machine learning methods that can be used to map human behavior in statistical models based on probability theory. This happens automatically based on observations of humans. In control engineering, however, we don't have any suitable methods that work with these kinds of data-driven, statistical models and which we can use to develop corresponding controls offering the necessary guarantees.

What kind of guarantees do you mean?

We want to guarantee that a robot will not make any unexpected movements, especially when it is in contact with a human. We have to be able to guarantee that a robot can interact safely with people. But we also have to guarantee that it can act intuitively with humans – and this is something that we still don't know how to formalize. Not only do robots need to act safely, their movements also have to be as natural and understandable for their human counterpart as possible. We have to prove that the robots will act in the correct way. This is the core of our project.

In other words, you need a design for an intelligent human-machine infrastructure so that both parties can interact without the robot harming the human or unintentionally destroying its environment?

Exactly. To ensure this kind of safety, we need to build suitable control mechanisms. So if you wanted to see the actual physical results of what we are building you would have to look inside the software, where the control technology is embedded. We do have a large variety of robots here at the Chair, but we develop the controls behind them, not necessarily the mechanics. We need to develop predictive models and implement these in the robot's software. The robot registers the movements a person makes and the forces they exert, for example via cameras and force sensors. Based on this information it can then use these predictive models to compute the requisite motor currents.

Could one say that you are looking to program a robot with everything that humans have learned to do intuitively based on years of experience?

Yes, you could say so. We have various options for doing this. Psychology offers models that describe simple human movements. However, we also want to predict more complex movement sequences. Because there is a wide spectrum of human behavior, we would ideally like robots to adapt to the actual person they are working with. In other words, the robot would be given a basic structural model. Through its own observations and learning, it would then continually improve the model and with it the predictions on this basic framework. In order to achieve this, we are collaborating with research groups specialized in the field of machine learning. Our part is to develop the controls that can work with these statistical, continuously improving models to compute the appropriate robot behavior.

Is it at all possible to predict complex human behavior when a robot is in a complex environment with constantly changing parameters?

Ultimately, this is what we want to achieve. But we start in a structured environment, where nothing unexpected happens. There are predefined patterns, for example, for transporting an object from A to B. In such a well-defined factory environment, the variance in movement is comparatively small. But this all changes in unstructured environments, especially when we start planning over longer timelines and also incorporate more complex human actions. Under these conditions, the number of possibilities increases exponentially. In our research we are starting with highly structured interaction. For example, if I tell the robot "give me a tool", it knows where we are and it also knows that there is a limited number of tools. The robot takes a tool and only has to predict how the human will move and where the handover point will be. Now, however, we are trying to move further away from this highly structured interaction to increasingly unstructured environments. We still have a long way to go but that is exactly what makes our research so fascinating.

What methods will you be applying?

We are researching analysis and design methods for controls based on data-driven statistical models. For linear, time-invariant dynamical systems, we have an established toolbox of analysis and control synthesis methods. At this point, I should say that in control engineering, what we call a system is actually an abstract description, in other words a mathematical model of a real-life process. This means that every model is an approximation of reality. What we want to do now is to embed human behavior in statistical models. This is why, for instance, we are using a mathematical class of models known as Gaussian processes (GPs) to capture human behavior. What has been missing so far are suitable systematic control design methods that deliver a control mechanism, based on GP models. As an example, the control mechanism will enable the robot to jointly move an object together with the human, with the robot following the movement intention of the human.

Can you briefly explain what a Gaussian process is?

A Gaussian process is a stochastic process that describes the Gaussian distributions of a continuum of random variables or functions. It can be used to mathematically describe random processes in time series. In machine learning, Gaussian processes (GPs) are used to provide a mechanism for inter- and extrapolation between input and output data. Starting with training data, the process uses each new input to predict the most probable output. GPs have the advantage of being able to approximate non-linear behavior while at the same time making a prediction on the degree of uncertainty. This makes them a very elegant solution. Using GPs, we can not only predict how a system will move in the next few seconds, but also say how certain we are about our prediction. It is this aspect that makes the methods we are developing so special. We want to specifically incorporate a degree of uncertainty about a prediction into the control – after all I can never be 100 percent certain about how a person will behave in the next few seconds. At the end of the day, we want to evaluate the certainty of predictions and give the robot a suitable level of decision-making power.

Evdoxía Tsakiridou

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

Multiple Sclerosis: **How Immune Cells Attack the Brain**

This is an article about immune cells that issue the wrong instructions. Instead of calling for assistance, they order destruction. It is also an article about the researcher who wants to track down these misguided cells. If he succeeds, we will be a step closer to finding better treatment options for multiple sclerosis and other autoimmune diseases.

Most of the time, multiple sclerosis is invisible. And when it does suddenly reveal itself, it remains disguised behind a variety of masks. No two patients present exactly the same symptoms. Some suffer from vision problems. Others lose their sense of balance, develop a feeling of paralysis or numbness in their arms and legs, or constantly feel tired and weak. The symptoms can often disappear by themselves, only to return with full force months later. Living with multiple sclerosis is unpredictable. And the cause of all this is nothing other than the patient's own immune system.

Many medical scientists believe that it can start with a harmless infection. A head cold, perhaps. Nothing too tricky for the immune system to handle. In the lymph node, a type of immune cell called a T cell identifies the intruder. Using its antenna-like receptor, it binds to an insidious virus protein. The T cell is activated.

Some immune cells, which should be protecting us against harmful viruses or bacteria, suddenly attack the body's own tissue. Instead of coming to the rescue, they go into destructive mode. They do this because they do not just recognize virus antigens, but also cross-react with the body's own molecules. The cells are autoreactive. Thomas Korn, Heisenberg Professor of Experimental Neuroimmunology at TUM's Department of Neurology, wants to track down these misguided or autoreactive cells as part of his EXODUS project. He aims to find out where they are activated, why they send incorrect signals, and how they can be stopped. Armed with this information, medical scientists will be able to develop more effective therapies for multiple sclerosis (MS) and other autoimmune diseases. Worldwide, around 2.3 million people are living with multiple sclerosis. The incidence of the disease is two to three times higher in women than in men. Geography also determines the likelihood of contracting MS: relatively few people suffer from the disease in equatorial regions, but the rate increases the further north or south one travels. No one knows the exact reason for this.

The activated T cells multiply at a rapid rate. They also release signaling substances that attract macrophages – the virus-destroying cells. While traveling through the bloodstream, the activated T cells also pass by the brain. And something that could not happen before suddenly becomes possible. ▷

Graphics: ediundsepp

Claudia Steinert

Multiple Sklerose: Wie Immunzellen das Gehirn angreifen

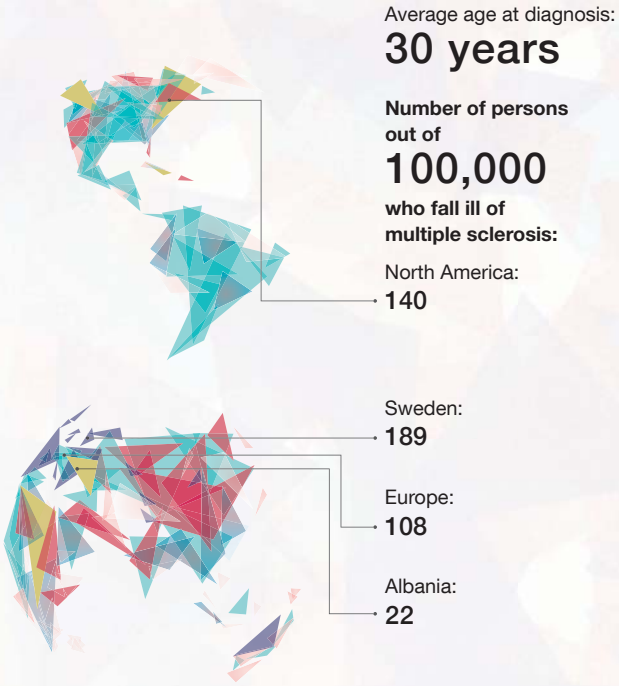
Weltweit sind etwa 2,3 Millionen Menschen an Multipler Sklerose (MS) erkrankt. Die Krankheit tritt vor allem bei jungen Leuten auf und betrifft das Zentralnervensystem. „Dabei ist das Gehirn eigentlich gesund, das Immunsystem ist krank“, erklärt Thomas Korn, Heisenberg-Professor für experimentelle Neuroimmunologie an der Neurologischen Klinik der TUM.

Bei MS erkennen sogenannte autoreaktive Zellen des Immunsystems nicht nur körperfremde Antigene (zum Beispiel Virus-Antigene) – wie es eigentlich sein sollte – sondern auch körpereigene Moleküle. Das hat fatale Folgen. Deswegen fressen bei MS-Patienten Immunzellen im Gehirn die Myelinscheide ab, die die Nervenfasern umhüllt und schützt. Ohne Myelinscheide aber können die Nervenzellen nicht mehr so gut miteinander kommunizieren. Thomas Korn interessiert sich vor allem für eine Sorte Immunzellen: die T-Zellen. Wenn das Immunsystem eine Verteidigungsarmee ist, dann sind die T-Zellen die Generäle. Das Problem: Wenn sie einmal aktiviert sind, schnappen sie nach allem, was ihren T-Zell-Rezeptoren präsentiert wird. Bei MS ist das die Myelinscheide im Gehirn. Dorthin gelangen autoreaktive T-Zellen jedoch nur im aktivierten Zustand. Experten vermuten, dass diese Aktivierung außerhalb des Gehirns stattfindet, zum Beispiel durch einen harmlosen Schnupfenvirus. Um diese Theorie zu prüfen, will Korn in seinem Projekt EXODUS den Weg der T-Zellen nachverfolgen. Dafür hat er Fördergelder vom Europäischen Forschungsrat (ERC) erhalten. Er markiert bei Mäusen T-Zellen, die sich in peripheren Lymphknoten oder in lymphatischem Gewebe im Bereich von Schleimhautoberflächen aufhalten, wie denen des Magen-Darm-Traktes. Wochen später schaut er nach, wohin die markierten Zellen gewandert sind.

Bei Mäusen, die an einer MS-ähnlichen Krankheit leiden, hofft Korn, solche markierten Zellen auch im Gehirn zu finden. Das könnte der Beweis dafür sein, dass die aktivierten, autoreaktiven T-Zellen tatsächlich von der Peripherie ins Gehirn einwandern. Damit wäre endlich klar, dass harmlose Infektionen sozusagen als Spätfolge einen MS-Schub auslösen können. In einem späteren Schritt will Korn auch den umgekehrten Weg testen: Immunzellen im Gehirn markieren und dann ihren Weg nachverfolgen. „Wenn diese Zellen das Gehirn tatsächlich wieder verlassen, dann könnten wir sie isolieren und genauer analysieren“, erklärt Korn. Vielleicht ließen sie sich sogar so manipulieren, dass zukünftige Schübe verhindert werden können. □

Graphics: ediundsepp

Picture credit: Jooss
Graphics: edlundsepp (Source: Atlas of MS 2013, Multiple Sclerosis International Federation)



Worldwide, around 2.3 million people suffer from multiple sclerosis (MS). The disease affects twice as many women as men. The likelihood of contracting MS is highest in North America and Europe, lowest in the equatorial regions.

At this stage, scientists do have a relatively good understanding of what causes the symptoms of multiple sclerosis. The disease wages war on the patient's nervous system. But instead of targeting the nerve cells themselves, it attacks the cells that surround them. The oligodendrocytes. These cells with their tricky name have an extremely important task. They wrap themselves around the projections of the nerve cells (axons), thus insulating them. In this way, they prevent short-circuits from happening in the brain. Information in the form of electrical signals is constantly dashing between our millions of nerve cells. It shoots through the axons at speeds of up to 200 meters per second. The axon can be compared to a power cable, with the myelin sheath formed by the oligodendrocytes corresponding to the insulating rubber jacket. It is the myelin sheath that enables fast and clear communication between the nerve cells. So it is a prerequisite for every deliberate movement and mental process.

The brain is a sensitive organ and must at all costs be defended against invaders. That is why we have the blood-brain barrier. It functions somewhat like a close-mesh mosquito net. Water and nutrients can pass through, but not much else. Activated T cells have a special type of anchor protein, however, which helps them cling on to the blood-brain barrier. They do, after all, want to check whether the brain also needs to be rid of viruses.

In multiple sclerosis patients, the myelin sheath becomes inflamed. Or rather: it comes under attack. "The central nervous system itself is healthy; the problem lies in the immune system," explains Thomas Korn. The immune cells destroy the protective insulation layer and expose the nerve fibers. Electrical signals are then only conveyed slowly or not at all. The fact that this occurs simultaneously at multiple locations in the brain means that a large variety of neurological deficits will become apparent. Problems with speech, distorted vision, numbness. The symptoms are often ambiguous. What is more, they usually disappear again, even without treatment. After a few days or weeks, the myelin sheath in the brain regenerates itself. However, the oligodendrocytes do not always succeed in remyelinating all of the nerve fibers. In such cases, some symptoms linger even after the attack has passed.

In healthy people, the immune cells turn back around halfway through the blood-brain barrier. Only the T cells that are activated and autoreactive make it as far as the brain tissue. Once there, they seek out insidious virus antigens using their receptors. There is a possibility, however, that as well as virus proteins, their receptors will also surround similar-looking myelin proteins. That is a serious mistake. But the cells do not notice this. They are activated and deploy macrophages to the brain. The autoimmune reaction begins.

Everyone has autoreactive T cells to a certain extent, even though this should not be the case. Precursors of T cells are formed in the bone marrow, but T cells only mature in the thymus, an organ of our lymphatic system. A kind of quality assurance takes place there. The thymus is supposed to prevent the creation of T cells capable of attacking the body. Self-antigens are presented to every new T cell in the thymus. If the cell recognizes it and binds to it, then it has pronounced its own death sentence. It cannot leave the thymus and dies in situ. This "quality assurance" is not 100% effective, however. Some autoreactive T cells escape the thymus. When a medic is explaining the immune system to a layperson, they often use war metaphors. Good guys versus bad guys, ▷

"Without funding from the ERC, I would not have been able to carry out this research."

Thomas Korn

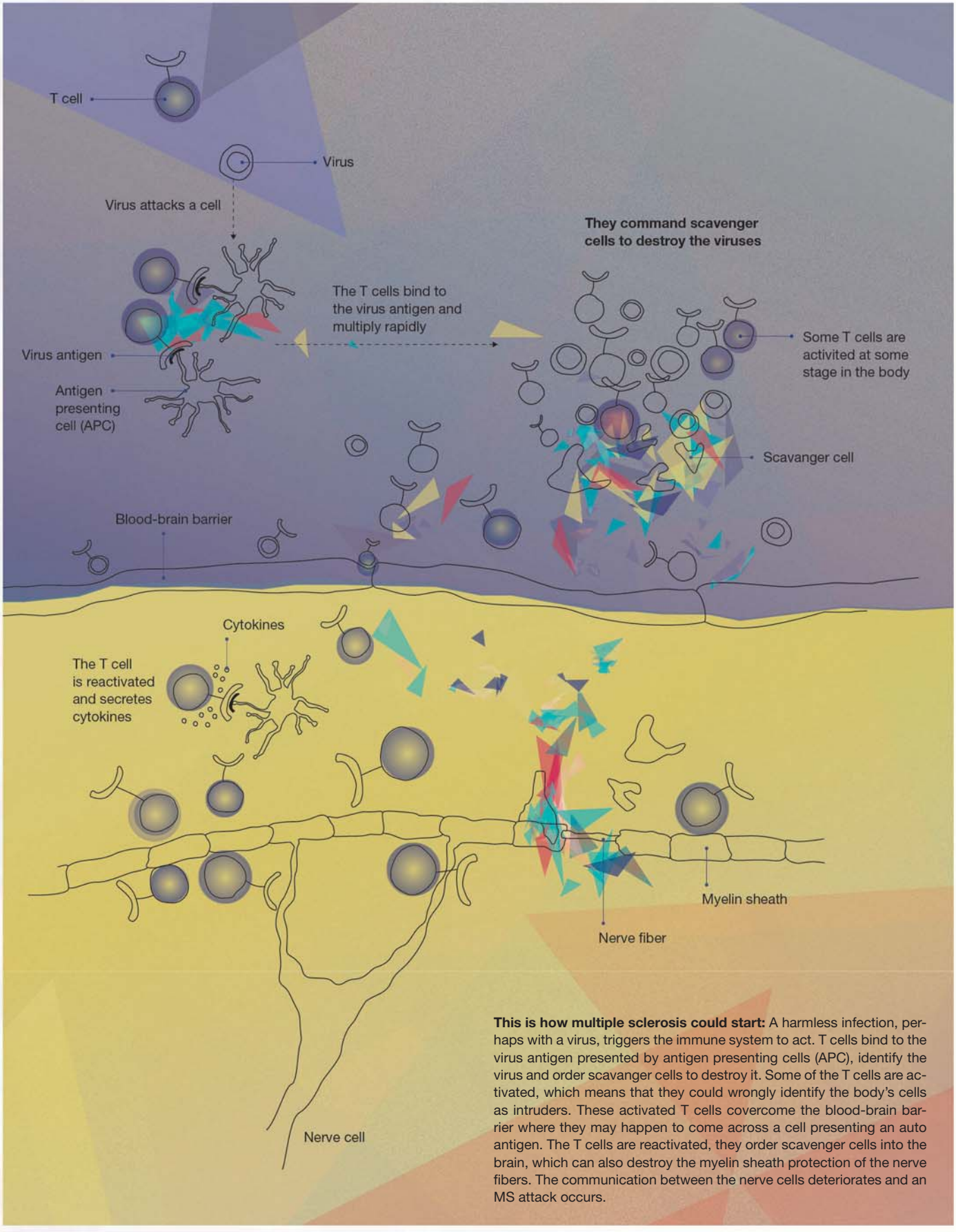
“There are many different immune cells in our immune system’s army. The T cells are like generals, directing the attack.”

Thomas Korn

Klaus Tschira Foundation donates 25 million euros for multiple sclerosis research

A new treatment and research center for multiple sclerosis will be established within the grounds of the TUM Klinikum rechts der Isar. The center will be unique in Germany with medics and scientists in areas ranging from clinical practice to basic research working under a single roof. Thomas Korn is one of currently four TUM scientists involved in the center. “The center provides us with the necessary infrastructure to efficiently drive our research forward,” he says. The project has been enabled thanks to a 25 million euro donation by the Klaus Tschira Foundation. The associated contract was signed on September 23, 2015.

Graphics: ediundsepp



This is how multiple sclerosis could start: A harmless infection, perhaps with a virus, triggers the immune system to act. T cells bind to the virus antigen presented by antigen presenting cells (APC), identify the virus and order scavanger cells to destroy it. Some of the T cells are activated, which means that they could wrongly identify the body's cells as intruders. These activated T cells covercome the blood-brain barrier where they may happen to come across a cell presenting an auto antigen. The T cells are reactivated, they order scavenger cells into the brain, which can also destroy the myelin sheath protection of the nerve fibers. The communication between the nerve cells deteriorates and an MS attack occurs.

immune cells fighting pathogens. Thomas Korn is also fond of these vivid comparisons, but he takes a slightly more detailed approach. He points out that there are at least as many different immune cells as subunits in the army. “The T cells are like generals, directing the attack,” he explains.

Macrophages migrate to the brain. They destroy the myelin sheath protecting the nerve fibers. The exposed axons start to lose their ability to conduct electrical signals. Communication between the nerve cells comes to a halt.

Korn wants to track down these generals. His objective as part of his EXODUS project is to discover the paths taken by T cells within the body and prove the theory that they are first activated at a peripheral location and only then migrate to the brain. This has only been a plausible but unproven assumption up to now. His work will be funded by the European Research Council, which is not afraid to back projects with a certain level of risk attached. “While our preliminary experiments have been promising, I still cannot rule out unforeseen problems,” admits Korn.

In order to trace the presumed path of the T cells to the brain from peripheral lymph nodes or lymphatic tissue, which are associated with mucosal surfaces like the gastrointestinal tract, Thomas Korn uses a very particular marking method. He makes genetically modified T cells glow with a red fluorescence. They will only do this, however, if they have been illuminated by blue light. The scientists push a blue light into the gastrointestinal tract of mice carrying these T cells, which suddenly glow like red lanterns.

The migration of the T cells from the gut to the brain is of particular interest because of indications that it is not just virus proteins, but also our own gut bacteria that could activate the T cells. Each individual’s microbiome, or the entire community of bacteria in the gastrointestinal tract, could therefore play a significant role in determining whether or not we are susceptible to autoimmune diseases like multiple sclerosis.

A few weeks after the light exposure, Korn intends to examine the mouse’s organs to locate the red-glowing T cells. This will make it clear that every red cell originated from the gut, or at least that the ancestral cells came from there. “In healthy mice, we will not find any red T cells in the brain – or at any rate, they will only have migrated as far as the blood-brain barrier,” explains Korn. The first step for the scientists, therefore, is to examine whether the system actually works in healthy animals. Only then will they turn to mice suffering from a disease similar to multiple sclerosis. These animals have a particularly large number of autoreactive T cells, which when activated pass into the brain and attack the myelin sheaths of nerve cells. If Korn does find glowing red T cells in the brains of these animals, he will have demonstrated that the activated T cells do indeed migrate from the periphery to the brain. This would finally prove that harmless infections can trigger an MS attack, as a delayed effect so to speak.

After a while, the activated immune cells slowly die off in the brain. Or they leave the brain. And migrate somewhere else. No one knows for sure. The only thing that is clear is that the MS attacks do come to an end at some stage. Just like that. Because the immune reaction ceases and the myelin sheath is repaired. Until the immune system is again mobilized and triggers the next attack.

A major problem when treating multiple sclerosis is that damaged brain tissue does not regenerate as easily as other organs. In the case of hepatitis, the immune response in the liver is so powerful that the response itself causes pronounced damage to the tissue. This is not a problem, however, because the liver is easily regenerated. But the brain does not have this ability. That is why all of the drugs used to treat multiple sclerosis up to now work outside the brain, and try to prevent a serious immune reaction from taking place within.

At a later stage, Korn intends to examine the opposite pathway by light-activating immune cells in the brain and tracking their progress. “If these cells do indeed exit the brain again, we will be able to isolate them and study them more closely,” confirms Korn. It might even be possible to manipulate them and prevent future attacks in MS sufferers. The first task at hand though, is to verify whether the generals do indeed behave as our theory predicts.

Claudia Steinert

Prof. Thomas Korn

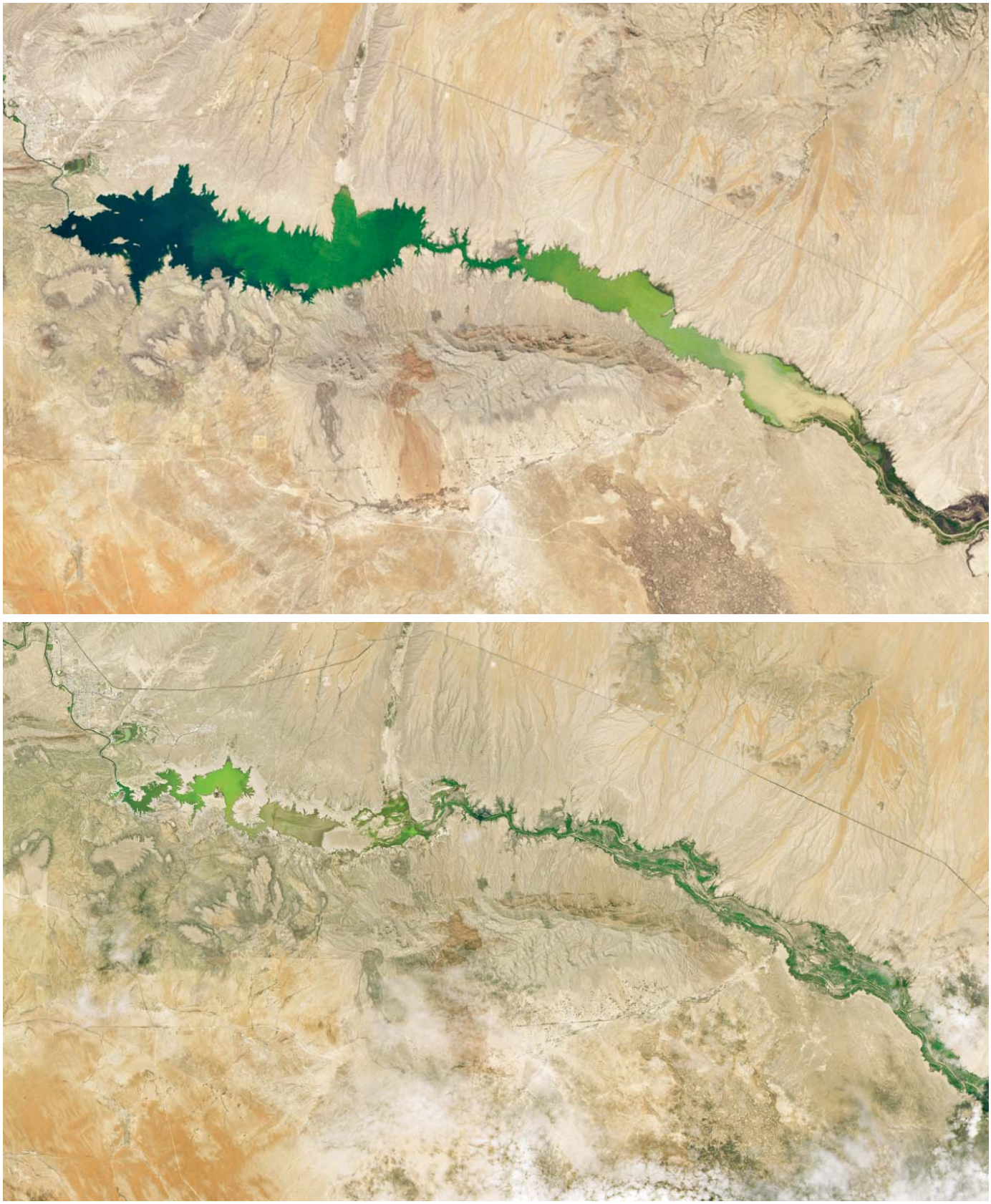
The courage to take risks

“Without funding from the ERC, I would not have been able to carry out this research,” declares Thomas Korn. So he is fortunate that the European Research Council (ERC) is not afraid to back riskier projects such as EXODUS. The majority of funding programs are risk-averse. “With other donors, there would have been no point in even applying with my idea,” Korn is convinced.

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 Würzburg, I spent six months per year caring for patients and the other six months working in the lab, which proved to be a very good balance,” recalls Korn. 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).

Picture credit: Jooss



Drought dries Elephant Butte Reservoir in New Mexico, USA. Two images taken in the summers of 1994 (top) and 2013 (bottom) show how the water level dwindled to its lowest value in forty years. Due to climate change, drought periods are projected to increase in the future.

Link
www.sysbiol.wzw.tum.de

Thought **for Food**

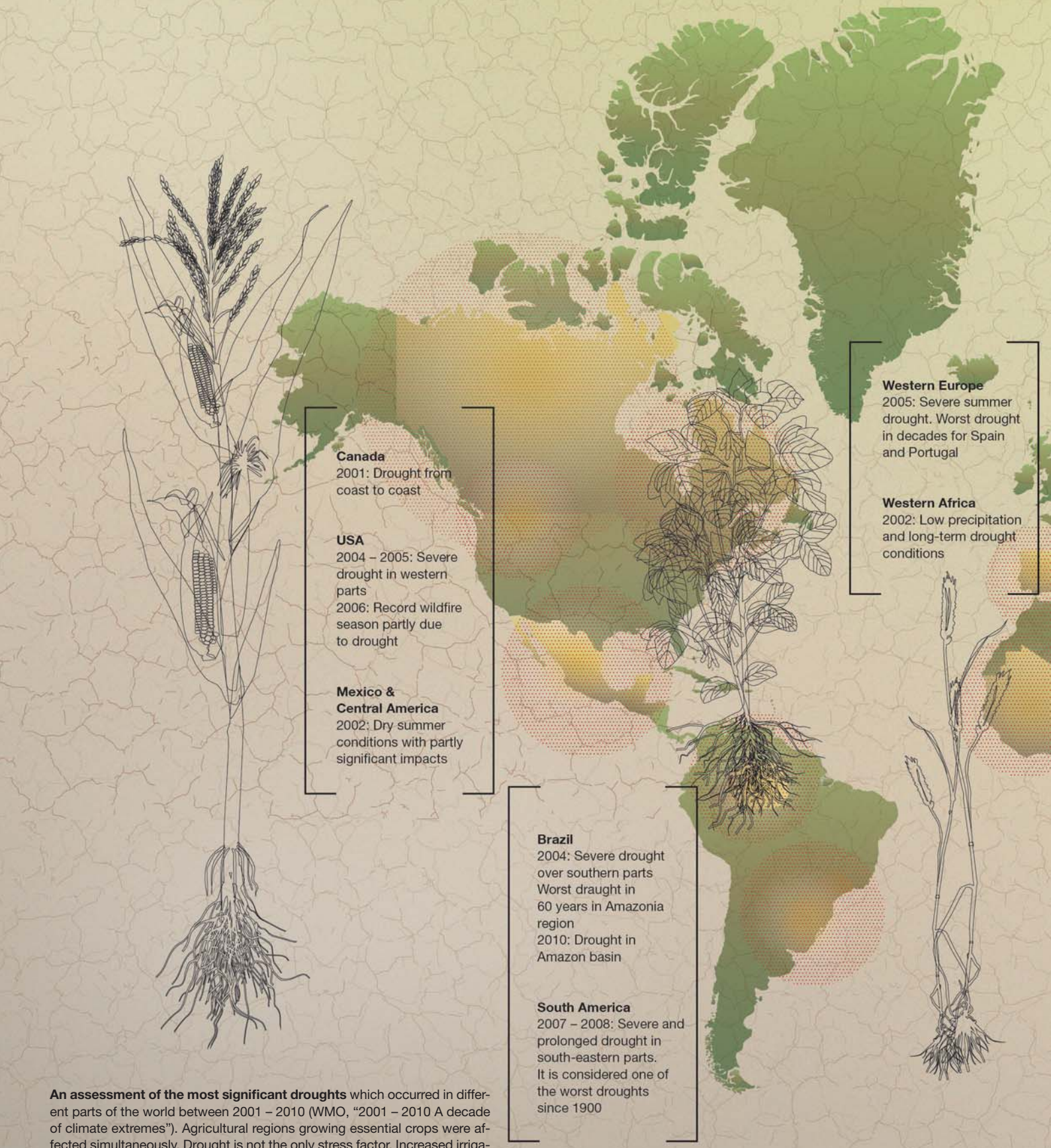
The StressNetAdapt project, led by Dr. Pascal Falter-Braun, investigates protein networks and complex signaling pathways in plant cells. Against the backdrop of climate change and its impact on food production, his research focuses on strategies that enable plants to overcome unfavorable environmental conditions such as water shortage or high soil salinity. The findings could pave the way to generate new, stress-tolerant crops using biotechnology.

Karsten Werth

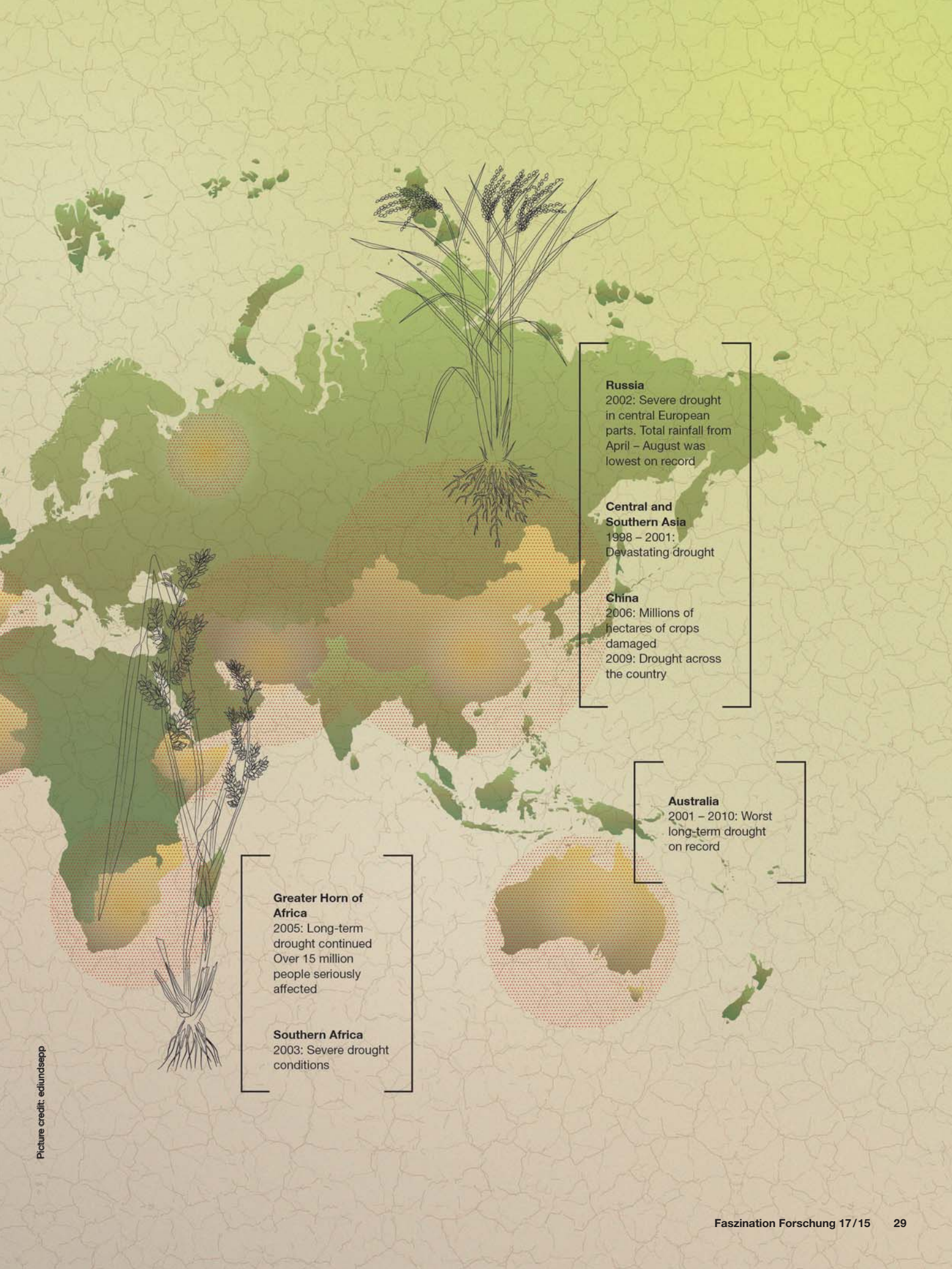
Netzwerkforschung für mehr Nahrung

In Zeiten des Klimawandels wird die Frage immer dringender, warum manche Organismen besser mit widrigen Bedingungen wie Trockenheit oder Krankheitserregern zurechtkommen als andere. Pascal Falter-Braun ist überzeugt: Das Erfolgsgeheimnis liegt in der Interaktion der Proteine, die sich in komplexen Netzwerken organisieren. Für sein jüngstes Forschungsvorhaben, das fünf Jahre lang solche Netzwerke untersuchen soll, erhielt er einen Grant vom Europäischen Forschungsrat (ERC) aus Brüssel. Am Wissenschaftszentrum Weihenstephan leitet Falter-Braun eine zehnköpfige Forschungsgruppe des Lehrstuhls für Systembiologie der Pflanzen. Ziel ihrer Grundlagenforschung ist es, herauszufinden, wie sich die molekularen Netzwerke von stresstoleranten Pflanzen von denen ihrer stressempfindlichen Verwandten unterscheiden. Die Forscher untersuchen jeweils 5.000 proteinkodierende Gene aus vier eng verwandten Arten der Familie der Kreuzblütler, kartieren molekulare Netzwerke und wollen anhand ihrer Überlagerung die Schlüsselproteine für die gewünschten Phänotypen identifizieren. Der biochemische Netzwerkvergleich ist zum Teil inspiriert von einer Ähnlichkeit der Proteinnetzwerke mit technischen oder sozialen Netzwerken, wie sie sich zum Beispiel in den sozialen Medien widerspiegeln. Die Erkenntnisse aus dem Projekt könnten langfristig dazu beitragen, durch Modulierung der Proteinnetzwerke und Züchtung stresstoleranter Arten die landwirtschaftlichen Erträge in Trockenperioden oder auf Böden mit hohem Salzgehalt zu verbessern und damit einem wachsenden Ernährungsproblem der Menschheit zu begegnen. □

Picture credit: NASA



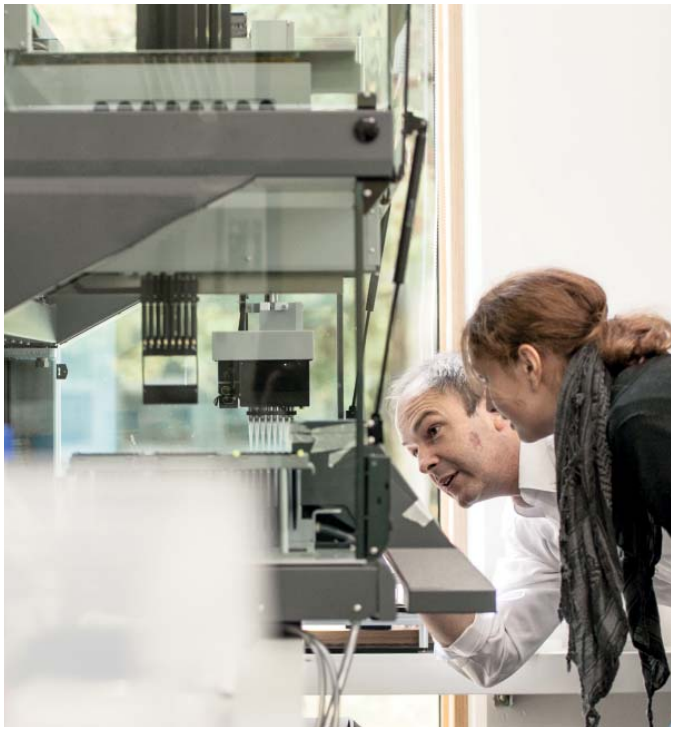
An assessment of the most significant droughts which occurred in different parts of the world between 2001 – 2010 (WMO, "2001 – 2010 A decade of climate extremes"). Agricultural regions growing essential crops were affected simultaneously. Drought is not the only stress factor. Increased irrigation – such as in California – can also gradually increase salt levels in the soil. High soil salinity has a very similar physiological impact on plants as lack of water.



Picture credit: ediundsepp

The prospects are dim: according to the 2014 report of the UN's Intergovernmental Panel on Climate Change (IPCC), weather extremes are projected to increase as the climate gets warmer. Experts see an increase in the frequency and extent of droughts as one of the greatest threats to global food production. Exemplifying the trend: historic droughts occurred between 2000 and 2010 in several key staple-food producing regions around the world including Brazil, North America and China. To reduce the risk of famines and resulting social unrest, it is critical to develop crop varieties that can thrive even in extreme climate conditions. TUM researcher Dr. Pascal Falter-Braun approaches the quest for stress-tolerant plants on a molecular level.

All living organisms owe their lives to the successful interplay of molecules inside their cells. But why do some organisms tolerate adverse environmental conditions better than others? Falter-Braun is convinced that the answer lies in the interactions between proteins, which are organized into complex networks. His latest research project will examine these networks over a five-year period – and has secured him one of the prestigious grants awarded by the European Research Council (ERC) in Brussels. At TUM's School of Life Sciences Weihenstephan, Falter-Braun leads a group of ten scientists at the Chair of Plant Systems Biology. The goal of their research is to determine how the molecular networks of stress-tolerant plants differ from those of their stress-sensitive counterparts. Thanks to his ERC Consolidator Grant of two million euros, Falter-Braun can focus on this question over the next five years. ▷



Dr. Pascal Falter-Braun

3 questions for …

Dr. Pascal Falter-Braun (43) was born in Essen, Germany, studied biochemistry at the Freie Universität Berlin and then spent over ten years engaged in research at Harvard University and Harvard Medical School in the US. He has been a research group leader at the TUM Chair of Plant Systems Biology since 2012 and a TUM Junior Fellow since 2014. Falter-Braun has published numerous papers in some of the most prestigious scientific journals such as "Science". He lives in Munich and is married with one daughter.

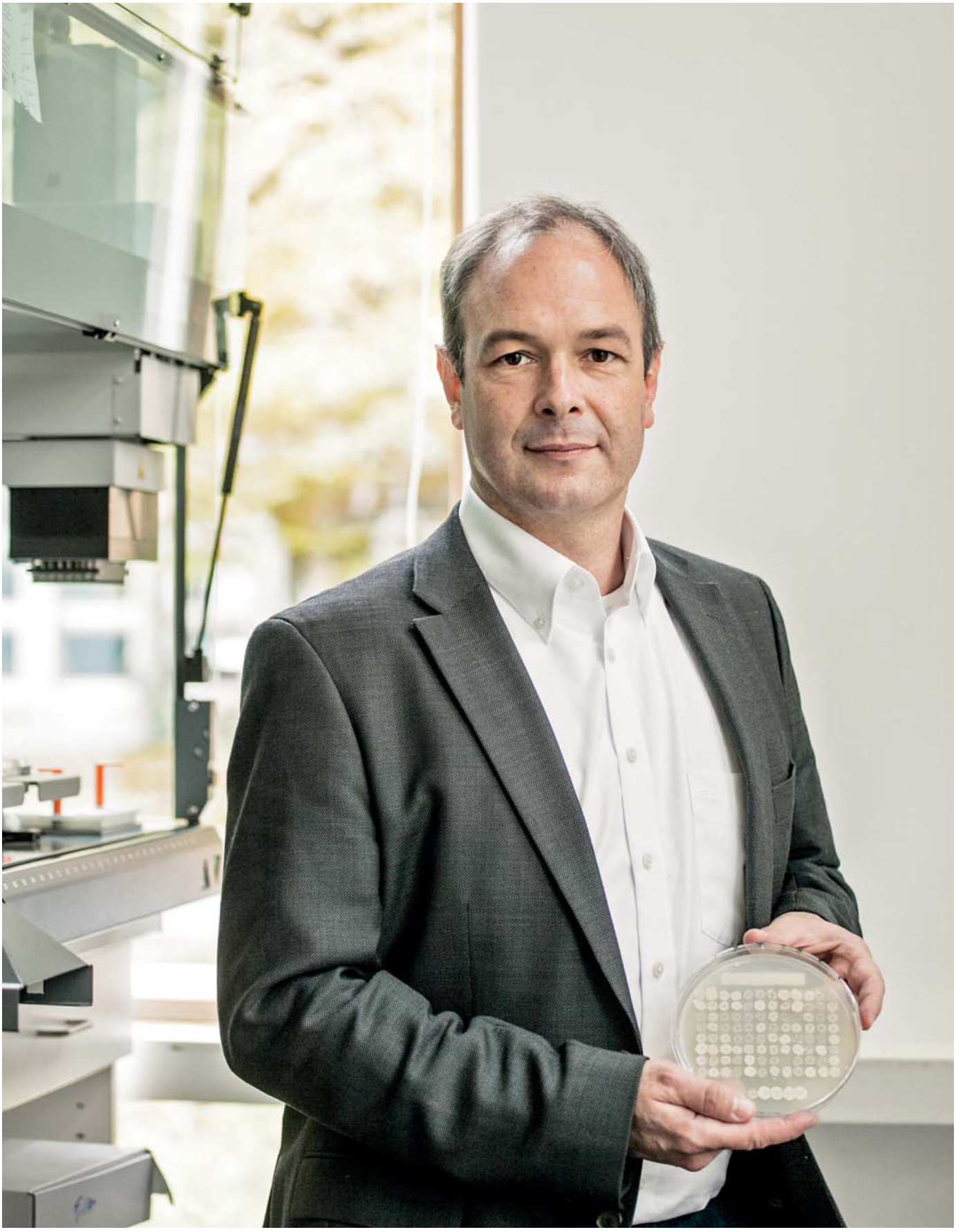
Dr. Falter-Braun, how did you get into your chosen subject?
My time in Boston coincided with the Human Genome Project, which brought me into contact with genome-wide research approaches very early on. I started on my first plant project in 2010, then working alongside colleagues from the Arabidopsis genome project; that was my first point of contact with plant science. Ultimately I came to the conclusion that, on a global scale, food and energy issues are the most important to me. Diseases certainly cause a lot of suffering but energy problems, water shortages, and related issues affect us all as a global community – and will certainly keep us on our toes for the next two decades. I was also drawn by the fact that not much research had been done in this area yet. So I switched to plant science fairly late in my career, as a newcomer to the field.

What does the ERC grant mean to you?
This is my most exciting project to date. We can make substantial progress here and it's great to have that recognition. I'm also very glad to be at TUM, where ERC grants lead to professorships through the Tenure Track system. That's obviously important when, like me, one is at the group leader level.

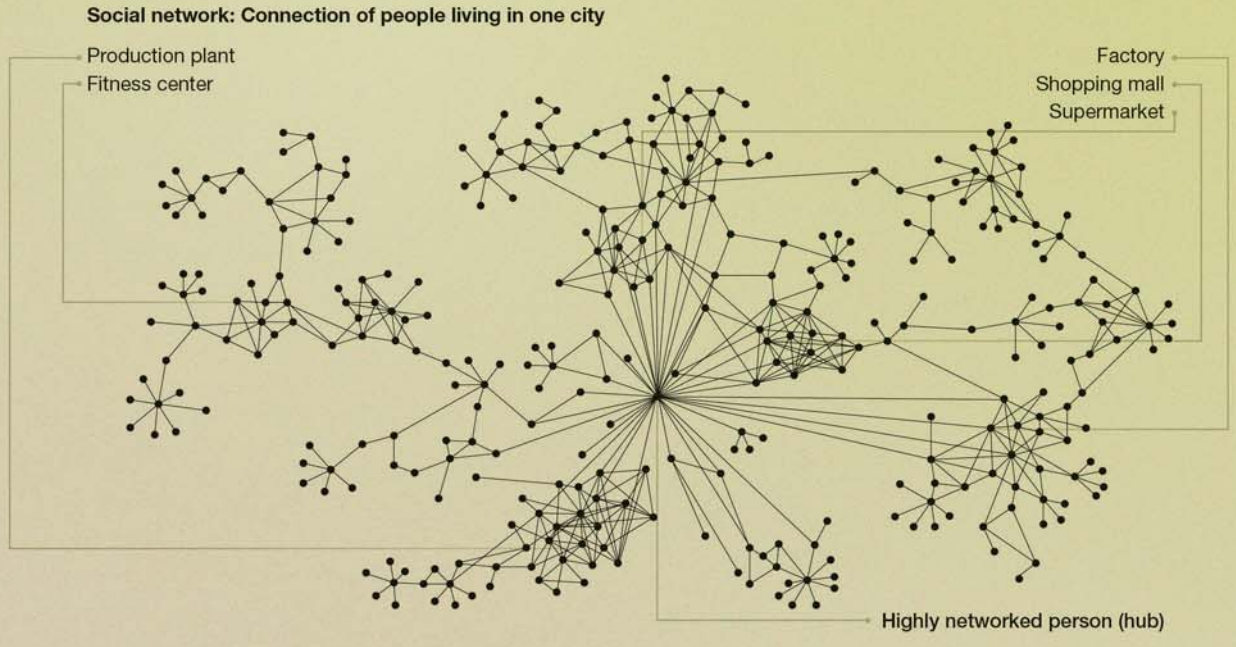
Would you encourage young people to become researchers?
Certainly, as long as they bring passion in addition to talent. It's not the best career path if you want to get rich quick. But as long as you have a certain amount of resilience, it can be a very rewarding and exciting path – especially when you reach the point where you can substantially realize your own ideas and find your own new and creative approaches. Not many careers afford that degree of freedom.

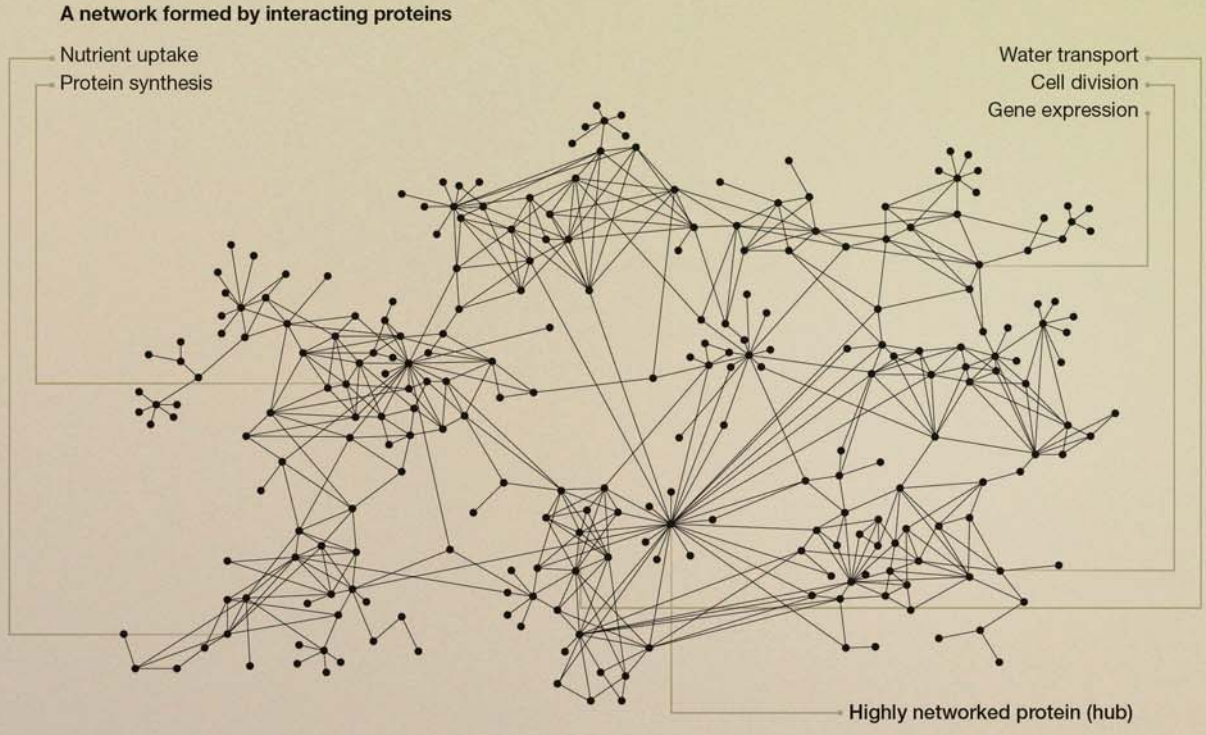
"Scientists have been trying to understand molecular networks for several years now."

Pascal Falter-Braun



Picture credits: ediundsepp





Social and molecular networks are similiar in various ways: They are comprised of several communities – in the case of proteins functionality clusters such as for water transport – connected via interaction between individual persons/proteins. Just like highly networked persons act as hubs and enable fast information flow throughout the network, highly networked proteins support the fast propagation of signals. Pathogens act on these hubs to effectively affect an organism.

Picture credits: ediundsepp

Mapping and understanding networks

Proteins are elementary to every cell of every living organism. They are responsible for transporting substances and signals, they interact with other molecules and they give structure to cells. “Scientists have been trying to understand molecular networks for several years now – since completion of the major genome projects,” says Falter-Braun. He continues: “All building blocks of life have now been identified. We know which proteins are encoded in a genome and have a complete parts list.” Yet sequencing the genome did not reveal the desired “circuit diagram” of life. A parts list alone does not tell us anything about the links between them and the way they interact. “It’s like a phone directory,” describes Falter-Braun: “We can’t use this list to find out which parties communicate and how.” However, this is precisely the crux of the issue. Translation of genomic information into plant characteristics results from the diverse and complex interactions among the components of the molecular networks. In crop plants, agricultural yield and stress tolerance are particularly important properties. Thus, the initial goal of Falter-Braun’s research is to map and understand these networks.

Similarity to social networks

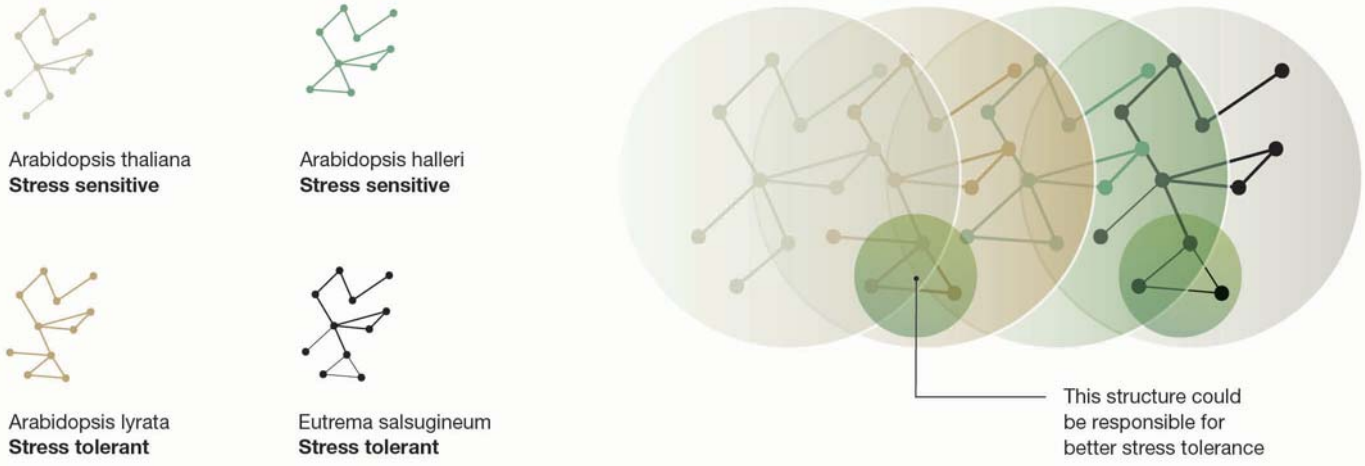
Insights gained into molecular networks to date have revealed their structural similarity to social and technical networks. Falter-Braun is particularly interested in information exchange and robustness. He gives an example: “In social networks many people have comparatively few friends. However, there are also a few people with very extensive contacts who are vital to the flow of information. On Facebook and Twitter, news spreads fastest via these highly networked participants. “Such strongly networked components, so-called hubs, are also found in complex technical networks, for example in air traffic. Here, most connections go through a few central hubs, such as Frankfurt, Charles de Gaulle and Heathrow. These hubs are important for the stability of air traffic operations. If several hubs were to go down at the same time, air traffic in Europe would collapse – with consequences around the globe. The complex molecular networks within cells have a similar structure: there are many proteins with few connections and a few major hubs.

Hubs as strategic targets for pathogens

The TUM researchers have already investigated how three evolutionarily diverse plant pathogens – representatives of bacteria, fungi and brown algae – attack plant networks. Falter-Braun summarizes: “We found that all three pathogens target the hub proteins of the host network. Moreover, we could show that the targeted host proteins have important functions – if we switch them off, the consequence is either increased resistance or increased susceptibility to the pathogen.” So there appears to be a “strategy” behind the attacks on these highly networked hubs. Falter-Braun considers the possibility of universal network laws, which may also apply to biological phenomena.

“On a global scale, food and energy issues are the most important to me.” *Pascal Falter-Braun*

For some plant species, the sequencing of many individual genomes has delivered significant insights into their natural genetic variation. To a certain extent, scientists today are able to watch evolution in action by identifying highly variable regions of the genome. “In our pathogen project, the results of this analysis surprised us,” says Falter-Braun. “Above all, we were expecting to see variability in the targeted hubs that would serve to thwart attacks by the pathogens. Instead, the most variable proteins turned out to be direct interaction partners of the hubs. This indicates that the network structure has a strong influence on evolutionary processes. The selection pressure that pathogens exert on the plant via the hubs appears to be intercepted and absorbed by proteins in the network environment.” Falter-Braun suspects that it is difficult for the hub proteins to change because they are so highly connected. Any changes in their shape would likely impact many different aspects of the network. Thus evolutionary adaptation of the network must take place in the neighborhood of the hub. This question continues to be investigated. ▷



The molecular networks of the four investigated plants are mostly similar but differ in details. Superimposing the networks reveals that Arabidopsis lyrata and Eutrema salsugineum share one specific structure which might be the key to more stress tolerance.

StressNetAdapt

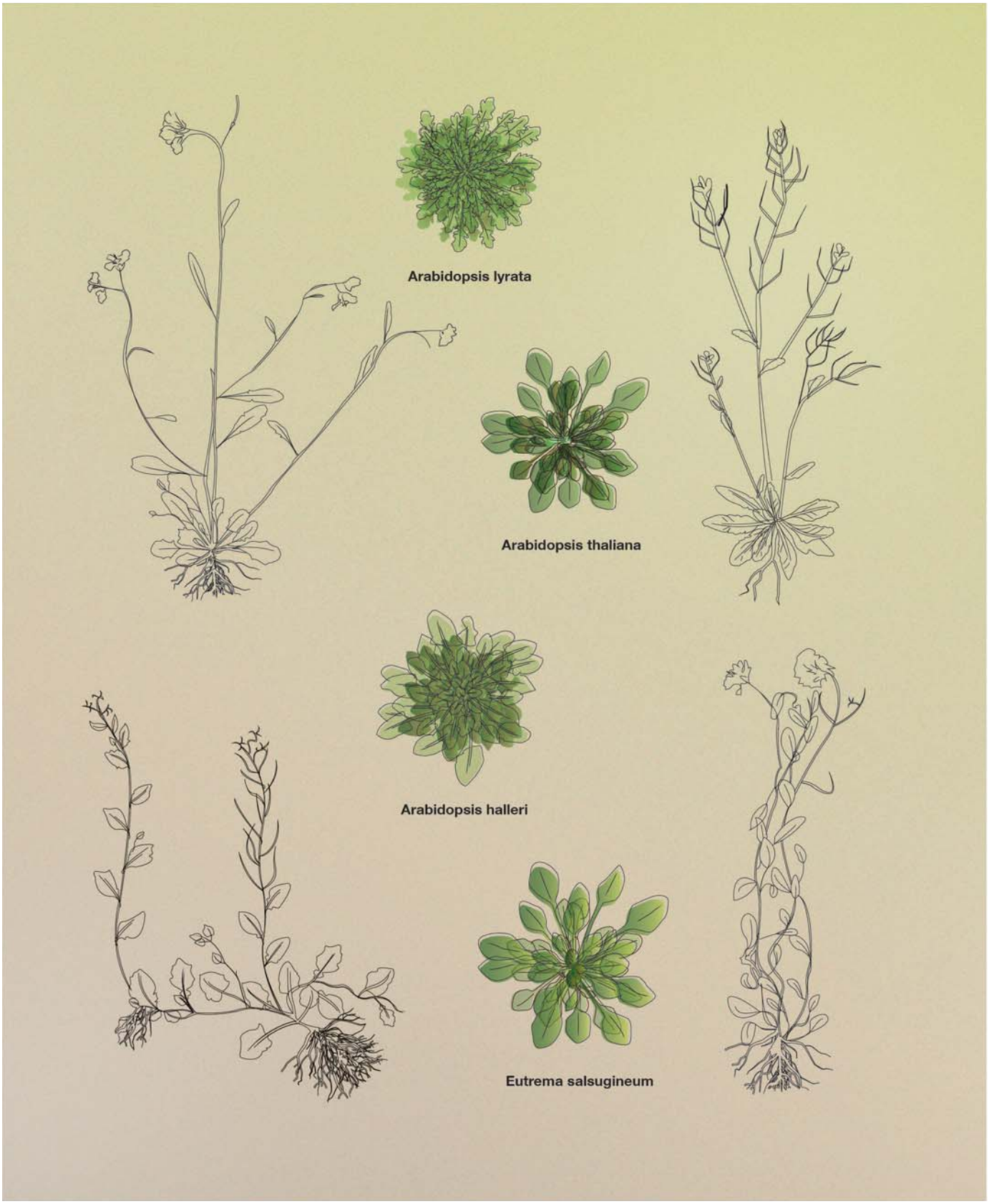
Falter-Braun's ERC project StressNetAdapt started in September 2015. In this project, the scientists will compare the protein networks involved in drought stress of four closely related cruciferous plants: Arabidopsis thaliana (thale cress), Arabidopsis lyrata, Arabidopsis halleri and Eutrema salsugineum. These plants are close relatives of rapeseed and cabbage varieties. Arabidopsis thaliana is one of the most important model organisms in plant research, analogous to the mouse in medical research. Falter-Braun and his colleagues generated an initial map of the protein interaction network for A. thaliana some years ago. In StressNetAdapt, the Weihenstephan researchers now attempt to find out why some of these evolutionarily close species are particularly tolerant to drought or salt stress and how plant breeding may benefit from this. Arabidopsis thaliana and Arabidopsis halleri are highly sensitive to drought stress, whereas Arabidopsis lyrata and Eutrema salsugineum can tolerate drought stress very well.

As a first step the molecular networks of these four species need to be mapped by protein-protein interaction analysis. To this end the researchers will examine 100 million protein pairs using a state-of-the-art pipetting robot and the yeast-2-hybrid system – a biochemical technique to identify protein-protein interactions. Since the four species are closely related, it is expected that the networks will be largely identical. At the same time some proteins may only occur in one species. In addition, some proteins may be differently connected. Falter-Braun's hypothesis is that on one hand there will be a core network that looks identical in all four crucifers, and on the other hand there will be network variations, of which some account for the increased tolerance to drought stress. The researchers aim to superimpose the four networks to reveal the differences. By this approach they hope to identify key proteins that could increase drought stress tolerance in sensitive plant species. The team then plans on introducing these to rapeseed to test their hypothesis. "Our research is intended to deliver a proof of principle for new biotechnological strategies that may be transferable to other crops in the future." According to Falter-Braun, the insights gained from this project could be used to modulate protein networks through selective breeding and thus deliver more robust crops. In the light of climate change and increasing food insecurity this could be progress that saves lives.

Karsten Werth

"Fascinatingly, all three pathogens that we investigated target the host's hub proteins – just as network theory predicted."

Pascal Falter-Braun



Picture credits: ediundsepp (source TUM)

Why are some plants more tolerant to stress than others? Pascal Falter-Braun compares the protein networks involved in tolerance to drought stress across four closely related plants. He hopes to find network structures that could lead the way to breeding more robust crops.

Pinning **Molecules Down**

Wilhelm H. Auwärter successfully investigates single molecules and the way they work by attaching them to tailored surfaces and examining them with a scanning tunneling microscope.

Picture credit: Jooss

Brigitte Röthlein

Moleküle unter Beobachtung

Ganz ohne Zwang, nur durch Selbstorganisation, bilden sich unter bestimmten Bedingungen Schichten aus Bornitrid, die nur eine Atomlage dick sind. Der Liechtensteiner und Schweizer Physiker Wilhelm H. Auwärter und sein Team stellen solche Schichten in den unterschiedlichsten Variationen her und benutzen sie dazu, Moleküle, die sich darauf festsetzen, mit dem Rastertunnelmikroskop abzutasten. Dies gibt ihnen die Möglichkeit, die Moleküle und ihr Verhalten auf atomarer Ebene zu untersuchen.

Im Vordergrund stehen dabei Porphyrine, organische Komplexe, die ein Metallion enthalten. Ihre chemische Struktur besteht aus vier Ringen, die zyklisch miteinander verbunden sind. Im Zentrum sitzt das Metallion. In ihren verschiedenen Ausprägungen spielen Porphyrine beispielsweise im menschlichen Stoffwechsel eine zentrale Rolle. So sorgen sie für den Transport des Blutsauerstoffs im Hämoglobin und kommen in vielen Enzymen vor. Sie zeigen ihre Wirkung aber auch im Chlorophyll, wo sie entscheidend an der Photosynthese beteiligt sind.

Die TUM Forscher fixieren diese Moleküle im Vakuum und bei tiefen Temperaturen auf der Bornitridschicht und setzen sie unterschiedlichen Bedingungen aus. Mit Hilfe des Rastertunnelmikroskops können sie dann beobachten, wie sich die Struktur der Moleküle verändert, welche Verbindungen sie eingehen und welche Varianten für bestimmte Zwecke besonders gut geeignet sind.

Mit diesem Verfahren lässt sich eine Vielzahl organischer und anderer Moleküle beobachten. Die Erkenntnisse helfen dabei, elektrische, magnetische und optoelektronische Eigenschaften von Materie zu optimieren. Anwendungen sind denkbar für organische Solarzellen, für reversible molekulare Schalter, für Sensoren oder neuartige Katalysatoren. Aufgrund der großen Bedeutung seiner Arbeiten erhielt Auwärter im vergangenen Jahr für seinen Projektvorschlag mit dem Namen NanoSurfs von der EU einen ERC Consolidator Grant, der mit knapp zwei Millionen Euro dotiert ist und seine Arbeit bis 2019 fördert. □

Link
www.e20.ph.tum.de

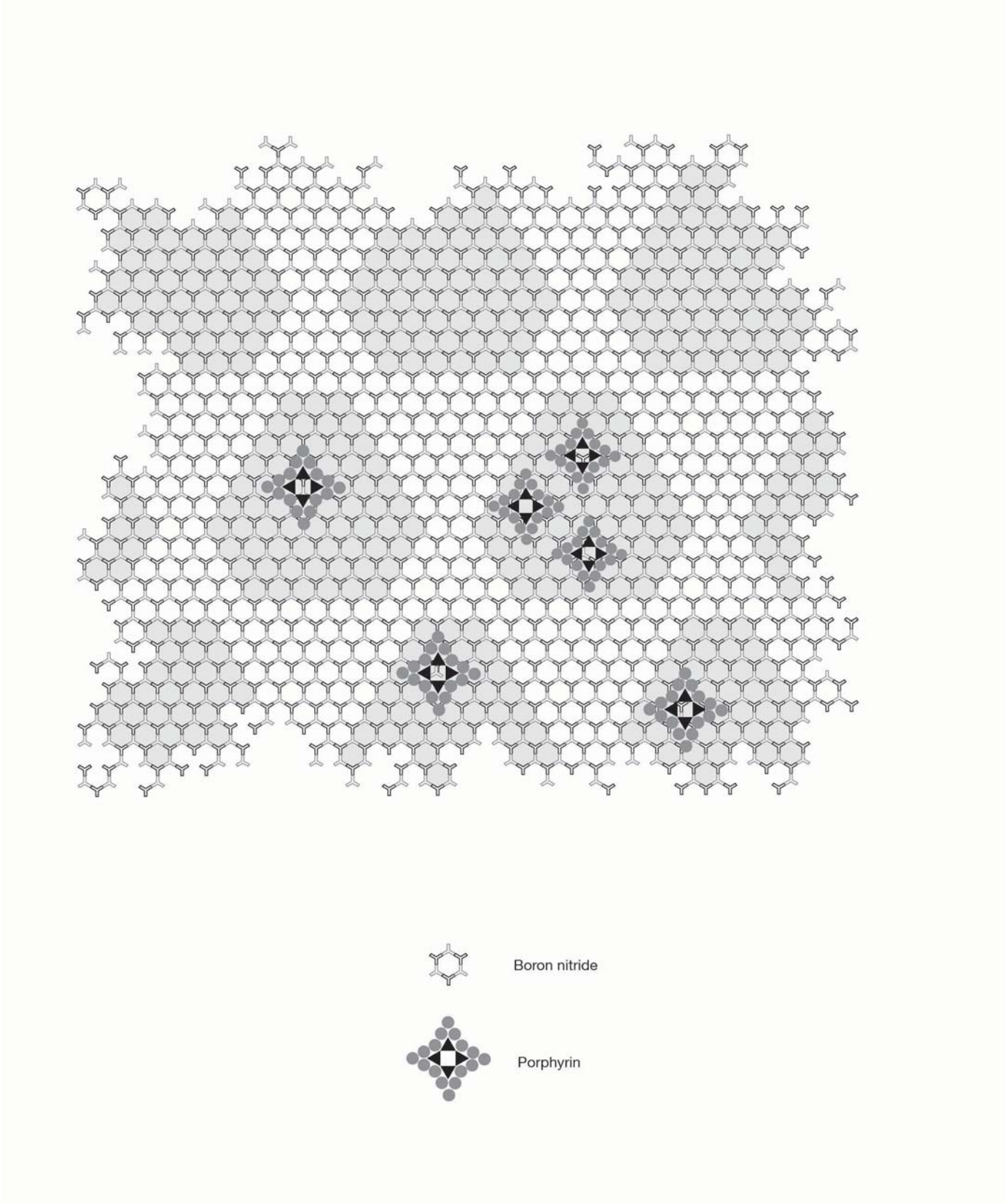
Insect researchers like to study their subjects by fixing them with pins and observing them at leisure. Wilhelm H. Auwärter does much the same thing with molecules – except that molecules are way smaller and remain “alive”. Which is the whole point of the experiment, in fact, as he is looking to observe the way they behave and perform various functions. And instead of pins, he uses the natural properties of the molecules to fasten them to a substrate.

The work of physics professor Auwärter at TUM is closing a gap in the study of organic molecules. Analytical methods exist to determine their chemical composition; X-rays can be used to establish their physical structure; and chemical analyses can test their activity patterns. All of that contributes to our current conceptual understanding of particular molecules. But nobody had ever really seen them before, because they are simply too small for optical microscopes. Now, though, Auwärter and his team are making these tiny structures and their functionality visible.

Growing layers one atom thin

In recognition of the importance of his efforts, Auwärter was awarded an ERC Consolidator Grant by the EU last year for his NanoSurfs project proposal. With funding of almost two million euros, the grant will support his research until 2019. “This is a tremendous boost to our efforts,” confirms the delighted scientist. “It means we can focus fully on our work and also acquire an atomic force microscope to supplement our analyses.”

At the heart of Auwärter’s work are ultrathin layers of boron nitride, vapor-deposited onto a base material, which is ▷



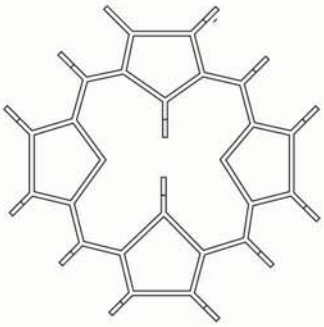
Picture credit: ediundsepp (Source TUM)

How to pin a molecule down (schematic illustration): Auwärter and his team grow ultrathin layers of boron nitride, which forms a honeycomb lattice much like graphene. Onto this substrate, they sublimate metalloporphyrin molecules, which attach themselves lightly to the boron nitride layer. With the help of a scanning tunneling microscope, one can then observe how these molecules behave, for instance when a gas molecule is in the vicinity.

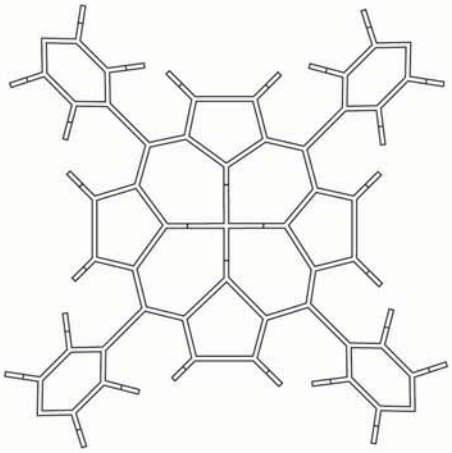
"The ERC grant is a tremendous boost to our efforts. It means we can focus fully on our work and also acquire an atomic force microscope to supplement our analyses."

Wilhelm H. Auwärter

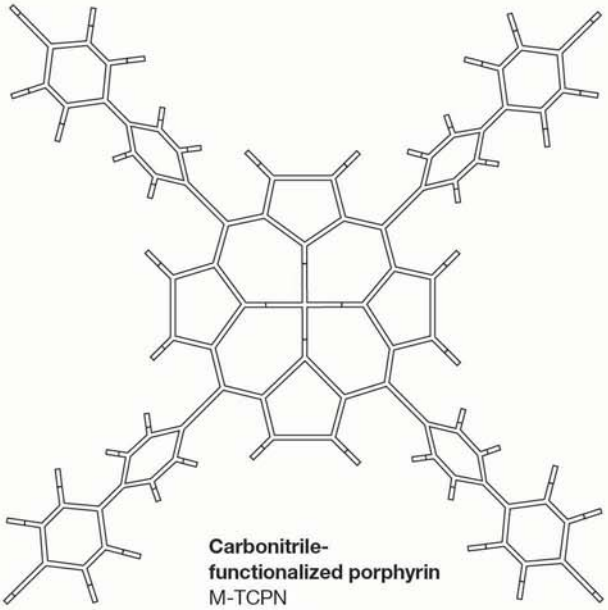
Picture credit: Jooss



Porphine
2H-P
free-base porphine



Tetraphenylporphyrin
M-TPP
metallotetraphenylporphyrin



Carbonitrile-functionalized porphyrin
M-TCPN
metallotetra
[(4-cyanophenyl)-phen-4-yl]
porphyrin

Three of the porphyrin molecules Auwärter works with. Porphyrins in their various forms play a key role in human metabolism, for instance, or in photosynthesis.

Picture credit: ediundsepp (Source: TUM)

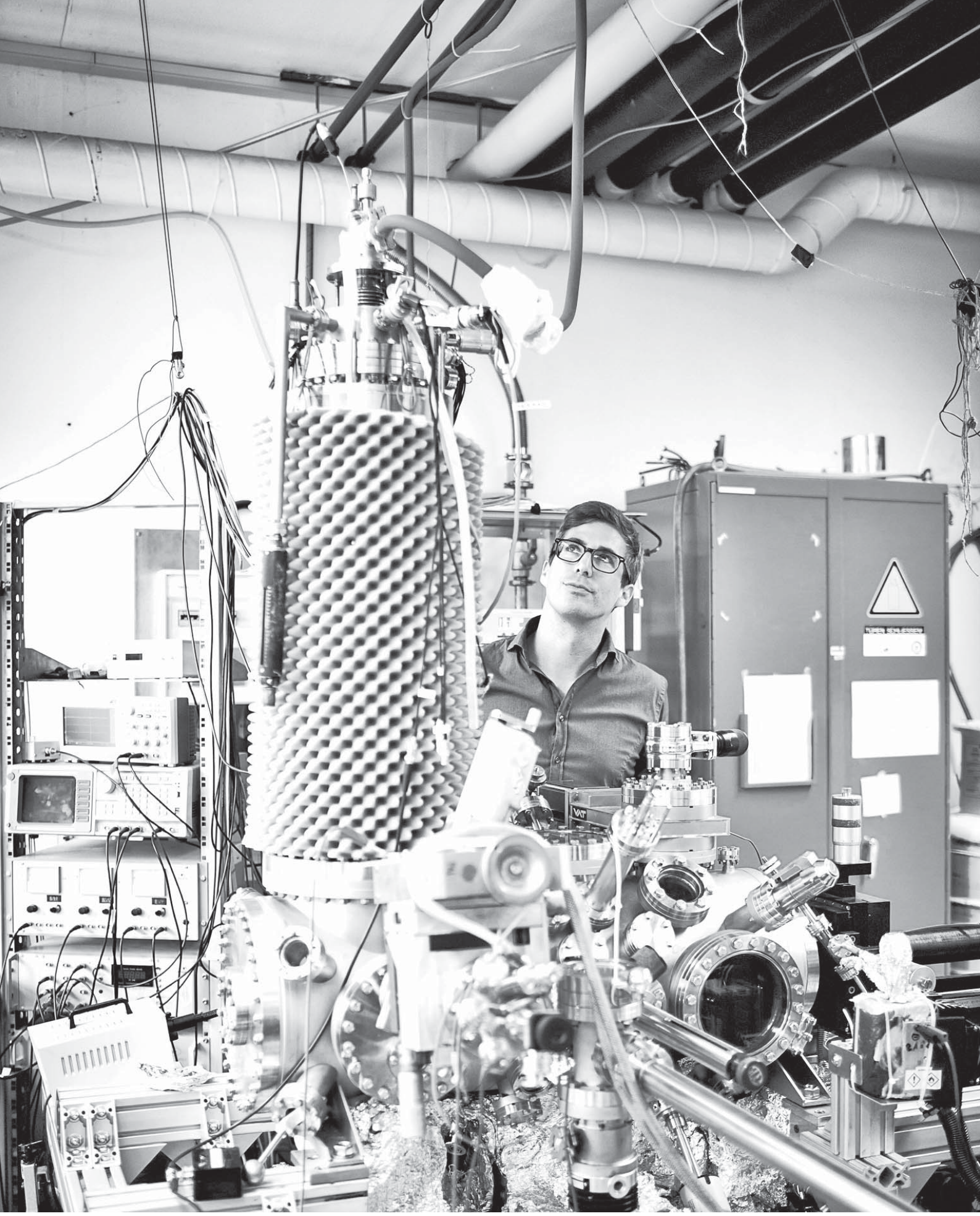
usually metallic. The process entails placing single crystals of the metal in a vacuum chamber, inside which a precursor substance containing boron and nitrogen is then evaporated. If this is done correctly, the resulting vapor settles on the monocrystal in a layer just one atom thin. The boron and nitrogen atoms are then compelled to arrange themselves in a certain way on the substrate and adopt a specific configuration. "This is a special property of boron nitride – and actually of graphene too," explains Auwärter. "As a rule, the layer can only spread out in two dimensions, so has no bulk."
The atomic structure of this lattice is revealed with a scanning tunneling microscope (STM). This device – "a cool invention" by subsequent Nobel Prize winners Gerd Binnig and Heinrich Rohrer – is capable of imaging surfaces so precisely that every single atom can be seen. Used to analyze the boron nitride layer, the STM reveals the formation of a flat, honeycomb lattice. By now, Auwärter and his team have become experts at producing this type of lattice in a wide range of variants. Nickel is most commonly used as the metallic base, but if this is substituted with rhodium, the two crystal structures do not overlap exactly and regular wrinkles form where the layer is slightly elevated. Other tricks can be used to produce wave and step effects or modify the electronic structure. The researchers are even attempting to insert other atoms or molecules between the base material and the boron nitride layer, with examples including silver and graphene.

Observing the behavior of metalloporphyrins

Onto this prepared substrate, Auwärter and his team then vaporize molecules such as metalloporphyrins. These are organic complexes containing a metal ion. Their chemical structure consists of four cyclically linked rings with the metal ion at the center. Porphyrins in their various forms play a key role in human metabolism, for instance. They enable hemoglobin in red blood cells to carry oxygen and also occur in many enzymes. They can be found in chlorophyll, where they make a key contribution to photosynthesis. "These molecules are so important that it is essential for us to understand exactly how they function on surfaces. Only then can we fully harness their technical potential," emphasizes Auwärter. Which is why he is attaching them to the boron nitride lattice in a high vacuum and usually at extremely low temperatures. He then observes how they behave as soon as a gas atom is in the vicinity. Since the molecules are placed lightly on the substrate, they can still move. And sometimes they also change structure, break up or bind with other molecules.
The primary tool for these observations is a scanning tunneling microscope, with an atomic force microscope planned as a future addition. At the core of the STM is a probe, consisting of an extremely fine tungsten needle, ideally with a point comprising a single atom. This is guided at close range across the surface whose atoms are to be examined. If the needle tip is directly above an atom on the surface, at a distance of approximately one nanometer, every now and then an electron will tunnel between the needle and the surface. A current, though miniscule, will flow – known as the tunnel current. If the probe systematically scans the surface and records the strength of the tunnel current at each point, it yields an image of that surface that is so precise it even shows the elevation of individual atoms. "We can see how the molecules cluster on the patterned boron nitride, for ▷

"These molecules are so important that it is essential for us to understand exactly how they function on surfaces. Only then can we fully harness their technical potential."

Wilhelm H. Auwärter



Picture credits: Jooss

Prof. Wilhelm Auwärter

From Zurich to Munich – via Vancouver

Doing the right thing at the right time can make a science career. In Wilhelm H. Auwärter's case, things seemed to fall into place automatically, although it is only now, many years on, that he sees it that way. "It was really all coincidental," remarks the 41-year-old Liechtenstein citizen and Swiss passport holder, now a Heisenberg Professor at TUM. "I used a scanning tunneling microscope to analyze boron nitride layers for my degree thesis in Zurich in 1998, but it didn't arouse all that much interest back then." It was only years later when graphene was discovered – which has an almost identical geometrical structure – and a Nobel Prize was awarded for that discovery, that Auwärter's findings began to interest many colleagues, leading to frequent citations of his earlier publications.

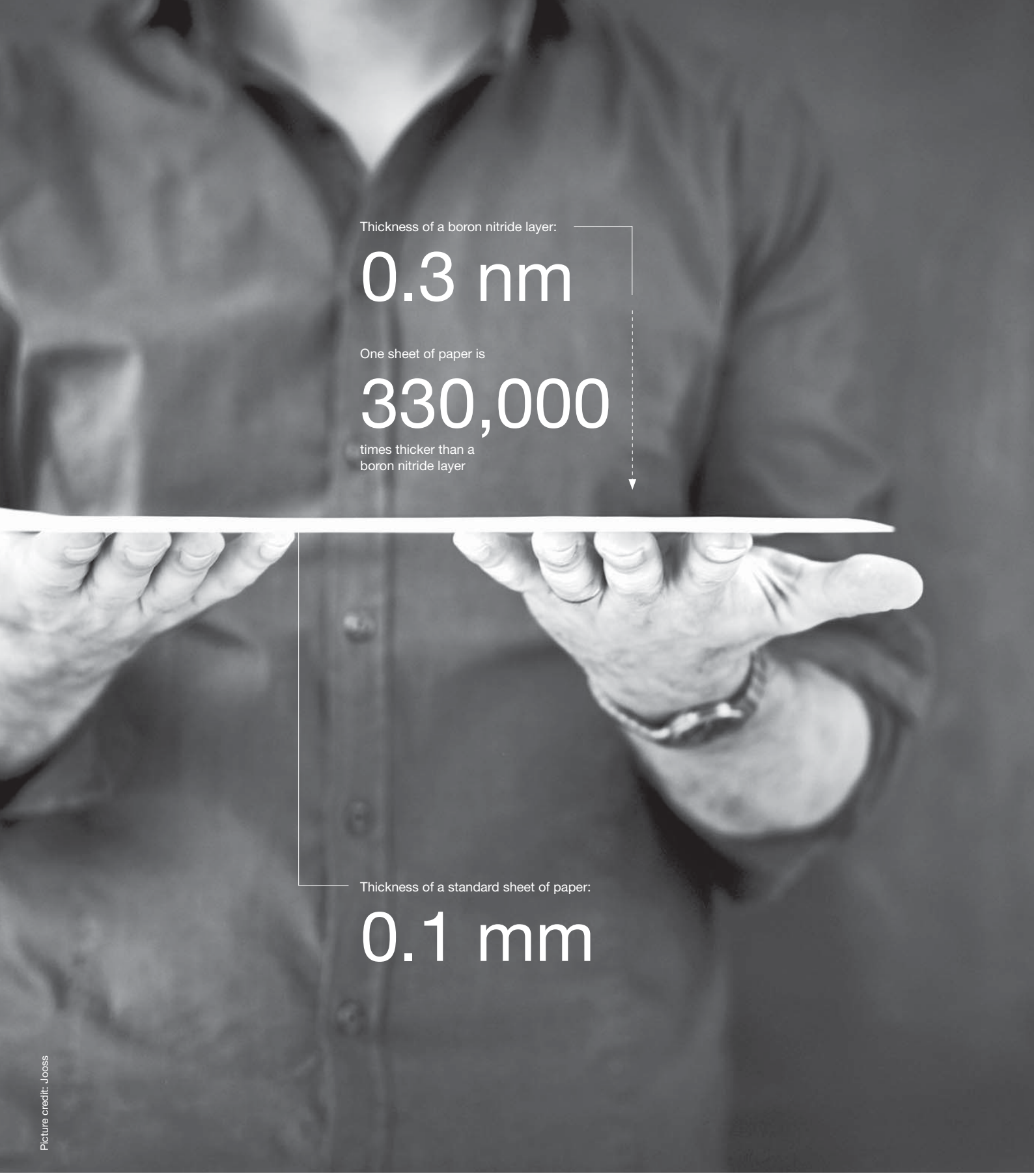
In the meantime, he continued pursuing the topic for his doctorate and developed his expertise in producing boron nitride layers and analyzing them with a scanning tunneling microscope. As a postdoc, he relocated to Vancouver due to the outstanding research framework on offer there. He and his wife remain very fond of that beautiful city surrounded by mountains and sea and still sometimes feel a bit homesick for it. "Maybe it will work out so that we can live there again, at least for a while," he hopes. Although, back in the day, it was no mean feat convincing his girlfriend (now wife) to give up her job in Zurich and go with him to Canada in the first place.

Now married, they have two children, aged three and five, who see visiting their dad at the university as a special treat: "They're delighted by the huge chalkboard and colored chalks in the seminar room and love it if they're allowed to pick up a wrench, since that's a grown-up tool."
In fact, a university career was not always Auwärter's aim – he could see himself working as a school teacher too. And although it turned out differently, he still enjoys teaching and does all he can to interest students in his physics lectures.

instance," describes Auwärter, adding, "Or we can determine which bonds our molecules form; how their 'feelers' interact with their neighbors." By conducting a tiny current through the tip of the microscope, the researchers can even induce vibration in the atomic structures and thus learn more about their structure.
At the moment, of course, all this is purely basic research – but with a real prospect of important applications in the long term. "Producing synthetic catalysts might be a possibility, for instance – that is, molecules that have the effect of provoking a specific chemical reaction," Auwärter reflects.

Atomic switches for extremely small sensors
As a concrete practical example, the TUM scientists are currently working with colleagues in Berkeley, California, to research processes inside novel organic solar cells. The aim is an atomic-scale investigation of the changes organic molecules in these solar cells undergo when irradiated with photons and how they transfer the released electrons to other molecules. Only when this information is established in detail will it be possible to set about optimizing the solar cell chemistry – similar to tiny Lego bricks you can use to build and modify the shapes you need. "This type of information is significant because, if we want to find molecules that are particularly fit for purpose, we need to know beforehand how they are oriented and coupled," Auwärter points out.
Another application for this method is atomic switches, created under specific conditions when molecules modify their structure – such as reorienting a bond – and thus suddenly change properties. Such reversible switches would be ideal for use in extremely small sensors.
Auwärter is well aware of the numerous possibilities open to him and his research team. However, he has made a deliberate decision to focus on his core competency, i. e. the study of molecules on suitable substrates like boron nitride. To achieve this, his team works in close collaboration with theoretical scientists, who interpret the results from a quantum-mechanical viewpoint and support them with simulations. "As labor-intensive as the ERC grant application was, it did give me a chance to consider where I've got to and what I want to achieve," says the physicist. "The hectic pace of day-to-day research means you never usually get the opportunity to take stock that way." When it comes to future research objectives, his plans are far-reaching, the aim being to create new ways of optimizing electric, magnetic and optoelectronic material properties at molecular level. The knowledge and hands-on experience Auwärter has gathered during his years of work in this field are surely unparalleled and will stand him in good stead in pursuing his goals. Even now, as a professor, he likes to spend a few hours here and there optimizing the microscope's scanning tips and imaging newly prepared surfaces. "You need experience and a good feel for what you're doing," he concludes. "And sometimes you just do something by intuition and couldn't really explain exactly why."

Brigitte Röthlein



Picture credit: Jooss

Just one atom thin are the boron nitride layers Wilhelm Auwärter produces in his lab. He and his team can even grow a wide range of variants of these layers, producing certain structures that allow them to capture molecules on the layer surfaces and study their behavior.

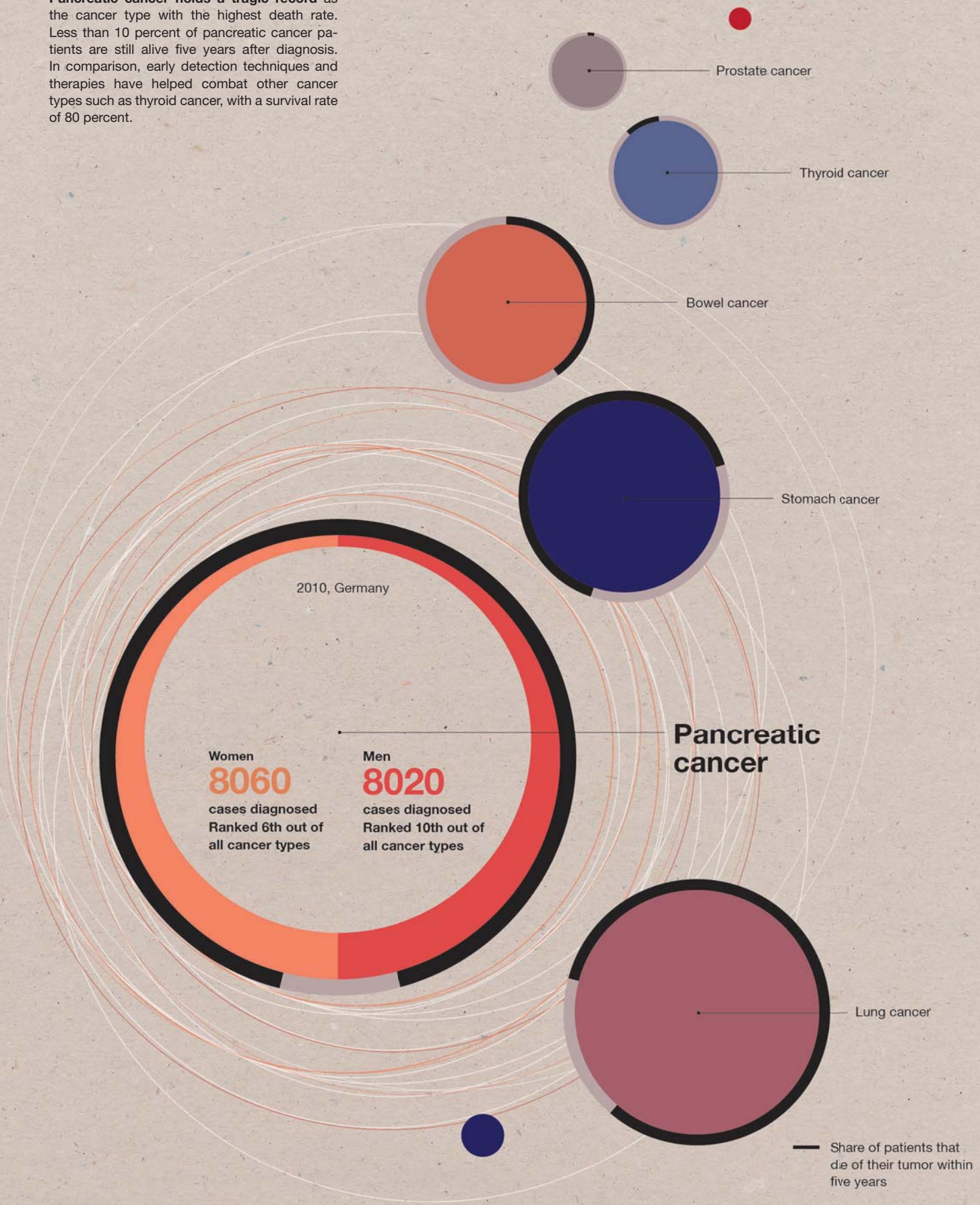
Link
www.med2.med.tu-muenchen.de

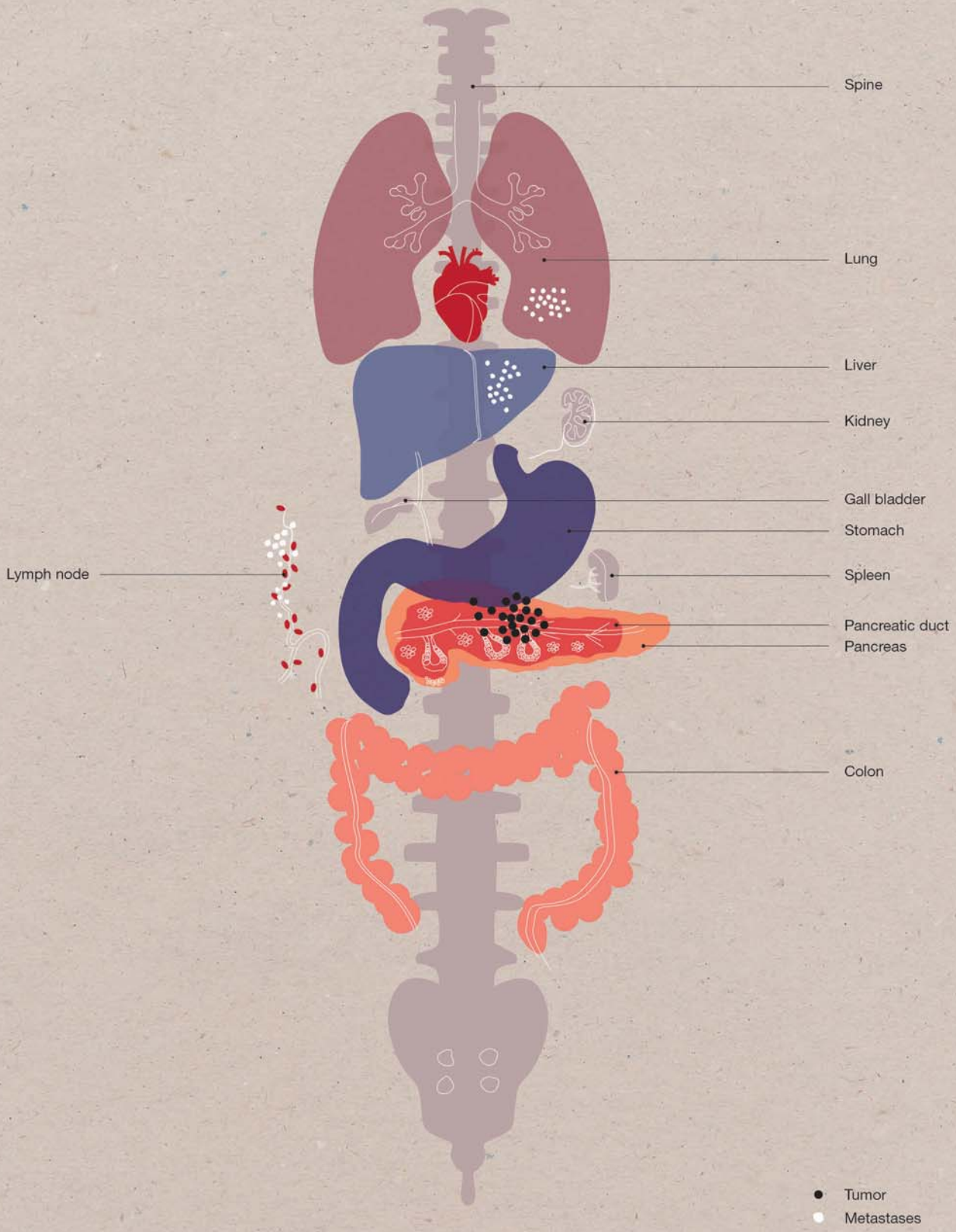
Pancreatic Cancer: New Approaches to Neutralize a Deadly Threat

By 2022, pancreatic cancer looks set to become the second most common cause of cancer-related death after lung cancer. Technically called pancreatic ductal adenocarcinoma, this type of cancer is relatively rare but screening and treatment options still leave much to be desired. In many cases, the disease thus proves fatal. Prof. Dieter Saur is pushing back the boundaries with his research, for which he recently received a much-sought-after ERC grant. In this interview, Saur explains how he hopes to improve the early detection and treatment of pancreatic carcinoma.

Graphics: ediundsepp, (Data: "Krebs in Deutschland 2009/2010", RKI 2013)

Pancreatic cancer holds a tragic record as the cancer type with the highest death rate. Less than 10 percent of pancreatic cancer patients are still alive five years after diagnosis. In comparison, early detection techniques and therapies have helped combat other cancer types such as thyroid cancer, with a survival rate of 80 percent.





By the time a pancreatic tumor can be clearly seen by various imaging diagnostic techniques, it is often too large for surgical treatment. Moreover, quite often the tumor has spread into the lung, liver or lymph nodes. Because it is so large, a pancreatic tumor can also grow into neighboring organs or tissue such as the spleen, stomach or back muscles.

Gerlinde Felix

Bauchspeicheldrüsenkrebs: Neue Ansätze um eine tödliche Gefahr zu entschärfen

Der Apple-Gründer Steve Jobs und der Medizin-Nobelpreisträger Ralph Steinman gaben dem Bauchspeicheldrüsenkrebs oder Pankreaskarzinom prominente Gesichter und verschafften einer lange wenig beachteten Erkrankung etwas mehr Aufmerksamkeit. Das Pankreaskarzinom ist nach wie vor eine Erkrankung mit geringen Heilungsaussichten. Obgleich nur 10 bis 16 Personen pro 100.000 Einwohner daran erkranken, ist es die fünfthäufigste Krebstodesursache. Während bei anderen Krebserkrankungen die Zahl der Todesfälle beständig sinkt, soll sie beim Pankreaskarzinom in den nächsten Jahren weiter dramatisch ansteigen. Zumeist wird die Krebserkrankung erst spät entdeckt, weil es an Früherkennungsmöglichkeiten fehlt und sich Symptome wie Rückenschmerzen und gürtelförmige Oberbauchschmerzen erst im fortgeschrittenen Stadium bemerkbar machen. Die Therapiemöglichkeiten sind derzeit sehr beschränkt. Die Fünfjahres-Überlebensrate liegt bei weniger als 5 Prozent. Der Gastroenterologe Prof. Dieter Saur vom Klinikum rechts der Isar, Kliniker und Forscher in einer Person, sucht deshalb mit seinen Mitarbeitern nach neuen Therapiestrategien und Früherkennungsmöglichkeiten. Er verspricht sich viel von einer Doppelstrategie, die den Tumor als Ganzes angreift. Der Tumor besteht zu 90 Prozent aus Körperzellen, die von den Tumorzellen so manipuliert wurden, dass sie fortan dem Wachstum des Tumors dienen. Das gilt auch für die in den Tumor eingewanderten Immunzellen. Nur 10 Prozent der Tumormasse sind bösartige Tumorzellen. Saur möchte mit einer Substanz die Tumorzellen gezielt bekämpfen. Mit der zweiten möchte er die Körper- und Immunzellen „entsklaven“. Neue Therapieansätze können künftig direkt an einem speziellen, ausgeklügelten Mausmodell erprobt werden, das Saur und sein Team bereits realisiert haben und das weltweit von vielen Forschergruppen eingesetzt wird. Es ermöglicht, Gene und Signalwege in den Pankreaszellen zu jedem Zeitpunkt zu aktivieren oder zu deaktivieren. Für die Erforschung neuer Therapieansätze unter Einsatz des neuen Mausmodells erhielt Saur einen der renommierten grants des Europäischen Forschungsrats (ERC). □

Prof. Saur, pancreatic cancer is currently the fifth most common cause of cancer-related death in Europe, despite being a relatively rare condition. The survival rate for patients five years after initial diagnosis is below five percent. Why is that?

We still don’t know enough about the causes of pancreatic carcinoma. There is no specific preventive check-up available that is cost-effective and simple to perform, and no early detection test. Part of the reason is clearly that, for a long time, pancreatic cancer received no real attention either in research or from the public. Then, ten to fifteen years ago, forecast mortality rates for 2020 and 2030 prompted a rethink in the US. And, in the wake of this development, willingness to support research into pancreatic cancer here in Germany also grew. This is extremely important because surgical removal of a tumor at an early stage can deliver a cure. Pancreatic tumors can usually be seen clearly using ultrasound or computed tomography and magnetic resonance imaging. But by the time tumors are diagnosed, it’s often too late for surgical intervention. Many symptoms only become apparent at a later stage – such as backache, weight loss and upper abdominal pain that radiates around the torso, sometimes accompanied by jaundice or pancreatitis and glossy, sticky, fatty stools. Sadly, our treatment options at these advanced stages are very limited.

What does that mean for patients?

If the tumor is inoperable, a patient has on average between six months and a year to live. All we can do at that point is try to alleviate their symptoms and delay the tumor growth. If the tumor can be surgically removed, average life expectancy is around two years, since tumor cells will often already have spread to the liver, lymph nodes or lungs – or the pancreatic tumor recurs. ▷

Picture credit: ediundsepp

How are you approaching early detection?
My colleagues and I are working to improve early diagnosis of pancreatic tumors, as well as of gastrointestinal cancers such as bile duct tumors. Our efforts here center on endoscopic molecular imaging, using fluorescent dyes that adhere to tumor components and light them up. In this way, we can render the tumor visible. We are also planning to develop an ultrasound contrast agent that binds specifically to pancreatic carcinomas. This would make even very small malignancies visible, enabling effective surgical removal.

You mentioned that treatment options for pancreatic cancer are limited – but to what extent?
It is only possible to remove the tumor in one in five patients. In the other cases, it will already have grown into surrounding structures such as the hepatic artery or surrounding structures, or metastasized into other organs. And that's where the problem begins: pancreatic cancer is relatively resistant to chemotherapy. Only a small segment of patients respond to chemotherapy with platinum-based substances. These target dividing cells by crosslinking the DNA and inhibit the mechanisms cells normally use to repair defective DNA strands. The effect of cell-growth-suppressing substances 5-fluorouracil and gemcitabine is limited too. Plus the patients in question are not a homogenous group. Rather, there are various subgroups with cancer caused by different genetic changes, requiring individual treatment. As it stands, we haven't even identified all the subgroups yet. ▷

Prof. Dieter Saur

Scientist and clinician in one person

Dieter Saur is a researcher who likes to question dogmas and does so with success. After earning his initial medical qualification, Saur stayed in Munich, transferring from Ludwig-Maximilians-Universität München to TUM in 1993. He then gained his doctorate in gastroenterology at TUM's university hospital (II. Medizinische Klinik), graduating summa cum laude and winning TUM's doctoral award. His doctoral thesis and postdoctoral qualification (2006) investigated neuronal control of the intestines, i.e. "gut-brain" function. A clinician and a researcher in one person, Saur still engages intensively with this topic. But when the hospital (II. Medizinische Klinik) established a new focus on tumor diseases of the gastrointestinal tract in 2002, he was also able to develop novel technologies and tackle completely new research issues. It became clear to him then that pancreatic cancer would be his primary focus in the future. The use of new endoscopic imaging procedures for early detection of gastrointestinal tumors is also a key topic for him.

A doctor of internal medicine specializing in gastroenterology since 2007 and a professor since 2013, Saur has accumulated a range of awards and grants along the way – most recently the prestigious Consolidator Grant from the European Research Council (ERC) for his work in pancreatic cancer. "The ERC grant is awarded to high-risk projects that promise groundbreaking results. It gives you the opportunity to purse completely new avenues." So just the thing for an adventurous researcher like Saur, who readily calls accepted doctrine into question – with great success. Personally, he also welcomes the resulting opportunity to network with many other researchers in receipt of ERC grants. His research goal for the coming years is to use optimized mouse models to develop innovative treatment strategies for pancreatic cancer. And a period abroad, perhaps? "The time has never been right – either my clinical work or my research always meant I couldn't leave. But now I've reached a point where a sabbatical might be feasible."

Picture credits: Jooss

Polychemotherapy containing multiple conventional cytotoxins seems to have a greater effect on more patients. However, it turns out that this combined treatment triggers inflammation within the tumor, which in turn reactivates it.

Ralph Steinman, Canadian winner of the Nobel Prize in Medicine, and Apple founder Steve Jobs had different types of pancreatic cancer, so their survival outlooks differed widely at the start …

Yes, there are various types of pancreatic carcinoma, linked to different prognoses. Around 90 to 95 percent of pancreatic tumors occur in the tissue that produces digestive enzymes, especially in the head of the pancreas. That was the case for Ralph Steinman. Their proximity to the bile duct, gallbladder, liver, stomach and duodenum means that these tumors can compress the bile and pancreatic ducts and tumor cells can also infiltrate these organs. A buildup of obstructed bile leads to jaundice. When Steinman was diagnosed with pancreatic cancer, it had already spread to the draining lymph nodes. The prognosis was poor. Steinman was only able to live with the condition for four years because an immunotherapy he himself developed prolonged his life to some extent. There are some case reports that describe patients responding well to this therapy, which could be a new treatment option for a certain subgroup, but not all patients. In around one to two percent of cases, tumors form in specific pancreatic cells responsible for producing hormones such as insulin and glucagon – both of which play an important role in the metabolism of sugars. These tumors are often relatively benign and respond well to treatment. But Steve Jobs' case involved a neuroendocrine tumor that became malignant. They managed to remove it completely and Jobs seemed to be cancer-free, but around three years later, metastases occurred in his liver. The tumor had already spread at the time of surgery.

What are the risk factors for pancreatic cancer?

Lifestyle factors such as smoking, alcohol consumption and obesity can increase the risk of pancreatic cancer. But other risk factors include type 2 diabetes and chronic inflammation of the pancreas (pancreatitis). Inherited predisposition plays a role in around 13 percent of pancreatic tumors. We hope to have all risk genes precisely identified in the coming five to ten years. Breast cancer genes BRCA 1 and 2 also increase the risk of pancreatic carcinoma. And we suspect there are more genetic risk factors too, as yet unknown.

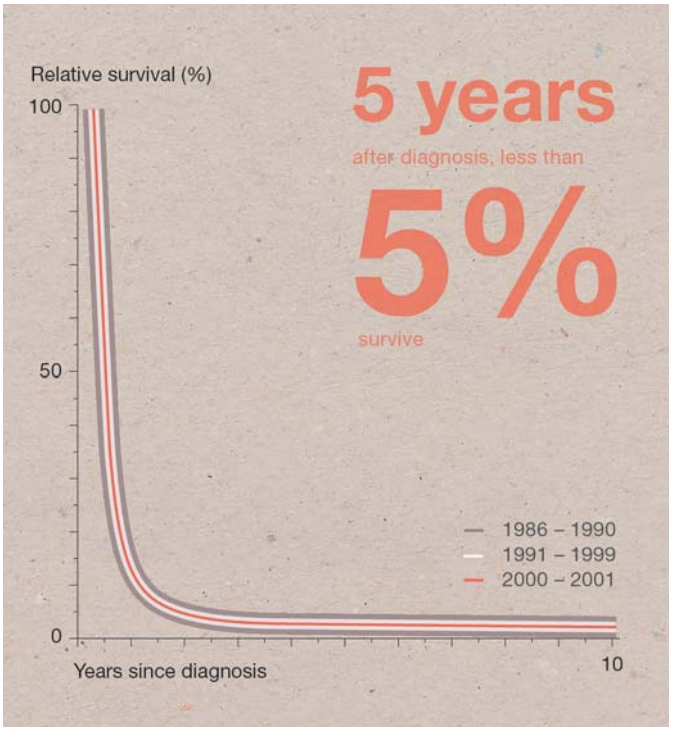
You're keen to strike out in a new direction with your research and have now received a much-coveted ERC grant to this end. What new treatment strategies are you and your team investigating?

Our approach takes account of the fact that pancreatic cancer differs significantly in structure to other types of tumor. It is an extremely complex condition. While other types of tumor primarily consist of malignant cells, 90 percent of a pancreatic ▷

"For the first time, our new genetic mouse models enable us to observe the effects of treatments and the strategies tumor cells develop to bypass such therapies." *Dieter Saur*

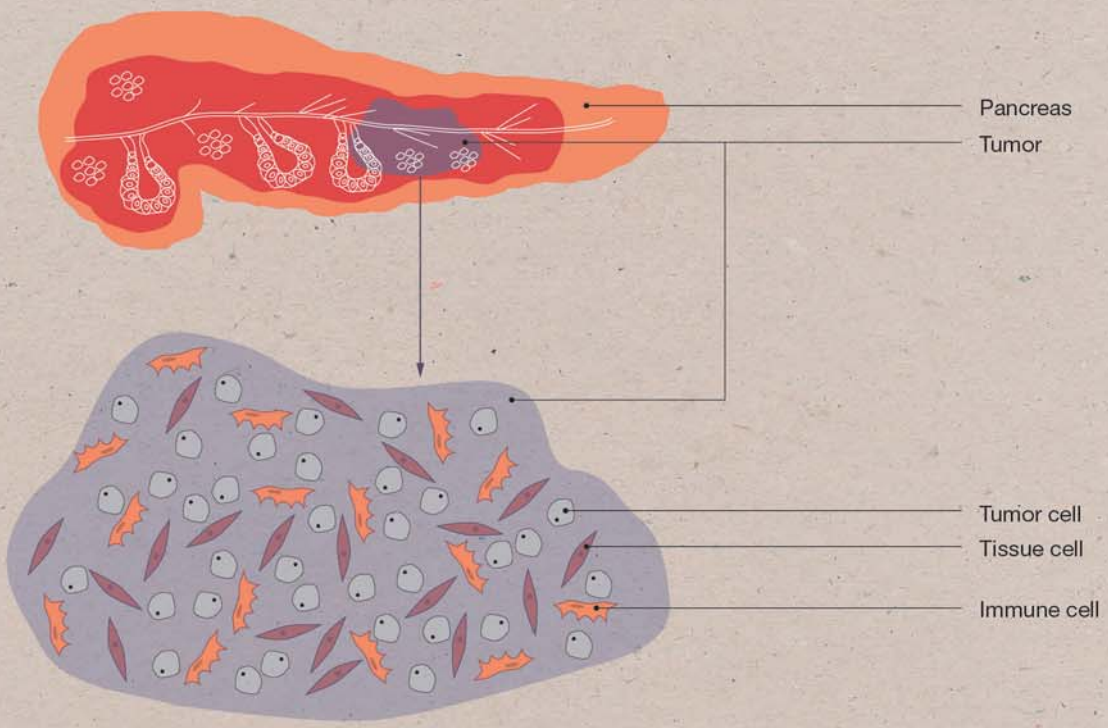
Picture credit: Jooss, Graphics: eigundeepp (Data: Ba… …rnal of Cancer, 2008)

Pancreatic cancer has been and still is extremely hard to combat. The tumor can go unnoticed for quite a while and by the time it is diagnosed, treatment options are still very limited. In the past 30 years, the chances of survival have not improved significantly.



"To target pancreatic cancer effectively, we aim to pursue a dual strategy with two different substances. One is designed to kill off the tumor cells, while the other should act on the connective tissue and immune cells in the tumor in such a way that they turn against the tumor cells again."

Dieter Saur



While most types of tumor primarily consist of malignant cells, 90 percent of a pancreatic carcinoma is made up of tissue cells, immune cells and an extracellular matrix such as collagen. Tumor cells account for just 10 percent. The carcinoma recruits tissue and immune cells to serve the needs of the tumor. Dieter Saur wants to attack not only the tumor cells, but also find a way to stop the tissue and immune cells from supporting the tumor.

carcinoma is made up of connective tissue cells, immune cells and an extracellular matrix such as collagen, with malignant tumor cells accounting for just 10 percent. Cancer therapies that target oxygen supply to the tumor via the bloodstream don't work on poorly supplied pancreatic tumors. The carcinoma can survive in the most adverse conditions and pursues a strategy that other tumor diseases do not use to the same extent. The tumor cells use specific proteins to recruit connective tissue cells to serve the needs of the tumor, contributing to its chemoresistance and even helping it grow. Chemoresistance means that the cells are not susceptible to a drug used in chemotherapy. Innate and adaptive immune system cells are also located in the vicinity. If they migrate into the affected pancreas, they secrete the transmitter substance Interleukin 6, for instance – which stimulates growth in the tumor cells. So instead of suppressing the disease, these substances actually facilitate it. To target pancreatic cancer effectively, we aim to pursue a dual strategy with two different substances. One is designed to kill off the tumor cells, while the other should act on the connective tissue and immune cells in the tumor in such a way that they turn against the tumor cells again. So this attacks the tumor on two fronts.

And the European Research Council is supporting your efforts – what role does this ERC grant play?

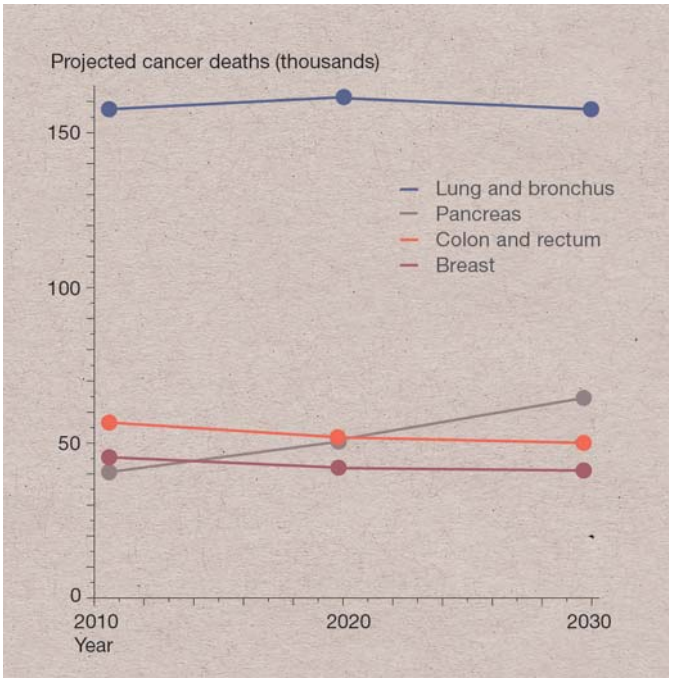
It makes it possible to test this treatment strategy using new genetic techniques. Over many years of work, we have put the building blocks in place one by one and developed genetic mouse models – that is, mice that have been genetically engineered in a specific way. A wide range of different genes and signal pathways can be activated or deactivated at any given time to test out therapeutic options. These innovative genetic model systems will enable us to reproduce and analyze many more tumor characteristics using mouse models than ever before.

How are the mouse models structured?

The mouse models carry various carcinogenic genetic alterations and use three different "cutting enzyme" systems and one short sequence of base pairs that enable gene recognition and allow the enzyme to cut DNA at a specific location in the genome. The genes are then flanked by these sequences so that we can initiate their removal specifically in the pancreas. As a result, the associated protein is no longer produced either. We can then investigate whether this has an impact on the effectiveness of a chemotherapy treatment, for instance.

Why was it important to develop new genetic model systems? And are they already in use?

The mouse model developed ten years ago enabled the study of cancer formation – but no more than that. For the first time, our new genetic mouse models enable us to observe the effects of treatments and the strategies tumor cells develop to bypass such therapies. That gives us insight into the way drug resistance evolves and allows us to develop strategies to prevent it. Our mouse model has already been implemented and works very well. Besides us, it is in use by thirty to forty research groups worldwide, who are investigating various aspects of this disease. Our hope is that international collaboration will improve the treatment landscape for pancreatic cancer as quickly as possible.



The number of people diagnosed with cancer will rise in the future. For most cancer types, screening and therapies have improved so much that – despite the higher number of patients – fewer people die of their tumor. This is not the case for pancreatic cancer, because of the limited treatment options once the tumor is detected. (Data: Rahib et al., Cancer Res. 2014)

That does sound promising. Will the findings be applicable to humans?

We have many indications that the results we are obtaining from preclinical animal models can be applied directly to humans. These range from the genetic characteristics of tumors through their growth patterns to their ability to metastasize. Additionally, tumors in mouse models show the same degree of resistance to established therapies as do human pancreatic carcinomas. However, it is still essential to test findings from animal models directly on human tumors. Only when we are certain that the results we obtain also apply to the relevant subcategories of pancreatic cancer in humans will we initiate clinical trials.

Gerlinde Felix

Graphics: ediundsepp (source: TUM)

New State-of-the-Art **Compact X-Ray Source**

Prof. Franz Pfeiffer devotes his scientific interest to developing new X-ray technologies for biomedical science and clinical use. He is a pioneer in phase contrast X-ray imaging and has laid the foundation for applications for this technique in medicine and industry, where it is expected to deliver improved image contrast with lower doses of radiation. Like all scientists presented in this issue, Pfeiffer, too, had been able to convince the European Research Council of his revolutionary ideas and had been supported by an ERC Starting Grant in the past. Now his group installed the world's first mini particle accelerator for high-brilliance X-rays, which offer much better image quality.

For some years now it has been possible to generate high-brilliance X-rays using ring-shaped particle accelerators (synchrotron sources). However, such installations are several hundred meters in diameter and cost billions of euros. The world's first mini synchrotron was inaugurated on October 29, 2015 at TUM. It can generate high-brilliance X-rays on a footprint measuring just 5 x 3 meters. The new unit will be used chiefly to research biomedical questions relating to cancer, osteoporosis, pulmonary diseases and arteriosclerosis.

Scientists and physicians are still routinely using X-rays for diagnostic purposes 120 years after their discovery. A major aim has therefore been to improve the quality of X-rays in order to make diagnoses more accurate. For example, soft tissues could thereby be visualized better and even minute tumors detected. For a considerable time, a team at the Technical University of Munich (TUM) headed by Prof. Franz Pfeiffer, Chair of Biomedical Physics, has been developing new X-ray techniques.

Starting October 29th, the scientists will now be able to use the world's first mini synchrotron for high-brilliance X-rays at their institute. The Munich Compact Light Source (MuCLS) is part of the new Center for Advanced Laser Applications (CALA), a joint project between TUM and LMU Munich.

New technique: collision between electrons and a laser beam

The California-based company Lyncean Technologies, which developed the mini synchrotron, employed a special technique. Large ring accelerators generate X-rays by deflecting high-energy electrons with magnets. They obtain high energies by means of extreme acceleration, and this requires big ring systems.

The new synchrotron uses a technique where X-rays are generated when laser light collides with high-speed electrons – within a space that's half as thin as a human hair. The major advantage of this approach is that the electrons can be traveling much more slowly. Consequently, they can be stored in a ring accelerator less than five meters in circumference, whereas synchrotrons need a circumference of nearly one thousand meters.

"We used to have to reserve time slots on the large synchrotrons long in advance if we wanted to run an experiment. Now we can work with a system in our own laboratory – which will speed up our research work considerably," says Pfeiffer.

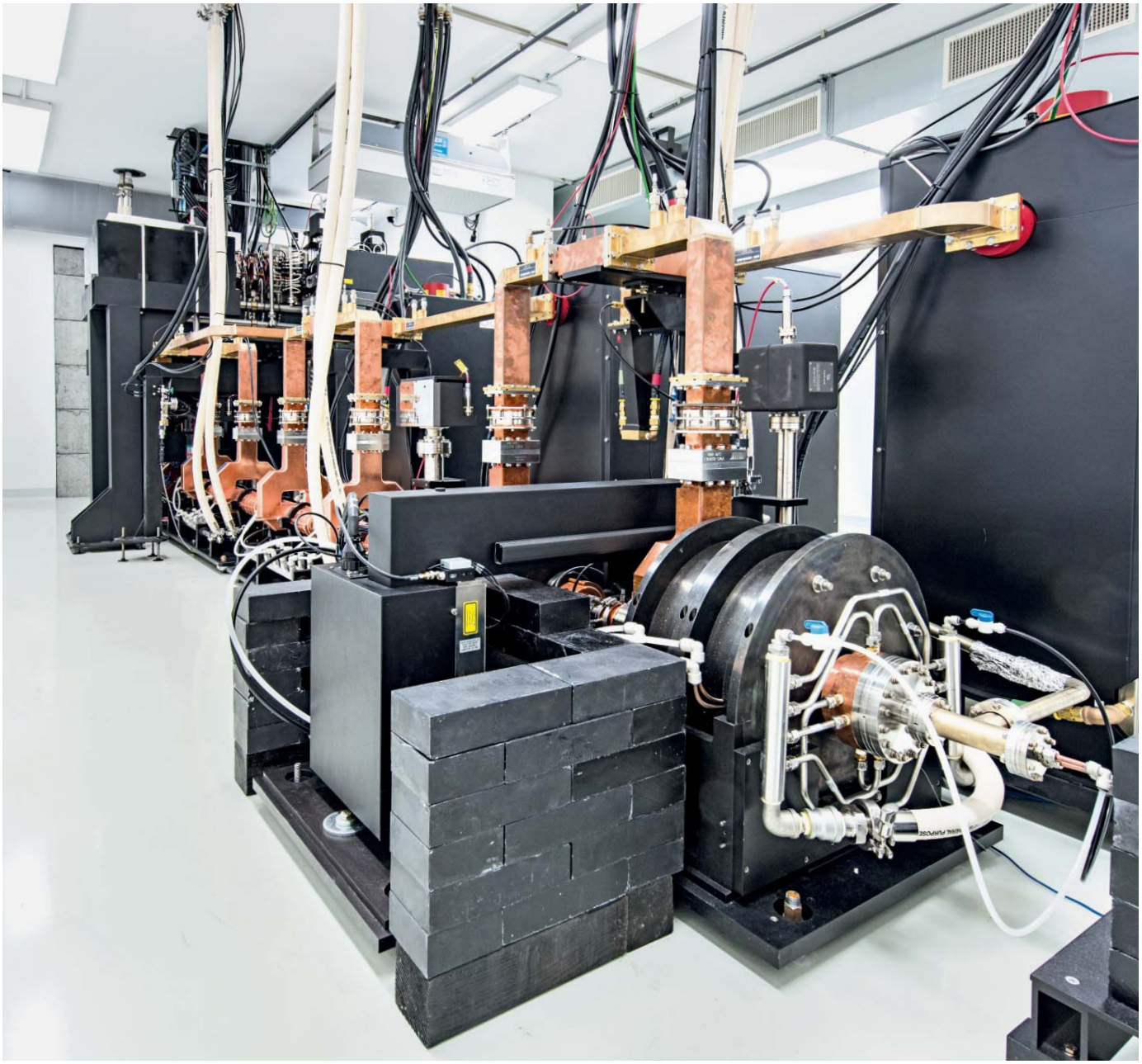
More intense, more variable and with better resolution

Apart from being more compact, the new system has other advantages over conventional X-ray tubes. The X-rays it produces are extremely bright and intense. Moreover, the energy of the X-rays can be precisely controlled so that they can be used, for example, for examining different tissue types. They also provide much better spatial resolution, as the source of the beam is less diffuse thanks to the small collision space.

"Brilliant X-rays can distinguish materials better, meaning that we will be able to detect much smaller tumors in tissue in the future. However, our research activities also include measuring bone properties in osteoporosis and determining altered sizes of pulmonary alveoli in diverse lung diseases," explains Dr. Klaus Achterhold from the MuCLS team.

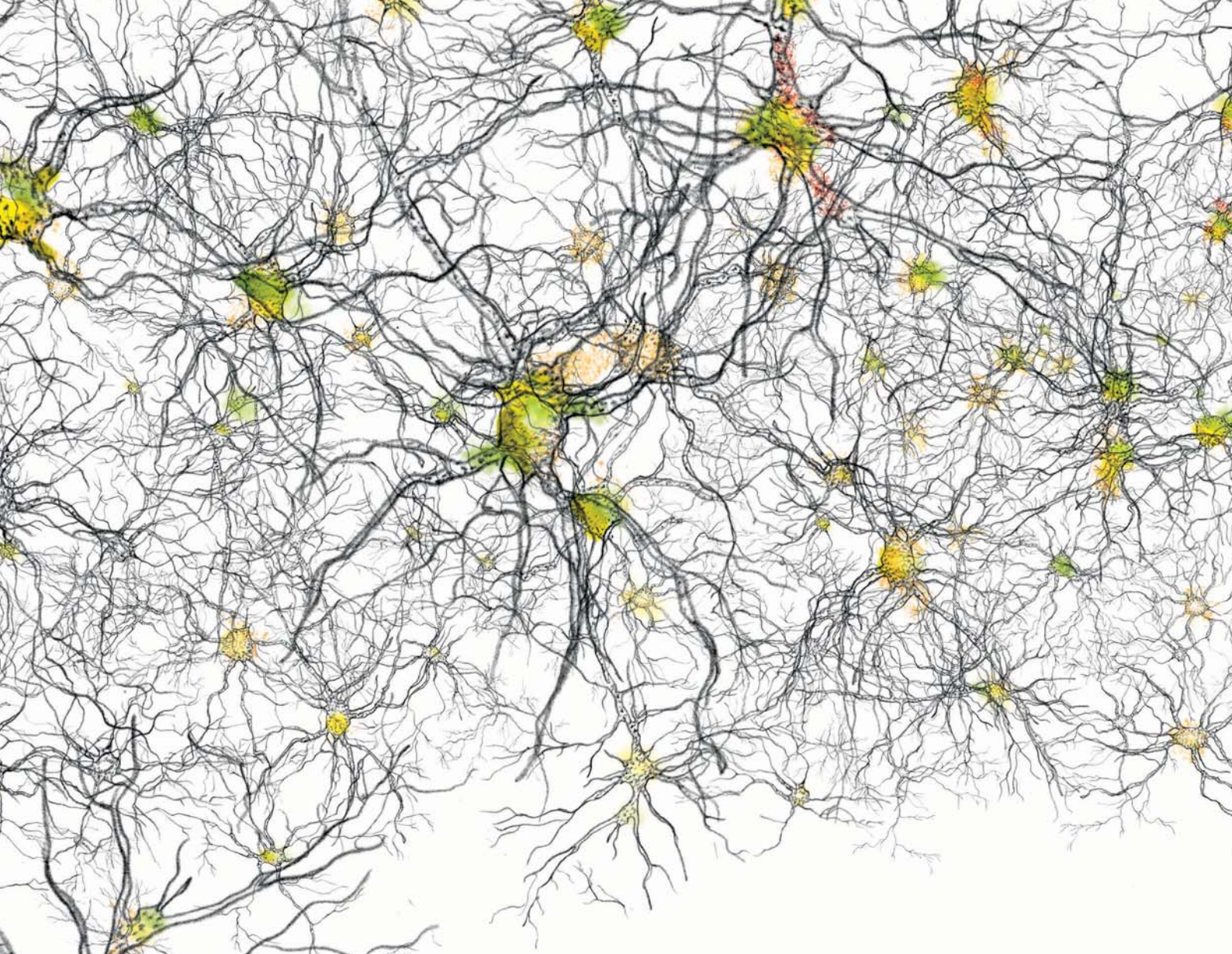
The scientists will initially use the instrument mainly for preclinical research, i.e. examining tissue samples from patients. They will also combine the new X-ray source with other systems, such as phase contrast. The group headed by Franz Pfeiffer has developed and refined the new X-ray phase-contrast technique. *Vera Siegler (TUM)*

Link
www.e17.ph.tum.de



The new mini synchrotron “Munich Compact Light Source” is the world’s first mini accelerator for high-brilliance X-rays. It is located in Garching at the TUM Institute of Medical Engineering (IMETUM).

Picture credit: Heddergott



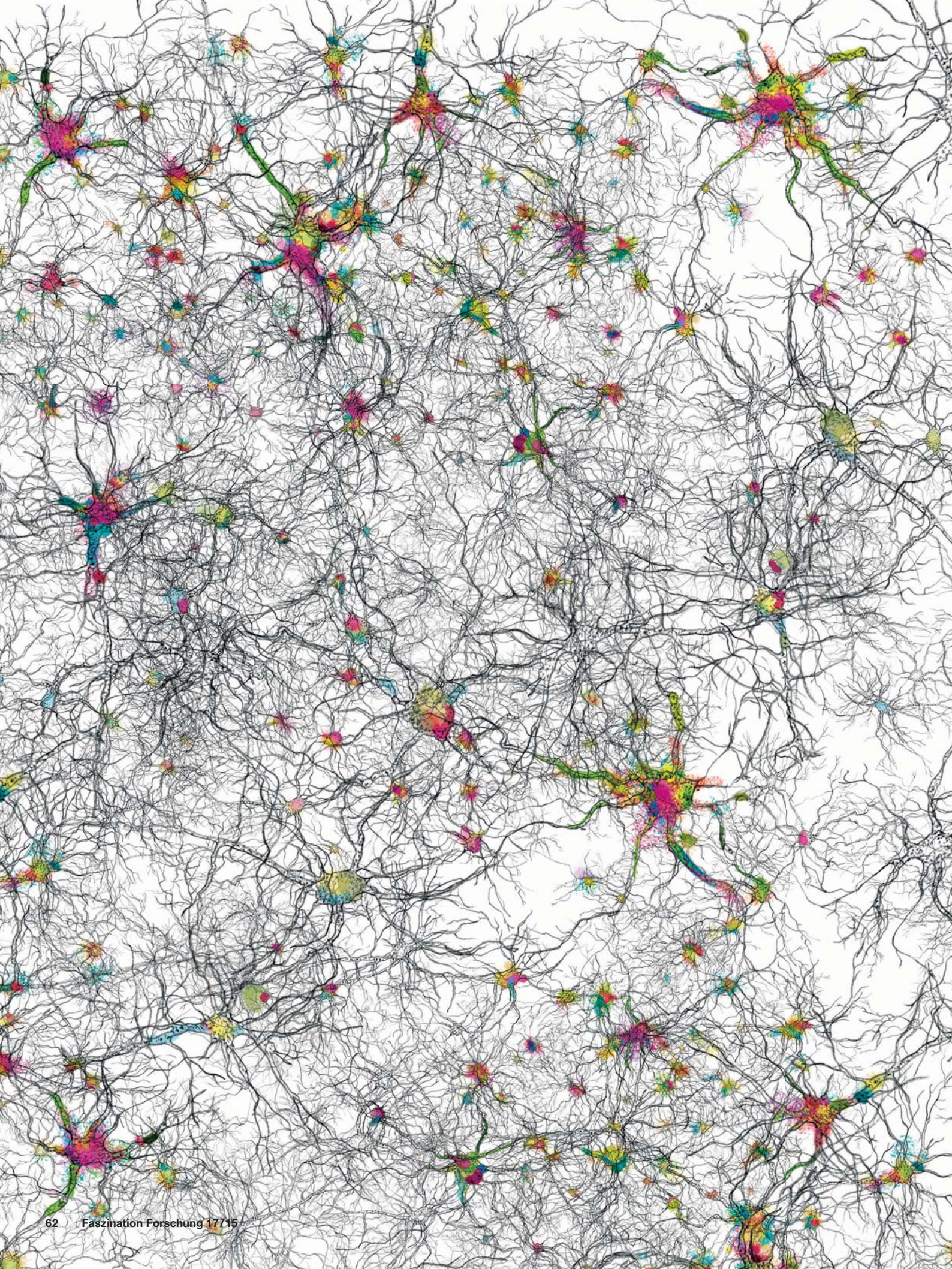
Link
www.misgeld-lab.me.tum.de

A Double-Edged Axe **in the Axon Forest**

There's rich variety of form and function among the hundred billion neurons that make up the human nervous system, yet almost every neuron has an axon. This extension from the cell body, typically resembling a trunk with many branches, carries electrical and chemical signals outward to other cells. During early development, the brain's axon "forest" is shaped by a pruning process that selectively cuts branches and clears the way for optimal neural networking. The same process shows a destructive aspect in old age, however, playing a role in neurodegenerative diseases. Prof. Thomas Misgeld is investigating the dual nature of axon loss.

When we are very young, as young as Thomas Misgeld is in this picture, our brain builds up a rich abundance of nerve fibers called axons, which transmit signals between nerve cells.

Graphics: ediundsepp



During childhood, our brains exhibit the highest number of synaptic connections and axons. Thereafter, the pruning of the axon forest sets in and excess connections are cut.

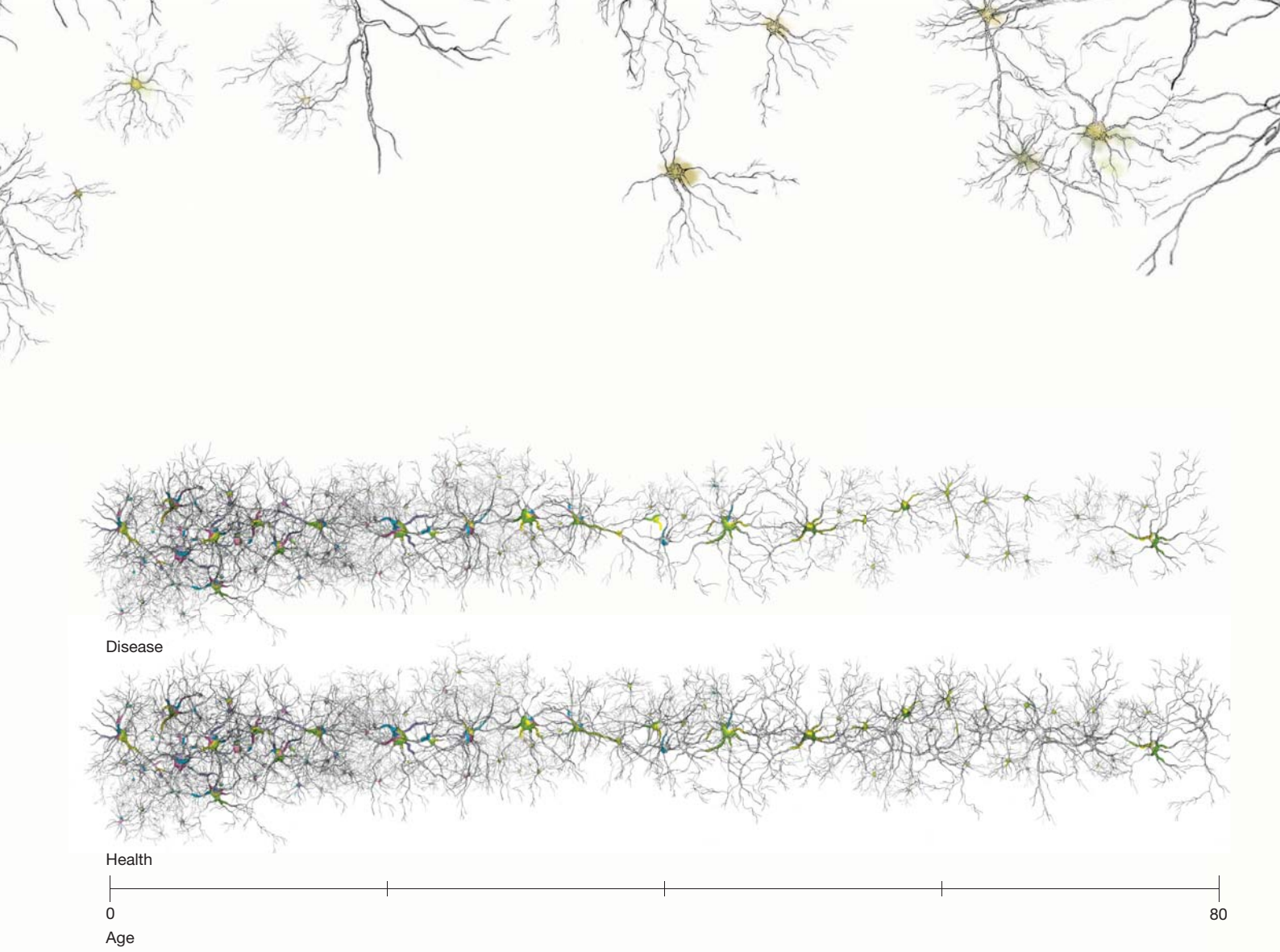
Graphics: ediundsepp

Patrick Regan

Eine zweischneidige Axt im Axonenwald

Wenn wir noch sehr jung sind, führt eine Wachstumsphase in unserem Gehirn zu einem Überschuss an Nervenfasern, den sogenannten Axonen. Diese Fortsätze von Nervenzellen leiten Signale von einer Nervenzelle zur nächsten weiter. Neurowissenschaftler ziehen oft den Vergleich zu einem Wald, in dem die Bäume den Nervenzellen, die Baumkronen den Axonen und ihre Verzweigungen den Synapsen entsprechen. In vielen Teilen des Gehirns werden bis zu 90 Prozent dieser Axonäste im normalen Verlauf der Entwicklung beseitigt. Dieser Prozess ist bisher nur teilweise erforscht. Unsere sensorischen und motorischen Systeme werden demnach während der Entwicklung verschaltet, indem die meisten der möglichen Nervenverbindungen abgebaut werden. Im hohen Alter besteht jedoch die Gefahr, dass derselbe Vorgang das Gehirn zerstört: Das Risiko, dass wir irgendwann im Leben an einem neurologischen Leiden erkranken, bei dem der Axonabbau eine Rolle spielt, ist sehr hoch. Der Abbau von Axonen ist also ein zweischneidiges Schwert – oder eine zweischneidige Axt, um im Bild des Waldes zu bleiben. Während unserer normalen Entwicklung gestaltet der Axonabbau unsere neuronalen Netzwerke, aber im Alter kann er bei verschiedenen Erkrankungen zur Zerstörung von kognitiven, sensorischen oder motorischen Funktionen beitragen.

Prof. Thomas Misgeld, Direktor des Instituts für Zellbiologie des Nervensystems an der TUM, will diesen Vorgang besser verstehen. Dafür hat er nun einen mit zwei Millionen Euro dotierten ERC Consolidator Grant eingeworben. Misgeld ist einer der Pioniere im Hinblick auf den Einsatz von Bildgebungstechniken, die moderne Mikroskopie und genetisch kodierte Biomarker kombinieren, um Veränderungen in der Struktur und der Funktion von Axonen *in vivo* beobachten zu können. In dem neuen Projekt werden die Mechanismen des Axonabbaus sowohl in motorischen Neuronen als auch im Zentralnervensystem während der normalen Entwicklung und der Krankheitsentstehung erforscht. Dabei handelt es sich primär um Grundlagenforschung, die Erkenntnisse über die Entwicklung und Anpassungsfähigkeit unseres Gehirns liefern soll. Obwohl die Forschung nicht primär darauf ausgerichtet ist, Therapien gegen neurodegenerative Erkrankungen zu entwickeln, so sind grundsätzliche Erkenntnisse dieser Art unerlässlich, um das Verständnis dieser häufigen Erkrankungen zu verbessern und damit mögliche therapeutische Ansatzpunkte zu identifizieren. □

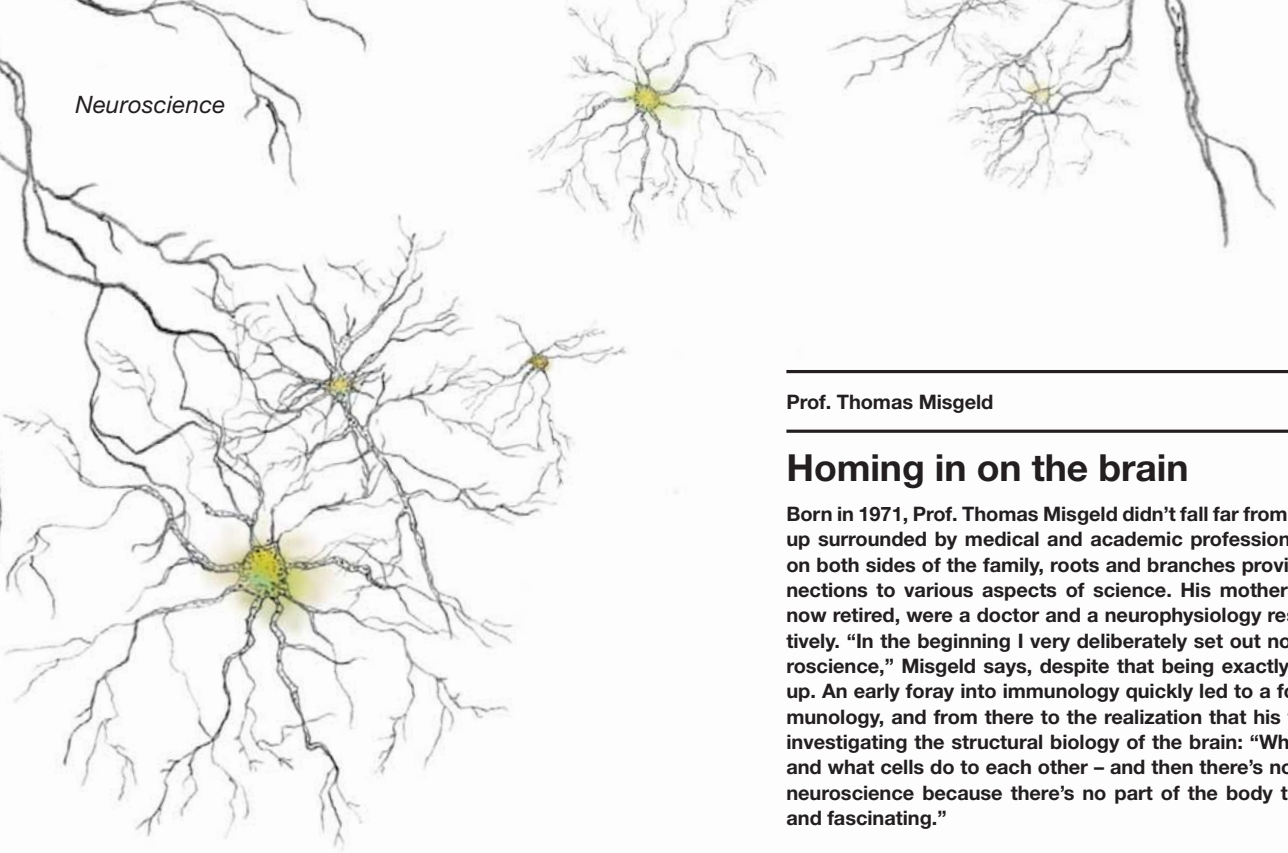


When your brain was very young, a period of exuberant growth produced a rich abundance of nerve fibers called axons – extensions of nerve cells that transmit impulses from one neuron to another – far more of them than would ultimately be put to use. Neuroscientists often liken this growth to a forest, with the trees being neurons and the canopy overhead consisting of axons and their synapse-bearing branches. Some of your young neurons, like trees growing in unsuitable places, were eliminated by apoptosis, a virtually universal mechanism for cell death. In addition, many of the remaining axon branches, up to 90 percent, were cleared away during the normal course of development through a "pruning" process that is only partly understood.

Largely in response to your specific environment and experience, your sensory and motor systems were wired up for life by taking down many of the possible connections. With old age, however, comes the danger that the same process will be the brain's undoing: If you grow very old, your lifetime risk of developing a disease in which axon loss plays a role – such as multiple sclerosis, amyotrophic lateral sclerosis, or Alzheimer's disease – could be very high.

Thus the mechanism is like a double-edged sword – or a double-edged axe, in keeping with the forest analogy – that both shapes and destroys. Axon loss can be observed sculpting neuronal networks during development and then, in a number of different diseases, contributing to the disruption of cognitive and neuromuscular functions. Gaining a more detailed understanding would be a big step in neuroscience and might also open new avenues for medical interventions against the looming epidemic of neurodegenerative disease. ▷

Graphics: ediundsepp



Ripe for discovery

There's no shortage of questions: How exactly does activity translate to morphology, leaving the imprint of experience on the circuitry of the nervous system? What kinds of signals set axon loss in motion? What mechanism allows a single branch to be selectively dismantled while leaving surrounding branches unharmed or even strengthened? What rules determine which branches will flourish and which will die off? If, as it appears, there is some kind of competition at play, what are the axons competing for? If competition alone can't explain the observations, what else is going on? Does the initial reversibility sometimes observed point toward a therapeutic window for disease-related axon loss? Will it be possible to identify pathways in axon loss that could be targeted for treatment?

"I don't understand it, and no one does" is a recurring refrain in conversations with Prof. Thomas Misgeld, director of the Institute of Cell Biology at TUM. He says this with excitement, never a hint of frustration. Every unknown could be an opportunity, and some of the most intriguing gaps in the neurobiological understanding of development and disease appear ripe for investigation using his techniques.

Misgeld's group and associated researchers have developed imaging techniques that make changes in the structure and function of axons observable *in vivo*. Two main areas of innovation come together here: novel approaches to microscopy and genetically encoded biosensors. Key examples would be two-photon microscopy and genetically encoded calcium indicators. Together, these lines of research have produced a versatile toolkit for making selected parts of individual ▷

Prof. Thomas Misgeld

Homing in on the brain

Born in 1971, Prof. Thomas Misgeld didn't fall far from the tree. He grew up surrounded by medical and academic professionals, with doctors on both sides of the family, roots and branches providing natural connections to various aspects of science. His mother and father, both now retired, were a doctor and a neurophysiology researcher, respectively. "In the beginning I very deliberately set out not to work in neuroscience," Misgeld says, despite that being exactly where he ended up. An early foray into immunology quickly led to a focus on neuroimmunology, and from there to the realization that his true passion was investigating the structural biology of the brain: "What cells look like, and what cells do to each other – and then there's nothing better than neuroscience because there's no part of the body that's as complex and fascinating."

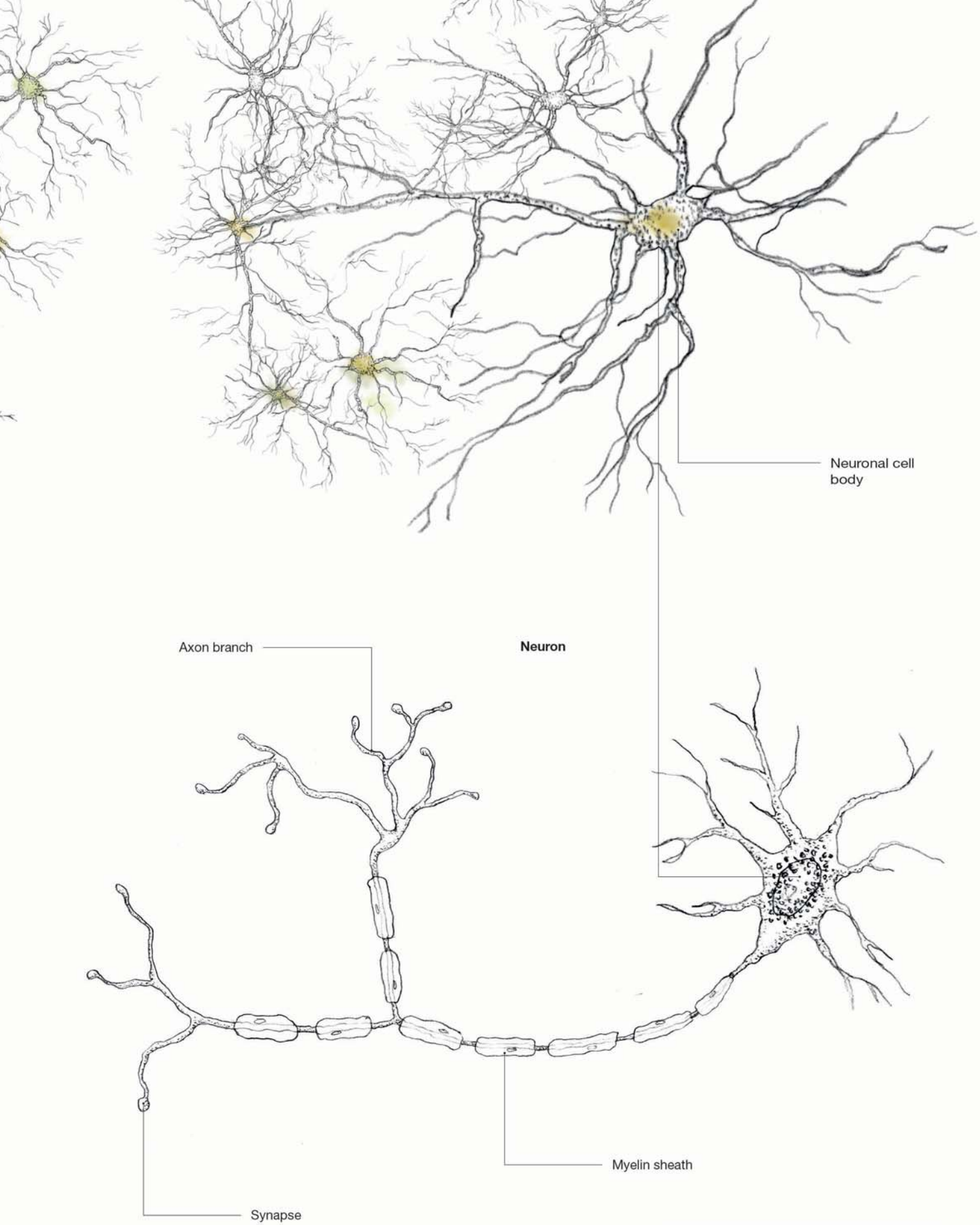
Following medical training in Munich, at TUM and the Max Planck Institute for Neurobiology, Thomas Misgeld did postdoctoral research in the United States. At Washington University in St. Louis and at Harvard, he acquired expertise in cutting-edge microscopy techniques for *in vivo* imaging that continue 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 of the TUM Institute of 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-coordinators of SyNergy.

While in America, Misgeld made a new family connection that would prove vital for his research as well. It was in St. Louis that he met his wife, Dr. Leanne Godinho. An accomplished scientist in her own right, Godinho is the anchor for much of the lab's work on developmental neurobiology, and particularly for research employing the zebrafish model. "Developing a dual career path in Germany is hard, as it is everywhere," Misgeld says, "but the environment here really allows us to do the kind of research we want, and to build up capabilities that will become increasingly important in the future."

Asked why he applied for an ERC Consolidator Grant, Misgeld first cites the obvious advantages: It brings in a substantial amount of funding (roughly two million euros in this case), and it's good for the prestige of the university. Beyond that, he stresses that the ERC offers one of the few "bottom-up" funding schemes in Europe. "That means you can do what you want rather than what some advisory committee – whether wisely or not so wisely – has recommended be investigated now." And the Consolidator Grant in particular fills an important gap, he says: Young scientists in Europe, especially in Germany, have a number of different ways to raise money for the first critical years of independent research, but very few third-party funding options that would enable them to continue at the same level. For Misgeld, these funds allow him to expand the more basic, biological side of his lab's research – while the more disease-oriented work continues – and to upgrade the lab's already formidable experimental infrastructure.

As an adult, our brains have substantially fewer axon branches and synapses than in our youth. Now, our neurons form a network of reliable and specific connections.

Picture credit: edlundsepp



Schematic representation of a neuron and its processes. The axon shown is not to scale; in reality it would be much longer.

In the healthy brain, the number of axons and synapses remains fairly stable, even in the adulthood. However, there is a risk that the process of axon degeneration may resume and contribute to diseases such as Alzheimer's disease or multiple sclerosis.

neurons – in animal models such as mice and zebrafish – reveal their location, status and function. Misgeld and colleagues pioneered *in vivo* single-axon microscopy and have, over the past few years, applied their methods to questions regarding axon degeneration.

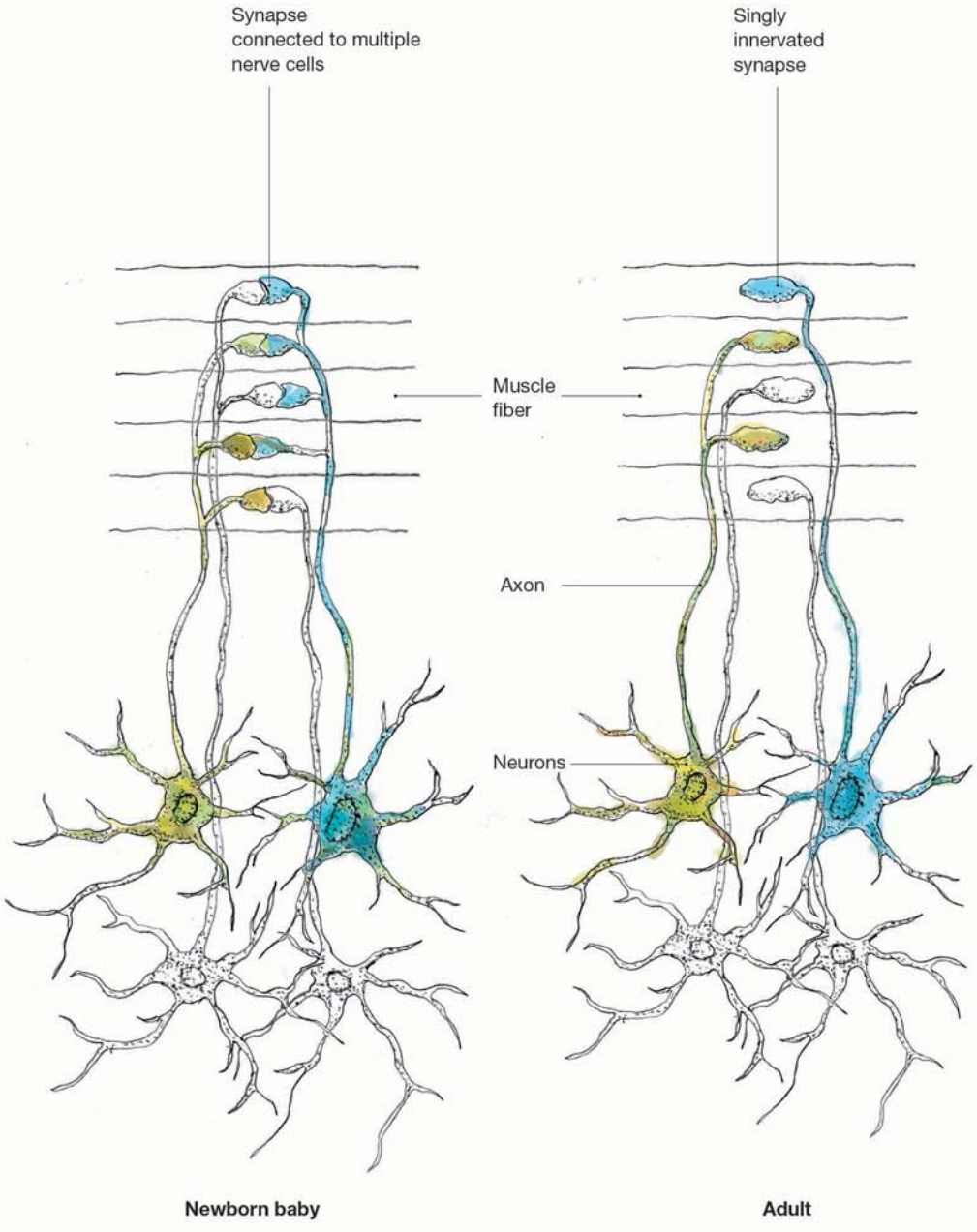
Models closer to nature

This effort is now being expanded and sharpened with support from the European Research Council, which awarded Misgeld an ERC Consolidator Grant to study "Mechanisms of Developmental and Injury-related Axon Branch Loss", a project nicknamed DIABLo. The mission is the further exploration of axon loss in the mammalian nervous system, developing and diseased, at the level of cellular and molecular biology.

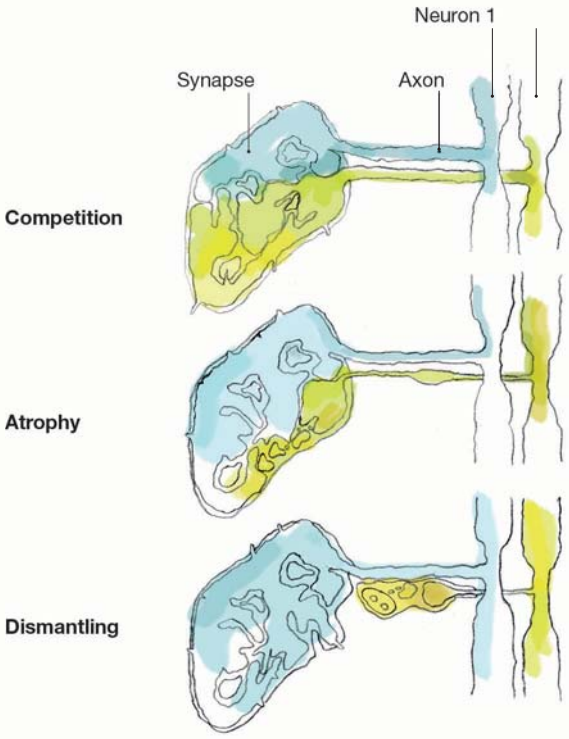
One distinctive feature of the project is a shift away from the standard way to trigger axon loss for study in the lab – an injury that completely cuts the nerves. "Except for a few specific cases, the approach of cutting something and then looking at what happens to the disconnected part doesn't seem so relevant to most neurological diseases," Misgeld says, "where that's not the initial mechanism. In most of the more common neurological diseases, something happens in the beginning, something that we don't even understand, to cause the axons to go away."

Not by chance, his group and collaborators already have experience with diverse animal models that share this common trait: Axons disappear without initially being cut. And they find more similarity between the responses to such ▷

Picture credits: ediundsepp



Innervation – meaning the "wiring up" of synapses – changes over a person's lifetime. For example, around the time of birth, each muscle fiber receives several weak inputs, which later remodel into a single, but strong input.



Axon branch loss occurs in distinct stages. In the normal "pruning" process, scientists assume that axons are competing. In disease as well as development, axons to be eliminated undergo thinning (atrophy) followed by localized swellings (dystrophy). In the final, dismantling stage, the axon is completely disassembled and cleared away.

"non-transecting" axon injuries in disease and development models than between either and the kind of axon loss triggered by a cut. One example is a process they have observed at developing neuromuscular synapses, which Misgeld suspects may be found to act elsewhere. Branches singled out to be disassembled go through a series of changes – overall thinning (atrophy), localized swellings (dystrophy), and local fragmentation at the tip repeated until completed – resembling the way an icicle melts. These individual steps also occur in diseases involving axon loss. Another characteristic that appears to be the same in development and disease is the role of glial cells, which surround and sheath neurons. Glial cells definitely do clean-up work by scavenging fragments of axon branches and might even – it remains to be seen – actively drive axon loss.

Four paths forward

Therefore, in DIABLo, Misgeld will concentrate on non-transecting models of axon loss, despite the increased difficulty of defining when exactly the process of axon dismantling begins. There are four main components of the project. The first, using developing motor axons as a model, will explore intrinsic mechanisms of axon loss. One set of experiments will focus on subcellular events that precede atrophy, particularly changes in axonal transport thought to destabilize selected, resource-starved branches while strengthening others.

The second component of the project, again using a motor axon model, will closely examine the role of glial cells in the death, breakup, and "self-digestion" of individual axon branches. During the initial atrophy phase, glial cells – which normally provide protective sheathing – "turn from friends to foes," Misgeld says. They first loosen their tight association with axons and synapses before engulfing fragments and finally disappearing – perhaps being digested by other members of the body's clean-up crew. The details of this sequence are unknown, and should be revealing.

The third and fourth experimental programs turn to the central nervous system in development and disease. The basic question is whether or not the mechanisms that operate in the brain and spinal cord are the same as those observed in the motor axon models. Misgeld suspects that they are. If so, the proof could expedite future research, since experiments with motor neuron models are technically less challenging than imaging individual cells in the central nervous system of living animals. In the development model, all of the group's prior experience will be brought to bear as they attempt to label corticospinal axons destined to undergo pruning and then to image the entire process *in vivo*. The fourth component of DIABLo will use a minimum-impact contusion technique to cause a non-transecting spinal injury and trigger axon loss, thus modeling disease in the central nervous system. This final element forms the most direct link between the ERC-funded project and other ongoing work in Misgeld's institute, including experiments involving models of multiple sclerosis, motor neuron disease and neuromyelitis optica. Such research is not aimed at developing cures, but it might yield knowledge that could lead in that direction.

"My group is not translational," Misgeld explains. "What we are doing is a step removed even from what most people call preclinical translation. My lab doesn't do quasiclinical studies, for example, where you look to see whether the mice in cohort A or cohort B are doing better. But we are always on the lookout for reasonable targets that other labs might want to study in that way."

Patrick Regan

"There's no part of the body that's more fascinating than the nervous system." *Thomas Misgeld*

Picture credits: ediundsepp (Source TUM)

Wir forschen für Ihren Erfolg

Pumpen und Armaturen langlebig und energiesparend zu konstruieren – das ist unser Ziel. Ob bei Hydraulik, Automation oder Werkstofftechnik, unsere Ingenieure schauen über die aktuellen Anforderungen des Marktes hinaus, analysieren Trends und adaptieren Technologien. Das Ergebnis: hochwertige Technik und innovative Produkte wie unser SALINO® Pressure Center, mit dem wir die Trinkwassergewinnung aus dem Meer revolutioniert haben. **www.unseretechnik.ihrerfolg.de**

Besuchen Sie uns auch unter www.ksb.com/sozialemedien

› Unsere Technik. Ihr Erfolg.
Pumpen ▪ Armaturen ▪ Service

KSB

Authors

Gerlinde Felix is a freelance journalist for medical and scientific topics. She holds a degree in physics and attended medicine courses at the university. Gerlinde Felix has been working as an author for newspapers, magazines and online publications for many years.

Patrick Regan has been a member of the TUM Corporate Communications Center since 2009. He came to TUM from PBS and NPR affiliate New Jersey Public TV and Radio in the US, where he produced 800 news reports on science and technology and hosted two interview series. In prior work at Bellcore and Bell Labs, he served as a science writer, magazine editor, executive speech writer, media relations manager and corporate spokesperson. He is a senior member of the IEEE.

Dr. Brigitte Röthlein has been working for many years as science author for magazines, TV and radio broadcasting and for newspapers. She holds a diploma in physics and a Ph.D. in communication science, education science and history of natural sciences. Her main interest lies in basic research.

Gitta Rohling, M.A., works under the brand name Auftrag Wort as a writer, editor and PR consultant. She supports mainly companies operating in technical and scientific fields in the areas of PR, press work and text.

Claudia Steinert 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.

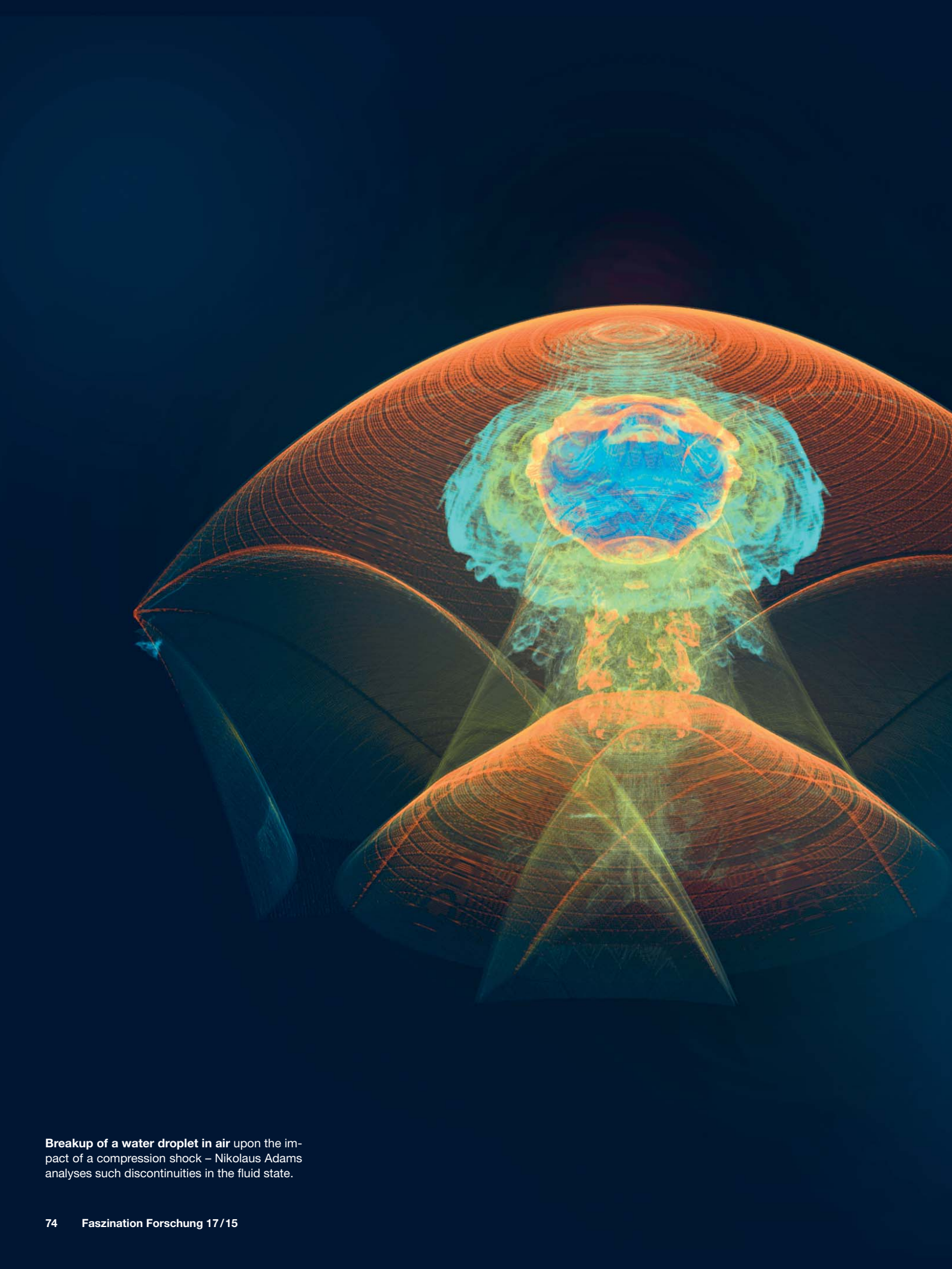
Dr. Evdoxía Tsakiridou studied philosophy and biology and completed a doctorate in brain research, followed by an internship at a daily newspaper. As a freelance science journalist, she writes for a variety of media, produces podcasts and also works in technical communications.

Dr. Karsten Werth is a freelance science journalist based in Munich. He studied history and American studies, writing his doctoral thesis on the US space program of the 1960s. He went on to gain experience with various industrial and media enterprises in the US, Canada and Germany, including as Editor-in-Chief at a PR agency.

Imprint

Faszination Forschung
Technische Universität München’s Science Magazine
Sponsored by the Excellence Initiative of the German federal and state governments

Publisher
Prof. Dr. Dr. h.c. mult. Wolfgang A. Herrmann, President of Technische Universität München
Editorial Office
Dr. Christine Rüth (Editor-in-Chief)
Translations
Capella & McGrath GmbH, Munich
Copy-editing
Baker & Harrison, Munich
Design
ediundsepp Gestaltungsgesellschaft, Munich
Authors in this issue
Gerlinde Felix, Patrick Regan, Dr. Brigitte Röthlein, Gitta Rohling, Vera Siegler, Claudia Steinert, Dr. Evdoxía Tsakiridou, Dr. Karsten Werth
Address of the Editorial Office
Technische Universität München, Corporate Communications Center, 80290 Munich
E-mail
faszination-forschung@zv.tum.de
Printing
Druckerei Joh. Walch GmbH & Co. KG, Augsburg
Circulation
45,200
ISSN: 1865-3022
Frequency
Twice a year
Responsible for editorial content and advertisements
Dr. Ulrich Marsch
Photographers
Astrid Eckert, Andreas Heddergott, Magdalena Jooss, ediundsepp
Cover photo
Astrid Eckert, Magdalena Jooss, ediundsepp



Breakup of a water droplet in air upon the impact of a compression shock – Nikolaus Adams analyses such discontinuities in the fluid state.

Link
www.aer.mw.tum.de

Spotlight on **Shock Waves**

An abrupt change in the density, pressure and temperature of a flow as opposed to a gradual increase is known as a shock wave – a phenomenon that could prove promising for a wide range of applications in industry and medicine. However, this would first require significantly greater understanding of the occurrence and impact of these shocks. Prof. Nikolaus Adams intends to devote the next five years to intensive research into their potential for biomedicine and nanotechnology – supported by an ERC Advanced Grant of EUR 2.4 million.

Shock wave expanding in gas: A bubble in a mixture of hydrogen, oxygen and xenon is exposed to a strong pressure wave, which swirls and ignites the gas mixture. A front of flames is created, which propagates through the mixture.

Picture credit: TUM/Adams

Gitta Rohling

Verdichtungsstöße – technisch gezielt einsetzbar?

Die Moleküle in einem Fluid streben nach einem Gleichgewichtszustand. Ändern sich Strömungszustände aber sprunghaft über sehr kleine Distanzen, entsteht ein thermodynamisches Ungleichgewicht in Form eines Verdichtungsstoßes. Ein typisches Beispiel ist der Knall, den der Mensch beim Überflug eines überschallschnellen Flugzeuges wahrnimmt. Die Moleküle der Luft müssen dem Flugzeug so schnell ausweichen, dass dies nicht mehr im thermodynamischen Gleichgewicht möglich ist. Es entsteht ein Verdichtungsstoß, der sich mit dem Flugzeug mitbewegt und den der Mensch als Knall wahrnimmt, wenn die sprunghafte Druckzunahme über ihn streicht. Mechanismen und Eigenschaften dieser Verdichtungsstöße wird Prof. Dr.-Ing. Nikolaus Adams in den nächsten fünf Jahren intensiv erforschen, gefördert durch einen mit 2,4 Millionen Euro dotierten ERC Advanced Grant. Verdichtungsstöße könnten für vielfältige Anwendungen in der Industrie und der Medizin interessant sein – beispielsweise für die Krebstherapie. Adams entwirft folgendes Szenario: „Nahe einer kranken Zelle werden winzige Dampfblasen erzeugt, die dann implodieren. Die so erzeugte Stoßwelle perforiert die Zellwände, sodass dank der nachlaufenden Strömung Medikamente schnell in die Zelle einströmen können. Ist die Perforierung klein genug, kann sich die Zellwand danach wieder schließen.“ Das wäre eine Therapie, die gezielt eingesetzt werden kann und die Dosierung von Medikamenten und damit auch die Nebenwirkungen deutlich reduziert.

Um solche Anwendungen zu ermöglichen, gilt es zunächst, das Verständnis über dieses Phänomen deutlich zu erhöhen. Adams interessiert ganz besonders, wie maßgeschneiderte Stöße erzeugt werden können und wie Stöße mit Phasengrenzen und Nanopartikeln interagieren. „Quantitativ und detailliert lassen sich diese Phänomene nur mit der numerischen Computersimulation untersuchen, die wir durch ausgewählte Experimente unterstützen werden.“ Einzelphänomene können die Wissenschaftler bereits gut simulieren; die Herausforderung liegt darin, mehrstufige Wechselwirkungen in komplexen Umgebungen nachzustellen – wie etwa in lebenden Organismen. „Oder ist die Komplexität so hoch, dass die Entstehung und die Auswirkungen der Verdichtungsstöße nicht vorhersagbar sind und diese sich daher nicht für die technische Beherrschung eignen?“, formuliert Adams die Frage, die ihn umtreibt. Erst wenn sich diese Frage verneinen lässt, können die Wissenschaftler untersuchen, welche Mechanismen und Eigenschaften eine kontrollierte Bildung von Stößen ermöglichen und wie sie sich auswirken. □

Molecules in a gas or liquid seek equilibrium. If the density, pressure and temperature of a fluid changes, the molecules usually have enough time to reach equilibrium – but not in the event of a shock wave. “In that case, the molecules cannot spontaneously achieve equilibrium. Instead, they are in a state of thermodynamic non-equilibrium,” explains Prof. Adams, Chair of the Institute of Aerodynamics and Fluid Mechanics at TUM.

Shock waves are sudden changes in flow states across very short distances. A typical example is the sonic boom we hear when an aircraft flies overhead faster than the speed of sound. The air molecules are forced out of the path of the aircraft so quickly that maintaining thermodynamic equilibrium is no longer possible. A shock wave forms that moves with the aircraft and is perceived as a boom by people on the ground when the sharp rise in pressure passes over them.

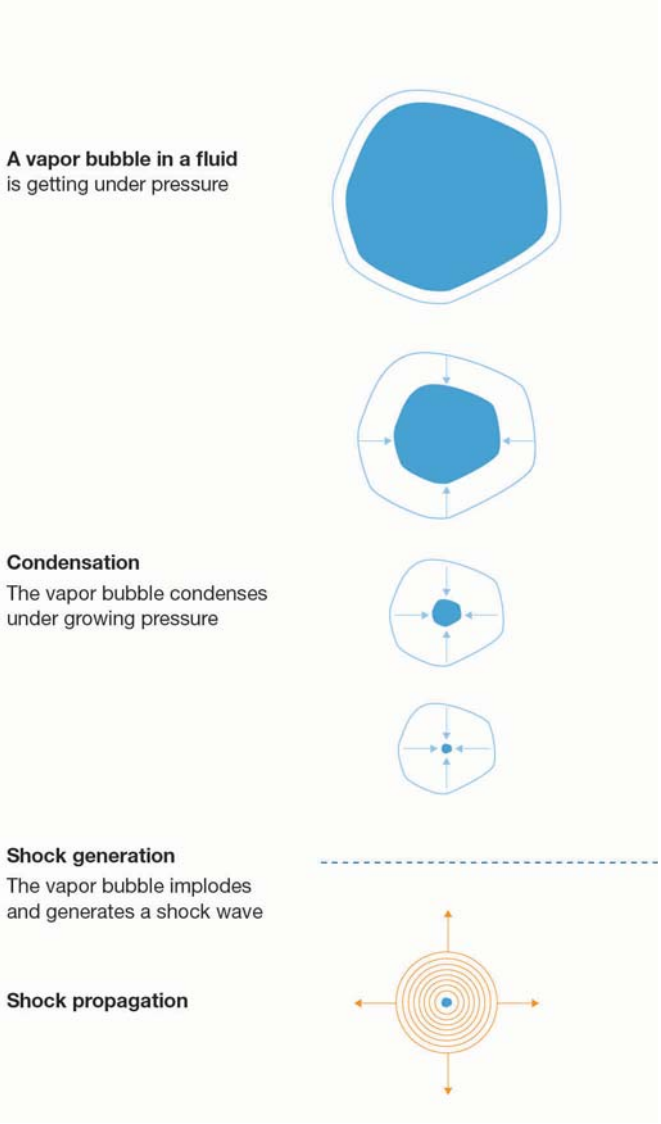
The formation, impact and potential for targeting shock waves is the focus of Adams’ research efforts, which he will now pursue intensively in a five-year project. This is facilitated by an ERC Advanced Grant – one of Europe’s most prestigious sources of research funding. The European Research Council awards these grants, endowed with EUR 2.4 million, to scientists who already have an outstanding track record and intend to pursue ambitious, pioneering and unconventional research.

From industry to medicine – of potential interest to a wide range of applications

Both the spatial localization and strength of shock waves means they hold potential for a wide range of applications. Direct fuel injection for diesel engines is a case in point. The automotive industry is keen to increase injection pressure as this would enable engineers to also reduce harmful emissions. However, extreme injection pressures result in extreme tensions in liquid fuel, which then evaporates without heating. Vapor bubbles, known as cavitation bubbles, form in the fuel and suddenly collapse (implode). This creates shock waves that are so strong, they can even damage hardened metals in fuel injector components on impact. This phenom-

"These phenomena are so tiny and fast that they are still largely unresearched and obtaining experimental data is a major challenge. Quantitative and detailed investigation is only possible by computer, using numerical simulation."

Nikolaus Adams



When a fluid containing vapor bubbles is exposed to higher pressure the vapor condenses and emits a strong shock wave upon final bubble collapse.

Picture credit: ediundsepp (Source TUM)

enon is called cavitation erosion and is also a familiar problem in the operation of marine propellers and water turbines. Yet what is a downside in engine technology could prove a benefit in medicine. "A fundamental problem in cancer treatment is that diffusion is a relatively slow process, so it takes time for drugs to reach the cancer cells, which have a higher internal pressure than healthy cells," describes Adams. In contrast to diffusion, shock waves are rapid processes and could be used to accelerate drug uptake significantly. Adams envisages the following scenario: "Tiny vapor bubbles are produced – for instance by ultrasound – in the vicinity of a diseased cell and then collapse. The shock wave this generates perforates the cell walls, with the subsequent flow allowing a rapid influx of drugs into the cell. As long as the perforation is small enough, the cell wall can close again afterwards." This would be a therapy that could be precisely targeted, substantially reducing the amount of medication required and thus also the side effects.

Mastering complexity through simulation

But before this type of scenario can become reality, scientists first need to improve their understanding of the physical processes involved. Adams is particularly interested in ways of generating tailored shock waves and how shocks interact with phase boundaries and nanoparticles: "These phenomena are so tiny and fast that they are still largely unresearched and obtaining experimental data is a major challenge. Quantitative and detailed investigation is only possible by computer, using numerical simulation."

In numerical simulation, scientists first formulate the basic properties of shock waves by means of physical and mathematical models, then implement these in dedicated programs on high-performance supercomputers. The decisive factor here is the number of degrees of freedom – that is, the number of variable data describing the flow. "The more degrees of freedom, the more accurate the simulation," Adams emphasizes. So this entails processing huge volumes of data. Thanks to improved processing power, the possibilities of numerical flow simulation have grown enormously over ▷

Prof. Nikolaus Adams

Research as a vocation

Inside Prof. Nikolaus Adams' office at the Department of Mechanical Engineering in Garching, near Munich, hangs a poster of aviation pioneer Otto Lilienthal with one of his flying machines. On it are printed three short phrases: "To know. To understand. To do." As far as Adams is concerned, Lilienthal represents the epitome of an engineer who acquires and analyzes knowledge to make it technically useful. "Lilienthal developed his flying machines without the possibility to rely on existing scientific knowledge, deriving knowledge and understanding from his observations of birds and his ability to turn those observations into technical solutions," recounts Adams, clearly impressed.

His ideal scientist, on the other hand, is Werner Heisenberg – due to the pursuit of scientific perfection that earned the physicist and founder of quantum mechanics his Nobel Prize in 1932. Heisenberg devoted himself to exploring the interplay between various findings in physics – such as the theory of relativity and quantum theory. As he recounted in 1970 in his talk" The Meaning of Beauty in the Exact Sciences": "In both cases, after years of vain effort at understanding, a bewildering plethora of details has been almost suddenly reduced to order by the appearance of a connection […]."

Adams uses similar terms to describe his fascination with numerical simulation – the computational process that allows exploration of complex physical flows and has thus become one of the most important tools in fluid mechanics today: "To carry out the simulation, we define a model in the form of a numerical algorithm, which serves as our working hypothesis. This involves reducing reality to the essentials based on assumptions and simplifications. I find that a fascinating form of research – we're trying to recreate reality, albeit well aware of the shortcomings of this approach. But that's the only way to understand what is actually happening."

Adams has been fascinated by this topic since his studies in aerospace engineering at the University of Stuttgart – making his path into research a matter of course. "Anyone wanting to improve our understanding of fluid physics essentially needs to work as a researcher. In industry the pressure for practical applications is high, which doesn't really allow for deeper examination of approaches and methods," he explains. Having received his doctorate with honors, he then took up a postdoctoral fellowship at the Center for Turbulence Research in Stanford, California. He went on to work as a scientist and lecturer at ETH Zurich and as a professor at the Dresden University of Technology, before transferring to TUM's Institute of Aerodynamics and Fluid Mechanics in 2004.

According to Adams, you know instinctively whether you would be well suited to research: "It's a vocation." As far as he is concerned, people who primarily view work as an obligation are not cut out for research careers. "But if you feel called to it and come equipped with the right skills, you'll make your way forward," he concludes with conviction.

"The ERC Advanced Grant gives us the freedom to redirect our research if unexpected results come up."

Nikolaus Adams

Picture credits: Eckert

the last few years. However, for large-scale simulations, the processes call for a lot more computational power – another area Adams is focusing on. As part of a team of researchers, he received the Gordon Bell Prize in 2013 for a flow simulation of a cavitation bubble cloud with 13 trillion degrees of freedom – the largest and most efficient ever performed at that time. The researchers simulated the simultaneous collapse of 15,000 gas bubbles within a liquid. To accomplish this, they used one of the world's fastest supercomputers, reaching a processing speed of 14 petaflops. That equates to 14 quadrillion (14,000,000,000,000,000) computer operations per second.

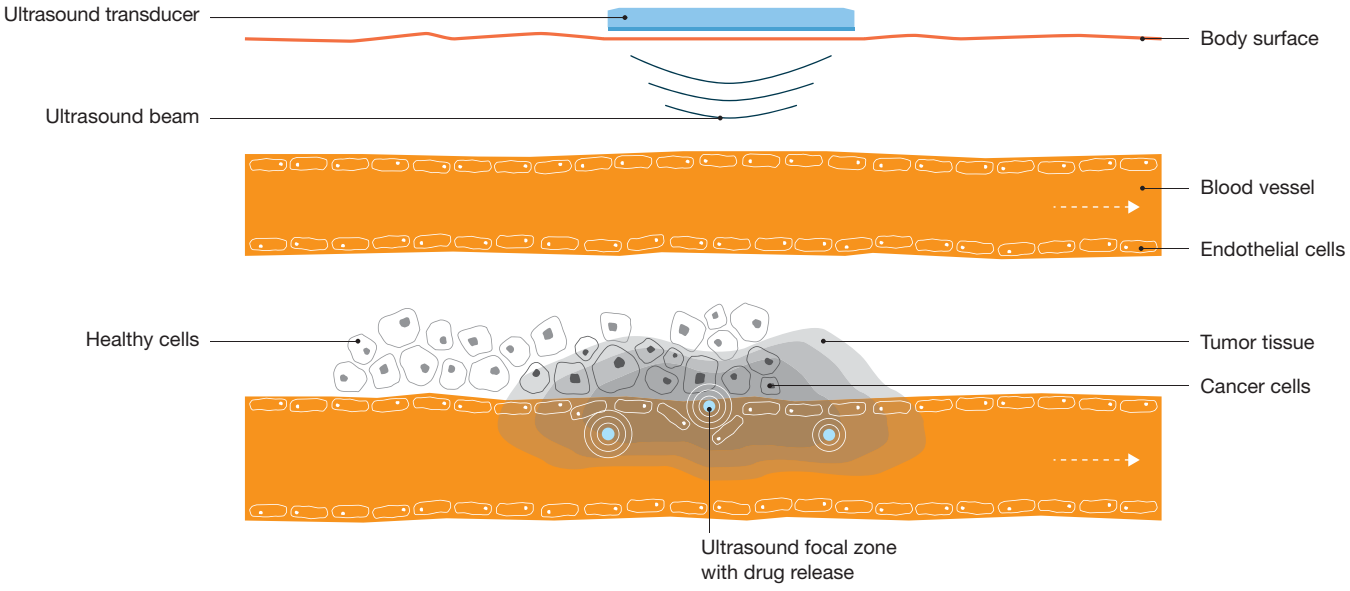
The burning question: can they be technically controlled?

The ERC Advanced Grant is crucial to Adams' ambitious research endeavors. Thanks to this funding, he is now able to extend an excellent research group by four doctoral students and one postdoc. Adams is particularly pleased to receive such "stable support over an unusually long period" and explains that, as a rule, grants tend to be smaller, shorter and thus more suited to incremental project proposals. In particular, the ERC Advanced Grant allows the scientists a fairly high degree of research freedom. "Disruptive research also becomes possible – we can redirect our efforts to pursue a new avenue if unexpected results come up," confirms Adams. The scientists will now start by using their simulations to address the burning question, namely can tailored shock waves be generated in complex environments such as living organisms? "We are already well able to simulate individual phenomena – the challenge lies in managing the complex interactions between them," clarifies Adams. Or, as he frames the question that drives him: "Is the level of complexity so great that the formation and impact of shock waves simply cannot be predicted, which means they cannot be controlled technically?" Only if he and his team succeed in managing this complexity can they then turn to investigating the mechanisms and properties that enable controlled formation of shock waves and their possible impacts – to the benefit of applications in industry and medicine.

Gitta Rohling

In the future, shock waves could help get medication exactly where it is needed: With the help of ultrasound, we could produce tiny vapor bubbles in the vicinity of a diseased cell and then collapse the bubble. The subsequent shock wave would perforate the cell walls, allowing a rapid influx of drugs into the cell.

Shock waves in medical applications



Picture credit: ediundsepp (Source: TUM)

Some said it couldn´t be done, but we didn´t get the message...

...so we did it.
Be part of our next challenges.

Consulting & Services

Technology & Products

Systems & Solutions

techSAT.com

Prof. Jean-Pierre Bourguignon

Jean-Pierre Bourguignon is President of the European Research Council. Prior to that, he was the Director of the Institut des Hautes Études Scientifiques (IHÉS) from 1994 till 2013. This international research institute located near Paris, France, was built as the European counterpart of the Institute for Advanced Study in Princeton. A mathematician by training, Bourguignon spent his whole career as a fellow of the Centre National de la Recherche Scientifique (CNRS). He held a professorship at École Polytechnique from 1986 to 2012. From 1990 to 1992, he was President of the Société Mathématique de France and President of the European Mathematical Society from 1995 to 1998.

Secure Funding **for Frontier Research**

In Horizon 2020, the EU's program to support research and innovation for the period 2014 to 2020, the need to develop frontier research has been fully recognized for its own sake and as a vital component for fostering innovation in the wider Europe. The three pillars (Excellent Science, Industrial Leadership, Societal Challenges) give Horizon 2020 a clear structure.

With the creation of the European Research Council (ERC) in 2007, representing about half the first pillar of Horizon 2020, the Union, for the first time, decided to support frontier research projects proposed by individual researchers on subjects of their choice, covering the whole field of knowledge, including the social sciences and humanities. Within the European scientific community, there is general agreement that this is having a real impact.

ERC grants quickly became highly coveted and competition for them is fierce. Around 11% of applicants succeed in the ERC calls and it is a fact that many excellent proposals remain unfunded as a consequence of the present level of the budget. But we see an undiminished demand, especially among the younger generation, and an equally undiminished quality in the applications the ERC receives. The ERC operates according to simple principles: it supports scientists from anywhere in the world, of any age and from any field of research with no predetermined targets or quotas. The ERC provides substantial, long-term funding of up to 2.5 million euros for up to five years. The only conditions are that ERC-funded researchers must be based in Europe and willing to be adventurous and to take risks in their research. And this to me is the real value of the ERC grants. Secure funding frees researchers from having to focus on immediate impact. From thinking about the next publication. From thinking about what to write in the next grant application. It allows scientists to really focus on the core of their research. In this way we hope that their work can lead to genuinely new knowledge, and in some cases even to radical breakthroughs. In other words, we encourage people to take risks, and we would like this approach to spread although we know that, spontaneously, the academic community tends to be conservative.

The hard part is to find a satisfactory balance between evaluating the credibility and the novelty of an idea. When you look for new ideas from scientists, then of course they must be evaluated by experts. But I think that it is critical to guide this process. I would therefore like to emphasize the need to give sufficient attention and respect to scientific diversity. One has to make sure that different ways of conducting research can be properly taken into consideration. Indeed, the critical number of people required to do significant work varies enormously from a single person to huge teams.

As a consequence, there is need for a great variety of effective programs to support research. Their evaluation must involve people with an inside knowledge of the practices of the discipline and of the environment in which researchers operate. The ERC assumes a very special role in this panoply, which needs to be properly understood and preserved. This is exemplified by the fact that the responsibility of defining how its budget is spent, as well as how its evaluation is conducted, has been given to a 22 member independent Scientific Council, a premiere among the programs of the European Commission. The ERC's peer review evaluation process has been carefully designed to judge applications on the exclusive basis of scientific quality, irrespective of gender, age, nationality or institution and other potential biases, while also taking career breaks and unconventional research career paths into account. The evaluation is monitored to guarantee transparency, fairness and impartiality in the treatment of proposals.

The most important impact is certainly the new opportunities for young and ambitious researchers that ERC offers, contributing to the development of a more dynamic and open community. □

Picture credit: ERC

swoboda
molding elements

www.swoboda.de

Von den Besten ausgezeichnet zu werden, ist kein geringes Lob.

Unsere Qualitätsmaßstäbe machen uns zu einem zuverlässigen Partner der Automobilindustrie. Wir hinterfragen selbstkritisch unsere Ergebnisse und arbeiten immer daran, einzigartige Lösungen zu entwickeln. Diese Leistung wird seit vielen Jahren von unseren Kunden mit Auszeichnungen honoriert. Das ist für uns Bestätigung und Ansporn zugleich, denn Stillstand bedeutet in unserer Branche Rückschritt.

Wir geben unser Bestes.
Wir sind stolz auf mehr als 2.600 Mitarbeiter weltweit, die ihr Wissen und ihre Erfahrung in die tägliche Arbeit einbringen. Innovation und Perfektion sind Ansprüche an unsere Arbeit. Als international gefragter Entwicklungs- und Fertigungspartner sind wir neben unserem Hauptsitz in Wiggensbach mit eigenen Werken in der Tschechischen Republik, in Rumänien sowie in den USA, Mexiko und China präsent.

Rund um den Globus etabliert.

Wir investieren in unsere Talente.
Dies gilt für die Ausbildung von Nachwuchskräften ebenso, wie für die Weiterentwicklung der Mitarbeiter. Wir arbeiten im Team und setzen auf gegenseitiges Vertrauen. Denn nur wer mit Leidenschaft dabei ist, kann Begeisterung entfalten. Auch deshalb fordern wir alle unsere Mitarbeiter auf, Verantwortung zu übernehmen. Für ihre Arbeit, für ihre Entscheidungen – und für das Engagement bei der permanenten Verbesserung von Prozessen und Produkten.

Swoboda – das sind wir.

Wir denken Zukunft.
Erfolg ist kein Zustand, Erfolg ist eine Aufgabe. Wir leben und denken Zukunft – und wollen deshalb auch weiter wachsen. Arbeiten Sie mit uns: an der Fortentwicklung unserer Produkte und an komplexen Aufgaben, die wir für unsere Kunden lösen. Kurze Entscheidungswege und hohe Flexibilität sind uns dabei sehr wichtig. Als Familienunternehmen schaffen wir Ihnen ein berufliches Umfeld mit Freiräumen und Perspektiven.

Willkommen im Team.

Wenn wir Ihr Interesse geweckt haben und Sie mehr über unser Unternehmen sowie unsere interessanten Stellenangebote erfahren möchten, besuchen Sie unsere Homepage **www.swoboda.de.**

Bitte richten Sie Ihre aussagekräftigen Bewerbungsunterlagen an: bewerbungen@swoboda.de

Gewinner Bayerischer Qualitätspreis 2014

BAYERISCHER QUALITÄTSPREIS 2014

Swoboda fördert das Deutschland STIPENDIUM

Partner der Hochschule Kempten University of Applied Sciences

DEUTSCHLANDS BESTE MITTELSTÄNDLER TOP 100 Swoboda KG Wirtschafts Woche

Mehr Raum für Sie.
Und Ihren Wissensdurst.

Was jemand kann, sieht man, wenn man ihm die Chance gibt, es zu zeigen. Deshalb lassen wir Ihnen vom ersten Tag an den nötigen Freiraum: Für Ihre Begeisterung, Ihre Kreativität und den Mut, Neues auszuprobieren. Egal ob während Ihres Praktikums, Ihrer Werkstudententätigkeit oder Ihrer Abschlussarbeit.

www.career.rohde-schwarz.com

ROHDE&SCHWARZ