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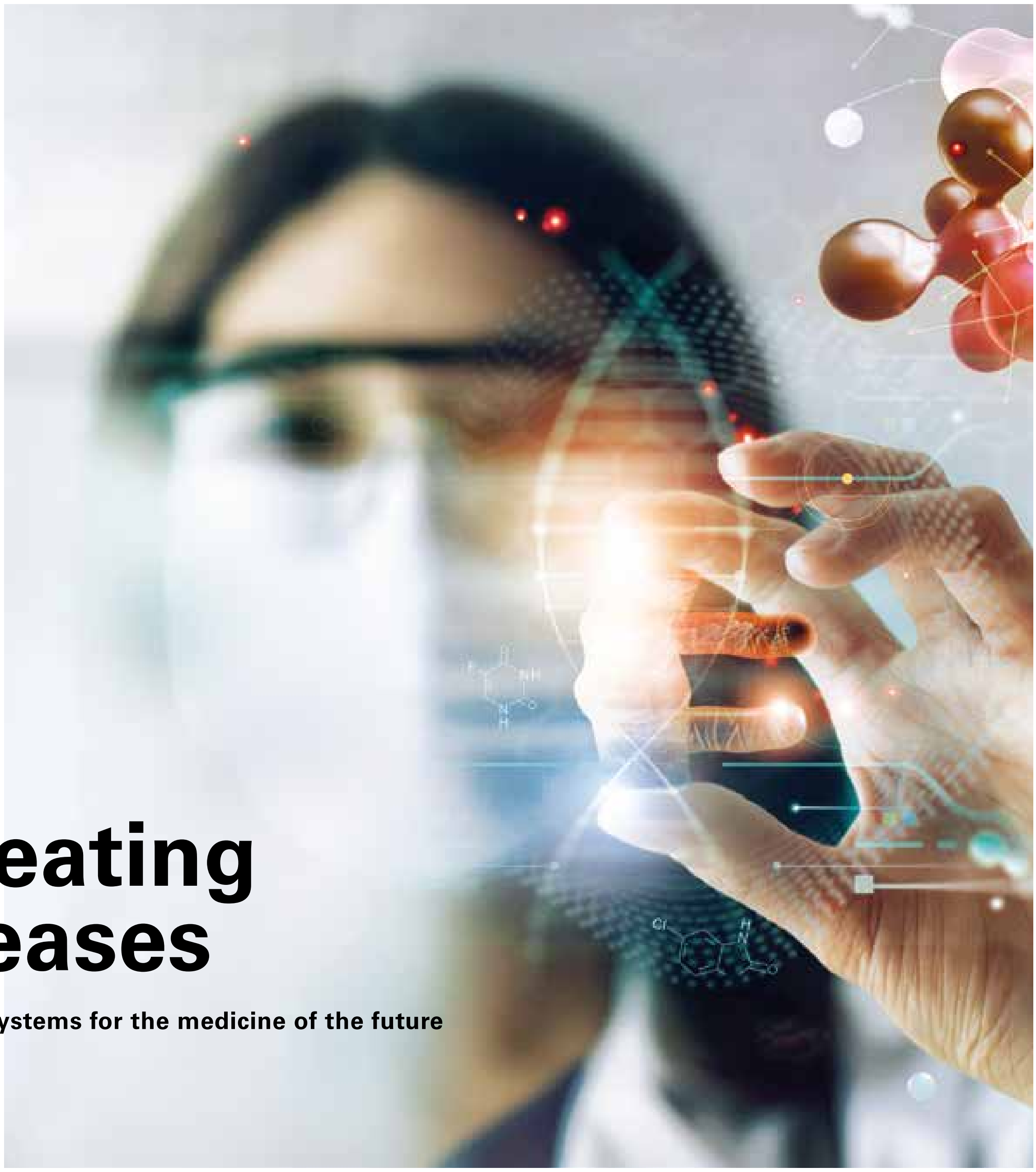


Defeating diseases

Intelligent systems for the medicine of the future

Biomedical systems
Merging the bio- and engineering sciences

DNA nanotechnology
Taking lessons from natural role models

Simulation science
The SimTech Cluster of Excellence – an interim review

Prof. Wolfram Ressel

"The war against disease is not only being waged in medical laboratories and hospitals. What is needed is interdisciplinarity, which is where the University of Stuttgart's strengths come into play."

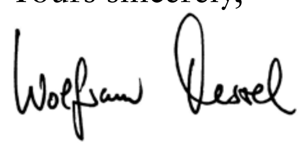
Dear Reader,

Photo: Matthias Schmiedel

Prof. Wolfram Ressel
Rector of the University of Stuttgart

As we all recall, it was almost exactly three years ago when the first Covid-19 cases plunged the entire world into a state of emergency. Since then, the initial horror of the pandemic has abated thanks to vaccines, immunization, and medications as well as our greater understanding about the complex nature of the disease profile. Yet, as is the case with many other widespread diseases, from cancer to heart attacks to back pain, we are far from beating SARS-CoV-2. This issue of *forschung leben* is about "defeating diseases", a title that represents a vision for the future but one, which researchers are getting a little closer to achieving with every day that passes through their expertise and heartfelt commitment.
The war against disease is not only being waged in medical laboratories and hospitals. What is needed is interdisciplinarity, which is where the University of Stuttgart's strengths come into play, for example through our "Biomedical Systems" research area, which is a merger between the biological and engineering sciences aimed at using intelligent systems to bring about a radical change in biomedical research and the technologies used within the health system.
As you read this issue, allow yourself to be drawn into the medical world of the future: discover how new methods and procedures are making it possible to provide personalized disease therapies with fewer side effects; be amazed by robotic assistants that assist doctors during surgical procedures, and enjoy the guest article by Prof. Mark Dominik Alscher, Managing Director of Bosch Health Campus GmbH Stuttgart in which he outlines his view of the challenges facing the healthcare sector.

I hope you'll enjoy this fascinating edition.
Yours sincerely,



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Bridging the gap between biology and technology

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EXPERIENCE RESEARCH

Paradigm shift in simulation science

WORLDVIEW

Opportunist

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Title: shutterstock
Photos: Sven Cichowicz, DFG Jakob Dürrwächter/Daniel Kempf/Claus-Dieter Munz, Max Kovalenko

NOTE PAD

AWARDS

GOTTFRIED WILHELM LEIBNIZ PRIZE 2023

PROF. ACHIM MENGES, Head of the Institute for Computational Design and Construction and spokesman for the University of Stuttgart's "Integrative Computational Design and Construction for Architecture" (IntCDC) Cluster of Excellence, has received the Gottfried Wilhelm Leibniz Prize 2023. This award, which is granted by the German Research Foundation (DFG) and endowed with 2.5 million euros, is considered the most important research prize in Germany. Menges received the award for his interdisciplinary research on digital planning methods and robotic manufacturing processes, both of which improve resource-efficiency and sustainability in the construction sector.

Menges' open-ended and basic research has led to the development of integrative design methods, innovative construction processes, and entirely novel construction systems. Examples include robotically wound, long-span, and extremely material-efficient fiber structures, digitally manufactured lightweight wood building systems, which can be adapted to various construction tasks, and adaptive 3D-printed facade elements that work without mechatronics or operating power.

ACM DISTINGUISHED MEMBER

The Association for Computing Machinery (ACM) has named **PROF. DR. MICHAEL PRADEL**, Managing Director of the Department of Computer Science at the University of Stuttgart's Institute for Software Engineering, a Distinguished Member, in recognition of his excellent research results, which software developers are already using in practice and in their tools. Pradel made a name for himself through his fundamental research on neural software analysis, automatic search and debugging technologies, and program analysis for web applications.

Photos: Uli Regenscheit, Katrin Binner

ERC STARTING GRANT

How do surfactants from glyphosate formulas affect the microbial degradation of the herbicide glyphosate in soil and how do surfactants affect important environmental cycles that have a bearing on emissions of climate-relevant gases such as carbon dioxide, methane, or nitrous oxide? In recognition of her research into these questions **PROF. DR. SARA KLEINDIENST** has been awarded one of the prestigious European Research Council (ERC) Starting Grants. Kleindienst has headed up the Department of Environmental Microbiology at the University of Stuttgart's Institute for Sanitary Engineering, Water Quality and Solid Waste Management (ISWA) since July 2022 and previously taught at the University of Tübingen. She will receive a grant of 1.5 million euros for her "MICROSURF" project. The ultimate goal of her research is to replace glyphosate surfactants with less harmful alternatives, or even to develop biological alternatives produced entirely by microorganisms.

THE WALTHER FLEMMING PRIZE

DR. ANDREW CLARK (Institute of Cell Biology and Immunology/Stuttgart Research Center Systems Biology) was awarded the Walter Flemming Prize 2022 by the German Society for Cell Biology (DGZ) in recognition of his contribution to the understanding of collective cell migration and the mechanical and biological properties of cells and tissues. The prize is named after Walther Flemming, a German cell biologist whose research was fundamental to our current understanding of cell division and replication.

Photos: Simon Kleindienst, private

NEW HONORARY DOCTORATE

PROF. DR. EBERHARD THEODOR GRÜN (shown on the right next to Rector Prof. Dr. Wolfram Ressel) was awarded an honorary doctorate at a special ceremony at the University of Stuttgart. Grün spent most of his career as a researcher at the Max Planck Institute for Nuclear Physics in Heidelberg, where he worked until 2007 and has been at the cutting edge of in situ cosmic dust research for around the world 40 years. He was the first to discover interstellar dust in the solar system before going on to found the science of dust astronomy. Grün collaborated with the University of Stuttgart's Institute of Space Systems on numerous related projects, including the relocation and construction of the Stuttgart Dust Accelerator, the only electrostatic dust accelerator of its kind in Europe, which provides scientists and students with new ways of simulating the conditions in outer space and opens up new possibilities in fundamental physics.

Video of the honorary doctorate award ceremony for Prof. Eberhard Theodor Grün

159+292

During the course of its energy-saving measures between October and December 2022, the University of Stuttgart managed to save the equivalent of the annual heat consumption of 159 single-family homes and the electricity consumption of 292 single-family homes; in absolute figures, this amounts to 3185 megawatt hours (MWh) of heat and 1459 MWh of electricity. This means that the total heat consumption was 12 percent and the electricity consumption 5.7 percent lower than the average value for the past five years.

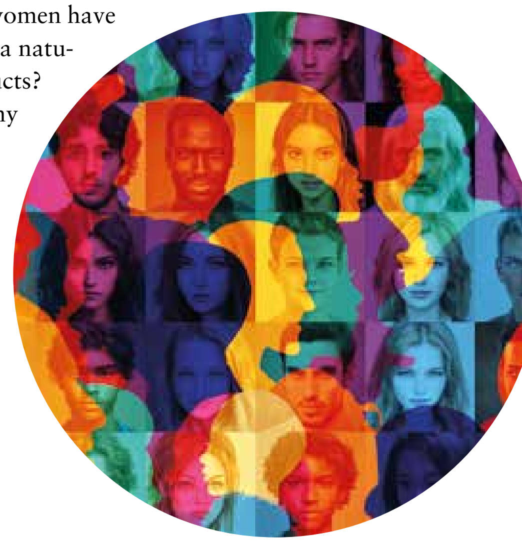
A key factor in this success was the university's energy-saving campaign, which was launched in October 2022 under the slogan "Think more. Use less. Save energy. Together!". Among the measures they employed were guidelines on lowering room temperatures, the reduction of lighting in non-safety-critical areas, and the operation of electrical appliances in addition to which most university buildings remained closed over Christmas and New Year's Day.

The campaign also includes helpful energy-saving tips for everyday university life, as small behavioral changes can often have a major impact: Just switching on the energy optimization function on half of the university's PC workstations saves around 22 MWh a year, which is the equivalent of the annual electricity consumption of about four or five single-family homes.

Information and figures on the University of Stuttgart's energy saving campaign

Photo: Uli Regenscheit

THE MANY FACES OF GENDER



16 events, 270 participants, 1620 minutes of lectures and discussions: these were the numbers for the first Gender Week in November 2022, which was organized by the University of Stuttgart's Gender Equality Center and the Equal Opportunities Officer. The discussion focused on the many faces of gender and the issues that these raise such as: Do women have a higher "mental load" (due to the roles they play)? Why is exhaustion a natural aspect of being a female? Are gender role models rigid social constructs? How can I cope with the day-to-day barriers that I face because of my gender or gender identity? And what if I'm not personally affected by any of this, but still want to show my solidarity to help improve the situation of affected individuals? "In its vision, the University of Stuttgart strives for a sustainable society and emphasizes the importance of diverse perspectives. What we wanted to achieve with Gender Week, says Gender Equality Officer Grazia Lamanna, was to create a space in which interested participants could explore these perspectives.

GRÜNDUNGSRADAR (START-UP RADAR) 2022

Out of the 48 participating major German universities, the Stifterverband ranked the University of Stuttgart 10th in the recently published ‚*Gründungsradar* (Start-up Radar) 2022'. The university did particularly well in the start-up activities category (9th place).

Commenting on this success, Prof. Peter Middendorf, Vice Rector for Knowledge and Technology Transfer at the University of Stuttgart, said that: "Science-based start-ups play a key strategic role for the University of Stuttgart as a knowledge transfer route, which is why we are delighted that focusing our transfer strategy on entrepreneurship and start-ups is bearing fruit and that we have not only been able to improve our "Gründungsradar" ranking from 12th to 10th place, but have also consistently achieved top rankings when it comes to the allocation of EXIST grants since 2019."

Photo: Gerd Altmann (pixabay)

WORLDWIDE REPUTATION

For the first time ever, the University of Stuttgart has been ranked among the 200 most prestigious universities in the world according to the British magazine *Times Higher Education*'s "The Reputation Ranking" rubric. It being placed in the 176 -200 ranking group makes it one of only 16 German universities to have made it into the "top 200" worldwide.

These reputation rankings, together with eleven other ranking indicators, form the basis for the prestigious "The World University Ranking" in which the University of Stuttgart's engineering departments were among the 125 best of 1306 universities listed around the world and 6th in Germany.

Researchers at the University of Stuttgart also repeated previous successes in terms of citations: for example, according to the recently published Stanford/Elsevier citation database, 121 of the more than 200,000 most-cited scientists in the world were working at the University of Stuttgart in 2021. Two physicists from the University of Stuttgart, Prof. Dr. Jörg Wrachtrup and Prof. Dr. Michael Saliba of the Department of Electrical Engineering, were awarded the rare distinction of "Highly Cited Researcher 2021" by Clarivate Analytics. This places them among the top one percent of the world's most influential researchers in the fields of Physics and Environment and Ecology. In addition, Prof. Dr. Alexander Brem was ranked 15th among the most research-intensive business economists in the German-speaking world in the "WirtschaftsWoche" 2022 ranking, whilst Prof. Dr. Philipp Schuster was ranked 100th among the under-40s.

NEW SPACE

Satellite development cycles have been greatly accelerated, which has had an impact on the requirements for their operating systems. Spaceflight launch costs have also come down sharply, and some satellites are smaller than shoe boxes. The on board sensor technology is getting less expensive, smaller, and better. Artificial intelligence makes it possible to effectively process and evaluate the large volumes of data.

Together, these improved conditions are helping more startups and small to medium-sized enterprises to grasp the opportunity and establish themselves in the space market as part of the so-called New Space movement. One start-up from the University of Stuttgart – sat:io – is right at the forefront of this development having come up with a concept for holistic, scalable solutions that enable multi-mission satellite operations. "Rather than a large expensive all-in-one system," the founders explain, "our tool suite includes a range of "standalone tools that can be used in or across project phases as required."

Photo sat:io

VIDEO AND PODCAST RESEARCH

How do Intelligent Systems help us in crisis situations? What is the role of haptic intelligence the operation of robots? How does muscle activity change in response to sensory interference? What does this reveal about diseases processes? And what are liquid crystals, anyway? As the following selection shows, the podcasts and videos on the University of Stuttgart's homepage shed a clear light on these and many other questions: https://www.uni-stuttgart.de/universitaet/aktuelles/video/ You can find even more videos on the University of Stuttgart's YouTube channel, where, among other things, you will also find recordings of lectures given by renowned external experts at the University of Stuttgart.

The University of Stuttgart's YouTube channel

3 QUESTIONS FOR

PROF. OLIVER RIEDEL

Head of the Institute for Control Engineering of Machine Tools and Manufacturing Units (ISW)

In the future, it may be possible to use personalized cartilage implants to treat cartilage damage resulting either from osteoarthritis or accidents. The artificial cartilage tissue would be specifically adapted to each patient and could accelerate the healing process. The Stuttgart Partnership Initiative – Mass Personalization (SPI-MP) research association is using an automated manufacturing process to produce this fabric as part of an interdisciplinary collaboration.

How does the collaboration work in this joint project?

The production of personalized cartilage tissue from biomaterial in an automated process is a challenge that we at the ISW cannot handle on our own, which is why we have partnered with other research teams at the University of Stuttgart and the Fraunhofer Society. The ISW is responsible for print web planning and control. The Fraunhofer Institute for Manufacturing Engineering and Automation (IPA) provides a so-called target geometry based on MRI images for this purpose. This is the only way we can print a precisely fitting implant. Both the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) and the University of Stuttgart's Institute of Interfacial Process Engineering and Plasma Technology are working on the development, production, and testing of the biomimetic material.

How is an implant printed?

At the ISW, we refined additive manufacturing – also known as 3D printing – into a 7-axis printing process. We use this multi-axis procedure to give the cartilage tissue the correct shape and structure for each patient. The implant is printed onto a customized bone replica using a print head specially developed for this purpose and a methacryl-modified gelatin solution. The main benefit of this approach is that it allows us to smoothly represent any geometric structure in more detail, greatly reducing the so-called step effects, which occur in layers during additive manufacturing, whilst increasing the accuracy of the implant fit.

What challenges do you still have to overcome?

The objective of the projects being carried out at the Center of Excellence for Mass Personalization is to develop manufacturing technologies for the cost-effective mass production of personalized products. What we are aiming to do is to use this approach to provide sustainable health care. To date, we have geared this procedure to the treatment of osteoarthritis of the knee, but going forward, we would like to apply the process to other parts of the body that need to be treated in different ways.

Video "Personalized imitation cartilage with multi-axis 3D printing"

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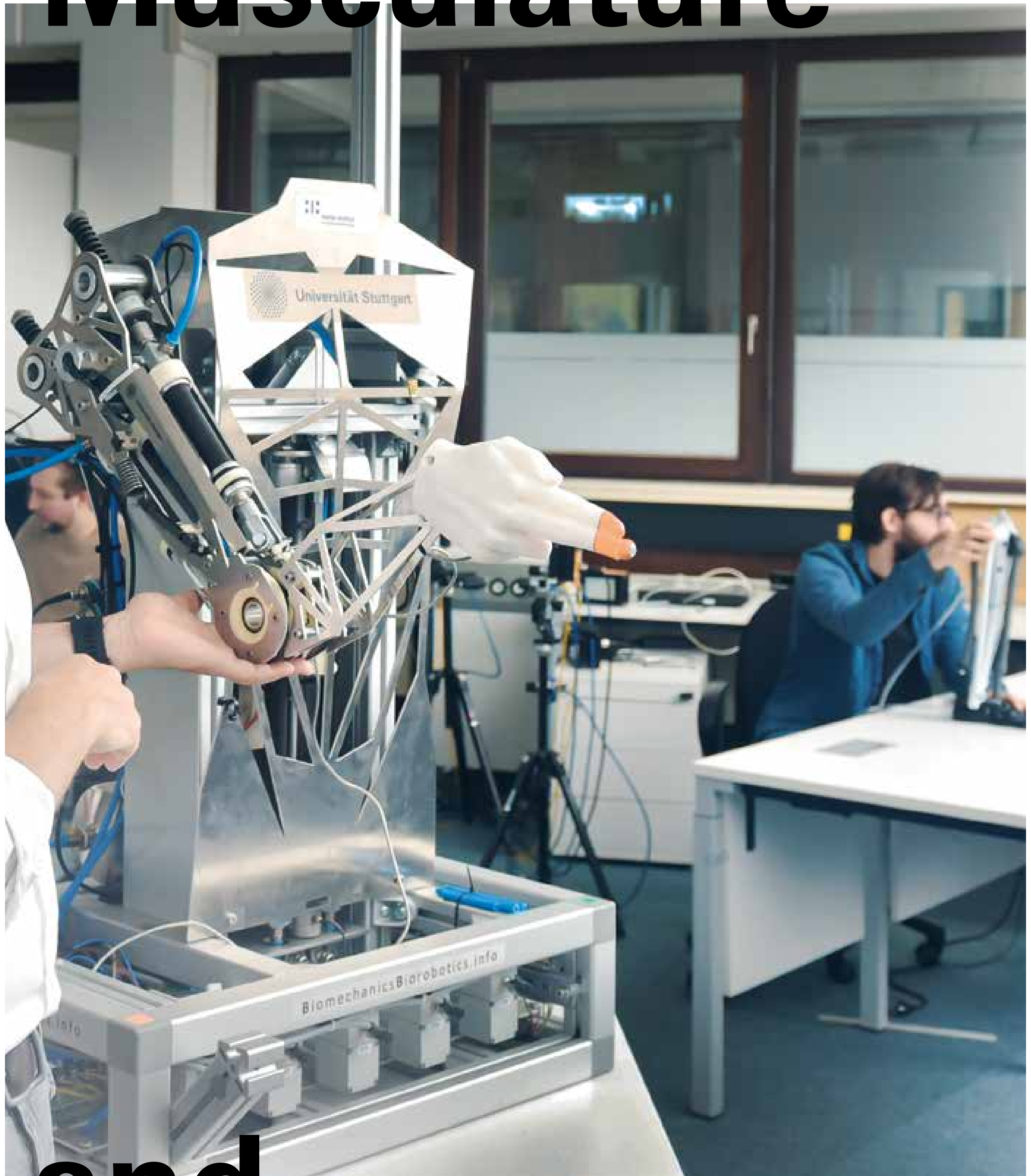
Photo: University of Stuttgart

Musculature and machinery



A team of researchers is working on computer-assisted biophysics and biorobotics.

Specialist in biophysical Research: Prof. Syn Schmitt

TEXT: DANIEL VÖLPEL
PHOTOS: MAX KOVALENKO

Prof. Syn Schmitt combines his enjoyment of sports and his passion for physics by simulating human movements, an activity that is not only laying the groundwork for the next generation of robots but may also provide evidence in a murder case.

If Prof. Syn Schmitt is asked to explain what he is working on, the 47-year-old points to a machine next to his desk in his office in the University of Stuttgart's Vaihingen campus and says: “This is a juggling robot.” The robot is equipped with two bars, each with a basket at the end, which serve as arms and hands. “It's basically just a motor that moves the arms up and down at a consistent speed,” explains Schmitt, who is the co-coordinator of the Emerging Field of Biomedical Systems and a researcher at the University of Stuttgart's Data-integrated Simulation Science (SimTech) Cluster of Excellence. “The reason this works is because the arms are just the right length and the hands have been designed just right.” Schmitt, who also heads up the Institute for Modelling and Simulation of Biomechanical Systems (IMBS) together with Prof. Oliver Röhrle is focusing his research on mapping human biology, formulating it in a set of rules, simulating it, and transferring it to technical systems. Another goal is to find criteria for evaluating a given technical design in terms of its similarity to the respective biological model based on similarity of shape and its dynamic properties.

STUDIES AND TRAINING SHAPED BY PHYSICS AND SPORTS

It was during his vocational training as a communications electronics technician at IBM that Schmitt discovered his passion for the things that hold the world together. As a trainee in the research center of the then computer manufacturer, he spent six weeks assisting a physicist who was experimenting with computer chip materials. Schmitt, who describes himself as an enthusiastic outdoor sportsman and passionate skier and grew up in Weil der Stadt in Baden-Württemberg, decided to combine physics and sports in a diploma and teaching degree program. After completing his traineeship, he earned a vocational baccalaureate.

The results of the biophysical research carried out by Schmitt's team of about 20 people are currently being incorporated into an intelligent assistance device for patients with neurodegenerative movement disorders (iAssistADL). The research group has set itself the goal of developing an aid device for people whose hands tremble →

The iAssistADL project

The University of Stuttgart's Institute of Industrial Manufacturing and Management (IFF) and Institute for Visualization and Interactive Systems (VIS) and the Institute for Modelling and Simulation of Biomechanical Systems (IMSB) are collaborating with the University of Tübingen's Hertie Institute for Clinical Brain Research (HIH) to develop an intelligent assistance device for people with neurodegenerative movement disorders in the iAssistADL project, which is led by Prof. Dr. Daniel Häufle of the HIH. The requisite software is being developed by a team led by Prof. Syn Schmitt of the IMSB and Prof. Andreas Bulling of the VIS at the Data Integrated Simulation Science Cluster of Excellence (EXC2075).

→ uncontrollably by 2024. As Schmitt explains: “People who suffer from this tremor in their arm can neither write nor drink from a glass. Our goal is to develop a robotic system that would be virtually invisible under clothing, but would still interact so closely with those affected that it would perform many of the arm's functions for them, recognizing whether they want to reach for a glass and drink or whether they want to pick up a fork and eat.”

The researchers use a robotic arm mounted on a chair, but first have to train it to carry out its respective functions. To achieve this, they intend to write a program that will evaluate sensor data and recognize the context the user finds them self in and what they are planning to do. “Whilst we can't peer into the brain," Schmitt explains, "we have to get as close as possible to the decision-making process,” which, he continues, is done by recording eye movements. Muscles tense up a few milliseconds before a given movement, which can be measured via the skin surface using electrodes. “If,” he says, “we can detect the activity early enough, we can merge that information with our biophysical models. Our hope is that this will give us a high probability of determining whether the person will reach for the glass, after which the robotic arm will be able to intervene before the person spills the contents of the glass.”

Schmitt only sees the chair with the clunky mechanical arm as an intermediate step in the development of conventional robotics in preparation for what modern, bio-inspired robotics will be capable of in ten to fifteen years' time. “In future, these will be soft-robotic, textile exoskeletons, which already exist in research environments,” he explains: “These will wrap around an arm like a sort of stiff pullover, which we refer to as bionic integration.”

EXPERT APPRAISAL RECEIVES NATIONWIDE ATTENTION IN THE "BATHTUB MURDER"CASE

Prof. Syn Schmitt

“Whilst we can't peer into the brain, we have to get as close as possible to the decision-making process.”

Although we already have artificial muscles, powering the computers and the energy supply are problematic, which is why Schmitt and his team are studying how information is processed in natural systems. “Biological systems can do it: we can hit a dartboard, run, or play the piano all without a huge fast central computer. Of course we have a brain with → millions of neurons but it has a relatively low signal processing speed.” Energy is stored in the muscles themselves as well as in the organs. “Everything would seem to suggest the use of distributed processing and energy storage for modern robotic systems," Schmitt explains.

Schmitt explains how the biomechanical simulation method was able to reconstruct the events of the "bathtub murder."

PROF. SYN SCHMITT

“Our goal is to develop a robotic system that would be virtually invisible under clothing.”

The idea of using simulations to prove things that people instinctively rule out first suggested itself to the researcher as he was preparing his dissertation in theoretical astrophysics in Tübingen under Prof. Hanns Ruder. Schmitt achieved nationwide fame with a simulation of the "bathtub murder" in Rottach-Egern when he demonstrated that it was highly probable that a senior citizen could have fallen into a bathtub and suffered the injuries noted in the autopsy, with no fault on the part of anyone else. Manfred Genditzki, who had been convicted of the murder, was released in 2022 partly on the basis of Schmitt’s expert opinion after the court accepted the simulation of human movements as a new form of evidence. The case is currently being retried. “Fundamentally, therefore,” says the researcher, “it would be a question of rethinking human forensics. Biophysical simulations could be used to account for the dynamics leading up to an important incident and come to objective conclusions.”

When Schmitt joined the Stuttgart-based Cluster of Excellence in 2008, he was already inspired by then SimTech Director Prof. Wolfgang Ehlers' idea of advancing biomechanics modeling. He founded a junior research group at the Institute of Sport and Movement Science, became a Junior Professor at the University of Stuttgart and was eventually given a professorship at the newly founded IMBS.

COMMITMENT TO EQUAL OPPORTUNITIES IN SCIENCE

The researcher took five months of parental leave for each of his two children and, having realized that this would not be without consequences for his research career, he temporarily took on the position of Gender Equality Officer at SimTech. “The reason I care about equal opportunities is because I believe that the only way to maximize success is to make opportunities equal for everyone and to remove any non research-related hurdles,” Schmitt explains. Where he feels most comfortable, he adds, is in a place where no one asks where you come from, but rather what ideas you bring to the table, which, he says, is how things are at SimTech, which is why he refers to the Cluster of Excellence as his "home town." “It's a new form of interdisciplinary university: our work depends on control engineering, mathematics, physics, electrical engineering, and computer science,” he explains: “In my opinion, the future will be all about breaking down the barriers between disciplines after which we can expect to gain fundamentally new insights.” ⇥

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SMARTER BAND-AIDS

TEXT: MICHAEL VOGEL
PHOTOS: SVEN CICHOWICZ

Functional polymers are opening up new possibilities in personalized medicine to which end an interdisciplinary team at the University of Stuttgart is working on new classes of materials and combining know-how from the fields of mechanics and chemistry.

New materials designed to enable the controlled release of active ingredients in band-aids.

Band-aids that deliver hormones or painkillers are already common in everyday medical practice. When applied to the skin, they serve as a reservoir for the active ingredient, which is gradually absorbed by the body. This absorption of active ingredients via the skin is expected to become increasingly important for the treatment of diseases and wounds. It would be possible to provide even more targeted treatments and eventually further personalize medicine through the use of smarter band-aids, which would make it easier to deal with the specific needs of individual patients. There are many approaches that could bring us closer to this goal, one of which involves functional polymers, which is where Prof. Sabine Ludwigs and Prof. Holger Steeb of the University of Stuttgart come in.

Ludwigs holds the Chair of Structure & Properties of Polymeric Materials at the Institute of Polymer Chemistry, while Steeb is Professor of Continuum Mechanics and Director of the Institute of Applied Mechanics (Civil Engineering). “We are currently developing a new class of polymer materials that will have important properties for future applications in personalized medicine,” says Ludwigs. “What makes our approach so effective is that our research combines our expertise in both mechanics and chemistry.”

Prof. Sabine Ludwigs of the Institute of Polymer Chemistry

BIO-COMPATIBLE POLYMERS FOR PHARMACEUTICAL APPLICATIONS

At first glance, it may seem surprising that polymers will play any significant role at all in the medicine of tomorrow; after all, in our everyday lives, polymers are primarily used in the form of plastics. Yet just as some polymers are used in Plexiglas or car tires, others are used in such things as the casings of enteric-coated capsules. Although they differ greatly depending on the intended use, the one thing that all polymers have in common is that they are huge molecules consisting of a large number of repeating atomic groups. These long polymer chains often form intertwined structures, not unlike a heaped plate of spaghetti, which can be cross-linked through the use of sophisticated chemistry.

Ludwigs and Steeb's teams are interested in so-called biocompatible functionalized polymers, which is to say that their chemical and physical properties are not harmful to living organisms or, as Ludwigs puts it more precisely: “What we're trying to identify are biocompatible polymers that are of interest to the pharmaceutical industry.” It is possible to store medically active substances in polymer networks, which can then be gradually released into the body in a controlled manner, always in the precise quantity that the body needs. These University of Stuttgart teams are involved in a research→ collaboration with pharmacists led by Prof. Dominique Lunter and Prof. Stefan Laufer of the Eberhard Karl University of Tübingen. →

Prof. Holger Steeb of the Institute of Applied Mechanics (civil engineering)

→ As Ludwigs explains: “The traditional approach in the pharmaceutical industry is to use polymers that are listed as approved polymers in reference works for pharmaceutical drug specifications (pharmacopoeias) and then to experiment with them.” Yet the requirements profile of these polymers is often limited, which is why Ludwigs and Steeb have chosen a different approach.

REGULATING THE RELEASE OF STORED ACTIVE INGREDIENTS IN A TARGETED MANNER

First they discuss any interesting properties that suitable polymers might have with their colleagues from the University of Tübingen, whereby "interesting" in this context refers to polymers that change their large-scale structure in response to an external stimulus. This change then enables the escape of the stored active ingredient. Oftentimes, a desirable feature, in such applications, is that the release of the active ingredient can be regulated, i.e., that the structural change of the polymer is reversible depending on the external stimulus. “The respective stimuli,” as Ludwigs explains, “could be pH, humidity, or temperature changes.” If, for example, a certain polymer reacts to moisture, it will be capable of absorbing a large number of water molecules without losing its structural properties. Such changes occur autonomously in the polymer network when a predefined stimulus threshold is reached. “However,”she continues, “it is also possible to manually trigger the change in the polymer network by applying an external stimulus, for example, by applying a weak electrical current,” which would require a suitable polymer to be electrically

Doctoral students investigate new materials in the laboratory.

conductive. Ludwigs' team first produces promising polymers in the lab, which not only have to exhibit the desired functionalization, but also meet certain elastic requirements, as they are supposed to adhere strongly to the skin in the final pharmaceutical product, even when the patient moves around. Steeb's team is studying whether the newly created polymers are able to do this by characterizing the polymer samples under mechanical tension. “That's how we determine their viscoelastic properties,” Steeb explains. “If, for example, the goal is for a polymer to absorb moisture, we can perform our measurements as the water molecules are being incorporated.”

Of course it takes a certain amount of know-how to make the measurements possible in the first place. As Steeb explains, "the polymer samples are often so small or so →

Prof. Holger Steeb

“Our unique selling point is the close integration of chemistry and engineering.”

focus on the use of polymers in medicine

→ fragile that they can't simply be clamped in a test setup like a metallic sample. Sometimes, for example, you have to apply the controlled force by rolling up the sample."

A CLOSE COLLABORATION BETWEEN TEAMS AT THE UNIVERSITIES OF STUTTGART AND TÜBINGEN

One potential outcome of the tests may be that the polymer sample does not retain the desired properties long enough, in which case Ludwigs' team will be called upon once again. If, however, the measured properties are promising, Steeb's team models the functional material on a computer to predict the polymer's causal relationships, which in turn the chemistry team can use to further improve it. Of course, more tensile tests then need to be carried out following the revision. “Ultimately,” Steeb explains, “it's about gaining a fundamental understanding of the rheology of the polymer in question.” Rheology reveals the conditions under which a material will deform reversibly, permanently, or not at all.

“As soon as we have a polymer at the University of Stuttgart that we are satisfied with,” says Ludwigs, “it’s over to the groups at the University of Tübingen who conduct experiments to measure its charging and discharging behavior.” In some cases, this will be followed by further refinements in the University of Stuttgart's chemistry and mechanics laboratories to further enhance the respective polymer.

Neatly arranged: various experimental materials for research

POTENTIAL APPLICATIONS IN PERSONALIZED TUMOR THERAPY

Ludwigs and Steeb have now been collaborating on this project for around four years. Functional polymers are the focus of a comprehensive and intensive field of research around the world. “Our unique selling point is the close integration of chemistry and engineering,” says Steeb. And this level of integration has recently become even tighter since the inter-faculty Functional Soft Materials Lab began operations at the start of the year. “This has brought our teams even closer together in their day-to-day work,” says Ludwigs. The laboratory is located at the Stuttgart Center for Simulation Science (SC SimTech), where Steeb is a member of the research management team.

The collaboration between Ludwigs and Steeb does not end with functional polymers as a drug delivery mechanism. In the future, as Steeb explains, functional polymers will also be in demand for 3D printing applications for personalized tumor therapies. “Among other things, 3D printing depends on the rheology of the polymers for optimal functionality.” ⇥

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How AI is changing the pharmaceutical sector

AI-based startup clusters are emerging in the pharmaceutical sector all around the world.

TEXT: HEIKE SCHMIDT-LANGER

Economists at the University of Stuttgart are looking into how well companies are exploiting the potential of artificial intelligence.

Given the fact that there are several million possible molecular compounds, finding the perfect compound for a new drug or vaccine experimentally requires lengthy and also cost-intensive laboratory work. But, in the future, digitalization and especially the rapid advances in artificial intelligence (AI) may make it possible to analyze active ingredients in a resource-efficient and accurate manner in the shortest possible time. Shortening the development time of new drugs creates major economic benefits for the pharmaceutical sector. Because, as things stand today, the development of an active ingredient to market maturity accounts for an average of seven years of the total 20 years of patent protection, meaning that the phase of economic exploitation under patent protection is reduced to about 10 to 15 years.

Researchers at the University of Stuttgart are among those studying the impact of AI on the pharmaceutical sector. More specifically, Dr. Johann Valentowitsch and Theresa Fritz of the Institute of Business Administration (BWI) have been investigating how →

Theresa Fritz is studying new collaborations within the pharmaceutical sector.

Johann Valentowitsch is analyzing the potential of AI from an economic perspective.

→ the use of AI in the pharmaceutical sector has led to new collaborations as global companies operating in this sector are increasingly collaborating closely with technology startups from outside the industry. Startups, which are often spun off from universities, need financial support, so they tend to partner with other stakeholders from the financial sector or access public research funding.

Using the available data, the researchers at the University of Stuttgart have been analyzing this new scenario in more detail. One of their striking findings is that the formation of clusters, i.e., the close collaboration between different stakeholders in networks, is significantly lower in the European Union than in other regions of the world. The researchers have found that the reasons for this include stricter regulations and less flexibility in directing funding initiatives. In this context, Valentowitsch points to the development of new battery technologies for electromobility, where other regions were often quicker off the mark, and says that it is important to use funding programs "to focus on the right projects rather than supporting things that are already available on the market."

FLEXIBLE ACCESS TO DATA PLAYS A CENTRAL ROLE IN TERMS OF

According to his colleague Theresa Fritz, even in the healthcare sector, the new skills are often already so advanced in these clusters that it is impossible to catch up. However, she adds, contrary to general expectations, the Asian market does not play a major role in this area although one might have expected to find the respective clusters there because of the more cost-effective production possibilities and the expertise in emerging technologies. But surprisingly, she says, these appeared in a completely different place, namely in Great Britain, a country, which had been at the forefront of funding and research based on Big Data applications. "This," as Valentowitsch explains, "is probably due to the different structure of the health care system in the UK, particularly the much more flexible data access regulations." "A competence gap has opened up within the EU" in the wake of the UK's secession from the EU."

THE DIFFERENT STARTUP CULTURES

Patient data is a key factor in exploiting the new opportunities in pharmaceutical research. "Without better access to data," Valentowitsch explains, "one cannot exploit the potential of digitization and AI. AI systems are only as good as the data they are fed." This tends to be hindered by the comparatively strict data protection rules in Germany.

Dr. Johann Valentowitsch

"AI systems are only as good as the data they are fed."

The economists' analysis also reveals a need to catch up in terms of funding. In countries, such as the USA and the UK, there are stronger links to third-party funding providers and so-called business angels. There, he says, there is "a totally different culture as well as a different startup culture, coupled with a willingness to simply take risks, even to fail from time to time, which, for some of us here is simply out of the question. We definitely need a rethink."

The researchers see more than enough potential for this. Fritz is convinced that there are "also opportunities for collaboration in Germany, but that we need to provide more support and try to break down the existing structures." ⇥

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Photos: private

HEALTHCARE FOR SHIFT WORKERS

A new program is designed to help create "healthy shift rosters."

The roster demonstrator was developed by Damian Kutzias.

Dimitri Evcenko of the University of Stuttgart's Institute of Human Factors and Technology Management

TEXT: DANIEL VÖLPEL

Shift work puts already stressed caregivers under even more strain. A program being run by the University of Stuttgart and the Fraunhofer Institute shows how to schedule the alternation between early, late, and night shifts in a way that does not compromise the health of the staff.

Computer programs for creating shift schedules have been around for a long time, but this one is different: not only are all the regulations, such as the maximum permitted working hours, stored in the “Demonstrator for the Design of Healthy Duty Schedules” but the program also offers additional recommendations to help caregivers remain healthy despite working rotating shifts. This includes such measures as not scheduling more than three night shifts in a row or not working a late shift on the eve of a vacation. Using the demonstrator to plan shift work for your team also provides you with an index, a health rating that ranks how well the rules have been complied with. The program displays all individual violations in a text field, which enables one to improve the plan and thus the well-being of one’s employees. →

Sandra Frings works at the Fraunhofer Institute for Industrial Engineering.

Sandra Frings

“The health of caregivers is extremely important both for themselves and for society as a whole.”

→ USING WELL-DEFINED KEY FIGURES TO OPTIMIZE SHIFT ROSTERS

The shift planner was developed as part of the "pulsnetz.de – healthy work" project run under the auspices of the Regional AI Future Center and funded by the German Federal Ministry of Labor and Social Affairs. Various partner organizations are working on projects that promote health in the social economy under the coordination of Diakonie Baden (a German protestant welfare organization). One of the partners is the University of Stuttgart's Institute of Human Factors and Technology Management (IAT), which is affiliated with the Fraunhofer Institute for Industrial Engineering (IAO) and the demonstrator was developed by a team of researchers from both institutes.

“The health of caregivers is extremely important, both for themselves and for society as a whole,” explains Sandra Frings of the Fraunhofer IAO. “Our key performance indicator for evaluating a healthy roster helps to optimize this, simply by making it visual,” adds Dimitri Evcenko, also of the IAT. The team had previously identified what care facilities needed in a series of seminars and surveys.

GREAT INTEREST IN THE SHIFT ROSTER DEMONSTRATOR

Both the identified requirements and real-world rosters and regulations were incorporated into the demonstrator as were recommendations from occupational science and practice. IAO employee Damian Kutzias then translated all the specifications into program code. The demonstrator was designed to work with AI methods in keeping with the Regional AI Future Center, under whose auspices the team was working. But training an AI requires practice data, historical rosters in this case, which however, lack any information about how well they performed in terms of health, which in turn would have prevented the system from learning which aspects to check so as to improve shift schedules. This is why Kutzias designed the demonstrator to be purely rule-based. “Clear rules are always better than an AI system,” he says. Software providers with historical rosters could use AI to refine the demonstrator to the point where it suggests improvements on its own or even generates the roster.

As part of the pulsnetz.de project, the team advises care centers by evaluating their historical shift rosters. It is possible, for example, to show how the health rating has changed over the course of a year. “The output is not just limited to a health rating,” Frings explains, ”you can break down how many times rules have been violated on a person by person basis.” The first care centers have now tested the demonstrator, the results of which can be viewed on the pulsnetz.de website.

There was a lot of interest when Kutzias showed what the program could do at a care service trade fair both among people responsible for producing shift rosters and works councils and employee representatives, because what the demonstrator ultimately shows is how well services are being planned and whether care provision services are functioning as they should be. “Everyone we've shown it to said it’s great and asked where they could buy it,” says Frings, but adds that: “This is just a prototype that software vendors would have to pick up and integrate.” The team created the demonstrator for everyone. Commercial providers could therefore base a product on the same principle and only need to contact the team to get the ball rolling. ⇥

Photos: Fraunhofer IAO

Dr. Mark Dominik Alscher specializes in internal medicine and is the Managing Director of Bosch Health Campus GmbH Stuttgart and a professor at the University of Tübingen. Following his medical studies at the University of Freiburg, where he also earned his doctorate, he began his career at the Robert Bosch Hospital and also worked in the USA for several years, including at Harvard Medical School. He became the Medical Director of the general clinics at the Robert Bosch Hospital in 2009, and has also been the Chairman of the Board of the Digital Health Baden-Württemberg Association since 2018. Alscher played a key role in the strategic realignment of Bosch Health Campus GmbH, which was founded in 2022.

RESPONDING EFFECTIVELY TO CHANGE

GUEST ARTICLE: MARK DOMINIK ALSCHER

The framework conditions for medical care in hospitals are changing rapidly due to various challenges ranging from demographic change and an aging society to the threat of pandemics. Technological innovations are also having a major impact on healthcare. In this article, Prof. Dr. Mark Dominik Alscher, a specialist for internal medicine and Managing Director of Bosch Health Campus GmbH, explains how hospitals can respond to these changes effectively and successfully.

Photo: Fotostudio M42

One of the most important factors currently affecting our planet is the strong influence of mankind on the conditions of existence, a fact, which is well described by the term anthropozoic era, which has been proposed to describe it. As the science of health maintenance and of disease prevention, diagnosis, and therapy, medicine is currently engaged in an open dialog with these changing conditions. Another thing that characterizes the current framework conditions is the speed of change, for example in medical services. This is reflected in terms such as "disruption" in respect to response and agility and doctors are among those affected by this steadily increasing complexity.

In terms of the general framework conditions, the main issues include population growth on the one hand, but also demographic change resulting in an increasingly aging society, and changes in Western lifestyles (especially in relation to diet and exercise), migration, and internationalization (e.g., pandemics) on the other.

In collaboration with the Robert Bosch Foundation, the Robert Bosch Hospital has implemented an organizational realignment in all areas relating to health in order to continue to be able to respond effectively under these conditions. In addition, a strategy was developed following the realignment, in which the aforementioned framework conditions were given the attention they deserve and which is intended to enable us to be effective, responsive, and successful in spite of these rapidly changing conditions.

The relevant measures are described below.

THE FOUNDATION OF THE BOSCH HEALTH CAMPUS

Internal discussions were held as far back 2017 in which the view was expressed that it is very difficult for outsiders to identify the various institutions under the non-profit Bosch umbrella. Another thing that quickly emerged from the discussions was that, in today's world of internationalization, globalization, and digitalization with the corresponding communication possibilities, it is essential to be visible and that the various divisions and departments must work together with as few barriers as possible in order to →

→ maximize synergies. Following these discussions, the decision was taken to bring all health-related areas together under the aegis of the Robert Bosch Foundation to which end Bosch Health Campus GmbH was founded in 2022, both as a holding company and as a structural framework. The Robert Bosch Foundation's Health Promotion Division, which has had a significant positive impact on health care over the decades, was separated from the Robert Bosch Stiftung and transferred to Bosch Health Campus GmbH. Other parts of the group that were transferred to the Bosch Health Campus include Robert-Bosch-Krankenhaus GmbH, Forschungs-GmbH (Robert Bosch Gesellschaft für Medizinische Forschung), and their respective subsidiaries. The collaboration between the various bodies has also been restructured through the formation of appropriate committees, such as the BHC Board of Directors, which includes the Managing Director of Bosch Health Campus and the Managing Director of the Robert Bosch Foundation, in order to expedite decision-making processes. This restructuring process was completed under company law on January 1, 2023.

BOSCH HEALTH CAMPUS STRATEGY

After this, a joint strategy was adopted over several stages in collaboration with all the internal committees, the executives and, in particular, the international Advisory Board.

Putting this strategy into practice reflects the guiding principle of Robert Bosch the Elder when he opened his hospital: "They will only achieve their full potential when they collaborate harmoniously with the best will in the world." Reformulated as a corporate vision this means that we are the visible enablers of the coming changes in healthcare whereby our mission is to focus all of our activities on the well-being of people.

In order to implement this effectively, a conscious decision was taken to be part of a network linked to the Bosch company with its vast capacity in the field of artificial intelligence and sensor technology and, of course, other fields. Another conscious decision that was included in the strategy was to collaborate with the Robert Bosch Foundation in the fields of international understanding, education, and other social issues. However, it was also specified that, rather than having to cover all areas itself, the Bosch Health Campus would be able to cover them via partnerships in an extended network, a so-called "Network Plus", a term used in Germany to denote an egalitarian collaboration between various partners on a win-win basis. The respective interactions should be based on:

⟶ **Partnership**
⟶ **Excellence**
⟶ **Relevance**

The rest of the strategy was then geared towards digitalization, global issues, demographic change, and technological progress. It is beyond the scope of this article to describe the entire strategy in detail, but I would like to mention a few of its key aspects by way of example.

THE VISION

We are the visible enablers of the coming changes in healthcare.

OUR MISSION

To focus all of our activities on the well-being of people.

TECHNICAL PROGRESS:

A conscious decision was taken to not only make clinical data available for science and research purposes at the Bosch Health Campus (Data Integration Center), but also to combine this with biological avatars, which primarily includes tissue and cell bio banks. This combination will also enable the rapid scientific processing of medical issues. The decision was taken to provide for the systematic provision of data for the use of the research community. →

PUTTING THIS STRATEGY INTO PRACTICE REFLECTS THE GUIDING PRINCIPLE OF ROBERT BOSCH THE ELDER WHEN HE OPENED HIS HOSPITAL:

> "They will only achieve their full potential when they collaborate harmoniously with the best will in the world."

→ Demographic change primarily concerns two areas in which action is needed.

– Shortage of skilled labor

Numerous projects, which are in alignment with the strategy, have to do with the shortage of skilled workers. Automation through such things as robotic infusion production and automated drug delivery could help with a more effective use of skilled labor.

– Aging

The other field of interest involves elderly patients with multiple morbidities, whereby we are looking at how we might be able to use sensory technology to enable them to remain in their homes for longer even if they have chronic illnesses.

In addition, there is a whole raft of measures intended to help with the effective use of contemporary digitalized products and services. One of these is to work with other institutions to offer the clinical data through appropriate interfaces for the development of algorithms. Another plan is to use digital technologies for things such as bridging language barriers, which is essential in the context of patient education, for example, but also in terms of preventive medicine. High-throughput technologies are used in the field of individualized therapies to create personal biomedical profiles.

The current disruptions in healthcare ultimately require decision-making structures based on such concepts as agility, participation, the exploitation of synergies, and flexibility. On the other hand, we need to create a technology transfer environment that facilitates the rapid delivery of digital and technical solutions to patients. This is why we have completely repositioned and realigned ourselves through the aforementioned organizational realignments, but also by taking advantage of the existing framework conditions. Another crucial aspect is the interaction with technical faculties, the assumption being that the most significant medical innovations are currently being driven by the technical disciplines. ⇥

BRIDGING THE GAP

BETWEEN BIOLOGY AND TECHNOLOGY

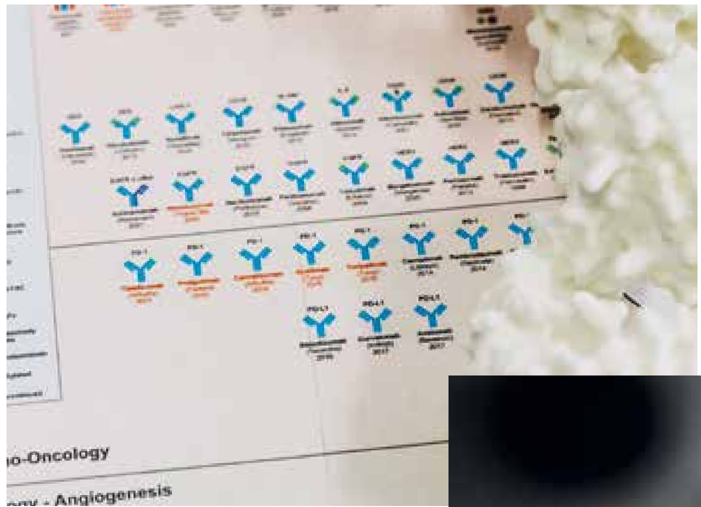
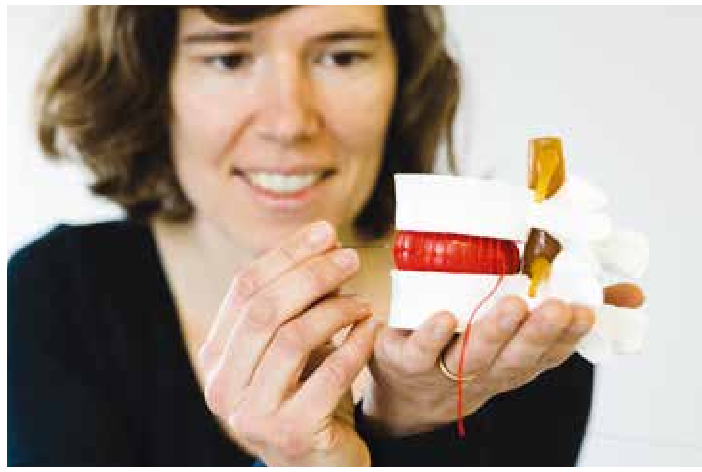


Photo: Günther Bayerl

From tailored antibodies to rebuilding injured tissue: internationally renowned scientists from various disciplines are working together to develop intelligent solutions for personalized healthcare under the leadership of Prof. Monilola Olayioye in the emerging field of "Biomedical Systems".



One of the things Dr. Andrea Toulouse and her team are working on is restoring destroyed tissue in spinal disks.

TEXT: JUTTA WITTE
PHOTOS: SVEN CICHOWICZ

They are investigating novel methods and procedures that could be used to provide personalized disease treatments with fewer side effects. As they work toward this goal, the researchers in the emerging field of "Biomedical Systems" are breaking new ground every day.

Nano- and microrobots that transport drugs inside humans; customized antibodies that attack tumor cells, and 3-D printers that rebuild injured body tissues are not science fiction, but the subject of cutting-edge interdisciplinary research at the University of Stuttgart. Researchers from the natural and engineering sciences are pooling their experience, expertise, and methods in the field of "Biomedical Systems" as they seek to raise biomedical research to a new level and make the treatment of diseases more effective and tolerable for all. “We are bridging the gaps between our various disciplines to jointly develop new personalized biomedical systems that will be of greater benefit to patients,” explains Prof. Monilola Olayioye, head of the scientific coordination team.

In order to achieve this, the researchers are looking at "all the building blocks of life" at the nano, micro, and macro levels, starting with genetic information, proteins, and individual cell types and ending with organs that communicate with one another. The potential fields of application for the innovations being developed there are just as wide-ranging as the research profile, because biomedical systems are needed in everything from diagnostics and therapy to rehab applications.

THE INCREASING IMPORTANCE OF THERAPEUTIC ANTIBODIES

A glance at Prof. Roland Kontermann's "antibody workshop" and at the therapeutic antibody map 2022 shows this. “Not only are there more and more, but the applications are also becoming broader,” says the expert in biomedical engineering, who works at the Institute of Cell Biology and Immunology (IZI). As he explains, over 130 of these proteins, which are produced by the immune system and designed for use in humans, have now been approved as drugs to fight cancer, inflammatory diseases, metabolic disorders, →

→ infections and even neurodegenerative diseases, and many more are currently at the clinical trials stage – tailor-made drugs of the kind that are also being developed in the IZI laboratory.

A current example is the “Atrosimab” molecule, which switches off proteins that trigger and repeatedly reignite the inflammatory process in diseases, such as rheumatism, in a targeted manner and without side effects. The so-called cytokine TNF, which is largely responsible for inflammation, has two receptors to which an antibody can bind in order to neutralize it. In addition to the pro-inflammatory one, there is another that prevents such things as the degeneration of cells or the re-germination of tuberculosis. The researchers have now succeeded in targeting and eliminating only the disease-causing docking station using "Atrosimab", which has just been successfully tested in the first clinical phase.

PIONEERING APPROACHES TO TUMOR THERAPIES

The IZI team is also following novel paths in the treatment of solid tumors such as breast or colon carcinomas. Whilst the use of antibodies has now become established in this area, sometimes in combination with other therapies, it is more challenging than, for example, the treatment of leukemias and lymphomas because solid tumor tissue is extremely complex, and the cells are difficult to access in addition to which, no two tumors are alike. So far, antibodies can attack them in three ways, either by inducing cell death in tumor cells, blocking the supply of blood vessels to the tumor, or activating the immune defense system. A so-called antibody-drug conjugate (ADC), which is an antibody chemically coupled with active substances, has been developed to target the so-called tumor stroma and thus a fourth predetermined breaking point. This connective tissue can account for up to 90 percent of a tumor.

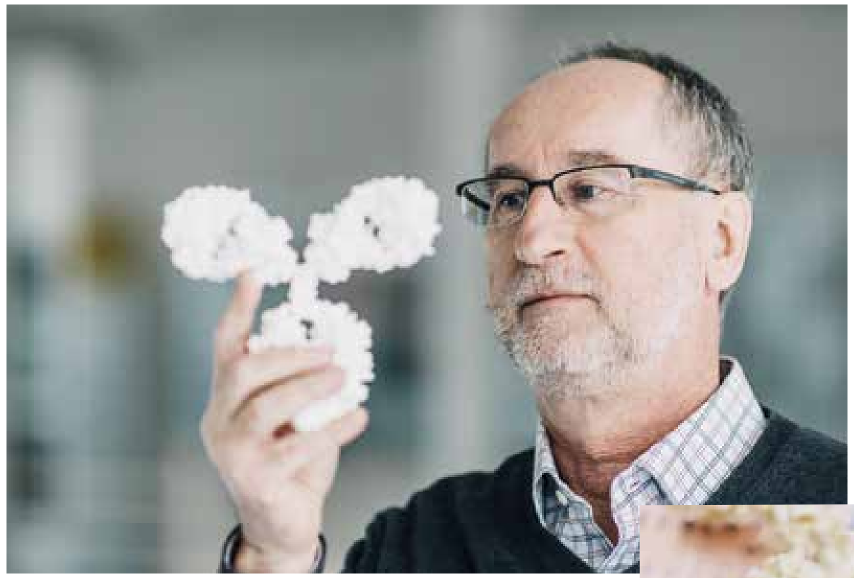
The new ADC, OMTX705, is thought to be the way forward, as it binds the connective tissue cells and simultaneously releases cytostatic drugs directly in the tumor. Clinical trials have just started: “If these clinical trials are successful," Kontermann explains, "this would be the first antibody to target the tumor stroma.”

MICROROBOTS FOR MORE PRECISE CANCER TREATMENT

Dr. Tian Qiu, a biomedical engineer at the University of Stuttgart's Institute of Physical Chemistry (IPC), and his "Biomedical Microsystems" research group are advancing cancer treatment from a different angle. In his VIBEBOT project, which is funded by the European Research Council (ERC), he is working on a micro robot that can penetrate human tissue in order, for example, to deliver chemotherapeutic agents precisely to the right spot on a tumor. “Usually when such drugs are administered orally or →

Prof. Roland Kontermann

"If these clinical trials are successful, this would be the first antibody to target the tumor stroma."



Prof. Roland Kontermann and his team are working on the use of tailored antibodies in the treatment of diseases.

Helena Nowack is a member of Prof. Kontermann's Biomedical Engineering team.

DR. TIAN QIU

"Our research has huge potential for the minimally invasive treatment of hard-to-reach regions in the body, such as the brain."

Biomedical engineer Dr. Tian Qiu is developing microrobots to deliver drugs precisely to the target areas.

→ intravenously," he explains, "only about one percent of the dose reaches its target." "The rest disperses throughout the body, causing side effects." Qiu likes to compare these drug delivery vehicles to fish in a net: they either have to be small enough slip through the meshes or able to destroy the net. To achieve this, the bioengineer takes inspiration from nature and his team has already achieved a first breakthrough. They have created a 500-nanometer robot inspired by Escherichia coli, which can "swim" through the tissue network of an eyeball. This "nano propeller" is controlled by a magnetic field. Its target is the retina, where it deposits the active ingredient. This method, which has been successfully tested in a pig's eye, represents a real advance in the treatment of eye diseases, which is usually done with drops that are difficult to dose and are slow-acting.

Other soft tissues are made up of a denser polymer network than that of the eyeball and are more difficult to penetrate. Thus, what is needed is a stronger robot with a different design. The researchers are now planning to build the 100-micrometer VIBEBOT (Vibrational Micro-robot), which will be modeled on another microorganism, namely the schistosoma (blood fluke), a parasite that can penetrate human skin within a few minutes by vibrating its body. "To penetrate biological tissues," says Qiu, "we need a similar system." But how could one navigate such a mini-machine through the body in a →

→ controlled, wireless manner? How should the drive system be designed? How could the micro-robot sense its surroundings? And how could it be reliably located? These are the questions Qiu and his team will be addressing over the next five years. However, he is already clear about one thing: "Our research has huge potential for the minimally invasive treatment of hard-to-reach regions in the body, such as the brain."

DEVELOPING THE WORLD'S SMALLEST 3-D PRINTER

Minimally invasive methods are already state of the art in surgery and orthopedics for the treatment of many diseases and injuries. But the projects being carried out in the Emerging Field of Biomedical Systems are revealing how much room there is for improvement and how much research remains to be done, for example, by the "EndoPrint3D" consortium. The physicists, bio-technologists, and engineers involved in the project have set themselves an ambitious goal: "We are currently collaborating on the development of the world's smallest 3-D printer," says collaboration coordinator Andrea Toulouse. The goal is for it to fit on the point of a needle and "reprint" destroyed tissue within the body from biogenic materials, i.e., materials known to the body, such as collagen or hyaluronic acid in order, for example, to restore parts of a spinal disk or an ear bone, or to close tiny holes in the cardiac septum of embryos. The intended aim of the procedure is to heal injuries quickly and with such precision that the surrounding tissue suffers as little damage as possible.

The printer is located at the end of a fiber optic endoscope, with a diameter of one millimeter, which is connected to a modified ultrashort pulse laser, used by a research group headed up by Prof. Harald Giessen at the 4th Physics Institute. This laser hardens the "bio-ink", which is delivered in a microfluidic process. A fine mesh of tissues, the extracellular matrix, which Michael Heymann, Junior Professor at the Institute of Biomaterials and Biomolecular Systems, describes as a "climbing frame", is reconstructed at the injured site, which can accommodate the cells needed for the regeneration process.

"The printing process," as his colleague Andrea Toulouse explains, "triggers a regeneration process, which the body must then continue on its own." →

Researchers want to improve minimally invasive interventions, for example on knee joints.

The "EndoPrint3D" team led by Dr. Andrea Toulouse (l.), Jun.Prof. Michael Heymann, and Prof. Harald Gießen (center).

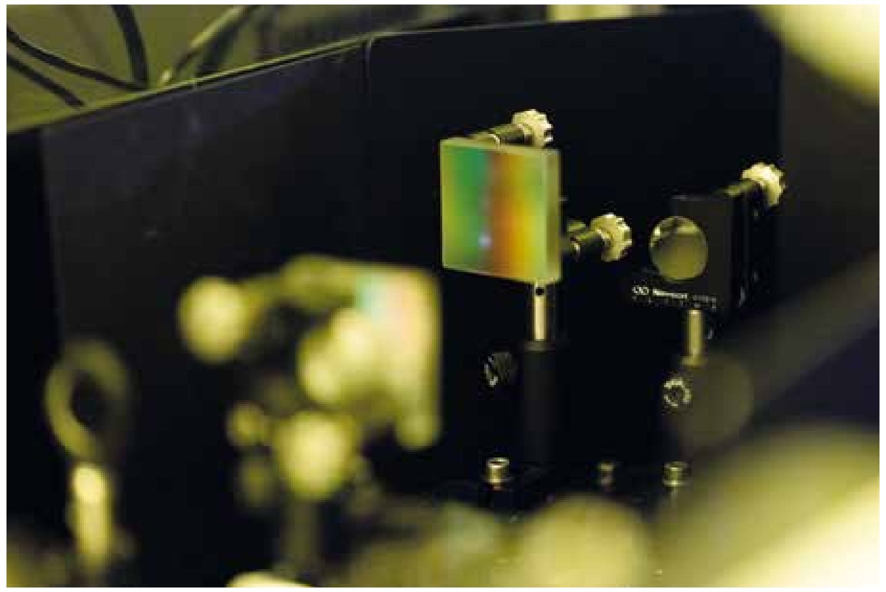
EXCELLENT, INNOVATIVE, NETWORKED, AND WITH AN INTERNATIONAL PROFILE

The Emerging Field of Biomedical Systems

The University of Stuttgart set up this department in 2018 as part of its application for excellence and it plays a decisive role in the University's structural development. "Our plan," says coordinator Monilola Olayioye, "is to drive progress to new promising fields of research, raise our international profile and attract talented Eerly Career Researchers to the University of Stuttgart by establishing additional tenure-track professorships to further expand this emerging field." The consortium is based on three pillars, which are biotechnology and bioengineering, sensor and nanotechnology as well as biointelligent devices and robotics. It builds upon our strengths in the natural sciences and engineering and their growing potential in biomedical research. The High Performance Computing Centre Stuttgart (HLRS) and the SimTech Cluster of Excellence also provide researchers with a unique infrastructure for handling large amounts of data, carrying out simulations, and developing valid model systems. They can also draw upon the University of Stuttgart's outstanding expertise in quantum technology. Among others, the consortium collaborates closely with the Bosch Health Campus in Stuttgart, the University of Tübingen, the University Hospital Tübingen, and numerous companies in the medical technology sector. Within the University of Stuttgart, they also collaborate with researchers working in the Emerging Field of Autonomous Systems and with the Quantum Sensors of the Future (Qsens) BMBF cluster.

Together with Prof. Laura Na Liu, Prof. Markus Morrison and Prof. Syn Prof. Syn Schmitt, Prof. Monilola Olayioye coordinates the emerging field of Biomedical Systems.

Photo: Günther Bayerl



Part of the pulse stretcher for preparing the laser pulses in the "EndoPrint3D" project

Jun. Prof. Michael Heymann (r.) and PhD candidate Kai Hirzel.

→ And, "relying more on the body's ability to heal itself rather than thinking in terms of replacement parts" is also the vision that drives Heymann. Two years from now, if all goes well, the complete system consisting of the laser, endoscope, printer, and bio-ink should be up and running, which will provide the proof of concept the team needs to further refine their innovation.

Atrosimab, OMTX705, VIBEBOT and EndoPrint3D are just a few examples from the large portfolio of excellent research being conducted in this emerging field. Above all, coordinator Monilola Olayioye relies on one thing to orchestrate them: a lot of communication. "To achieve scientific success and for a diverse set of teams to develop products together, you need a common language." And a lot of stamina: It took the IZI team 15 years to get its new antibodies into human trials. On the other hand, according to Tian Qiu's estimates, it will take at least a decade before the nano- and microrobots being built in the IPC's labs will be ready to be deployed in patients – and that's being optimistic. "Many things are possible and are already being implemented in clinical practice," says Prof. Olayioye. "But we also need to think big and ultimately develop intelligent systems that are not only customizable, but also easily constructed, adaptable, and affordable." ⇥

Prof. Monilola Olayioye

> "But we also need to think big and ultimately develop intelligent systems that are not only customizable, but also easily constructed, adaptable, and affordable."

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TEXT: HEIKE SCHMIDT-LANGER

Researchers at the University of Stuttgart are searching for new combination therapies to make the treatment of cancer more precise and effective.

Tearing down the safety nets of cancer cells

New strategies to kill off cancer cells: The researchers plan to combine different mechanisms that cause cell death.

The quickest way to collapse a house of cards is to remove two cards at the same time. This is roughly analogous to the approach taken to cancer therapy by Prof. Markus Morrison, Dr. Daniela Stöhr and their team of the University of Stuttgart's Institute of Cell Biology and Immunology (IZI). The scientists combine different methods to kill cancer cells. "When it comes to aggressive tumors in particular," says Stöhr, explaining the basic approach, "you need combination therapies in order to get around the cancer cell's safety nets.

PIONEERS IN THE STUDY OF CELL DEATH MECHANISMS

Specifically, the researchers are targeting two different cell death mechanisms known as apoptosis and ferroptosis. Apoptosis is the conventional cell death process triggered by so-called BH3 mimetics as well as by the majority of other anticancer drugs. BH3 mimetics have been shown to be particularly effective against various tumor cells by inhibiting the ability of tumor cells to avoid cell death. Oncological drugs of this class are proving to be extremely effective, particularly in a certain form of leukemia. Ferroptosis is → another alternative signaling pathway that has been known for about ten years and can damage cancer cells by causing a failure of antioxidant systems. The researchers plan to combine BH3 mimetics with ferroptosis-inducing substances (RSL3) to achieve the best possible treatment efficacy even in resistant cancer cells and

the researchers are among the pioneers in this field. "For the first time," says Morrison, who is also a member of the scientific coordination team of the University of Stuttgart's Emerging Field Biomedical Systems, "we are recognizing that these cell death mechanisms, apoptosis and ferroptosis, which are actually considered to be completely separate, are intertwined in this case." The potential consequences for therapy are far-reaching, as the scientist explains: "Using these substances to stimulate and stress the cell in both directions brings about a cell death synergy, and many more cells die than the sum of the cells that could be killed with the two distinct treatments."

However, certain questions remain to be answered. A more in-depth analysis of previously unstudied cancer cell types, for example, revealed an unexpected result: rather than dying, the cells suddenly began thriving more than before. So whereas in some cases cancer cells are effectively eliminated, the administration of certain BH3 mimetics in combination with RSL3 can also have the exact opposite effect and the treated cells develop a resistance to ferroptosis and survive.

Dr. Daniela Stöhr

"We should never stop exploring alternative treatments because cancer cells can adapt, too."

Prof. Markus Morrison is head of the Institute of Cell Biology and Immunology.

COLLABORATION IN A NATIONWIDE RESEARCH PROJECT

Why and how this happens is the subject of a nationwide research project initiated by Morrison and Stöhr in which other researchers from the University of Stuttgart, the University of Cologne, and the Helmholtz Institute in Munich are collaborating. Prof. Sabine Laschat of the University of Stuttgart's Institute of Organic Chemistry, for example, is working on synthesizing more suitable BH3 mimetic variants. The underlying question behind the studies is how neutralizing effects can occur in combination therapies. Daniela Stöhr is certain about one thing at least: "We should never stop exploring alternative treatments because cancer cells can adapt, too." ⇥

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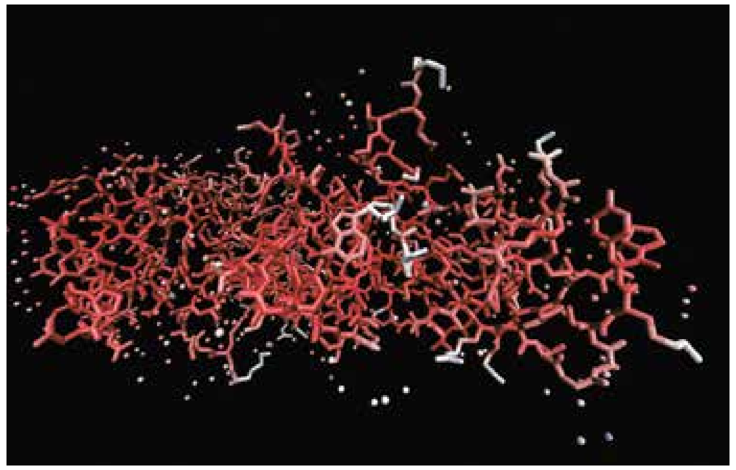
Photos: unsplash, Sven Cichowicz, private

NEW STRATEGIES FOR ATTACKING VIRUSES

A so-called pro-drug intermediate in the active center of an enzyme.



TEXT: CHRISTIAN HEINRICH

Infections, such as hepatitis C and HIV, are already being treated effectively with so-called nucleoside analogues. Prof. Clemens Richert of the University of Stuttgart is researching ways to extend their range and effect on other viral diseases.

What makes viruses so dangerous is that they are small, only need to carry a light load, and are hard to catch. They are parasites that invade other cells and take full advantage of the opportunities they offer. Whereas bacteria are independent cells, viruses are little more than a genome within a shell structure, which makes developing drugs that effectively target them very difficult. But even viruses need to replicate their genome, which makes them vulnerable to attack.

STOPPING THE REPLICATION OF THE VIRAL GENOME

The term nucleoside analogue applies to a group of agents that specifically target the replication of the viral genome. They are the subject of research being conducted by Prof. Clemens Richert, managing director of the University of Stuttgart's Institute of Organic Chemistry (IOC). His parents were both medical doctors and had told him as a child that bacteria could be treated with antibiotics but that nothing could be done against viruses. “Fortunately, that has changed,” says Richert with a smile. Richert and his team are researching nucleoside analogues to ensure that this development continues. Due to their strong resemblance to the eponymous building blocks of the virus' own genome, the virus' enzymes incorporate them into the genome during replication after which they unleash their effect. The built-in nucleoside analogue inhibits the attachment of further nucleosides, which brings the genome replication to a halt. “It's like inserting a railroad car on a freight train with a missing →

Researchers at the Institute of Organic Chemistry are doing lab work on the basics for novel viral treatments.

→ coupling: You can't put anything else on it,” says Richert, which, he says, means that the genome of the virus cannot be copied or can only be copied with errors.

The efficacy of nucleoside analogues has been demonstrated by drugs that show this effect and have already been approved and used such as azidothymidine (AZT), which is used to treat HIV, sofosbuvir, which doctors prescribe for the treatment of hepatitis C, and molnupiravir and remdesivir, which are sometimes used to treat COVID-19. Richert is convinced that: “This is a promising start to the use of nucleoside analogues. But just a start.”

Prof. Clemens Richert

“This is a promising start to the use of nucleoside analogues. But just a start.”

Two projects being carried out by Richert's working group have already yielded promising results. One of them involves research into the development of so-called C-nucleosides, which are better than conventional nucleoside analogues in that they bind more strongly to DNA and RNA, i.e., to the genome. And there is a possibility that using C-nucleosides as drugs against viruses may be more effective than previous nucleoside analogues, as they always compete with naturally-occurring nucleosides. “What this means,” says Richert, “is that we don't need to introduce as much of the nucleoside analogue substance to get the same effect, which is a major benefit, because the amount of nucleoside analogue administered is critical in terms of potential side effects.” Researchers at the University of Stuttgart are advancing the development of C-nucleosides in a project funded by the German Research Foundation (DFG) and the Volkswagen Foundation.

Prof. Dr. Clemens Richert is Managing Director of the Institute of Organic Chemistry.

MULTIPLE APPLICATIONS FOR NUCLEOSIDE ANALOGUES

The second project mentioned above involves the activation of nucleoside analogues at the target site. Nucleoside analogues only become active in the cell after phosphorylation, i.e., after a specific sub-form of phosphoric acid has been attached to them. If the analogue is packaged in a so-called pro-drug, which is taken in tablet form, fewer steps are required because the molecular packaging helps the active agent to reach the target site. However, endogenous enzymes are required to unpack the nucleoside analogues at the target site, which means that nucleoside analogues usually only work well in parts of the body that contain larger quantities of the corresponding enzymes, such as in the liver, but cannot be used as efficiently in parts of the body that contain fewer of them. “What we are doing,” Richert explains, “is modifying the nucleoside analogues and their packaging in such a way that it takes fewer enzymes to unpack them enabling them to unfold their effect, which should enable us to use them in more parts of the body.”

The work being carried out by these researchers at the University of Stuttgart could pave the way to the use of nucleoside analogues in a broader range of diseases, because, basically, any virus that uses an auto-encoded apparatus to replicate its RNA or DNA can be targeted via nucleoside analogues. In addition to approved indications for combating diseases such as hepatitis C and HIV, there are a number of other viruses that should be being tackled more effectively, Richert explains: “Herpes simplex, for example, could be treated effectively with nucleoside analogues.” But nucleoside analogues could also be used to target novel viruses. ⇥

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Photos: Clemens Richert, Marga Kowarowski, Peter Schüle

NOTEPAD

COMBINED FLOOD PROTECTION AND COOLING

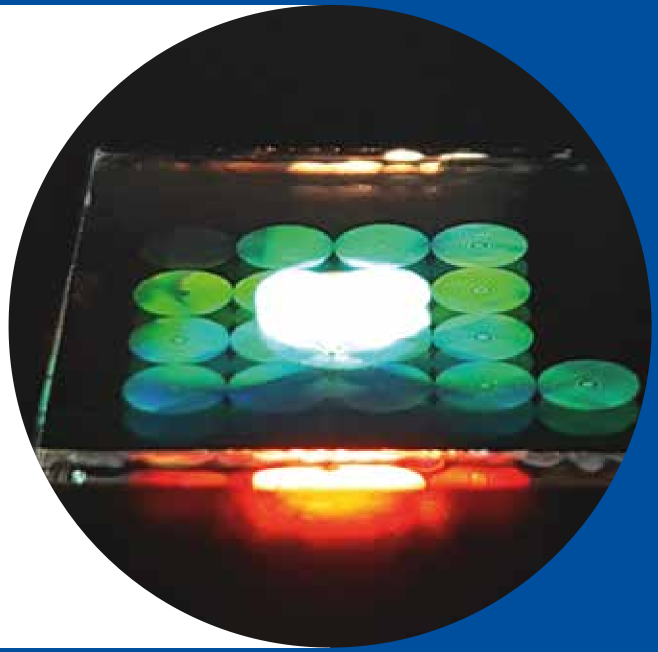
The glass façade of a high-rise building can get so hot that one could fry fried eggs on it, which is a major factor in the overheating of our cities. On the other hand, flooding causes billions of euros of damage every year. The University of Stuttgart's Collaborative Research Center 1244 has come up with a solution to both problems in the form of a hydroactive façade that not only cools exterior walls and the interior of the building, but also the surrounding urban space. For this purpose, textile facade elements called "HydroSKIN" absorb water while it is raining and releases it on hot days for evaporative cooling.

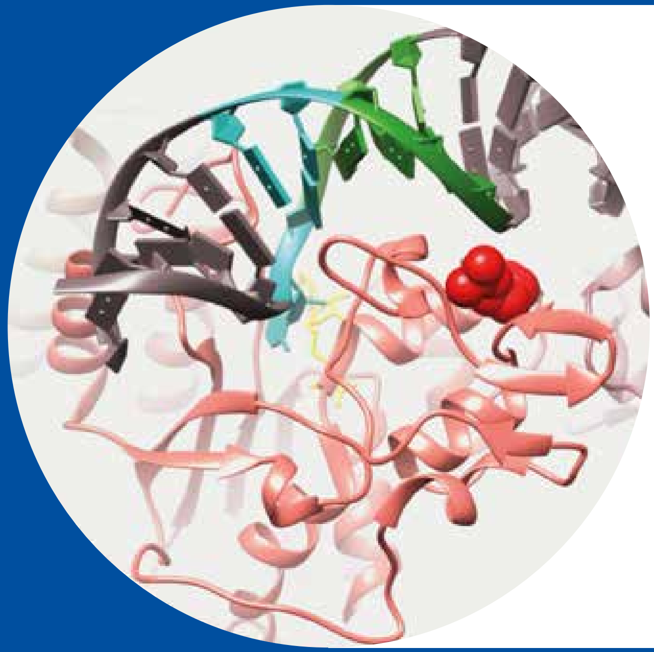
HydroSKIN is built around a textile spacer consisting of two textile layers, kept apart by threads, which ensures good ventilation. The high rate of air circulation facilitates the evaporation of water and enhances the cooling effect of the facade. The woven fabric is enclosed in an outer textile cover, which allows almost all raindrops to penetrate whilst protecting it from contamination and an internal film drains the water into the underlying profile layer from where it can either be stored in a reservoir or used directly to help reduce water consumption in the building. On hot days, the water can be returned to the façade element, where it evaporates, thus generating a natural cooling effect.

CELL PHONES: ZOOMING IN LIKE WITH AN OPTICAL LENS

The only way to zoom in on conventional smartphones is usually by swiping two fingers across the screen, but this only increases the size of the image, which becomes visibly pixely. This is why the newest generation of smartphones are often pre-equipped with multiple lenses with various fixed focal lengths to take higher-quality photos, similar to the earlier interchangeable lenses of 35 mm cameras that enabled one to take both wide-angle and telescopic photos.

Researchers at the University of Stuttgart's 4th Physics Institute recently presented the first ever electrically switchable meta lens in the journal *Nature Communications*. The device consists of two metalenses that can be switched independently at the touch of a button, which means that several combinations are possible, which translate to different focal lengths. This type of lens could be used in flat smartphones in the future, without the need for additional mechanical components or complicated, failure-prone mechanisms.





NEW APPROACHES TO THE TREATMENT OF LEUKEMIA

Up to 25 percent of patients suffering from acute myeloid leukemia (AML) have mutations in DNMT3A DNA methyltransferase, an enzyme involved in the regulation of DNA methylation. A group of scientists at the University of Stuttgart, led by Prof. Albert Jeltsch, are currently using a recently developed "deep enzymology technology" to investigate the mechanisms through which cancer mutations influence cellular activity. Understanding the biological effects of these mutations could lead to new approaches to the treatment of this kind of tumor.

USING ULTRASOUND TO MONITOR HAND MOVEMENTS

Contactless operating element operation is increasingly becoming the norm: in cars, machinery, and operating theaters, whether it be through eye movement, hand gesture tracking, or voice control. The newest communication technologies are both intuitive and allow additional degrees of freedom in human-machine interactions. So far, however, users have only received feedback on the controls in the form of indications on displays or acoustic signals, which can be confusing and annoying, and the user has no way of knowing whether the system has executed the instruction correctly.

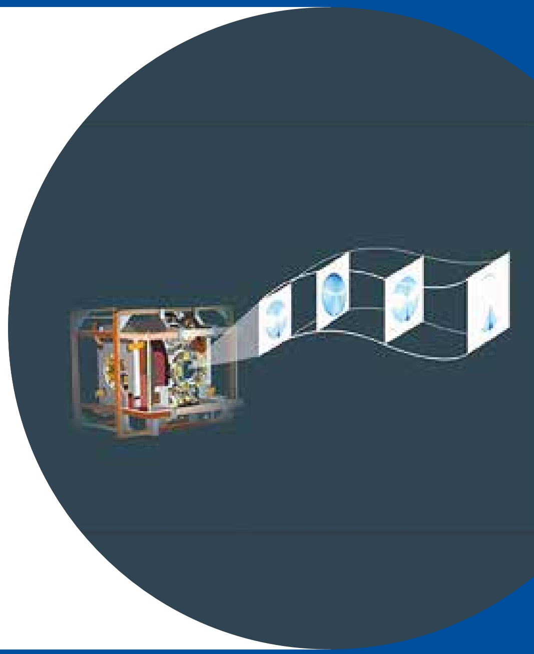
Researchers at the University of Stuttgart's Institute for Engineering Design and Industrial Design now want to optimize the transfer of information between man and machine, whereby they are using ultrasound waves projected onto the palm of the hand, where they cause a tingling sensation. Once the user has learned to interpret these signals, the sensation helps them move the hand with the right speed in the right direction.

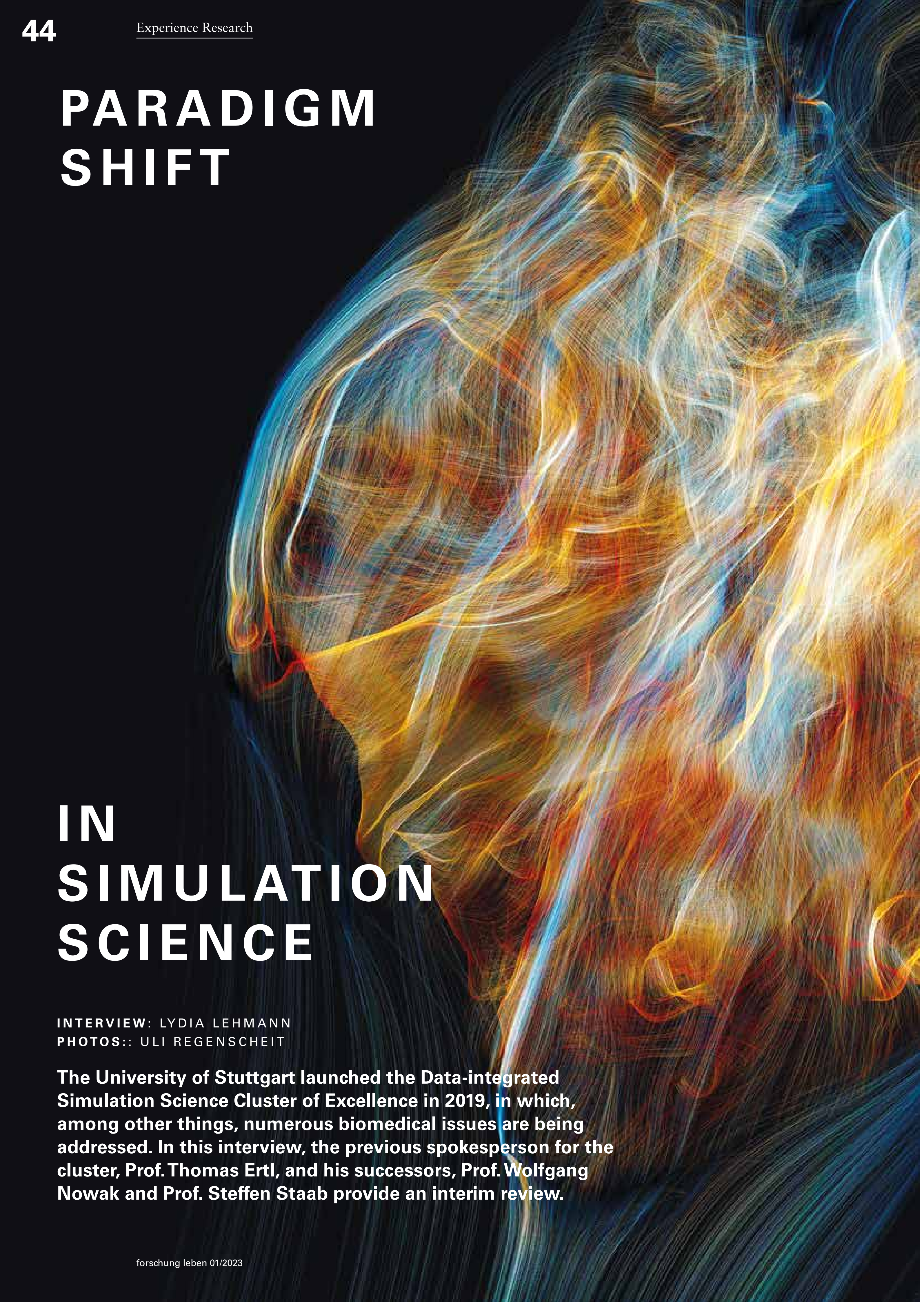
Photos: Sven Cichowicz, Albert Jeltsch, 4th Physics Institute, IKTD/Peter Schmid, Keilyn Ureña-Alvarado

MOLECULAR VIBRATION IN SLOW MOTION

Simple molecules consist of two atoms whose atomic nuclei are only separated by a nanometer or even less. At these tiny length scales, dynamic processes occur rather quickly, too quickly, in fact, to enable the molecular vibrations to be observed. Rydberg ion molecules, which consist of a charged particle – an ion – and a so-called Rydberg atom, are quite different. One of their key characteristics is that the outermost electron is situated extremely far away, in relative terms, from the atomic nucleus. Owing to their enormous size, they vibrate about once every microsecond, which is virtually in slow motion compared to the oscillation speed of normal molecules.

Researchers at the University of Stuttgart's 5th Institute of Physics were able to observe the molecular oscillation in an ion-Rydberg molecule for the first time and display it in a series of snapshots at different points in time. Going forward, the methods they applied could be used to improve our understanding of dynamic processes in molecules and may even enable direct tracking of chemical reactions down to the atomic level.





PARADIGM SHIFT IN SIMULATION SCIENCE

INTERVIEW: LYDIA LEHMANN
PHOTOS:: ULI REGENSCHEIT

The University of Stuttgart launched the Data-integrated Simulation Science Cluster of Excellence in 2019, in which, among other things, numerous biomedical issues are being addressed. In this interview, the previous spokesperson for the cluster, Prof. Thomas Ertl, and his successors, Prof. Wolfgang Nowak and Prof. Steffen Staab provide an interim review.

The three co-spokespersons for the SimTech Cluster of Excellence: Prof. Dr. Thomas Ertl (l.), Director of the Stuttgart Center for Simulation Science, Prof. Dr. Wolfgang Nowak (r.o.), Head of the Institute for Modelling Hydraulic and Environmental Systems, and Prof. Dr. Steffen Staab (r.u.), Head of Department at the Institute for Parallel and Distributed Systems

The halfway point of the funding period for the University of Stuttgart's Data-integrated Simulation Science Cluster of Excellence was recently reached. What have you achieved so far?

PROF. WOLFGANG NOWAK (WN) Conventional simulation technology involves the numerical simulation of physical principles on computers. Huge amounts of experimental data have recently become available that can improve such simulations. This is why we had set ourselves the goal of bringing about a paradigm shift away from traditional simulation technology towards "data-integrated simulation science"...

PROF. THOMAS ERTL (TE) ...yes, we incorporated data science and machine learning with a view to merging simulation science and data science to establish a more advanced simulation discipline.

WN That was a really radical change and what we now know is that this paradigm shift has played a central role in all of the 80 projects we have successfully completed during the first half of the project. Comments from our researchers, such as: "I am among the foremost researchers doing data-integrated simulation science in my field", which we hear again and again, show that it has been successful both at the collective and personal levels.

TE The heterogeneity and breadth of SimTech's research successes can be seen in all seven project networks; focusing on individual ones is almost pointless. All in all, simulation science has coalesced and matured over the past 15 years from isolated approaches into an independent discipline. →

A vortex formation simulation on a plate with air flowing in obliquely from below. Slow flows are shown in red and fast flows in blue.

Photo: DFG / Jakob Dürrwächter, Daniel Kempf, Claus-Dieter Munz

Prof. Thomas Ertl

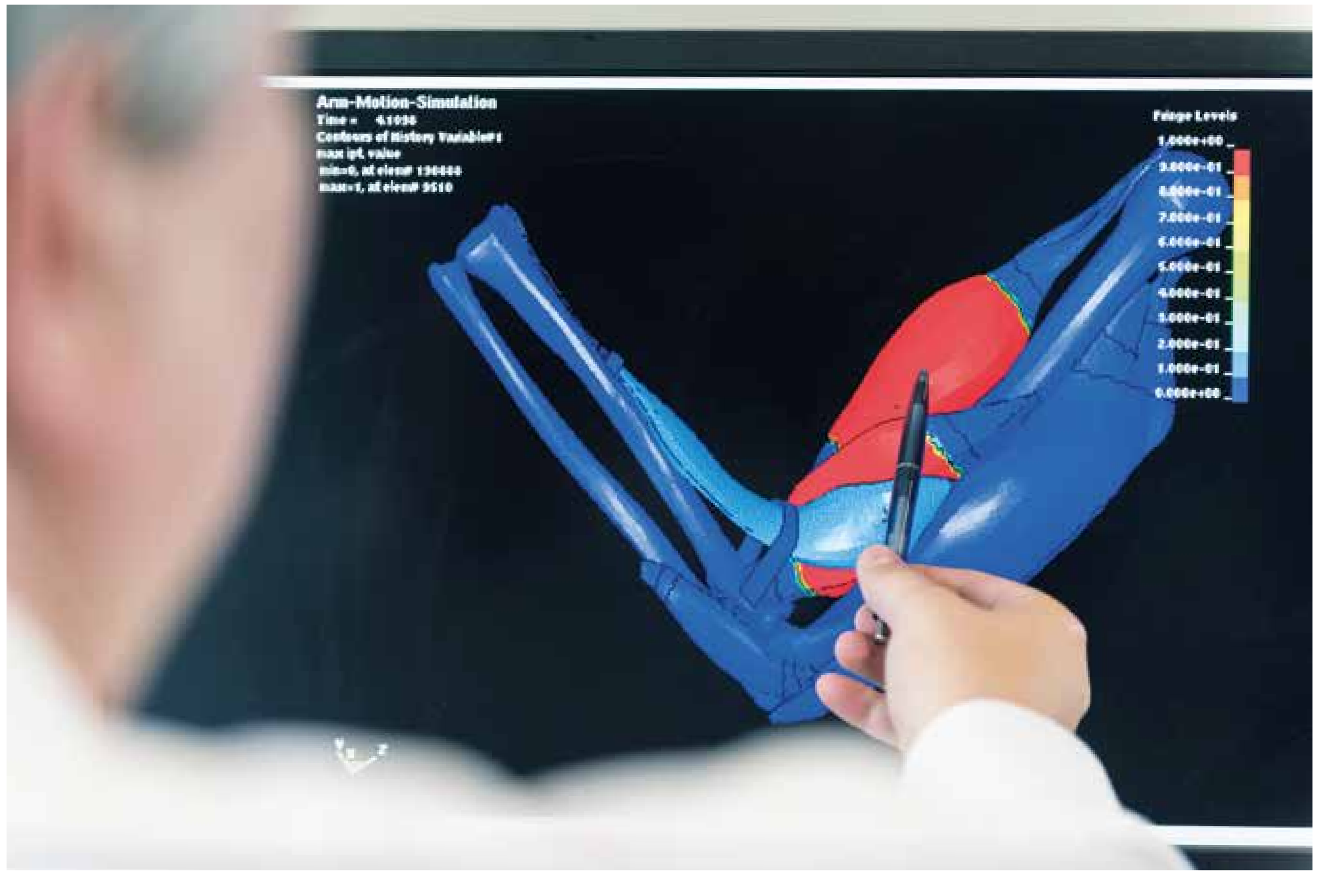
“The fact that SimTech is an internationally established trademark of the University of Stuttgart is a unique selling point.”

→ We run our own SimTech bachelor's and master's study programs, host our own graduate school where more than 200 people have earned doctorates in simulation science, and are proud to have ten post-doctoral habilitations in simulation science. There is a funding structure in place for post-doc projects, and we have established seven junior research groups: we have been joined by four men and three women, mostly from outside the university, who are now leading their research groups with great success. We also announced six new professorships, all of which have since been taken up by excellent researchers. The fact that SimTech is an internationally established trademark of the University of Stuttgart is a unique selling point.

What do you personally like most about SimTech?
TE Even as a veteran of almost 20 years, what fascinates me is the level of collaboration and personal interaction – and the fact that we have been so successful on this basis. The development over the years of such an excellent culture of collaboration in a cluster of this size, which still leaves room for many idiosyncrasies and in which everyone is on an equal footing, is not something that can be taken for granted. I'm saying that now as the spokesperson, but this is the lived reality across all status groups.
WN Yes – how did one of the reviewers put it during our last review? Ah yes: “This degree of team spirit cannot be faked.”
TE (laughs.) Yes, that was a phrase from someone from outside the group that sums it up nicely.
PROF. STEFFEN STAAB (SST) What always impresses me are our annual SimTech status meetings in Bad Boll, which are attended by around 200 active SimTech researchers. That's where you get a physical sense of the size of the undertaking as you walk the corridors and how enthusiastic everyone is about it.
WN I like the interdisciplinarity on an equal footing and having our own SimTech vocabulary. As an environmental engineer and porous-media researcher, I stroll into the math building, and after enough discussions with mathematicians, I no longer feel out of my depth. Then I head over to the computer science building with new questions and experience the same thing. (laughs.) And I sit on the board of directors alongside a theoretical chemist, a systems biologist and others, where discussions also take place on various professional levels. I love that!

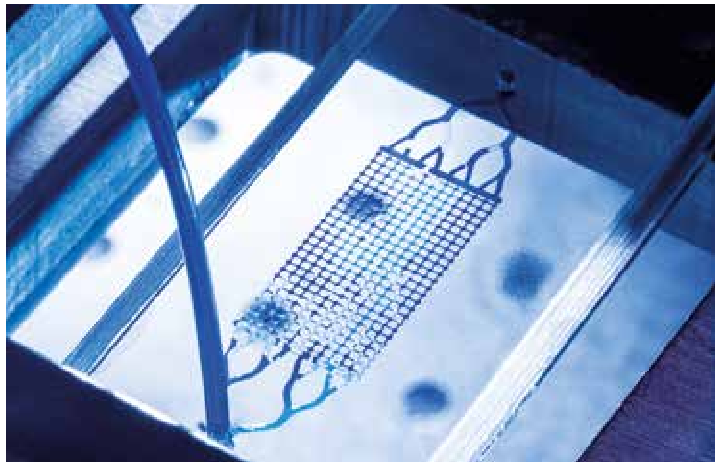
So SimTech is the living embodiment of the "Stuttgarter Weg (Stuttgart way)" of doing interdisciplinary research. And, in keeping with the University of Stuttgart's vision, why is your simulation research important for society and for the future?
TE Simulations are run by people and don’t take place in a vacuum. We want to make simulations and the data they yield available for different application contexts – think "pervasive simulation and visualization": not only on a supercomputer or at a lab desk, but also for a geologist taking pictures on a tablet with built-in sensors outside in the real world, → collecting data and feeding it directly into a simulation that then runs remotely on a supercomputer before feeding the results back to the user. The issues involved include the interfaces between supercomputers and mobile devices as well as more compact displays for tablets.
WN The Digital Human Model is another example, where our researchers are working on personalized prognoses on a per-patient basis. A patient with a spinal disk injury is admitted to the hospital to have a prosthesis implanted. We need to quickly calculate the exact forces acting on the bones and spinal disk due to nerve stimuli, muscles, and tendons in this specific patient. A simulation can then be used to predict which implant would be the best.

Is this just a distant dream for the future, or are we on the verge of using such personalized spinal disk implants?
WN We at SimTech are basic researchers; the systems we program are not immediately used in hospitals. There is one more technology transfer stage in between. However, we can already use real CT data to show that the necessary calculations can actually be done. And we can use augmented or virtual reality glasses to visualize the force conditions that occur during movements as well as which part of the muscle they affect and how.
SST There are several transfer-oriented application projects that are not funded by the Cluster of Excellence, but which build on SimTech's methodological innovations. For example, one project with the University Hospital of Jena is just getting underway, which →



Right from the start, one of the key research areas of the SimTech Cluster of Excellence has been the simulation of complex processes in the human musculoskeletal system.

Photo: Max Kovalenko



The University of Stuttgart's Porous Media Lab is a central experimental platform, used by the "Data-integrated Simulation Science" Cluster of Excellence, (EXC 2075, SimTech) and other institutes.

Photo: Uli Regenscheit

→ involves simulating processes in the liver and simultaneously using machine learning to support the tumor board, in which doctors with expertise in various specialist areas consult with each other on the diagnosis and treatment of liver tumors. Incidentally, the industrial sector is already using SimTech's methodological findings as the result of transfer activities of this kind.

What will change at SimTech in the second half of the funding period? What would you like to focus on?

TE I will be retiring in October. We started the SimTech generation change last year, since which time Wolfgang Nowak and Steffen Staab have been co-spokespersons for the cluster, my successor duo. Holger Steeb will be assuming the position of director at the Stuttgart Center for Simulation Science. With these three individuals, an excellent team is in place to prepare and hopefully lead SimTech's next application for excellence status to success.

SST We're aiming for a combination of evolution and revolution. Whilst data-integrated simulation science does indeed represent a new paradigm, we will of course continue to think beyond it. To what extent will simulation science undergo a fundamental change? That's a challenge because there is only one simulation science, yet many contributing disciplines all with their own different vernaculars. I believe that achieving success here will enable us to make a considerable difference, because we will have an impact on various disciplines.

WN The opportunity is already there to pick up on certain topics right now in order to redirect SimTech's focus for potential follow-up funding as a cluster of excellence. One such area of interest is our new "Quantum Computing for Simulation" project network, where we are working closely with theoretical chemists as well as theoretical and experimental physicists to make quantum computers fit for our simulation runs and to tune the algorithms accordingly.

SST The second thing we want to focus on is "Knowledge-Infused Simulation Science," or knowledge integration. We want to make simulation systems as intelligent as possible, for example by having them learn from experience or by incorporating expert knowledge into our simulations, which would save computing power and time.

WN And we are aware of what the science-supporting structures have accomplished so far – for example, when it comes to promoting young scientists, internationalization, diversity, study programs, the management of scientific data, public relations, and reflecting on one's own work. We would like to continue our success and surpass what we have achieved so far. ⇥

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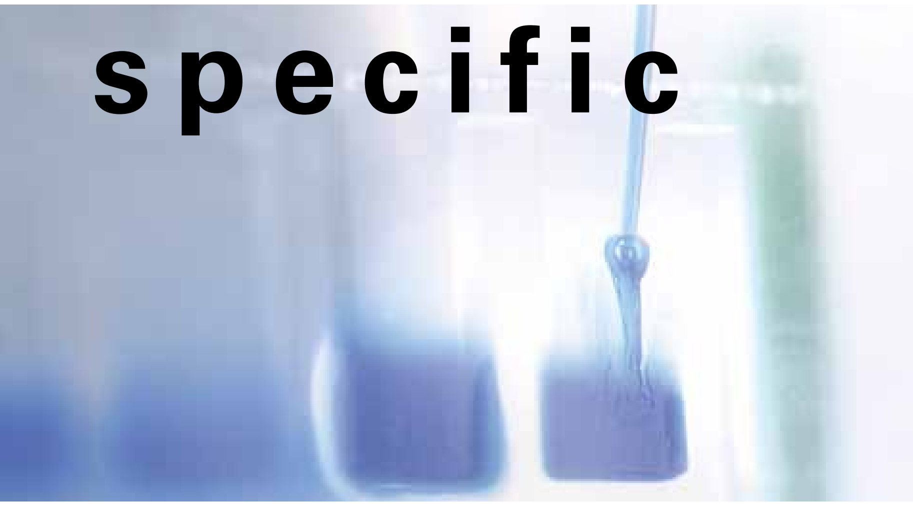
Simulations are helping to investigate the smallest building blocks of life, such as enzymes.

Photo: Max Kovalenko

Prof. Steffen Staab

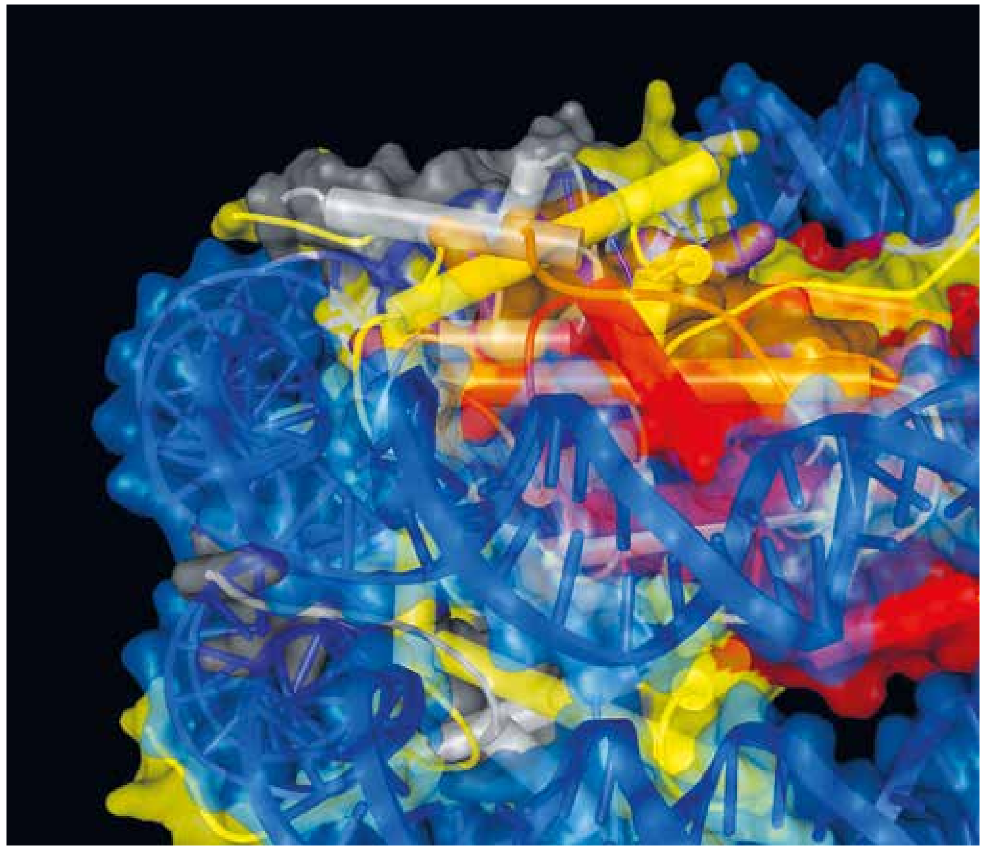
"We're aiming for a combination of evolution and revolution. Whilst data-integrated simulation science does indeed represent a new paradigm, we will of course continue to think beyond it."

Switching off in a targeted manner specific genes



Using gel electrophoresis to perform complex protein analyses.

The structure of a nucleosome, the elementary structural element of the genome.



TEXT: FLORIAN BAYER

Researchers at the University of Stuttgart are using modified genetic scissors that have been converted into a gene regulator to develop novel therapies for SARS-CoV-2 and Parkinson's disease, two diseases that otherwise have little in common.

Prof. Albert Jeltsch heads up the Institute of Biochemistry and Technical Biochemistry.

The third anniversary of the Covid-19 pandemic occurred earlier this year. In spite of extensive research around the world, much of the background to the spread of the virus in the body remains unclear. As of today, only a single drug – Nirmatrelvir, which is a virostatic agent – has been approved for the treatment of SARS-CoV-2. On the other hand, the only treatments available for Parkinson's disease to date only treat the symptoms rather than the cause. Parkinson's disease is characterized by the progressive loss of the nerve cells that produce the hormone dopamine resulting in increasing movement disorders and muscle tremors as the disease progresses.

Prof. Albert Jeltsch and his team at the University of Stuttgart's Institute of Biochemistry and Technical Biochemistry (IBTB) are taking a new approach to treating SARS-CoV-2 by using a method they also use to develop new therapies for Parkinson's disease, which involves using a modified molecular biological "genetic scissors" known as CRISP/Cas9 to knock out certain genes. This is an extremely efficient way of precisely modifying, deactivating, or completely removing certain DNA building blocks in a targeted manner.

REDUCING THE ACTIVITY OF DISEASE-RELEVANT TARGET GENES

The objective when treating both SARS-CoV-2 and Parkinson's disease is merely to silence the target genes, which means that no genetic modification is required. The target genes in the case of SARS-CoV-2 are ACE 2 and TMPRSS2, which the virus uses to gain entry into epithelial cells and to replicate itself within the cell. This would make the cells resistant to the pathogen, which would prevent or at least slow down any further spread of the virus in the body as well as indirectly slowing the spread of SARS-CoV-2 throughout the population.

In the case of Parkinson's disease things are very different because, unlike the treatment of SARS-CoV-2, the goal is not to stop the spread of the virus but rather to attenuate the neuropathological symptoms in the brain. To achieve this, the researchers at the University of Stuttgart are attempting to reduce the transcription rate of the so-called SNCA gene in the hope of reducing the formation of SNCA protein clumps in neurons. "In both cases," Jeltsch explains, "we are attempting to target natural intracellular gene regulatory mechanisms in cells in order to reduce the activity of disease-relevant target genes."

CONCENTRATED RESEARCH ON THE APPROPRIATE GENETIC SCISSORS

Nevertheless, the mechanism, i.e., the precise targeting and editing of the affected genetic sequences, is similar to that being used in the SARS-CoV-2 research project. Commenting on the research being conducted on a SARS-CoV-2 therapy, Jeltsch says': "We are confident that we will be able to achieve a stable and durable repression of both target genes through a clever selection of EpiEditors." The team is currently working hard to identify these specific EpiEditors, i.e., the specific type of "genetic scissors". The next steps will be to test appropriate drug applications, first in the laboratory and later in clinical trials.

The researchers also want to identify and test specific vectors that will ultimately be used to introduce the new active ingredient into patients' cells. The most promising approach for SARS-CoV-2 is to target the epithelial cell layer in the nasal cavity, which would enable the drug to be delivered in the form of an aerosol or nasal spray.

Initially, the project at the University of Stuttgart is scheduled to run until 2024, at which point the findings could be used for further clinical development and validation. Everyone now agrees that the Covid-19 virus will be a fact of life for the foreseeable future. ⇥

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HOW CELLS MAKE DECISIONS

Peering into cellular processes: Prof. Stefan Legewie

TEXT: ANDREA MAYER-GRENU

Systems biologist Prof. Stefan Legewie and his team at the Institute of Biomedical Genetics and the Stuttgart Research Center Systems Biology are combining cell biology, computer science, biophysics, and mathematics to develop a systemic understanding of intracellular processes.

The central focus of systems biology is the holistic analysis of complex biological data sets, which helps to give us a better understanding of important questions in such areas as cancer research, for example: how do cells respond to changes in their immediate environment, and how is genetic activity controlled during this process? “Our primary focus is on signal transduction cascades, which transmit information from the cell membrane to the cell nucleus,” says Legewie, summarizing the scope of his research. “After that, we're interested in processing, by which I'm referring to the modification of ribonucleic acids (RNA).” In an attempt to answer these questions, the working group is not only using experiments but also mathematical modeling and artificial intelligence.

UNDERSTANDING THE DECISION-MAKING PROCESSES INVOLVED IN CANCER

In terms of cancer research, the group is investigating a specific signaling pathway with a tumor-suppressive effect, i.e., it is able to block the growth of tumors. One way to picture this is to imagine a hormone-like protein called TGFß, which attaches to receptors on the cell surface. Once this signal has been transmitted to the cell nucleus it activates genes that inhibit cell growth but if the signaling pathway changes, due to mutations for example, TGFß can no longer inhibit the growth leading to excessive cell growth and ultimately cancer. Other changes in the same signaling pathway can cause cells to migrate and a tumor to metastasize.

The primary goal of Legewie's research group is to gain a better understanding of these decision-making processes in the TGFß signaling pathway that play a role in cancer, whereby they exploit the fact that not all cells in a cell population behave in the same way: some stop growing, whereas others migrate or do not respond in any way at all. “So, what we do,” as Legewie explains, “is to analyze a large number of individual cells and → exploit their heterogeneity to understand the underlying decision-making principles.” The findings, which were obtained in collaboration with the University of Darmstadt, were recently published in the scientific journal "PNAS".[1].

Several

10,000

of mutations can be characterized using a novel screening process.

Ultimately, the scientists are trying to identify potential targets that can be targeted to reverse the process of tumor development and metastasis. The hope is that it will eventually be possible to develop drugs that will be able to shrink metastasizing tumors. Legewie's second field of research, which involves the processing of messenger RNA in cellular protein synthesis, is already much closer to use in therapeutic settings. The result of this processing, which is referred to as alternative splicing, is that human cells have many more protein variants than such things as yeast cells or other lower organisms, which becomes Important in treatments, such as CAR-T cell therapy, which is used for end-stage leukemias when the patients' own immune cells (T cells) are extracted and reprogrammed to make them attack leukemia cells after they are reintroduced to the body. This treatment is extremely efficient in principle but sometimes the leukemia cells simply don’t respond to the T cells, because T cells are programmed to target a specific receptor on the surface of the cell. This is the very receptor that is processed in a different way in resistant leukemia cells as a result of mutations in the genome, which renders the therapy ineffective.

PREDICTING THE EFFECTS OF COMPLEX MUTATIONS

Legewie's team, is collaborating with groups in Mainz and Frankfurt to gain a better understanding of the principles of resistance development by devising a screening approach that can be used to characterize several tens of thousands of mutations in a high-throughput mapping process, which was reported on last year in the journal *Nature Communications*.[2]. What they found was that processing mRNA is enormously complex, as even a relatively short genetic segment of the surface protein gives rise to about 100 variants that could potentially confer resistance. There are also numerous potential combinations of mutations and it is difficult to predict how they will interact. Mathematics has been instrumental in interpreting the relevant data: the research group used various approaches based on systems biology to develop quantitative models that accurately predict the effects of complex mutations on the products of gene transcriptions.

“Going forward,” says Legewie,“ we may be able to use this data to predict whether a patient will develop resistance as soon as the treatment starts.” The findings also indicate which other therapeutic approaches CAR T-cell therapy could be combined with in order to guard against resistance. ⇥

Institute of Biomedical Genetics

The Systems Biology Chair is part of the University of Stuttgart's recently founded Institute of Biomedical Genetics (IBMG), which conducts research into the fundamentals of how genes and genetic regulatory networks contribute to human disease. The Institute's other divisions include the Department of Eukaryotic Genetics (Prof. Jörn Lausen), which studies the basic molecular mechanisms involved in stem cell differentiation, and the Department of Computational Biology (Prof. Björn Voß), which combines expertise in RNA biochemistry, "next generation sequencing" (NGS), and the development of algorithms for analyzing RNA structures. Going forward, a professorship in genome editing, which has yet to be filled, will develop novel methods for the targeted manipulation of genetic activity.

1 Bohn et.al.: State- and stimulus-specific dynamics of SMAD signaling determine fate decisions in individual cells. *Proceedings of the National Academy of Sciences* (in press), https://doi.org/10.1073/pnas.2210891120

2 Cortés-López et.al.: High-throughput mutagenesis identifies mutations and RNA-binding proteins controlling CD19 splicing and CART-19 therapy resistance. *Nature Communications* 2022, https://www.nature.com/articles/s41467-022-31818-y

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Photo: Uli Regenscheit

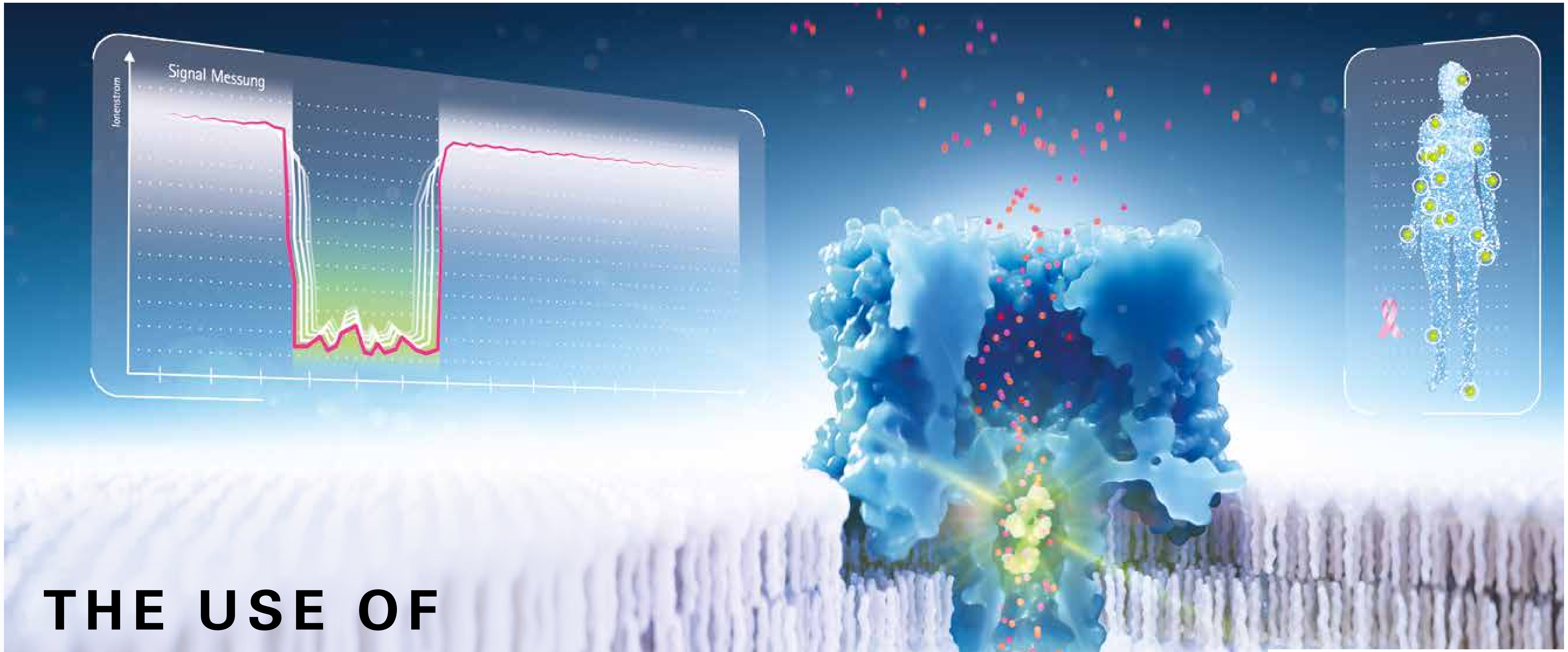


Photo: Hahn-Schickard

THE USE OF NANOPORES TO DETECT POTENTIAL DISEASES

TEXT: MICHAEL VOGEL

A new type of bioanalysis could be used to expand the field of prognostics but this would requires a much deeper fundamental understanding of molecular processes. The so-called Cluster4future nanodiag BW (Next generation innovation network Nanodiag BW), which includes two working groups from the University of Stuttgart among others, has set itself the goal of achieving this.

This diagram shows how the electrical conductivity of a nanopore temporarily decreases as a protein fragment passes through the pore.

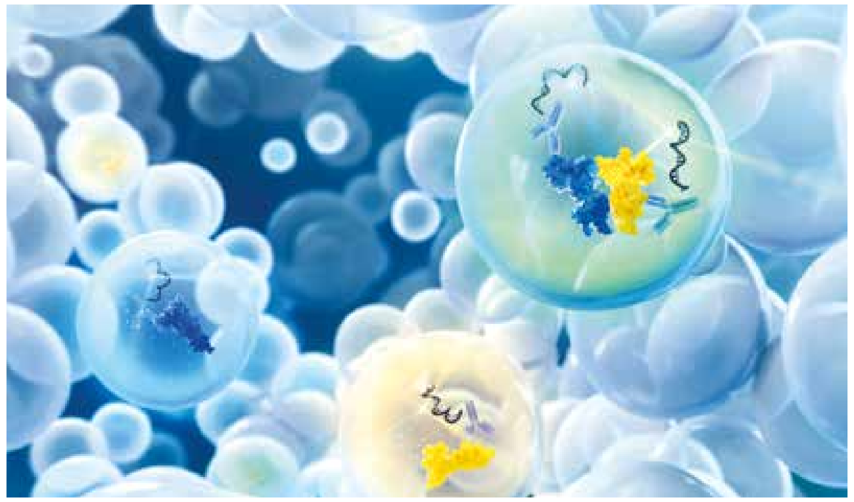
The human body is made up of 100 trillion cells, each of which performs a specific task within the body. Because cells have a limited life span, they divide on a regular basis in a highly complex process that produces incredibly accurate copies of the parent cell. “However,” as Prof. Stephan Nußberger explains, “medical scientists now also know that even our lifestyles can cause minimal changes in a gene or in the formation of new proteins within a cell.” This can lead to uninhibited cell proliferation and potentially to poorer resistance to pathogens. “They can also cause diabetes, cancer, or infectious diseases,” says the biophysicist, who conducts his research at the University of Stuttgart's Institute of Biomaterials and Biomolecular Systems. “Whilst diagnosing such diseases is often straightforward,” says Nußberger, “medical scientists are hoping to augment diagnostics with prognostics going forward.” This, he explains, would make it possible to detect the problem at an early stage and to initiate a less aggressive treatment to counteract it in good time.

CLUSTER FOR A NEW KIND OF BIO-ANALYTICS

Achieving this is the goal that Cluster4future nanodiag BW (Next generation innovation network nanodiag BW) has set itself. The project group includes the Hahn-Schickard-Gesellschaft für angewandte Forschung (Hahn-Schickard Society for Applied Research), which is closely associated with the University of Stuttgart, seven other universities and several non-university-affiliated research institutes, as well as nine commercial enterprises. The University of Stuttgart is represented by Nußberger's research group and a group led by Prof. Christian Holm of the Institute for Computational Physics. The specific aim is to develop a new type of bioanalysis involving the use of nanopores to analyze biomolecules. →

→ The process exploits the way cells work. “All cell walls include pores through which metabolism takes place,” Nußberger explains. These enable the passage of things such as ions, sugar molecules, and biomolecules. “Pores have diameters ranging from 0.1 to five nanometers, depending on what they transport.” 0.1 nanometer is equal to one atomic diameter and one nanometer is one millionths of a millimeter.

The engineered replication of this transport mechanism can be used to detect single molecules: an electrically conductive liquid chamber is separated into two areas by a porous membrane. The molecules to be analyzed are in the liquid, which is usually a saline solution. Applying an electrical voltage causes a current to flow through the porous membrane, because the ions in the liquid migrate, whereas the current drops if a molecule gets trapped in the pore or passes through it. The specific characteristics of the change will indicate what exactly has blocked or passed through the pore.



The pore being studied is divided into millions of micro droplets in a process known as "emulsion coupling".

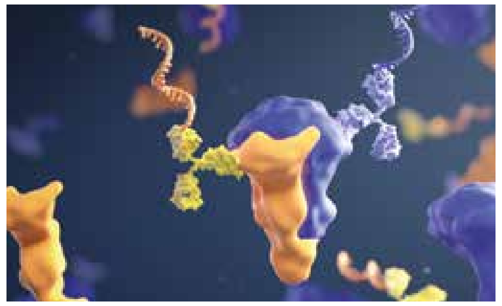
Prof. Stephan Nußberger

“Whilst diagnosing such diseases is often straightforward, medical scientists are hoping to augment diagnostics with prognostics going forward.”

MEASUREMENTS IN THE MILLISECOND RANGE

“So far,” says Christian Holm, “nanopore technology has only been used commercially for the analysis of DNA. But what our research is about is the characterization and even the direct sequencing of proteins.” Sequencing, in this context, means determining the sequence of amino acids that make up a protein. Initially the project team will be studying bionanopores, which are specially produced biological pores. The molecules that will be analyzed will only differ slightly from one another, for example, by a handful of atoms at a specific location – analogous to the aforementioned lifestyle-related changes, to which end the project partners will need to be able to measure minuscule current differences in the millisecond range. The currents in question might differ by one trillionth of an ampere. To put this in perspective the current that flows when charging a smartphone is about one ampere.

“For us to succeed in all of this,” Holm explains, “we need to have a comprehensive understanding of nanopores and how they interact with proteins.” And comprehensive in this case really does mean comprehensive: the relevant events take place in just a few cubic nanometers, although tens of thousands of individual particles are involved in this process at the atomic and molecular level, some from the aqueous solution, some from the protein to be analyzed, and some from the pore surface. “We still don't → understand the details of the processes involved,” says theoretical physicist Holm, which is where his working group comes in.



The so-called PICO method uses two distinct, DNA-labeled antibodies that target specific proteins, shown here in blue and yellow.

“We model the proteins, the pore, and the fluid on the computer,” he explains. The model reflects such things as which parts of a protein are more rigid or more flexible, and how strongly its atoms interact with each other as well as the relevant mechanical and electrical forces. “Then we use the model to simulate the passage of proteins through the nanopore to see how the proteins move within it and which interaction we would expect to produce which electrical current signal.”

The cluster members continuously compare the results from these simulations with those from experiments being carried out in Freiburg. “The aim then is to collaborate with a team at RWTH Aachen University to develop a program that can reliably analyze real-world electrical current signals,” says Holm. Artificial intelligence will be used to perform the analysis, because the signals will be noisy and will often result from protein changes that have never been empirically measured before, because of the huge number of variants.

Nußberger's team's task will be to provide control measurements to help develop the electrical current measurement technology. “We already have an optical system that can detect whether a pore is currently open or closed,” says Nußberger. “But when it comes to the production of bionanopores, we still can't check whether a single pore is created in the relevant area of a membrane, which is what we want, or whether several pores are created, which means that measuring just the current alone could falsify the result.”

Prof. Christian Holm

"For us to succeed in all of this, we need to have a comprehensive understanding of nanopores and how they interact with proteins."

FROM BASIC RESEARCH TO PRODUCT DEVELOPMENT

The cluster members are then planning to extend the process to solid-state nanopores in a follow-up project. Nanopores, as Holm explains, "are pores in artificially produced thin membranes made of substances such as graphene." The pores would be only one atomic layer thick, because graphene is a two-dimensional material. "This," as Holm explains, "would mean that there could really only be exactly one protein building block migrating through a pore at any given time, which would enhance the signal resolution.” But, up to now, this is only a theoretical possibility, because we cannot yet produce these pores in a sufficiently reproducible manner. It would also be more of a challenge to measure the signal because it would be even weaker and shorter than that of bio-nanopores and there would be more background “noise”. But, on the other hand, solid-state nanopores would be more robust and would lend themselves to a greater range of uses and could be integrated into electronic systems. It would also be possible to place a large number of solid-state nanopores next to one another on a membrane, which would enable the measurements to be carried out in parallel: the optimal analyzer.

The cluster will operate for three three-year periods and will receive 45 million euros of funding from the German Federal Ministry of Education and Research. “What we want to do in the first three years,” says Holm, “is to lay the development foundations after which we'll turn our attention to the most promising approaches in the following three years, before devoting the final three years to creating the product.” ⇥

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Photos: Hahn-Schickard, Actome GmbH

MEDICINE OF THE FUTURE IN FIGURES

Whether it be cancer, heart attacks, diabetes, infections, rheumatism, or pneumonia, the list of common diseases that are far from being conquered despite all the medical advances is long. And this is in spite of the fact that Germany is spending more and more on health care every year and hit new highs during the Covid-19 pandemic, when significant amounts of money were spent on research and teaching, for instance in the search for new therapies, active ingredients, and substances, or to increase the level of digitalization in health-related research.

One key factor for achieving success in this field is the convergence of biology and engineering as well as computer and social sciences, a degree of interdisciplinarity that is daily reality at the University of Stuttgart, for example in the field of biomedical systems. So, even forgetting the direct training of physicians or the fact that it has its own clinic, the University of Stuttgart is making a considerable contribution to medical progress.

43 researchers are currently employed at the University of Stuttgart's Emerging Field of Biomedical Systems, where they are working in the fields of biotechnology and bioengineering, sensors and nanotechnology, and biointelligent devices and robotics.

> 100

To date, the German Research Foundation has initiated well over 100 research projects relating to the Covid-19 pandemic.

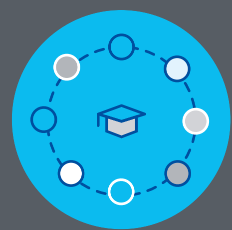
611 The University of Stuttgart's bachelor's degree program in medical engineering has produced 611 graduates since it began in the winter semester of 2010/11 since which time 452 students have completed the follow-up master's degree program. (Based on the latest figures from the summer semester 2022)

441,000,000,000

According to figures from the German Federal Statistical Office, healthcare spending in Germany totaled 441 billion euros in 2020. A further strong increase is predicted for the following years due to Covid-19.

1446 In Germany, there were medical technology manufacturers in 2020, whose total sales amounted to 34.25 billion euros – 2.9 percent more than in the previous year.

2007 The University of Stuttgart's "Simulation Technology" (SimTech) Cluster of Excellence was approved in 2007 and has been continuing to operate as the "Data-integrated Simulation Science" Cluster of Excellence since 2019. Right from the outset, the research carried out there into digital human models has made a lasting contribution to medical progress and continues to do so.



8 The University of Stuttgart offers 8 degree programs at the interface of medicine and technology, which cover Motion Science, Chemistry, Chemical and Bioengineering, Materials Science, Medical Technology, Simulation Technology, Engineering Biology, and Engineering Cybernetics.

REPAIRING BROKEN "SHOCK ABSORBERS"

TEXT: BETTINA WIND

Cartilage is hardly able to heal itself, and current therapeutic treatments leave much to be desired, which is why researchers are working on biomimetic and personalized solutions.

Joint pain is a common complaint that is often rooted in damaged cartilage.

Painful joints, swelling and limited mobility: some five million Germans are currently suffering from osteoarthritis, which is the world's most common joint disease. In medical terms, osteoarthritis means that wear and tear on the cartilage layer of the joints is greater than what would normally be expected given the patient's age and could even be caused by an accident or fall. "The forces acting between the bones are enormous. Healthy joint cartilage acts as a protective layer as well as a shock absorber, which enables the bones to glide across each other," explains Prof. Günter Tovar, who heads up the University of Stuttgart's Institute of Interfacial Process Engineering and Plasma Technology (IGVP), where researchers are collaborating with the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB to explore ways of repairing damaged cartilage.

By itself, cartilage only has a very limited ability to regenerate naturally due to the lack of blood supply and the small number of cells it contains. As Tovar explains, current treatments are not wholly adequate due to the fact there are different types of → cartilage with different structures: we have hyaline cartilage, which acts as a shock absorber between bones, elastic cartilage in the auricle (outer ear), and fibrocartilage, which serves as an anchor point for tendons and ligaments.

Prof. Günter Tovar heads up the Institute of Interfacial Process Engineering and Plasma Technology.

THE CHALLENGES ASSOCIATED WITH MODERN TREATMENTS

The fact that there are three subtypes of cartilage makes therapeutic interventions much more difficult. When treating joint cartilage damage, for example, surgeons deliberately damage the bone to cause a blood clot to form that contains stem cells, from which new cartilage cells can form. But what the body makes is fibrocartilage, which, by its very nature, is not designed to withstand the same compressive stresses as articular cartilage.

Another procedure involves taking articular cartilage from another part of the body and using it to construct new cartilage. Although these pieces of cartilage have near-optimal mechanical properties, they form a cartilage mosaic because they are the product of an injury to another part of the body. A different method involves extracting cartilage cells from the patient, cultivating them in vitro, multiplying them, and reinserting them after a few weeks, but this requires two operations, and it is not easy to create the right kind of cartilage.

Given these difficulties, the team at the IGVP is initially focusing on the internal structure of cartilaginous tissue. Articular cartilage consists of a macromolecular extracellular matrix whose key components are water and collagen, and is based around a triple helix, a structure that gives it high tensile strength and has virtually no elastic properties. The research team is using medical gelatin, which consists of fragments of collagen, to rebuild this triple helix structure. "What we're doing," Tovar explains, "is to give the cartilage cells the appropriate biochemical signals to make sure that they continue to differentiate and form the correct cell types giving us the basic frame, as it were, for intact articular cartilage tissue." The scientists make building blocks at the molecular level, which behave in as biomimetic a way as possible. "As long as the cells feel comfortable in the artificially engineered tissue, they can do their job and facilitate the regeneration of cartilage."

The researchers also want to make the soft cartilage structures compatible with other processing technologies to which end they apply a chemical treatment to the gelatin to make its consistency suitable for use in, for example, 3-D printer additive manufacturing. The researchers then work in interdisciplinary teams to complete the subsequent processing steps. "We rely on interdisciplinary team play," says Tovar, "especially when it comes to interfacial engineering."

PROF. GÜNTER TOVAR

"Healthy cartilage in joints serves as a protective layer as well as a shock absorber, which enables the bones to glide across each other."

FOCUS ON TISSUE REGENERATION

TriAnkle is an EU project that goes one step closer to practical application. "The objective of all of this," explains Pinar Koca, a doctoral student at the IGVP who is contributing to the project by researching cartilage regeneration, "is to develop clinically useful and personalized biological scaffolds for tissue regeneration in weight-bearing joints." This research consortium is composed of twelve partners in five European countries and includes organizations such as the Sports Clinic and the FC Barcelona Foundation. "Professional athletes and the clubs they play for," says Koca, "have a particularly strong interest in healing cartilage injuries rapidly and lastingly, which is why we are pleased to be able to contribute to the project by bringing in our findings from application-oriented basic research." ⇥

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Photos: Shutterstock, IGVP

Connecting the physical and digital worlds

Prof. Cattaneo and Dr. Qiu are working on the creation of next-generation in vitro models.

TEXT: JUTTA WITTE
PHOTOS: SVEN CICHOWICZ

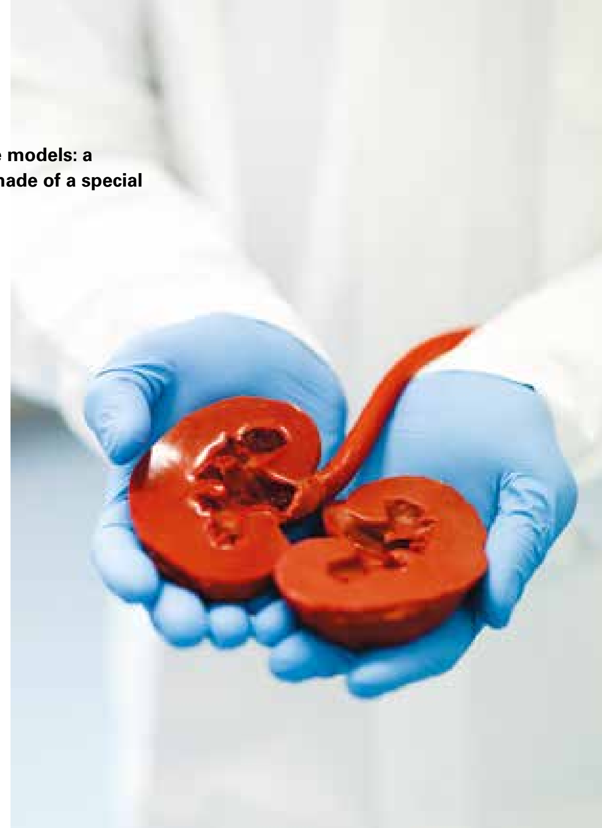
Models being developed by researchers working in the fields of medical and biomedical engineering will help to develop new therapies for increasingly complex minimally invasive procedures and will at the same time improve training for surgeons.

Before new medical devices, such as stents and catheters, are used in surgery, they undergo preclinical testing in models and animals. “However,” as Prof. Giorgio Cattaneo, head of the University of Stuttgart's Institute of Biomedical Engineering (BMT), says, “the models we've been using so far are too unrealistic.” One of the things he and his team are studying is microsystems used in the treatment of strokes and heart attacks. Normally, for example, stents, which are inserted via catheters into narrowed blood vessels in order to dilate them, are first tested in plastic models with simplified geometries and artificial blood. The problem with this, however, is that these models do not properly represent the anatomy of the vessels, the mechanical deformation they undergo when the heart beats, or the interaction between the material and the biological tissue.

Other concerns that biomedical engineer Cattaneo has is that the subsequent testing of the implants in animals is not only ethically problematic, but is also time-consuming and, given the differences between other animals and humans, not always conclusive. “There are a lot of factors that influence the mechanical, fluid dynamic, and biological behavior of vessels and contribute to the success and undesirable side effects of any minimally invasive procedure,” Cattaneo explains. Researchers are currently working on new models that adequately reflect the essential geometric, mechanical, and biological parameters in order to be able to analyze the interactions between technical and biological systems in a reliable manner.

Expert in Soft Material Engineering: Dr. Tian Qiu

Cattaneo has recruited the help of an expert in soft material engineering. Among his other commitments, Dr. Tian Qiu heads the Cyber Valley research group for "biomedical microsystems" at the Institute of Physical Chemistry (IPC) where he is advancing the development of so-called organ phantoms, i.e., anatomically correct models of human tissue, which not only look like real organs but also feel real. These "phantoms" which are equipped with sensors also provide the data needed to make the work →



Accurate models: a kidney made of a special plastic

Prof. Giorgio Cattaneo

“These models could help us to develop a new generation of medical devices."

Director of the Institute of Biomedical Engineering: Prof. Giorgio Cattaneo

→ performed by surgeons measurable and comprehensible, which means that they meet two different requirements: on the one hand, they provide insights into how any tissue created by the biomedical engineers responds to a given medical intervention and, on the other hand they provide important feedback on the surgical procedure, which means that they can help to improve surgical training.

"Students and junior doctors," as Qiu explains, "can use the hybrid models to familiarize themselves with new surgical instruments and try them out." The first of his "digital tutors" was created in collaboration with the University Medical Center Freiburg and consists of a, now commercially viable, model of a male urinary tract made up of three phantom organs: a kidney, urinary bladder, and prostate. Surgeons can use it to practice things like endoscopic bladder examinations.

Researchers welcome the new generation of models because they not only enable them to generate data, visualize organs, and document research progress in a practical manner and in real time but also give them the basis for the construction of a standardized training platform in which all conceivable scenarios including "worst cases" that even experienced physicians rarely encounter in real life can be experienced. Both researchers, who collaborate closely with the medical engineering sector on various projects, predict that in vitro models will soon bridge the gap between the physical and digital spheres. Cattaneo is convinced that "they could help us to develop a new generation of medical devices." Recently, he has been collaborating with Tian Qiu to integrate these models into his master's program. “Introducing aspiring medical engineers to the hybrid models of the future now is a good thing.” ⇥

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Tiny crystals to diagnose cancer

TEXT: MICHAEL VOGEL

Perovskite detectors could potentially improve radiological examinations. A team at the Institute for Photovoltaics is cultivating suitable crystals.

Radiological examinations are standard practice in the treatment of cancer. A frequently used technology for this is the computed tomography or CT scan, which whilst rendering a 3-D image of an organ, provides no information about its metabolism, which is unfortunate because one of the important indicators of the presence of a malignant tumor is a sharp increase in metabolism as the body needs a lot of energy to sustain uncontrolled cell growth. This is where so-called PET scanners come into play, which are used in Germany to diagnose various types of lung cancer and certain types of lymphomas.

PET scanners are huge and laypersons would find it hard to distinguish them from a CT scanner based on their outward appearance. Before the examination, patients have to drink a dextrose solution containing a radioactive marker, which provides energy to the cells, which is exactly what a tumor needs to continue its growth in the affected organ. This radioactive marker triggers reactions within the body, each of which produces two gamma quanta that move in opposite directions from one another. Gamma quanta are even more energetic than X-rays.

HIGHLY VERSATILE: PEROVSKITE SEMICONDUCTORS

The PET scanner uses specific crystals arranged in a tube shape around the body region to be examined to detect the gamma quantum pairs: these absorb the gamma quanta and convert the absorbed energy into light spectra, which can be used to determine the location of their origin in the body provided that the light spectra of both gamma quanta can be detected.

Each of these so-called scintillation crystals is only a few centimeters long, and a PET scanner tunnel needs around 60,000 of them to function. The basic idea is for the crystals to absorb as many of the gamma quanta as possible and convert them into visible light, in addition to which they need to be ready to receive a new gamma quantum as quickly as possible once this process is completed, i.e., to use the technical term, they need to have a short "dead time", which

is where Prof. Michael Saliba, a physicist who heads up the University of Stuttgart's Institute for Photovoltaics (IPV), comes in. He and his team are investigating potential applications for perovskites in the future including such things as PET scanner crystals. Perovskites, which are named after the Russian mineralogist Lev Alexejewitsch Perowski, are a newly discovered class of semiconductors in whose development Michael Saliba played a major role. "Perovskite semiconductors," he says, "are a class of materials that have fueled scientific research in countless fields within just a few years. Everything from solar cells to light-emitting diodes to lasers can be made from perovskites." Or scintillation crystals to use another name.

Perovskites contain heavy elements, such as lead, which means that they are really good at absorbing the gamma quanta emitted by PET scanners. "We've been able to → → grow suitable crystals for this purpose," Saliba explains. "They convert a high number of gamma quanta into visible light at low temperatures (around –196 °C) whilst still

Prof. Michael Saliba is head of the Institute of Photovoltaics. One of the expected results or his research on perovskite semiconductors is an improvement in PET scanners.

About

60,000

Scintillation crystals are needed in every PET scanner tube.

having a low dead time. That sounds like it could be costly to use these crystals in a PET scanner," the physicist continues, but we can use liquid nitrogen to get down to these temperatures, which is nothing unusual in medical practice. We cool things even further in hospitals to operate superconducting magnets."

INTERNATIONAL INTEREST IN RESEARCH BEING CARRIED OUT AT THE UNIVERSITY OF STUTTGART

A US-based company has taken an interest in the crystals being developed at the University Stuttgart and Saliba's team is now collaborating with them and the two project partners have already applied for a joint patent. "According to the data from the manufacturers," Saliba explains, "modern PET scanners can reliably achieve resolutions of 1.5 centimeters." "However," he emphasizes, "the lower dead time of our perovskite crystals may enable us to improve the resolution to less than a centimeter." And whilst a few millimeters difference may not sound like a lot, "it could be crucial for the early detection of a tumor." Philips, a PET scanner manufacturer, recently estimated the number of PET scans performed in the USA alone to be not far short of two million per year. "So this means that this development could potentially help a lot of patients and possibly save lives," Saliba said. ⇥

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Photos: Uli Regenscheit, Radiologie München

A new assistance system is designed to take the strain off surgeons during operations

TEXT: DANIEL VÖLPEL

**Surgeons who perform minimally invasive operations often have to remain in an uncomfortable position for extended periods.
A new personal assistance system designed by a team at the University of Stuttgart could relieve the strain on their arms and muscles.**

Technical Design expert: Prof. Thomas Maier

Operations on the brain or minimally invasive procedures in the abdominal cavity place heavy physical demands on medical personnel as Prof. Thomas Maier explains: “Laparoscopic and neurosurgical operations involve extremely long periods of holding still.” Maier is head of research and teaching in the Technical Design Department at the University of Stuttgart's Institute for Engineering Design and Industrial Design (IKTD). Ferdinand Langer, one of Maier's research colleagues, is all too aware of the potential consequences of frequently performing operations of this kind: “These prolonged and uncomfortable arm and upper body postures can cause long-term musculoskeletal disorders.” They also increase the risk of unintentional movements by the surgeons.

This is why Maier, one of the founders of the University of Stuttgart's medical engineering program, joined a research team a few years ago to look into how machines could support surgeons during operations, or more precisely, how they could lend them a helping hand. Their research resulted in a prototype for an arm-assist system, which was then developed in a joint project involving the commercial sector, the gynecological clinic and the Institute for Occupational and Social Medicine at the University Hospital in Tübingen, and the University of Stuttgart's IKTD and Institute for System Dynamics.

Langer, who has a master's degree in medical engineering, has been using the arm support device to conduct research on man-machine interfaces since November 2020. With funding from the German Research Foundation, he is exploring the question of how to create the best interface between this device and humans. “Surgeons,” as Langer →

→ explains, “have to be able to perform at any time, whether it be to carry out a minimally invasive procedure, an open surgical procedure, or to resuscitate a patient.” This is why we cannot have a quasi permanent connection between the user and the machine, as would be the case with a robotic suit (exoskeleton).

To demonstrate the arm assister system, Langer takes up a position in a setup that resembles the lifting mechanism of a forklift truck. As soon as he rests his forearms on the ends of two horizontal rods, the clumsy-looking device immediately follows his every movement instantly and fluidly. Better still, the system relieves him of up to 50 Newtons of the load that would ordinarily have been borne by his arms and can be adjusted as required thus counteracting the force of gravity.

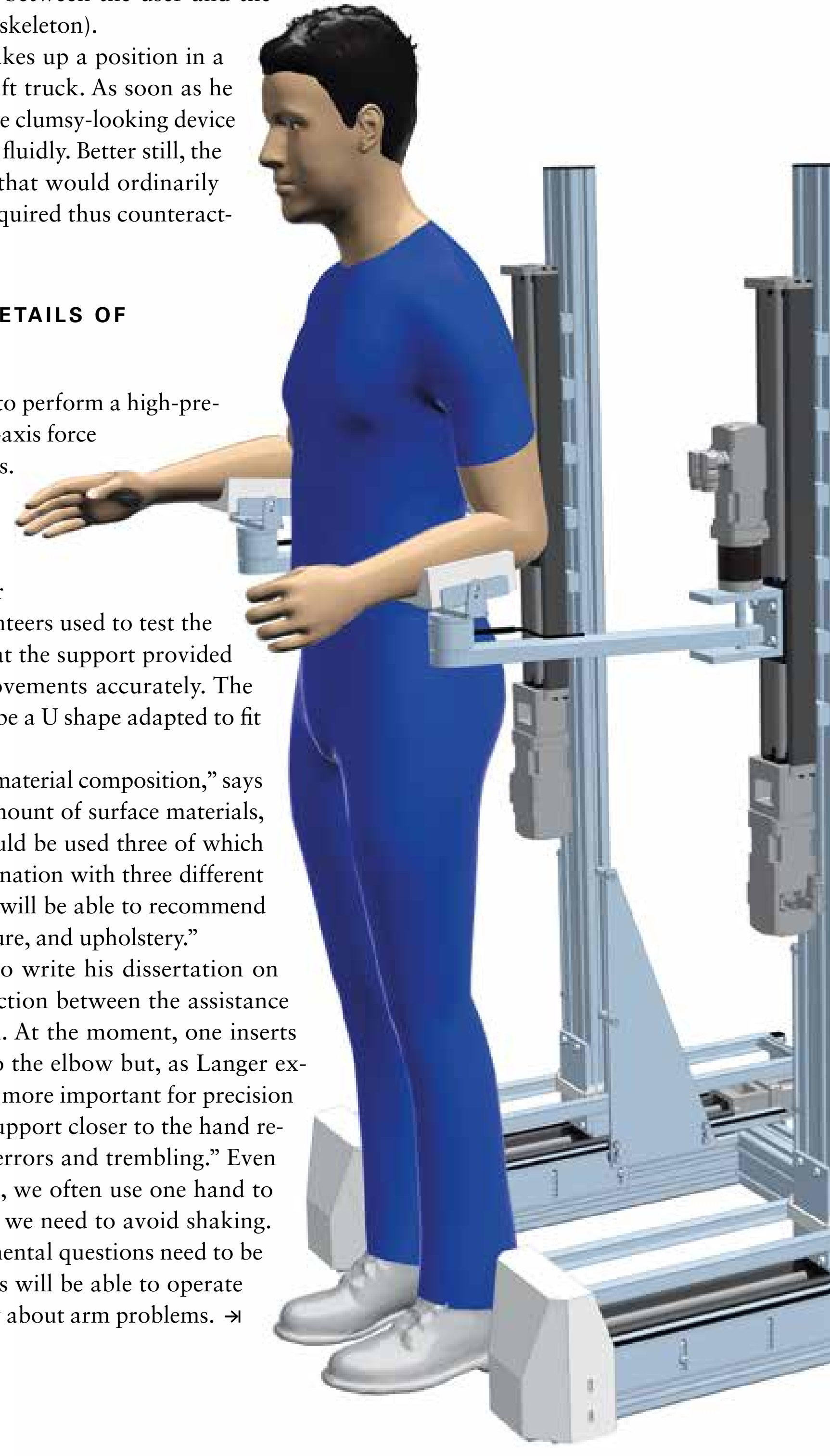
TEDIOUS DETAILED WORK ON THE SMALL DETAILS OF AN ASSISTANCE SYSTEM

But just resting one's arms on the device is not enough to perform a high-precision operation: directly below the forearm rest is a six-axis force sensor that measures every one the surgeon’s movements. “The wearer can move about a large radius and control the system through this interface, the force sensor,” Langer explains. To enable this, the sensor has to precisely detect all of the arm's movements. The researcher used 3D printing to create various arm rests that volunteers used to test the assistance system and one of the things he found is that the support provided by flat surfaces is insufficient and does not track movements accurately. The optimum and most comfortable armrest was found to be a U shape adapted to fit the human arm.

“Apart from the shape, we are also interested in the material composition,” says Maier, describing the subsequent research task. Any amount of surface materials, from artificial leather or cork, to rubber or plastic, could be used three of which Langer and at least 30 subjects will be testing in combination with three different padding designs in the spring of 2023. “In the end, we will be able to recommend certain design features in terms of shape, surface structure, and upholstery.”

Ferdinand Langer is researching man-machine interfaces.

Langer then plans to write his dissertation on how to form the connection between the assistance system and the surgeon. At the moment, one inserts one’s arms almost up to the elbow but, as Langer explains: “wrist support is more important for precision surgery as placing the support closer to the hand reduces the frequency of errors and trembling.” Even in everyday life, he says, we often use one hand to support the other when we need to avoid shaking. These and other fundamental questions need to be resolved before surgeons will be able to operate without having to worry about arm problems. ⇥



A new arm-assist system is helping to relieve the strain on surgeons' arms during operations.

Photos: Uli Regenscheit, Tobias Atzkern, University of Stuttgart/IKTD

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INTELLIGENT SURGICAL ASSISTANTS

TEXT: CLAUDIA ZÖLLER-FUSS

For the past 20 years or so, surgical robots have been common in German operating theaters. In this article, Prof. Peter P. Pott explains why autonomous surgery is still science fiction for the time being and why we still need surgeons.

Prof. Pott and his team are working on the development of robotic assistance systems.

Prof. Peter P. Pott grabs himself a coffee before the interview starts, which would usually take a couple of minutes – but not for the head of the Institute for Medical Device Technology (IMT). “It's hard for me to make it to the coffee machine without being stopped on the way,” he says with a laugh when he gets back to his small office. He takes his students seriously, which is immediately apparent when he talks enthusiastically about a student's bachelor's thesis that was recently discussed in the press. The student participated in the development of a robotic assistance system, or more accurately, a robotic scrub nurse, which hands the correct medical instruments to surgeons exactly when they are needed during operations. This is made possible through the use of artificial intelligence (AI). The integration of AI in operating theaters is one of three research priorities at the Institute for Medical Device Technology (IMT), which Pott has headed up since it was founded in 2017.

MEDICAL ROBOTICS HAS BEEN A TREND FOR THE PAST 20 YEARS

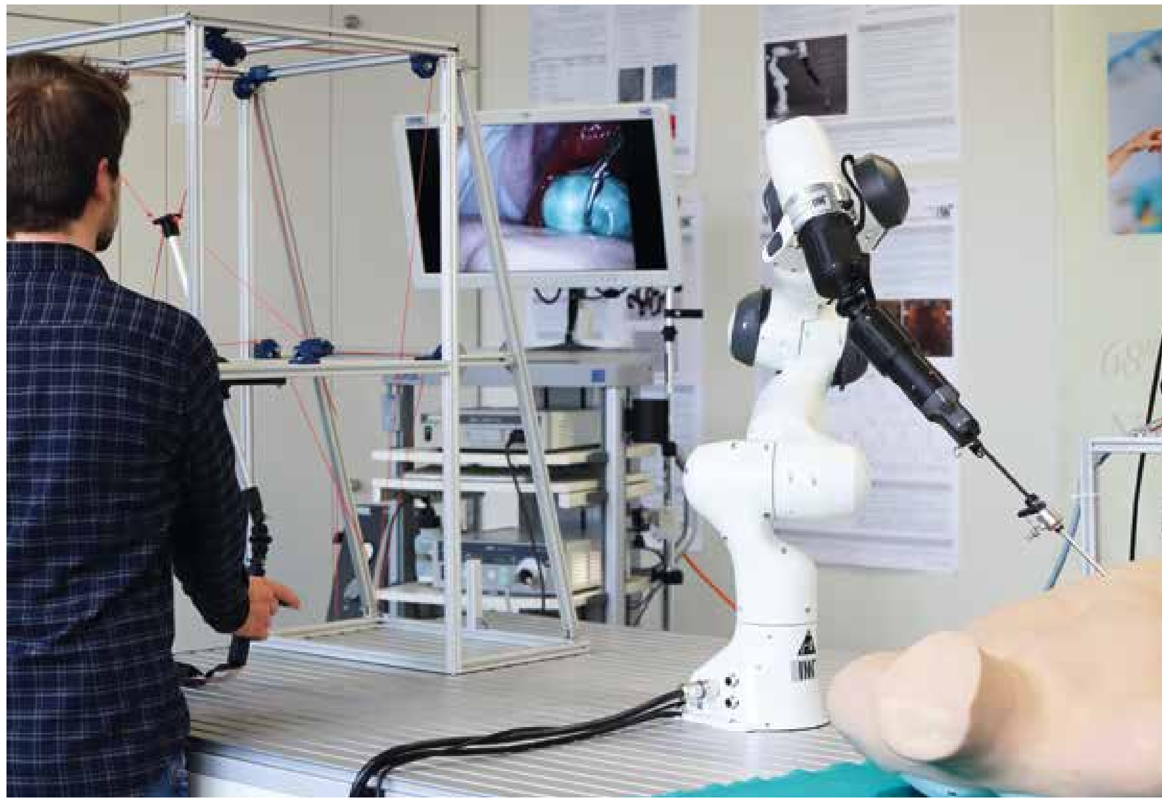
Robots have been standard in many German operating theaters since the late 1990s, which all began with a robot known as Robodoc, which was used in hip operations. It was one of a group of so-called automatic systems and was able, at least in part, to perform autonomously in the operating theater by following a set of predefined movement sequences. “Robodoc only performed a single process step autonomously,” Pott explains. So, although Robodoc was an innovative device, its use also resulted in some serious → injuries: many of "its patients" developed a limp after the operation, which came to be known as "Robodoc hip". So Robodoc was consigned to the scrap heap, and nobody wanted to talk about or hear anything about a medical robot for quite some time afterwards. Even today, Pott explains, we usually talk about assistance systems as opposed to robots.

DaVinci, a telemanipulation system on which the IMT is also conducting research, has been enjoying commercial success for the past 15 years. Unlike Robodoc, it does not act autonomously, but is instead operated by a surgeon throughout the surgery using a control console equipped with joysticks. “Nobody anywhere is pushing the idea of unmanned operating theaters at this point,” says Pott. “Mechanical aids will be controlled by human operators for a long time to come.” So nothing has really changed in operating theaters except that certain mechanical aids are now being used.

The main benefits of these systems are that they give surgeons a better view and improve their posture during surgeries. The operators sit at the operating console and guide the instruments via the control unit whilst a stereoscopic image is shown on a 3D monitor. “This greatly improves concentration and posture – and that's not to be underestimated,” says Pott. The main drawback he sees with this is that although the operators can see everything, they can't feel it – the connection is missing.

The IMT is trying to address this issue by developing mechatronic systems, which support the surgeons during the procedure, but without keeping them at a distance (alienating them). “Alienation can be thought of as a local anesthetic on a finger: you can still see it and maybe even move it, but you lose your sense of touch,” says Pott, explaining the approach. The MIT is attempting to resolve this problem, for example, by developing a system that measures the forces acting on patients during surgery and reporting them back to the surgeons, for example by replicating them in the joystick. To achieve this, it is equipped with tiny bidirectional motors that transmit pressure or resistance to the operator by mimicking the forces involved.

Indirectly, the IMT's second research approach, which involves proximity to the patient, is also intended to make the production of telemanipulation systems more cost-effective and thus more available. “In effect, if we develop technology that works excellently, but ends up being too expensive then it is only going to be used in industrialized countries, which,” as Pott explains in summary, “excludes large “swathes of humanity.” IMT researchers refer to this approach as "low cost", but he stresses, this does not →



A surgery being carried out with the aid of robotic assistant, which is controlled via an input device.

Photos: Giuliano Giacoppo, Bha Aldan Al-Abboodi

The robotics laboratory at the Institute of Medical Device Technology

→ mean cheap. Instead, it reflects an attitude in which, for example, the cost of healthcare systems in emerging countries is taken into account when considering new developments, the idea being to enable patients to access new technologies all around the world.

In addition to patient proximity and cost-effectiveness, the third of the IMT's research priorities concerns the use of AI in the operating room. The shortage of skilled workers is particularly noticeable in clinical settings. "In the past," Pott explains, "people used automation to cut costs; today, they use it because they don't have enough staff." The IMT's approach of using assistance systems to relieve staff, thereby freeing them to focus on more complex and important activities, is intended to help solve this problem.

The robotic scrub nurse mentioned above is one such assistance system. It is designed to hand surgical instruments to the surgeon in exactly the same anticipatory manner as an operating theater assistant, which sounds easier than it actually is because handing over and receiving surgical instruments and consumables is usually done under high time pressure and requires an understanding of the specific processes being carried out. "Operating theater assistants know exactly what the surgeons need at any given time, without having to be told," Pott explains, "they work as a team." "Surgeons simply don't have time for a robot that has to be told what to do."

Prof. Peter P. Pott

"Operating theater assistants know exactly what the surgeons need at any given time, without having to be told: they work as a team."

The robotic scrub nurse also has to solve a number of other problems such as distinguishing between sterile and non-sterile materials, coping with the limited space in the operating theater, being aware of the specific preferences of the surgeon performing the operation, and, of course, ensuring the safety of the personnel. "We are trying to use assistance systems, such as the robotic scrub nurse, to emulate these challenges," Pott explains. It uses a camera to get an overview of the entire surgical area, analyzes all the moves made by those performing the operation and compares them with its data, which enables it to understand the current surgical phase. Collaborative robotic arms enable safe interactions with humans in confined spaces. "Researchers are currently making great strides," says Pott, who is confident that the robotic scrub nurse and other assistance systems will one day be capable of performing even more complex tasks and that, with increasing experience, surgeons will also be able to use them for less common operations. He suspects that both →

Millimeter precision: a novel system for use in the intestine

→ augmented reality (AR), which is the computer-based enhancement of human perception, and instrumentation developed specifically for robots, will be used in the future. He also believes that some level of autonomy, comparable to a lane departure warning system in a car, will be feasible.

However, he is also convinced that the responsibility and surgical procedures will continue to be the preserve of humans for a long time to come. "The future is becoming more autonomous, but it will be some time before it is completely autonomous. I don't expect to see it any time in the next 10 years." ⇥

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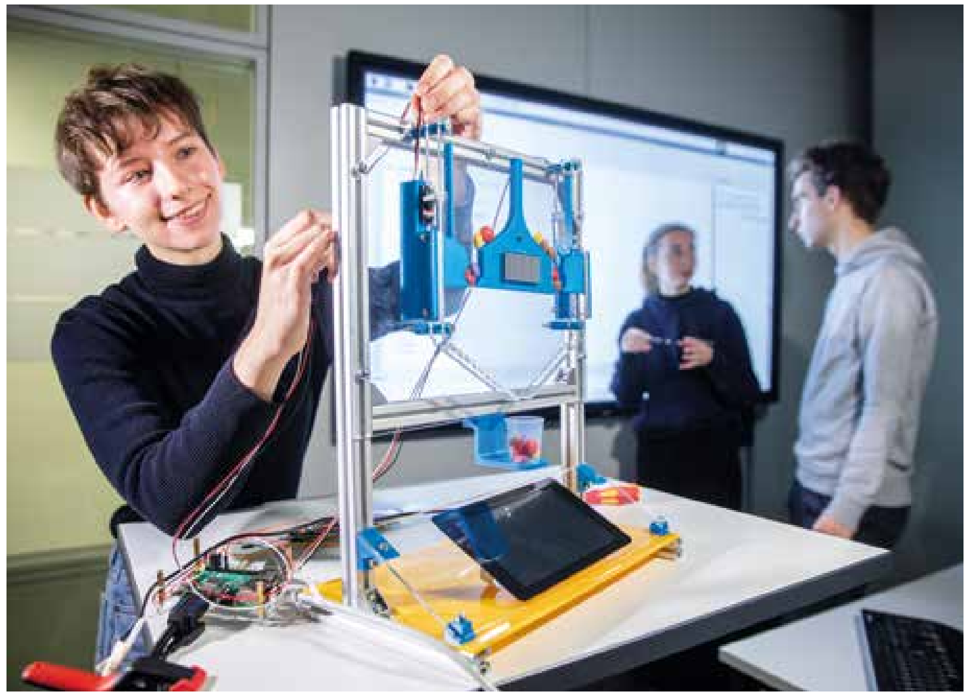
Photos: Max Schäfer, Giulano Giacoppo

Encouraging independent experimentation



Students are working on a novel drug dispensing model for Alzheimer's patients.

TEXT: MIRIAM HOFFMEYER
PHOTOS: ULI REGENSCHEIT

The MEDtechBIO program gives particularly talented students the opportunity to develop and implement their own project ideas: from drug delivery systems for people with Alzheimer's disease to researching pigments with antibacterial properties.

At first glance, the device looks like a marble run behind Plexiglas. Two small servo motors start moving as Feline Herrmann taps a touchpad. A Smartie separates from the colorful supply, slides down a chute, and lands in a small medicine beaker. A medical technology student collaborated with three of her fellow students to construct the prototype of a dispenser that reminds Alzheimer's patients to take their medication. “This project,” says David Kreickmann, “is a great opportunity for us to gain practical experience before we even complete our third semester; we are learning a lot here.”

The group of four successfully presented their dispenser idea as part of their successful application for a place at the MEDtechBIO "School for Talents" in the winter semester of 2022/23 – a program offered by the University of Stuttgart for particularly high-achieving students and funded by the German Research Foundation as part of the German federal and state excellence strategy. There are currently nine faculty projects being run at the School for Talents, as well as the "Annual Program," in which students work on innovative interdisciplinary projects. In addition to professional training, the program also includes personal development coaching.

TOGETHER FROM THE INITIAL IDEA TO THE END RESULT

Since 2020, almost 30 bachelor's and master's students in medical technology and technical biology have taken part in MEDtechBIO, where they gain project experience, prepare for competitions, and are given the opportunity to write their first papers for publication. MEDtechBIO is headed up by Prof. Peter P. Pott, head of the Institute for Medical Device Technology (IMT), and Jun. Prof. Michael Heymann of the Institute of Biomaterials and Biomolecular Systems (IBBS). “The idea is to teach students how to exploit their theoretical and practical knowledge,” says Heymann. “They are encouraged to break their projects down into a number of small steps as they move from the initial idea to the final → result, and to find solutions to problems on their own. At the same time, the students learn important lessons about teamwork and experience the success of working together to accomplish a common goal.”

The four students in the dispenser group first stripped down a dispenser for sweeteners, which they then used as a model to design a device adapted to Smartie dimensions. They used a laser cutter to cut some of the components to size, and modeled others to be 3D printed. The group is currently working on a particularly ingenious feature of their prototype, which involves programming simple memory and arithmetic tasks, which the patients are asked to complete on the touchpad before the medicine is dispensed as a kind of reward. Whilst these short tests are designed to be fun and to stimulate the brain, they also collect daily data on the development of Alzheimer's disease. “This,” as Kreickmann explains, “makes it possible to produce a very precise individualized record of the course of the disease.”

TRYING OUT NEW THINGS WHILST GAINING VALUABLE EXPERIENCE

Another ongoing MEDtechBio project involves research into pigments that have antibacterial properties. Eight students studying for bachelor's and master's degrees in technical biology are working on the production of melanin and carminic acid using bacteria and yeasts. The resulting pigments could be used in things such as vegan lipsticks or in dressings to promote wound healing. Carminic acid is a red dye currently obtained from dried cochineal lice, and eumelanin is a dark dye obtained from the ink sacs of cephalopods. Other substances are usually substituted in industrial production, but some of them are suspected of being carcinogenic.

Most days, the group gathers in the laboratory at the Institute of Biomaterials and Biomolecular Systems to continue their ambitious experiments. “We all help and motivate one another, and everyone contributes ideas,” says Fatma Caliskan, who is studying for her bachelor's degree. After the students isolate lice DNA, they use PCR equipment to amplify it and incorporate the DNA fragments into plasmids, which are ring-shaped double-stranded DNA molecules that can be absorbed by coli bacteria. “If everything goes according to plan,” Caliskan explains, “the bacteria produce an enzyme, which we can detect.” A number of challenges still need to be overcome, both when it comes to incorporating the DNA into the plasmid scaffold and in the detection of the enzyme, but this does not faze the group. “The laboratory practicals we do during our studies involve experiments with known outcomes,” says Caliskan. “But here we have the chance to try new things and design our own experiments. It's a great experience!” ⇥

One the groups at MEDtechBIO is studying pigments with antibacterial properties.

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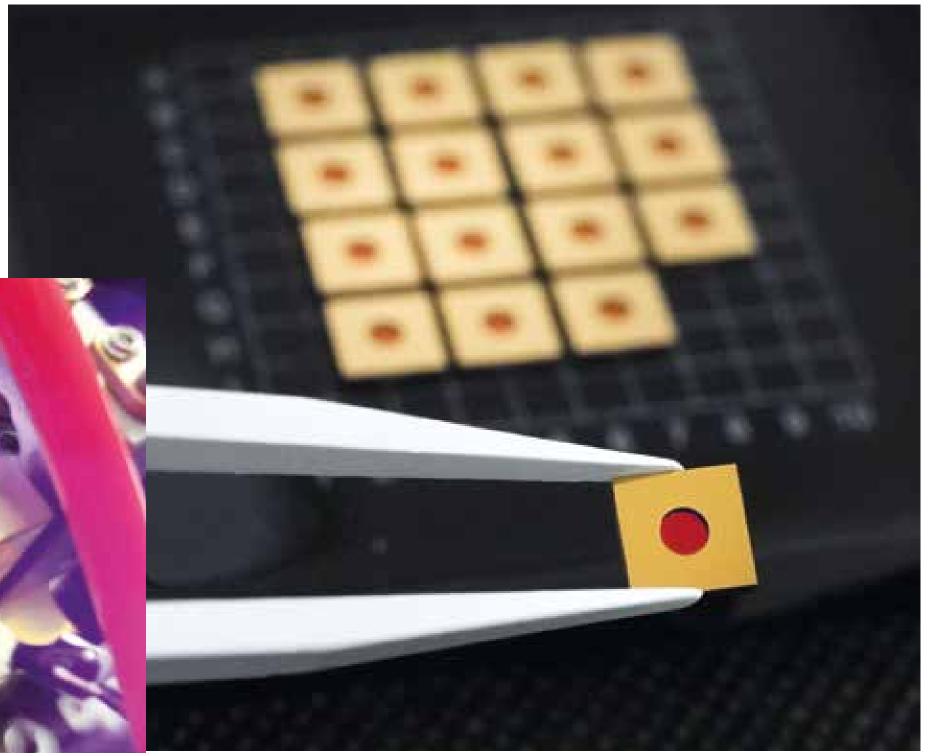
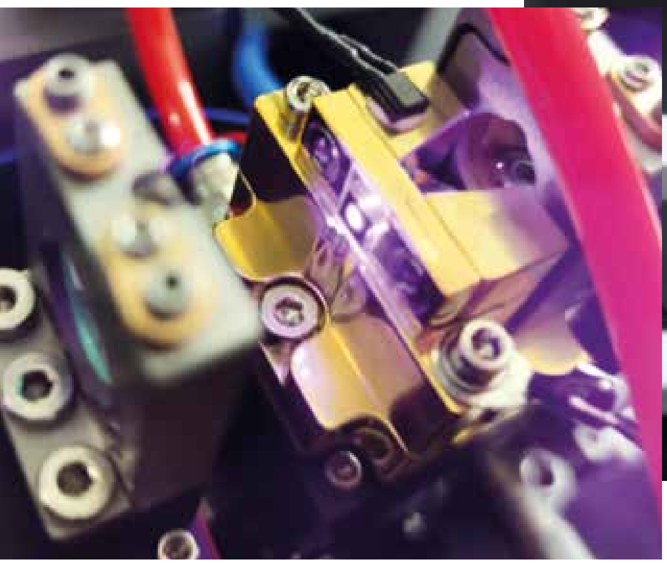
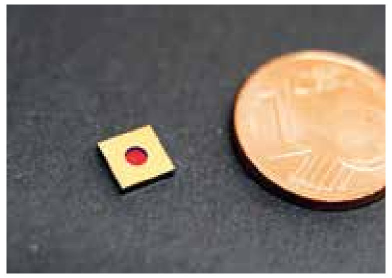
Special crystals for biomedicine





Quality assurance: laser crystals are scrutinized in a test module



Tiny MEXL crystals are one of the core components of lasers used in biomedical cell analysis.

TEXT: JACQUELINE GEHRKE

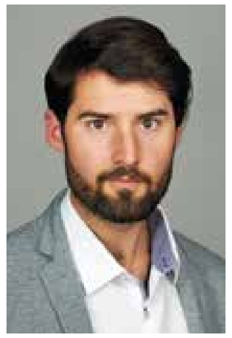
A University of Stuttgart start-up is using laser crystals to create new ways of performing biomedical cell analyses. The founders of Twenty-One Semiconductors became enthusiastic about laser technology during their physics studies.

At five by five millimeters, the crystal is smaller than a one-cent coin, but notwithstanding its minute dimensions, it could make a big difference for example for cancer patients, because this minuscule membrane external cavity laser (MEXL) crystal is the core component of lasers, which can be used to test the efficacy of therapies. These novel semiconductor membrane lasers are being developed for biomedical applications by Twenty-One Semiconductors (21S), a start-up spin-off from the University of Stuttgart. The company's founders, Dr. Roman Bek and Norbert Witz-Haszler, both alumni of the University, are developing them for new diagnostic and therapeutic applications in diseases, such as cancer.

Lasers generate light in different color spectra, whereby in the field of biomedical cell analysis, the yellow spectral range is particularly interesting as it enables researchers to → obtain much more information about the ratio of diseased to healthy cells. “Such cell analyses are performed regularly during a therapy to determine the ratio of healthy and diseased cells, which enables one to draw conclusions about the effectiveness of the therapy,” explains Bek, chief technology officer at 21S.

NOVEL LASER CRYSTALS ARE IMPROVING CELL ANALYSIS

“The unique feature of our MEXL crystals is that they can be used to produce compact laser systems, which emit light in the yellow spectral range,” says managing director Witz-Haszler. Many of the lasers used in biomedicine emit light in the visible range of the spectrum between 300 and 700 nanometers. We already have some highly developed semiconductor technologies for generating lasers in the red or blue range, for example, but not in the green-yellow range of the spectrum, which leaves the so-called yellow gap. “The reason for this,” Witz-Haszler explains, “"is that it is extremely difficult to manufacture efficient semiconductor lasers that emit yellow light, because of the materials involved. “However," he continues, "this part of the spectrum can be used to obtain essential information about diseased cell tissue, which is particularly useful for biomedical cell analysis. And it is precisely this information that our MEXL technology enables us to access by enabling the production of compact laser systems for the green-yellow spectral range.”



The company founders Norbert Witz-Haszler (l.) and Dr. Roman Bek

FROM STUDYING PHYSICS TO FOUNDING A START-UP

Founders Norbert Witz-Haszler and Dr. Roman Bek studied physics at the University of Stuttgart and were already enthusiastic about semiconductor and laser technologies at that time. They took the first step towards realizing their idea of starting their own company in late 2018. “Originally," says Witz-Haszler, "we only manufactured and sold semiconductor layers.” An EXIST-Gründerstipendium (a start-up grant available to German entrepreneurs) gave them the financial support they needed as well as free access to laboratories and equipment at the University of Stuttgart's Institute of Semiconductor Optics and Functional Interfaces (IHFG).

Eventually the two physicists went on to found Twenty-One Semiconductors GmbH in May 2019. “By the end of 2019, our sales had already put us in a position to fund ourselves,” says Bek. Then, in late 2020, they received a further cash injection from the High-Tech Gründerfonds to enable them to develop the MEXL crystals into a finished product.

“The great thing about our work,” says Witz-Haszler, “is that we get to apply what we've learned to launch technologies that make the world a better place.” The young entrepreneurs sell 95 percent of their laser crystals to manufacturers in the biomedical sector and are currently working on standardizing the production process. They also want to open up other fields of application. Witz-Haszler is confident about the future: “I don't think we've realized the full potential of our technology yet. There's still a lot that could be done with it." ⇥

Norbert Witz-Haszler

"The great thing about our work is that we get to apply what we've learned to launch technologies that make the world a better place."

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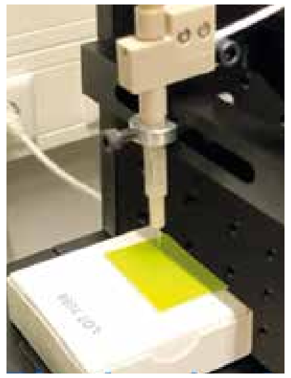
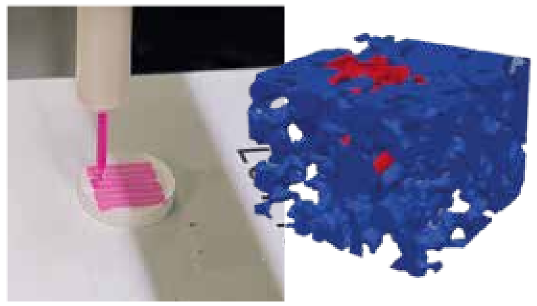
Photos: 21 semiconductors/Marieke Lienert

PRINTED MEDICATION





Experiments for precise dosages: colored drops of water are applied to a tablet.

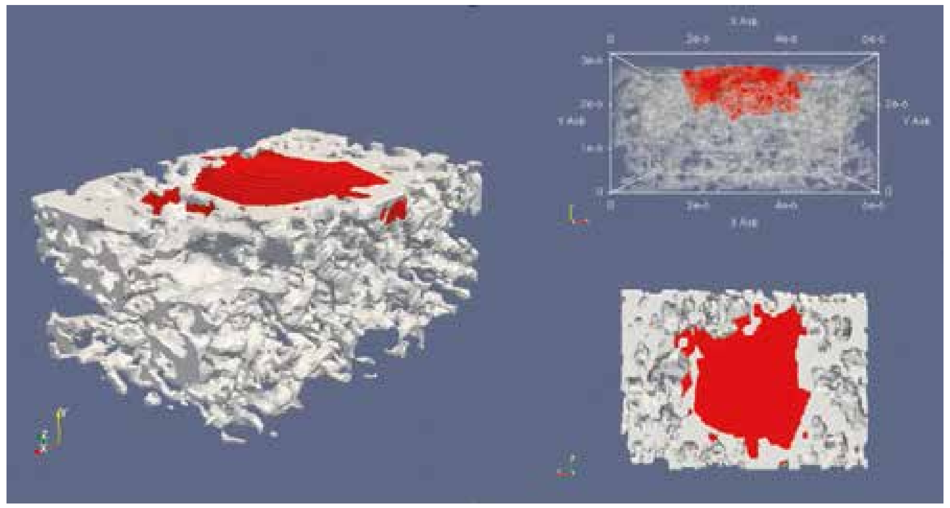
TEXT: FLORIAN BAYER

It will soon be possible to print precise doses of active ingredients onto tablets using special printers. Researchers at the University of Stuttgart are developing the basic tools for this in the "Printing personalized medicines on demand" (PrintMed) ERC project.

Most drugs are sold in standard sizes according to the "one size fits all" principle: painkillers, for instance, are available in tablets or capsules of 200, 400, and 600 milligrams. In some cases, the tablets can still be broken along a groove, and liquid active ingredients can be administered in the form of counted drops for more precise dosing. But what if there is a need to dose active ingredients even more precisely? Prof. Majid Hassanizadeh, Prof. Rainer Helmig, and Prof. Oliver Röhrle are conducting research into this issue at the University of Stuttgart. They are collaborating in an ERC project called "PrintMed" to develop a method for applying a specific strength of the active ingredient to tablets using special "printers", which are similar in principle to inkjet printers. The aim is to be able to give patients the correct dose depending on their age, gender, weight, and diagnosis.

The project is still in the transition phase from theory to practice. Hassanizadeh, a fluid mechanic who holds a senior professorship at the University of Utrecht in the Netherlands, is primarily concerned with the physical properties of the active ingredients and tablet bases, whereas Helmig and Röhrle, both modelers, are mainly interested in mathematical simulations. The task they have set themselves is anything but trivial because the plan is to spray the active ingredients onto the surface of the tablet blank in the form of tiny droplets that will then seep into it. This raises the question of what the consistency of the powder from which the tablet is made needs to be: too porous and the tablet will crumble apart too soon; too hard and the droplets would not be able to be absorbed into it.

An initial version of the tablet blanks, which could be printed in the future, was developed during an earlier phase funded by an ERC Proof of Concept Grant, which Hassanizadeh received for the project, which he completed in collaboration with Hamed Aslannejad. The researchers used theoretical simulations performed on supercomputers, as well as innumerable practical experiments, whose results they observed using high-precision imaging, to create a tablet powder that is neither too porous nor too solid. They were also able to determine the optimum parameters for the printing process, for example with regard to the air flow during printing. →



A liquid seeping into a porous substrate.

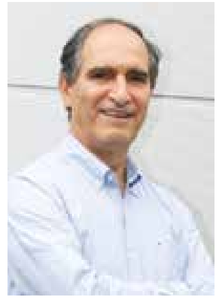
→ HUGE POTENTIAL FOR PERSONALIZED MEDICINE

Initial tests using an active ingredient known as clonidine were successful. Clonidine is used to treat high blood pressure as well as elevated intraocular pressure and a range of other conditions. The studies found that the active ingredient contained in the tablet was released in under 15 minutes, which the researchers consider to be a satisfactory result.

"The potential for additive manufacturing technologies, such as the machine printing we are studying, to transform personalized medicine is enormous," says Majid Hassanizadeh. "In particular, liquid printing facilitates a rapid and accurate delivery of liquid active ingredients." Originally from Iran, Hassanizadeh has been researching at the University of Stuttgart on and off for almost 20 years and holds an honorary doctorate from the University. He has also been working closely with Rainer Helmig for many years.

"Our extensive scientific exchanges over the past two decades have put us in the fortunate position of being able to open up entirely new fields of research related to porous media and to train some excellent young researchers," says Helmig. Along with his colleague Oliver Röhrle, he draws particular attention to his close, interdisciplinary collaboration with Hassanizadeh at the Data Integrated Simulation Science (SimTech) Cluster of Excellence as part of the International Research Training Group (ITRG 1938) "Non-linearities and Upscaling in Porous Media (NUPUS)" and the "Interface-Driven Multi-Field Processes in Porous Media – Flow, Transport and Deformation" Collaborative Research Centre" (SFB 1313).

The researchers are currently focusing all their efforts on ensuring that the printers will soon be able to produce targeted and precisely dosed medications on the premises of pharmacies or hospitals, and are hoping to succeed in this as early as 2024 or 2025. ⇥



Fluid mechanics engineer Prof. Majid Hassanizadeh

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Photos: University of Utrecht / Uli Regenscheit

The opportunist

Prof. Laura Na Liu and her team are working at the interface between nanophotonics and DNA nano engineering, which

requires a lot of finesse as the researchers use nano-engineering processes to create test devices.

TEXT: MICHAEL VOGEL
PHOTOS: MAX KOVALENKO

Laura Na Liu, a native of China, is an internationally renowned scientist, who works in the field of DNA nanotechnology. She is currently conducting basic research at the University of Stuttgart which, among other things, could also prove beneficial to medicine in the future.

Natural selection has produced many ideal solutions to various problems, Cells, which house the perfectly tuned machinery of life, being just one example. They can grow, divide, move around, metabolize food and energy, and respond to stimuli. “Our goal is to mimic some of the crucial properties and functions of cells,” says Laura Na Liu. The physicist wants to study natural models in order to develop artificial nanosystems – bionics at the nano scale. Liu has been a professor at the University of Stuttgart since 2020 and is the director of the 2nd Physics Institute. Her 15-strong research group is conducting → research at the interface between nanophotonics, i.e., using nanometer-sized structures to manipulate light, and DNA nano engineering.

In one example, she and her team drew inspiration from the ATP synthase enzyme's mode of operation, which can transport hydrogen ions across cell membranes in a highly energy-efficient manner. The way the enzyme works is similar to a motor driving a pump. Liu and her team are using DNA strands, which they assemble and fold in a highly refined process, as the building blocks for mimicking this molecular motor. This creates new molecular bonds between the strands of DNA, which produces the desired structure, which could be either two- or three-dimensional. “It's a bit like knitting a sweater,” Liu explains: “You begin with a lot of individual threads, which you then artfully weave together to create the desired shape.”

Liu's team is also taking another approach in addition to this one, which involves the use of semiconductor technology to produce metallic nanostructures, which can, for example, be coated with a functional polymer. An electrical voltage can then be applied to control the optical properties of these hybrid structures. In the future, the basic research that Liu is conducting could result in new types of minuscule but highly sensitive sensors, or perhaps in new ways of transporting active substances to the desired location within the human body.

Liu has received numerous awards for her work as well as funding from the German Physical Society (DPG), the German Research Foundation (DFG), the Max Planck Society, the EU, the Alexander von Humboldt Foundation, the European Optical Society and the Optical Society (now Optica). At the University of Stuttgart, she is a member of the "Biomedical Systems" Profile Area coordination team, in which various faculties collaborate on an interdisciplinary basis, not least with a view to attracting young scientists to this exciting field of research.

FROM NORTHEAST CHINA TO SOUTHWEST GERMANY

Liu was born in Shenyang in northeastern China in 1979. Shenyang is located 700 kilometers from Beijing, 250 from the North Korean border, four hours by plane to Hong Kong, and an 18-hour flight to Stuttgart. Although she had already displayed a talent for physics in secondary school, she did not initially intend to pursue a degree in the subject. Eventually, however, she did enroll in a bachelor's degree program in physics at a university in a neighboring city before going on to complete her master's degree in Hong Kong.

Towards the end of her studies, Liu had made up her mind to go abroad to work on her doctorate: “I wanted to see the world out there.” She considered the USA and Singapore as possible destinations but that was before she was visited by a friend who →

→ was pursuing his doctoral studies at the University of Stuttgart. “He told me how much he enjoyed the working group he was in and that Europe was an interesting place to travel to because of the many different cultures there,” Liu recalls.

The working group he was referring to was headed up by Prof. Harald Giessen, then head of the 4th Physics Institute. Following a single phone call to Giessen, Liu had been accepted for the doctoral position. “He then gave me carte blanche to do whatever I wanted,” she says. “If something caught my interest, I was allowed to pursue it.” This turned out to be a productive arrangement: doctoral candidates are expected to publish three papers – Liu published eleven!

Yet, she recalls her relocation to Europe as a "culture shock." Apart from the names of some of the car makes manufactured there, she knew nothing about Stuttgart. "My first Sunday downtown after arriving was unsettling," she recalls. "Where were all the people? All the shops were closed. I grew up in Asia and was used to always seeing people, everywhere." Fortunately, she says, there was a very good, international atmosphere in her work group, which helped her to settle in.

IMPETUS FOR A NEW RESEARCH FOCUS IN THE USA

Around the time she was finishing her doctoral studies, a chemist named Paul Alivisatos, who was then working at the University of California at Berkely at the time, came to Stuttgart to give a lecture on the synthesis of nanostructures from molecular building blocks. Liu got talking to him after his presentation, and he invited her on the spot to become a postdoc in his research group. This opened up a whole new world for her, as this way of producing nanosystems was completely different. “That period triggered my current research focus,” says Liu.

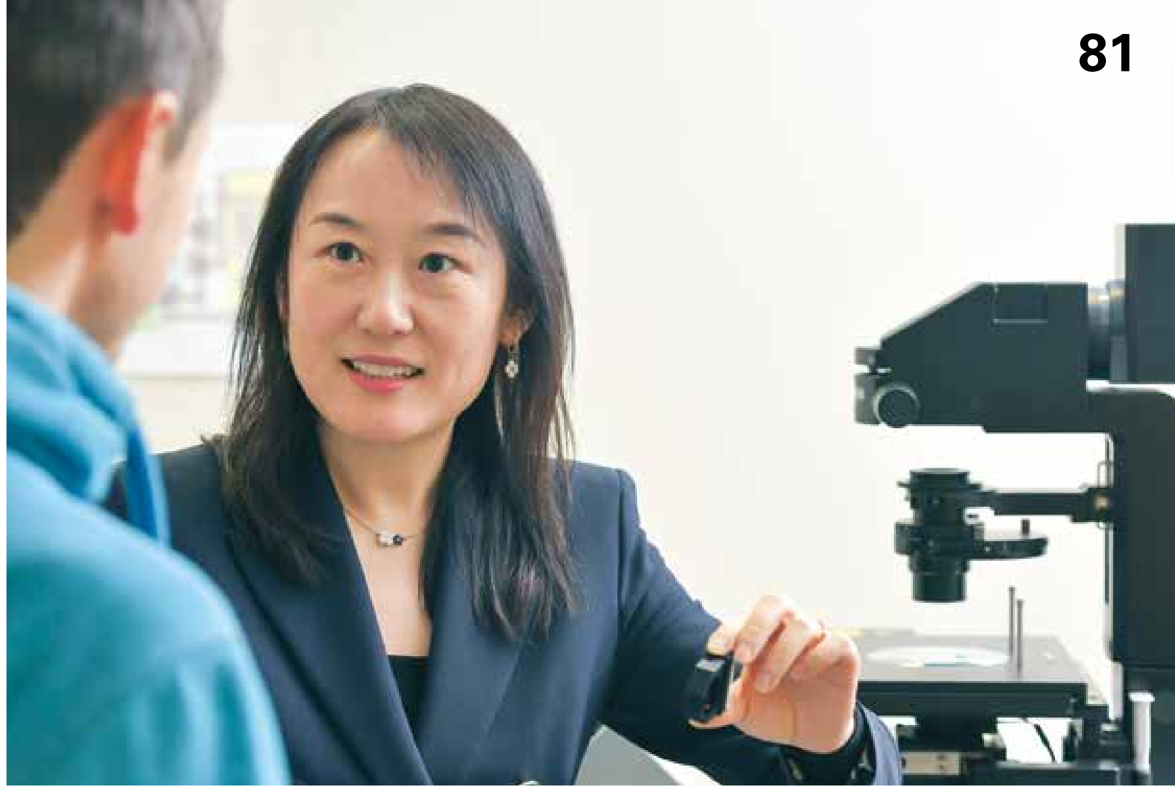
Following her time at Berkeley she completed another postdoctoral period at Rice University in Houston, Texas, where “working with Naomi Halas, another renowned nanophotonics researcher, I learned that success doesn't last forever, nor are all mistakes fatal, but that courage, perseverance, and enthusiasm are essential.”

RESEARCH AT THE MAX PLANCK INSTITUTE

All told, Liu spent about three years in the USA before returning to Germany. “I received an offer from the Max Planck Institute for Intelligent Systems to head up a financially independent research group, which was too tempting to turn down.” The Max Planck Society institutes”, she says, are "a total paradise" for scientists adding that these →

Prof. Laura Na Liu

“Whenever an opportunity came up, I grabbed it.”



Laura Na Liu heads up the 2nd Physics Institute at the University of Stuttgart and is a leading researcher in the field of meta materials.

Prof. Laura Na Liu

“By now, Stuttgart has become my second home.”

→ are world leading research institutes, which enable one to carry out cutting-edge research and participate in extremely attractive collaborations.

Apart from the job offer, she also had private reasons for returning to Stuttgart: her husband, also a physicist, whom she had met and married whilst studying in China, was working in Europe and is currently working at one of the Max Planck Institute for Medical Research’s sites in Stuttgart.

After heading up the Max Planck group for three years, Liu accepted a professorship at the Ruprecht Karl University of Heidelberg in 2015, and was offered a professorship at the University of Stuttgart in 2020, back where she first put down roots in Germany. None of this was planned: “It’s just the way it panned out,” says Liu looking back. “Whenever an opportunity came up, I grabbed it.” And, she adds, she always looked for jobs that would give her a lot of freedom. “By now, Stuttgart has become my second home.” ⇥

Laura Na Liu talks about the importance of nanotechnology and offers advice to young scientists in the University of Stuttgart's "Made in Science" podcast.

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AN ENGINEER DEDICATED TO A WIDE RANGE OF GOALS

Photo: Carl-Zeiss-Stiftung

TEXT: MIRIAM HOFFMEYER

Having completed his studies at the University of Stuttgart, medical engineer Lukas Findeisen now works at the interface between science and society.

Lukas Findeisen has been interested in how new technologies might contribute to a fairer and healthier society since the first semester of his medical engineering studies. “I believe that engineers have a huge responsibility to the public,” says the 30-year-old, who has been working as a program manager for Artificial Intelligence (AI) and Life Science Technologies (LST) at the Carl Zeiss Foundation in Stuttgart since late 2021, where he helped to develop the foundation's new ten-year strategy. “Working at the intersection between politics, science, and business is incredibly exciting,” says Findeisen.

The new development strategy prioritizes AI, LST, and resource efficiency each of which, as the medical technology expert explains, will be focused on four action areas. “For the life science technologies, that means sensors, surfaces, data, and synthetics,” he explains, “appropriate projects might cover such things as ingestible diagnostic robots, implant surfaces, the AlphaFold AI, which can be used to design proteins, or the production of tissue fragments that can be used in the development of personalized medicines.” University research projects in each of the four action areas will be eligible for support as will transfer projects at universities of applied sciences. The first calls of tender in the field of sensor technology have already been published. “ carry out the formal review of the applications received and oversee both the selection and implementation of the projects,” says Findeisen, whose responsibilities also include 21 ongoing projects, which are receiving support: “This gives me an insight into an extremely wide range of cutting-edge research topics, which is incredibly rewarding for me!”

Findeisen grew up in Bochum before relocating to the southwest in 2012 to complete a joint bachelor's program in medical technology at the universities of Stuttgart and Tübingen after which he completed a master’s degree at the University of Stuttgart in 2020. “Not only did I receive an excellent professional education and learn many technical skills,” he says, “but I also met some great people such as Prof. Stephan Nußberger, who supervised my bachelor’s studies. My class was only the second intake to complete the bachelor's program. I was involved in setting up the student council at the time and am very grateful that we were given such a free hand. We students were involved in everything, from shaping the curriculum to evaluating the quality of teaching.”

Lukas Findeisen

"I'm convinced that groups in which power is distributed fairly make better decisions."

Findeisen spent almost two years as Manager of Innovation and Digitization Projects at the Baden-Württemberg State Association of the German Red Cross, which he continues to advise, before switching to the Carl Zeiss Foundation. He does volunteer work for "Decentrale," an organization that he co-founded, which develops workshops and other learning events on issues such as intersectionality and inclusive leadership from a feminist perspective. “I'm convinced that groups in which power is distributed fairly make better decisions,” he explains. “One of the overriding concerns for our generation is to challenge the overall distribution of roles to improve things for everyone.” ⇥

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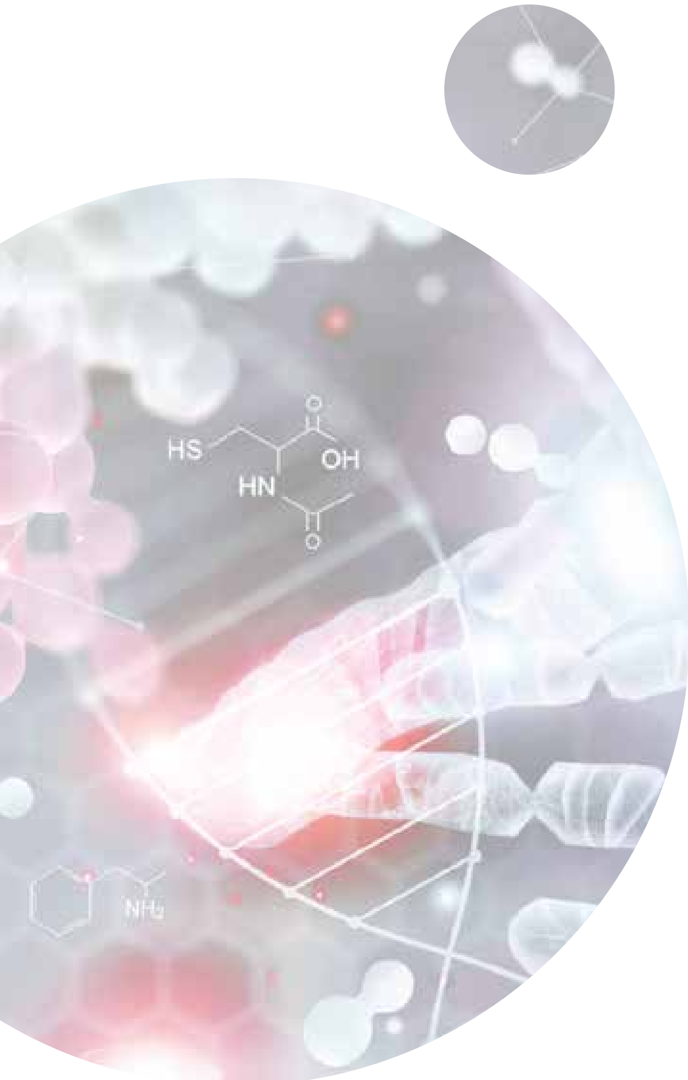

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