

Faszination Forschung

TUM Research Highlights

Technical University of Munich

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Inorganic Chemistry: Gold Therapy

Nanophysics and Virology – Quarantine for Viruses

Cryptography – Data Security Now and in the Future

Neurology – Teamwork to Regain the Power of Language

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Dear TUM friends and associates,

An unconventional mindset free from the constraints of individual subject areas, with people at the heart of our aspirations – these are the cornerstones of the TUM Agenda 2030, which is guiding the transformation of our research and education. The TUM Innovation Networks act as focal points for creative research. They provide the scope to adopt visionary research approaches, explore uncharted scientific territory and put potential to the test.

In this issue of Faszination Forschung, you'll get to know two creative minds who serve as spokespeople for individual Innovation Networks. Simon Jacob works with researchers in the fields of medicine, natural sciences and informatics to understand complex brain functions such as language and develop methods to help stroke patients to regain the power of speech. Angela Casini is conversant with the untapped potential that inorganic chemistry holds for the development of novel drugs. She uses organometallic complexes to deliberately inhibit the flow of water through tiny channels in cell membranes, an approach that could lead to new cancer medications.

Hendrik Dietz is developing an innovative technology for the fight against viruses, namely encapsulating viruses in tiny DNA shells. Virologist Ulrike Protzer believes this is an exciting approach that could render even novel viruses harmless.

Additive manufacturing is already employed in numerous fields. This technology enables the development of new designs and the use of new materials. Katrin Wudy analyzes the entire process, from materials development through to quality management. Artificial intelligence is considered a valuable tool in the evaluation of immense volumes of data. Xiaoxiang Zhu harnesses AI to identify relationships and as yet unknown phenomena in earth observation. She develops algorithms supporting the analysis of satellite data.

Antonia Wachter-Zeh has dedicated her work to data protection. She looks ahead to the age of quantum computing, which will require new encryption methods. Her error-correcting codes are designed to repel attacks from quantum computers. Gil Westmeyer is striving to understand how learning processes function at the neural level. By deploying new markers for electron microscopy, he is making molecular processes in nerve cells visible.



When translated into products, research becomes practical, tangible and usable. Mahmoud Masri has developed a process to extract oil from yeast cultures – as an alternative to palm oil. He has founded a start-up with the aim of producing yeast oil in large-scale bioreactors in the near future.

I am certain that this issue of Faszination Forschung will once again provide exciting insights into our researchers' ideas and innovations. I hope you enjoy reading our latest issue!

Yours sincerely,

Thomas F. Hofmann
President

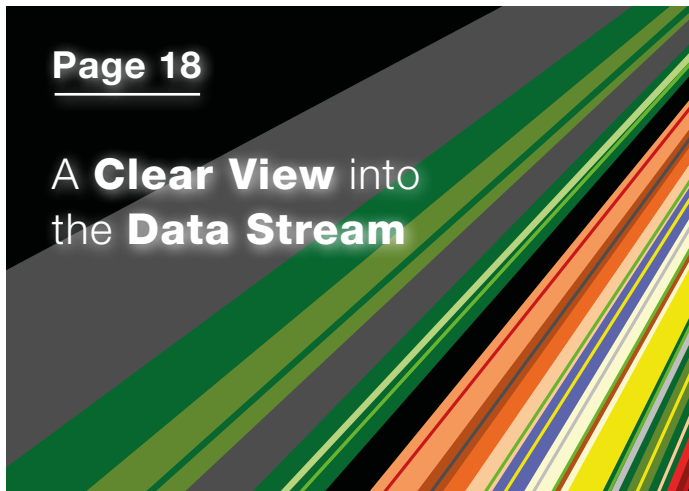
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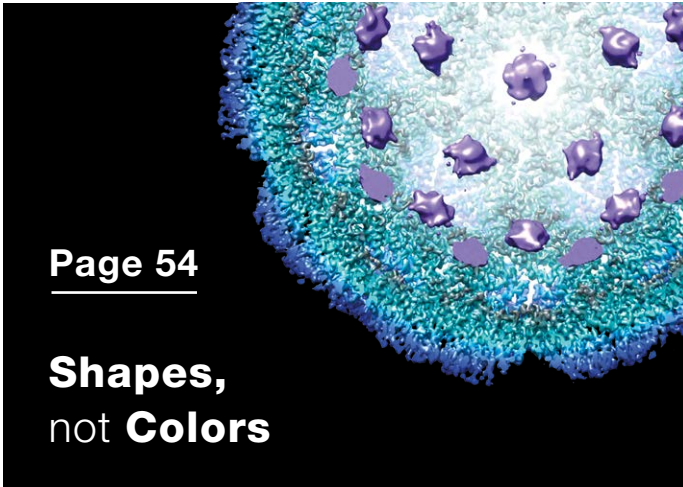
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Angela Casini sees considerable potential offered by inorganic chemistry for the pharmaceutical industry. Her research is laying the groundwork for novel therapies and new drug delivery strategies.

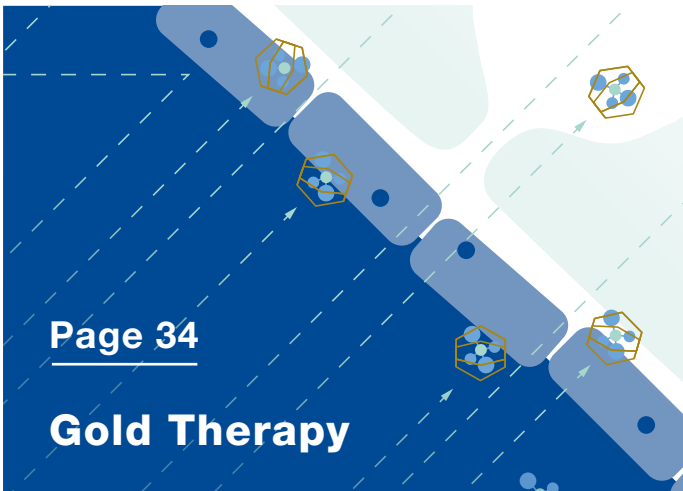
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Katrin Wudy drives the processes for series production with 3D printing. Her research focuses on powder bed fusion of both metals and plastics.



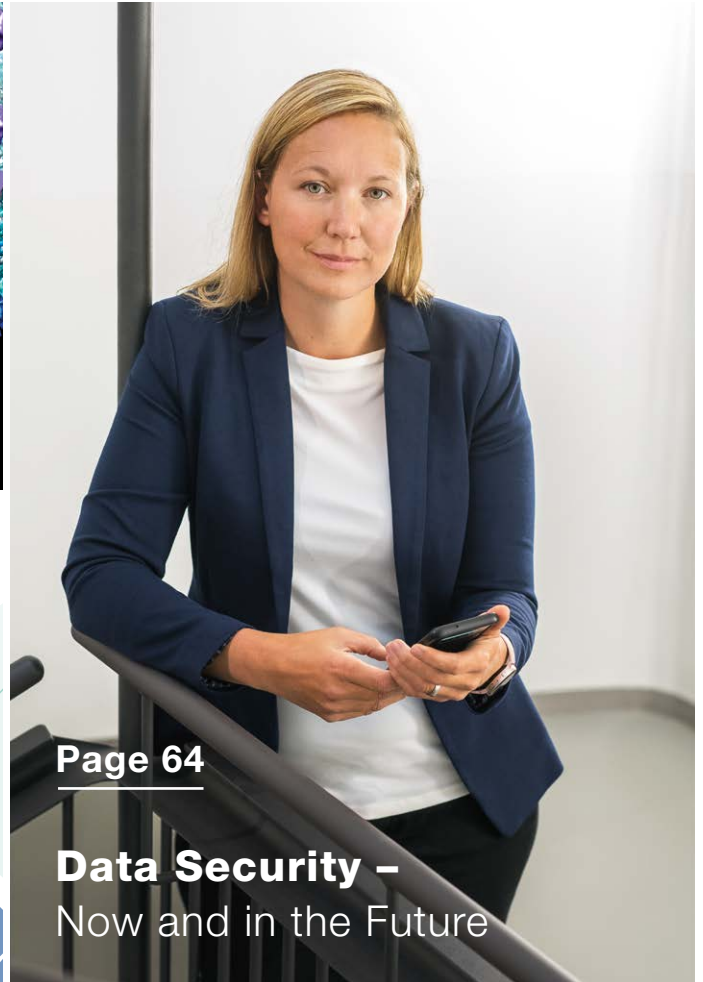
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not Colors**



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Picture credits: Juli Eberle, Stefan Woidig, Astrid Eckert/TUM; Graphics: edlundsepp (source: TUM), ACS (full credit see p. 54)

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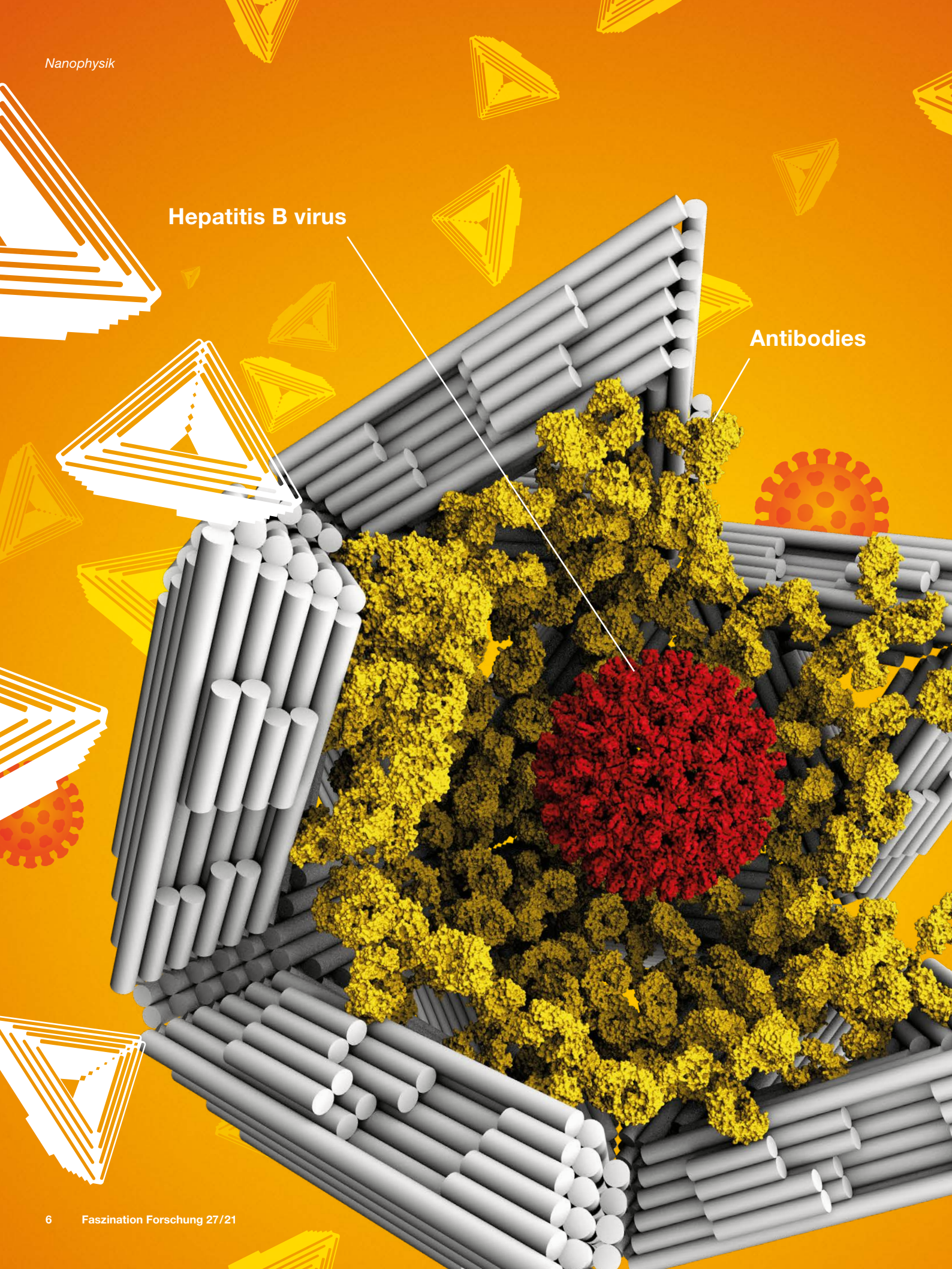
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German edition available as a PDF here:
www.tum.de/faszination-forschung-27

Hepatitis B virus

Antibodies



Link

www.dietzlab.org

Quarantine for Viruses

Though it might seem like an idea from the world of science fiction at first, it could soon become reality: Researchers hope to capture viruses in minute DNA capsules that prowl through the human body. TUM Professor Hendrik Dietz and his team have already laid the foundations for such a technology.

Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Quarantäne für Viren

D

In dem von der EU geförderten Projekt VIROFIGHT entwickelt Hendrik Dietz, TUM Professor für Biomolekulare Nanotechnologie, zusammen mit seinem Team und Fachleuten aus angrenzenden Gebieten eine radikal neue Technologie zur Bekämpfung von Viren. Das Team macht sich dabei die jüngsten Fortschritte in der supramolekularen Chemie, der molekularen Nanotechnik und der Virologie zunutze. „Unser Ansatz betrachtet ein völlig neues antivirales Konzept“, betont der Forscher. „Anstatt wie die derzeitigen antiviralen Medikamente auf die Funktion virusspezifischer Proteine oder Enzyme zu zielen, wird VIROFIGHT ganze Viren mit synthetischen Nanokapseln einschließen, um den Erreger effizient zu neutralisieren.“ Dies wäre eine absolut neue therapeutische Lösung, die verschiedene Viren auf derselben Plattform bekämpfen könnte, und würde im Erfolgsfall einen echten Durchbruch für die antivirale Medizin darstellen. Das innovative Konzept könnte viele Leben retten und enorme Gesundheitskosten für die Gesellschaft einsparen. □

DNA capsule



Prof. Hendrik Dietz

was born in 1977, grew up in Berlin and studied physics at LMU Munich. After being awarded his doctorate in protein mechanics, in 2007 he moved to Harvard Medical School where he joined a group of researchers led by William Shih seeking to produce three-dimensional objects from DNA. Together with computer scientist Shawn Douglas and other colleagues, he became known as a pioneer of DNA origami. In 2009, he accepted a position at TUM as Extraordinary Professor for Experimental Biophysics, and was made a full professor in 2014. Dietz has received numerous awards and grants for his work, including the Gottfried Wilhelm Leibniz Prize from the German Research Foundation (DFG) in 2015. He received a Starting Grant from the European Research Council (ERC) in 2010, followed by a Consolidator Grant in 2016 and an Advanced Grant in 2021. Dietz was made an honorary member of the North Rhine-Westphalian Academy of Sciences in 2019.

The coronavirus crisis has emphasized the point that while antibiotics are available to treat bacteria, we have far fewer drugs at hand to treat acute viral infections. While vaccinations have been created to counter some viruses, the process of developing such preventive measures is a tedious one and each vaccine has to be precisely tailored to the properties and characteristics of each virus.

What if we had a general-purpose weapon to fight and eliminate viruses, from COVID and influenza to hepatitis and HI viruses? Researchers are on track to make it a reality. Hendrik Dietz, Professor of Biomolecular Technology, and his team have developed minute traps that capture viruses in the body and “swallow” them. This is an utterly novel concept that sounds brilliantly simple. “As far as we know, what we are proposing has never been attempted before,” the researchers say, in prosaic language typical of scholars. “If successful, it would represent a disruptive advance.”



“The procedure could prove useful against new types of viruses.”

Ulrike Protzer



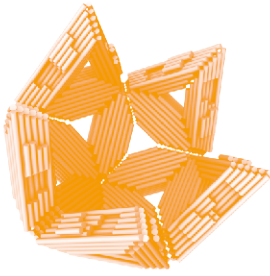
“As far as we know, what we are proposing has never been attempted before.”

Hendrik Dietz

Prof. Ulrike Protzer has accompanied Hendrik Dietz's project from the beginning. The virologist, who is Director of the Institute of Virology at TUM and the Helmholtz Center in Munich, provided inactivated hepatitis B viruses that enabled Dietz and his team to trial the process of capturing viruses in DNA capsules.

Professor Protzer, you must have been astonished when a physicist came to you with the concept of capturing viruses in tiny shells?

Ulrike Protzer: A little, yes. But I was already familiar with Hendrik Dietz and his work. That said, I was impressed by the highly complex objects he and his team had been able to construct; I had imagined they would be far more primitive. ▶



DNA triangles assemble into shells



DNA origami triangles

There are two main methods to build virus-trapping capsules.

- 1 One builds fully prepared half-shells that capture viruses.
- 2: Smaller building blocks bind to a virus particle across its entire surface, ultimately covering it to form a complete shell.

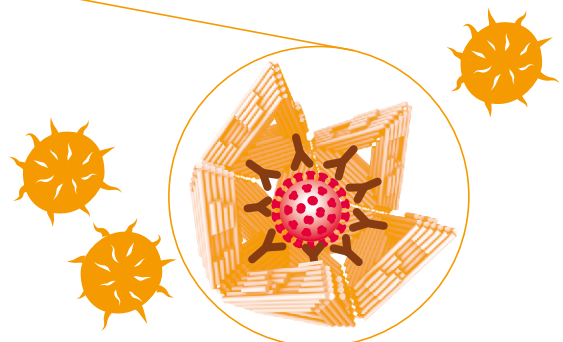
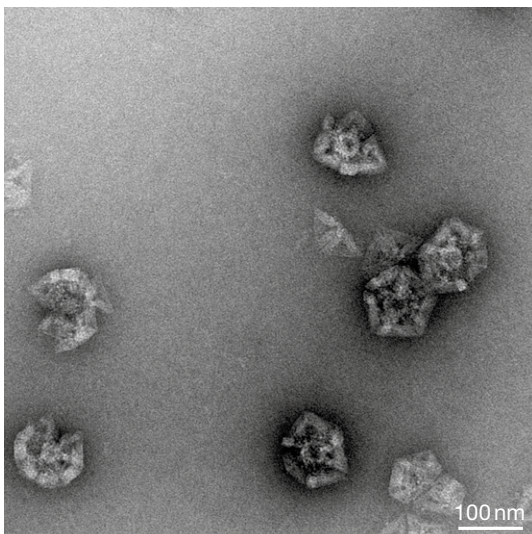


Antibodies in the shell's interior bind to the viruses

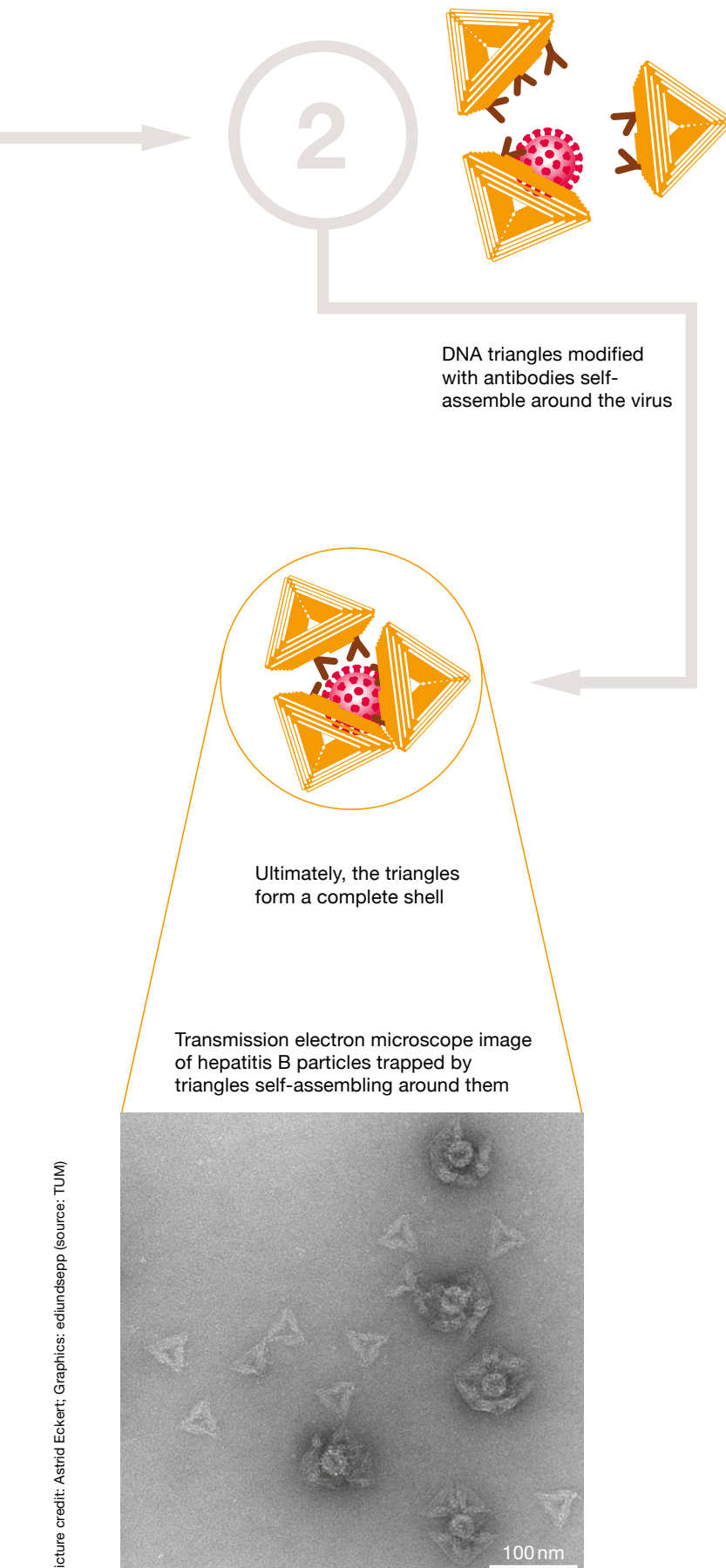


The virus is captured and neutralized

Transmission electron microscope image of hepatitis B particles trapped in half shells



The body's own phagocytic cells eliminate the shell containing the virus



Picture credit: Astrid Eckert; Graphics: edlundsepp (source: TUM)

How do you introduce the DNA capsules into the body?

There are different methods depending on where you want them to elicit an antiviral effect. One can inject them intravenously if an effect in the bloodstream is wanted. Alternatively, a patient can inhale them if the aim is to capture viruses in the airway mucosa or lungs. The best way to reach viruses in the gastrointestinal tract will probably be using a type of capsule that you swallow.

Assuming that you actually capture the viruses, what happens next?

The body's own phagocytic cells will eliminate them.

Are there any risks involved? Can the body reject these artificial structures or produce an allergic reaction?

We can't exclude that possibility, but I wouldn't expect so. The material that makes up the capsules is DNA, which is not foreign to the human body. However, it may activate the body's innate immune system. But that might actually even be helpful in fighting viruses. That's something to be investigated in further studies.

Do you believe the project has a realistic chance?

I think it's absolutely fascinating. We need to see whether it can win out over the antibody therapies currently in clinical trials. However, such antibodies always need to be developed specifically against a certain type of virus. In my view, this new approach has an advantage in that it is more universal. We could use these as ready-made kits to capture all kinds of viruses, including new viruses for which no antibodies have been developed yet.

Realistically, how long should we expect development of this treatment to take?

First of all, the project needs to complete preclinical studies, which take three to five years, followed by a clinical trial phase that will last approximately ten years on top. So, it will certainly take a lot of patience and a lot of funding. □



An epiphany in August

It began in summer 2019 – long before anyone was talking about the coronavirus – in Dietz’s office at the north end of the Garching research campus. The biophysicist and his team had just managed to build nanoscale capsules from DNA material. The institute is specialized in this field: Over the last ten years, researchers there have refined technologies that use DNA building blocks to form highly complex yet ultra-miniaturized objects. These processes are further evolutions of a nanofabrication concept known as 3D DNA origami, a development Dietz was already involved in as a postdoc at Harvard. What initially had looked a bit like “a technology searching for an application” could now become a vital tool in combating viruses. The researchers based the design for their capsules on viruses and their shells. Back in 1962, the American biologist Donald Caspar published a paper with British biophysicist and Nobel Prize laureate Aaron Klug, outlining how the capsid – the outer shell of a virus – is made up of proteins. They identified that these shells are regular, hollow bodies that correspond to strict geometric rules. Hendrik Dietz and his colleagues Christian Sigl, Elena M. Willner and Wouter Engelen “copied” these geometric specifications together with colleagues Seth Fraden and Michael Hagan from Brandeis University to create their nanoshells and were thereby able to construct a series of stable capsules composed either of

3D DNA

origami

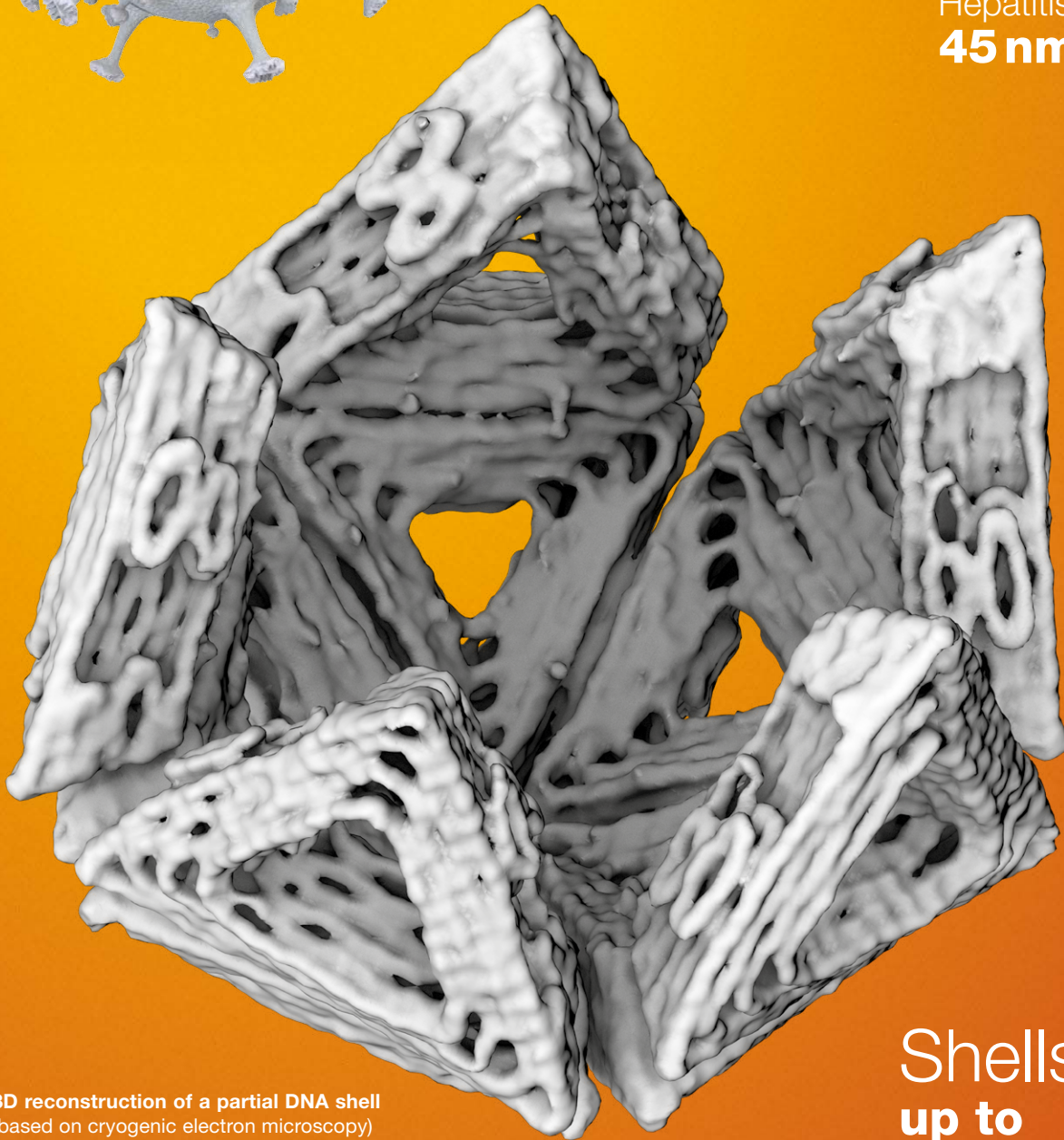
uses a DNA building block to form highly complex, ultra-miniaturized objects.



Coronavirus
80–140 nm



Hepatitis B virus
45 nm



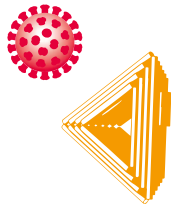
3D reconstruction of a partial DNA shell
(based on cryogenic electron microscopy)

Shells
up to
280 nm

Each of the

20 faces

forming the icosahedron is represented by a triangular piece of DNA.



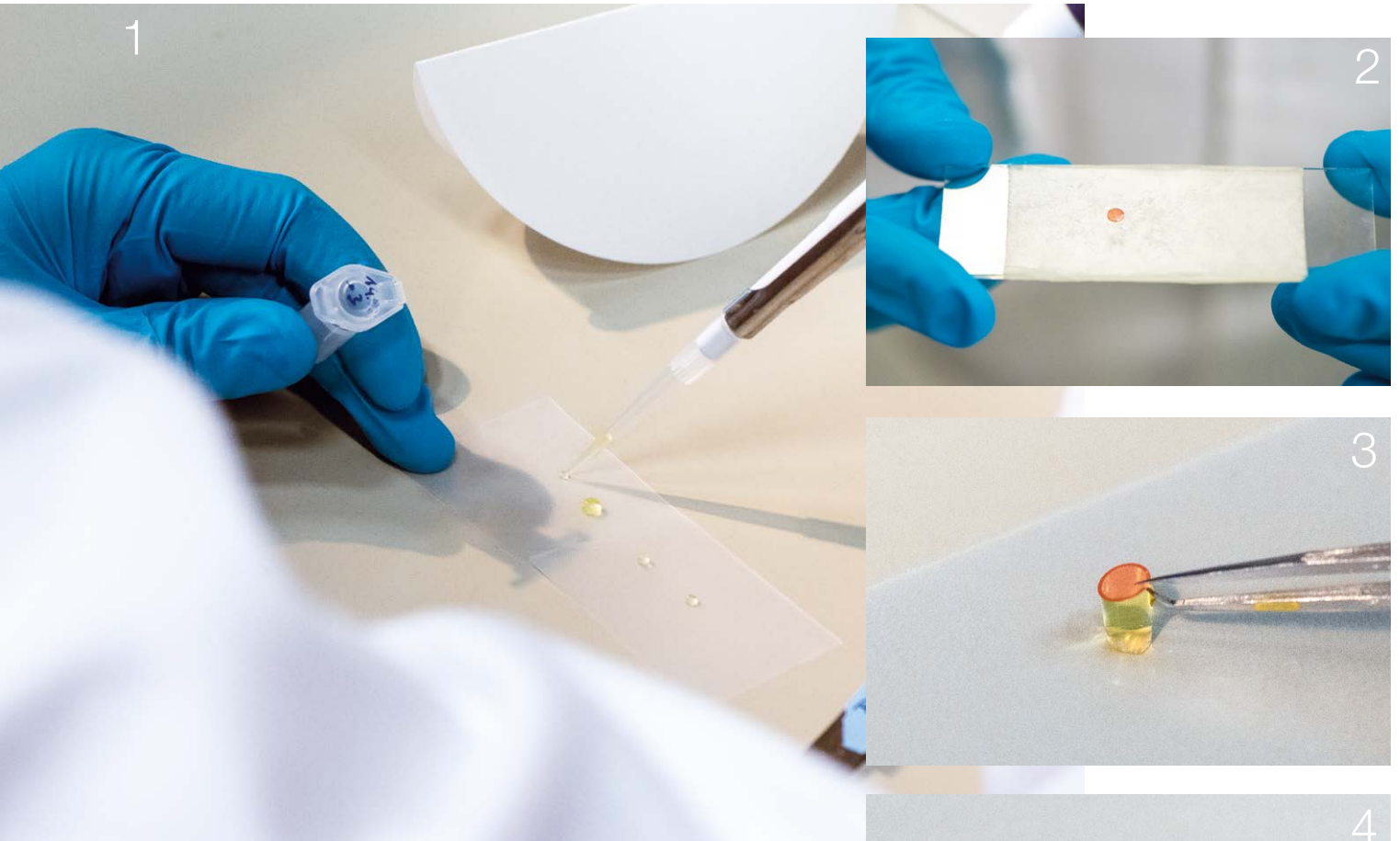
half-shells or smaller pieces of shell. Similar to natural viral particles, these shells are hollow bodies with 20 sides (icosahedrons), but are made from triangular, multi-layered pieces of DNA. Each shell comprises many million individual atoms. By using a sort of click mechanism, the researchers managed to cause the shells' complex building blocks to combine of their own accord. This process of self-assembly thereby creates the spherical shells.

“People have perhaps become a little tired of DNA nanotechnology,” explains Dietz. “Although we have made magnificent advances in recent years, we still lacked real-world applications for our technology.” Last year, however, a lucky coincidence that researchers like to call serendipity provided an answer. In August 2019, as he looked at his screens showing the newly formed hollow bodies on one side and the similarly structured virus on the other, the thought flashed through his mind that the virus should fit perfectly inside the artificial capsule.

Shells with adhesive interiors

Dietz and his team immediately set about exploring this idea. They created building blocks for shells of various sizes, procured inactivated hepatitis B particles from TUM virologist Ulrike Protzer to act as a model system, and tested whether these particles could be captured in their capsules. “In order for the viruses to stick to the inside of the shells, we equipped the interiors with antibodies that stick to particular features on the surface of the viruses,” explains biophysicist Dietz. In principle, however, it should be possible to use any molecule that binds with virus particles, such as short peptide chains or aptamers. These are DNA sequences that can be obtained using a selection process in a test tube. “You then have two different strategies to choose from. First, you can build fully prepared half-shells that combine to form complete, closed capsules after they capture a virus. Or, as a second option, you can use smaller building blocks that dock with the virus particle across its entire surface, ultimately covering it to form a complete shell.” Viruses encapsulated in this way would no longer be infectious and could be “disposed of” within the body. Currently, the researchers are working on “virucidal shells”, shells whose interiors are coated with an enzyme that can digest virus surface molecules once encapsulated, similar to the way Venus flytraps “eat” the prey they trap.

With the help of their cryogenic electron microscope, the researchers have been able to demonstrate that these



Preparation of DNA nanostructures for imaging with transmission electron microscopy (TEM): The nanostructures are applied on a metal disk (“grid”) and stained with fluid die (uranyl formate).

nanoscale virus traps work in test tubes. In other tests, they have proven that viruses captured in this way were prevented from interacting with other surfaces by up to 99%. Experiments with infectious Adeno-associated viruses were able to show the neutralizing effect of the shells with living cells.

These laboratory experiments are important initial steps. The technology, however, must now be tested in living organisms. In separate work, Dietz and his team have learned to produce their nano-objects in large volumes and at acceptable costs and can also stabilize them for use in physiological conditions. ▶

Up to
99%

of interactions between captured viruses and other surfaces were blocked.



EU-funded project

VIROFIGHT

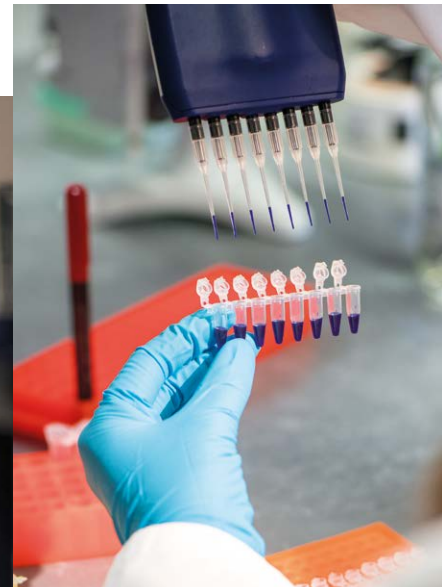
The interdisciplinary consortium integrates experts on supra-molecular chemistry, molecular nanoengineering, and virology across Europe.

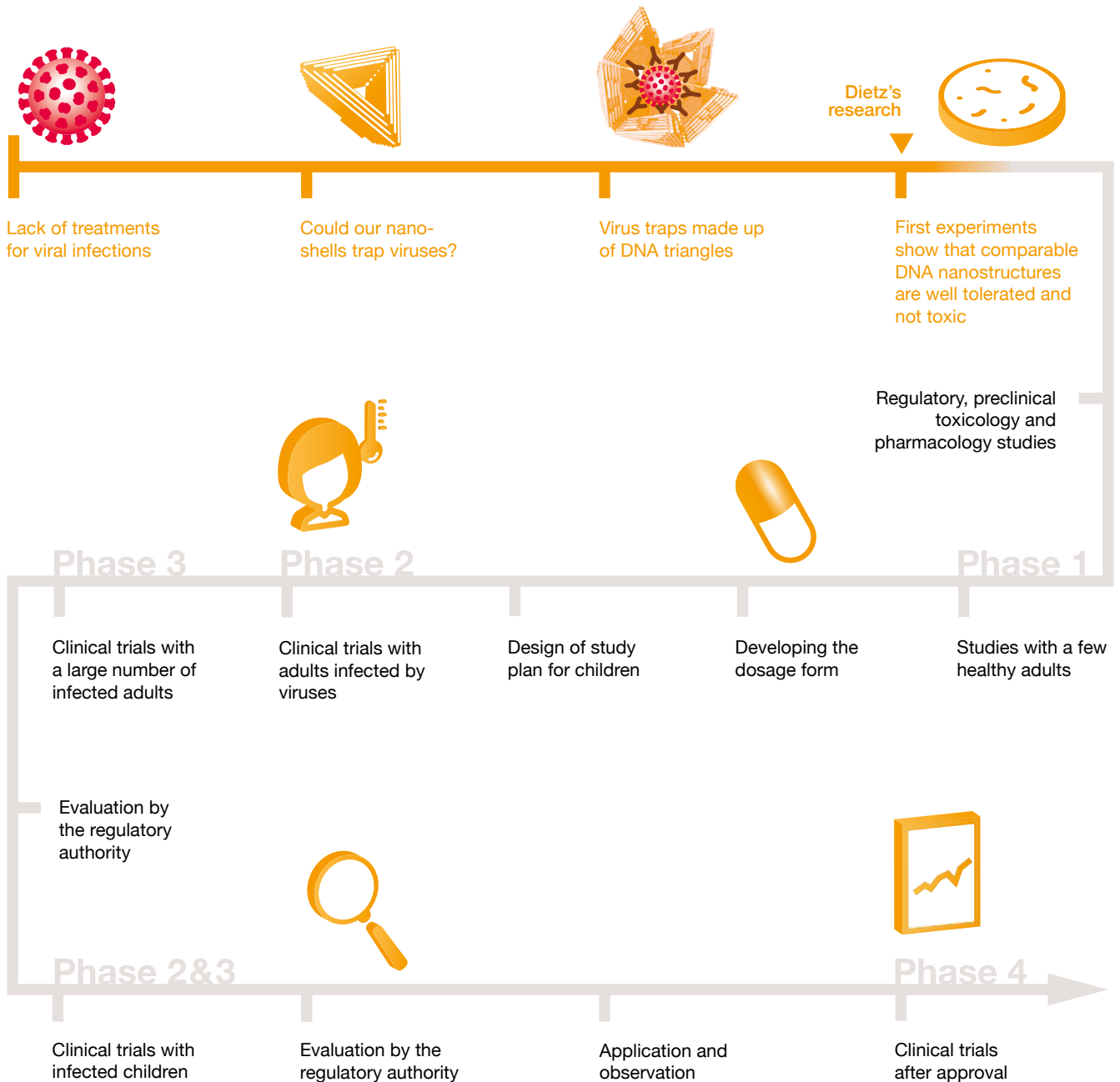
Experiments on mice soon

In light of the coronavirus pandemic, the research has suddenly taken on an unforeseen currency and urgency. Dietz and his team have been acutely focused on how their concept could be realized in practice; they have discussed it with numerous experts to ascertain whether the concept has a realistic chance as a treatment for viruses. “Of course, we’re working to overcome some of the weaknesses and press ahead with practical testing,” says Dietz. “There are many viral infections for which we have no therapy so far. To find new therapies we must explore avenues off the beaten path. Our concept is unusual but, in principle, resembles in part aspects of the adaptive immune response. As I understand it, we typically return to health when our body has managed to ‘coat’ viral pathogens with neutralizing antibodies.”

Preliminary experiments on mice at the Helmholtz Center in Munich have already shown that comparable DNA nanostructures are well tolerated and not toxic. The EU has now committed to support the next stages of research as part of a project called VIROFIGHT. An interdisciplinary consortium of doctors, virologists, biophysicists, molecular biologists, chemists and experts in DNA origami and protein design will now get to grips with the concept.

Freezing viruses for long-term storage and preparing DNA nanostructures for gel electrophoresis analysis.





Their task will be to test the virus trapping process that successfully beat the hepatitis B virus and Adeno-associated viruses in test tubes with other viruses and in mice. “As soon as we see that encapsulation has positive effects in the mouse model, it will probably make sense to explore setting up a company and look for investors,” says Dietz, outlining his plans.

And then – if everything goes to plan – in a few years’ time, there could be a universal family of medications capable of fighting viruses, created for the good of humanity. After all, this will not be the last pandemic humanity will face.

Brigitte Röthlein

How Hendrik Dietz's idea could eventually turn into medical treatment – if it proves itself in the many tests on the way. Currently it is at stage 4.



A Clear View into the Data Stream

In an effort to ensure that we make optimal use of the incredible amounts of data generated by satellites, researchers from nine nations have come together to work on AI4EO, a project spearheaded by TUM. The project's output is publicly available and, it is hoped, could help to tackle many social challenges – such as in megacities – and visualize changes in land use and the impact of climate change.

Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Durchblick im Datenstrom

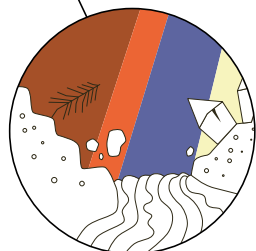


Im Projekt AI4EO entwickeln Forscherinnen und Forscher aus neun Nationen neuartige Methoden des Maschinellen Lernens und Lösungen für die Analyse von großen Datenmengen, um so den stetig anschwellenden Satellitendatenstrom zu analysieren. Xiaoxiang Zhu, Professorin für Data Science in der Erdbeobachtung an der TUM und am DLR, leitet das Projekt. □

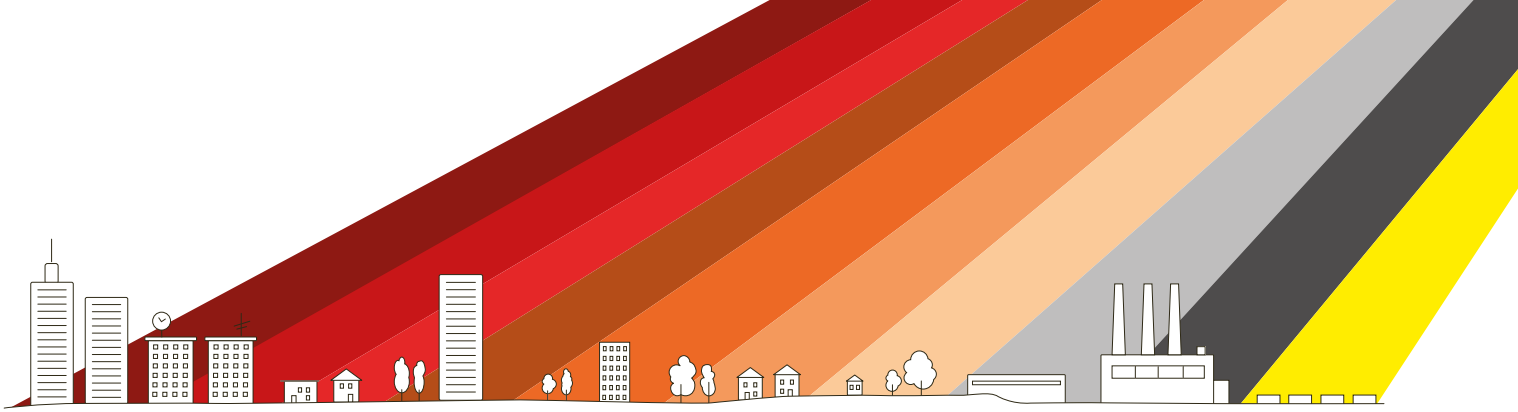


Xiaoxiang Zhu is Professor of Data Science in Earth Observation at TUM as a joint appointment together with DLR.

In recent years, satellite data has become one of the most important sources of data for earth observation. It reveals how fast megacities around the world are spreading, where arable land is disappearing and nature reserves are shrinking. The problem, however, is that satellites nowadays send so much data down to earth that it is impossible to maintain an overview without technological assistance. For instance, around 40 billion megabytes of data are currently stored at the Remote Sensing Data Center (DFD) at the German Aerospace Center (DLR). This data volume could fill the storage capacity of 625 million smartphones and is forecast to more than double by 2030. In the last year, researchers from nine countries have come together to launch AI4EO (Artificial Intelligence for Earth Observation), an international future lab directed by TUM aiming to facilitate effective use of this data in future. These researchers have pooled their expertise to develop novel machine learning methods and big data analytics solutions, thereby making it possible to analyze the ever-rising tide of satellite data. “Artificial intelligence enables us to identify unknown objects and relationships – but that’s not all,” emphasizes Prof. Xiaoxiang Zhu, data scientist at TUM and director of AI4EO. “The algorithms we have developed are also able to uncover unidentified phenomena. This will make it possible to use satellite data in an even more multifaceted manner in future.”



Machine learning and other artificial intelligence techniques help extract specific information from the great wealth of satellite data.

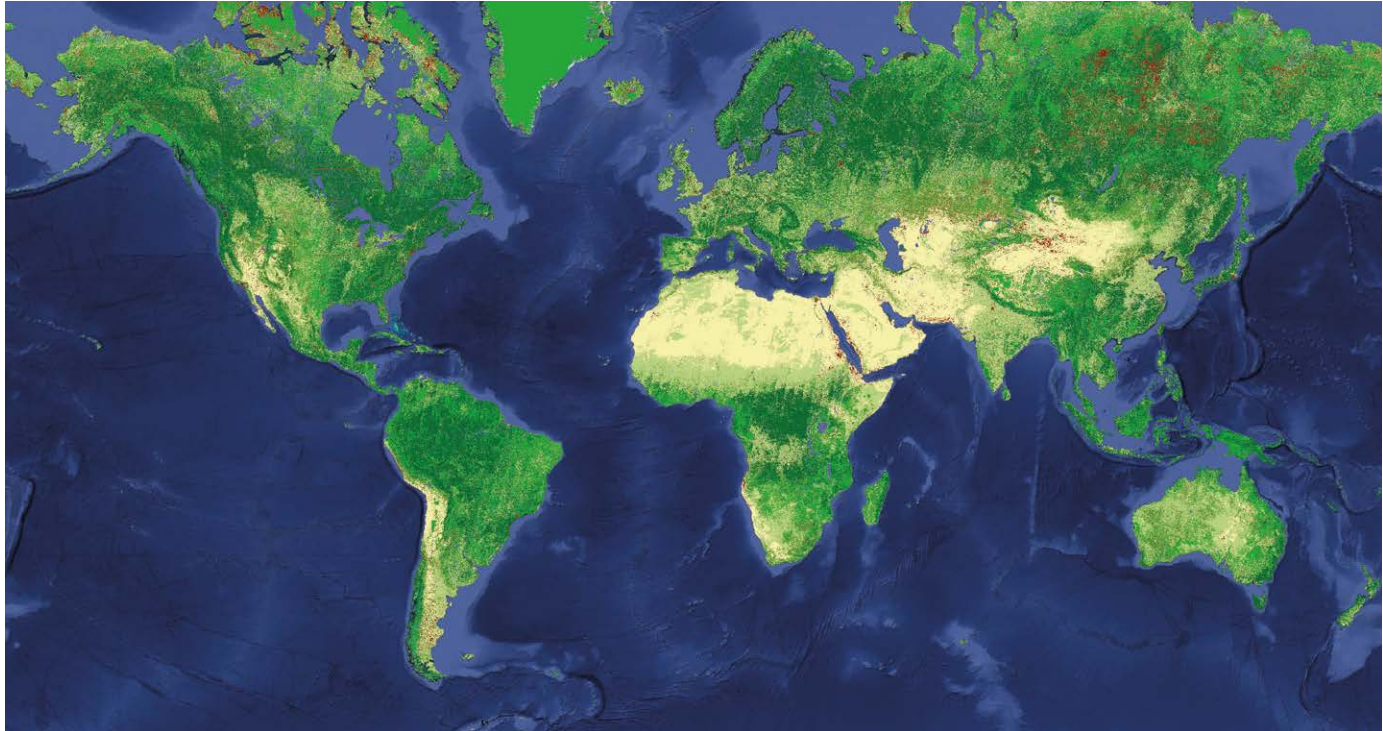
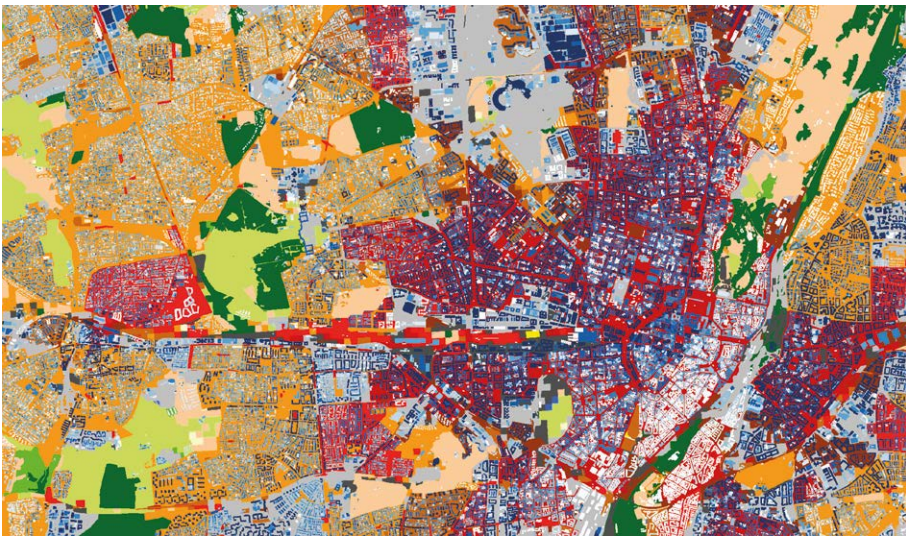


- Compact high-rise
- Compact middle-rise
- Compact low-rise

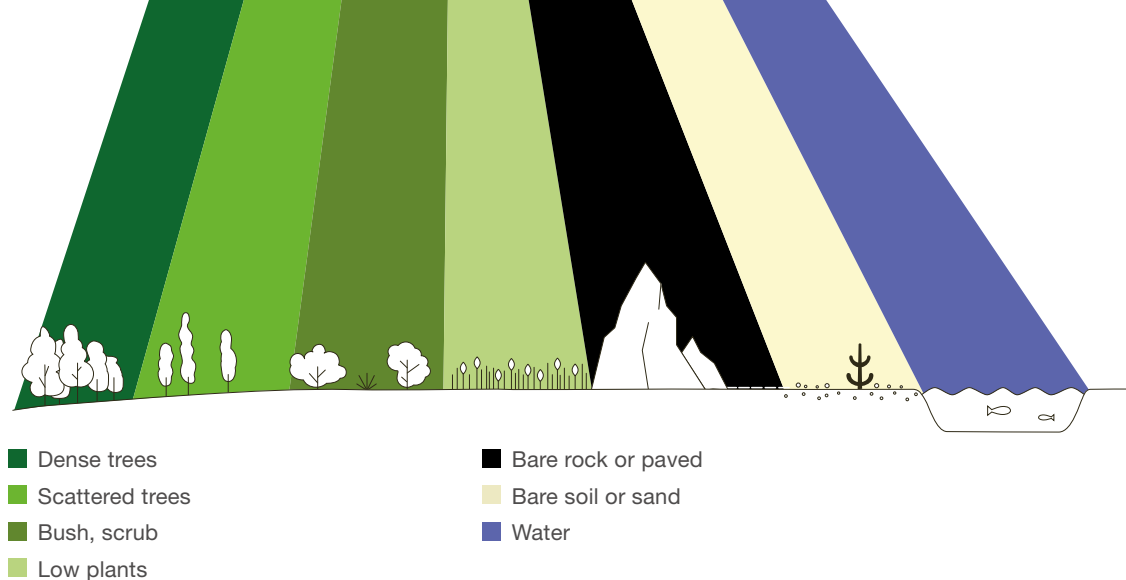
- Open high-rise
- Open middle-rise
- Open low-rise
- Sparsely built

- Large low-rise
- Heavy industry
- Lightweight low-rise

With the help of AI, urban climate zone classes could be automatically extracted from satellite data. The pictures show the world's first global urban local climate zone map (below) and the local climate zone map of Munich overlaid on the 3D building model (right).



Graphics: edlundsapp (source: TUM/Zhu); Picture credits: TUM/Zhu



Recording three billion buildings worldwide

Examples of this type of valuable new information can be found in the machine learning methods and big data analytics solutions developed by Zhu and her colleagues, which have made it possible to create a complete map of all buildings around the world for the first time. Map services like Google Maps and OpenStreetMap also provide detailed maps. However, they often identify built-up spaces simply as “urban areas” – and only depict individual houses and buildings to a limited extent. “This data is enormously important for urban planning,” says Zhu. One example is cities in which “informal settlements”, or slums, are constantly growing. Experts estimate that there are around three billion buildings around the world. Yet only 16 percent of these buildings are individually depicted in OpenStreetMap, with information on building height only available for 0.5 percent. In the So2Sat project, the TUM team successfully harnessed intelligent algorithms to extract detailed building information and produce maps complete with individual buildings for locations around the world, including Cairo and other major African cities. “We make our datasets publicly available,” underscores Zhu, “which means they can be used in different ways.”

The urban microclimate

Researchers at the AI4EO future lab use an abundance of these datasets, which developers around the world can also utilize to design new satellite information services. One example is So2Sat LGZ42, a dataset in which Xiaoxiang Zhu’s group combine satellite data on cities with particularly current information: the urban structures that shape the urban climate, namely densely packed high-rise buildings that cause the summer heat to build up, and green spaces that provide fresh air. The team has identified 17 such characteristic urban climate zone classes

that are now automatically extracted from satellite data using artificial intelligence. This tool and the dataset are also particularly valuable for urban planners.

The TUM group in the AI4EO future lab has developed other solutions, such as a program that provides information updated daily on changing land use – areas that have been built on or lost due to flooding. Other outcomes include a machine learning pipeline that automatically removes intrusive clouds from satellite images and a complex analytical algorithm that compares satellite images to predict future events – such as streets that could soon be covered by rising waters. “In a film sequence taken from observation cameras, you quickly see what’s changing,” says Zhu. “However, we have to work with individual images that satellites take during several flyovers. Identifying a development from these images is much harder. But our algorithm can do it.”

The algorithms identify far more events than the naked human eye. Like everything produced by the AI4EO future lab, these innovations and datasets are publicly available. Further tools are set to be added in the near future, among them a visual question answering (VQA) system based on natural language processing. It can examine satellite images directly and answer questions like “What changes have happened in this image?” in a way that people can understand. This system is the first of its kind, a sort of Alexa or Siri for earth observation, and will screen the wealth of earth observation data to evaluate the highly dynamic changes underway around the world.

■ *Tim Schröder*

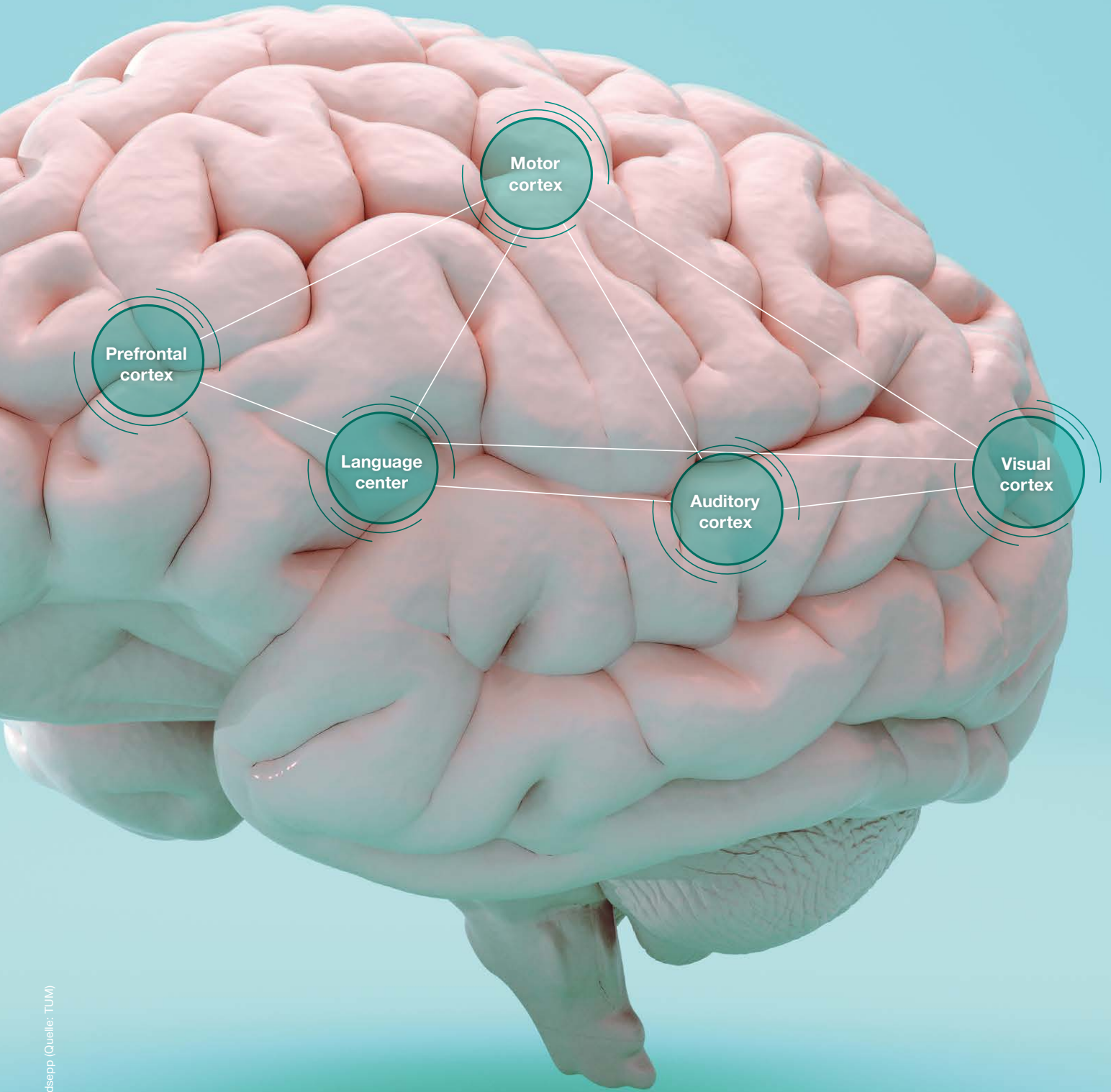
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Teamwork to Regain the Power of Language

Cognitive brain functions such as language and a powerful memory are what make humans unique. But the mechanisms behind them are still poorly understood. Neurologist Prof. Simon Jacob is working closely with specialists from other disciplines to change this. Using knowledge gained from many years of research with animals and humans, his team is now embarking on a study aimed at helping stroke patients regain their ability to understand and produce speech.





Grafiken: turbosquid.de, edtundsepp (Quelle: TUM)

Link
simonjacob.de

Gemeinsam gegen Sprachlosigkeit

D

Kognitive Hirnleistungen wie Sprache und ein leistungsfähiges Gedächtnis auch für komplexe, abstrakte Informationen entstehen durch ein exakt koordiniertes Zusammenspiel verschiedener Hirnbereiche. Diese Funktionen finden sich so nicht bei anderen Tieren und prägen uns als Menschen. Sind sie infolge einer Krankheit oder Verletzung gestört, ist das für die Betroffenen sehr belastend. Damit Ärztinnen und Ärzte diesen Menschen helfen können, müssen zuerst die entsprechenden Prozesse im Gehirn genau verstanden sein. Ihre Erforschung wird jedoch dadurch erschwert, dass vielen Tiermodellen bestimmte kognitive Hirnfunktionen fehlen. Bei Menschen wiederum dürfen aus ethischen Gründen meist nur nicht-invasive Methoden eingesetzt werden, welche die neuronalen Vorgänge nur unzureichend abbilden. Der Arzt und Neurophysiologe Prof. Simon Jacob setzt deshalb auf eine Kombination aus Experimenten im Tiermodell und Untersuchungen bei Menschen, die sich aus medizinischen Gründen einer neurochirurgischen Operation am Gehirn unterziehen. In enger Zusammenarbeit mit Spezialisten mehrerer Fachrichtungen möchte er unter anderem Verfahren entwickeln, mit denen Patientinnen nach einem Schlaganfall ihre Sprachfähigkeit zurückgewinnen können. □

Stimulus processing
in a healthy brain



Hello.
How are you?

Sensory input

Stimulus processing
in the brain of a neurological patient



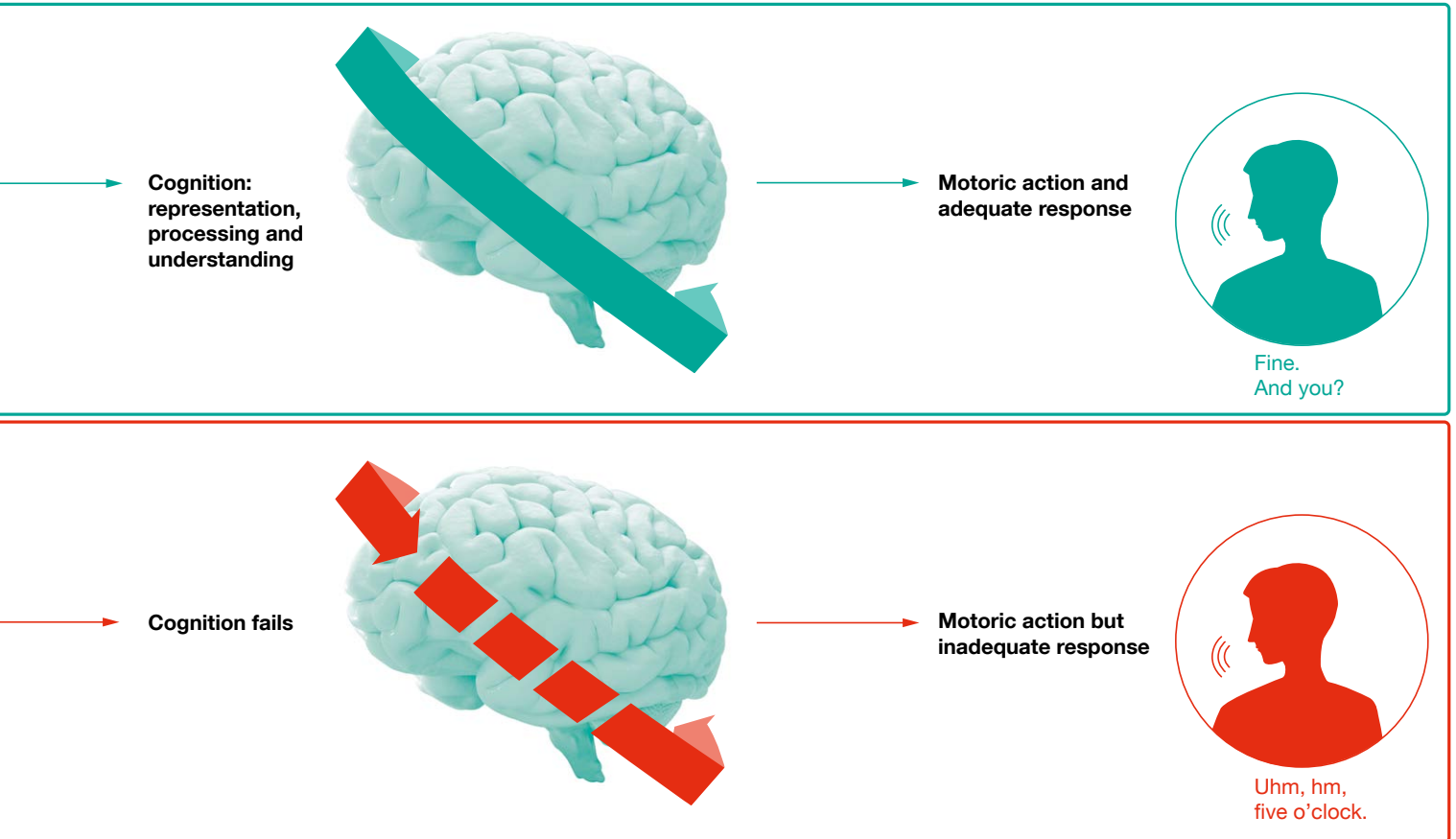
Hello.
How are you?

Sensory input

Humans are the only animals able to reflect on their position in the animal kingdom. We are able to do so because of complex brain functions such as active perception, memory, and language. The umbrella term for these functions is cognition. “Cognitive processes translate sensory stimuli in our environment into purposeful, planned action and enable us to, for example, respond in completely different ways to a repeating situation. The key brain region for these processes is the frontal lobe,” explains Simon Jacob, who, as TUM Professor of Translational Neurotechnology, researches cognitive functions at TUM. As a neurologist and neurophysiologist, he has the perfect qualifications for the post. “Translational” means turning scientific insights into treatments, and Jacob is one of those rare basic researchers who – as a qualified doctor – is actually familiar with medicine in practice. “Medicine is and remains the inspiration behind

and the motivation for our research,” stresses Jacob. “We hope that our results will be translated into practical applications.”

Cognitive impairment is a feature of a number of psychiatric and neurological disorders, ranging from depression, schizophrenia, and dementia to stroke and head injury. From his interactions with patients, Jacob knows how difficult this can be for sufferers and their relatives. “When our cognitive functions are impaired, we are no longer ourselves,” he explains, noting that there are still no effective treatments for many of these conditions, as we still do not understand exactly what’s going on in the brain in these disorders. “We have a very good understanding of how individual nerve cells or neurons work, but we don’t yet understand how exactly they work together in networks.”

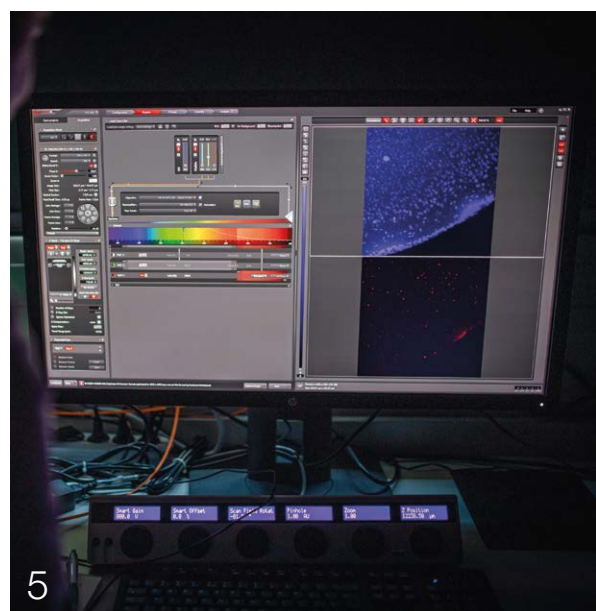
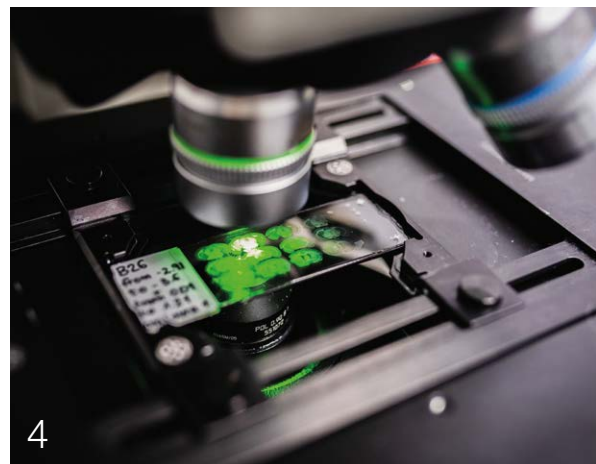
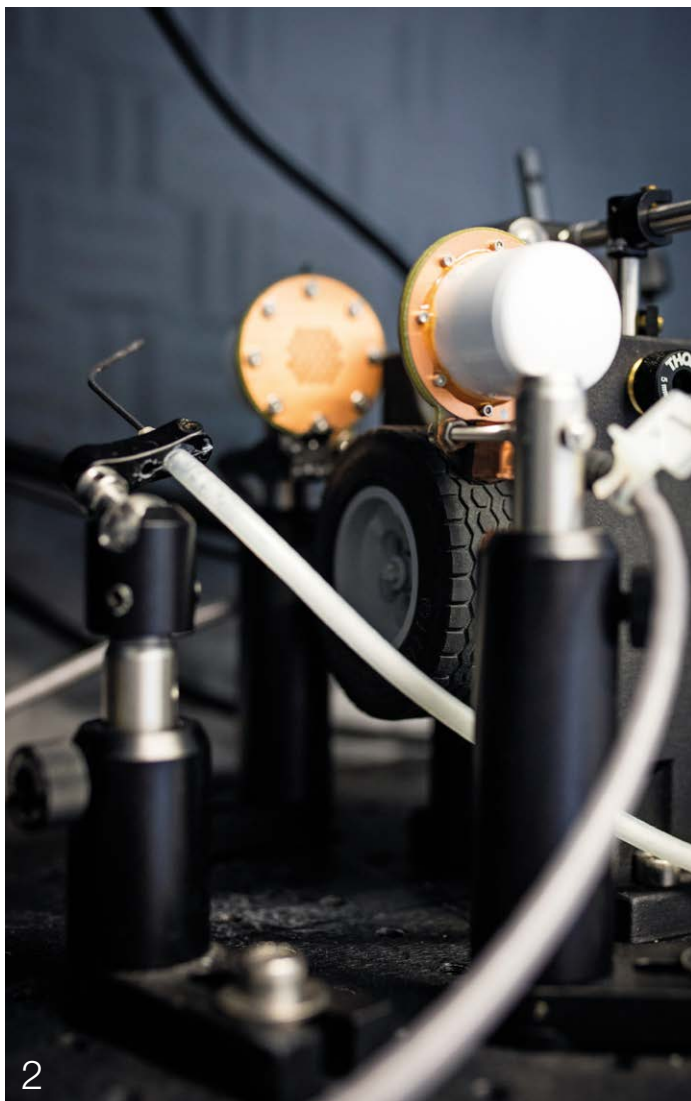


Cognitive processes translate sensory stimuli into purposeful, planned action. There are still no effective treatments for persons suffering from impaired cognitive functions, such as after a stroke.

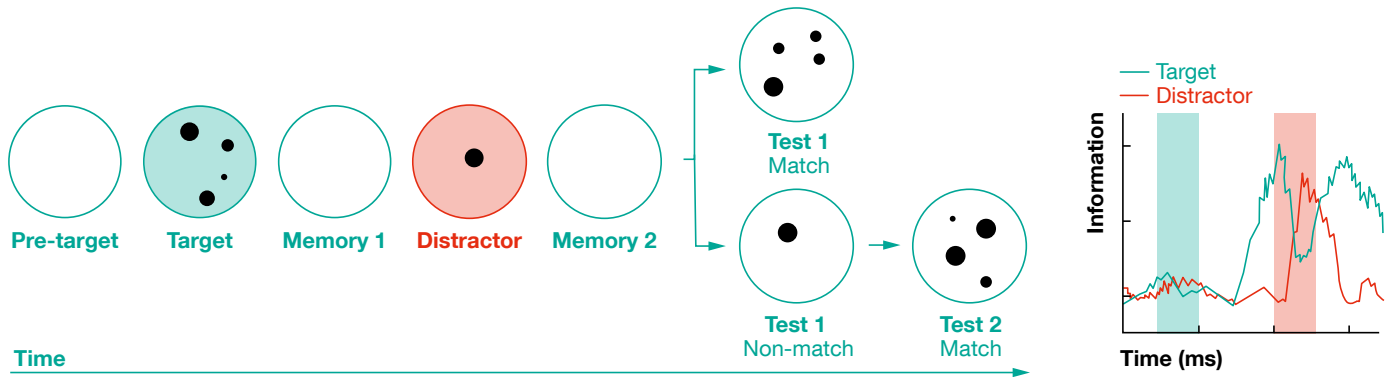
Understanding cognitive processes in monkeys

One reason for this is that reproducing the complexity of cognition – which arises from interactions between different brain regions – in a cell culture dish is simply not possible. In addition, because few animals have cognitive abilities comparable to humans, there are few animals capable of serving as animal models for research. Ethical considerations rule out using invasive methods to measure the activity of individual neurons in humans. “In healthy people, we are limited to measuring brain waves or using MRI to map the activity of specific brain regions,” explains Jacob. “But these methods don’t have very good spatial resolution.” In other words, you can see which brain regions are at work, but not what’s happening at the level of individual brain cells. But to understand disease processes with enough precision to be able to help people who are ill, you need to do exactly that.

That’s why, before coming to Munich, Jacob worked with non-human primates, where invasive techniques are permitted. “Research using non-human primates as an animal model is incredibly important for medicine. It goes without saying that all experiments must be licensed by the relevant supervisory authority and are monitored very closely,” says the researcher. “We anesthetize and prepare the animals for neuronal measurements in the same way as we would humans.” Rhesus monkeys can be trained so that in some domains they exhibit cognitive abilities approaching those of humans. Through research like this, Jacob has gained important insights into a key cognitive function – working memory. Working memory stores information online for a few seconds before having to decide which items need to be acted on and which do not.



Distracting inputs are not suppressed in working memory. Instead, the prefrontal cortex registers them along with relevant inputs and selects the correct answer later on. In this experiment, animals were trained to memorize the number of dots in the target visual display and resist the distracting numerosity. Electrical activity in a typical neuron shows that both pieces of information are represented.



Jacob's experimental animals learned to memorize and later recognize stimuli consisting of varying numbers of dots. During the task, the monkeys were also presented with distracting stimuli, which they needed to ignore. Using electrodes implanted in the monkeys' brains, the researchers were able to measure what was happening in brain cells during this task. "The measurements don't cause the animals any pain, as the brain has no pain receptors. This is why neurosurgeons are able to perform awake brain surgery," explains Jacob.

The researchers had hypothesized that the brain directly filters out distracting stimuli, but it turned out that these irrelevant stimuli were encoded in the frontal lobe in the same way as relevant stimuli, albeit in distinct groups of cells. While it remains unclear for now how the brain subsequently selects relevant information, Jacob is confident that, "Cognitive performance is not based on blindly blocking irrelevant information, but on purposefully selecting relevant information."

1 Jacob works with mice to understand the functions of individual brain cells and their networks. **2 Animal training setup** with ultrasound speakers. **3 Miniature fluorescence microscopes** register neuronal activity. **4 + 5 Microscopic examination** of brain networks after termination of the neuronal recordings.

In addition, his team was able to show that the neurotransmitter dopamine improves working memory. This is reflected in the symptoms experienced by patients with altered dopamine signaling. "We tend to think of Parkinson's disease, which is characterized by dopamine deficiency, as being primarily a motor disorder, but patients with Parkinson's often also have memory problems and other cognitive anomalies. Significant cognitive problems are also a feature of schizophrenia, and this condition is also treated with medication that affects dopamine metabolism."

From mouse to human

To gain a deeper understanding of brain cell function and neuronal networks, Jacob has also begun to work with mice. "Today we have the technology to record from hundreds of neurons simultaneously and process the large volumes of data produced," explains Jacob. "In mice, we can look at how different brain regions interact by, for example, interrupting the connection between these regions with very high anatomical and temporal precision." In addition, many expedient molecular biology techniques have been developed for use in mice. It is, for example, possible to genetically modify neurons so that their activity can be up- or downregulated by light impulses, so that only certain groups of neurons are visible under a microscope, or so that neurotransmitters can be measured optically. This offers significant potential. "It means that, for example, we can directly observe the role dopamine plays in cognitive processes in the brain," explains Jacob. ▶

Basic research to the benefit of us all

An important step for the neurophysiologist was transferring his findings from animal models into humans. The key to doing so was to take advantage of neurosurgical operations in which, in order to improve the accuracy and safety of the operation, patients choose to remain awake. Awake brain surgery is used, for example, when removing brain tumors close to the language centers in the left-brain hemisphere. “By having the patient awake during the operation, the neurosurgeon can use electrical stimulation to identify areas involved in speech production and comprehension, enabling the surgeon to take extra care when operating in those areas,” explains Jacob. Many patients also consent to take part in behavioral experiments during the operation – they are happy to support research, and they know that the results will benefit other patients. Jacob and his team are extremely grateful: “We are unfailingly impressed by the dedication shown by our patients.”

By way of tiny electrodes introduced into the tissue around the tumor, the researchers can measure what’s going on in the human brain during cognitive processes. Their measurements are as accurate, both temporally and spatially, as in their animal model. The TUM University Hospital is the perfect place for these studies. As a major national cancer center, dozens of awake brain surgeries are performed there every year. The fact that Jacob, as a physician, is familiar with the ins and outs of day-to-day clinical practice, with its last minute changes of plan and short lead times, and speaks the language of the neurosurgeons carrying out the operations, has proved invaluable. “This interdisciplinary approach is enabling me to bridge the gap from laboratory animals to humans,” notes Jacob, before adding, “Also in my role as basic and blue skies researcher, my aim has always been about working with and for people.” Bringing research and medicine closer together is very much the trend right now, says Jacob.

“Being physically close to other specialists, as we are at TUM’s Center for Neuromedicine, is hugely important.”

Simon Jacob

Prof. Simon Jacob

is a neurophysiologist and board-certified neurologist. He studied medicine on a scholarship from the Studienstiftung des deutschen Volkes at the Universities of Freiburg and Heidelberg, at University College London (UK), and at Harvard University (USA). In the course of his experimental doctoral thesis at Yale University (USA), he became strongly attracted to scientific work. He subsequently trained as a neurologist and systems neuroscientist at University Hospital Tübingen and the Charité in Berlin. Jacob joined TUM in 2015, and in 2019 was appointed Professor of Translational Neurotechnology. He has received numerous awards for his work, which is currently funded by a prestigious ERC Starting Grant.



“Being physically close to other specialists, as we are at TUM’s Center for Neuromedicine, is hugely important.”

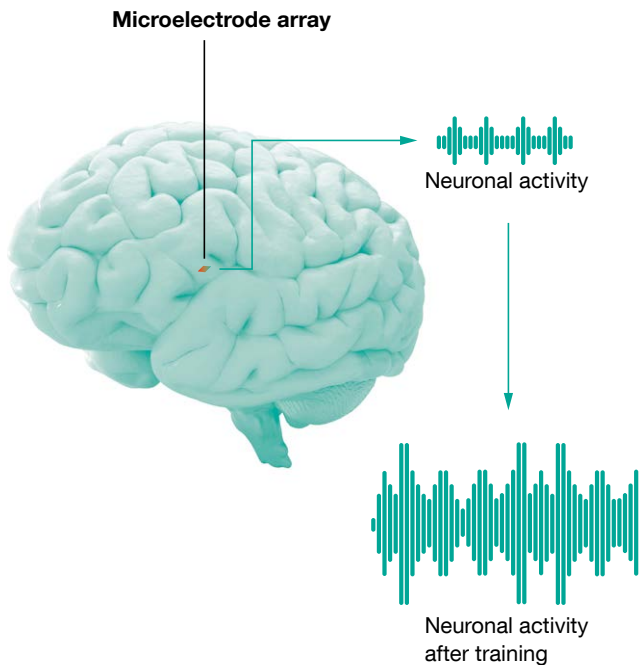
Helping stroke patients with language disorders

The excellent conditions at TUM are now enabling Jacob to carry out a study which will, for the first time, examine whether this invasive procedure can be used to treat language disorders (aphasia). In this study, electrodes will be implanted into the brains of patients who have had a stroke which has affected their ability to understand and, in particular, produce speech. The electrodes record neuronal activity when the patient speaks, which the re-

searchers can also translate into audible and visible cues. These cues can be used to help study participants. “Language is the noblest, most human cognitive function. In common with all other cognitive functions, it is about processing sensory stimuli and responding appropriately to this information,” explains Jacob. “As a physician, I find the suffering of people with aphasia, who find themselves unable to communicate with those around them after a stroke, very affecting. We hope that participants in our biofeedback treatment study will learn to steer their brain activity so that they can learn to once again speak more fluently.” ▶



Bildquelle: Juli Eberle

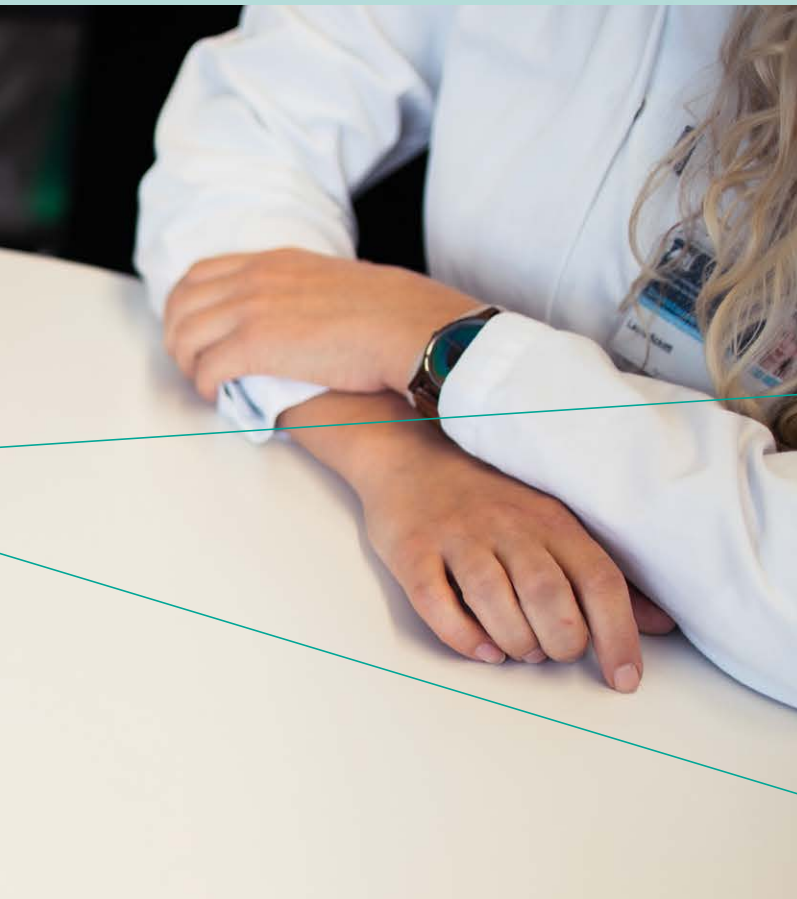


This project too has a strongly interdisciplinary flavor. “We will not make any further progress in aphasia using conventional methods,” believes Jacob. “We have to now trust ourselves to put our insights from basic research into practice and work together across different disciplines.” Consequently, as well as neurophysiologists, with their understanding of the processes in the brain, and the neurosurgeons who carry out the surgery, the work also involves computer scientists who are analyzing the data produced, engineers who are designing new probes, and technicians who are developing measuring devices able to communicate with the electrodes wirelessly and non-invasively. Jacob is confident that the future will see better technologies for treating cognitive disorders. “There are a lot of technical issues to be resolved, but we now have a new generation of physicians who have learned to think along interdisciplinary lines,” he explains. ▶

Biofeedback could help study participants improve speech production. Neuronal measurements from the implanted Utah array can be translated into audiovisual signals that are presented to the patient. In multiple training sessions, patients learn to use the feedback signals to specifically control their brain activity.

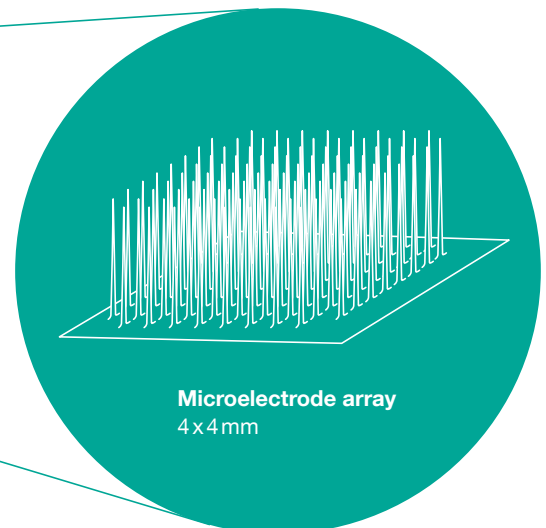


Bildquellen: -Juli Eberle; Grafiken: edlundsepp (Quelle: TUM)



△ **Being both a basic researcher and a clinician** enables Jacob to build bridges between lab bench and bedside and to transfer his scientific findings from animals to humans.

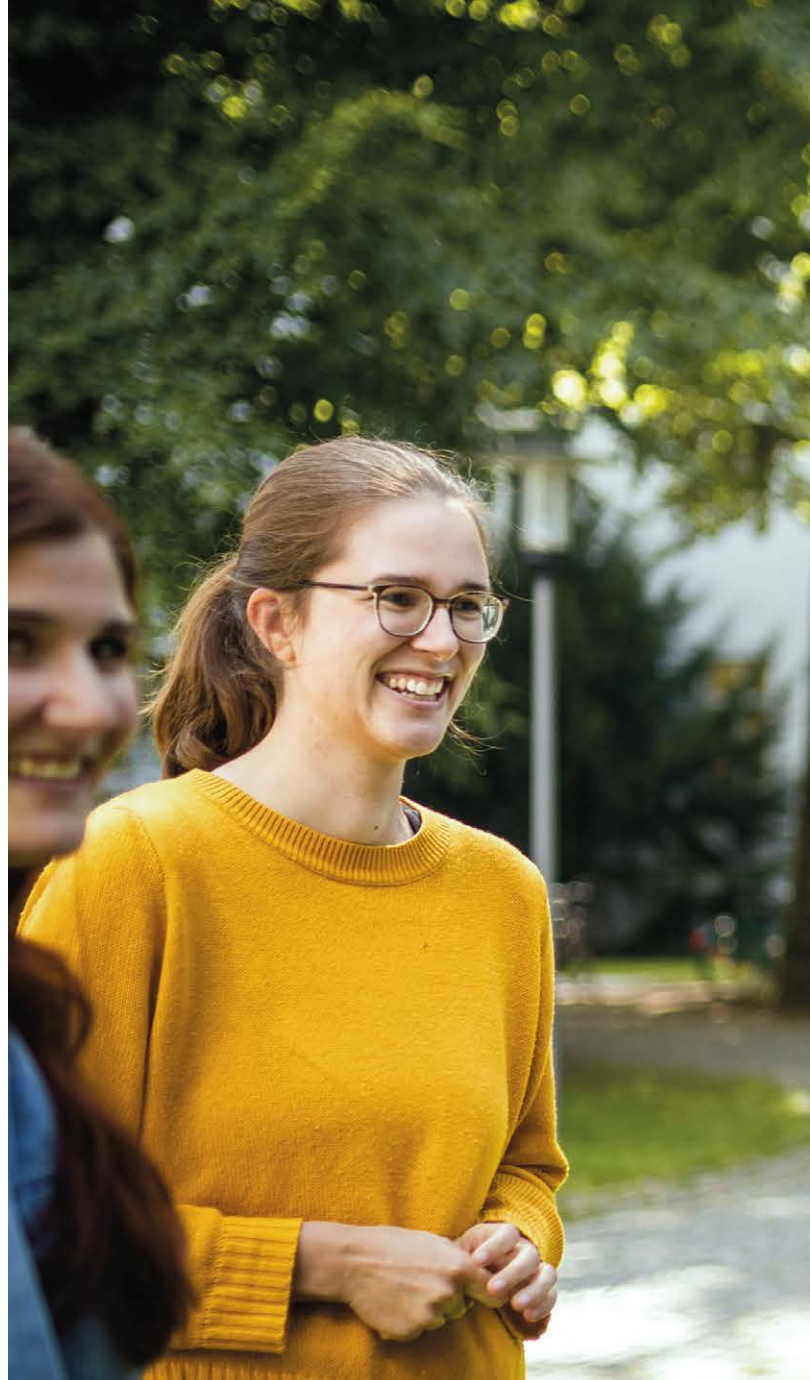
◁ **A study designed to help stroke patients** regain their ability to produce speech: a microelectrode array (Utah array) implanted into participants' brains records neuronal activity while the patients speak.



Scientific thinking and interdisciplinary collaboration

His own team is a broad mix of physicians and scientists, including biologists, psychologists, neuroscientists, and computer scientists. There is also a special doctoral program which enables interested medical students to dive deeper into scientific methods. Jacob is confident this will help change the perspective of aspiring neurologists, neurosurgeons, and psychiatrists. “By recognizing the value of neuroscience and building our medical practice on a solid foundation of neurophysiology and neurobiology, we are able to achieve more for our patients.” The newly founded TUM Innovation Network for Neurotechnology in Mental Health, which Jacob is coordinating, is also aimed at facilitating interactions between disciplines. “Our network will be leading the way as a flagship project internationally,” says Jacob. As a technical university, TUM is perfectly positioned for this approach, as it can involve researchers from the engineering, artificial intelligence, data modeling, ethics, and social sciences fields. “When such different cultures talk to each other, there can sometimes be a little friction,” admits Jacob. “But it is very enriching and I find it a constant inspiration.”

Larissa Tetsch



TUM Innovation Network for Neurotechnology in Mental Health (NEUROTECH)

Part of the TUM Excellence Initiative, TUM Innovation Networks are intended to nurture innovative research fields straddling multiple disciplines. The interdisciplinary teams are made up of seven to ten principal investigators and up to ten PhD students and postdocs. Each network is granted around €3 million in funding over a four-year period.

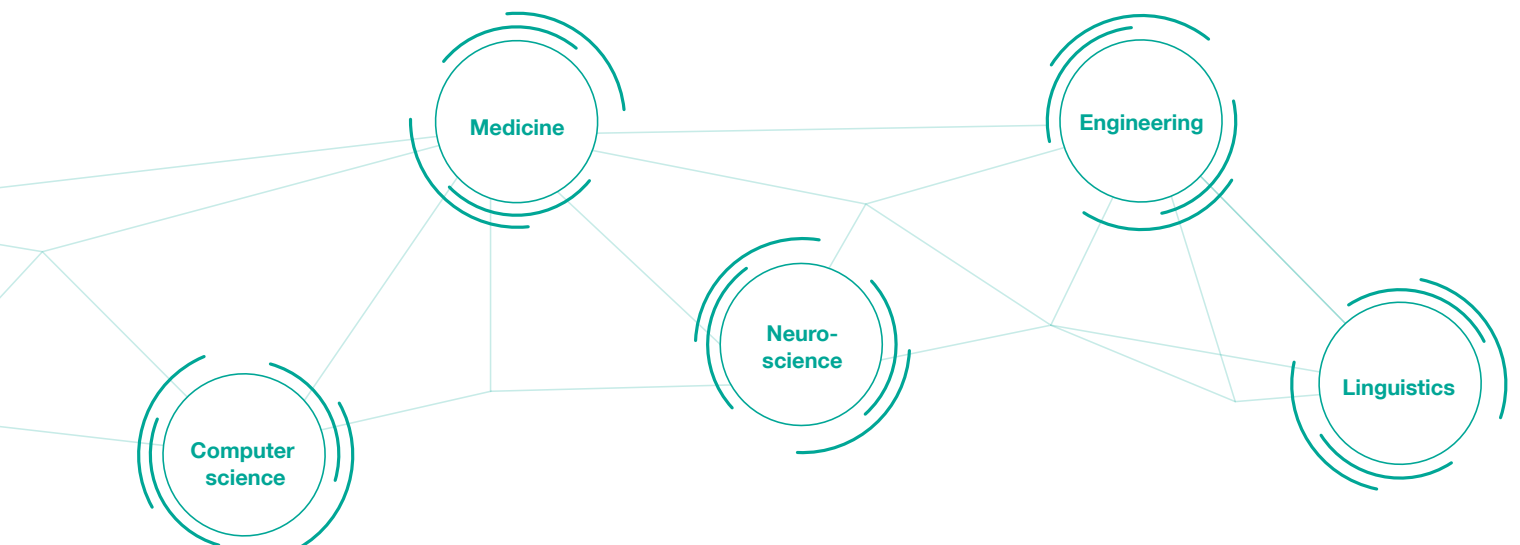
NEUROTECH, the transdisciplinary Network for Mental Health, was selected from 32 applications as one of the first three networks to receive funding. Led by Professor Simon Jacob, it started work on April 1, 2021. The aim of the researchers is to improve our understanding of psychiatric and neurological disorders to enable more reliable diagnoses and individualized treatments.

Simon Jacob is convinced that progress in treating brain disorders requires working across many disciplines. Consequently, his team is made up of scientists and clinicians with expertise in various fields.





Bildquelle: Juli Eberle



Gold Therapy

The pharmaceutical industry is always in search of new drugs to treat diseases. However, despite the huge diversity of inorganic compounds and materials, the potential offered by inorganic chemistry is largely ignored. Promising results being produced by the TUM research group led by Angela Casini could be about to change that. Her research is laying the groundwork for novel therapies and new drug delivery strategies.

Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Heilen mit Gold

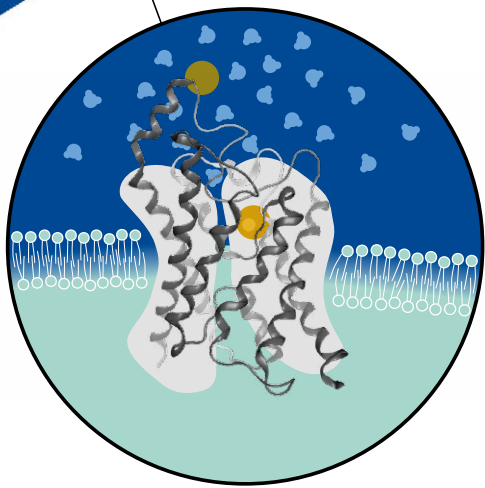
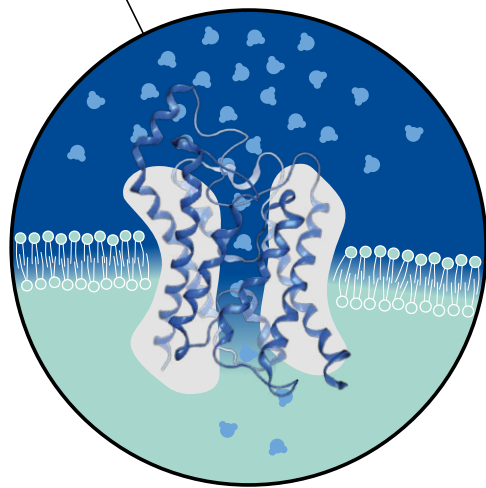
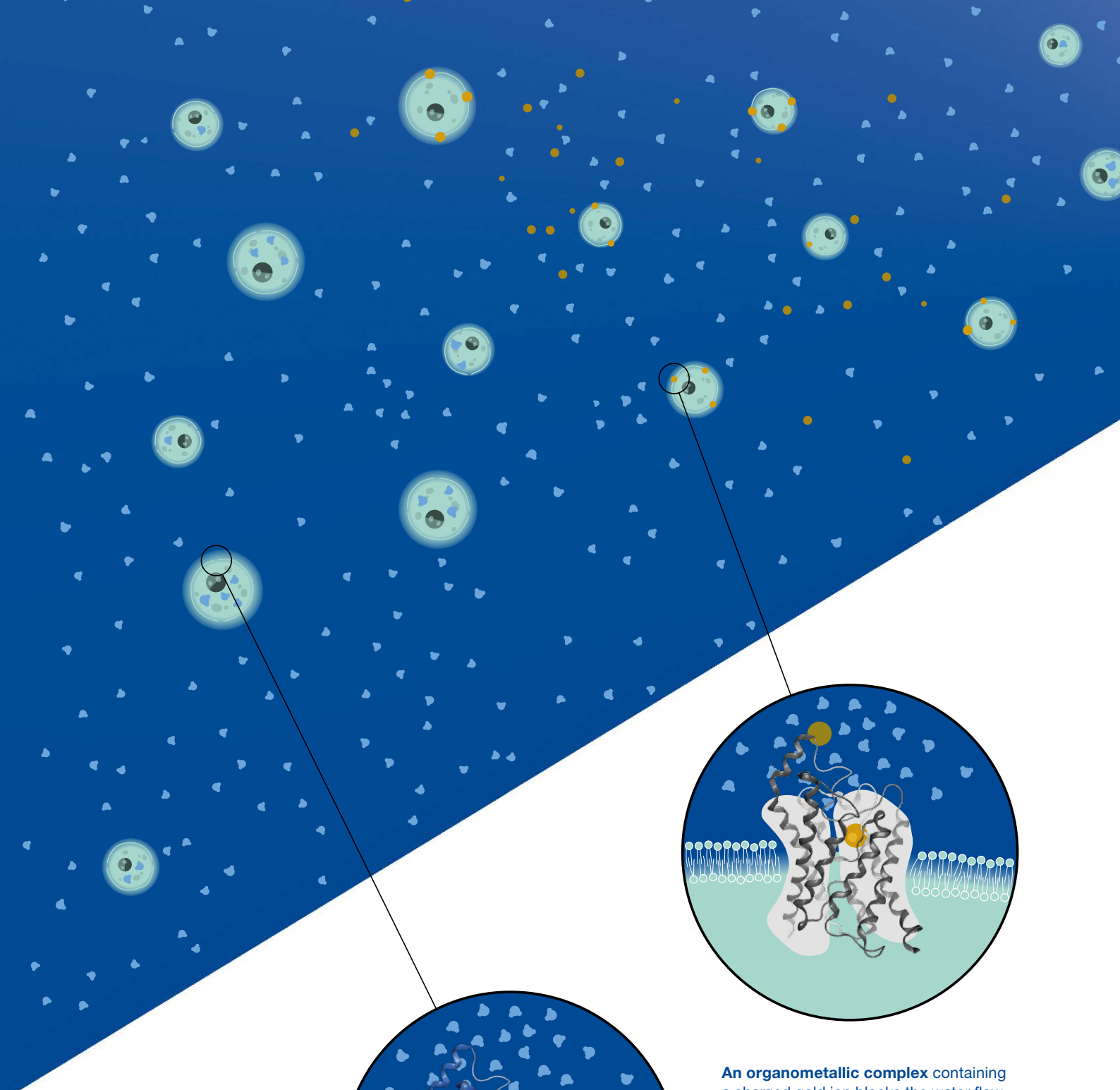
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Fast alle bis dato zugelassenen Arzneistoffe beruhen auf organischen Substanzen. Anorganische Verbindungen kommen heute nur bei wenigen medizinischen Anwendungen zum Einsatz. Das will Prof. Angela Casini mit ihrer Arbeitsgruppe für Medizinische und Bioanorganische Chemie an der TUM ändern. Sie sieht ein großes Potenzial in anorganischen Wirkstoffen, da Metallionen essenzielle Schlüsselrollen in biologischen Systemen einnehmen. So gelang es ihrem Team, mit metallorganischen Goldkomplexen winzige Wasserkanäle in Zellmembranen – sogenannte Aquaporine – selektiv und irreversibel zu hemmen. Ein erster Schritt für einen neuen Ansatz in der Krebstherapie. Sogenannte supramolekulare metallbasierte Strukturen sind ein weiteres Forschungsfeld der anorganischen Chemie mit Potenzial für verbesserte zielgerichtete Therapien und einen optimierten Wirkstofftransport. Neuartige supramolekulare metallbasierte Käfigkomplexe sollen dabei Arzneistoffe oder Radiopharmaka für bildgebende Verfahren einkapseln und zu vorgegebenen Wirkorten transportieren. Wie molekulare trojanische Pferde im Körper eines Patienten könnten sie etwa die Aufnahme von Medikamenten in Krebszellen erhöhen. Durch erfolgreiche Wirksamkeitsstudien konnte Casinis Arbeitsgruppe bereits eine große Hürde überwinden und den Transport einer von Käfigkomplexen eingekapselten radioaktiven Verbindung durch die Blut-Hirnschranke in das Gehirn von lebenden Mäusen bewerkstelligen. Parallel ist die Gruppe stets auf der Suche nach neuen Materialien und therapeutischen Wirkstoffen für die regenerative Medizin. □

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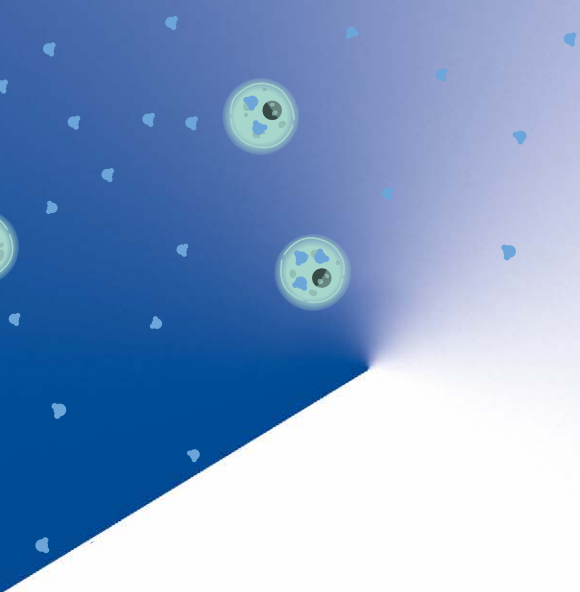
www.department.ch.tum.de/mbc





An organometallic complex containing a charged gold ion blocks the water flow through an aquaporin. Casini's group was the first to develop a gold-based inhibitor acting selectively on tumor cells.

Aquaporins form small channels in the cell membranes. Forming hourglass pores, they enable water and other substances to flow into the cells. Aquaporins play an important role in a number of diseases.



Prof. Angela Casini is using gold to stop water. But it is not raging waters that the Italian professor has in her sights; it is actually the water that flows through tiny channels in the cells that make up our bodies. In the process, her Medicinal and Bioinorganic Chemistry group at TUM is pioneering a completely new approach to fighting cancer and other diseases. Small water channels in tumor cell membranes play an essential, but largely overlooked, role in helping cancer spread around the body. Organometallic complexes, consisting of organic molecular groups clustered around a charged gold ion, are able to block the flow of water through these channels and, the hope is, neutralize tumor cells.

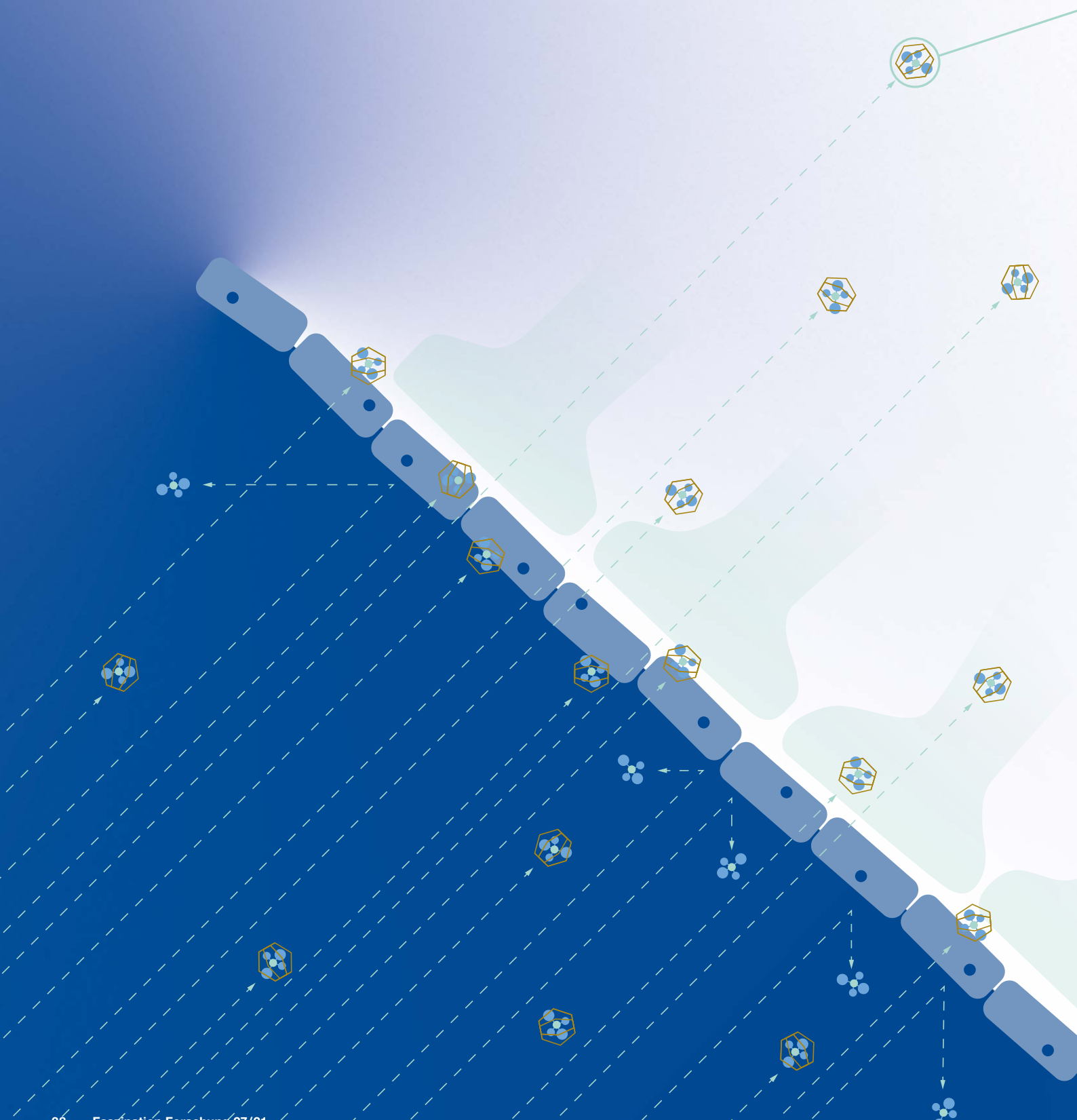
“Metal ions play a key role in biological systems,” explains Casini. Having the exact dosage is, however, extremely important. A metal ion concentration that is too high can be harmful, but so can too low a concentration. Casini is therefore aiming for the “golden” middle ground. And her work is coming to fruition: “We were the first group to develop a selective gold-based inhibitor for these channels,” says Casini. The membrane channels she is blocking are known as aquaporins. They are complex transmembrane proteins in which the amino acids are arranged in a series of helices to form a narrow hourglass channel. These proteins are built into the cell membrane, where they form small pores which narrow to a diameter as little as three tenths of a nanometer. They perform the essential task of maintaining the cell’s osmotic balance. Up to three billion water molecules can flow through an aquaporin channel per second – many times more than would diffuse through the semi-permeable membrane which surrounds the cell alone.

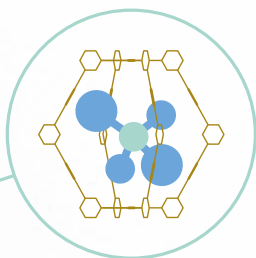
Small water channels through the cell membrane

Aquaporins were discovered by US physician and molecular biologist Peter Agre – a discovery for which he was awarded the 2003 Nobel Prize in Chemistry. About 30 years ago, he realized that a previously identified protein performed an important role as a water channel through the cell membrane. Since then, aquaporins have been identified in a wide array of different cells and organisms ranging from bacteria to plants, animals and humans. Water molecules are not the only substrates that pass through aquaporins; there are also variants, called isoforms, which additionally transport small molecules such as glycerol, hydrogen peroxide, and urea. Aquaporins have been implicated in a number of diseases, including cancer and obesity. Nonetheless, they serve important purposes in a wide variety of organisms. In plants, they support water transport through stems and leaves. In humans they facilitate rapid diffusion of water in cells of the salivary glands, kidney and the crystalline lens of the eye, among other tissues. However, they also facilitate tumor cell mobility and have been identified in more than 20 different tumor types. Tumor cells use these highly efficient water channels to spread rapidly through the body and form fatal metastases.

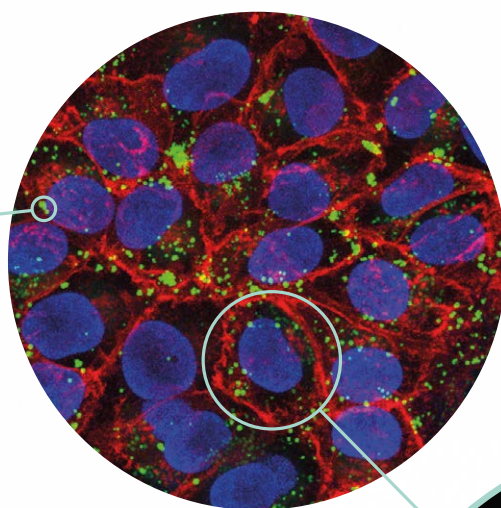
And this is where the work of Angela Casini, along with several international collaborators from the fields of biochemistry, biology, and physiology, comes in. “Selectively blocking tumor cell aquaporin channels could potentially offer a new approach to cancer therapy,” says Casini. She has recently succeeded in using organometallic gold complexes to selectively and irreversibly inhibit cancer-associated aquaporins. This could be used to







Supramolecular metallacages can encapsulate drugs and deliver them to specific targets such as cancer cells.



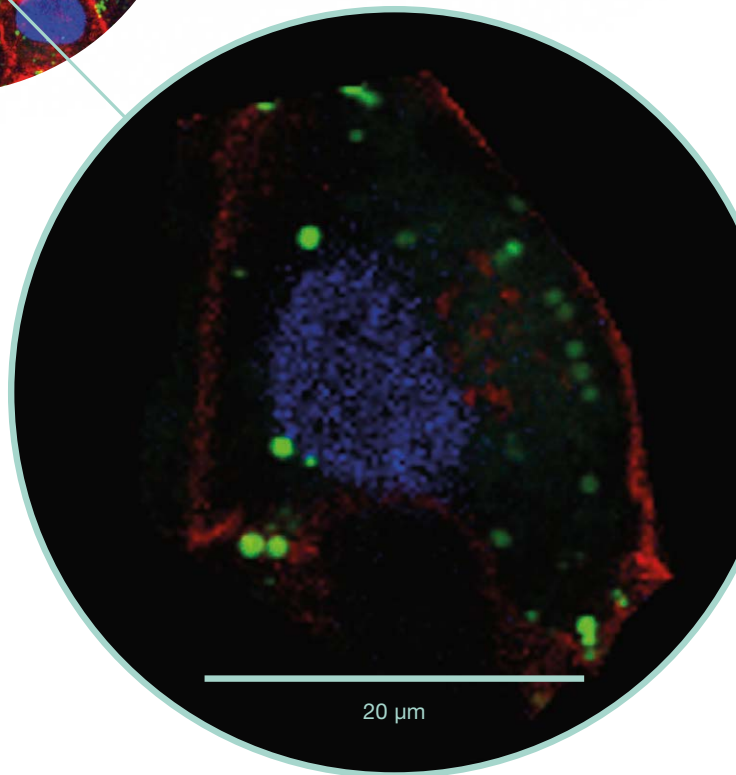
Fluorescent microscopy image of fluorescent metallacages (green) entering human cancer cells (red membrane, blue nucleus).

reduce tumor cell mobility, which could in principle form the basis for a future therapy aimed at stopping tumors from spreading within the body. Casini has not yet optimized these gold inhibitors to maximize their effect on tumor cells, but it is not unreasonable to hope that she might one day identify organometallic complexes able to act more or less exclusively on tumor cell aquaporins.

As promising as this work is, Casini's ideas and experiments extend much further. "Inorganic chemistry has a huge untapped potential for medicine," says Casini. Right now, the vast majority of drugs are organic compounds, i.e., compounds based on the element carbon. Inorganic substances occupy at best a small niche. Examples include the alkali metal lithium, used to treat depression, and radioactive isotopes of rhenium, yttrium, and zirconium, which are employed in nuclear medicine for imaging and therapy. "Medicinal inorganic chemistry will play a big role in future drug development for personalized medicine and will enable major advances in predictive medicine, i.e., predicting disease risk," asserts Casini confidently.

"Trojan horses" deliver drugs to their targets

Similarly, Casini is also very excited by the potential of supramolecular inorganic chemistry. The field was established by the French scientist Jean-Marie Lehn – work for which he was awarded the 1987 Nobel Prize in Chemistry. He discovered that individual molecules can assemble into complex supramolecular structures. Supramolecular chemistry could potentially be used to develop novel systems for targeted drug delivery to specific sites within the body. Casini's research group has already developed supramolecular metallacages able to encapsulate drugs or radioactive agents for imaging procedures. By acting as a kind of molecular "Trojan horse", these cages could be used to boost drug uptake by cancer cells.



Casini has performed initial experiments which prove that this approach is feasible. These involved functionalizing her metal cages with molecular targeting groups, designed by the TUM research group headed by Prof. Horst Kessler. Initial *in vitro* experiments showed increased uptake of encapsulated cisplatin – a cytotoxic drug containing a bound platinum atom in the center – by cancer cells. These metal cages have also been used *in vivo* in mice to transport an encapsulated radioactive compound (pertechnetate) across the blood-brain barrier into the brain. This overcomes a major hurdle to administering drugs into the central nervous system. Because metal-based supramolecular structures permit a wide range of variations and can be adapted for specific tasks, Casini expects these complex chemical systems to prove useful for many other biomedical applications in the future. ▶

“Medicinal inorganic chemistry will play a big role in future drug development for personalized medicine and will enable major advances in predictive medicine.”

Angela Casini

TUM Innovation Network for Artificial Intelligence Powered Multifunctional Materials Design (ARTEMIS)

Part of the TUM Excellence Initiative, TUM Innovation Networks are intended to nurture innovative research fields straddling multiple disciplines. The interdisciplinary teams are made up of seven to ten principal investigators and up to ten PhD students and postdocs. Each network is granted around €3 million in funding over a four-year period.

ARTEMIS, led by Prof. Casini and Prof. Gagliardi, brings together a team of TUM chemists, physicists, bioengineers and computer scientists. They will use machine learning techniques to generate new materials and give new impetus to two research fields prominent at TUM: energy and medicine.

A transdisciplinary Innovation Network to develop new materials

In the search for other supramolecular inorganic materials, Casini and her colleague Alessio Gagliardi have recently set up and now coordinate the Artificial Intelligence Powered Multifunctional Materials Design network ARTEMIS. The network will focus on using artificial intelligence to develop novel materials for energy research and regenerative medicine. All new metal-containing supramolecules will be studied by Casini's research group to determine their suitability for use as new multifunctional materials in regenerative medicine. To this end, the group will use biophysical and analytical techniques as well as pharmacological methods. In addition, they will harness atomistic computer simulations to help predict interactions between metallic active substances and target molecules in the body.

Angela Casini hopes that all these approaches will help to raise awareness within the pharmaceutical industry of the potential offered by inorganic chemistry. “Right now, there is a lack of knowledge concerning the possible use of metals to develop new drugs,” she says. “We need to disseminate this knowledge more widely, starting by training a new generation of chemists who are familiar with interdisciplinary studies.” One step towards achieving this goal could be the renowned Gordon Research Conference “Metals in Medicine” due to be held in summer 2022, which Casini, as one of the conference chairs, is organizing. Inorganic chemistry provides a fantastic set of tools for biomedical applications. “Failing to take advantage of the variety offered by the periodic table would be such a waste,” says Casini. ■ *Jan Oliver Löffken*



Picture credit: Magdalena Jooss

Prof. Angela Casini

obtained her PhD at the University of Florence in 2004. Following a one-year postdoc at the University of Pisa, Casini attained the role of Principal Investigator at the Swiss Federal Institute of Technology in Lausanne. The post was funded by the Swiss National Science Foundation (SNSF). In 2011, she joined the University of Groningen in the Netherlands as an assistant professor for four years. During that time, she also conducted research as a visiting professor in Italy and France. Between 2015 and 2019, she held the Chair of Medicinal and Bioinorganic Chemistry at Cardiff University in the UK. Since 2019, she has headed the Medicinal and Bioinorganic Chemistry research group under the distinguished Liesel Beckmann Professorship at TUM.

Casini has received numerous awards for her pioneering work in the field of bioinorganic chemistry, including the European Medal for Biological Inorganic Chemistry, the Burghausen Diamond of Chemistry Award, and the renowned American Chemical Society Inorganic Lectureship Award. Here, she recently initiated the Artificial Intelligence Powered Multifunctional Materials Design network (ARTEMIS). Together with other researchers at TUM, she is coordinating the ARTEMIS network, which aims to use artificial intelligence to identify new materials for energy research and regenerative medicine.



Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Grenzenlose Fertigungsfreiheit

D

Ob als Zwischensohlen von Turnschuhen, Triebwerkskomponenten von Flugzeugen oder Knochenimplantate: Die additive Fertigung ist bereits Teil unseres Alltags. Sie bietet sich immer dann an, wenn besonders komplexe, filigrane Geometrien gefragt sind und herkömmliche Verfahren an ihre Grenzen stoßen. „Alles, was vorstellbar ist, ist additiv herstellbar“, fasst Prof. Katrin Wudy zusammen. Gemeinsam mit ihrem Team erforscht sie die vielfältigen Möglichkeiten für die additive Fertigung von Serienbauteilen aus Kunststoff und Metall. Sie analysieren, wie sich Prozesse verbessern und neue Werkstoffe verarbeiten lassen. Ihr Fokus liegt auf dem sogenannten pulverbettbasierten Schmelzen (Powder Bed Fusion). Hier wird der eingesetzte Werkstoff als Pulver verarbeitet, das aus vielen Partikeln besteht, die einen Durchmesser von gerade einmal 50 Mikrometern aufweisen – was dem Durchmesser eines menschlichen Haares entspricht. Damit wollen Katrin Wudy und ihr Team die Prozesse für die Serienfertigung voranbringen und neue Materialien erschließen. □



Picture credit: Stefan Woidig; Graphics: edlundsepp

Unlimited Freedom in Manufacturing

Link

www.mw.tum.de/lbam

If you come across a particularly complex filigree part, chances are it was made by way of additive manufacturing, also known as 3D printing. Additive manufacturing technologies are becoming firmly established in industry and enabling a much, much wider range of components to be produced. But there's still a great deal of research to be done. Prof. Katrin Wudy and her team want to drive the processes for series production forward and tap into new materials.



Prof. Katrin Wudy

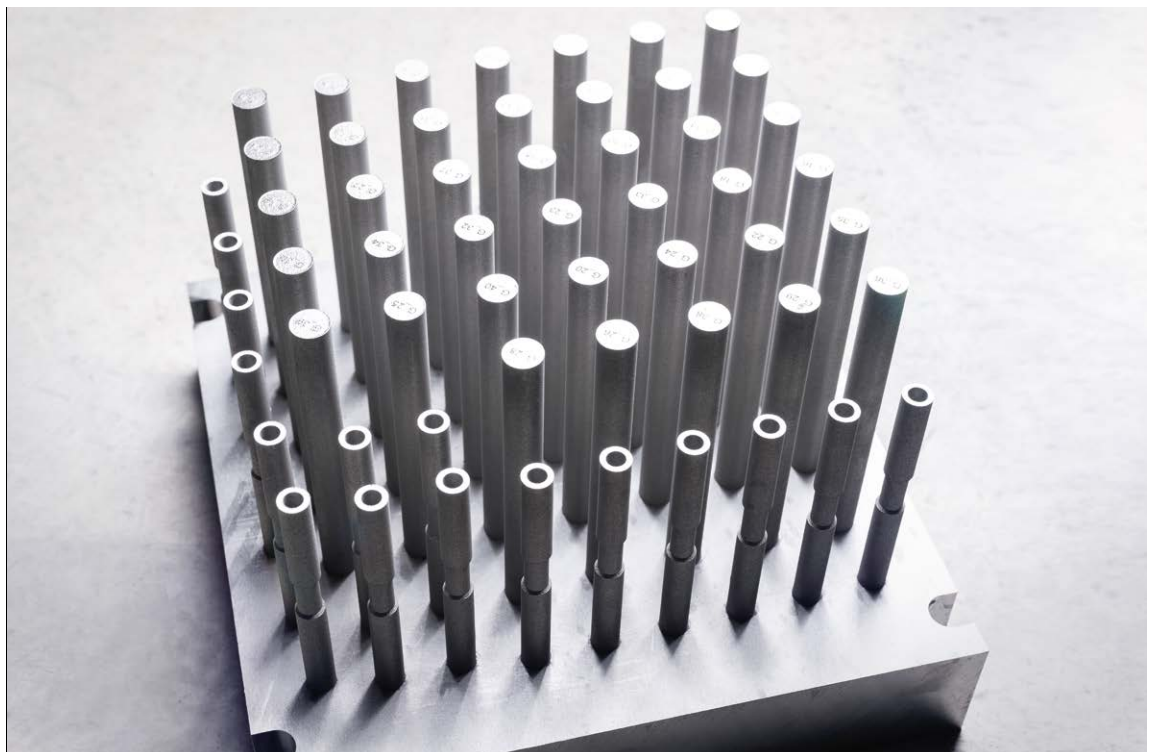
obtained her PhD in powder- and beam-based additive manufacturing from Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) in 2017. From 2015 to 2019, Katrin Wudy was Managing Director of Collaborative Research Centre 814 “Additive Manufacturing” at FAU. She was appointed Professor for Laser-Based Additive Manufacturing at TUM in 2019. The industrial and practical relevance of her research is very important for Katrin Wudy. That’s why she and her team bridge the gap between fundamental research and application-driven projects with industrial partners.

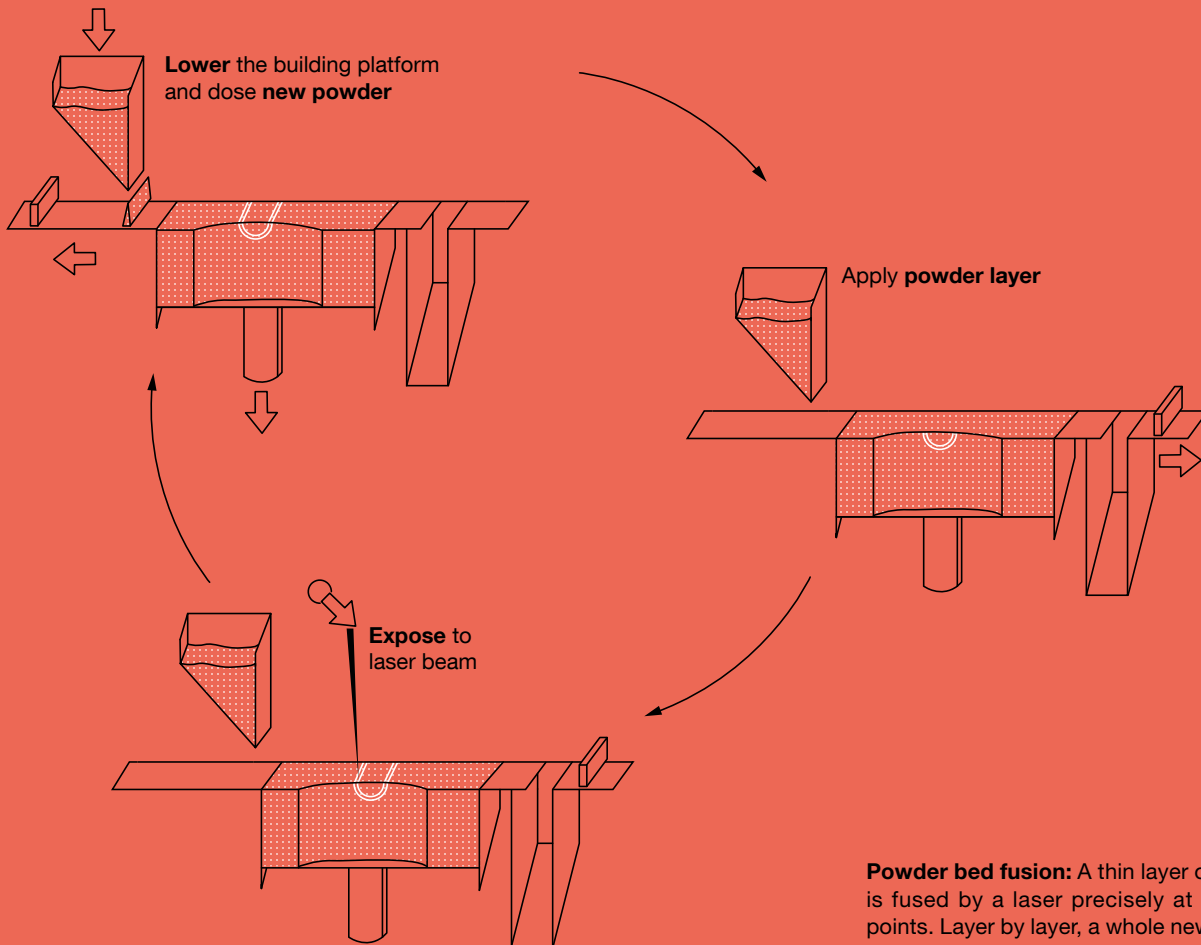
“Additive manufacturing has become part of our everyday lives,” Katrin Wudy says, pointing to her shoes. The trainers she’s wearing have white midsoles with a lattice structure that ensures the shoes can cushion impacts effectively. “Very comfy,” says Wudy, smiling. And that’s not all. Most importantly, they’re also 3D printed.

Whether it’s in the form of these midsoles, fuel nozzles, mascara brushes or bone implants, we find the results of additive manufacturing almost everywhere. They often have complex, intricate geometries that conventional techniques struggle to cope with. Just why is this the case?

Additive manufacturing offers virtually unlimited design freedom, because the components are built up layer by layer based on a digital data model – with no need for any tools or molds whatsoever. It also allows materials to be used that would otherwise push traditional manufacturing methods to their limits. “If you can imagine something, you can use additive manufacturing to make it,” says Wudy, putting it in a nutshell. “That’s what I find fascinating about my area of research,” she adds. ▶

Powder bed fusion of metals: Printed parts with support structures on a build platform.





Powder bed fusion: A thin layer of powder is fused by a laser precisely at specified points. Layer by layer, a whole new component emerges.

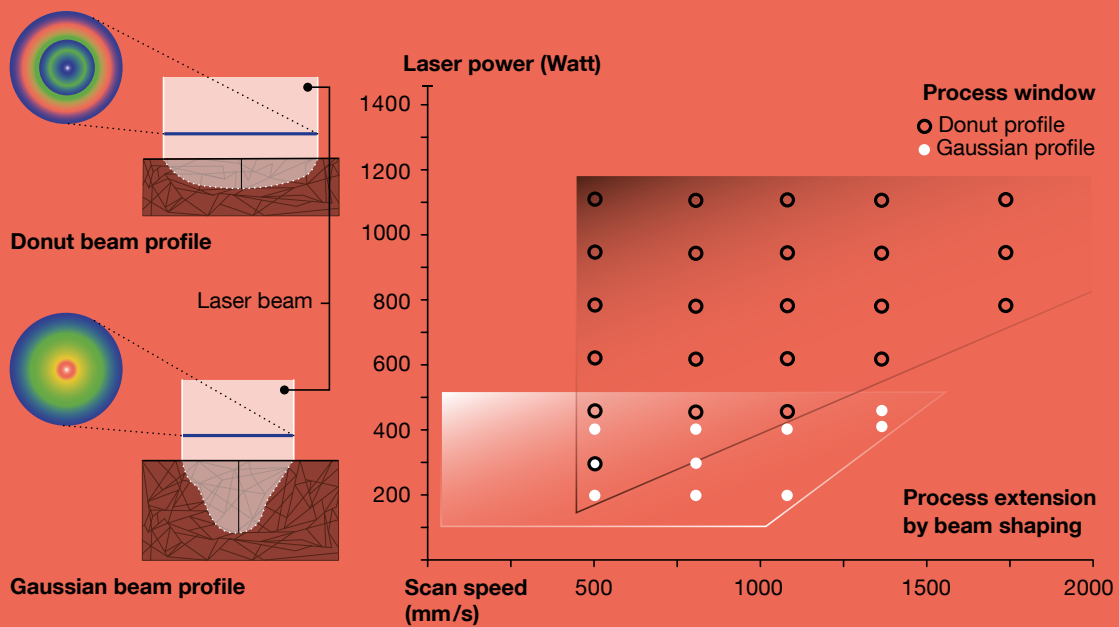
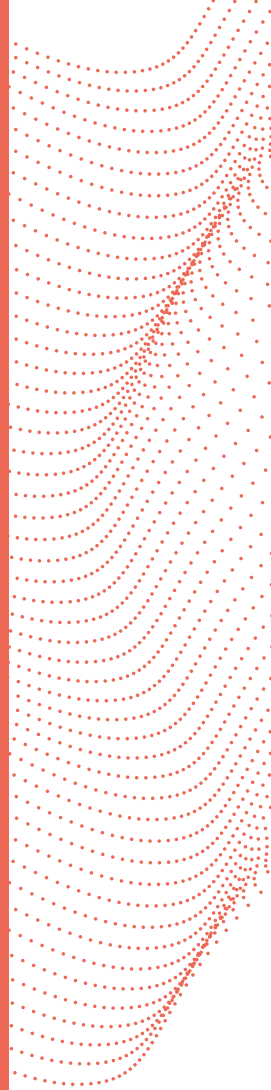
Dual focus as global USP: Wudy's group researches additive manufacturing for both plastics and metals. Shown here: powder bed fusion of plastics (1) and metals (2) together with analyzing methods (3: plastics; 4: metals).

Mass-producing components

When they think of additive manufacturing, most people see a desktop 3D printer manufacturing different figures. There are several processes, however, that industry can draw on to make technically highly sophisticated products out of different materials. And this is precisely what Wudy and her team are interested in: they are analyzing laser- and powder-based additive techniques for mass products and studying how processes can be improved and new materials processed. Their focus is on "powder bed fusion", which uses as its material a powder consist-

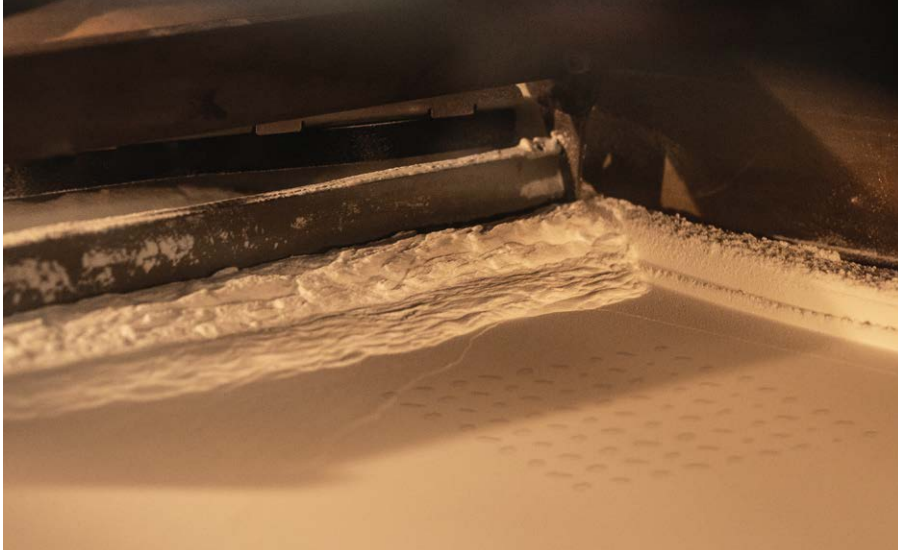
ing of spherical particles each just 50 micrometers in diameter – as thin as a human hair.

How does it work? First, a thin layer of powder is applied to a building platform of a production system, before a laser beam fuses this powder bed precisely at the points specified by the digital data model. The building platform is then moved down a layer, another thin layer of powder is added, and it too is fused on. In this way, a whole new component is created, one layer at a time. ▶

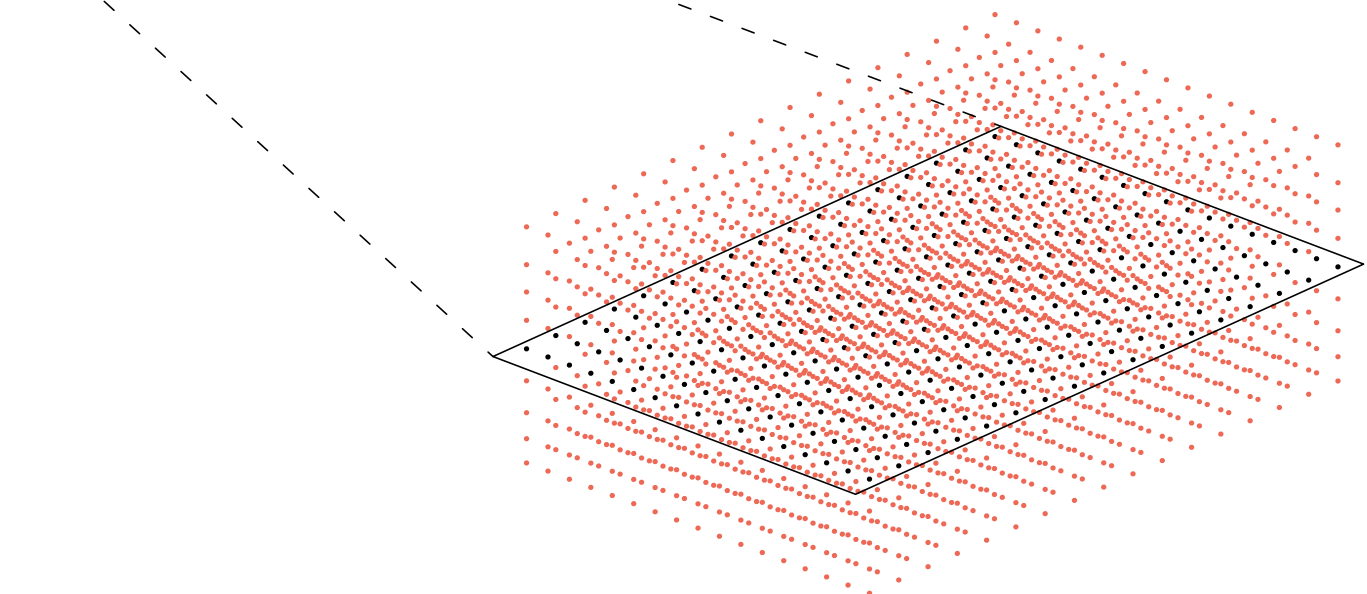
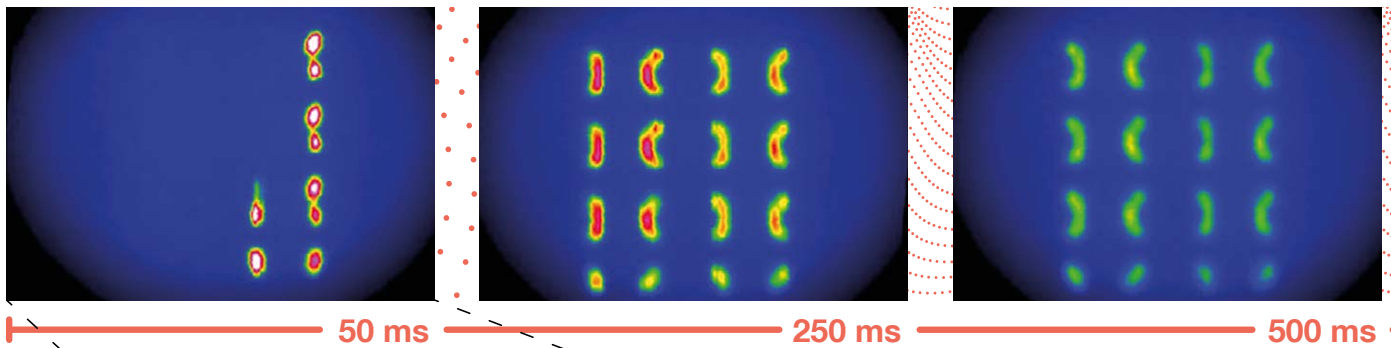


Speeding up metal additive manufacturing by varying the shape of the laser beam: A donut beam profile yields a large process window and thus allows for a faster laser process.





Thermographic observation of the melting process as the laser beam moves across the powder bed.



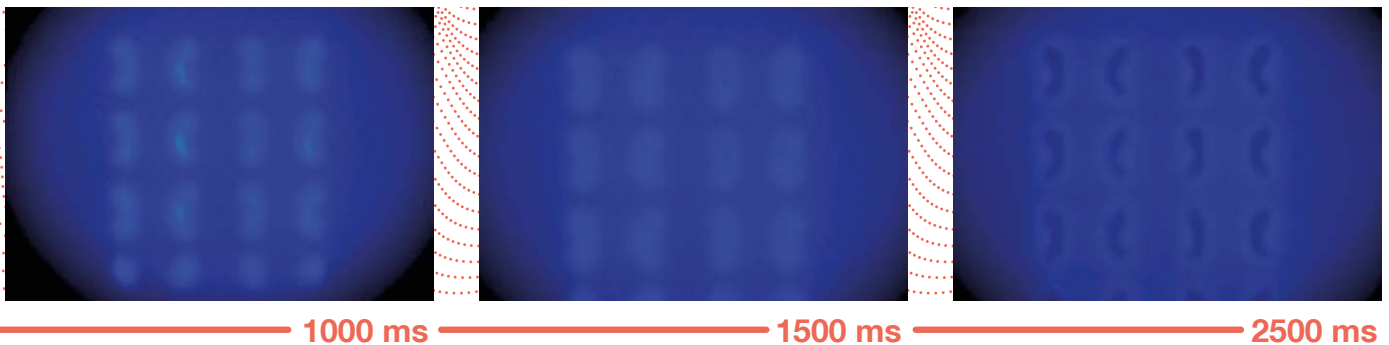
Implementing a new monitoring system for powder bed fusion of plastics to observe the thermal development of the melting process.

A focus on metal and plastic

The laboratory that Wudy shares with the Institute for Machine Tools and Industrial Management at TUM is home to five such machines plus a number of test benches. Here, she and her team are researching the additive manufacturing of plastics and metals in particular. This dual focus is a global USP for Wudy's professorship. "The industries are at different stages of research and manufacturing, so knowledge transfer is possible," she emphasizes. For instance, monitoring systems have already become well established in the metals sector but not for plastic powder bed fusion, where there hasn't been monitoring of the fusing process to date. This means that you don't know whether a component has been successfully manufactured – or not – until you take it out of the building process.

"If you can imagine something, you can use additive manufacturing to make it."

Katrin Wudy



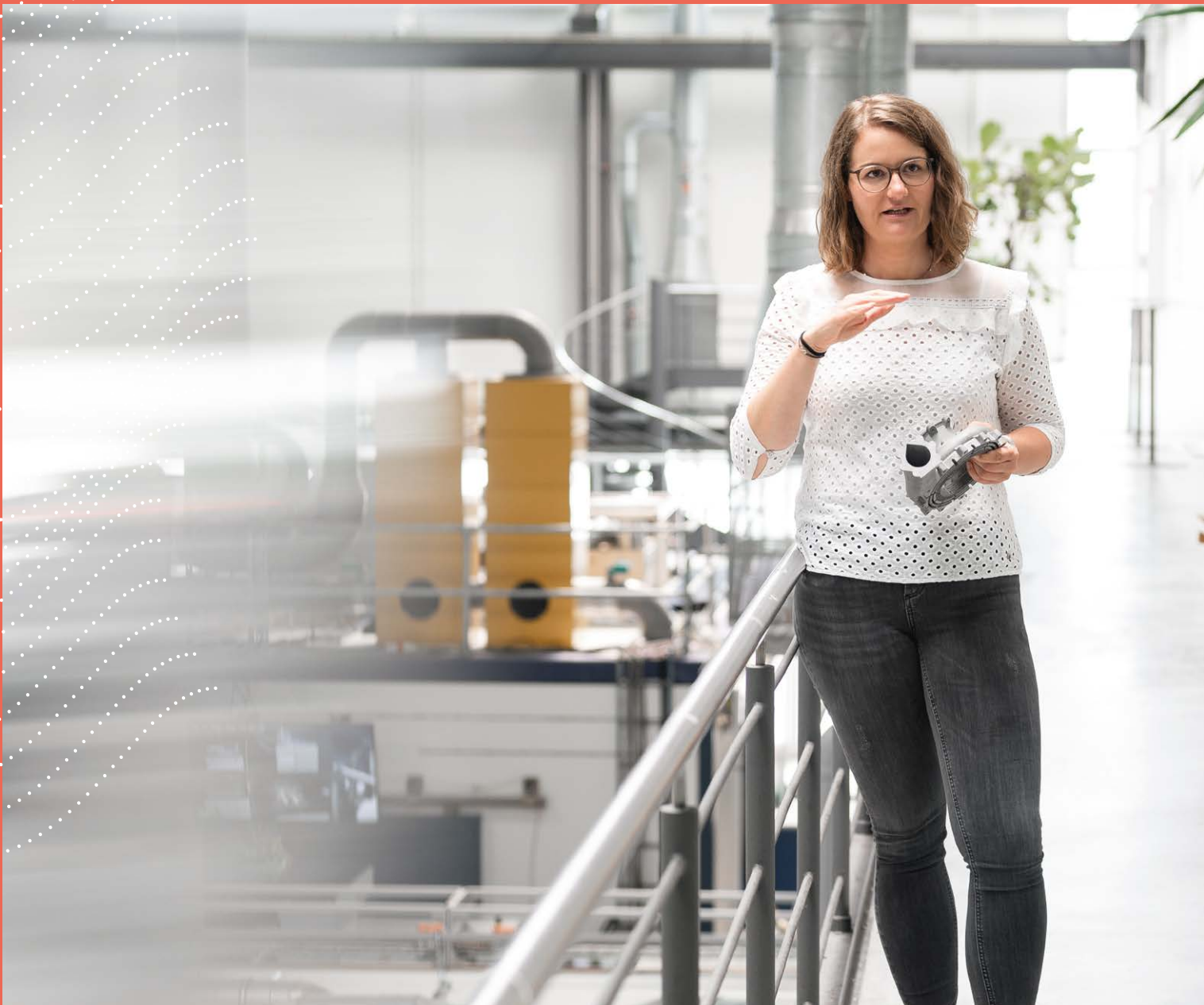
A great many process studies are needed, in other words. Wudy and her team are therefore keeping a close eye on various process parameters during manufacturing or processing so that they can evaluate the materials before the process has even finished. They are aiming high: in the future, hopefully, it will take a matter of days rather than months to develop stable additive processes for new materials. The questions that Wudy is seeking to answer are: What process parameters do I need to take into account for a stable additive process? How do I create a correlation with component properties? The critical factors include how the temperature changes over time and space during fusing and solidification. In order to monitor the temperature of the material during laser exposure, Wudy creates thermography images, which she analyzes in terms of how the fusing process develops over time.

When it comes to metals, Wudy and her team want to modify the melting process itself. The laser beam moves over the powder bed at speeds of up to a meter per second with a spot size of around 60 μm . This means that a very large amount of energy is delivered to a tiny area in an ultra-short space of time. Spatter and powder particles are flung out of the melt pool, which can introduce defects into the component. "We're now working on adjusting the energy input, such as by using different beam profiles, which is making the melt pool bigger and less volatile," Wudy explains. Today's state-of-the-art laser beam sources have an intensity profile that takes the shape of a Gaussian profile in their cross-section (see p. 47). In her tests, Wudy changed the energy input to a ring and donut profile and discovered that this enables her both to fuse larger areas and to speed up the process. A further benefit is that, since these ring and donut profiles allow the temperature gradient to be reduced during laser exposure, new materials can be processed. These include materials susceptible to cracking, such as hot-work tool steels. ■

Gitta Rohling

“We want to develop novel additive manufacturing process strategies in order to realize the first-time-right production and to create products for the future.”

Katrin Wudy



What position is additive manufacturing in today?

Some questions for Prof. Katrin Wudy

Additive manufacturing is now part and parcel of everyday production in many industries. Where do some of the current challenges lie?

As well as optimizing the processes, we're also working on automating them. This is because many of the steps that come after the actual manufacturing process haven't been automated yet, such as releasing the components from the powder and then sorting them, or reusing the powder. We want to develop automated processes for this and get them stable.

Another challenge that we're working on solving is the fact that the range of materials that we could theoretically use in additive manufacturing has always been limited so far. Why's that? Because the micro-scale powder used in powder bed fusion has to exhibit decidedly specific properties, which makes sophisticated demands.

What's going to be studied in the future?

One issue that's going to be taking up more of our time is artificial intelligence (AI), which is becoming increasingly important in additive manufacturing, just like in many other industries. It'll definitely help us answer many of our research questions in the future. Right now, however, it's a question of analyzing and evaluating our datasets – and then gaining a better understanding of our processes and optimizing them. There's an awful lot of data to analyze on the components, which are often made up of thousands of layers. The advances made in AI for image recognition and analysis are proving particularly helpful for our monitoring, so we'll be working closely with our colleagues in Informatics going forward.

Overall, there's a lot of research needed in the field of additive manufacturing. After all, it's still quite a new research area. Although early additive manufacturing techniques were developed as far back as 1985, the first industrial applications only came about within the past ten years. There's still a great deal of progress we can make in research. The community that's researching and working here is young, dynamic, innovative – and keen to transform the world of manufacturing.

■

Gitta Rohling



Picture credit: Stefan Woidig

Palmöl aus dem Bioreaktor

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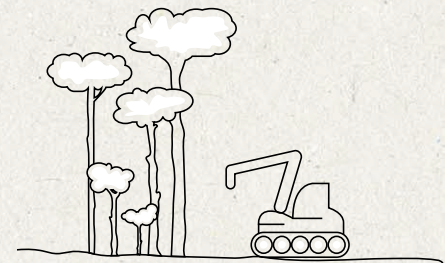
Auf der Suche nach einer umweltfreundlichen Alternative zu Palmöl hat der Biochemiker Dr. Mahmoud Masri ein Verfahren zur Gewinnung von Öl aus Hefekulturen entwickelt – gentechnik- und lösungsmittelfrei, basierend auf organischen Abfällen. Mit seinem Start-up Global Sustainable Transformation will er bald Hefeöl in großen Bioreaktoren produzieren. □

How to Grow Palm Oil in a Bioreactor

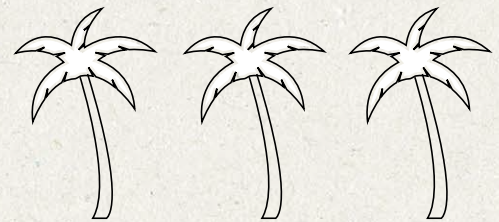
Palm oil would be a great product – if it wasn't for the huge tracts of rainforest that are cut down for oil palm cultivation. Biotechnologist Dr. Mahmoud Masri has now developed a palm oil substitute that can be produced in a yeast culture. He has founded a start-up with the aim of making his vision of environmentally friendly yeast oil a reality.

Eleven years ago, Greenpeace released a gruesome video raging against the use of palm oil in food. In it, a young man, taking a break from the office, reaches for a chocolate bar. He absent-mindedly tears open the packaging, but fails to notice that it contains not a chocolate bar but the finger of an orangutan, into which he unwittingly bites. The ape's blood is then seen running down his chin. The video was intended to draw attention to the fact that his chocolate bar contains palm oil, and that the orangutan's rainforest habitat is being destroyed to make space for oil palm cultivation. In addition to its impact on biodiversity, palm oil cultivation also releases large volumes of CO₂. In 2018/19, the EU decided it was time to take action. From 2030, palm oil, once considered a sustainable product, will no longer be permitted in biodiesel. Despite its image problems, the global market for palm oil is booming. Since 2010, production has grown by nearly 50% to 74 million tons per year.

For manufacturers of processed foods in particular, palm oil has some very appealing properties. It is tasteless, keeps well, can be used for pan and deep-frying, and is cheap, cholesterol free and vegan. It is also used in skin creams, lipsticks, detergents, shower gels, paints and varnishes. In addition, by comparison with oilseed crops such as soya, rape and sunflower, yields from oil palms are a great deal higher. Much less land is required to obtain abundant harvests. This land, however, has primarily been obtained by clearing rainforests in Indonesia and Malaysia – a process that is still going on today.



Rainforest logging



Palm oil cultivation



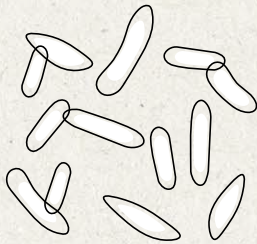
Palm oil

74 million

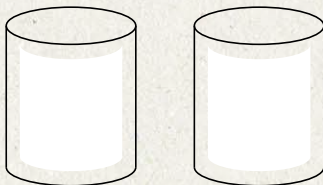
tons of palm oil were produced worldwide in 2018/19

50%

more palm oil was produced in 2018/19 compared to 2010



Yeast cultures ...



... produce oil in a bioreactor

50,000

times more oil per hectare of space



Enzymes help in extracting a palm oil equivalent

As a result, those looking for palm oil alternatives have a very high bar to clear. But that hasn't deterred Mahmoud Masri at TUM. He is using a tiny single-celled organism – yeast – to produce oil in huge culture vats. "Bioreactors take up a lot less space than oil palms. Yeast cultures are able to produce 50,000 times more oil per hectare than oil palms," explains Dr. Masri.

That yeast can be induced to produce oil has long been known. But the oil produced is a long way from being able to compete with palm oil. Yields are low, oil extraction requires the use of toxic solvents, and the yeast require very specialized nutrient media.

Dr. Masri started by turning his attention to the solvent problem. "I tried a number of enzymes to break open the yeast and extract the oil without using solvents," he explains. "None of them really did the trick." Finally, he tried an enzyme extracted from a specific fungus. The result was as much a surprise to him as it was to his supervisor, Werner Siemens Professor of Synthetic Biotechnology Thomas Brück. "Following enzyme treatment and centrifugation, the test tube I held in my hand had a clear oil layer on top," says Masri. "What's that?" asked Thomas, and I replied 'It's the oil'. This was a major breakthrough, since it meant we had succeeded in entirely dispensing with organic solvents."

The second problem was a bit trickier. As Masri explains, "Yeasts can grow on practically any type of organic waste if that waste has first been treated with enzymes to break it down into some basic building blocks. That's the big advantage of using yeast." The sticking point is nitrogen concentration. Too low and the yeast grow too slowly, too high and the yeast switch to producing carbohydrates rather than oil. Masri tried many different approaches, before coming up with the idea of adding small quantities of organic acids to his cultures, which the yeast rapidly metabolize into fatty acids. "The yeast cultures grew incredibly dense and thick, irrespective of the amount of nitrogen."

The end of the story brings us back to the beginning. The team submitted patents, founded Global Sustainable Transformation, was awarded the TUM's IDEAward 2020 innovation prize and received financial support in the form of a TUM Bridge-to-Innovation Grant. Masri is now negotiating with investors and carrying out research to determine the best organic waste to use for large-scale oil production.

Markus Bernards

Shapes, not Colors

Prof. Gil Westmeyer visualizes molecular information that imaging techniques have not yet been able to access. One prime example is the molecular processes involved in signal transmission between nerve cells, such as when the connections between neurons strengthen during learning. Together with his team, Westmeyer is developing new markers for electron microscopy.

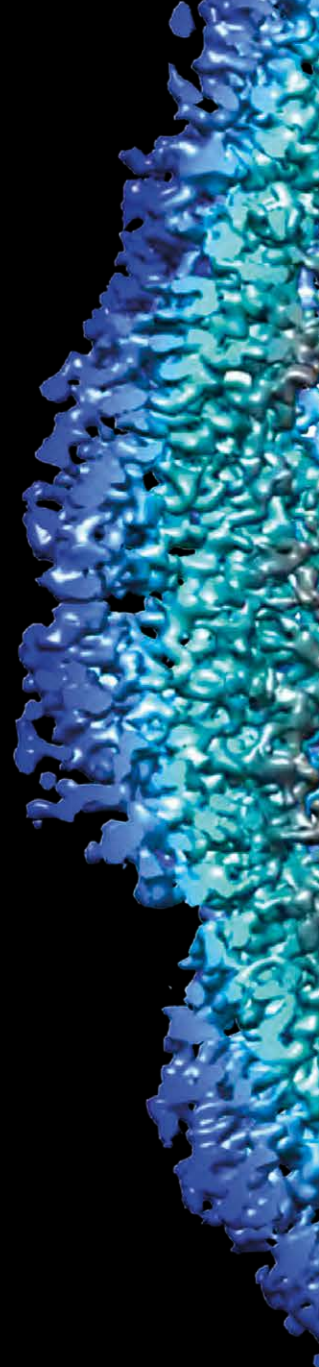
Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Formen statt Farben

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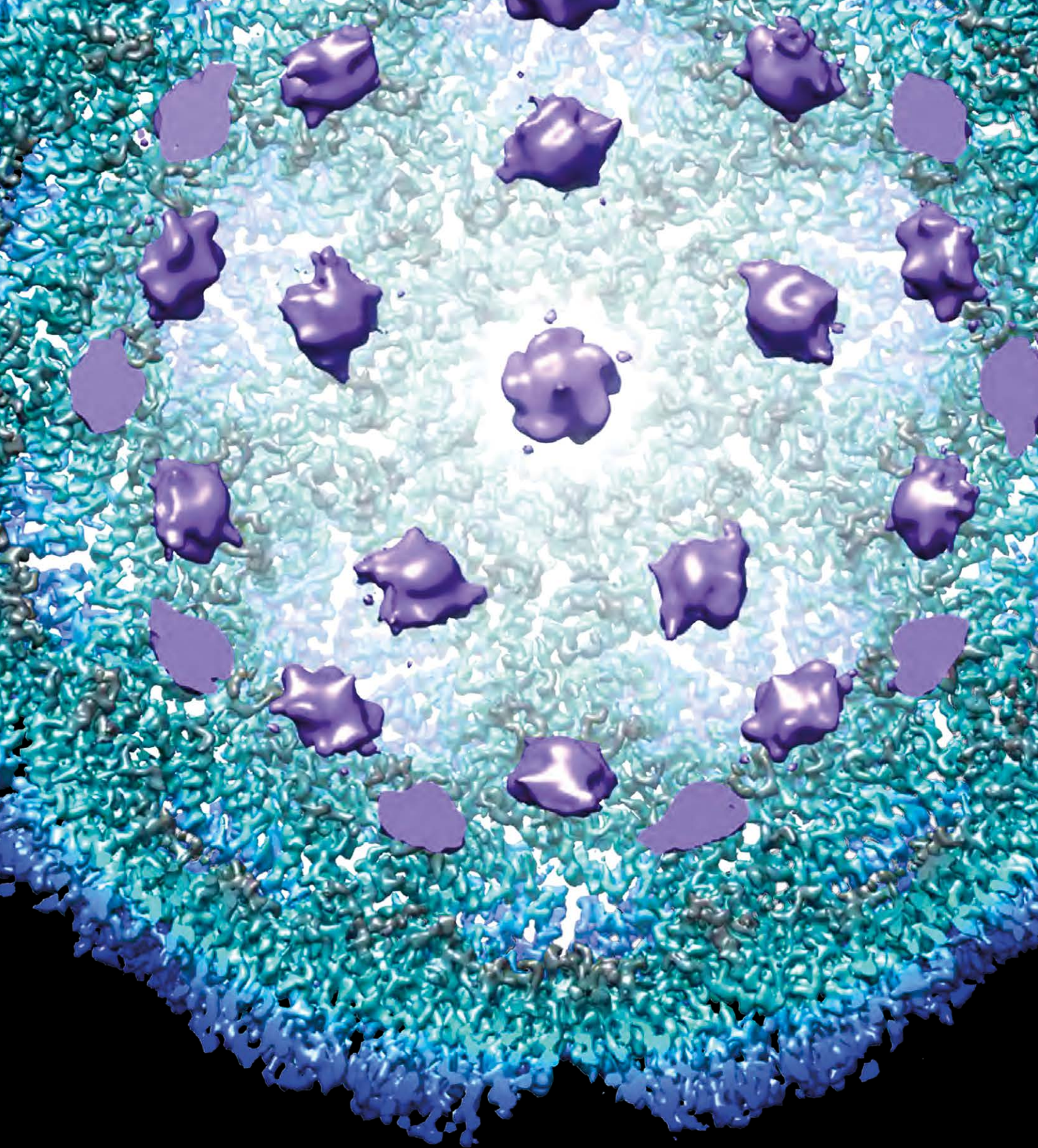
Wenn Zellen aktiviert werden, verändert sich ihre Genexpression und damit ihre Proteinproduktion. Das ist auch bei Nervenzellen der Fall, wenn im Rahmen von Lernprozessen die Signalübertragung verstärkt wird. Außerdem produzieren die Zellen dann unterschiedliche Proteine, etwa für die Veränderung von Synapsen. Bisher ist es nicht möglich, diese molekularen Veränderungen mittels Hochdurchsatz-Mikroskopie zu visualisieren, da die Fluoreszenzmikroskopie zwar Methoden zur Markierung von Molekülen bietet, aber nicht die notwendige Auflösung liefert.

Prof. Gil Westmeyer hat mit seinem Team deshalb neuartige Marker für die Elektronenmikroskopie entwickelt. Sie ermöglichen, eine Vielzahl „molekularer Spieler“ parallel in sehr hoher Auflösung zu visualisieren. Dafür nutzt der Forscher Designer-Proteine, die von Nervenzellen in Zellkulturen oder von gentechnisch veränderten Modellorganismen produziert werden, etwa wenn die Zelle aktiviert wird. Die Proteine bauen sich in der jeweiligen Zelle dann selber zu Nanostrukturen zusammen. Das Aussehen dieser Strukturen lässt sich durch geschicktes Design der Proteinbausteine variieren. Im Elektronenmikroskop können auf diesem Weg unterschiedlichste molekulare Informationen parallel ausgelesen werden. Die Methode lässt sich vielseitig nutzen, etwa um molekulare Vorgänge von Lernprozessen zu untersuchen oder um das Verständnis für neuropsychiatrische Erkrankungen zu verbessern. Eine wichtige Rolle könnte die Technologie außerdem bei der Entwicklung zukünftiger Zelltherapien und der Entwicklung von Schnittstellen zwischen Nervenzellen und Computern spielen. □



1 nm

Source: Reprinted (adapted) with permission from "Iron-Sequestering Nanocompartments as Multiplexed Electron Microscopy Gene Reporters". Copyright 2019 American Chemical Society.



Asked about the applications for the latest methods he has developed, Gil Westmeyer first outlines the bigger picture. The connections between nerve cells, known as synapses, have a hugely important role to play in memory formation. New synapses develop, and existing synapses become more receptive to signals. The next time the same cell is stimulated, the response from the receiving cell is significantly stronger.

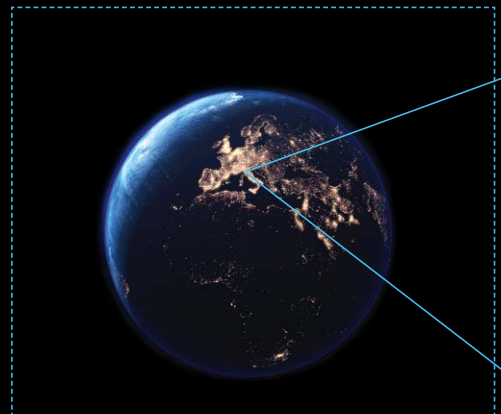
Researchers worldwide hope that by revealing the connections between nerve cells, they can infer their functions. This impetus has led to the emergence of a new branch of neuroscience called connectomics – a reference to genomics, which considers a complete set of genes. Scientists in this field are working to create the connectome – akin to a wiring diagram for the brain – by eventually mapping all synapses of a brain. Some researchers even believe that the connectome is at the core of what we are – in other words, our memories, our cognition, and our thoughts.

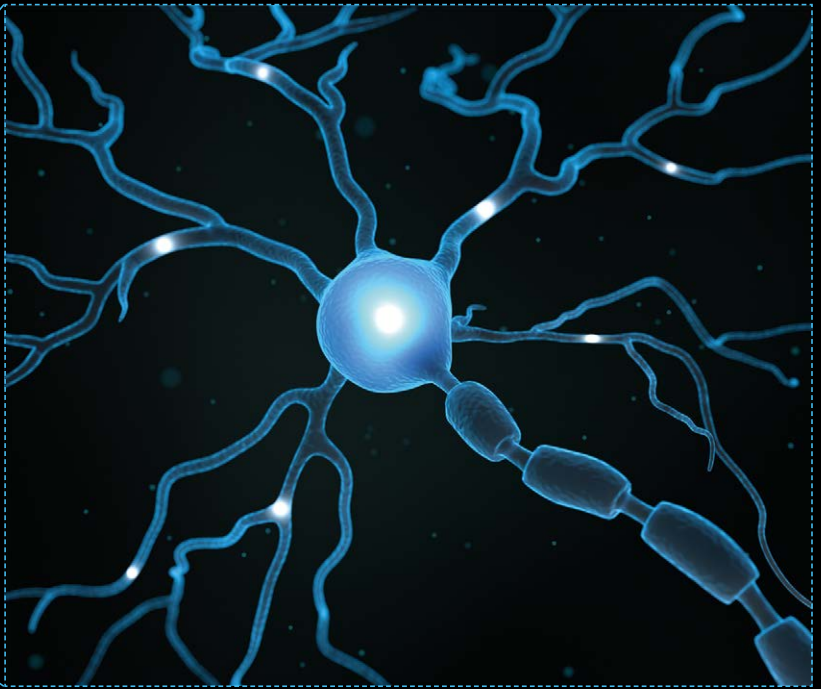
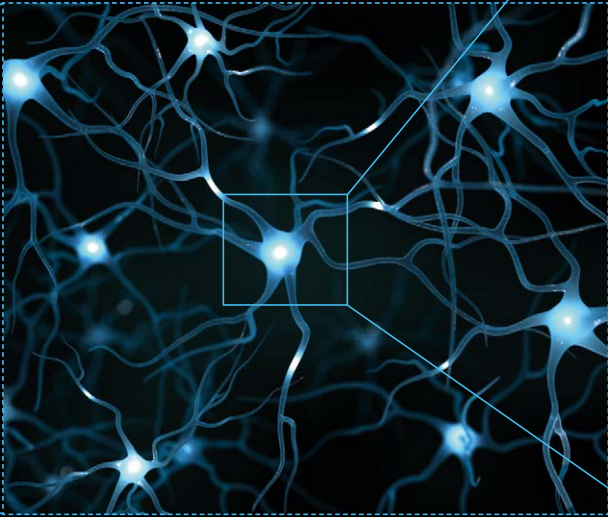
The connectome – a wiring diagram for the brain

Scientists have already successfully mapped the connectomes of certain model organisms, such as the roundworm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*. With around 100,000 neurons, a fruit fly's brain is compact enough for researchers to examine in its entirety. By comparison, a human brain has around 100 billion nerve cells. Westmeyer compares the overview provided by the connectome to a street map of a large, dynamic city. "While we can see the major anatomical connections, we want to zoom in even further and see what traffic volumes are located where, how the traffic light intervals are organized, and where road construction zones crop up and disappear," he states.

Gil Westmeyer heads up the Institute for Synthetic Biomedicine at Helmholtz Zentrum München and is Professor of Neurobiological Engineering at TUM. His research program focuses on developing biomolecular and genetic methods for capturing and controlling fundamental cell processes. Such techniques make it possible to visualize the underlying patterns in molecular mechanisms and refine current models of information processing. These insights will also help us understand the mechanisms involved in a biological learning process. ▶

In analogy to a detailed road map, a brain's connectome details the connections between all of its neurons.





Fluorescence microscopy

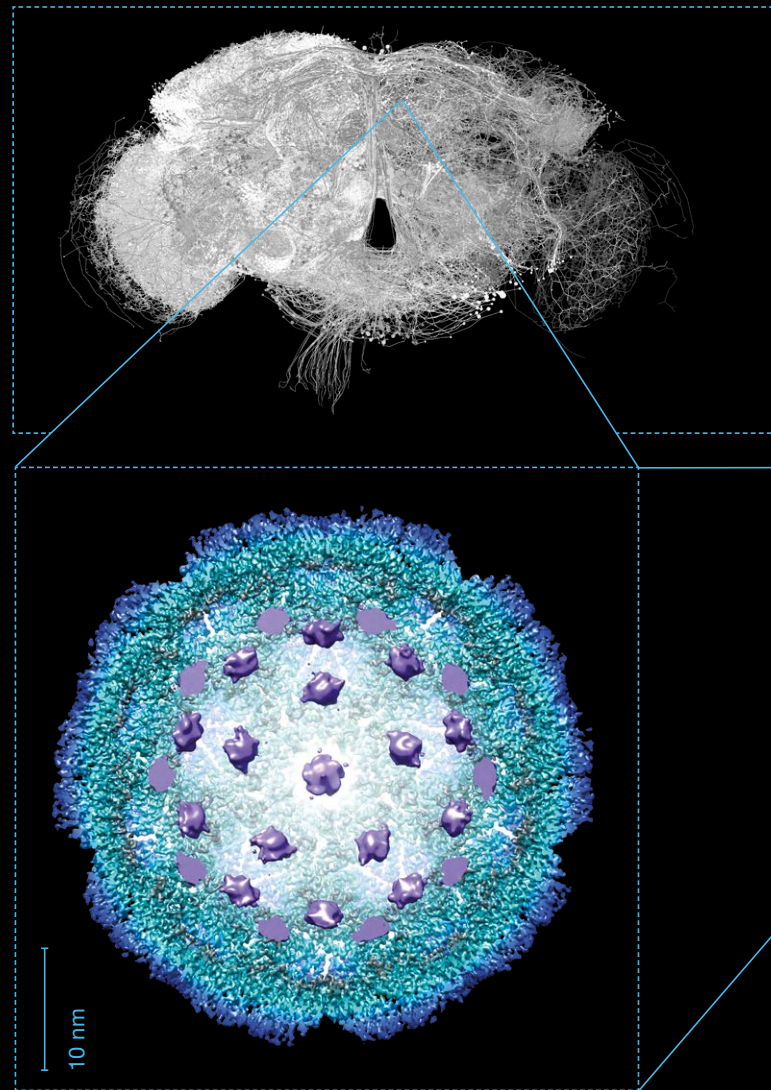
Fluorescence microscopy is a specific form of optical microscopy based on the physical effect of fluorescence. When fluorescent compounds are excited with light of a certain wavelength, they emit light of a different, longer wavelength. This form of microscopy uses fluorescent dyes that attach themselves to certain structures with the help of, say, antibodies or fluorescent proteins produced by genetically modified cells. Light has wavelengths of well under one micrometer. Due to the diffraction barrier, an optical microscope cannot distinguish between objects smaller than several hundred nanometers in size. By spatially restricting possible fluorescence emissions or isolating the fluorescence signals, super-resolution fluorescence microscopy can overcome the resolution barrier and localize fluorophores measuring just a few nanometers across.

Volume electron microscopy

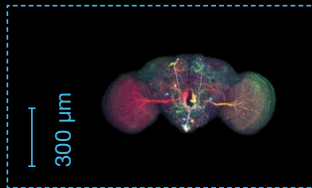
For visualizing cell-cell contacts and intracellular organelles in a block of tissue with nanometer resolution, the block is ablated (with either diamond knives or ion beams) and analyzed sequentially using scanning electron microscopy on either the individual sections or the block remaining after each section is removed. The tissue is then virtually assembled from the 2D sections into a 3D digital model. Computer algorithms help to identify the individual cell structures.

Source: *Drosophila* Brainbow: a recombinase-based fluorescence labeling technique to subdivide neural expression patterns Reprinted (adapted) from 2011 Springer Nature; EM reconstruction of *Drosophila* neurons by the Full Adult Fly tracing community. Visualisation by Philipp Schlegel (Drosophila Connectomics Group, University of Cambridge) 2018 Springer Nature, Reprinted Zheng, Lauritzen et al., Cell Resource (2018); Reprinted (adapted) with permission from "Iron-Sequestering Nanocompartments as Multiplexed Electron Microscopy Gene Reporters". Copyright 2019 American Chemical Society

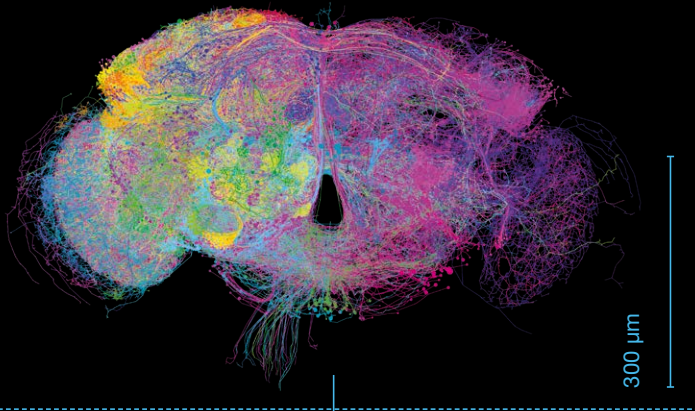
High-throughput volume electron microscopy reveals the "connectome" of a fly's brain, i.e., all connections between its neurons.



Nanosized gene reporters are genetically expressed by defined nerve cells under specific conditions.



Fluorescence microscopy can reveal cell function but lacks the resolution to resolve the exact contacts between nerve cells.



Gene reporters for electron microscopy augment the brain's wiring diagram with "multicolor" information on cell function.

Learning processes at the molecular level

Any change of state in a cell is closely associated with changes in gene expression and, consequently, protein production. The fact that signal transmission intensifies after a learning process is partly based on the synthesis of new proteins, both in the cell body and in the processes of nerve cells, which branch out considerably.

Electron microscopy (EM) is the imaging technique of choice for mapping the trajectories of nerve cells. "Volume electron microscopy provides detailed information about the connections within neural networks. However, the images produced in high-throughput microscopy are imprecise depictions of the molecular players on the cell's playing field, such as mRNA or proteins," explains Westmeyer.

To capture these molecular cell processes, fluorescence microscopy (FM) is a suitable technique. FM uses special fluorescent proteins to provide multicolored markings and has established itself as an indispensable technique in the field of biomedicine. Unfortunately, FM does not offer the resolution required to examine the nerve cells' delicate processes. Westmeyer and his team hope to resolve this issue with a new method they have developed for electron microscopy. It involves markers that can visualize information in a similar way to fluorescent proteins, just with an electron microscope instead – therefore offering considerably higher resolution.

In order to achieve this, the scientists rely on protein complexes that self-assemble within the nerve cells. They use these complexes in neurons, in cell cultures, or in model organisms such as fruit flies, in which nerve cells are genetically modified to produce corresponding

markers, for instance, when they are activated or produce certain proteins for new synapse formation. One class of protein complexes is known as encapsulins, which self-assemble into hollow nanocompartments with defined sizes of 20, 30, or 40 nanometers. Nerve cells, with diameters of several micrometers, are around 1000 times larger than these nanocages.

Proteins or enzymes, such as the enzyme ferroxidase, can be encapsulated inside the nanocages. The enzyme catalyzes the oxidation of iron ions that enter the nanocages through their pores, creating iron-oxide species of low solubility that are trapped in the nanocages. Metals have a higher density than proteins and therefore improve the contrast so that the nanocages are clearly visible in EM images. What is even more ingenious is that, by skillfully designing the proteins' building blocks, scientists can create nanostructures with different contours that are distinguishable in EM imaging. "This means we can generate a whole range of structures, which allows us to examine several parameters of a cell's state at the same time. Given the complexity of the nervous system, this is a significant advantage," says Westmeyer. It is all made possible by the fact that the nanocages are non-toxic and so small and inert that they do not hinder or disturb cells. The protein complexes serve as markers for genetic activities (gene reporters), which means that different molecular states of cells can effectively be visualized with different "colors" in an electron microscope. The project has received a prestigious Consolidator Grant from the European Research Council.

Westmeyer thinks one step further. An electron microscope cannot visualize activities in living cells. To bridge

this gap and make it possible to examine dynamic processes in the future, fluorescent proteins will also be added to the nanocages inside the nerve cells. "This will allow us to make the markings so bright that we could even conduct measurements on living cells using high-performance, super-resolution fluorescence microscopy – with a potential resolution of several nanometers," says Westmeyer. Theoretically, a subsequent step could see cells examined under a fluorescence microscope being additionally examined under an electron microscope so that the cell structures can be analyzed in even greater detail. "It might sound simple, but the validation required means it is still a long way off," notes Westmeyer.

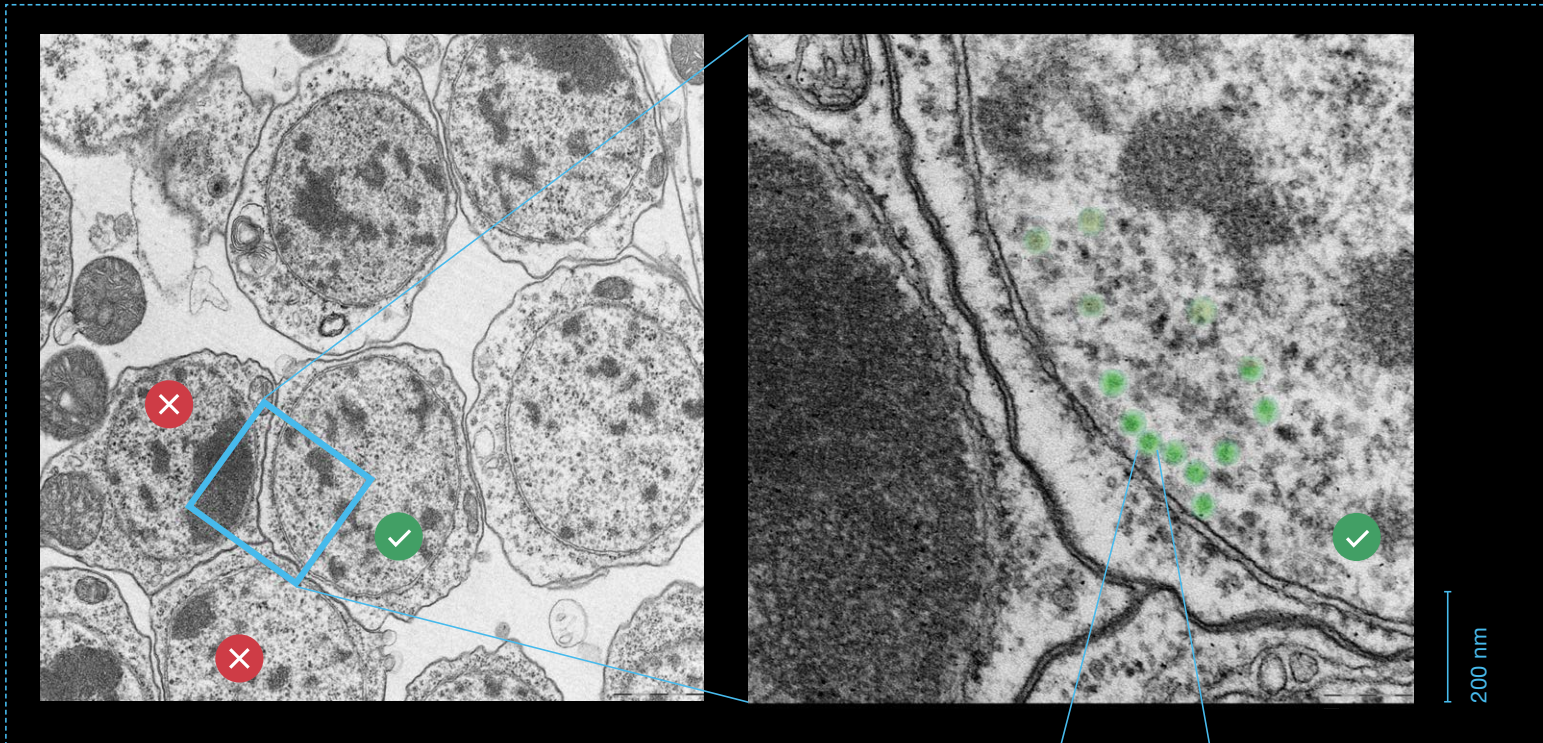
Monitoring human-computer interfaces

Westmeyer is fizzing with ideas of other use cases for his methods. For instance, insights gained into the dynamic interactions between patterns of brain activity – i.e., the cell states identified by markers – and connections between nerve cells, in other words, the paths of nerve cells identified from EM images, could improve our understanding of neuropsychiatric disorders such as autism and Alzheimer's. The novel marker methods could also contribute to the development of future cell-based therapies. The aim is to use a combination of different molecular methods to visualize as many aspects of cellular processes as possible, thus enabling researchers to refine and support these innovative treatment approaches. Westmeyer's method could also help uncover the architectural principles of neuronal circuitry, which could then provide inspiration for the design and development of neuromorphic computer chips. This chip architecture ▶

“Our method allows us to augment high-resolution anatomical brain maps with ‘multicolor’ functional information.”

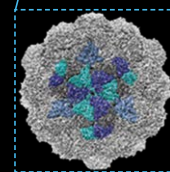
Gil Westmeyer





Visualizing molecular information in neurons.

Left: Electron microscopy of a section through a fruit fly's brain. EM gene reporters are expressed in the nerve cell labeled with the green checkmark to report on the cell's genetic state.



Link
www.westmeyerlab.org

seeks to recreate the circuitry optimized over the course of biological evolution and would then, for example, be able to perform pattern recognition algorithms very efficiently at the hardware level.

Furthermore, the EM markers could prove helpful in creating new interfaces between nerve cells and computer chips. In a new project at the Munich Institute for Biomedical Engineering (MIBE) at TUM, conducted in collaboration with the Technical University of Dresden and Bernhard Wolfrum of TUM, Westmeyer hopes to grow nerve cells directly onto the circuitry of computer chips. The scientists want to measure the electrical and electrochemical properties of the nerve cells and deliver electrical stimulation in return. They then plan to use electron microscopy to examine and improve cell-chip contacts. The marker systems Westmeyer's team has developed for electron microscopy could provide crucial additional information about the functional state of the nerve cells used in the experiment, thus allowing scientists to monitor and optimize the interfaces. This iterative approach could make future interfaces between neurons and a connected device, such as a computer, safer and more precise. One potential application for this technology would be to control a paralyzed patient's bionic arms or legs.



Karoline Stürmer



Prof. Gil Gregor Westmeyer

studied medicine and philosophy in Munich. He conducted his doctoral work on the molecular basis of Alzheimer's disease in Prof. Christian Haass' laboratory before receiving a part of his clinical education at Harvard Medical School in Boston, Massachusetts (USA). He then worked in Prof. Alan Jasanoff's laboratory at MIT before being appointed to TUM in 2012. Gil Westmeyer is currently Professor of Neurobiological Engineering at TUM. He is also Director of the Institute for Synthetic Biomedicine at Helmholtz Zentrum München.



Security – Now and in the Future

Information is long established as a vital business asset – and protecting this information is a key challenge for the 21st century. Prof. Antonia Wachter-Zeh wants to use mathematical codes to develop new encryption techniques able to withstand attacks from even the most powerful quantum computers. Her methods could also help enable long-term data storage using DNA.

Link
www.ei.tum.de/en/Int

Gesamter Artikel (PDF, DE): www.tum.de/faszination-forschung-27

Sichere Daten – auch in der Zukunft

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Das Verschlüsseln von Daten verhindert das Auslesen und den Missbrauch sensibler Informationen. Mit dem Bau von Quantencomputern ist die Sicherheit gängiger Verschlüsselungsmethoden in Gefahr. Die auf der Quantenphysik beruhenden Rechner können aktuelle Kryptoverfahren knacken – was die gesamte Kommunikationssicherheit in der IT in Frage stellt. Zwar sind leistungsfähige Quantenrechner erst im Stadium von Prototypen, doch die Zeit für die Lösung des Problems ist schon heute kritisch. Antonia Wachter-Zeh, Professorin für Codierung und Kryptographie an der TUM, entwickelt mit algebraischen Codes neue Verschlüsselungsmethoden, die auch Quantencomputern standhalten sollen. Dieses Konzept der algebraischen Codes wendet Wachter-Zeh auch auf die neue Methode der DNA-Speicherung an. Bei diesem Speicherungsverfahren werden Daten direkt in DNA-Strängen abgelegt. Die dabei auftretenden Lese- und Schreibfehler will die TUM Professorin mit algebraischen Codes korrigieren. □

In an ever more digital world, data security is hugely important. To protect data and guarantee the security of data transfer, data for applications such as home banking, online shopping, and sharing business documents is encrypted. A number of different encryption schemes are used, depending on the application.

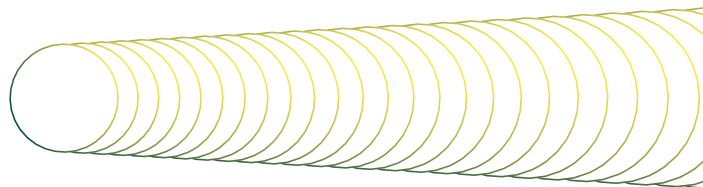
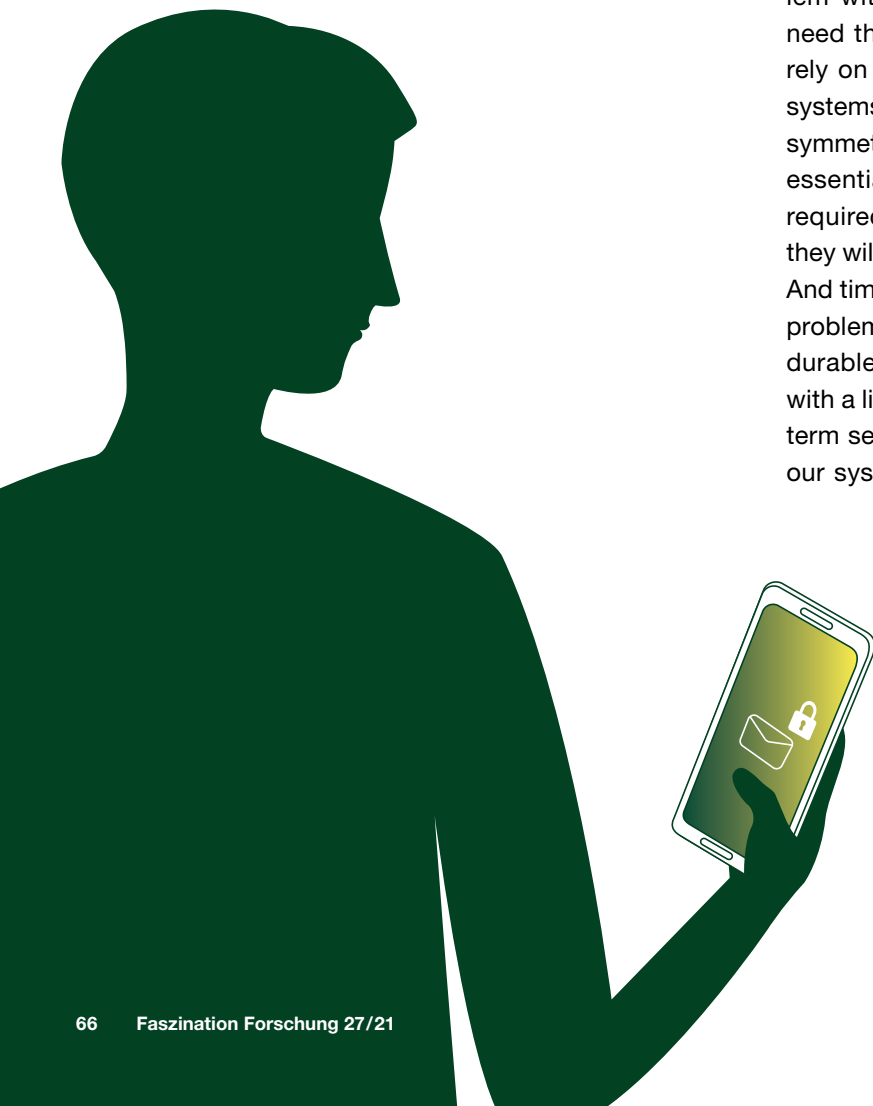
Asymmetric cryptography is one widely-used cryptography system. Asymmetric cryptography algorithms feature a public key and a private key and form the foundation of many crypto-procedures at work in today's IT world. We rely on public key systems when we send an email, do our internet banking, or communicate with a web server. From a mathematical perspective, public key encryption is predicated on the fact that calculating the private key from the public key is extremely difficult – in fact it's beyond even the most powerful modern supercomputers. But that may not be the case for much longer. The advent of quantum computers means that widely-used public key algorithms such as RSA and elliptic curve cryptography are no longer secure. It's not yet clear when quantum

computers powerful enough to crack these algorithms will be available, but it's clear that they're coming. Google, IBM and other IT companies have already developed early prototypes. The German Federal Office for Information Security expects machines able to crack public key encryption to be available by the early 2030s.

The quantum menace

TUM Professor of Coding and Cryptography and DFG Heinz Maier-Leibnitz Prize winner Antonia Wachter-Zeh is very clear about the significance of this threat. "As soon as powerful quantum computers with sufficient qubits become available, widely-used public key cryptosystems have a big problem," she explains. As part of the ERC Starting Grant project inCREASE, her research group is seeking to develop new cryptographic systems that are also resistant to attack from quantum computers.

It's worth noting that quantum computers are not a threat to all cryptography systems. For very efficient symmetric cryptography algorithms, such as AES, quantum computers pose relatively little threat. Increased computing power can be counteracted by using longer keys. The problem with these systems, however, is that both parties need the same key. And to share this key, they need to rely on public key cryptography. In practice, public key systems are generally "only" used for exchanging keys for symmetric cryptography systems. But key exchange is an essential part of these systems. Because the schemes required for this key exchange are completely broken, they will no longer be usable within the foreseeable future. And time is already running out now if we are to solve this problem. The issue particularly affects manufacturers of durable products, such as cars, aircraft, and satellites, with a life span well in excess of 10 years. "We want long-term security for the data we are transferring today, plus our systems are going to be used for a very long time,"



says Wachter-Zeh. “Satellites in orbit, for example, are very difficult to update. But we still want the data transferred via those satellites to be secure in 20 years’ time.” Another reason Wachter-Zeh believes we need to deal with this problem now is that today’s communications are often stored. “We need to make sure that even in 10 or 20 years’ time, no-one will be able to decrypt data transferred today.”

Post-quantum cryptography

Moving to quantum computer-resilient cryptographic systems is therefore something we need to do now. Faced with this problem, the US National Institute of Standards and Technology (NIST) launched a quantum-resilient cryptography competition, which has now entered its final round. The goal is to standardize “post-quantum cryptography”, i.e. cryptographic systems that can’t be cracked even by quantum computers.

Development of post-quantum cryptography is based on mathematical concepts which can be divided into a number of groups. Antonia Wachter-Zeh’s group is researching secure encryption techniques that use error correction codes. This promising approach is based on correcting errors which arise during data transfer or storage. Error correction codes enable error-tolerant data encoding. How many errors can be corrected depends on the type of code.

“Codes like this are used in conventional communications technology. In the simplest case they involve adding redundancy to a message,” explains Wachter-Zeh. “In communications engineering, if you transfer a codeword and the communication channel introduces an error, then you want the recipient to be able to resolve the error and compute the correct message. This principle can also be used for encryption. You deliberately introduce a specific error, so that it can’t be decrypted by anyone else.”

Wachter-Zeh is an expert on a specific class of error correction codes called rank metric codes. The NIST classes rank metric-based techniques as extremely promising, but thinks a lot more research is needed. Wachter-Zeh’s research group has developed some of the world’s most efficient rank metric decoding techniques and has proposed a new public key system based on rank metric codes (LIGA).

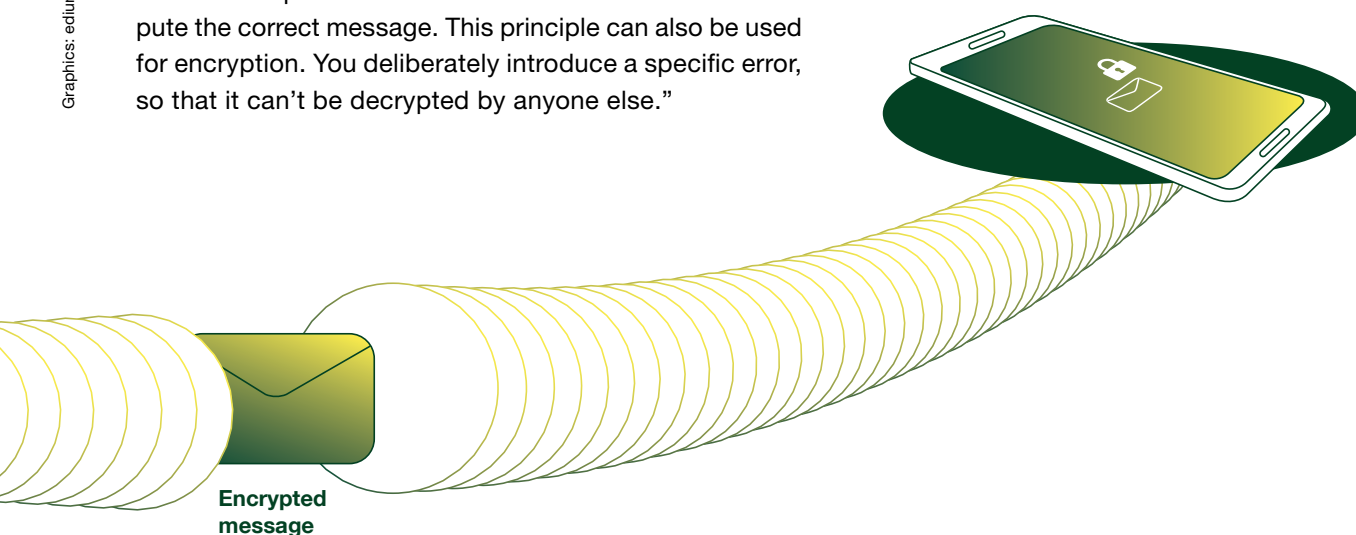
DNA-based storage

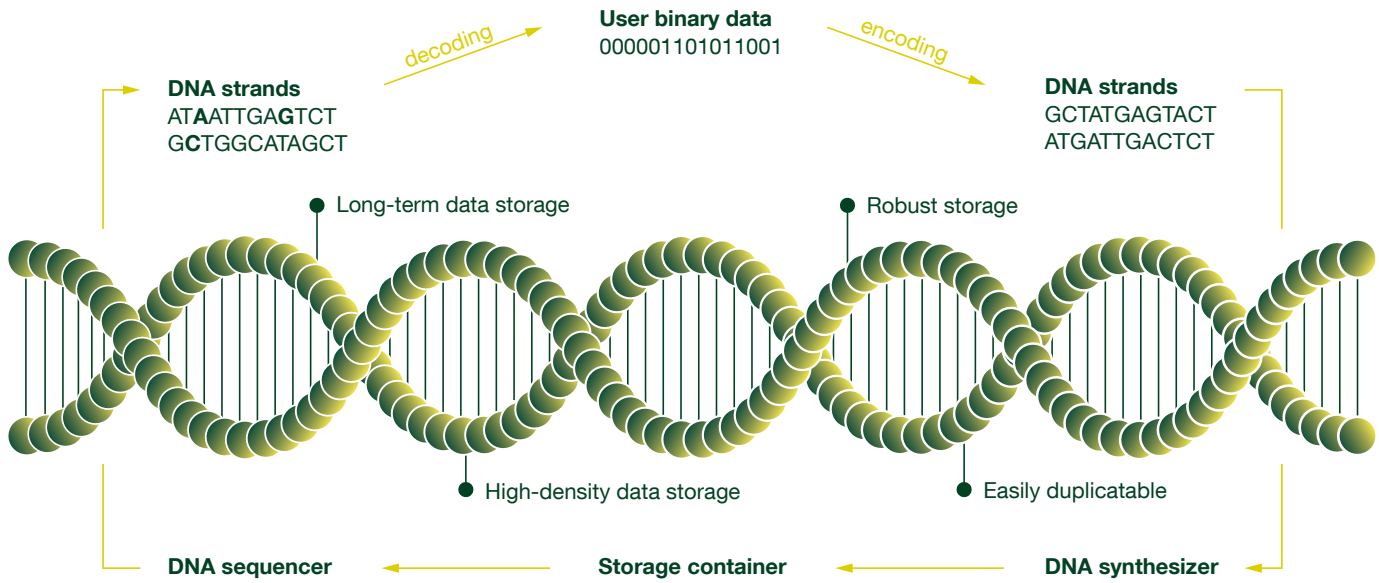
Wachter-Zeh hopes that error correction codes will also provide solutions to another highly topical problem – data storage using DNA. This new storage technique involves storing data in strands of DNA. The zeros and ones of digital data are converted into the four bases found in DNA: adenine (A), cytosine (C), guanine (G) and thymine (T). In the simplest case, two digital bits are combined into one DNA base.

Storing data in DNA strands has the potential to solve an increasingly pressing problem – conventional storage media such as DVDs and hard drives have a very limited life span. Where data needs to be stored for longer periods – several decades for example – there is a high risk of data loss.

With DNA storage, data keeps for much longer – as demonstrated by the fact that we are able to extract DNA from ancient mammoth bones. “The ability of fossils to store DNA implies that DNA could be used for archival data storage. If we want to store data for generations, DNA-based storage is an excellent option.” ▶

Graphics: edlundsepp (source: TUM)





Storing data in strands of DNA involves converting the zeros and ones of digital data into the four bases of DNA: adenine (A), cytosine (C), guanine (G) and thymine (T). DNA storage has the potential to solve several problems such as life span and capacity of conventional storage media.



Prof. Antonia Wachter-Zeh

is a professor in the TUM's Department of Electrical and Computer Engineering. She completed her MSc in communications technology at Ulm University in 2009. Wachter-Zeh completed her PhD at Ulm and the University of Rennes in France in 2013. From 2013 to 2016 she worked as a postdoctoral researcher at the Technion-Israel Institute of Technology in Haifa, Israel, and from 2016 to 2020 was Tenure Track Assistant Professor at TUM. Wachter-Zeh has been awarded the DFG's Heinz Maier-Leibnitz Prize and is funded by an ERC Starting Grant. Her research interests are coding theory, cryptography, and information theory and their application to storage, communication, privacy, and security.

Another advantage of DNA-based storage is that gene sequences are very dense and enable the storage of a great deal of data in a very compact space. “The maximum data density for the medium currently used for archival storage – tape – is 100 GB per cubic millimeter. For DNA it’s 10^9 GB per cubic millimeter,” explains Wachter-Zeh.

Eliminating errors

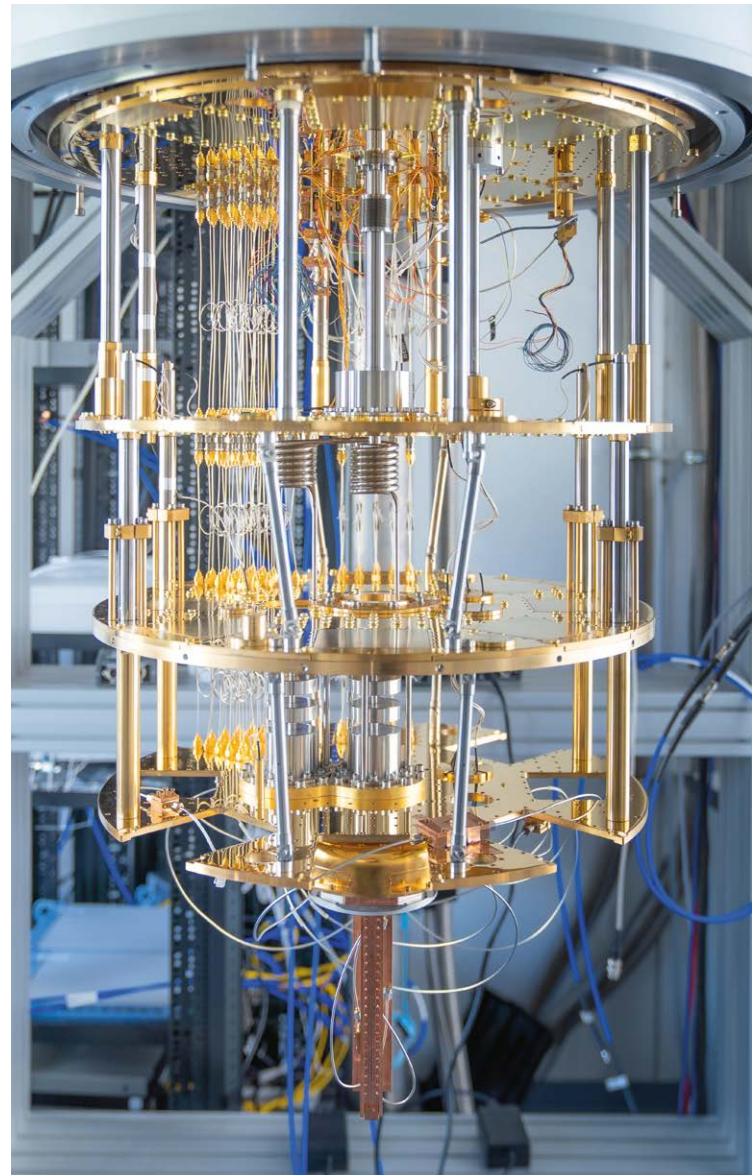
Before DNA-based storage can be used in practice, however, a number of obstacles need to be overcome, particularly in the areas of reading and writing the data. Writing data to DNA using DNA synthesis is currently the costliest part of DNA storage. Wachter-Zeh’s research group is trying to make this process more efficient. “We want to write multiple sequences simultaneously and as rapidly as possible,” explains the TUM researcher. “If a machine can do this in parallel, the question is what is the theoretically best way of doing this?” She is therefore examining synthesis techniques in which multiple strands are constructed step by step and in parallel using a fixed supersequence.

The second focus for her research group is reading the data. This is currently the biggest challenge for DNA-based storage. Basically, data is read by sequencing the DNA. Because each DNA strand is replicated many times, the read sequences are always clustered around the written data. The sequencing process sequences a large number of DNA strands which then need to be reassembled in order.

In addition, various errors can occur. Sequences can go missing, because they have not been read. The order of the sequences can also be lost. Within sequences, it can also occur that bases are inserted, deleted, or duplicated. When reading the data, all of these errors need to be corrected. “Researchers have found that without error correction it is almost impossible to reconstruct data from DNA systems,” explains Wachter-Zeh. “There are simply too many errors. Error correction is therefore essential – for which we can use known communications engineering techniques.”

Here again, Wachter-Zeh is relying on error correction codes. The existence of base deletions and other errors mean, however, that she is having to develop completely new techniques. For her research group, her methodological expertise is invaluable. Her group has developed a general principle to enable coding using unordered sequences. Wachter-Zeh is also a world leader in the development of codes for correcting insertions and deletions.

Klaus Manhart



Cryogenic infrastructure for operating a superconducting quantum computer at the Walther Meissner Institute, funded by the Munich Cluster of Excellence MCQST. Many surfaces and electrical contacts are coated with gold to achieve minimum electrical resistance and maximum thermal conduction.

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Note on photos

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