B56133

Max Planck RESEARCH

The Science Magazine of the Max Planck Society 2020

Max Planck Innovation

MAGNETIC RESONANCE IMAGING
A live link to the root of the disease

DRUGS
Brake for breast cancer

NEW MATERIALS
Ivory from a test tube

SPECIAL

STIFTERVERBAND

TOGETHER WE CAN DO IT!

At the Stifterverband, corporations and foundations have been working together for 100 years to make our country competitive and innovative. We make it possible to explore new worlds. We are working towards leading our schools, universities and research into the future. Support us in this endeavour – become a part of the Stifterverband.
www.stifterverband2020.de

Ad multos annos: to the next 50 years

Prof. Dr. Dr. Andreas Barner, President of the Stifterverband für die Deutsche Wissenschaft and Vice President of the Max Planck Society

Experience has shown that translating the knowledge generated by basic research into practice is by no means an easy task. For this reason, it is all the more important to have efficient, continuous innovation chains that bridge the gap between business and basic research. In this situation, it is quite often necessary to engage with questions raised by applied research in order to prepare ideas for implementation. Functional innovation chains are of particular, even fundamental importance, particularly in Germany with its outstanding basic research and globally competitive economy.

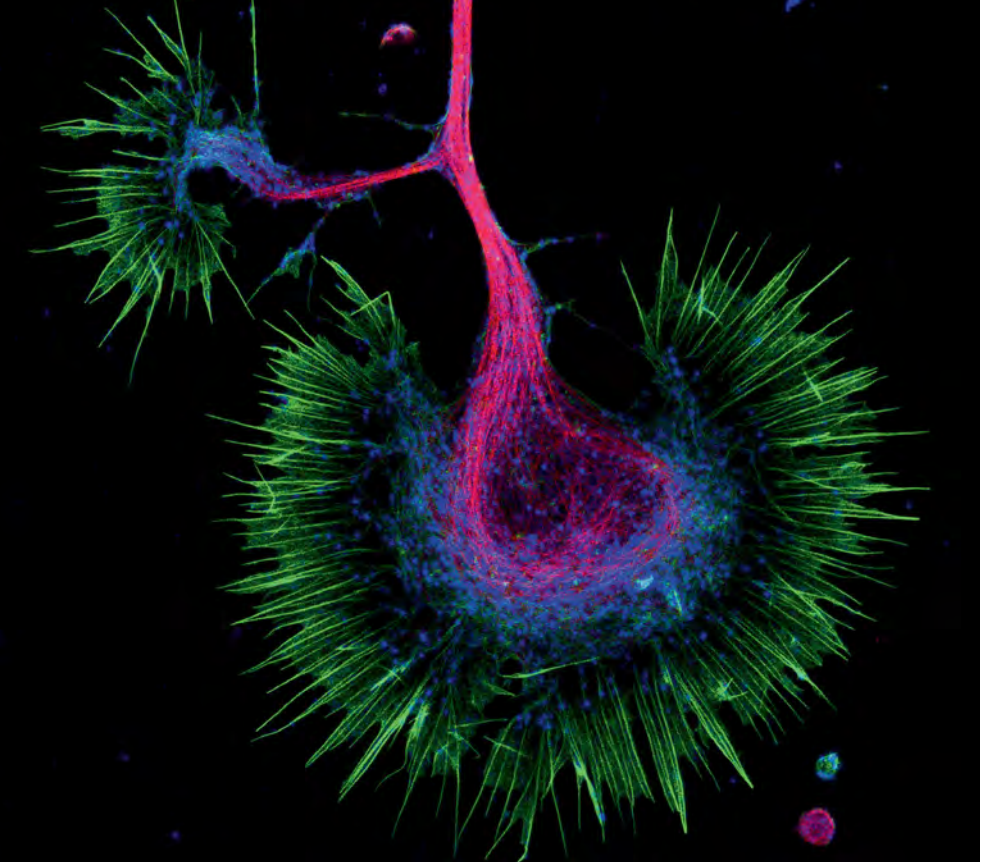
Basic research has one goal: to make crucial discoveries and advance human knowledge. Its value comes from its exploration of the unknown, and its significance in practice is often not immediately recognizable. During the 20 years or more of research history that led to the discovery of genome editing systems such as CRISPR-Cas, it would have never been possible to "ask for" the invention of an easy to use and precise gene editing tool. Over the course of many years, during a process of free, unplanned interaction between numerous scientific stakeholders, a large body of seemingly "useless knowledge", relating for example to unusual, repetitive DNA sequences and an exciting type of immune system in bacteria was generated – until finally a "eureka" moment occurred and the scientists reached an understanding of individual gene editing mechanisms. Today, the resulting technology has not only revolutionized genetic research, but also opened up new treatment options in the field of medicine along with many other applications.

This example not only shows the value of basic research but also illustrates how important it is to be able to digest and question the opportunities that arise from basic research findings, also in terms of possible applications. It also displays the courage to enter into dialog with scientists who have basic research in their sights and applications or applied research in mind. Here, Max Planck Innovation (MI) plays an essential role, not only formally as a technology transfer organization, but also as an institution that is changing perspectives in basic research.

MI understands the excellent basic research conducted independently by the Max Planck Institutes and can apply it at the right time in a way that is solution-oriented and "driven by the product". The organization is therefore an important bridge builder between science, business, and society. As reflected by its collaboration with Boehringer Ingelheim, MI is open to new models of cooperation between research facilities and start-ups, SMEs and larger companies, for example in certain areas of indication where the goal is to identify and optimize novel, therapeutically effective substances and develop them to the stage of validated leads that are effective in in-vivo model systems. Joint efforts are also being made to establish spin-offs from Max Planck Institutes. The Boehringer Ingelheim Venture Fund is involved in the early rounds of financing for such spin-offs. This is in keeping with Boehringer Ingelheim's strategy of investing in groundbreaking biotechnology companies that focus on therapeutic products and create innovations in biomedical research.

The professional work of Max Planck Innovation is making a highly favorable impression in this respect. As a rule, the quality of the patents is exceptionally high. In their capacity as competent contacts, the staff at MI understand the needs of both company founders and investors while ensuring that the MPG is involved as needed. As negotiating partners, they are tough but invariably fair, with sound judgment and consideration for all those involved. In terms of content and processes, MI is also more than competitive when compared with international transfer offices. As the central point of contact, MI brings together the creativity and pioneering spirit of scientists and start-up founders and the expertise of the business world with the aim of finding new solutions to the challenges facing society. In this way, it encourages us to try out more new things, leave the well-trodden paths and take more risks in Germany. We will need Max Planck Innovation for another 50 years at least.

Photo: Boehringer Ingelheim



24 The axon of a nerve cell uses a growth cone to search for its target.

CONTENTS

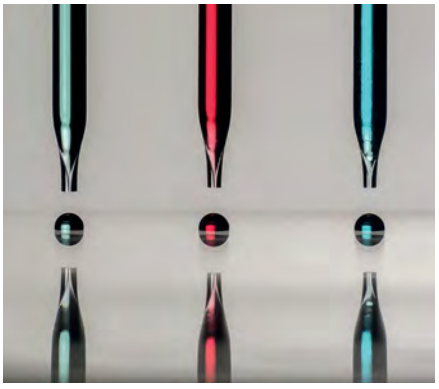
06 With more risk capital, it would be easier for ideas from basic research to be put to practical use.

Max Planck **Innovation**

The technology transfer organization of the Max Planck Society has forged a link between science and business since 1970. Max Planck Innovation advises and supports Max Planck scientists in assessing the potential of an invention and applying for patents. It also markets patents, technologies and know-how to industry and is on hand to help new entrepreneurs set up their business who convert the research results from the Max Planck Society into products and services.

Photo: Abberior Instruments GmbH; illustration: designergold

44 Katharina Landfester is researching new applications for nanocapsules in industry and medicine.



54 Scienion prints biomolecules on carrier media – and has now become very successful in this area.

58 An Evotec scientist during an electrophysiological experiment.

Photos: Frank Vinken; Scienion; Evotec (left to right)

We have to do a better job of utilizing our own ideas

The Max Planck Society is a basic research institution with a mission that the theoretical physicist Max Planck, after whom the MPG is named, once expressed as follows: "Insight must precede application." The insights gained into the laws of nature and society, into structures and contexts, are what create the basis for true innovation. The world of tomorrow and the day after tomorrow will build on the knowledge gained through this research.

TEXT **MARTIN STRATMANN**

Basic research is the most important way to find innovative solutions to major problems. However, the wealth of new ideas first has to be sifted in order to filter out those with potential for practical application. Next comes the lengthy journey from idea to marketable product, a journey that is not only risky and potentially doomed to failure, but also extremely expensive.

Back in 1970, with this in mind, the Max Planck Society established one of the first technology transfer institutions in Germany; formerly named Garching Instrumente, this company is now known as Max Planck Innovation GmbH. Over the last 50 years, the company has supervised more than 4,500 inventions and concluded 2,500 license agreements. Almost 80 percent of the roughly 160 spin-offs supervised by Max Planck Innovation are still in business today; seven of them have even made it to the stock exchange. Measured by its income of approximately EUR 500 million, Max Planck Innovation is one of Germany's leading technology transfer organizations, the other being Fraunhofer.

Germany has enormous scientific potential. We have to mobilize this for innovations in all sectors. In its expert opinion of 2019, the Commission of Experts for Research and Innovation (EFI) directed by Dietmar Harhoff of the Max Planck Institute for Innovation and Competition emphasized the special part played in the innovation system by start-ups whose new business models and products provide important stimuli for the economy.

Over the last few decades, the Federal Government has set up various funding lines for start-up founders in order to foster greater enterprise. Nevertheless, the German enterprise birth rate remains unchanged at 4.97 percent; Germany's performance in the Global Entrepreneurship Monitor for 2018/2019 is only mediocre. One of the key recommendations of the EFI is therefore to continue accelerating the country's start-up culture in order to promote start-ups from within the scientific community.

> Start-ups provide important stimuli for the economy

The Max Planck Society accordingly wishes to encourage young researchers to explore the potential applications of their scientific findings in greater depth. Here scientific excellence and economic success are

Illustration: designergold

not mutually exclusive. On the contrary, the Max Planck Society's Nobel Prize winners in particular have always kept potential applications in their sights. They include Manfred Eigen, for example, who was awarded the Nobel Prize in Chemistry in 1967 at just 40 years of age. In the 1980s, he put his theories about the self-organization of complex molecules into practice by developing so-called evolutionary machines. The company Evotec based its business model on bioreactors capable of accelerating this natural process. This makes it possible to identify new molecular substances, which can then be used to develop new pharmaceutical drugs. In 1993, Eigen not only gave the new biotech company his patents and the necessary machinery, but also furnished it with capital and became one of its co-founders. It is now one of the most successful on the MDAX stock index.

Theodor Hänsch, who was awarded the Nobel Prize in Physics in 2005, developed the optical "frequency comb synthesizer", with which it first became possible to count the exact number of light pulses per second and thus to determine light wavelengths with absolute precision. This Nobel Prize winning technology is now used as the basis for optical frequency measurements in numerous laboratories worldwide and is the core business area of the company Menlo Systems, which was founded by Hänsch and his staff.

Scientific excellence and economic success are not mutually exclusive

The most recent Max Planck Nobel Prize laureate, Stefan Hell, is also an entrepreneur. The STED microscopy developed by Hell, for which he received the Nobel Prize in Chemistry in 2014, has catapulted light microscopy into a new dimension and made optical resolution possible down to a few nanometers. However, the STED microscope was to be just the first of a whole family of diffraction-unlimited light microscopes. Hell established no fewer than two companies, Abberior and Abberior Instruments, one of which develops fluorescent dyes while the other manufactures microscopes.

However, start-ups require more than just an innovative idea or invention – they also need an environment in which they can grow and thrive. Today there are already areas in Germany that meet the basic requirements for this, for example the region in and around Stuttgart and Tuebingen with its outstanding research facilities and innovative industrial landscape. Our aim – with the help of spatial consolidation – is to intensify the flow of knowledge between research facilities and companies while creating sufficient scope for companies and the science sector to test new technology and business models in practice. We seek to create locations where high-risk projects and business models can be piloted, and where a failure is not perceived as a threat.

Here the Cyber Valley research consortium initiated by the Max Planck Society is to show the way forward, with the Max Planck Institute for Intelligent Systems in Tuebingen and Stuttgart at its core. It is currently developing into a creative hot spot for scientific progress and economically successful innovations in the field of artificial intelligence – and is attracting companies both large and small. Cyber Valley recently established a start-up network with the aim of creating a community of start-up entrepreneurs.

The corporate technology groups Bosch and Amazon are also investing heavily in this area. Bosch, for example, has announced that it will be constructing a new campus in Tuebingen at which research is to be carried out by around 700 AI experts, while Amazon is planning to establish a research and development center with a workforce of around 100 within the next five years.

Yet even if we succeed in inspiring more entrepreneurial spirit, there is one thing aside from inventors and managers that we need above all: capital. Germany is strong on basic research. However, German investors have very little appreciation of the possibilities this opens up for product development and commercialization. Instead, German start-ups are becoming increasingly dependent on foreign backing. The growing interest being shown by U.S. investors confirms the quality of the research being carried out in our country, but this also entails a risk that our expertise and value creation potential will migrate still further in the long term.

The Max Planck Society can already point to numerous examples of this, one of them being Anthony Hyman, Director at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden. At the end of 2018, he founded the biotech company Dewpoint in cooperation with the Whitehead Insti-

tute at the MIT in Boston. This company is pursuing a new approach to the treatment of diseases such as cancer. With the support of lead investor Polaris Partners, the start-up established its headquarters in Boston and a subsidiary in Dresden, and secured USD 60 million in start-up funding. Start-up founders in Germany can only dream of such sums.

Germany needs more risk capital

Another example is the first RNAi drug, which was licensed in 2018 and which is based on technology developed at the Max Planck Institute for Biophysical Chemistry. We would have liked to keep this technology in Germany. For this reason, the U.S. biotech company Alnylam was initially only granted a co-license, while a second license went to the German company Ribopharma AG. However, this company was taken over by Alnylam back in 2003, which meant that all the associated rights went to the U.S. Alynlam now has a stock market value of more than EUR 14 billion (around USD 15.8 billion) and employs more than 1,000 people.

Furthermore, the most successful life sciences invention in the history of the Max Planck Society, the pharmaceutical drug Sutent, was commercialized through a start-up in the U.S. named Sugen Inc. The company was finally taken over by Pfizer – another U.S. pharmaceutical group. Its active principle was discovered in the 1990s by Axel Ullrich and his team at the MPI of Biochemistry.

In order to improve the level of funding start-ups in Germany, we would therefore welcome a national initiative that increases the risk capital available across sectors and makes it easier to supply start-ups with sufficient functional equity capital.

Technology transfer, like research, thrives on change. New instruments have to be developed to translate academic research into practical application, and new research focuses have to be set. In recent years, this has been accomplished with great success in the early-phase drug development sector. The LDC and its partners have just secured funding amounting to EUR 60 million for promising projects.

In future, it seems likely that more and more of these projects will be put to practical use, not only by classic licensing, but also by start-ups – an area which Max Planck Innovation aims to become even stronger in the years to come. At the MPG, we intend to work together on improving the culture of innovation and entrepreneurship at the Institutes, for example by increasing the presence of Max Planck Innovation and taking steps to raise awareness for this topic.

Start-ups are to receive support in the form of largely standardized, flat-rate licensing conditions featuring positive stakeholder and entrepreneurial terms, deployment of industry experts, their own "company building" activities with experienced external management ("founding without founders") and improved training in entrepreneurship. Close cooperation with Cyber Valley in the area of IT is planned. These and other measures will enable Max Planck Innovation to continue playing a leading role in technology transfer in Germany. ◂

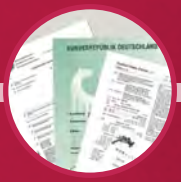
Martin Stratmann, born in 1954, studied chemistry at the Ruhr University Bochum. He completed his doctorate in 1982 at the Max-Planck-Institut für Eisenforschung. Following on from a postdoctoral position in the U.S., he became a Group Leader at the Max-Planck-Institut für Eisenforschung. He habilitated at the University of Dusseldorf and then taught at the University of Erlangen-Nuremberg from 1994 to 1999. In 2000, he accepted the appointment of Scientific Member and Director at the Max-Planck-Institut für Eisenforschung. He has received numerous awards, including the U. R. Evans Award presented by the British Institute of Corrosion in 2005. Martin Stratmann was appointed President of the Max Planck Society in June 2014.

Illustration: designergold; photo: Axel Griesch

50 years of Max Planck **Innovation**

1970

Founding of "Garching Instruments" with headquarters at the IPP [Max Planck Institute for Plasma Physics] in Garching (March 20, 1970)



1985

Filing of patent for FLASH

1991

First start-up with MPG as a participant: Sugen, Inc. (U.S.)

1992

First approved drug from MPG technology: Miltefosine (Miltex) for treating cutaneous metastases of breast cancer

evotec

1993

First German start-up with MPG as a participant: Evotec (Hamburg)

1993

Company name changed to "Garching Innovation GmbH – Technology from the Max Planck Society"

1996

All major medical technology companies have licensed FLASH
➜ Large revenue growth

Photos: MPG/collage based on draft by Jens Frahm (left); Evotec (right)

2000

"Tuschl patents" filed for RNA interference

2002
2004

Approval of miltefosine (Impavido) for treating leishmaniasis

2006

Company name changed to "Max Planck Innovation GmbH"

Max-Planck-**Innovation**

2006

Approval of Sutent as a cancer drug

2007

Life Science Incubator founded at caesar in Bonn

2008

Lead Discovery Center (LDC) founded in Dortmund

2018
2019

Approval of Onpattro and Givlaari by Alnylam → First RNAi-based drugs

Photos: Pixabay; Max Planck Innovation Lead Discovery Center; Alnylam (from left to right)

Thanks to Jens Frahm and his team, MRI examinations can be completed in a relatively short time.

A live link to the root of the disease

It is thanks to magnetic resonance imaging MRI – and not least **Jens Frahm** – that doctors are better able to diagnose diseases among patients than they could 30 years ago. The research conducted by the Director of the non-profit making company Biomedizinische NMR Forschungs GmbH at the **Max Planck Institute for Biophysical Chemistry** in Goettingen has succeeded in significantly improving the images made of the body. In the interim, the team from Goettingen has even been able to push MRI from photography to filming.

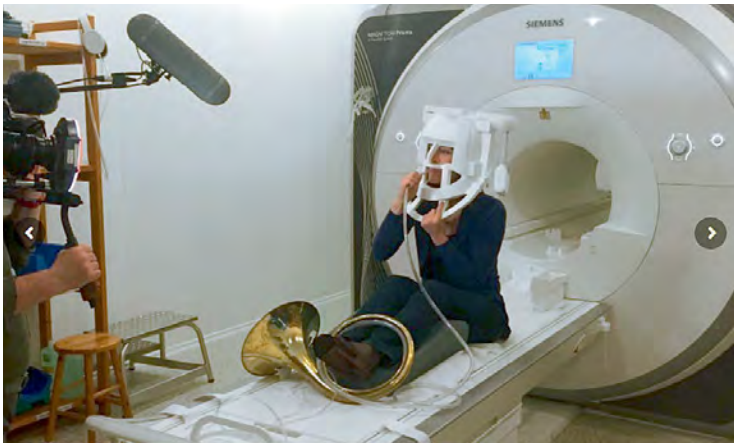
TEXT **ROLAND WENGENMAYR**

If you ever find yourself lying in the tube of a MRI system, you can be thankful that the examination only takes a few minutes and not several hours, even though one part of the body is scanned from a large number of different perspectives. This is the result of the work contributed by scientists from the Max Planck Institute for Biophysical Chemistry to the development of MRI during the 1980s. The first generation of these devices, which can look inside the human body without using harmful radiation, took several minutes to take just one picture. Not only that, the person needed to lie still for the whole time to ensure that the images were sharp enough.

In principle, this could be compared to the initial stages of photography, when people had to hold still for long periods of time to prevent the pictures from becoming blurred. However, photographic technology improved at an incredibly fast rate, and eventually led to the creation of films. A comparable development towards moving images is now occurring in MRI. And for around forty years, Jens Frahm and his colleagues have helped make major improvements in this respect.

One key discovery made by the researchers in Goettingen was the FLASH technology, which from 1985 onwards drastically reduced the measurement time required for a single image. In so doing, they helped MRI make its big breakthrough. Today, there are over 60,000 devices in use, with 100 million examinations made every year. Thanks to their contribution, the technology is now able to record images of the inside of the body within a relatively short period of time, even in three dimensions, and in addition provide insights into metabolic processes in the

Photo: Frank Vinken



Sarah Willis, a horn player in the Berlin Philharmonic Orchestra, is one of the musicians whose tongue movements are being analyzed using real-time MRI. During the tests, a radiofrequency antenna circumscribes Willis' head while she lies in the MRI device and blows into a horn made of a non-magnetic alloy via a tube. During the entire procedure, she is monitored by researchers who evaluate the data on a computer (from left to right).

tissue with the aid of the chemical information from the MRI signals. This means that brain diseases can be better understood, for example.

A LIVELY INTEREST IN HUMAN STORIES

For several years, researchers have been working to create magnetic resonance images of moving organs. The Goettingen real-time MRI technology now makes it possible to obtain live videos from inside the body. Beating hearts, swallowing and speaking can now be monitored, as well as tongue movements while playing brass instruments. These are just some examples from Frahm's research. The physicist combines a warm-hearted interest in human stories with a fascination for the medical technology to which he has dedicated his life's work as a researcher.

MRI as it is now used in clinical practice is still not a particularly fast way of obtaining images from inside the body. On the other hand, it has the great advantage that it does not expose the body to harmful radiation. Since biologic tissue contains a large amount of water, the MRI method offers another advantage: it works with signals from the water, or more precisely, from the nuclei of hydrogen atoms. This makes it possible to differentiate between tissue such as bones, muscles and organs due to their different water content. By contrast, with X-ray technology, it took a long time before the method was able to show not just bones, but also soft tissue, although often only with the aid of contrast agents. Even so, the first medical imaging technology was such an important step forward that Wilhelm Conrad Röntgen was awarded the first Nobel Prize for Physics in 1901 for discovering the radiation that was named after him. Even at that time, therefore, basic research helped provide completely new opportunities for conducting medical examinations, and this is what Jens Frahm aims to achieve with his research into MRI.

In theory, the Director of the Biomedizinische NMR Forschungs GmbH at the Max Planck Institute for Biophysical Chemistry has already reached an age when professors retire. "I'm already into the extension period," he jokes. The Max Planck Society has made sure that Frahm can continue his work for the next three years.

In so doing, it is helping a researcher who was accepted into the "Hall of Fame of German Research" in 2016, and who has received one award after another, such as the European Inventor Award for Research in 2018. It is also thanks to Frahm that the Max Planck Society was granted the most lucrative patent in its history. However, before the license revenues from

Photos: sarah-willis.com

Photo: sarah-willis.com

this patent began to roll in, there was a bitter dispute over the patented FLASH technology used. Frahm fought this legal battle to the bitter end with a will of iron – something you wouldn't think was compatible with his affable, friendly nature.

YEARS OF PATENT DISPUTES

In the mid-1980s, the researchers in Goettingen under Jens Frahm succeeded in accelerating examinations with the MRI devices one hundred-fold thanks to the FLASH procedure. Obviously, all the medical technology companies wanted to use this idea, and big names such as General Electric, Philips and Siemens immediately jumped onto the bandwagon. However, the companies initially refused to recognize the patent owned by the Goettingen scientists and to pay the license fees due to the Max Planck Society. In fact, the Max Planck Society only made moderate demands. "We wanted just one percent of the total turnover," explains Bernhard Hertel, who at that time worked at Garching Instrumente, the predecessor of today's Max-Planck-Innovation GmbH. "Then the major disputes began."

For seven years, Hertel, who is now 79, worked with Frahm to prepare court cases against the device manufacturers. General Electric proved the most obstinate opponent. Hertel flew to the U.S. dozens of times to pursue the legal fight against the medical technology company from Wisconsin. He decided not to use an interpreter, since "that would only have led to unnecessary delays in the proceedings." However, his strategy was not entirely risk-free, since just one careless remark would have caused the Max Planck Society to lose the protective rights to the patent claims. This is exactly what the opposing side hoped would happen, and they arranged for extremely precise minutes to be taken of the negotiations. In some cases, this yielded some strange results, according to Hertel. In the official minutes of the proceedings, it is stated that a dog was barking in the courtroom, and that it was made to stop with a loud "Shut!" by its owner, Frahm's attorney.

The opposing side certainly left no stone unturned. They employed dozens of attorneys, submitted falsified documents and even paid money for the services of a Nobel Prize winner in chemistry, who was presented as a scientific expert. However, he was not very familiar with the imaging variants of the nuclear magnetic resonance technology that were the subject of the dispute.

It was only in 1992, when the European patent was granted in full and when Hertel succeeded in negotiating a license agreement with Siemens, that General Electric finally admitted defeat. A figure of 0.7 percent of the total turnover was agreed, with a down payment of USD 20 million. Licenses were also issued to Toshiba, Hitachi, Philips and other medical technology companies. Ultimately, therefore, the Max Planck Society won the day. The fight was worth the effort: while the legal proceedings through to the final judgment in 1993 may have cost three million Deutschmarks, the license fees for the FLASH patent owned by the Max Planck Society brought in a total of EUR 155 million. To these were added other patents from Frahm's research, which also led to revenues of several million euros.

To understand why FLASH marked such a breakthrough, the basic principle of MRI needs to be taken into account. The signals come directly from the nuclei of the hydrogen atoms, which are present in different concentrations for different types of tissue. The hydrogen nucleus consists of a single proton, which behaves like a tiny magnet in a magnetic field. An MRI device has a strong magnetic field of this type. The magnet that generates this field is usually the large tube into which you are pushed. The magnetic field aligns the protons in the body like small compass needles. A radiofrequency antenna, which is placed on the upper body for examinations of the chest area, for example, is responsible for the measurement itself. The antenna sends a brief radiofrequency pulse into the

body, which excites the protons out of their equilibrium position.

Where does the information about the tissue properties come from? After the excitation of the protons, they gradually return to their equilibrium state, like compass needles turning northwards. While doing so, they emit the energy absorbed from the radio pulse, and this signal is recorded by the radiofrequency antenna, which is now switched to receiving mode. Put simply, the key information is contained in the frequency and duration of the water proton signal, which is influenced by the local tissue surrounding it.

SHARP, CLEAR IMAGES ONE HUNDRED TIMES FASTER

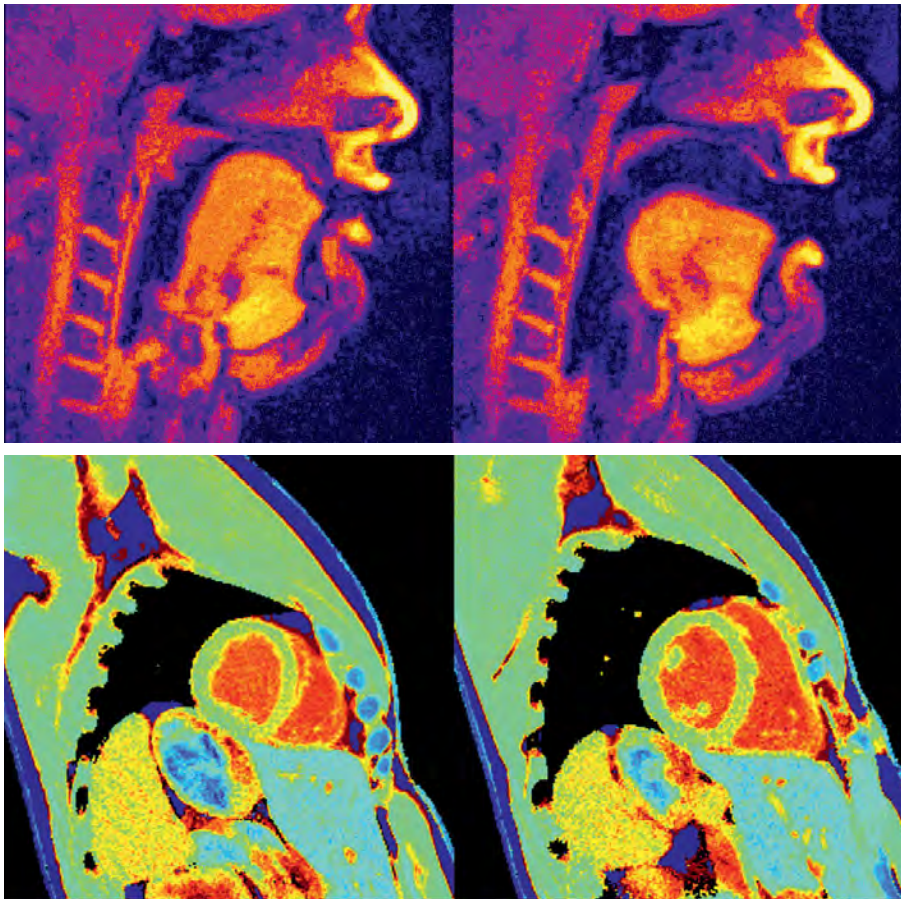
During the initial stages of its development, MRI needed a large number of individual measurements in order to build up a single image, with each measurement requiring two radio pulses. In addition, long waiting times were necessary between the measurements, since all protons were excited in order to produce useful images. Therefore, a long time was needed for them to return to their initial position.

The researchers in Goettingen then succeeded in conducting a measurement with just one radio pulse. Moreover, the FLASH technology excites only a small portion of the protons for each individual measurement by just a low-energy radio pulse. This makes it possible to take the next measurement immediately afterwards. As a result, FLASH technology records clear, sharp images in one-hundredth of the time originally needed to make a recording.

Since then, the researchers in Goettingen have even made sufficient progress with their technology to enable MRI to make the leap from a static image to film recordings. Short sequences made up of individual images have already become an established feature in the clinical field, albeit only with periodic processes such as the beating of the heart. Until now, films of this type were created subsequently from a series of measurements that can take several minutes. When examining the heart, the individual MRI data is synchronized with an electrocardiogram (ECG) recorded at the same time. With this trick, the computer can then correctly assign the images to the right phase of the heartbeat in the video that is retrospectively created. Since MRI and the ECG can interfere with each other, this recording method is subject to error. In addition, patients also have to be wired up with ECG electrodes – and they commonly have to hold their breath to ensure that the images are sharp.

In the real-time MRI technology, i.e. FLASH II developed by Frahm's team, this lengthy process and the discomfort involved are a thing of the past. The new technology delivers serial images or MRI movies from the body in real time, live and directly, without an ECG. The patients can breathe freely, since the system records live videos from inside the body with 30 or 50 images per second and in extreme cases even with 100 images per second.

The bottleneck on the way to achieving real-time MRI was the enormous mathematical effort required to calculate the images. A computer has to convert the MRI measurements into a high-resolution video in real time, in



Studies of singing and quantitative tissue maps: with FLASH II technology, MRI can be used to monitor the tongue movements of a singer, for example, and in so doing to diagnose speech defects (upper half). However, it is also a useful method for differentiating between different types of tissue. The almost round wall of the left heart chamber is light green, while the blood in the chamber is shown in red. The skeletal muscles are shown in green, while the liver is green-blue and the fat tissue is blue.

Photos: Jens Frahm / MPI for Biophysical Chemistry

» The bottleneck on the way to achieving real-time MRI was the enormous mathematical effort required to calculate the images.

other words, almost without any delay. If it fully recalculates each image, the process takes far too long. That's why the technology developed in Goettingen generates the images from only a very small dataset, which then can also be recorded far more quickly. For example, if only 5 percent of the original data needs to be acquired, the measurement becomes 20 times faster.

The procedure used to reduce the data is a distant relative of a technology used for rapid video transmissions. Here, algorithms analyze those areas from the image in a series that have changed in comparison with the previous image. Only these changes are transferred, leading to significant savings in data quantity. The researchers in Goettingen are pursuing a similar strategy. In simple terms, the computer uses the information from the preceding images that hasn't changed, and only calculates the areas of the image that have changed in order to create the new image.

With this trick, Frahm's team succeeded in shortening both the acquisition and computing time. Yet despite this, these MRI video images are sharp and accurate. Two former doctoral researchers, Martin Uecker (now a professor at the University Medical Center Goettingen) and Shuo Zhang (now an employee at Philips in Aachen) played a key role in enabling this new development.

Frahm's team demonstrated just how well the FLASH II technology works with live recordings of a beating heart. With this method, the researchers have found a way around one problem that arises with the standard ECG-synchronized heart MRI procedure that has been used to date. Contrary to requirements when the ECG and MRI are synchronized, the heart does not beat entirely evenly. "If it were to do so, this would result in mechanical problems, and it would never hold out for an entire lifetime," Frahm explains. "Naturally, in all cases of arrhythmia, the old technique has gone wrong," Frahm says. "And these are precisely the patients who need to be examined."

MUSICIANS CAN IMPROVE THEIR PLAYING TECHNIQUE WITH FLASH II

That's why clinics are becoming increasingly interested in the real-time MRI technology from Goettingen. However, the manufacturers of the MRI devices are still not ready to start production, since every new technology must be clinically tested and certified. Even so, Jens Frahm and his staff members, in cooperation with the University Medical Center Goettingen, have already used the FLASH II technology to help their first patients. They include people with swallowing difficulties, or professional brass players who can no longer play properly due to embouchure dystonia, for example, leading to tongue problems due to a lack of muscular control.

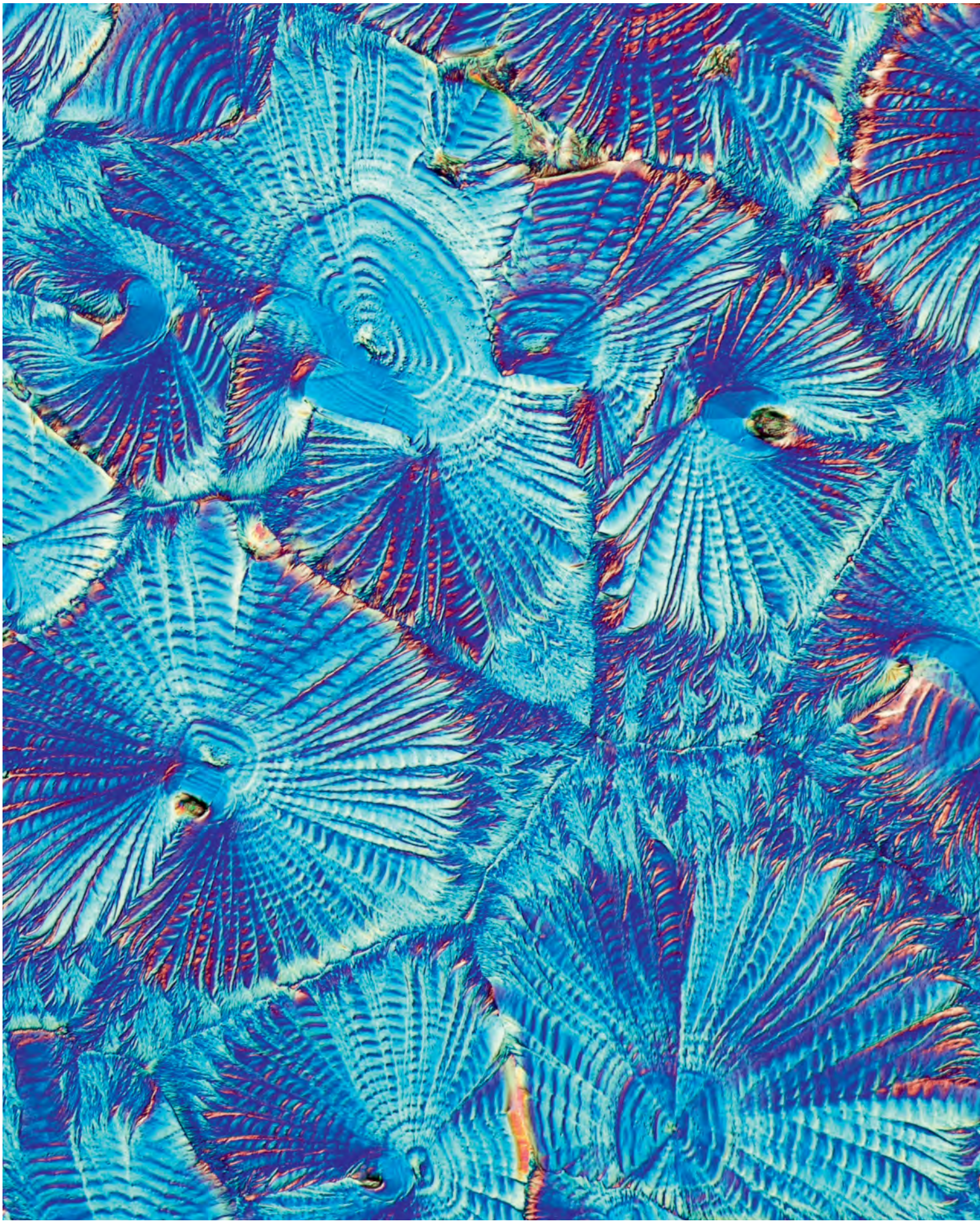
It was more or less a coincidence that the researchers discovered that FLASH II can also help these musicians. For one project, Frahm's team recorded the playing technique of professional horn players so that the MRI videos of their tongue movements could be used for educational purposes. "It emerged that even top-notch musicians don't always do the same thing," Frahm explains. "That's because we humans have no sensors in the rear part of our tongue, which would otherwise enable us to control its precise position." However, when the musicians themselves don't exactly know what their tongue is doing, this naturally has an impact on their teaching. It is hoped that the films recorded in Goettingen can now be studied to help teach players the right technique.

During the course of the project, the researcher came across a horn player from California who had speech problems and who also was no longer able to play correctly. In the MRI video, it emerged that while playing, the musician positioned his tongue in a completely different way to other horn players. He was only able to change this after Frahm's group projected back his own live recordings in real time, while playing in the MRI tube. On the basis of this experience, Frahm's team began investigating how useful the visual feedback might be when treating patients with speech deficiencies and brass players with dystonia.

The opportunity of using basic research to help people in a direct and practical way has motivated Jens Frahm for four decades. Now he firmly intends to get real-time MRI up and running in clinics. "I want to see this through to the end!", he says. Enabling doctors to see what is going wrong in the body, live. ◂

GLOSSARY

Magnetic resonance imaging: The technology uses the nuclear spin of hydrogen atoms. The nuclear spin is a quantum mechanical property and virtually turns the atoms into tiny rod magnets. How they behave in an external magnetic field depends on their chemical environment. The imaging technique makes it possible to differentiate between individual types of tissue, since they contain different amounts of water.



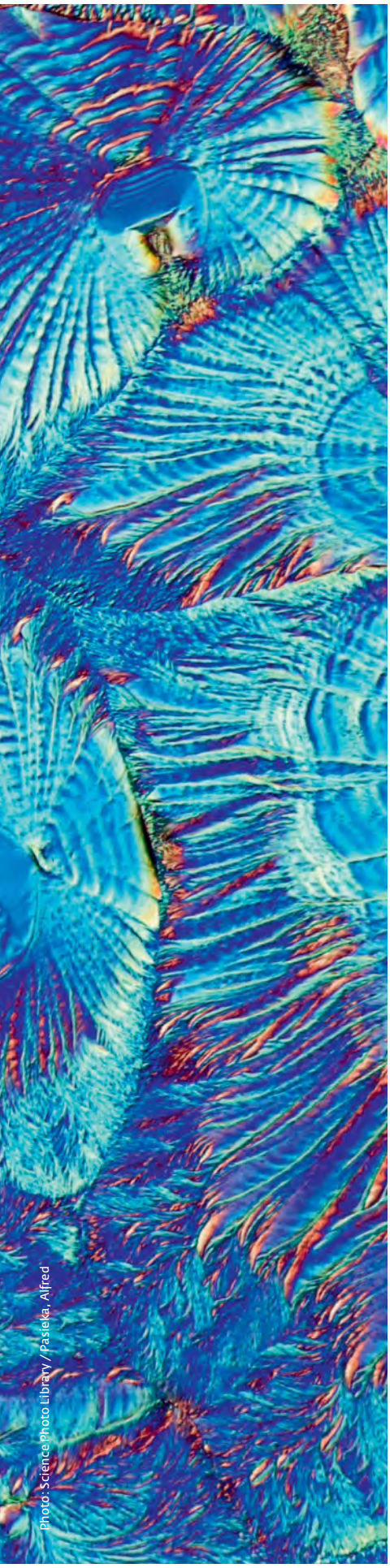


Photo: Science Photo Library / Pasieka, Alfred

Brake for breast cancer

Researcher or entrepreneur – thanks to **Axel Ullrich**, this is no longer a contradiction for the Max Planck Society: he's both. This is proven by countless publications and honors, two cutting-edge cancer drugs, six start-up companies and over 100 patents. Ullrich, a former Director of the **Max Planck Institute of Biochemistry** in Martinsried has been instrumental in promoting the combination of basic and applied research at the Max Planck Society.

TEXT **HARALD RÖSCH**

To outsiders, it didn't seem like a big deal when the Max Planck Society announced in 1988 that a scientist from California would be transferring to the Max Planck Institute of Biochemistry in Martinsried. But Axel Ullrich's appointment did cause a stir in specialist circles. While he was widely regarded as a brilliant scientist on the one hand, on the other, he had joined the biotech start-up Genentech after completing his doctoral thesis in Heidelberg and a research stay at the University of California. At that time, switching sides from academic research to the private sector was still frowned upon in Germany.

Trastuzumab crystals under the microscope. The approval of this antibody against a certain form of breast cancer in 2000 marked a milestone in cancer treatment.

CLONING EXPERT

Genentech, which was founded in 1976, had set itself the goal of genetically modifying microorganisms in such a way that these could produce vital proteins for medical research and practice. Back then, Ullrich was regarded among his colleagues as an expert in the isolation of genes and their incorporation into bacterial genomes, a process known as cloning. In 1977 at the University of California, he developed a method that enabled him to transfer a copy of the human insulin gene to bacteria, which then went on to produce the signal substance. This made it possible to produce

human insulin on an industrial scale for the first time: a huge relief for millions of diabetics who had been dependent on animal insulin until then, which is not always tolerated so well by the human body.

As a renowned cloning expert, he was of course very welcome at Genentech where, he joined a group of talented and well-disciplined, although sometimes eccentric, young researchers who set out to revolutionize molecular biology. Anyone who reading the recollections of those involved will, to a certain extent, be reminded of the Silicon Valley computer kids who invented the PC at about the same time.

As a private investor, Ullrich, with his keen sense for a worthwhile research project, first had to lose some of the money he invested: short of cash and desperately in need of a car, he sold his Genentech shares for a few thousand dollars – too soon, as it turned out in retrospect; they would have been worth several million dollars following the company's IPO. From then on his friends always made joking reference about his "million dollar Volkswagen".

This anecdote symbolizes the carefree spirit of the "wild youngsters" at that time. Yet, it also clearly shows their willingness to dare to do something new and not to allow themselves to be discouraged. They met with considerable resistance, because as brilliant as they were, many of these researchers were stonewalled by their scientific colleagues following their transition from the noble pursuit of academic research to industry.

MOVING INTO THE BUSINESS SECTOR

Fearing that he may no longer be able to get a job in basic research, Ullrich himself initially shied away from switching sides. But he eventually took the risk and never regretted it: he stayed with Genentech for nearly ten years. The company, which was taken over by the Swiss pharmaceutical giant Roche in 2009, is now regarded as an "elite school" from which countless other biotech start-ups have emerged. For the American science journalist Robert Bazell, Ullrich is an example of how science works: "As so often happens in science the research that led to this breakthrough did not begin with hundreds of scientists working towards a stated goal, but a lone researcher trying to satisfy his own curiosity."

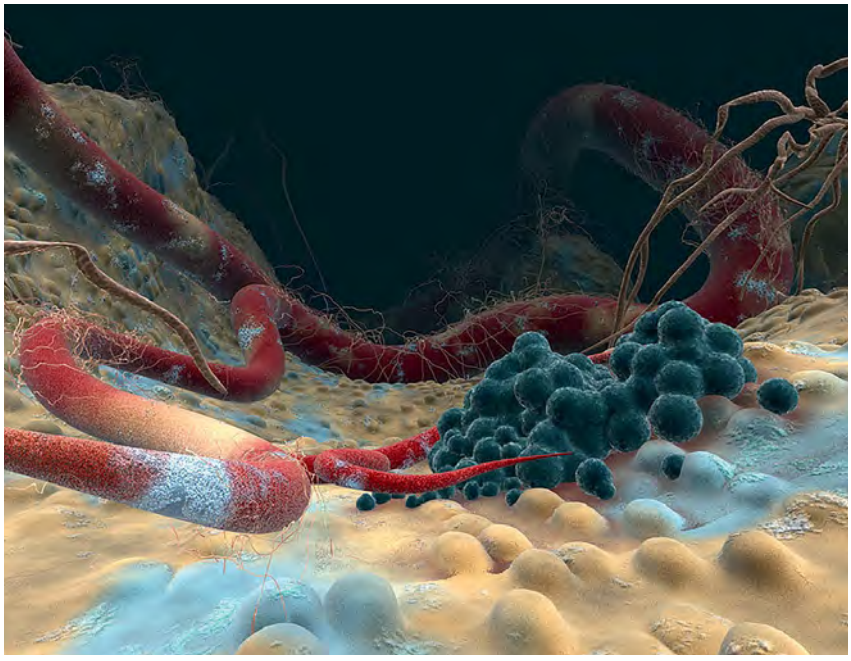
When the Max Planck Society asked Ullrich whether he would transfer to one of its Institutes in the late 1980s, he made his return to Germany conditional, an unusual demand at the time: he wanted to continue to make his research available to medical practice going forward. He had learned in the U.S. that this would only be possible with the support of private companies. Although there were no anxieties about contacts between academic and applied research, this represented a paradigm shift for the Max Planck Society. Its researchers had not been allowed to hold shares in private companies until then for fear of conflicts of interest.

From that point on, Ullrich strove to combine basic and applied science, an approach that has made him one of the ten most cited scientists worldwide throughout the past 25 years, as well as a highly successful entrepreneur whose current companies include Sugen, Axxima, U3 Pharma, Kinaxo, Blackfield and SciMab. He also still holds the record for having registered the most patents within the Max Planck Society.

His career as an entrepreneur began in 1991 when he founded Sugen, which was also the Max Planck Society's first spin-off. The name of the company evokes the names of the founders, Joseph Schlessinger from New York University and Axel Ullrich. Because there was no relevant start-up scene in Germany at that time, the company was

Axel Ullrich carried out his research at Genentech in San Francisco from 1979 to 1988. He and his colleagues transferred human genes to bacteria thus converting them into production machines for novel drugs; a revolution for the pharmaceutical industry.

Photo: MPI of Biochemistry - Axel Ullrich



Tumors need a food and oxygen supply via the bloodstream, to which end they release substances that stimulate the growth of blood vessels. Vascular cells can detect these signals with the aid of tyrosine kinase receptors.

Photo: MPI of Biochemistry - Axel Ullrich

founded in the U.S. It was not until 1993 that Evotec, a company based on technologies developed by Nobel Prize winner Manfred Eigen, became the first German company in which the Max Planck Society purchased shares along with its scientific founders.

The Max Planck Society's knowledge transfer subsidiary, Max Planck Innovation, has been supporting Ullrich's spin-offs right from the start. With Sugen, Ullrich broke new ground for the Max Planck Society, as Jörn Erselius, Managing Director of Max Planck Innovation since 2005, explains: "Contract and investment negotiations, discussions with investors – none of these things had ever existed at the Max Planck Society before. At that time," he continues, "there was still a rule under which a given scientist was only allowed to hold a minor shareholding in a company up to the same number of shares held by the Max Planck Society."

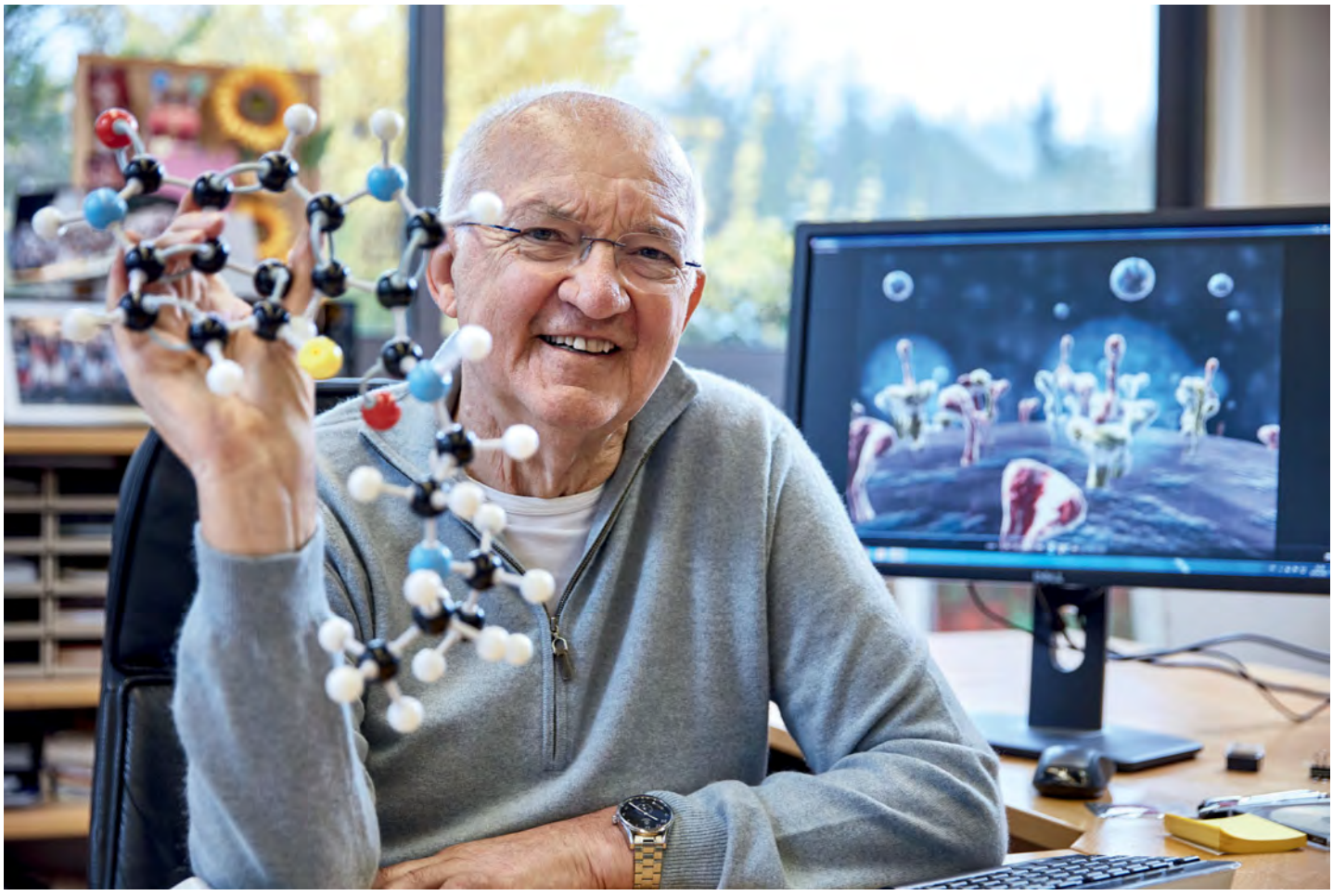
SUCCESSFUL SPIN-OFF

The young Californian company continued its close collaboration with the Max Planck Institute of Biochemistry in Martinsried, which resulted in 30 joint patents, and went on to be extremely successful. The Swedish pharmaceutical giant Pharmacia bought Sugen out in 1999 for USD 650 million and the Max Planck Society received several million euros by selling its shares in the company. The income generated from the license agreement with Sugen now totals well in excess of EUR 100 million, making Sugen its most financially successful spin-off to date. "What Axel Ullrich has shown," Erselius explains, "is that there is no contradiction between excellent basic research and successful applied science."

The secret of Sugen's success was based on so-called receptor tyrosine kinases, receptor molecules that protrude through the membrane into the cell's interior. Whenever a growth factor docks on to the receptor, it transmits phosphate molecules, which activate various signaling pathways that control gene metabolism and other gene activity. When doing this, receptor tyrosine kinases ensure, for example, that blood vessels can grow, which is a prerequisite for the supply of oxygen and nutrients to tumors.

Ever since his time at Genentech, Ullrich has been pursuing the idea that drugs that target these tyrosine kinases may be able to switch off cancer cells and cure the disease. He then went on to study several hundred types of proteins within this family.

The success of this strategy has been impressive: two cancer drugs that target receptor tyrosine kinases, so-called kinase inhibitors, have emerged from his laboratory: Trastuzumab (Herceptin) was approved in Germany for a specific type of breast cancer in 2000, followed by sunitinib, which is sold under the product name Sutent for the treatment of advanced kidney cancer in 2006. Ullrich has received countless awards for his findings. They earned him a place in the European Inventor Award finale in 2017, among other things. He was awarded the highly prestigious Lasker Prize for his discovery in 2019. >



Axel Ullrich in his office in Martinsried with a model of the tyrosine kinase inhibitor sunitinib, an active agent that is considered to be one of his most significant discoveries.

Yet tyrosine kinases also play a role in diseases other than cancer. In 1997, Ullrich and Heinrich Kuhn, the then Managing Director of Max Planck Innovation, decided to found another company to investigate these further. This company, Axxima, which is based in Martinsried, focused on the role played by tyrosine kinases in infectious diseases such as AIDS, hepatitis and influenza. The relevant pathogens use these receptors to infect body cells. The intention is to use kinase inhibitors to shut off this gateway. The Company was acquired by GPC Biotech in 2005.

Ullrich founded another company in 2001, his third after Sugen and Axxima, to conduct research into other tyrosine kinases that are involved in cancer. Among other things, the purpose of U3, which stands for Ullrich 3, was to study the "Fibroblast Growth Factor Receptor" (FGFR4) and its role in the development of cancer. From the outset, the company collaborated closely with Daiichi Sankyo, a Japanese pharmaceutical company that acquired U3 in 2008 for EUR 150 million.

By contrast, Kinaxo, which was founded in 2005, has been focusing on a technology developed in Ullrich's laboratories to analyze the targeting accuracy of kinase inhibitors, which is an important building block for the development of cancer drugs with fewer side effects. Kinaxo collaborated with many pharmaceutical companies and was therefore able to make the relevant technology available to other development programs in the field of cancer research. The company was sold to Evotec in early 2011. Ullrich still comes up with ideas and acts as a point of contact for his most recent start-ups, Blackfield (which was sold in 2016) and SciMab, which was founded in 2017.

The turn of the millennium was a goldrush period for the biotech scene. "Back then," says Erselius, "investors were much more willing to take risks than they are today, and raising venture capital was relatively easy." But that was soon to change: when the dotcom bubble burst in 2000 and many venture capitalists lost their investments, the necessary capital also dried up in the field of biotechnology. New start-ups fell by the wayside as developers of novel active agents. Suddenly it had become almost impossible to develop new drugs from laboratory findings.

Photo: Heinz Troll / EPO

It was at that point that Max Planck Innovation came up with the idea of the Max Planck Society's Lead Discovery Center (LDC) in Dortmund, which was set up with the aid of several employees from Ullrich's laboratory. As Erselius explains: "Axel Ullrich provided significant support for the foundation of the Lead Discovery Center in 2008 both in terms of his research and his ideas. Once again, he came up with ideas and served as the driving force for knowledge transfer within the Max Planck Society."

FROM THE LABORATORY TO THE PATIENT

The LDC is now an independent company that picks up on basic research findings to develop active pharmaceutical agents, which licensed or collaboration partners test in clinical studies to determine whether they are suitable for use as therapeutic drugs. Ten years after its establishment, the LDC can look back on some impressive results: one of its research projects has managed to make the leap to the clinical stage and is currently being tested in a phase 1b study; two others will be following soon. All in all, the LDC has filed 23 patent applications and granted licenses to collaboration partners to carry out research into 15 additional substances.

One licensed project is based on a molecule called Axl that can block the tyrosine kinase, an enzyme that is overactive in most forms of highly invasive breast cancer. Ullrich had discovered that this kinase has an influence on the formation of metastases. The LDC then identified a molecule that is able to block the Axl kinase and is suitable for use as an active therapeutic agent. Qurient, a Korean pharmaceutical company, has acquired a license from the LDC to develop the substance and is currently testing it in preclinical trials.

The initial euphoria of cancer researchers has now given way to a certain degree of disillusionment: the kinase inhibitors have not led to the anticipated big breakthrough in spite of the many different research approaches. Although many of these drugs are currently in use, their success in the battle against cancer is only partial. Ullrich was initially convinced that cancer could be defeated during his own lifetime, a prognosis that has sadly not yet been borne out.

It is possible that future cancer treatments will entail a combination of different approaches that can be tailored to individual patients, which may, in addition to kinase inhibitors, involve such treatments as drugs that target other cancer genes and those that switch on the suicide program of cancer cells. The current standard cancer treatment program also includes drugs that stimulate cancer patients' own immune systems to fight tumors.

It is possible that certain forms of cancer will never be completely curable. Rather than hoping for a cure, some cancer researchers are therefore focusing on simply slowing down the progress of the disease to such an extent that patients will no longer suffer the terminal stage of the cancer. In this case, Ullrich and his fellow frontline comrades will have succeeded in achieving something similar to what AIDS researchers had previously accomplished: transforming an acutely fatal disease into one that is chronic but controllable. ◀

Top To thrive, cancer cells need growth factors (blue), which bind to tyrosine kinase receptors (yellow, red) on their surfaces and activate signaling pathways within the cells. Herceptin (brown) blocks the receptors, thus preventing the further multiplication of cancer cells.

Bottom Sutent (orange) blocks a molecule that supplies the tyrosine kinase receptor with energy (green), thereby interrupting the intra-cellular signal transduction. Meaning that the active ingredient can prevent the cancer cells from dividing and block the formation of new blood vessels to feed the tumor.

Photos: MPI of Biochemistry - Axel Ullrich

Molecular bright spots

STED microscopes can produce extremely detailed images of everything from the transport of individual proteins or tiny membrane vesicles in living cells to the synapses of neurons or the skeletons of tumor cells. The technique was invented by **Stefan Hell**, Director at the **Max Planck Institutes for Biophysical Chemistry** in Goettingen **and Medical Research** in Heidelberg. Now, the spin-off company Abberior Instruments sells the highest-resolution fluorescence microscope on the market – and researchers at both the Institutes and the company continue to push the resolution to its ultimate limit: the single nanometer size scale of a molecule.

TEXT **JANOSCH DEEG**

The black box measures almost one and a half meters square and has a height of perhaps 40 centimeters. Usually, black boxes are associated with disasters – but not so in this case. Here, it stands for a real success story from physical research. The box contains an assortment of lasers, lenses, mirrors, and numerous other components, which together make up the latest microscope from the company Abberior Instruments. Going by the name of MINFLUX, it will soon be available worldwide and will once again take fluorescence microscopy to a new level. In fact, the company's existing models have already set new standards, producing images around ten times sharper than experts thought possible just 20 years ago.

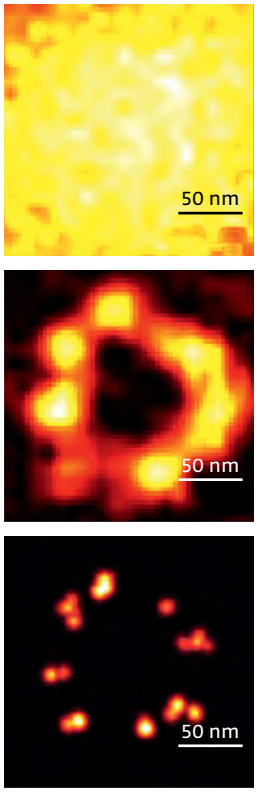
This ultrasharp form of optical fluorescence microscopy was invented by one of the company's seven founders, and he was even awarded a Nobel Prize for it. With his work, he proved all of the experts wrong in their belief that optical microscopy had already reached the limits set by the laws of physics in the 20th century. It's no wonder, therefore, that the company has seen impressive rates of growth. Its latest innovation is MINFLUX, a fluorescence microscope that will peer down into even smaller dimensions, reaching as far as the size of a molecule. But first things first. You could say that the story of Abberior Instruments actually began with a setback if not with a series of small disasters.

In the 1980s, a physicist in his mid-twenties by the name of Stefan Hell was working on his doctoral thesis

A sprouting neuron: the axon of a nerve cell uses a growth cone such as this to search for its target. Captured using a STED microscope, this image offers a detailed view of the fine projections (green), with which the rounded end of the axon explores its environment. The red and blue staining reveals proteins of the cytoskeleton, which provide the growth cone with its structure and mobility.

Photo: Abberior Instruments GmbH

Breakthroughs in the resolution of fluorescence microscopy: developed by Stefan Hell and colleagues, STED microscopy (center) achieved a resolution about ten times higher than the widely used confocal microscopy (top) over a decade ago. Now, with MINFLUX (bottom), the researchers have once again increased the definition by a factor of ten – making this technique 100 times more powerful overall and allowing it to image the molecular scale.



in Heidelberg. Using laser scanning microscopes, he was examining semiconductor chips at Heidelberg Instruments, a company his doctoral supervisor had recently founded with a group of other professors. Things were looking good, and wealthy financial backers were coming on board. Everything revolved around the new technology, however, and too little attention was paid to customer requirements. The company was ultimately broken up, and its workforce of almost 100 employees were either laid off or split up among successor companies by the investors. But this no longer affected Stefan Hell's plan. With his doctorate almost under his belt, he was ready to dive into the world of science – although he took one valuable piece of experience away with him: "I saw what not to do when founding a hi-tech spin-off," the researcher smiles. "Ideally, you design products for which customers already exist. And you don't rely on financial backers who don't really understand the subject matter," he says, lounging casually in his chair in a conference room at Abberior Instruments. He knows he chose a better approach.

By the early 1990s, Hell was working as a young scientist in Finland. Up there in the cold north, he was chasing a hot lead: what if the resolution limit of optical microscopes could be overcome with the help of a quantum optical effect? This was a radical idea at the time, because the resolution limit of optical microscopes was carved in stone. In fact, this had been the case since 1873, when the physicist Ernst Abbe formulated the relevant law: an optical microscope cannot visualize structures smaller than half the wavelength of visible light. This diffraction limit meant that optical microscopes could only resolve structures down to a size of 200 nanometers (nm) – fine enough to discern individual cells and their larger components, such as the nucleus or other organelles, but not the cell's molecular machinery. Modern electron microscopy can penetrate down to this scale, but only if the cells are first killed and prepared in a laborious process. This wouldn't be necessary with the device that Hell had in mind – which would therefore be especially useful in biomedical research.

When Hell became a Junior Research Group Leader at the Max Planck Institute for Biophysical Chemistry in Goettingen in 1997, he was able to build a microscope based on his ideas. Around the turn of the millennium, the device was ready – and it could ultimately resolve details with dimensions of just 20 to 30 nanometers. Since then, the technology has been known as STED microscopy (see box on page 27).

STED WINS THE RESOLUTION RACE

In 2004, another young physicist was looking for a topic for his doctoral thesis and was impressed by Hell's invention: "I was fascinated to see how you can bypass a law of physics," says Gerald Donnert, who is now Managing Director of Abberior Instruments. The same year, he persuaded Stefan Hell, who was by then Director of the Department of NanoBiophotonics at the Max Planck Institute for Biophysical Chemistry, to take him on as a doctoral researcher.

The young scientist found Hell to be not only highly focused but also a very exacting boss – a great match for the ambitious and highly motivated Donnert, who was tasked with building the highest-resolution STED microscope ever built. "It was an extremely exciting time," he recalls – after all, the year 2006 saw the emergence of another high-resolution form of fluorescence microscopy in the U.S. It was a bit like a race between top athletes, he says: "Who had the highest resolution? >

Photos: MPI for Biophysical Chemistry

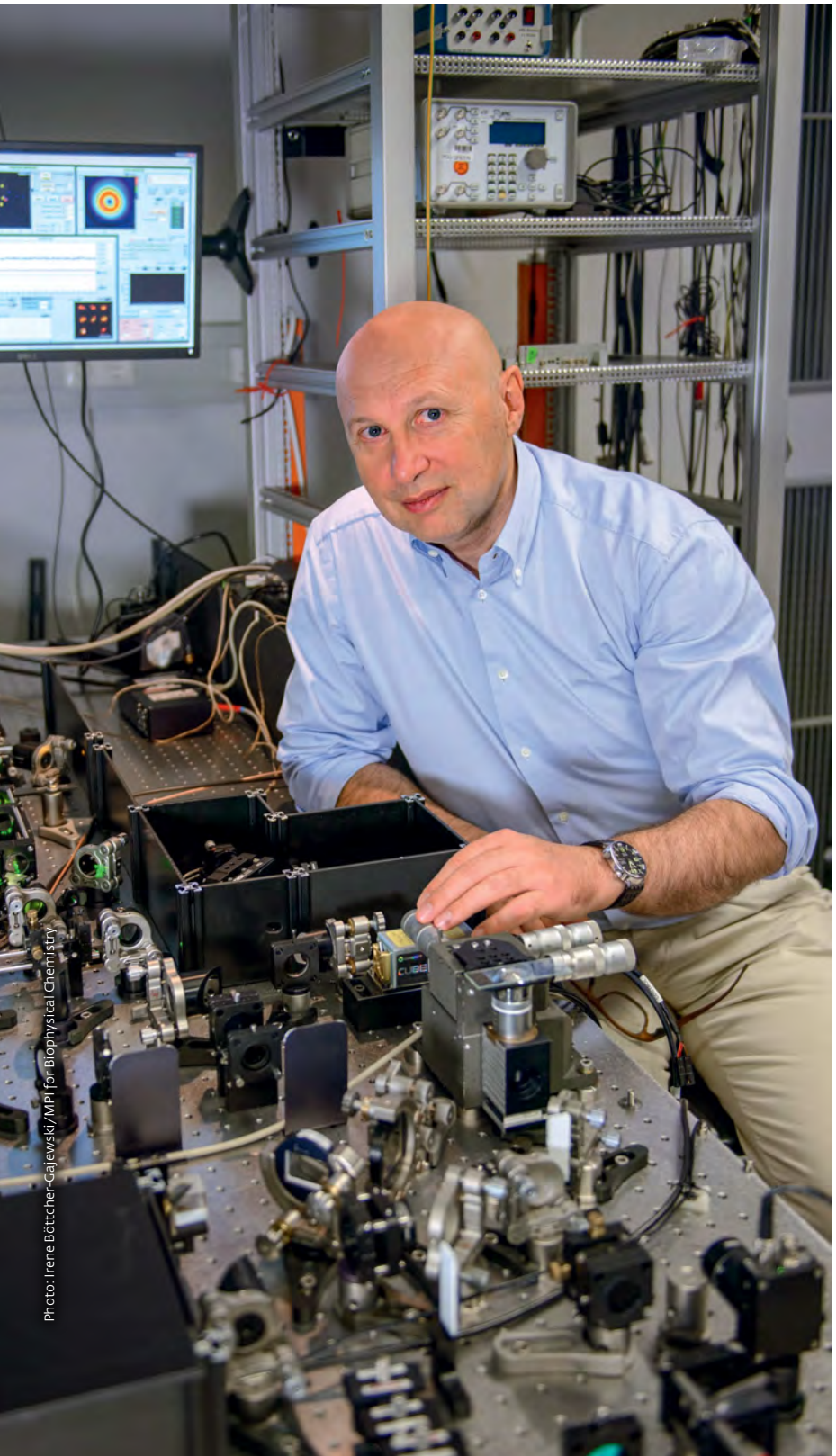


Photo: Irene Böttcher-Gajewski/MPI for Biophysical Chemistry

STED

STED stands for "stimulated emission depletion" and is a high-resolution form of fluorescence microscopy that involves the specific, temporary deactivation of tiny fluorescent dye molecules. In fluorescence microscopy, the interesting areas of the sample – such as specific structures of a cell – are generally marked with fluorescent dyes prior to examination. After the sample is briefly illuminated with light, these areas begin to glow. But two fluorescent molecules that are very close together can only be distinguished in this way if the light waves produced during fluorescence do not overlap too strongly. For this reason, the resolution is limited to around 200 nanometers (nm) at best.

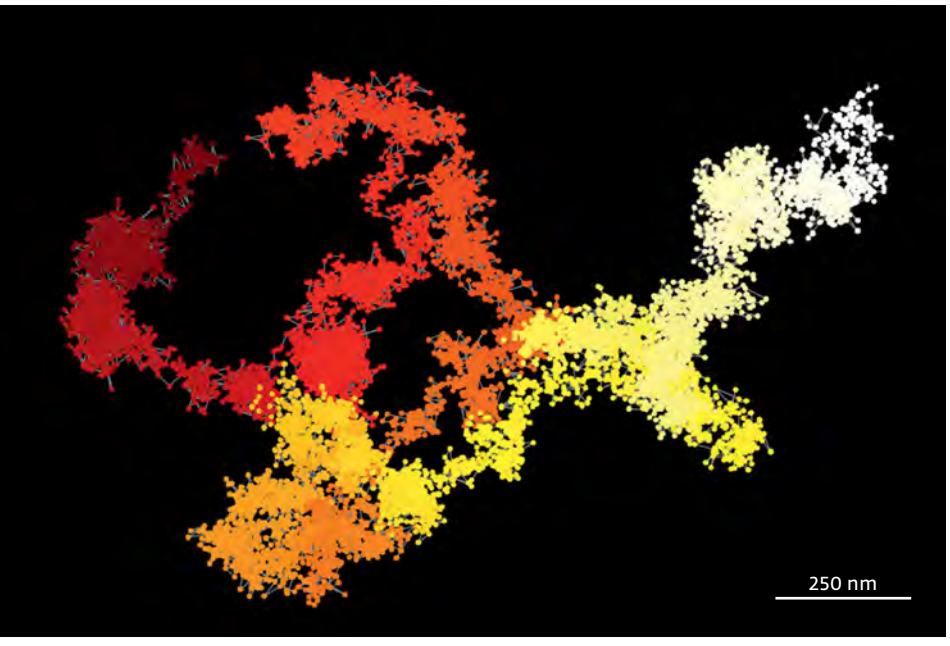
The special thing about STED is that it ensures that fluorescent molecules in close proximity to one another do not emit light at the same time. To achieve this, a donut-shaped laser beam switches some of the molecules off so that light is only emitted by those in the hole of the donut beam. Nearby molecules that have been switched off can no longer interfere with those that are glowing. By scanning across the sample, this method produces a fluorescence image with a resolution of 20 to 100 nanometers, depending on the configuration.

A result of basic research: the first STED microscope was built by Stefan Hell at the Max Planck Institute for Biophysical Chemistry.

Whose method would be the most useful one?" Donnert completed his doctoral thesis in under three years – an exceptionally short time in a subject like physics – and his microscope ultimately won the race.

The U.S. National Academy of Sciences invited him to Washington and presented him with a prize for his work. But despite this success, he initially felt an urge to get away from science: "I wanted to experience something different," he says. When he was offered a job at McKinsey & Company, a top address in the world of management consulting, it was an opportunity he could not refuse. During his time at the company, he learned how business works and realized that you have to be willing to take risks in order to achieve success. In the meantime, he stayed in touch with Hell. The two researchers had a hunch that the potential market for ultrasharp microscopes was much bigger than the established microscope manufacturers believed.

Track of a molecule diffusing within the cell membrane. Its position was determined approximately 10,000 times a second to a resolution of 20 nanometers (nm).



Indeed, in the hope of quickly popularizing the technique, Hell had initially teamed up with a well-known company that had acquired the patent license for STED microscopy. But there wasn't as much demand for the devices as he'd hoped. Nor did the idea of marketing STED microscopy through a smaller and more versatile joint venture come to fruition, an approach suggested by Dieter Treichel, Senior Start-up & Portfolio Manager at Max Planck Innovation. "Large companies are more interested in selling their well-established products for as long as possible," says Treichel. "STED was seen as the icing on the cake, rather than the new standard in confocal fluorescence microscopy. In this situation, it made sense to found a start-up, even though we lacked sales channels of our own at first."

With that in mind, Hell wasted no time in teaming up with his former doctoral student Gerald Donnert to improve the availability of the most powerful fluorescence microscopes in the world. Donnert's considerable knowledge of business strategies, which he had acquired during his time at McKinsey, would now be a priceless asset. But as well as a watertight business plan, the two researchers took another key factor into consideration: "The success of a company depends on its people." They brought a further five colleagues on board as co-founders of Abberior Instruments GmbH, bringing together a range of different skill sets from the worlds of physics, chemistry, and biology. All of them were former doctoral students with Hell and knew they could work well as a team. All of them were familiar with STED technology from the ground up and believed in its potential. Stefan Hell, their former mentor, would continue to support them as an advisor.

The team received assistance from Max Planck Innovation to found the company, especially from Dieter Treichel,

Photo: Stefan Hell/MPI for Biophysical Chemistry

MINFLUX

MINFLUX (from "minimal fluorescence flux") is a combination, so to speak, of the fundamental strength of STED and another high-resolution strategy – PALM or STORM. These techniques use a burst of light over a wide area of the sample to switch on a few molecules at random – just enough so that the probability of two dye molecules in close proximity fluorescing at the same time is small. By bringing together a large number of individual images, computer algorithms can then reconstruct the positions of the fluorophores – provided that they glow very brightly. Since this is rarely the case, however, PALM and STORM seldom deliver a higher resolution than 20 to 40 nanometers. MINFLUX also switches the fluorescent molecules on individually, but the molecules are scanned using a donut-shaped laser beam in order to determine their definitive position. Unlike in STED, the donut laser beam doesn't switch the molecules off but rather excites them to emit fluorescence.
The closer the center of the beam comes to the molecule, the less light the molecule emits, as no excitation occurs in the dark center of the donut. If the molecule's fluorescent signal disappears, its position can be determined with utmost precision because it must coincide with the known position of the donut center. Together with the single molecule switching, this localization results in a spatial resolution of about one nanometer.
For the first time, MINFLUX also allows researchers to capture precise images of molecular paths, such that videos with high spatial and temporal resolution can now be captured of proteins diffusing rapidly, for example, within the interior of a living cell.

The MINFLUX microscope, which combines the conceptual strengths of STED with that of another microscopy technique, is the latest commercial product from Abberior Instruments. It is the first commercially available microscope to achieve a resolution of one nanometer, i.e. the size of a molecule.

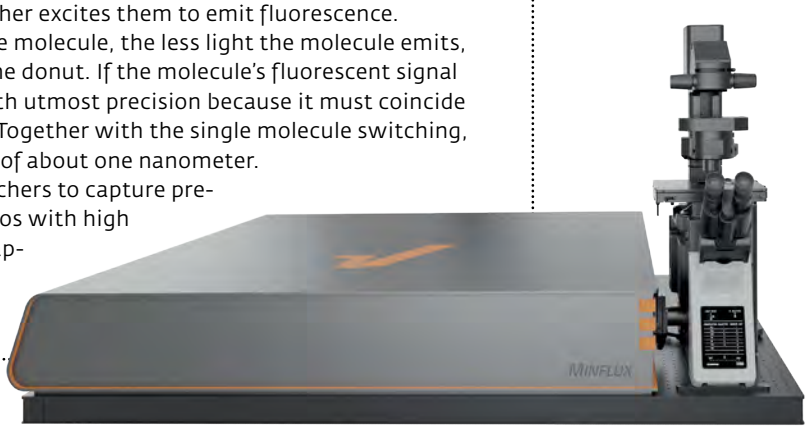


Photo: Abberior Instruments GmbH

both in the early days and when they came to establish a U.S. subsidiary a few years later. The young entrepreneurs deliberately made do without external financial support and instead opted to pull together the seed capital from their own savings: EUR 200,000 in total. In other words, there were no external backers, because Hell was keen to avoid a repeat of his experience at Heidelberg Instruments.

ALMOST TWICE AS MANY ORDERS FROM YEAR TO YEAR SINCE 2014

Abberior Instruments was recorded in the register of companies in 2012. Two orders had already been received verbally – from "family and friends," as Hell jokingly refers to the company's first customers: overseas research colleagues who knew him personally and needed high-resolution microscopes for their research. In the early days, the team met in what they called the "garage" – an approximately 25-square-meter room that they had rented on the ground floor of a rather unassuming three-story building on the University of Goettingen campus. It was here that the researchers built the first microscopes. Although they offered customers from the world of science more capabilities than established devices on the market, they were not yet STED microscopes, since the patent licenses were still held exclusively by the big company. Even so, everything was going to plan, although one risk remained: "If a customer hadn't paid for a microscope that they'd ordered, we'd have run into serious difficulties. At that time, the capital was all tied up in the shipped devices," Donnert recalls. But the customers were satisfied and paid their invoices, allowing the young company to build more devices and grow.

Word of their success got around: in January 2014, Abberior Instruments was awarded the Innovationspreis der deutschen Wirtschaft (German Business Prize for Innovation) in the "Start-up" category. And in spring of the same year, the exclusive patent license of the major company expired, clearing the way for Abberior Instruments to offer STED microscopes as well. And then came the news that no one was

» "Abberior Instruments has the world's best development team in the field of laser scanning microscopy," says Stefan Hell.

really expecting: in fall 2014, Stefan Hell was awarded a Nobel Prize for the invention of STED microscopy. According to Donnert, interest in the devices rose significantly as a result: "From that point onwards, our rate of growth has been remarkable." Hell disagrees, though: "The Nobel Prize affected our growth less than you'd imagine." He believes it had more to do with the power of the microscopes, as well as their fair price and the company's expert customer service. "In 2014, the price of STED microscopes almost halved thanks to the presence of Abberior Instruments as a second supplier. That was not only good for the researchers and the grant funding agencies, but also boosted demand. And it had nothing to do with the Nobel Prize." In any case, the number of orders has almost doubled from year to year since 2014.

The company's rapid growth also called for bigger premises, and the "garage" became an entire floor of the same building, with several offices, laboratories, workshops, a showroom, a meeting room, and a break room equipped with a coffee machine and a football table – in other words, everything you need to provide a relaxed, creative working environment for 40 people. In addition, there were now a further 20 staff members working at three smaller locations – Heidelberg, Basel, and Jupiter in Florida. Incidentally, the Heidelberg branch just happens to occupy the rooms where Hell worked on his doctorate some 30 years ago.

The staff members of the research and development Department, who are responsible for developing new methods and devices, make up an unusually large proportion of the workforce – and they're good: "Abberior Instruments has the world's best development team in the field of laser scanning microscopy," says Stefan Hell. As Donnert has also found, this is something that customers value: "We're perceived as being the most innovative company in superresolution fluorescence microscopy."

ABBERIOR INSTRUMENTS LEAVES THE START-UP PHASE

The Abberior Instruments range offers something for every requirement: "For those who want to obtain good, high-resolution images as quickly as possible as well as for experts who want to derive the maximum benefit," explains Hell. The products therefore range from very easy to operate, compact STED microscopes to more powerful models and even tailor-made solutions. In addition, an independent sister firm by the name of Abberior markets the fluorescent dyes that go with the microscopes. That's also part of the strategy – everything comes from a single source in order to ensure the best possible results for researchers.

There was just one problem: many potential customers were still unaware of Abberior Instruments. The team therefore stepped up their efforts to establish contact with interested parties. Here too, rather than simply attending scientific conferences, they explored new approaches. In 2015, for example, a number of employees embarked on a two-week tour of Germany. They installed an STED microscope in a container and did the rounds of universities across the country. Every day, at a new location, they followed the same routine: set up, demonstrate, dismantle. "People were quite impressed that our systems produced top-notch superresolution in a movable container – reliably," says Donnert.

To improve their positioning in the major markets of the U.S. and Asia, the company has also teamed up with two industry giants. Since 2019, Abberior Instruments' compact STED model has been marketed by Nikon in the U.S. and Zeiss in China. Donnert is proud to report that the companies examined the devices thoroughly and were very impressed. At least now that Abberior Instruments has begun collaborating with these major players, the company evidently has left the start-up phase. Hell is amazed at how fast the company has grown in the space of seven or eight years. "Most people overestimate what they can do in one year and underestimate what they can achieve in ten years," he says, quoting Bill Gates. "The same thing happened with Abberior and Abberior Instruments."

That said, it hasn't even been ten years since the company was founded, and everything suggests that it will continue on a steep upward trajectory. The market for STED microscopes continues to expand, and the

Part of the Goettingen team with Managing Director Gerald Donnert (front row, fourth from left). In total, Abberior Instruments employs around 60 members of staff, many of whom work on ongoing research and product development.

next high-end product is already waiting in the wings: MINFLUX will be able to resolve tightly packed individual molecules in three dimensions (see box on page 29). This seemed unthinkable not all that long ago and will take biomedical microscopy in particular to a whole new level. Here, too, it was Hell who came up with the idea that underpins the method. The Max Planck Society secured the patent rights back in 2011, and the first scientific publication on MINFLUX came at the end of 2016. Abberior Instruments then acquired the licenses from the Max Planck Society – with the promise that it would develop a product from the physical concept as quickly as possible. And that's precisely what it did. Just over three years later, the prototype in the black box is so advanced that it is now a microscope that biologists can use. "That's only possible because Abberior Instruments is a slender, streamlined company in which everyone making decisions about a product also has a detailed understanding of it. And that goes for everything from the technology to its application," says Gerald Donnert. "And because all of the decision-makers are hand-picked and don't depend on financial backers," adds Stefan Hell. Once again, this goes to show that it was the right decision to found a start-up in which no one has a say but the expert scientists. ◂

GLOSSARY

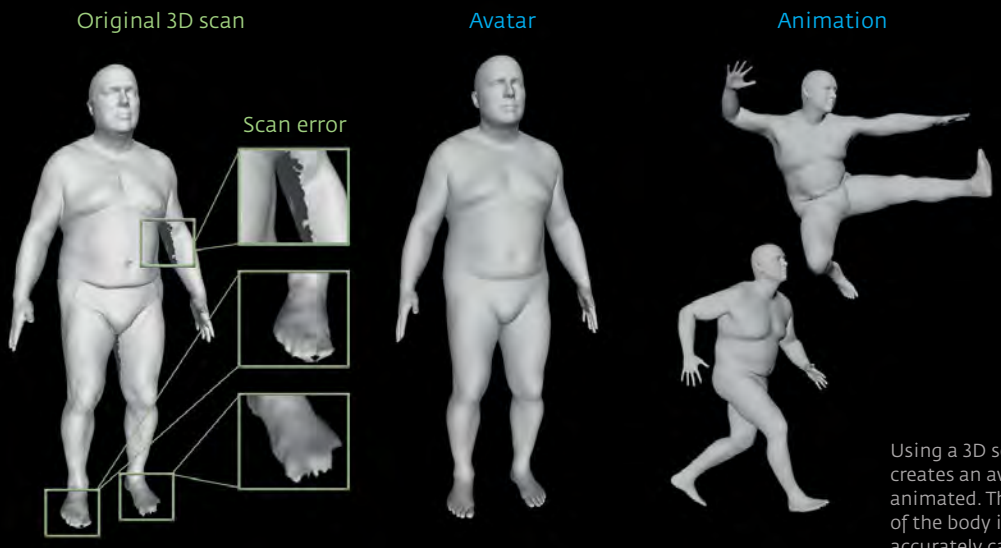
Fluorescence microscopy: In this special variant of optical microscopy, fluorescent molecules are used as tags to highlight the molecules of interest, such as specific proteins. To this end, the sample is illuminated with light, causing them to glow. As the emitted fluorescence light has a longer wavelength than the illumination light, the latter can be filtered out so that the image shows the fluorescent structures only. Individual organelles – such as the Golgi apparatus, for example – can also be marked with fluorescent molecules.

Confocal laser scanning microscopy: In this form of microscopy, the sample is scanned with a focused laser beam rather than being illuminated all at once. The laser beam excites suitable markers point by point in the sample, causing them to fluoresce.

Photo: Abberior Instruments GmbH

Avatars for everyone

Meshcapade creates 3D models of human bodies – and not only for animation in movies and computer games



Using a 3D scan, Meshcapade's software creates an avatar that can be realistically animated. The program can correct the parts of the body in the 3D model that are not accurately captured by the 3D scan – in this case a region of the upper arm and a few toes.

The startup from Tuebingen produces software that makes it easier than ever before to create animated three-dimensional models of human bodies. Meshcapade was founded by Michael Black, the Director of the Max Planck Institute for Intelligent Systems, along with Naureen Mahmood and Talha Zaman, two of his former coworkers. "Our software generates realistic avatars and movements that customers can utilize in a wide range of applications," says Naureen Mahmood, the company's Managing Director.

Such models can be used to create convincingly animated characters in films and computer games and realistic protagonists in virtual and augmented reality. Online clothing retailers scan these avatars to allow their customers to try on clothes virtually, on a model of their body that can vary in terms of both shape and activity. Robots can also use the avatars to train how to interact with people. And that's not all that 3D models have to offer.

Meshcapade is extremely versatile, chiefly because it's able to create avatars from data of widely varying quality. Motion analysis is probably the most comprehensive data collection method. Cameras record the paths of 30 to 40 reflective markers at key points on the body worn by a person in motion. The Meshcapade software converts the movements of the markers into a 3D model of the person. Meshcapade, however, can also analyze 3D scans of individuals. Since such scans are often poor in quality, the relevant software can only create static models from them. "We can even generate fairly realistic models from simple body measurements such as height, weight, and hip and shoulder circumferences," says Naureen Mahmood.

Soon Meshcapade will even be able to create 3D avatars using photos and videos. "We are continuing research into making the techniques more robust and versatile, but we can already create 3D models from photos, paving the way for many exciting applications," says Naureen Mahmood. As a result, frequenting cyberspace using virtual representations of our own bodies may become increasingly common. At the very least, we'll be meeting figures online more often with realistic body proportions that move realistically.

Graphic: Meshcapade

Reliable DNA copier

A biochemical trick to prevent errors during DNA amplification

Some scientists achieve breakthroughs by combining familiar ideas from different fields in surprising ways. Igor Ivanov is a case in point: his combination of two standard molecular-biological methods started a genuine revolution.

The story, which the scientist describes as a fairytale come true, begins in the early 1980s. While working on his diploma thesis, Ivanov, originally a physicist, spent several months in a molecular biology laboratory in Moscow, where he became acquainted with a method of cross-linking separate DNA strands using formaldehyde. Years later, he was conducting postdoctoral research at the Max Planck Institute for Molecular Genetics in Hans Lehrach's Department. Then as now, everyday laboratory work was dominated by the polymerase chain reaction (PCR), a standard technique for amplifying DNA. DNA polymerase plays a key role in PCR. It is a thermostable enzyme that copies the desired DNA section at 95 degrees Celsius or when additional reagents are added. However, the polymerase is active at much lower temperatures causing non-specific amplification errors. Confronted with this problem in the laboratory, Ivanov came up with a revolutionary solution. He recalled the cross-linking technique from his time in Moscow and added formaldehyde to the polymerase reaction mixture. Aldehyde, a molecule with the chemical formula CH_2O, would bind to the DNA, reasoned Ivanow, and thus block access to the polymerase. Once the higher temperature had been reached at which correct DNA copies are produced, these links would break and the chain reaction would be able to start.

After only a few trial runs, he realized that his method had immense potential and could be successfully marketed. The patent experts at Max Planck Innovation provided him with support, and eventually the decision was made to collaborate with Qiagen, a biotech company with which Igor Ivanov had previously worked. HotStar polymerase became a major money-earner, making a lasting impact on molecular biology. It was a technical – and a financial – success story. By the time the patent expired in 2018, the Max Planck Society had generated revenues in the millions.

Gene ferries for plant breeding

Plasmids derived from bacteria can be utilized to transfer DNA into plants

The "Ti plasmid" is a small, ring-shaped DNA molecule that is transferred into plants by the bacterium *Agrobacterium tumefaciens*. The molecule can trigger genetic changes, and thus tumors, in plants. In the 1970s, researchers at the Max Planck Institute for Plant Breeding Research in Cologne and at the University of Ghent in Belgium developed a novel method that used the plasmid to introduce new genes into plants. This technique substitutes tumor-inducing genes with selected genes in the plasmid. In 1989, Max Planck Innovation granted the marketing license for the Ti plasmid patents to the biotech company Plant Genetic Systems. After several takeovers, Bayer CropScience now holds the patents and still receives royalties for them. Ti plasmids have, for example, allowed crops to be developed that are more resistant to drought and pests.

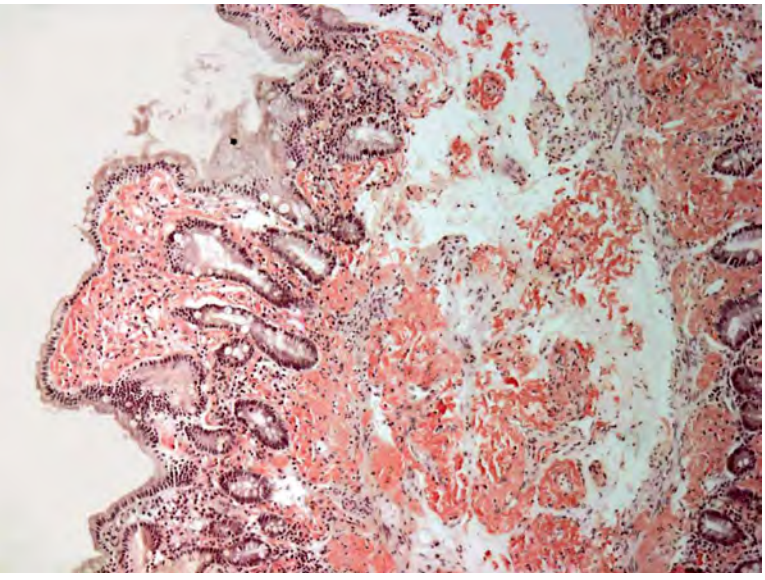
New wheat varieties have been developed to be more resistant to pests, drought and soil salinity. The plants are also expected to produce even higher yields.

Photo: Michael Callaghan / unsplash

New drug class

The drugs patisiran and givosiran are based on a process known as RNA interference and are used to treat rare genetic diseases

Patisiran and givosiran are two completely new drugs to treat rare hereditary diseases and were launched in 2018 and 2019 by the U.S. pharmaceutical company Alnylam Pharmaceuticals. Their discovery was based, among others, on two research projects on RNA interference (RNAi), whose results were patented by the Max Planck Society in 2000. Two years later, Max Planck Innovation granted Alnylam Pharmaceuticals a license to use the RNAi method in clinical medicine.



In amyloidosis, pathologically transformed proteins are deposited outside cells, as seen here in the connective tissue of the duodenum. The deposits are visualized as light red material.

Drugs based on RNAi act at an earlier point in the disease process than other drugs; they prevent the synthesis of disease-causing proteins by silencing the RNA molecules that code for them. RNA molecules are copies of sections of DNA and, among other things, serve as blueprints for protein synthesis. In the late 1990s, two U.S. scientists discovered that the nematode C. elegans can silence RNA molecules and thus genes. Thomas Tuschl and his colleagues from the Max Planck Institute for Biophysical Chemistry in Goettingen analyzed the structure of the molecules involved and discovered that the process of RNA interference also occurs in humans and other mammals. In this way, the researchers laid the foundation for the development of RNAi drugs.

Patisiran, which is being sold under the trade name Onpattro, is the first treatment for patients with transthyretin-related hereditary amyloidosis. It has so far been approved in the U.S. and many European countries, including Germany. The disease is hereditary and leads to progressive disability and, frequently, to death within five years. Patisiran is used to treat nerve damage caused by the disease. Before its authorization, no other drugs were available to treat patients.

By contrast, Givosiran is used to treat patients with acute hepatic porphyria. This rare hereditary disease causes the build-up of toxic porphyrin molecules during the synthesis of the blood pigment hemoglobin. This can result in severe pain, paralysis, respiratory arrest, and seizures.

Givosiran inhibits the formation of these toxic substances. A phase III study found that monthly subcutaneous injections could reduce the frequency of disease attacks by 70 percent. The drug has already been authorized in the U.S. and is currently under review for authorization in Europe.

Approximately one thousand patients have so far been treated with the RNAi drugs. “We anticipate that in the next few years, even more RNAi drugs will be granted authorization,” says the Managing Director of Max Planck Innovation, Jörn Erselius. “The technology represents a textbook example of how basic research can yield completely new treatments. However, patience is sometimes needed; it usually takes ten to fifteen years for a discovery to reach patients.”

In addition to clinical medicine, RNAi is an indispensable tool in basic research. Beyond licenses for use in medicine, Max Planck Innovation has also granted licenses to companies manufacturing research reagents. RNAi enables scientists to investigate the function of genes.

To ensure that the technology would also be further developed outside the U.S., the German start-up company Ribopharma was also granted a license. The following year, however, Alnylam acquired its competitor, so that the company now holds the exclusive commercialization rights. The German RNAi research site was later taken over by Roche and abandoned a few years later when the company withdrew from RNAi technology.

RNAi is therefore a prime example of foreign companies bringing a technology developed in Germany to market maturity and going on to earn substantial profits. However, even though it proved impossible to keep RNAi drug development in Germany, the Max Planck Society has nevertheless made substantial financial gains from the licensing income and the stock flotation of Alnylam in 2004.

Photo: Michael Feldman, MD, PhD, University of Pennsylvania School of Medicine

Corrosion protection to order

The company Enviral manufactures a coating containing tiny capsules that prevent corrosion – as employed, for instance, in the Bauhaus Museum in Dessau

The Bauhaus set standards not only in art and architecture, but also in novel building materials. Its successor institutions, such as the Bauhaus Museum in Dessau, inaugurated in 2019, are no exception. Brandenburg-based company Enviral utilized particularly sophisticated corrosion protection for the steel structure behind the glass facade of the museum. The coating, known as SmartCorr, is composed of nanocapsules containing an anti-corrosion agent. If the coating is scratched, corrosion occurs and the pH value changes, causing the tiny capsules to open. They then release their corrosion-inhibiting contents. The SmartCorr coating is based on a technique developed by a research team led by Helmuth Möhwald at the Max Planck Institute of Colloids and Interfaces in Potsdam. In 2018, Max Planck Innovation licensed the technology to Enviral. Together with three manufacturers of coatings, Enviral has already developed coatings incorporating the nanocapsules as additional corrosion protection. In addition to the Bauhaus Museum in Dessau, the coating, technically a "powder coating", has also been used on other buildings, such as the Thomas Mann House in Los Angeles. The house is on the coast of the Pacific Ocean and is exposed to particularly corrosive conditions. Together with other coating manufacturers, the company is also investigating the capsules as an additive for coatings. The products will benefit both customers and the environment. "SmartCorr coatings are not only more cost-effective but also more sustainable," says Rainer Rogovits, Managing Director of Enviral. "By dispensing with powder coating, we can save materials and energy."

Scratches of coated surfaces often speed up corrosion – but not if the steel is coated with SmartCorr.

Cure for leishmaniasis

One of the world's most devastating infectious diseases was defeated by an anti-cancer drug

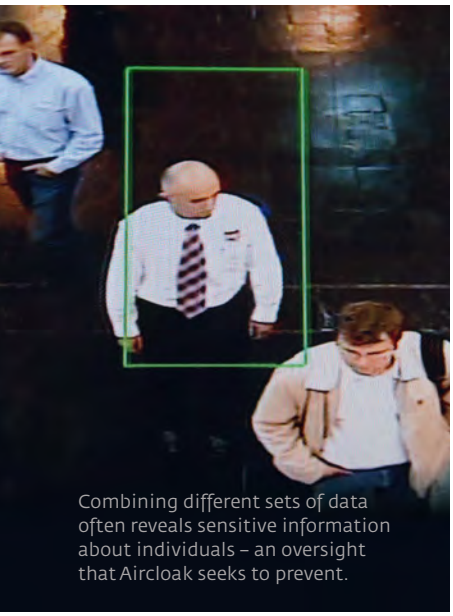
By chance, while searching for a cure for cancer, scientists discovered a cure for leishmaniasis. That's the story of miltefosine, developed in the 1980s by Hansjörg Eibl at the Max Planck Institute for Biophysical Chemistry and Clemens Unger at the University of Freiburg. Marketing authorization for the drug, under the trade name Miltex, was first granted in 1992 to the pharmaceutical company Asta Medica to treat skin metastases in breast cancer patients. However, biochemists also investigated miltefosine's effect on parasitic protozoa such as leishmanias or trypanosomes, since the immune system recognizes these in a similar way to tumor cells. They soon realized that they had struck gold. The drug makes short work of leishmanias, the pathogens that cause visceral leishmaniasis. Every year millions of people fall ill with the disease. Also known as black fever or Dumdum fever, the infection is always fatal if left untreated. However, help is now available: miltefosine, marketed by Zentaris and authorized under the trade name Impavido in India in 2002 and in Germany in 2004, has a success rate of 98 percent when administered as a four-week course of treatment.

At the Max Planck Institute for Biophysical Chemistry, Hansjörg Eibl (right) and Clemens Unger give a lecture on the synthesis of miltefosine, which is effective in treating both breast cancer metastases and visceral leishmaniasis.

Photos: iStock (above), MPI for Biophysical Chemistry (right)

Privacy protection in data treasure troves

Software by the company Aircloak enables customer information to be flexibly anonymized but still evaluated statistically



Combining different sets of data often reveals sensitive information about individuals – an oversight that Aircloak seeks to prevent.

Data is a source of new ideas. Companies can develop products for their customers using information they have on record for them. But data can also be easily misused. Banks, insurance companies and companies in the healthcare sector are obliged to handle their clients' sensitive data with particular care – and not just since the advent of the European General Data Protection Regulation, which strengthened the relevant legislation. However, anonymized customer information is frequently all such companies need to target their services to customers. Since 2016, the Berlin start-up Aircloak, which currently employs a staff of ten, has been marketing software to facilitate this. It allows companies such as financial service providers to reliably extract anonymized information from their data records. Companies employing Aircloak software can formulate a question, which will then be answered by means of a statistical analysis. The steps the software takes to anonymize answers vary depending on the nature of the question asked. Combinations of questions that are more likely to identify individuals, for instance, result in an increased blurring of answers by the the software. For example, an employee could potentially ask for the total income of a group of people followed by information on the total income of this group excluding data from a person "X". Aircloak adapts the answers it provides to these two questions to ensure that while its answers retain some statistical value, they can't be used to calculate the income of X based on the difference between the two answers.

The idea of having data flexibly anonymized by an independent entity, namely a piece of software, was the brainchild of Paul Francis, Director at the Max Planck Institute for Software Systems in Kaiserslautern. "Our software was developed based on this idea," says Felix Bauer, a former employee of Paul Francis and now Managing Director of Aircloak. "We solve the problem that deleting a person's data such as name, date of birth and complete residential address from data records is often not enough to ensure data protection." As things stand, it's possible to reveal data about individuals, both by performing multiple queries on a data set and by linking data from different sources. Aircloak's software prevents this. It helps companies to unearth the treasures in their databases while still safeguarding privacy.

Photos Caro / Oberhaeuser (left); MPI for Extraterrestrial Physics (below)

Cold plasma to combat germs

Ionized gas to sterilize wounds and surgical instruments

What are the various states of matter? Most people would probably give the following standard answers: "solid, liquid, and gas." Gregor Morfill is always keen to add a fourth: plasma. As an astrophysicist, Morfill initially studied plasma – a state in which atoms are present as ions and electrons – because that's what stars are composed of. The interest of the emeritus Director of the Max Planck Institute for Extraterrestrial Physics has now extended to "cold plasma." Unlike the plasma in stars, cold plasma is at a moderate temperature and – as Morfill recognized – can be used as a disinfectant. He developed this concept into a concrete medical application that streams a breath of cold plasma over a wound or target to be disinfected, killing all bacteria and viruses in just minutes. Based on this idea, Gregor Morfill founded the company terraplasma in Garching in 2011.

In addition to wound disinfection and sterilization of surgical instruments, Gregor Morfill's team of researchers has identified several other fields of application. The antibacterial effect of cold plasma can also be used to treat water, for instance to sterilize drinking water. Furthermore, it eliminates molecules that cause odors as well as allergens. Cold plasma can also be used to purify air or reduce exhaust emissions, fields which are currently being investigated by terraplasma and its spin-offs.

Among other things, wounds can be efficiently sterilized using the pale-blue, glowing cold plasma.

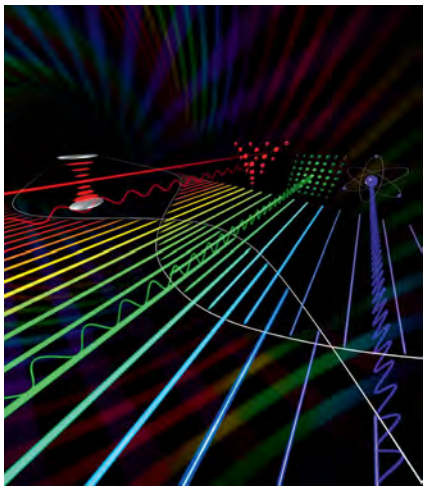
Light combs as yardsticks

A Nobel Prize-winning technology that can improve satellite navigation and measurements of time and distance

Atomic clocks are trailblazers – and not just as timekeepers (they can be accurate to within one second over 30 million years), but also in the more literal sense of the word. That's because atomic clocks are an essential element in satellite navigation systems such as GPS or Galileo. Their accuracy determines how well such systems can pinpoint our position. However, clocks known as optical clocks can be even more accurate than atomic clocks. Optical clocks employ the frequency of a light wave that an atom can absorb or emit when it passes from one energy state to another as a timekeeper. A device known as an "optical frequency comb" enables such transitions to be recorded with extraordinary accuracy. Each "tooth" of the comb is a different color of the rainbow, and the even spacing of these teeth can be specified with extreme precision. Frequency measurements using the optical frequency comb make optical clocks not only more accurate, they also allow different clocks to be compared.

The techniques underlying optical frequency combs were developed by Theodor W. Hänsch, Director at the Max Planck Institute for Quantum Optics in Garching and Professor at the Ludwig Maximilian University in Munich. In 2005 he was awarded the Nobel Prize in Physics for his contributions. Back in 2001, together with Ronald Holzwarth and Michael Mei, he founded Menlo Systems in Martinsried near Munich, which today employs more than 100 people and is the world market leader in optical frequency combs.

The technology can be deployed wherever light frequencies need to be measured with extreme accuracy. In addition to the field of atomic clocks, optical frequency combs can, among other things, also improve the accuracy of pure physics experiments involving spectroscopy and the sensitivity with which trace gases can be analyzed in the atmosphere. Precise frequency measurements can also improve the accuracy of the information garnered from the starlight captured by telescopes, and thus the properties of the stars. Crucially, the light emitted by a star depends, among other things, on the temperature and composition of its surface. Since light wave frequencies can readily be used to determine distances – as evidenced by standard tools from hardware stores to measure distances – frequency combs can also be used in all situations where extremely precise distance measurements are vital, for instance to coordinate swarms of satellites.



Optical frequency combs with their accurately fanned out lines of differently colored light have many applications, for example in spectroscopy.

In addition to optical frequency comb technology, Menlo Systems also offers numerous other advanced products for optical applications, such as femtosecond fiber lasers, which efficiently generate exceptionally short flashes of light. These can be used to shed light on neurological processes or to process materials. The company based in Martinsried also manufactures systems that generate optical frequency combs in the terahertz range. One area of application is in quality control, for example in the plastics and food industries.

Graphic: Menlo Systems

Genetic fingerprinting

Particular fragments of DNA can be used to reliably prove paternity

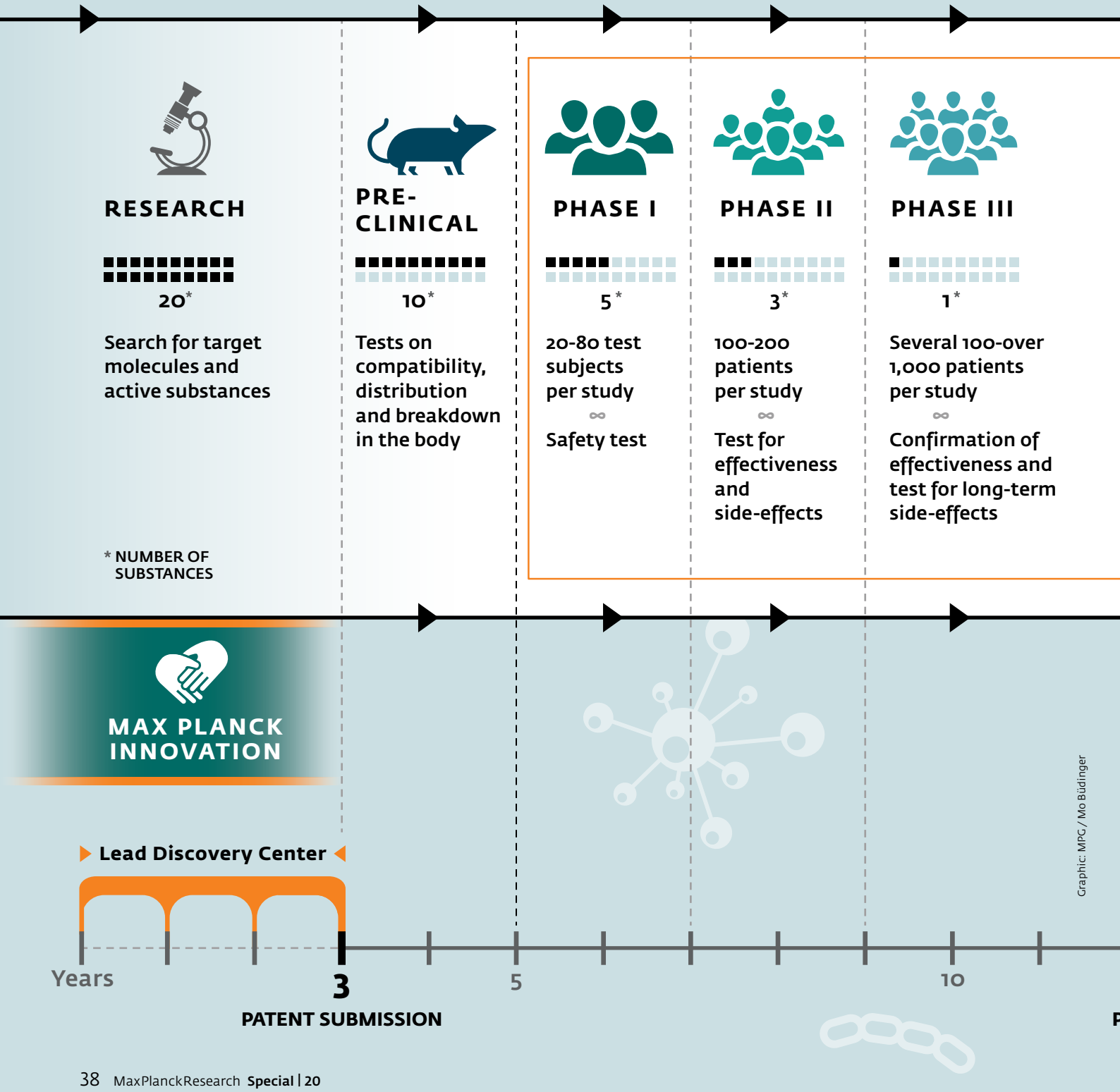
"Luke, I am your father!" – not all fathers are as open as Star Wars' Darth Vader in admitting the paternity of their children. In cases where doubt has been raised, the matter needs to be settled in court by means of a paternity test, comparing the mother's, father's and child's genetic material.

Diethard Tautz might justifiably be regarded as the father of this technique. A biologist, and now the Director of the Max Planck Institute for Evolutionary Biology in Ploen, Tautz identified specific DNA fragments in the genome of the fruit fly *Drosophila* as part of his doctoral thesis. These fragments known as "short tandem repeats" are short regions of repeated, extremely short DNA sequences. Tautz discovered that each individual possesses a characteristic set of these tandem-like repeats, inheriting these genetic traits half from the father and half from the mother. As a result, they can be used in kinship analysis. Together with Herbert Jäckle, Director at the Max Planck Institute for Biophysical Chemistry, Tautz developed the short-tandem repeat method, a genetic fingerprinting technique that enables paternity to be proven with absolute certainty. This method has also established itself as the standard in forensic science to reveal identities.

The Max Planck Society granted a license for this to the U.S. company Research Genetics in 1993 and a sub-license to Promega, also based in the U.S., in 1996.

From the lab to the pharmacy

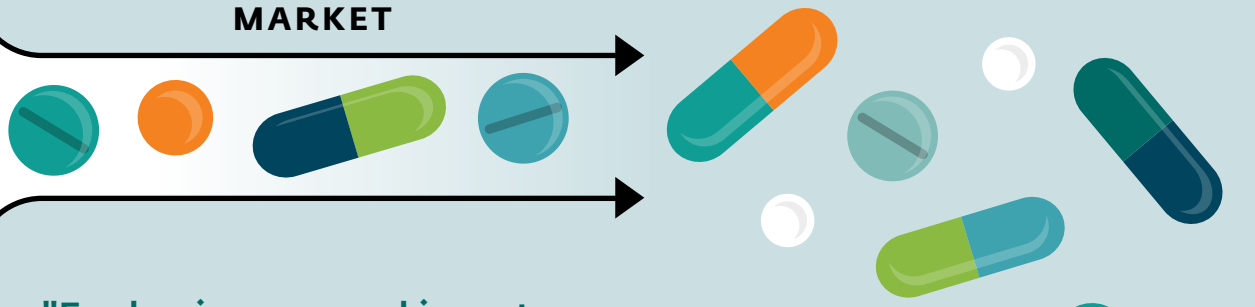
Before an active substance discovered in the laboratory reaches the market as a drug, it must first prove its worth in lengthy tests. This can take up to ten years or more. Most candidates fail: on average, only one in 20 active substances is developed into a new drug.



Graphic: MPG / Mo Büdinger

Clinical development

MARKET



"For businesses and investors, it is often too risky to draw on results from early academic research. The purpose of the Lead Discovery Center is to bridge the gap between research, industry and risk capital."

JÖRN ERSELIUS, MAX PLANCK INNOVATION

DRUG

Generic drugs

PATENT GRANTED

PATENT EXPIRES

Just a spoonful of sugar

Peter Seeberger has founded nine start-ups to date. With these companies, the Director of the **Max Planck Institute of Colloids and Interfaces** in Potsdam wants to put the results of his basic research into practice. One goal is to introduce sugar-based vaccines against multi-resistant bacteria.

TEXT **CATARINA PIETSCHMANN**

Peter Seeberger bursts in through the door. His last meeting, dealing with his latest company, took a little longer than expected. But then he gets straight into the subject at hand without slowing down. He speaks extremely quickly since he has no time to lose. The ideas that keep bubbling out of the 53-year-old just have to be implemented.

The subject is sugar. This is not about the fine, white crystals of the ubiquitous sweetener that spring to mind. Nor is it diabetes. Actually, Peter Seeberger is interested in the biological functions of longer-chain sugar molecules, the oligosaccharides. These molecules surround every living cell like a fine fur, no matter whether human, animal, or plant.

Here they form parts of large molecules, namely glycoproteins and glycolipids, that project out from the cell surface like small antennae. Cells use these antennae to communicate with their surroundings. Messenger substances dock here, triggering cascades of signals inside the cell. And, they serve as a critical checkpoint for friend-or-foe identification. Bacteria and viruses also have these antennae and use them to dock onto human cells. This is what makes these sugar chains, known as glycans, so interesting for medicine – as antigens in new vaccines or as diagnostic tools, therapeutic antibodies or drugs. Peter Seeberger, Director of the Biomolecular Systems Department at the Max Planck Institute of Colloids and Interfaces in Potsdam since 2009, is one of the pioneers of molecular glycobiology.

A SYNTHESIZER FOR VACCINE CANDIDATES

It all started in Boulder, Colorado, where the native of Nuremberg earned his doctorate in biochemistry after studying chemistry in Erlangen, Germany. There he asked himself, why are there machines with which we can synthesize any type of DNA, but nothing comparable for glycans? First, he familiarized himself with the chemical aspects of the question in the New York laboratory of sugar synthesis specialist Samuel Danishefsky. At the Massachusetts Institute of Technology (MIT) in Boston, he then modified an old DNA synthesizer to assemble oligosaccharides and founded his first company, Ancora Pharmaceuticals, in 2002. This company produces custom-made glycans. GlycoUniverse in Potsdam, which Seeberger founded in 2013, provides easy access to the world of glycans for scientists in academia and industry with the Glyconeer 2.1, developed by his team as the first commercial synthesizer for oligosaccharides.

The synthesizer now makes it almost child's play to reproduce key sugar structures from pathogens and thereby generate candidates for vaccines that stimulate the human immune system to produce antibodies. To get closer to clinical application in the development of sugar-based vaccines than is possible at a Max Planck Institute, Seeberger founded Vaxxilon AG in 2015. This company specializes in targeting resistant hospital germs.

Photo: David Ausserhofer

Chemist Peter Seeberger experienced starting companies as a completely normal act during his time at MIT. This is one reason why he is pursuing developments with several start-ups, especially in the field of glycobiology.

These include *Klebsiella pneumoniae* (triggering pneumonia and sepsis) and *Clostridium difficile* (intestinal inflammation), which are especially dangerous due to their resistance to many drugs.

THE FAST TRACK TO MALARIA DRUG ARTEMISININ

Seeberger's role models include U.S. physician and microbiologist Maurice Ralph Hillemann (1919-2005), who developed nearly 40 vaccines. These include vaccines against measles, chickenpox and hepatitis A and B. "In the end, he managed to make the world a little bit better," says Peter Seeberger. This statement also describes his own motivation: to make the world "a little bit better" through his research, especially in regions of the world that lack comprehensive medical care.

In his Department in Potsdam, Seeberger conducts basic research out of scientific curiosity. "But when we find something interesting, we continue to pursue it. And yes, I do always ask myself if there is an application." As a re-

Automated sugar synthesis: the synthesizer brings the reactants together at the right time and in the right quantity. Seeberger commercialized this method at the Ancora Pharmaceuticals and GlycoUniverse companies.

sult, nine companies have been founded as of January 2020.

With one company, ArtemiFlow GmbH, founded in 2013, the chemist has taken up the fight against malaria. This disease kills nearly 500,000 people every year – most of them children. In an effort to do something about it, a team headed by Peter Seeberger also left the tried and tested path of sugar-based vaccines. The researchers developed a flow synthesis device using UV light to take a critical step towards developing the malaria drug artemisinin, which enables the conversion of a substance from the sweet wormwood plant to the active ingredient within 15 minutes. ArtemiFlow uses this process to produce artemisinin on a large scale.

In the meantime, the subsidiary ArtemiFlow USA was founded. "We are now growing sweet wormwood in former tobacco fields in Kentucky," explains the chemist. The scientists also want to investigate artemisinin as a potential active substance in fighting cancer. "There are now clinical studies that show this substance to be effective against 114 different types of cancer as well as several autoimmune diseases."

FluxPharm, founded in 2016, is also developing commercial flow synthesis. The company also wants to use this method to produce important drugs cost-effectively – also directly in developing countries. Just recently, Peter Seeberger's group even developed and patented a device for autonomous chemical synthesis. These are small systems that can be located anywhere and controlled from a laptop. This would make it possible to produce drugs on demand in developing countries in the future. But production in industrial nations would also be more cost-effective. "No pharmaceutical company would have to continue producing its drugs in low-wage countries like China or India. Instead, they could be produced fully automatically in Germany."

Together with partners in Denmark, Seeberger founded Draupnir Bio ApS in 2017 for the preclinical development of new sugar-based agents to lower cholesterol. Stimulated by an inquiry from a Danish colleague, Seeberger's team, with its comprehensive glycan library, launched the search for a sugar that binds effectively to PCSK9. This enzyme plays a very important role in lipid metabolism. "It is important to inhibit this in people with high cholesterol levels to prevent potential heart attacks. Unfortunately, statins, the classic cholesterol reducers, do not work in one out of five patients." Seeberger identified a sugar that blocks PCSK9 by a different mechanism from that of statins and which can be taken orally.

A very recent addition is Tacalyx GmbH, founded in Berlin in 2019. With this company, Seeberger wants to take on a heavyweight opponent: cancer. Even malignant tumors have glycan structures on their cell surfaces. Could it be possible to vaccinate against cancer by using sugar structures from tumor cells to provoke an immune response in humans?

As a postdoc, Seeberger learned about a candidate vaccine that was

Photo: David Ausserhofer

then tested 20 years later in Asia. It protected 50 percent of the test subjects from cancer because their immune system generated antibodies against cancer cells. The other half of the study participants did not respond to these sugars. Tacalyx is now developing monoclonal antibodies against sugars on the surface of cancer cells to specifically target them.

CLOTHING FROM CRUSTACEAN SHELLS AND RICE STRAW

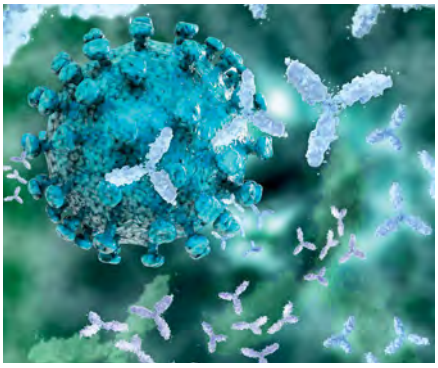
Peter Seeberger's repeated implementation of results from promising basic research in start-ups is due in part to the attitudes of established companies towards these developments: "We usually develop something completely new that is associated with a paradigm shift," the chemist explains. "Industry often has difficulty handling this." In addition, it comes naturally to him to combine research and entrepreneurship. This also has to do with his past experience. Early in his career, he was a professor at MIT in Cambridge, Massachusetts. "Starting up companies is an everyday event there."

Seeberger's wide-ranging experience with start-ups has also highlighted the biggest hurdles: "Finding the right people for management and, of course, obtaining solid financing." Now, he knows many people and knows who, and in which position, can move something forward. The work of Max Planck Innovation has also been very helpful. Seeberger greatly appreciates their support in matters such as selecting appropriate licensing models or in financing companies. More than that, however, he appreciates the freedom that the Max Planck Society generally provides him in his research.

The search for sugar-based vaccines could have just simply continued. But Seeberger's research took a new turn after the working group relocated from its temporary quarters on the campus of the Free University of Berlin to a building expansion at the Max Planck Institute in Potsdam in 2015. There, his focus shifted to carbohydrate-based materials. This area of interest essentially imposed itself upon him since the biomaterials experts are right next door in Potsdam. "I had hardly looked at structural aspects before, only the biological function," he says. "80 percent of biomass on Earth is made of sugars – and most of these sugars have structural functions! Typical examples are cellulose in wood or chitin in crustaceans."

So could cotton, which requires large land areas and large quantities of water to grow, be replaced by a fabric made from crustacean shells? "We are also considering how we could combine chitin with cellulose. Both are flexible and both form fibrils." This would yield unconventional, sustainable hybrid materials: T-shirts, clothing and bed linen that simply lands on the compost pile and turn into humus once they are worn out.

Today, crustacean shells from shrimp farming are simply thrown back into the sea. And in Vietnam alone, 170 million tons of rice straw, which also consists largely of cellulose, are burned annually. What a resource! "Our vision is to develop a completely new recycling economy based on renewable raw materials, away from oil and towards producing everything based on sugars. And all of this from ordinary animal and vegetable wastes!" Peter Seeberger is just getting started in this field. There is therefore a good chance that one, two or three more start-ups will result based on these resources over the next few years. ◂



Sweet defense: Peter Seeberger and his team are searching for sugar-based vaccines that stimulate the immune system to produce antibodies with specialized targets, such as the glycoproteins of pathogens.

GLOSSARY

Flow synthesis is a chemical process whereby the reaction medium is routed through an apparatus in which the conversion takes place. Since the reaction products can be separated out relatively easily at the end of the process, the chemical industry prefers this type of process over one in which the reaction takes place in a closed container.

Glycan: A polysaccharide comprising a chain of simple sugars, such as glucose or fructose. An example is cellulose. Polysaccharides also occur in signal molecules on the surfaces of cells in connection with proteins in the form of glycoproteins or in combination with fat molecules as glycolipids.

Photo: Adobe Stock

Researcher with ingenuity: Katharina Landfester has already registered more than 50 patents for nanocapsules. And because her team is continually pursuing new ideas, there will be more to come.

The all-purpose capsule

Katharina Landfester, Director at the **Max Planck Institute for Polymer Research** in Mainz, has opened the door to numerous applications. She has developed a technology whereby tiny containers can be specifically manufactured for almost any substance and equipped with various functions. Her team is now working on using nanocapsules as transporters for pharmaceuticals, as medical sensors, or as fungus treatments in wine production.

TEXT **TOBIAS HERRMANN**

When Katharina Landfester first held a glass of the milky liquid in her hand, she had no idea what was in it. The receptacle contained a mixture as unremarkable as its name: a mini-emulsion. Milk is a well-known example of a mini-emulsion. Tiny droplets of fat are distributed in a large quantity of water. These are held in suspension by proteins and lipids. But a mini-emulsion from Katharina Landfester's laboratory can do much more than milk. The chemist's team uses the droplets to produce nanospheres and nanocapsules that can be used as vehicles for numerous purposes. The particles can transport medications through the body or provide medically relevant data from the body. They are also useful for pest control in agriculture and for countless other technical applications.

The history of the multi-functional particles began in 1997. Back then, Landfester was working as a junior scientist in the Department of Markus Antonietti, Director at the Max Planck Institute of Colloids and Interfaces in Potsdam-Golm. There, she researched colloids and developed the first prototypes of the mini-emulsion droplets. However, she faced some obstacles along the way. "It was clear that we would have to take a close look at the physical-chemical processes in the mini-emulsions," explains Landfester. If these could be understood more precisely, it might be possible to produce a wide variety of nanoparticles in a targeted manner, controlled by the composition of the mini-emulsions. >

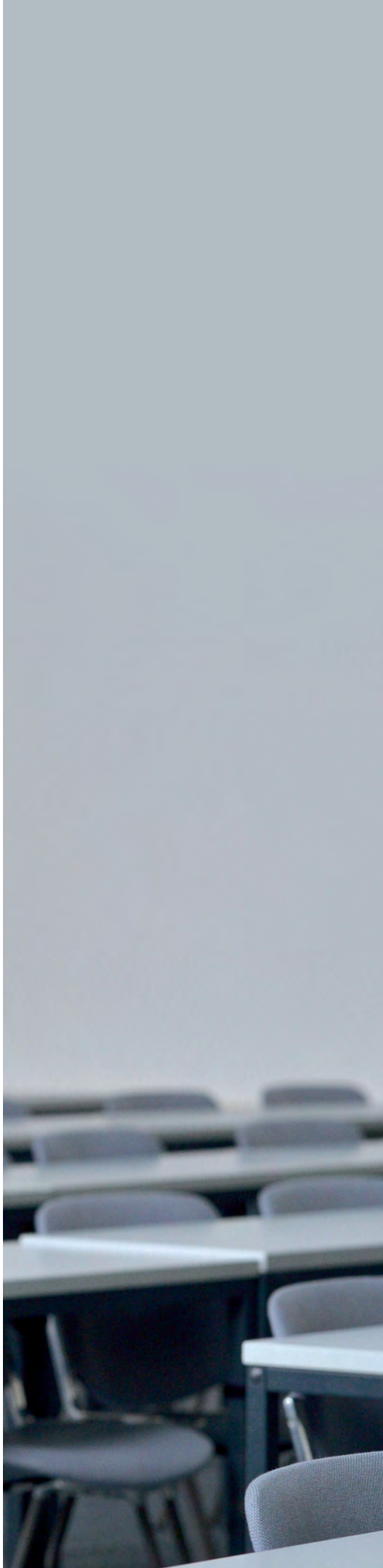
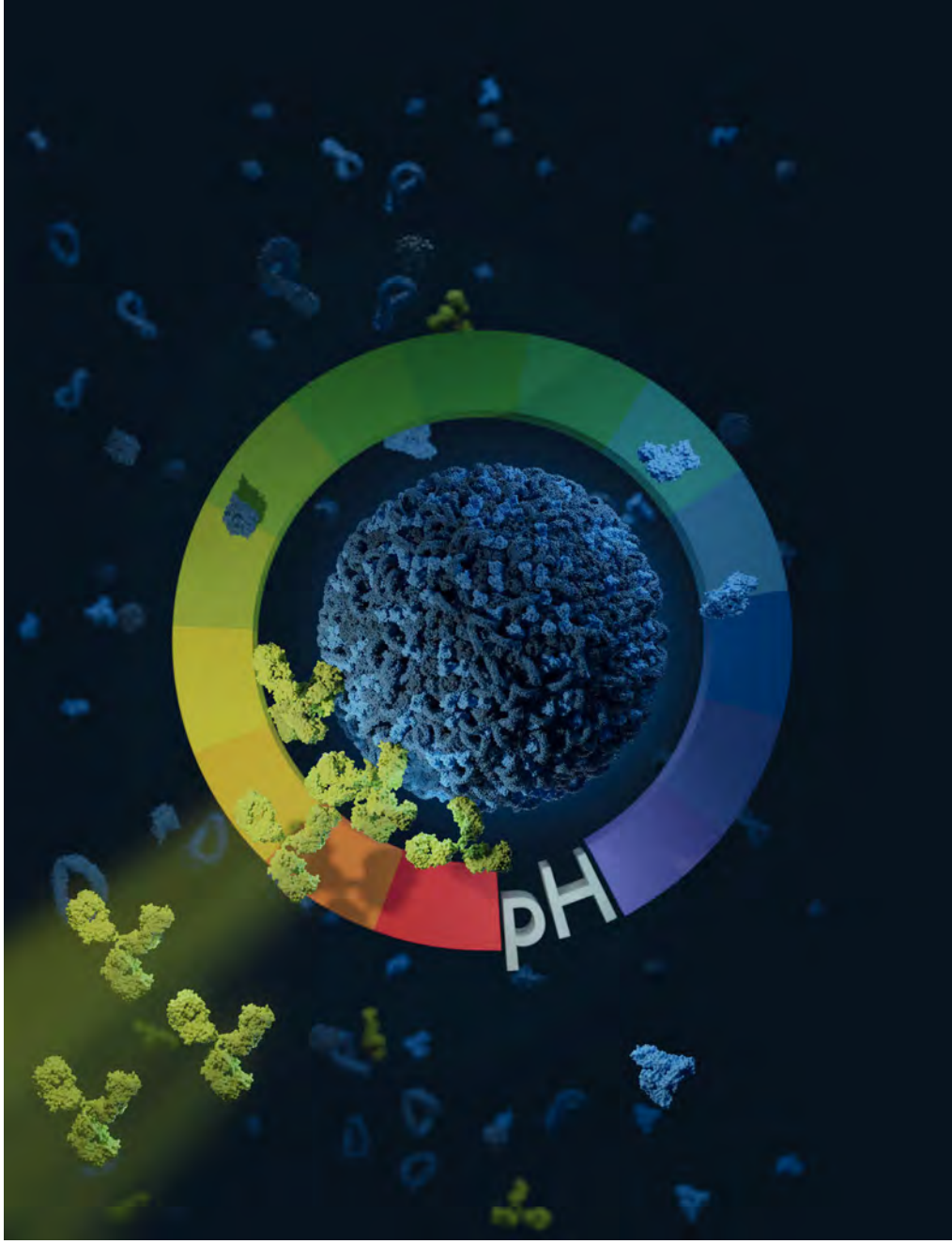


Photo: Frank Vinken



A question of environment: in an acidic solution (i.e. at a low pH), antibodies (yellow) attach themselves to nanotransporters (blue) without being damaged. In previous attempts to create a compound through chemical activation, the antibodies lost their function.

In 2003, Landfester – by now a professor at the University of Ulm – developed a method for producing emulsions in which all the droplets are nearly the same size. This worked both with emulsions of oily droplets in an aqueous environment and with mixtures of water droplets in oil. Landfester turned the emulsions into a versatile means of producing nanoparticles by allowing chemical reactions to take place on the surface of the droplets. For the first time, she succeeded in producing stable nanocapsules for various different purposes. Or, as Landfester puts it: "This allowed us to encapsulate virtually anything."

The chemist explains that the most important element of nanospheres is the shell. "The shell, which is only about 10 nanometers thick, must be absolutely leak-proof so that the encapsulated substance cannot diffuse out. But as soon as required, it must be possible to reliably open the shell." The researchers use enzymes, a change in temperature or pH value, or irradiation with UV light to do this.

THE CAPSULES NEED COVER AND A GUIDE SYSTEM

In her laboratory in Mainz, where she was appointed Director of the Max Planck Institute for Polymer Research, Landfester has been refining the chemical processes that turn nanocapsules into highly functional tools since 2008. Together with her colleagues, she has further developed the tiny capsules for various potential applications. Three ideas are particularly promising: a transporter for pharmaceuticals, a thermometer for cells, and a vaccine for grapevines.

The nanocapsules, which are intended to deliver an active ingredient to a specific focus of a disease, are perhaps the best example of how nanocontainers can be modified as required. This would allow the dose to be significantly increased where the active ingredient is most needed. The rest of the body would receive much less, and the side effects would be reduced to a minimum. This is a major advantage, particularly when determining the dose of cancer drugs for which there must be

Photo: Volker Mailänder / MPI for Polymer Research

an appropriate balance between damage to the tumor and damage to the surrounding tissues.

Landfester's research team has already overcome several obstacles on the way to developing a cancer drug that is both more effective and better tolerated than other drugs thanks to the targeted delivery of active ingredients. Together with a team led by Volker Mailänder, who is both a doctor at the University Hospital in Mainz and a researcher at the Max Planck Institute, she has spent several years exploring the possibilities of the capsules. For example, they coated the surface of the capsules with proteins that immune cells or macrophages do not recognize as foreign. The camouflaged nanoparticles can then move through the human body unhindered by immune cells. And to ensure that the capsules penetrate only the target cells, they have built a kind of navigation system into them.

For this purpose, the researchers equipped the capsule shell with antibodies that are meant to guide the nanocapsules to the desired target. Nevertheless, it was precisely at this step that the scientists initially hit a brick wall. Mailänder remembers the difficulties well. "We wanted to chemically bind the antibody to the nanotransporter. In this process, also known as targeting, the surface of the nanotransporter is first chemically activated so that the antibody can dock to the carrier." However, this process always ended up altering or destroying the antibody, thus causing it to lose its effect. The researchers ultimately found a solution, albeit more or less by accident. "In order to be able to measure how effectively the antibody binds to the capsule, we performed a control experiment in which we did not activate the surface of the transporter but rather mixed nanocarriers and antibodies in a buffer solution." The scientists hypothesized that the antibody would be unable to bind to a non-activated surface and be easily removed by various washing processes.

To their great astonishment, the supposed negative control produced a better result than the actual experiment. However, this was not due to errors in the experiment: "Contrary to all previous findings, the non-activated nanocarrier obviously binds the antibodies to itself more strongly than the modified one," explains Mailänder. "We were faced with an enigma."

THE NANOTRANSPORTERS WORKED WELL IN MICE

The team found the answer in the slightly acidic buffer solution in which the antibodies unfolded easily and thus adhered firmly to the nanotransporter. This compound persisted even in media with a high content of other proteins – including blood. In contrast, the chemically activated carrier-antibody complex almost completely lost its effect.

After also overcoming this obstacle, the researchers tested their transporters in living organisms – and were successful. "We had already used nanotransporters in mice to transport some substances to the desired location," says Landfester, "and also released them there." The second step is performed primarily by enzymes. "We usually design the capsule shell so that it can be opened only by enzymes present in the target cells," says Landfester. The opening of some nanotransporters also differs depending on the pH value, which is different in cancer cells than in healthy tissue. So far, the scientists have encapsulated anti-inflammatory agents and drugs designed to specifically trigger immune cells. This vaccination should enable the immune system to more effectively fight cancer. However, before physicians can use this nanotherapy in practice, various tests, refinements, and clinical studies are needed. In the long term, however, the nano-submarines of Volker Mailänder and Katharina Landfester could make some treatments more effective and more tolerable.

The nanocapsules could not only improve therapy, but also biomedical research and diagnosis. To this end, Katharina Landfester and Stanislav Balouchev have developed a dual nanosensor that measures the temperature and oxygen content of a cell in real time. These two pieces of information are of particular interest for medicine. Whether protein synthesis, DNA repair, or signal molecules that dock to receptors – these constantly recurring biochemical processes that occur in every cell can be successful only if the temperature is right and the cell has the right amount of oxygen available. Deviations from the values may sometimes be the result of diseases. The appropriate measurements can therefore improve the understanding of what is wrong and also enable a diagnosis of the disease. >

For both measurements, dyes, which are transported in nanospheres consisting of a mixture of oil and wax to the diseased cells, play a decisive role. The dyes are stimulated to emit under red light, which also penetrates into deeper layers of the body. When measuring temperature, the color of the light that the dye molecules emit depends on how well they can move in the waxy nanospheres. These become increasingly soft, especially in the physiologically relevant range between 35°C and 42°C. The dye molecules come closer together more often in warmer environments. Because one molecule absorbs energy from the other during such an interaction and then emits more energetic light, the dye molecules emit yellow rather than red at a higher temperature of the tissue under investigation. In this way, they can be used as nanothermometers.

The nanospheres become an oxygen sensor because they contain dye molecules that bind a precisely known amount of activated oxygen contained in the sphere itself when excited with light. The resulting concentration gradient is balanced by oxygen diffusing into the cell. The more oxygen is present in the capsule environment, the faster the capsule refills with oxygen. As with a thermometer, the scientists calibrate their oxygen meter beforehand. They therefore know how fast

Photo: Christian Schneider / MPI for Polymer Research

An employee from Frederik Wurm's group drills a hole in a vine and attaches a plastic cup containing a few milliliters of a cocktail containing nanocapsules with a fungicide against the esca fungi, which is a dreaded vine pest.

this process takes place at a certain concentration. This enables them to deduce the oxygen concentration in the cell from the time when the capsule refills with oxygen.

The nanocapsules consist of biologically compatible components and are therefore harmless to the cell. However, this characteristic is accompanied by a significant disadvantage: within a few hours, they are degraded by enzymes. The dual nanosensor already works quite well in cell cultures, where it could one day help to investigate the effectiveness of active ingredients, for example. The researchers recently carried out the first experiments with mice. However, before they can test the method in human tissue, a lot of researching and experimentation is required. For this reason, Landfester describes the approach as "somewhat visionary."

Photo: Christian Schneider / MPI for Polymer Research

NANOBAIT WITH FUNGICIDE FOR LIGNIN-EATING FUNGI

An application beyond medicine that is already close to implementation is the protection of vines against fungal attack. This could help wine growers overcome their greatest adversary: esca. This is a group of fungi that eat their way through the trunk of the vine and decompose it – resulting in considerable financial losses every year.

The fungi ravenously attack the lignin, one of the main components of the vine. A team of researchers led by Frederik Wurm, group leader in Katharina Landfester's Department, take advantage of this. Using mini-emulsion technology, they produce tiny capsules of lignin and fill them with fungicides. For the treatment, they drill a hole in the trunk and attach a small plastic container containing a few milliliters of a suspension toxic to the fungi. The cocktail of nanobait is then drawn into the vine. There, the esca fungi are attracted by the lignin-containing shell of the nanocapsules and eat them. "They effectively dig their own grave," says Wurm. Because as soon as they open the capsule, the active ingredient escapes and does its job.

In the past, fungicides were simply sprayed on the vines. However, this treatment did not work for long and had to be repeated regularly. As a result, fungicide residues were detected in the grapes. And even with repeated applications, the plant protection agent did not effectively combat esca.

This novel method eliminates the fungus reliably and sustainably, even though significantly less of the fungicide is used here than in the spray treatment. "We conducted the first experiments five years ago, and the vines we treated then are still doing well," says the scientist. Because the fungicide was used sparingly, no traces of the fungicides were found in the grapes. A further advantage of the nano-fungus treatment is that it is a form of upcycling: the lignin for the nanocapsules is a by-product of paper production.

The method has been met with great interest from winegrowers and agrochemical companies alike. Talks are already underway with several companies about possible cooperation, says Wurm. A spin-off is also conceivable. The scientists are still carrying out various tests but hope to market the product soon. The esca fungi could then literally get their last meal.

"WE STILL HAVE PLENTY IDEAS"

The treatment of grapevines, the deployment of nanosensors and the transport of pharmaceuticals are just a few of the many possible applications of nanocapsule technology. Among other things, Katharina Landfester and her colleagues have already developed corrosion protection for airplanes, adhesives that gain and lose their adhesiveness as required, and a printer's ink with which electrically conductive polymers can be printed. Katharina Landfester has already filed around 50 patents in connection with the nanocapsules – the first during the late 1990s. While she was at Max Planck, she received ongoing support from the patent experts at Max Planck Innovation. Some patents for developments that Landfester made in Ulm were later transferred to the Max Planck Society. Her team will continue to employ patent experts at Max Planck Innovation: "We still have plenty of ideas about what we could do with the nanocapsules," says the researcher. ◂

The profiler

Lothar Willmitzer, a scientist at the **Max Planck Institute of Molecular Plant Physiology** in Potsdam, had never thought about the commercial application of his research. Nevertheless, he founded three companies during his career. He is particularly pleased that his research has also been able to benefit humans.

TEXT **CATARINA PIETSCHMANN**

Scientists can read the metabolism of an organism like a book. It reveals stress, diseases, environmental toxins, and nutrient deficiencies as well as which nutrients an organism needs and which medicines work in the case of illness.

In contrast to the metabolism of humans, little was known about the metabolism of plants for a long time. This is why, in 1994, Lothar Willmitzer and his colleagues at the Max Planck Institute of Molecular Plant Physiology in Potsdam-Golm, which had just been founded at the time, began to investigate the metabolic pathways of plants such as *Arabidopsis thaliana* and potato. It soon became clear just how extensive this project was. The uptake of nutrients, the formation and storage of constituents, plant growth, and seed formation are all part of the metabolism.

Even the formation of starch in a potato plant proved to be much more complicated than expected. "Once we had identified genes for starch production, we modified their activity in such a way that they were able to produce more and higher quality starch," says Willmitzer. "However, the daughter plants produced less instead of more starch." Willmitzer concluded that he would have to switch off one gene after another in order to truly understand starch metabolism.

AUTOMATED METABOLIC ANALYSIS

Countless samples of plant extracts soon covered the lab benches. Each of them was composed of different metabolic substances. To analyze them all would have been a Herculean task. "We quickly realized that we would have to automate this so we wouldn't get bogged down in routine tasks," says Willmitzer. But the chemists were skeptical. They thought that analyzing hundreds of unpurified samples in parallel would produce results that were far too inaccurate.

"We didn't want to precisely determine one substance in the sample but rather the ratio of as many substances as possible to each other," says Willmitzer. The aim was to detect the change in metabolism when a gene is switched off. Willmitzer then wanted to compare this pattern with that of other genes and thus obtain a comprehensive picture of the metabolic activity of a plant.

He called his method "metabolic profiling". He started with *Arabidopsis*. Crop plants such as potatoes, corn, or rice would follow. The initial test results suggested that the plan would work in principle. But it would take years to switch off the approx. 30,000 genes of *Arabidopsis* one by one and measure the effect.

Willmitzer thus began his second career as a company founder. It all began in 1998 with his spin-off, Metanomics. Funded by BASF and the German Federal Ministry of Education and Research, Willmitzer and four former employees developed the initial technology platform.

Before then, it was common practice to process all biochemical levels

Photo: Till Budde, Economic Development Agency Brandenburg (WFBB)

Lothar Willmitzer is successful not only as a scientist but also as a founder of spin-offs. The companies he founded now employ around 55 people.

completely and successively: from the gene and DNA to the messenger RNA to the protein synthesis and the metabolic products. In the case of Metanomics, however, the scientists switched off a gene and then observed only the effect on the metabolic cocktail of sugars, amino acids, enzymes, and vitamins. Each sample provided a mixture of 350 different substances. Approximately 40% of the substances were completely unknown. Metanomics is now an independent subsidiary of BASF.

SERVICES FOR THE INDUSTRY

In the years to follow, Willmitzer repeatedly asked companies whether he could analyze plant metabolites for them. But services for industry are not part of the scope of a Max Planck Institute. Willmitzer therefore founded Metasysx in 2012. The company, which is located within view of the Max Planck Campus, now has around a dozen employees analyzing the metabolic profiles of plants. In addition to complete metabolic profiles, the small company also determines the fatty acid profiles of a plant, integrates genetic and protein data, and produces metabolic products as reference standards.

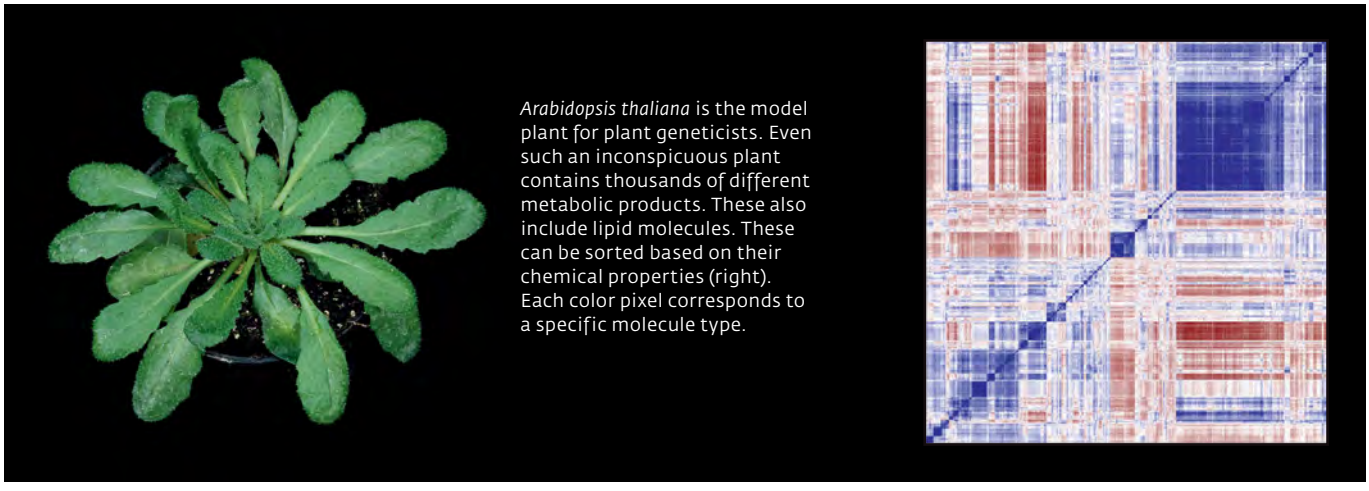
"Start-up companies are often very much driven by people, and developments are sometimes coincidental," says Willmitzer. For example, his Chinese doctoral researcher, Yan Li, was initially part of the Metasysx team and then returned to China. "We had considered building a laboratory there. But that wouldn't have been easy for a foreign company." But now with a Chinese pharmaceutical company as a partner, it is. Metasysx now has a subsidiary company called Metanotitia in Shenzhen. It further develops metabolic profiling for both acute and predictive diagnostics of various diseases.

Metabolic analysis for medical applications is now also becoming more important in Germany. "Metasysx also collaborates with the Charité hospital in Berlin. We hope to improve the dosage of drugs that suppress the immune system after transplantation so that the new tissue is not rejected by the body," explains Willmitzer.

MORE PRECISE DOSAGE

There is still no precise information on the quantities in which these products should be administered, so Metasysx now analyzes the metabolic profiles of blood and urine samples of patients treated with various doses. "We want to develop mathematical models in order to be able to more accurately predict the effect on individual patients."

Another joint project between Metasysx and the Charité could be the treatment of depression. "Doctors still diagnose the disease mainly by interviewing the patients. It is not possible to predict which drugs a patient will respond to. Doctors must therefore experiment with different active ingredients," explains Willmitzer. Metabolic



Arabidopsis thaliana is the model plant for plant geneticists. Even such an inconspicuous plant contains thousands of different metabolic products. These also include lipid molecules. These can be sorted based on their chemical properties (right). Each color pixel corresponds to a specific molecule type.

Photo: MPI of Molecular Plant Physiology; graphic: Lothar Willmitzer

products in the blood reveal which active ingredient is effective in a patient. The aim is to be able to determine the right antidepressant via blood tests prior to therapy.

Another application of metabolic profiling is the development of improved herbicides. The pharmaceutical and agrochemical company Bayer initially wanted to cooperate with Willmitzer's Department at the Max Planck Institute. But Willmitzer declined. "In our field of research, everything is public. In contrast, industrial research is usually a trade secret. We would have had 20 employees who were not allowed to talk about what they do. This sort of thing is not good for the working environment." Willmitzer therefore founded Targenomix in 2013. The company analyses what exactly in a plant is triggered by pesticides.

The potato plant uses its tubers to store starch. So many genes are involved in the production of this substance, which is also important for human nutrition, that researchers can only decipher the starch metabolism only with the help of automated methods.

FOUNDER WITH HEART AND SOUL

According to Willmitzer, spin-offs face three challenges: "First, developing an idea; second, obtaining funding; and third, finding the right employees – because the success of a project depends on them." Especially in the first year after founding them, he had to put a lot of his heart and soul into his companies. "Ideally, you should then be able to gradually withdraw from the day-to-day business because the young team doesn't want the old fossil to keep showing up," says Willmitzer with a smile. Moreover, research at the Institute must continue unabated.

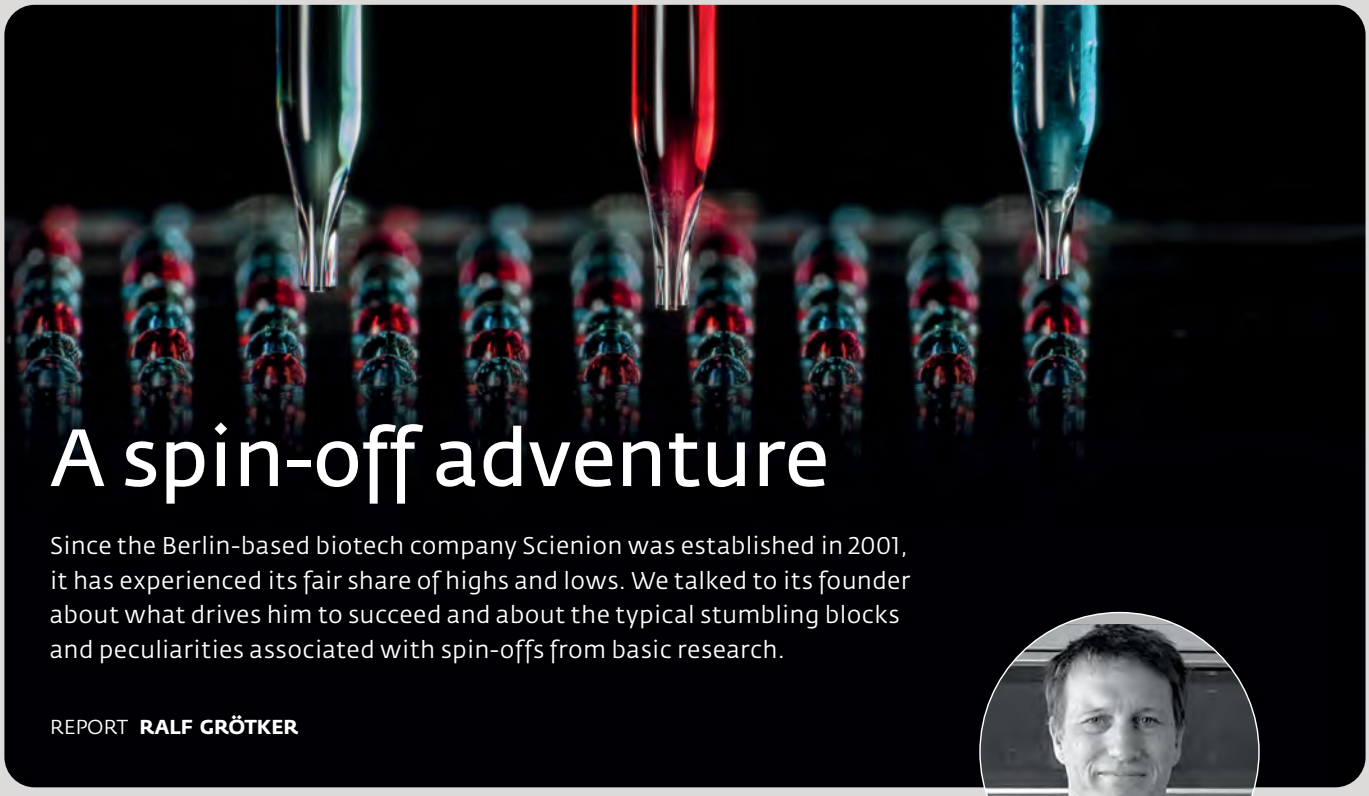
Three years ago, the 68-year-old chemist once again took on something completely new. He was driven by a provocative question: "Is it possible that all the small metabolic molecules with which the cells gain energy or form lipids, sugars, and amino acids also control these processes? That they are not only part of these processes but also play an important role in diseases?" Nobody had thought about that before.

But how do you obtain access to such control molecules? If they carry out these functions, they would require a partner – most likely a protein. In this case, the substances would have to occur as single molecules and be bound to a protein.

"Nobody believed us at first," says Willmitzer. But his suspicions proved to be correct. Five such protein-metabolite duos have already been found. "This approach could one day become very important. When a pharmaceutical company targets a protein for therapy, it first tests countless different compounds stored in huge molecular databases. However, if there is already a natural binding partner in the body and we know its structure, this greatly simplifies the search for active substances."

Willmitzer has also passed on this project to a younger colleague, Aleksandra Skirycz, who currently heads a research group in his Department. "But she has been offered a position in the U.S. and will take the subject with her. So, it looks like I won't have a project for my last two years here," says Willmitzer, laughing. But definitely a new idea! ◀

Photo: MPI of Molecular Plant Physiology, Josef Bergstein



A spin-off adventure

Since the Berlin-based biotech company Scienion was established in 2001, it has experienced its fair share of highs and lows. We talked to its founder about what drives him to succeed and about the typical stumbling blocks and peculiarities associated with spin-offs from basic research.

REPORT **RALF GRÖTKER**

The company

Scienion deposits DNA, peptides, antibodies, enzymes, and proteins to substrates in such a way that the biological activity of the molecules is preserved. In principle, the devices are ink-jet printers for biological molecules and living individual cells.
For example, corporate customers use them to manufacture pregnancy tests, allergy tests, tools for cancer diagnostics, or biosensors for glucose measurement.

scienion
ENABLING LIFE SCIENCE

The founder

Holger Eickhoff actually spends his entire time at the company from Monday morning to Friday evening. Weekends are family time.
"When our children were still young, we lived in Berlin, in the district of Zehlendorf, close to the Max Planck Institute for Molecular Genetics, where I was doing my postdoc research. After that we moved to Syke, near Bremen, where we had more family around. With parents and parents-in-law on hand, my wife was able to return to work, and I've been commuting by train since then." The children have since left home.

"I LIKE IT WHEN SUCCESS IS CLEARLY DEFINED."

Whenever he can, Eickhoff goes swimming three times a week, racking up at least three kilometers each time. He was a competitive swimmer until his mid-20s: "My best time for the 200-meter butterfly used to be two minutes two seconds. Now it takes me 2:30." He never regretted not staying in academia. "I like it when success is clearly defined. In a company, this means generating growth and earning money. But when you publish something as a scientist, the response is always: 'Interesting! But ….'" Does he want to take early retirement in his late 50s? "No chance," he says. Scienion is still not nearly well-enough known – and that's something he wants to change. "For our customers, the devices we sell them are a huge source of income. We'd like a bigger share of that part of the success story."

Note: at that time, the world record was 1:56, but now it is 1:51.

Photos: Scienion AG

The idea

In the mid-1990s, Holger Eickhoff was a postdoc in Hans Lehrach's group at the Max Planck Institute for Molecular Genetics. Lehrach had started building up DNA libraries back in the 1980s, and the technique of dispensing biomolecules onto a membrane via a dot-matrix printer was his invention. "We improved on this idea and commercialized it," says Eickhoff. "When we worked with Hans, we had already begun printing not only on membranes but also on glass, because it's a better substrate for fluorescent detection." Of course, they weren't the only ones. Indeed, they were up against competitors with the same plan. One such competitor was Oxford Gene Technology. "They later took aggressive action in the marketplace because of potential patent infringements and even paid us a visit – but they had nothing on us." And how did he come up with the idea of founding a company in the first place? "We were inspired to act by a business plan competition in Berlin. A colleague came to me and suggested that we should take part.

"WE NEEDED SIX MILLION TO LAUNCH."

I thought: this is quite different from an application for research funding. We entered the competition with a plan for a biochip company, which we called Biomatrix. When we lost, it only increased my desire to succeed." During his doctorate, Eickhoff had already founded a trading company that imported optical tables, microscopes, and cameras from the U.S. "So I already knew how to set up a company." While in Berlin, he heard about Max Planck Innovation: "We were doing basic research but using an industrial approach, enabling high throughput. Uli Mahr and Jörn Erselius from Max Planck Innovation were very helpful when it came to overhauling our original plan." Finally, they were ready to go: Biomatrix was dead; long live Scienion! "We submitted a concept to the Berlin Brandenburg Innovation Award scheme – and we won. We needed EUR 6 million to launch – that would allow us to pay the salaries of 30 employees for the first three years as well as the rent on the premises, and to buy equipment such as centrifuges and automated pipetting systems. By March 9, 2001, we'd obtained all the signatures from our investors and shareholders." And so the rollercoaster ride began.

Plan A

Just half a year after the company was founded, the world was shaken by the news of 9/11. After that, nothing was quite the same. A sense of disillusionment set in. "One of our main investors pulled out of all investments in the life sciences sector," says Eickhoff. "And suddenly, there was no money." It wasn't easy to instigate changes in the company strategy with a partner who was still there but wasn't available for joint decision-making. Ultimately, the shares were bought up by the remaining shareholders, and new ones came on board in 2006. The Max Planck Society also participated in subsequent rounds of financing – sending an important signal to the other investors. Of course, there were also other factors at play: "We believed market studies that said the biochip market was experiencing astronomical growth! We set our sights on a market share of 2%." That may sound modest, but arithmetically, you get gigantic numbers. The biochips from Scienion were technically outstanding and were being offered at an attractive price. However, they were not a diagnostic tool but rather a product that, in those days, was primarily being bought by researchers – and there were other and above all bigger suppliers on the market, who had greater marketing capacities and could also offer more customer service. "We invested vast resources in order to generate biological content of our own – DNA, proteins, antibodies. And then we discovered that our customers already had biological content themselves. Sometimes they asked us: what about the technology you have for producing biochips? Our answer was: that's not for sale – it's our proprietary competitive advantage! As we hit rock bottom, I halved the size of the company. I had to let a quarter of the employees go, and another quarter subsequently quit because the whole situation had become too uncertain for them."

"WE BELIEVED MARKET STUDIES THAT SAID THE BIOCHIP MARKET WAS EXPERIENCING ASTRONOMICAL GROWTH!"

Plan B

The balance sheet for 2005 told a sobering story: it wasn't possible to achieve any revenue growth by selling biochips. It was time for plan B. "We designed, built, certified, and marketed the first device on a very tight budget," says Eickhoff. Not long afterward, Scienion found itself at the center of a review by the U.S. Food and Drug Administration (FDA). "A customer who we'd supplied with a device was audited by the FDA, and we and our technology were caught up in the middle of it. It was very exciting, and the necessary documentation almost stretched us to our limits." News of the procedure's positive outcome attracted new investors. "Whereas before, we had two people producing print heads for our own requirements, there are now 30 people working on this task." In 2010, Scienion sold a proper production system for the first time, allowing biochips to be produced on a conveyor belt. This gives the company a key advantage for many applications. "Take antibiotics in milk, for example," says Eickhoff: "In a cheese factory, antibiotics kill the cheese cultures, so you already have to check the milk trucks for antibiotics – for every single delivery. In turn, that means you need thousands of assays in the broad application. That's where our technology gets stuck in!" Could anyone have predicted that sales of biochips wouldn't be successful in the early 2000s? "Certainly not us," Eickhoff admits. "We were very well versed in the technology and very enthusiastic about it. We suffered from tunnel vision and developed products that failed to reflect the needs of the market. We were excited by chips with 3,000 proteins on them, but no one wanted them – or at least they didn't want to pay for them." At some point, they began listening to their existing and potential customers. "That was a key step forward, as was the moment when we stopped defining ourselves solely by our technology. Instead, we started to look at the demand that existed on the market and where we could be of use."

"WE WERE VERY WELL VERSED IN THE TECHNOLOGY AND VERY ENTHUSIASTIC ABOUT IT. WE SUFFERED FROM TUNNEL VISION AND DEVELOPED PRODUCTS THAT FAILED TO REFLECT THE NEEDS OF THE MARKET."

Tailwind

Since 2005, a lot of the changes in the market for diagnostic tools have benefitted Scienion as a supplier. "We first discussed the HPV test for detecting papillomaviruses in 2004/2005." The test can be used to determine whether a patient is infected with viruses from that family. "But you actually want to know the exact type of virus, as not all of them are carcinogenic," Eickhoff explains. "And companies that have offered tests for typing viruses have worked with our technology." The entire field has grown steadily since then – with the occasional new virus strain being added, as well as vaccines that are only active against a few types of virus. "When it comes to diagnosis, physicians therefore want to know exactly which viral populations are present in a patient. We then developed a panel that allows you to search for sexually transmitted diseases in swabs taken for the HPV test."

Takeover attempt

Over the last few years, Scienion has been subject to a series of takeover bids by other companies. "From the outside, we may look like a bargain," says Eickhoff, "because investors from the early years are still on board, and an outside observer suspects they may want to sell up at a low price." The first offer came from a company based in Canada that wanted to finance the purchase price with a capital increase on the stock exchange. The company was listed on the Toronto Stock Exchange and wanted to move to Wall Street. "This meant we had to audit our business figures extensively, first according to German law and then according to Canadian and finally American law," says Eickhoff. "Several auditing firms made a small fortune in the process. But in the end, the Canadian company was unable to finance the acquisition, and we carried on alone."

Photo: Scienion AG

New markets

Scienion has since begun to address other segments of the market: "Veterinary diagnostics are hugely important for us nowadays. It's an attractive market because it always involves large numbers of units and payment is always immediate. For example, one of our customers produces thousands of diagnostic tests every day for dogs, allowing dog owners to check whether ticks can be detected in the animals' bloodstreams," says Eickhoff. If necessary, they can then buy a spray to control the ticks. "This application in companion diagnostics is something none of us had in mind. It's completely different from the clinical sector, where research into new active substances or the individual adaptation of medications is carried out on a relatively small number of patients." In retrospect, the company's initial approach was not entirely incorrect. "We were just too far ahead of the curve," says Eickhoff. "Back then we were developing surfaces that were 100% repellent for all sorts of things, and we now use these surfaces in a process known as single-molecule handling. But no one saw a market for them in those days." In fact, Scienion is now also selling biochips as a successful side business – in other words, resurrecting its original business model. "Especially when larger customers want to see how our technology works, they buy our chips before deciding on a device," says Eickhoff.

Advertising/ customer acquisition

Every year, Scienion appears at about 30 trade fairs, conferences, or events, as well as in publications. "Not in publications where we're named as authors, but rather where we are featured in the 'Materials and methods' section," explains Eickhoff. "When we do business with a new customer, we usually begin by investing two or three days' work that we don't charge for. This has benefits for both parties: the customer gets to see how we work, and we see what the customer already has and what they need, allowing us to make a good assessment of own efforts and revenues that await us. In the case of biochips, this can range from a few thousand euros to EUR 100,000 or 200,000. The devices start at EUR 50,000 or EUR 150,000-200,000 for larger models, with production devices costing between EUR 500,000 and several million euros."

Looking to the future

"For many years, we were driven by concerns about how we would survive the next quarter," says Eickhoff. Thankfully, that's no longer the case, he says. "Now that we have more wind in our sails, we can plan strategically." Scienion founded a U.S. subsidiary in 2011, followed by a French subsidiary called Cellenion in 2016/17. "Unlike the otherwise 'dead' molecules that we've dispensed over the course of the company's history here, we dispense live material. Single or multiple cells, such as three-dimensional cell groups, can therefore be dispensed alive and in a fully functional state for use in analysis. With this technique, we've really hit a home run in terms of demand!," Eickhoff explains. Analysis at the individual cell level – in the field of oncology, for example – is currently a major area of interest. "Our technology can be used to analyze tumors to determine which cells that they contain are responsible for what. This is another area in which we're further expanding our range of biochips. That's where our future lies." Other sectors include the personalized dosing of drugs for patients on special edible paper, as well as artificial noses – silicon components that are able to detect tuberculosis in the patient's breath. And the company is also interested in exploring new sales regions. "Right now, we're looking at China," says Holger Eickhoff.

"NOW THAT WE HAVE MORE WIND IN OUR SAILS, WE CAN PLAN STRATEGICALLY."

Drug evolution riding high

Evotec's history illustrates that biotechnology made in Germany can set standards worldwide. The Max Planck Society is one of the company's founders and continues to shape it to this day.

TEXT **DIRK BÖTTCHER**

In the early 1990s, few people had heard of evolutionary molecular biology, this field was a source of inspiration for entrepreneurs and investors. Co-founded by the Nobel Prize Laureate Manfred Eigen from the Max Planck Institute for Biophysical Chemistry in Goettingen in 1993, Hamburg-based Evotec Biosystems set out to investigate pharmaceutical substances using the technique Eigen had developed. In a nutshell, the technique is based on utilizing evolutionary processes such as selection by random variations to research and develop drugs. Such an approach, it was hoped, would allow scientists to conduct automated analyses of the effects of a large number of substances on specific target structures or directly on cellular processes. Novel drugs, for example, could then be developed faster, more precisely, and at a lower cost.

Evotec is one of Germany's most successful biotechnology stories. The company is growing at a breathtaking pace, utilizing unique technologies, and its approach based on highly-automated, industrial-scale translational research has revolutionized the industry. Most notably, the company has been shaped by some of the most remarkable scientists of our time.

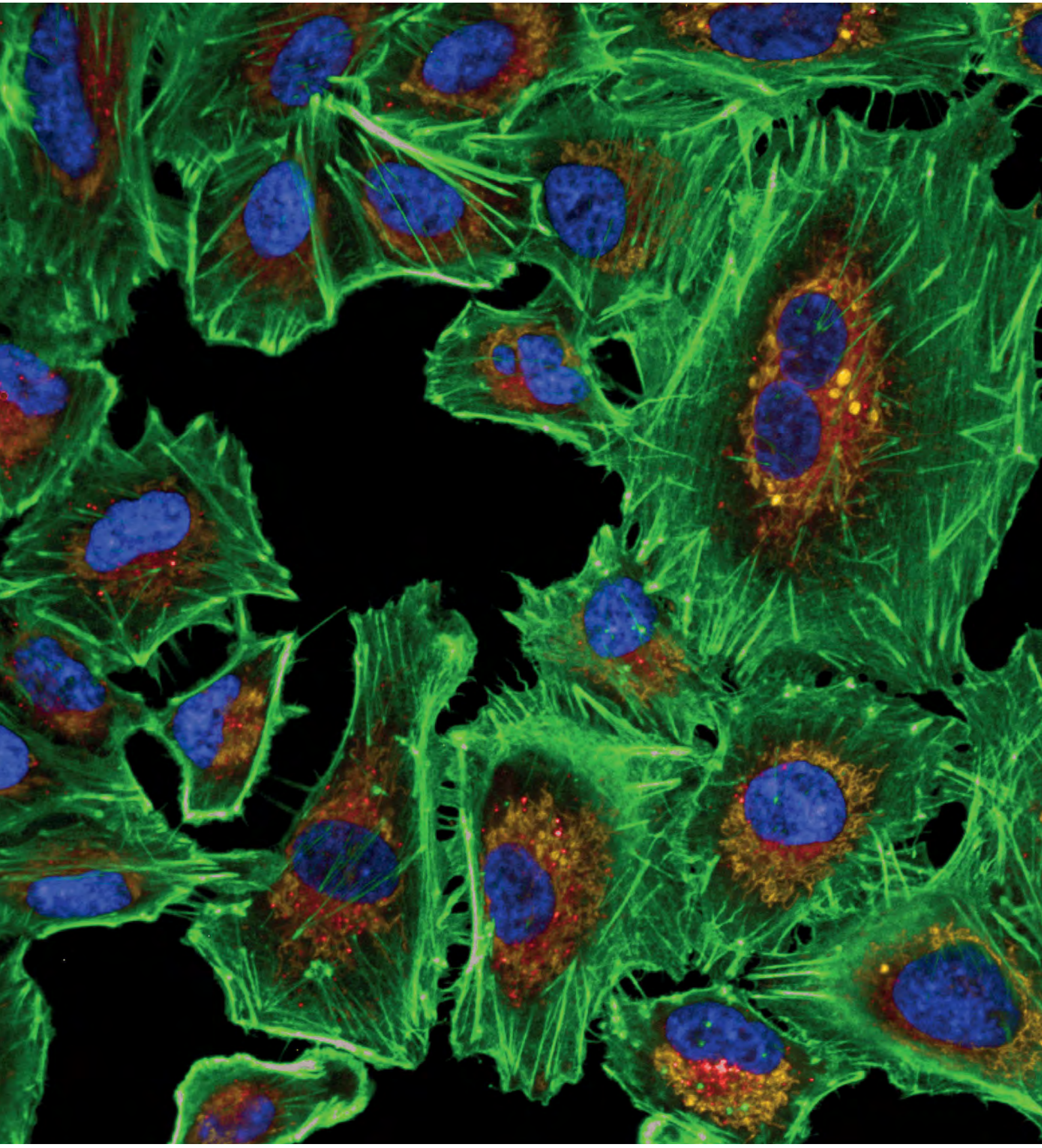
FOURTEEN SITES, SIX COUNTRIES, 3,000 EMPLOYEES

First and foremost, they include Manfred Eigen (1927–2019), co-founder and Chief Scientist of Evotec. In 1994, he described the hopes researchers had for the future of evolutionary molecular biology, a technique he was instrumental in developing, in the scientific journal Science: "You can solve problems in ways you never would think of." Up until that time, scientists had focused their research on individual molecules, using their knowledge of biochemistry to try to achieve specific binding properties – and, by extension, a desired effect. Just what might they achieve, however, if they could investigate a vast number of these molecules using a quasi-evolutionary process in a single device? Eigen's vision, previously unimaginable, would come to fruition.

Visiting Evotec in Hamburg today shows how brilliant his idea was. Established as a small company with a starting capital of EUR 7 million and a handful of employees, the company

Using technology to fight tumors: among other things, Evotec utilizes lung cancer cells to develop assays that can be used to develop more effective cancer treatments. Visible in the cells are the nuclei (blue), mitochondria (orange), lysosomes (dark red), and actin filaments (green).

Photo: Evotec



A flair for promising discoveries: in 1967, aged just 40, Manfred Eigen was awarded the Nobel Prize for Chemistry for the development of a method for studying extremely fast chemical reactions. He became the founding Director of the Max Planck Institute for Biophysical Chemistry and co-founder of several companies. He was able to quickly recognize how to harness the economic potential of unexpected findings.

now occupies several buildings at its headquarters and has grown to become one of the world's leading providers of research and development services. More than 3,000 employees work at fourteen locations in six countries, annual sales are approaching EUR 500,000, and its current CEO, Werner Lanthaler, claims that the company is only just embarking on its development (see the interview on page 63).

DRUG SCREENING ON AN INDUSTRIAL SCALE

Since Lanthaler took over as CEO in 2009, the value of Evotec shares has increased by more than 3,000 percent, its workforce has increased tenfold, the company is in the black, and its market capitalization is more than EUR 3,000,000,000. The evidence for Lanthaler's optimism can be seen in a small room in the laboratory wings of Evotec's headquarters. The multi-story building with its imposing glass facade has Manfred Eigen's name emblazoned above the entrance. Inside a window provides visitors with a glimpse into the laboratory. Enclosed in a glass box, a robot arm moves back and forth, grips small sample containers, pipettes, sorts, empties containers with tiny plastic tubes, and places them in incubators – a miracle machine that cultures and analyzes "induced pluripotent stem cells" (iPSC).

Using a combination of four genes, then coding for specific transcription factors, adult (already differentiated) cells can be reprogrammed to become iPS cells. The Japanese scientist Shinya Yamanaka, among others, was awarded the 2012 Nobel Prize for Medicine for the development of these techniques. They have huge potential, particularly in the field of regenerative medicine, because iPS cells can proliferate indefinitely and can differentiate into all the body's cell types. With its iPSC platform, Evotec is aiming to scale up drug screening to an industrial scale, while meeting the highest standards for throughput, reproducibility and robustness.

Sitting in Manfred Eigen's Goettingen office back at the beginning of 1993, did Evotec's founders genuinely anticipate the scale of the company's success? It's possible that they did not, even though two of them, Karsten Henco and Ulrich Aldag were perhaps among the most ambitious entrepreneurs of the day. As founder and manager respectively, they had recently had recently successfully launched the renowned biotechnology company Qiagen – still one of the few highly successful German biotech companies. The fact that both of them took their leave from this meteorically successful venture to found a new company with Manfred Eigen and the Max Planck Society shows how convinced they were by the idea and by Eigen's technology.

LOOKING FOR MARKETABLE INNOVATIONS

"As Max Planck Society employees, we were certainly slower certainly slower than the other founders might have wished, but we were venturing into completely new territory," recalls Jörn Erselius. Erselius is the current Managing Director of Max Planck Innovation GmbH (MI) and was involved in founding the spin-off company Evotec. At the time, MI had only just founded a company, Sugen Inc. in the U.S., in which the Max Planck Society also held shares. At Evotec's founding, Eigen, Henco, and Aldag proposed that the Max Planck Society should also take a five percent stake in the company and contribute a good dozen of its patents. "We had never owned shares in a German company. As far as patents were

Photo: Inge von Kruse

Dedicated to its founder: Evotec is located on its own campus named after Manfred Eigen in Hamburg-Langenhorn.

concerned, some belonged solely to us, while others were jointly owned with Qiagen. Before Sugen and Evotec, the statutes of the Max Planck Society prohibited the acquisition of shares in companies by their founders to prevent conflicts of interest. This complex mixture of interests turned out to be a great challenge, but a future-orientated solution was arrived at with the Max Planck Society," says Erselius.

Today, spin-offs are common practice in the science community. MI now employs five start-up managers with a predominantly business management background who support spin-offs in interdisciplinary teams. Since the early 1990s, in addition to Evotec, over 150 other companies have been spun off from the Max Planck Society. These employ thousands of people. Many companies have reduced their own research and development expenditure in recent years, for example in the pharmaceutical industry. "More than ever before, such companies are now looking for market-ready technologies; our basic research is frequently still underdeveloped for the market," says Erselius. Start-ups are therefore often an ideal way "to translate know-how from basic research onto the marketplace." In his view, they are like incubators, frequently enabling technologies to be brought to the marketplace faster and with greater agility. "Our network of investors and experienced managers is now very extensive and a great resource for such start-ups."

FOURTEEN MILLION COMPOUNDS SCREENED IN 2019

When Evotec was founded, plans were made to develop three business divisions: pharmaceutical research, diagnostics, and technical enzymes (for example in detergents). In the medium to long term, the plan was to float each of these again on the stock market. In 2000, this was achieved with Direvo, which manufactures technical enzymes. Just one year earlier, in 1999, Evotec had itself successfully gone public. It was the first time that the Max Planck Society had held shares in a German company, and, as a research facility, it needed to decide how it should manage such investments. According to Erselius, it was decided at that time "to hold on to the stocks initially to send a signal to the market that we had confidence in the business model." It was only after a few years had passed that

Photo: Evotec

the Max Planck Society gradually sold its stocks worth several million euros. An innovative regulation was also found to solve the complex problem of the patents it held. "Ultimately, we combined all the patents into one portfolio and entered into a comprehensive license agreement with Evotec."

In 2019, Evotec screened more than 14 million new compounds at its facilities in Hamburg. Each of the company's devices screens as many as 40,000 samples a day – three of these are located at the Hamburg site alone. That's equivalent to the jobs of several hundred technicians. At Evotec, such comparatively simple operations are performed by robot arms in glassed-in workspaces. They load and unload samples, while on a monitor the analyses are displayed as graphs and color gradients. In one installation, strong light-gathering microscopes automatically deliver high-resolution images of cell samples. They enable scientists to observe how both tumor cells and healthy cells react to the drug under investigation; the goal, after all, is to kill cancer cells rather than healthy tissue. Other devices measure the binding forces between the active substances and cells. The laboratory machines work 24 hours a day, the larger assays running by night and the smaller ones by day, as these require more staff involvement.

The samples are stored in huge freezers, from where they are, as it were, fired into the assay devices under air pressure through pipes, a spectacle that is as efficient as it is fascinating. Evotec has the facilities to store more than 400,000 compounds. At its Toulouse site, a library containing a further 1.7 million compounds is shared by Evotec and the pharmaceutical company Sanofi. Maintaining such a library of samples offers a key advantage: reproducibility. Should an active ingredient need retesting, this can be done with precisely the same samples. The two data sets can thus be compared with complete consistency. Evotec charges many of its customers on a traditional performance-based basis. For many of the jointly developed projects, Evotec has also concluded "co-owning" agreements with its customers, whereby both co-owners benefit from any subsequent marketing success. Evotec also receives traditional milestone payments when specific research objectives have been reached.

An automated device for all-rounders: Evotec tests potential drugs using induced pluripotent stem cells in a high-throughput process. It has developed a particularly effective method for cultivating such cells.

Photo: Evotec

TESTING ELECTRICAL CURRENTS FOR ANTI-ALZHEIMER DRUGS

The monitors in Evotec's laboratory show just how advanced techniques have become; current flow through single ion channels of individual cells can be visualized. The equipment can detect spikes of current of as little as five nanoamperes. On a computer monitor, visitors can observe the alternating flashes of activity of individual nerve cells in a group, indicating that the cells are communicating with each other. Perhaps one day, this research will lead to the discovery of a drug to treat Alzheimer's or a new painkiller.

In contrast to such ultra-modern, fascinating technology, the garish orange laboratory console on display in the entrance area looks like a relic from yesteryear, as though it has come straight from the original *Star Trek* series. In fact, the crude system with its small monitors and simple manual controls was state of the art just 16 years ago. It was one of the first systems that Evotec built and marketed itself. Evotec developed it in an attempt to enter the market itself as a manufacturer of technology. In the end, however, only six of the devices were sold, and Evotec lacked the resources to market them worldwide. The division was sold to the technology manufacturer Perkin-Elmer, from whom Evotec is still purchasing important equipment. Even a company like Evotec can't possibly produce everything. ◀

"We're aiming to broaden the range of technologies we can offer."

Werner Lanthaler, CEO of Evotec, discusses new forms of cooperation with basic academic research and the right target customers.

Werner Lanthaler

Dr. Lanthaler, who are Evotec's typical customers?
Werner Lanthaler: Our partners are pharmaceutical companies that outsource research into their innovations, smaller biotechs that develop products virtually, and basic academic research institutions looking to evaluate potential industrial applications.

And the customers benefit from lower research costs?
No, nobody comes to us on account of our prices. However, we turn fixed research costs, such as expenses for personnel and facilities, into flexible costs incurred solely due to research operations and advances. That didn't exist before Evotec. It's a mega-trend of the future, and, alongside Evotec's technological expertise, identifying it has been one of the key reasons for the company's successful development.

Why should companies or institutes outsource research?
It's to do with the way we support research; our work is of the highest quality and is unbiased – without conscious or unconscious interference. That's crucial, because companies often actively guide their research in the particular direction in which they feel themselves to be well positioned. Evotec delivers meaningful results very quickly, which can be worth hard cash for customers, because this allows them to quickly abandon projects that are not promising, or to accelerate them if they do prove encouraging. This helps companies become more agile.

Do you also have expectations of your customers?
Our motto is: "First in class, best in class." We're a natural fit for companies whose research is aimed at developing an entirely new therapeutic approach or whose products are more innovative than those of their competitors.

Can you give me an example?
One of the products we have co-developed in a broad-based partnership with Bayer is a drug to alleviate abdominal pain in women; up to now, drugs have only treated the symptoms of such pain but not the underlying cause. Evotec has analyzed the first molecule that makes a completely new treatment approach conceivable.

When you became CEO of Evotec, the company was making a loss of more than EUR 50 million; now it generates over EUR 100 million in profits. A classic success story?
That's one way of looking at it, but it's a story that is only just beginning.

Why?
The market for the services we provide is estimated at around EUR 30 billion; less than ten percent of research is currently outsourced, and the growth potential is correspondingly high. We expect annual growth rates of up to ten percent. We also have more than a hundred drug targets in our pipeline that we co-own with our customers.

What about the competition?
We do have competition in individual services, but we're the only company with a business model of providing all assay services under one roof.

How would you characterize Evotec's relationship with basic academic research?
Certainly, we can help our academic partners to translate basic research into practical applications. One of our goals is to cooperate even more closely with research institutes.

What do you expect such partnerships to look like in the future?
Our Academic BRIDGEs* concept was developed to foster joint projects with leading research institutions and funding partners. The first of these BRIDGE projects, LAB282, was launched in 2016 together with the University of Oxford. There are now five more BRIDGEs in North America, France, and Israel.

What do these involve precisely?
One of our tasks is to validate initial experiments based on the data. And, once again, it's crucial that we quickly determine which experiments should be continued and which should be terminated.

Do you have a focus?
Above and beyond traditional life sciences research, we want to broaden the range of technological services we provide. The research conducted by the Max Planck Society, for example, is much broader than ours. Would it, for instance, be feasible to share capacities?

What drives you?
In my daily work I experience new technologies that are currently used to research drugs for 3,300 diseases, whose causes at present cannot be treated. Along with being able to foster the growth of companies, I find that highly motivating. I am particularly fascinated by our pluripotent stem cells – they will dramatically transform research worldwide. I envisage a time one day when when we will be able to conduct clinical trials in a dish.

Interview: Dirk Böttcher

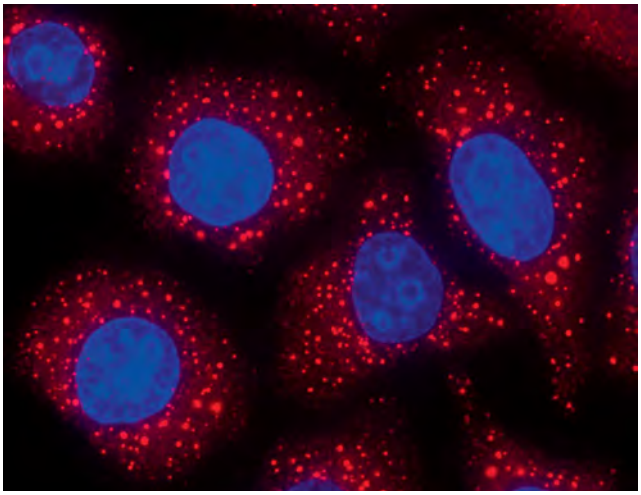
*The acronym BRIDGE stands for Biomedical Research, Innovation & Development Generation Efficiency.

Photo: Evotec

Order is half the battle

Dewpoint Therapeutics is working on a way to help diseased cells regain efficient control of their biochemical processes

Even cells have to be organized if their internal processes are to function smoothly. They can for example cause certain biomolecules to accumulate in a specific area of their cytoplasm, even though there is no membrane separating this area from the rest of the cell. These localized increases in concentration improve the efficiency of vital reactions. In many diseases, such as neurodegenerative and cardiovascular diseases or cancer, the formation of so-called biomolecular condensates is presumably disrupted. Correcting this defect could therefore be a promising starting point for possible treatments.



Dewpoint Therapeutics, established in 2018, is researching the form these treatments could take and pursuing various approaches to this end. Small molecules could for example restore order in the condensates and thus alleviate the symptoms of disease. The condensates could also possibly be used in a process known as targeting. In simplified terms: if a certain condensate were found to contain a pathogenic substance, an active substance could be guided directly to the site affected.

However, an even more detailed understanding of biomolecular condensates is necessary to implement this and other ideas. Dewpoint Therapeutics has a mission to improve this understanding. After all, it was the company's founders, Anthony Hyman and Richard Young, who discovered the medicinal potential of condensates in the first place. Since Hyman is a Director at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden and Young a researcher at the Whitehead Institute in Boston, Dewpoint was conceived as a German-American concern. At present, 15 staff members are employed at each of the branches in Boston and Dresden, and more staff are to be recruited at both locations. The concept is convincing: in 2019, the company secured up to USD 60 million in funding, and just recently, in November 2019, a research and license agreement was negotiated with Bayer according to which Bayer will invest up to USD 100 million.

Concentrated stress management: if cells lack the ATP that supplies them with energy, the RNA of certain proteins accumulates in stress granules (red) close to the cell nucleus (blue).

Making the leap to quantum security

InfiniQuant aims to develop compact, cost-effective quantum cryptography systems

Until now, the use of quantum mechanics to protect communication has been an extremely exclusive affair. Researchers at the Max Planck Institute for the Science of Light want to change this. A team led by Imran Khan, who until now was a member of the group led by Christoph Marquardt, is therefore preparing to establish a company under the name InfiniQuant. The physicists aim to use the company as a vehicle to offer compact, cost-effective data encryption that utilizes quantum cryptography and is compatible with existing communication technology. This process exploits the fact that it is impossible to eavesdrop on certain quantum states without being detected. From now on, the team behind InfiniQuant aims to miniaturize the building blocks of quantum communication still further, thus positioning them for a wider range of applications. Possible customers could include banks and government institutions, which work with particularly sensitive data. Until now, there has been only one provider offering systems to protect this data traffic; however, these systems are expensive and not miniaturized. The price of a single device runs into six figures, and the data network of a bank, for example, would need roughly as many devices as it has branches.

Photo: Ina Poser / Dewpoint

Ivory from a test tube

Ivory from elephant tusks, a substance that has been banned from trade, can be produced synthetically, e.g. for piano keys

This will make pianists feel good – and others as well: a team from the Department of Solid State Quantum Electronics at the Max Planck Institute for Solid State Research has found a way to produce synthetic ivory. This feels as warm as its natural equivalent, is similarly effective at absorbing moisture from the fingers, and has similar non-slip properties. The material's grip can also be adapted to meet the pianist's individual requirements.

International trade in ivory from elephant tusks was banned in 1989 in order to protect the animals from extinction. Until now, piano manufacturers have been unable to find a material that felt the same as natural ivory, even though its tactile properties depend to some degree on its origins and the animals' diet. However, Sarah Parks, Dieter Fischer and Jochen Mannhart can control the properties of synthetic ivory with the utmost precision. They were the ones who developed the material at the Max Planck Institute for Solid State Research, in cooperation with the piano manufacturer Sauter in Spaichingen, Germany.

The right conditions, such as temperature and the concentration of each component, are critical when producing this material. "We started by thinking about which parameters could be important for direct synthesis," says Dieter Fischer. "And our choices turned out quite well right from the start." The actual manufacturing process is very easy. The researchers simply mix gelatin dissolved in water and hydroxylapatite powder suspended in ethanol. Gelatin is derived from collagen, the organic component of ivory, while hydroxylapatite is the mineral component of both ivory and bone. Once the researchers have mixed both the ingredients, they let the mixture dry in flat trays. A couple of post-processing steps – and the covering for the piano keys is ready. "I was surprised, for as far as we know, nobody else has ever tried to make synthetic ivory in this way," says Dieter Fischer.

In all previous attempts, the scientists had apparently assumed that they had to let hydroxylapatite crystals grow in a collagen lattice. This is how natural ivory is formed. However, this process is not only complicated in the lab – and even more so during technical production – but has so far also failed to yield the desired result. Piano makers have therefore been making do with other alternative materials, often plastics, which do not have the same tactile properties as ivory.

By modifying the process slightly, the Max Planck researchers have also succeeded in producing the synthetic ivory in cylinder form. They have already had chess pieces and copies of prehistoric artifacts carved from it. In July 2019, the researchers established the company Ivortec to exploit the many uses of this nature-identical material other than piano keys. "Max Planck Innovation gave us excellent support while we were applying for patents and starting up the company," says Jochen Mannhart.

David Butcher, the Managing Director of Ivortec, is now raising venture capital, forming collaborative relationships with possible production companies and sounding out demand for the material, which could in many cases replace both plastics and wood. "Furniture manufacturers and yacht builders have expressed great interest in ivory, not only because it looks elegant but also because it doesn't combust until it reaches 1000 degrees Celsius – so you could say it's a decorative type of fire protection," explains Butcher. The material surpasses plastics, not least in terms of sustainability. For one thing, it is not manufactured using fossil resources; for another, it biodegrades at the end of its lifecycle. Synthetic ivory allows pianists to enjoy a sensation while playing that would otherwise be denied them due to the need to protect elephants; furthermore, unlike plastic alternatives, it leaves no waste.

Almost natural: piano keys covered with synthetic ivory feel warm, absorb moisture and have a grip similar to that of the natural material obtained from elephant tusks.

Photo: iStock

Gentle electrical pulses

Patients with cardiac arrhythmias could benefit not only from treatment with low-energy electric shocks but also from a new imaging technique

Some patients are more afraid of resuscitation than they are of death. This is because the electric shocks used to resuscitate people suffering from cardiac arrest caused by fibrillation are extremely painful. They also damage the tissue, thus increasing the risk of further potentially fatal cardiac arrhythmias. Stefan Luther and his team at the Max Planck Institute for Dynamics and Self-Organization in Goettingen are seeking a new approach. They are developing a form of defibrillation which requires significantly less energy, since the electrical field used is specially formed and pulsed.

Fibrillation is the most common cause of death worldwide; it causes one person to die of sudden cardiac arrest every five minutes in Germany alone. The new method could be particularly beneficial for patients who have a known history of cardiac arrhythmia and have consequently had a defibrillator implanted. Devices of this type automatically administer life-saving electric shocks in emergencies. However, some patients have these life-saving devices removed – not least because they sometimes trigger electric shocks that are absolutely unnecessary.

The technology can also be integrated into external defibrillators, such as those now available in many public spaces. It could then be used as a gentler alternative to conventional treatment with high-energy electric shocks. The defibrillator can still administer strong electric shocks if the fibrillation cannot be stopped with weak electrical pulses.

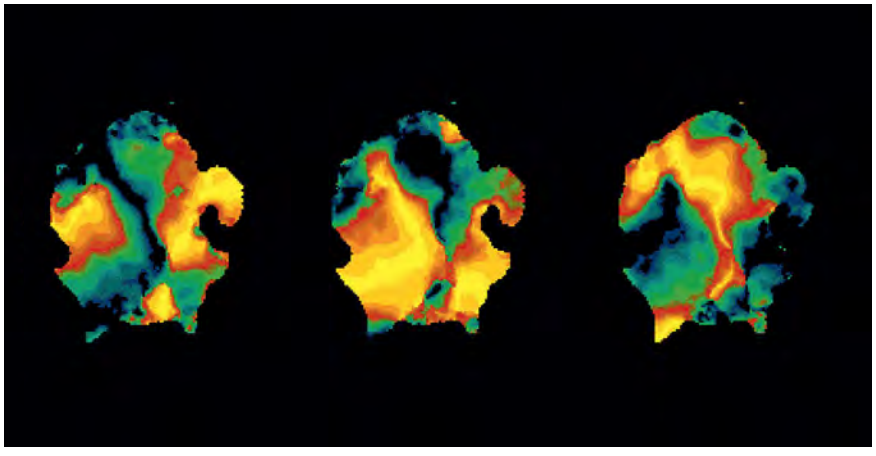
"We haven't yet finished investigating the tissue damage, but we already expect it to be significantly less due to the reduction in energy we have achieved so far," says Stefan Luther. "However, whether or not we can reduce the energy used during the fibrillation by about 90 percent and thus make the treatment less painful largely depends on the position of the electrodes." Here the scientists are currently still seeking a feasible solution.

The team in Goettingen will be testing low-energy defibrillation on pigs until mid-2020. The scientists then intend to perform the first clinical study on heart patients. After completing the basic research at the Max Planck Institute, their plan in the medium-term is to use a subsidy from the founding initiative GO-Bio to establish a company that will transfer this treatment from research to medical practice. The Federal Ministry of Education and Research set up the two-phase GO-Bio program to provide support for promising biomedical concepts, initially while they are being investigated at a scientific institution and later when starting up a company.

As part of their work on low-energy defibrillation, the scientists have already developed a new diagnostic method which promises to be useful in a number of medical applications. In order to find out how a low-energy electric field can stop fibrillation, they first have to understand exactly what happens in the heart. It is already known that electrical excitation in the fibrillating heart muscle rotates in a vortex-like pattern rather than passing through it like a wave. This means that the organ can no longer contract properly and stops pumping. However, doctors have until now been unable to gain a full picture of the disturbed dynamics in everyday medical practice. An international team of researchers led by Stefan Luther, Jan Christoph, who is also carrying out research at the Max Planck Institute for Dynamics and Self-Organization, and Gerd Hasenfuss, cardiologist at Goettingen University Hospital's Heart Center, has therefore developed a method with which the necessary examinations can be carried out. This now enables doctors to track cardiac arrhythmias in real time on 3D images generated by standard ultrasound equipment.

The researchers in Goettingen are currently using the method in a study carried out jointly with cardiologists at the Hamburg-Eppendorf University Hospital in order to better identify those areas in the heart muscle that are susceptible to cardiac arrhythmia. This is because the three-dimensional vortexes tend to occur in the vicinity of heterogeneous tissue such as a scar, a

Cardiac fibrillation on film: three images taken in quick succession of the chaotic excitation (black – resting, yellow – excitated) that can lead to cardiac arrest.



Graphic: MPI for Dynamics and Self-Organization

blood vessel or a small quantity of fat. As part of a second study conducted in cooperation with Goettingen University Hospital, the researchers intend to investigate ventricular fibrillation in patients who have had to undergo heart surgery; this phase is likely to commence in mid-2020. This surgery requires the patient's heart to be stopped, which also causes it to fibrillate.

"We are holding talks with industrial companies with the goal of putting the new imaging technique to practical use in the medical field," says Stefan Luther. Companies could use the new technology to enhance their ultrasound diagnostic equipment in such a way that doctors can look still deeper into the heart. This would not only benefit patients with cardiac arrhythmias but also those with cardiac insufficiency. This diagnostic method could therefore help improve the treatment of heart disease in several ways.

You are the bus stop!

A software program for on-call buses is designed to make public transport more attractive

Public transport has a chicken-or-egg problem: on the one hand, it is not worth operating an extensive transport service if only a few people use it. On the other, people – especially in rural districts – are unlikely to switch from their own cars to public transport if the network is not made more attractive. A team led by Stephan Herminghaus, Director at the Max Planck Institute for Dynamics and Self-Organization in Goettingen, now intends to find a solution to this dilemma. The researchers have programmed a software for on-call buses with which passengers can be collected from a location of their choice and taken straight to their destination at a certain time.

Under the name 'Ecobus', they have already tested the service in the Harz region in cooperation with the local transport companies. "However, we don't want to offer just another public transport system that then cannibalizes other means of transport," says Stephan Herminghaus. Another pilot scheme which combines on-call buses with regular bus services is currently operating in Leipzig under the name 'Flexa' Taxis can also be integrated into the system if the need arises. During the first half of 2020, the team in Goettingen aims to start up a company that offers software first and foremost but also operates its own minibuses if necessary.

The scientists, who normally carry out research into the dynamics of complex fluids, are using statistical physics in their practical tests to determine the conditions in which these on-call bus systems can work best. A separate software program is required for this, since the operators of existing on-call bus services do not share information about the exact way in which they function. In contrast, the researchers are familiar with all the components of their own software and can also control them. Their goal is to provide an optimum service that will encourage people to switch to public transport. "We want our work to help discourage people from sitting alone in their cars," says Herminghaus. If the scientists manage to achieve this, it would mean less traffic, healthier air and lower CO_2 emissions.

The EcoBus in the Harz region picked up passengers anywhere they liked – without them having to hold up a sign.

Photo: MPI for Dynamics and Self-Organization

Phantoms for surgeons

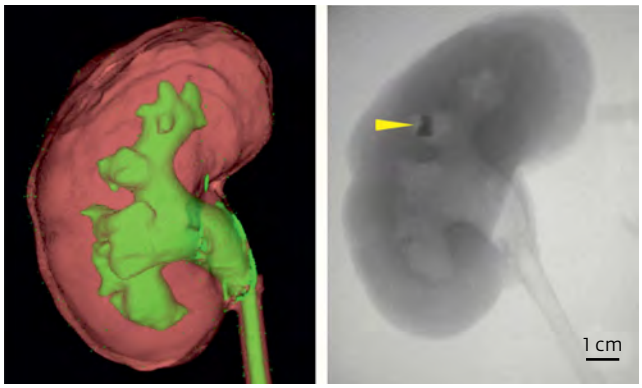
Organ models made of a hydrogel compound may improve medical training

Before pilots are allowed to fly airplanes, they have to spend many hours in a flight simulator. Here the trainee pilots experience situations they may encounter later in their career and also receive detailed feedback on their actions. In contrast, trainee surgeons usually have to "learn by doing". Peer Fischer from the Max Planck Institute for Intelligent Systems in Stuttgart wants to develop a new solution. In cooperation with his research group at the Institute, Tian Qiu from the University of Stuttgart and Arkadiusz Mernik from the University Medical Center in Freiburg, Fischer is developing true-to-life models of human organs that could radically change surgical training.

The scientists originally focused on the development of innovative robotic surgical procedures. In order to test these, they ordered replicas of human organs from an endoscope manufacturer but were anything but satisfied with the quality. "The organ models had a balloon-like structure; they had absolutely nothing in common with the human anatomy and also behaved differently to real organs. They were completely useless for the investigations we were planning," says Fischer.

The researchers accordingly decided to develop artificial organ models themselves. For this, they created high-resolution images of a kidney using computer tomography and then used this data to fabricate the basic framework of a so-called organ phantom using 3D printing technology. The cavities in the model were subsequently filled with a hydrogel compound which imitates natural tissue in terms of its consistency, haptics, water content and electric conductivity. They then removed the framework. "In this way, we made an artificial kidney which doctors could not distinguish from a real kidney when they viewed it by ultrasound," says Fischer. Models of the bladder and prostate have now also been created; other organs and tissues are currently in development.

Fischer uses the prostate to illustrate just how valuable the models can be. If the prostate becomes enlarged, the patient has to undergo a so-called transurethral prostate resection. During this procedure, a loop-like instrument is inserted into the body through the urethra. This loop is heated with alternating current and the surgeon uses it to scrape away excess prostate tissue – while avoiding injury to the prostate capsule, nerve fibers and blood vessels. This is a difficult undertaking which requires plenty of practice. Fischer and his team used their method to create an artificial model that not only looks and feels exactly like the human prostate but can also be operated on. The surgeon can then use imaging techniques to examine how precisely the operation was performed and whether the surrounding tissue was damaged. "Our phantoms make it possible to perform repeatable tests on medical instruments and procedures and to improve them," Peer Fischer explains. The researchers are currently cooperating with various medical technology companies and developing other organ phantoms for surgical training purposes. They plan to launch their own start-up in the medium term.



Phantom kidney: on the left a 3D design, on the right an x-ray of a printed organ model in which a tumor has been positioned (arrow).

Photos: Dr. Tian Qiu (Uni Stuttgart/MPI) and Prof. Arkadiusz Miernik (Uni Medical Center Freiburg)

A copper fleece for batteries

Batteries are to become more powerful and last longer – thanks not least to technology developed by the Max Planck Institute for Medical Research in Heidelberg. The researchers, who are actually investigating how living cells react to nanostructures and mechanical stimuli, have found a way to create sponge-like networks from ultra-fine metal wire.

"The metal networks are so fine yet so robust that we are now also investigating their potential as efficient conductors in batteries," says Joachim Spatz, Director at the Max Planck Institute for Medical Research. They can for example evenly penetrate the actual electrode material in a lithium battery and shorten the electrical exchange

Effective against tuberculosis and cancer

Max Planck researchers have developed a promising vaccine candidate that is also being tested as a possible cancer treatment

Research into curing tuberculosis has made no real progress in almost 100 years. Only since the beginning of the 21st century has this gradually started to change. Several vaccine candidates are currently undergoing clinical trials as the only available vaccine (BCG) was originally developed in 1921 and does not afford sufficient protection against the most common form of pulmonary tuberculosis through which the disease is mainly spread.

So far, the best results have been obtained from a vaccine candidate known as VPM1002. The scientific foundation of this success was laid by Stefan Kaufmann at the Max Planck Institute for Infection Biology in Berlin. The vaccine candidate is based on the BCG vaccine and contains attenuated bacteria similar to those that cause tuberculosis. These are genetically modified in such a way that immune cells can better recognize them. VPM1002 therefore affords better protection from tuberculosis than the old vaccine, and will one day replace it for vaccinating newborns. VPM1002 could also be used as a booster vaccine in adults.

In 2004, the Max Planck Society granted the license for the vaccine to the company Vakzine Projekt Management (VPM). From 2012 on, the company continued developing the vaccine in cooperation with the Serum Institute of India, which has now completely taken over VPM.

In 2018, a phase II study confirmed that the vaccine is effective and well-tolerated by newborns, both of which is now to be investigated in greater depth. At present, VPM1002 is being tested on adult subjects in India as part of another phase II study. This should be completed by mid-2020. Researchers are also investigating whether the vaccine could prevent people who come into close contact with tuberculosis patients from becoming infected.

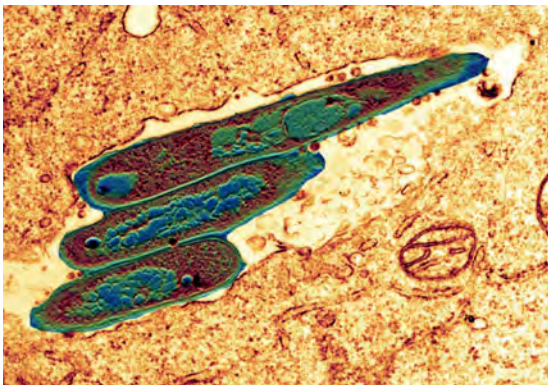


Photo: MPI for Infection Biology – CF Microscopy / Volker Brinkmann

Bacteria from the attenuated strain used in tuberculosis vaccines (BCG) inside a macrophage, one of the immune system's scavenger cells.

Activating the immune system can protect patients from cancer as well as tuberculosis. The traditional tuberculosis vaccine BCG, for example, is effective against bladder cancer, one of the most common cancers in Europe. The vaccine is absorbed by the immune system's scavenger cells, which can then kill cancer cells more efficiently. However, the cancer does not disappear completely in all of the patients treated with BCG: the tumors recur in 30 to 40 percent of cases.

A clinical study of bladder cancer patients has now shown that treatment with VPM1002 can prevent the bladder tumors from recurring: almost half of the patients who had previously failed to respond to conventional treatment with unmodified BCG were tumor-free by the end of the study. In order to ensure that these patients do not have to wait too long to benefit from VPM1002 treatment, the developers are holding talks with the European Medicines Agency to have the vaccine licensed throughout Europe as soon as possible.

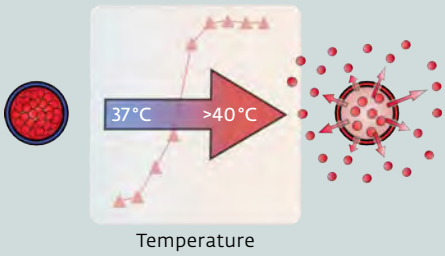
paths between the conductor and the electrode material. This accelerates the charging and discharging processes. The battery's capacity can also be increased in certain cases since the active material is utilized more efficiently. "We assume that a battery with conductors that penetrate the active material is mechanically stabilized and withstands more charging cycles than present-day batteries," says Joachim Spatz. The main reason why the capacity of conventional batteries decreases over time is because the active material expands or contracts during charging or discharging and ultimately separates from the metal foil that serves as a conductor. The researchers believe that a metal web embedded in the active material would change shape in the same way.

The new battery design is being made possible thanks to an advanced procedure in which large quantities of microscopically fine metal fibers are spun from drops of molten metal. During this procedure, the metal atoms also form a structure which enables the fibers to be melded into networks at low temperatures.

The metal sponges created in this way could be useful not only for batteries but also for other applications, e.g. for catalysis in the chemical industry or as an electromagnetic shielding material.

A hot drug

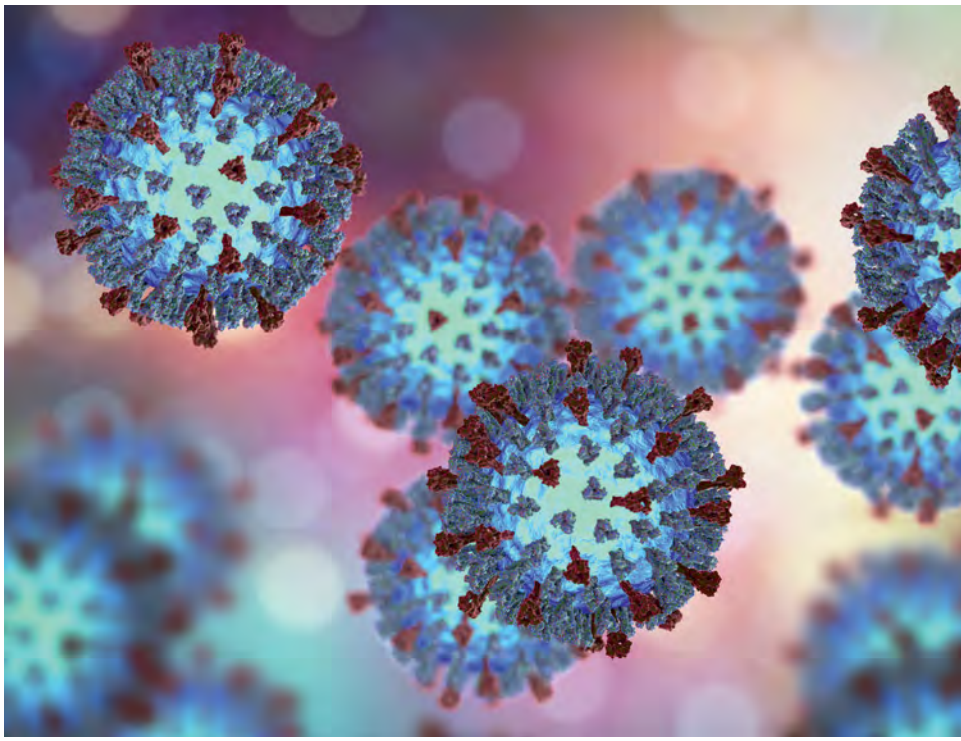
Much of the effort expended on pharmaceutical research focuses on making drugs more effective and reducing side-effects. Hansjörg Eibl, former Director of the Max Planck Institute for Biophysical Chemistry, is also pursuing this goal. It occurred to him that an active substance cannot trigger side-effects as long as it is well encapsulated. He accordingly put this idea to practical use by utilizing thermosomes. These are temperature-sensitive nanotransporters which are charged with active substances, administered intravenously and which initially circulate unnoticed in the bloodstream. The active substance is only released when these mini-transporters reach the target tissue, which is warmed to a temperature of 40 to 42 degrees Celsius by an external heat source (the body's normal temperature is around 37 degrees Celsius). Up to 15 times the local concentration can be achieved in this way, thus appreciably reducing the substance's adverse effects. Various animal studies of a chemotherapy drug carried out in cooperation with the LMU Munich have already shown that the concept works, at least in animals. Thermosome GmbH, based in Martinsried, has been developing these temperature-sensitive nanotransporters for medical use since 2015.



Heat-sensitive nanotransporters charged with the active substance circulate in the bloodstream. They discharge their load once they reach their target, which is warmed to 40 degrees by an external heat source.

Measles against cancer

Genetically modified viruses could fight tumors



Beneficial viruses: a specific strain of the measles virus, which is used in vaccines and cannot attack healthy cells, is genetically modified in such a way that it reproduces in tumor cells and effectively destroys them.

Viruses are usually seen as dangerous – they can destroy computer hard drives and cause a wide range of diseases in humans. However, they can also be useful. Molecular biologists have been using modified viruses for many years as an effective means of infiltrating foreign DNA into living cells – a technique that doctors now also use in gene therapy. Wolfgang Neubert, former Research Group Leader at the Max Planck Institute of Biochemistry, is also using viruses for medical purposes.

The scientist is treating tumors with a measles virus that naturally inhibits cancer growth. Together with researchers from the University of Tuebingen, he genetically modified a measles virus that is used in a vaccine and cannot attack healthy cells; this otherwise harmless vaccine now turns into a potent cytostatic agent when it penetrates cancer cells. It then reproduces unchecked in the cancer cells and oncolysis occurs: the cell bursts and releases measles viruses, which then attack the nearest cancer cells. The viruses also activate the immune system; in ideal circumstances, this causes tumors to be effectively destroyed.

In 2018, the Max Planck Society granted a license to the Austrian biotech company Themis Bioscience, allowing it to use the technology to develop and manufacture this type of cancer treatment. The out-licensed oncolytic virus is now being tested on cancer patients in an early clinical study.

Graphics: Thermosome (left); shutterstock (right)

Deformed proteins

A drug to treat Parkinson's disease is being developed from a substance that prevents the formation of toxic protein clumps

Proteins have to assume the correct spatial structure if they are to properly perform their tasks in the body. The fatal consequences of defective folding are shown by diseases such as Parkinson's: so-called synuclein proteins in the brain cells do not fold correctly and consequently form toxic clumps. This causes the death of the affected cells.

Christian Griesinger and his team at the Max Planck Institute for Biophysical Chemistry in Goettingen are analyzing the spatial structure of proteins. In cooperation with Armin Giese from the Ludwig Maximilian University of Munich, they have also been testing and optimizing molecules that prevent the protein alpha-synuclein from clumping. One substance is proving to be particularly promising: the molecule known as anle138b dissolves toxic clumps of synuclein and prevents new ones from forming. This active substance accordingly tackles the disease at its source.

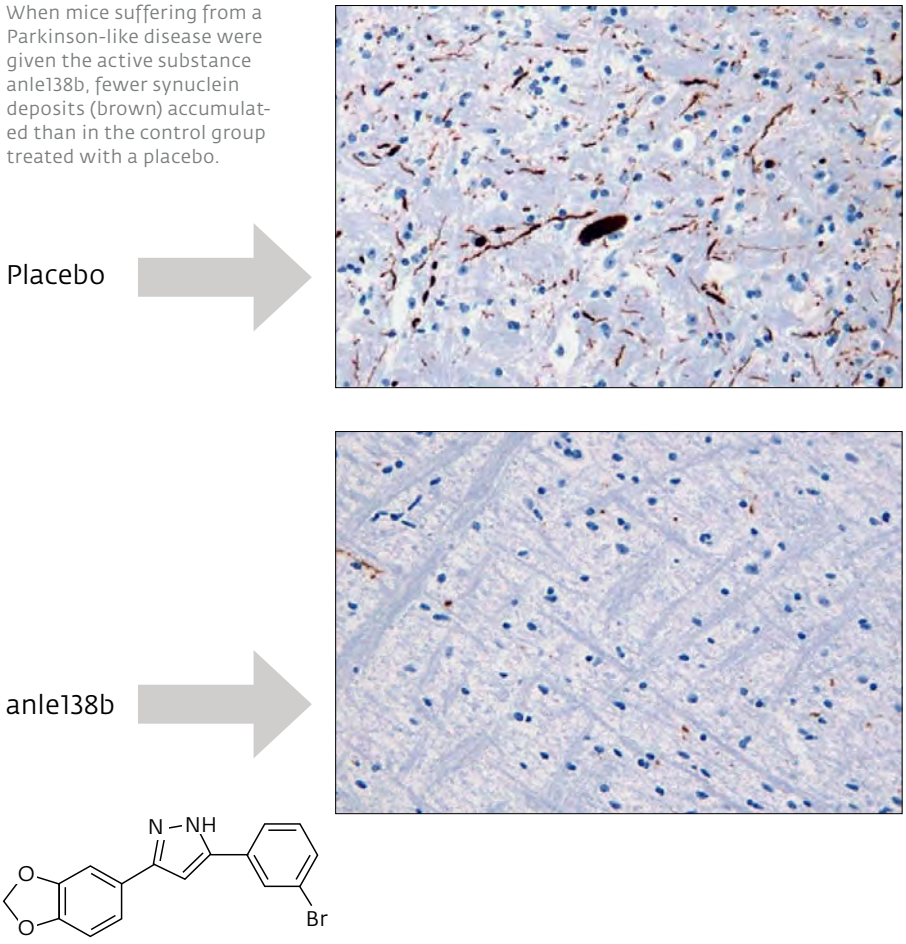
If genetically modified mice suffering from Parkinson's disease are treated with anle138b, they can coordinate their movements better and remain symptom-free for a longer period. Mice with Alzheimer's disease and so-called multiple system atrophy can be treated with similar success.

In 2013, Max Planck Innovation and the Ludwig Maximilian University of Munich out-licensed the further development of the active ingredient to the newly-established pharmaceutical company Modag. Pre-clinical studies showed that anle138b is very well tolerated by animals. Furthermore, the active ingredient has been developed in such a way that it will in future be possible to administer it to humans in pill form.

A clinical phase I study of anle138b got under way at the end of 2019. The goal is to investigate the safety and tolerability of the substance in human test subjects. If this study is successful, Modag is planning to treat patients with multiple system atrophy as part of a phase II study; this is a rapidly progressing disease in which alpha-synuclein forms clumps in various parts of the brain and leads to death within four to eight years. However, the active ingredient will also be used to treat other neurodegenerative diseases such as Parkinson's, Alzheimer's and Creutzfeldt-Jakob disease.

In the fall of 2019, Max Planck Innovation also granted Modag a license for a technology with which the company can develop successors that are chemically slightly modified versions of anle138b and are even better suited to oral administration. With anle138b and its successors, we may one day have a new type of drug that could inhibit or even stop the development of diseases such as Parkinson's, Alzheimer's or multiple system atrophy.

When mice suffering from a Parkinson-like disease were given the active substance anle138b, fewer synuclein deposits (brown) accumulated than in the control group treated with a placebo.



Graphics: Giese, LMU Munich

Bert Klebl, CEO of the Lead Discovery Center in Dortmund.

Photo: Hardy Welsch

"The LDC bridges **the valley of death"**

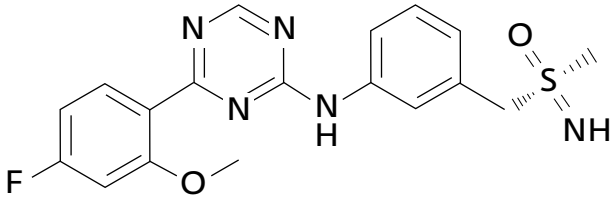
Founded in 2008, the **Lead Discovery Center** (LDC) closes the funding gap between basic research and drug development. In this interview, CEO **Bert Klebl** describes the close cooperation with scientists and the LDC's role-model function.

TEXT **TOBIAS HERRMANN**

Mr. Klebl, the Max Planck Society concentrates on basic research. How does a drug discovery organization such as the LDC fit with this?
Bert Klebl: For me there's no contradiction. Of course, the first goal of basic research is to create new knowledge and expand on what we already know. But this often generates results with a practical application. If researchers discover a molecule that seems medically relevant, for example, they should definitely pursue this idea. The substance could turn out to be a cure for a fatal disease. And this is were the LDC comes in.

How does your collaboration with the research scientists work exactly?
Usually it's the scientists who get in touch with us. The LDC was founded 12 years ago and by now we are well known at all the institutes in the biology and medicine section, as well as in the chemistry, physics and technology section. Our members of staff immerse themselves in the topic, talk to experts and have the scientists explain their hypothesis. Then we bring in our drug development expertise and examine whether or not the project can be realized. Once this hurdle has been cleared, we sit down with the researcher and write up their idea and all the drug-relevant information in an investment proposal. This sets out verifiable milestones and states the aim of the project. A committee on which staff from Max Planck Innovation and investment fund participants are equally represented then decides if and how the project is to be supported financially.

What is the aim of the project usually given by the researchers? In other words – up to which stage do you accompany the project?
Basically we accompany the drug development from the initial idea up to "proof of concept." If the molecule has proven its worth in an animal model, we consider our job done, and license the product together with the appropriate patents to a pharma company. >



The chemical formula of Atuveciclib. This molecule, a member of the class of so-called CDK inhibitors, is currently in a Phase I study and is therefore the most advanced LDC project. It has been developed together with Bayer since 2011 and could be used in cancer therapy.

Why do companies get on board so late? Couldn't a scientist with a promising idea start cooperating with a biotech company at an earlier stage?
I'm afraid they wouldn't have much luck. With a few exceptions, there are hardly any biotech or pharma companies still actively engaged in research in the transition area from basic research to early drug discovery. Most biotech companies have long since become service providers, as this is considerably more lucrative in the short run, and pharma concerns concentrate on later developmental phases. The wheels in drug development turn slowly. It can often take 4 or 5 years for an initial idea to become a finished product for "proof of concept", which will ideally be ready for clinical testing 2 or 3 years after that. Companies get on board later, when the value chain is shorter and the perceived entrepreneurial risk is not so great.

The probability that an idea proves to be a failure is therefore greatest early on. At the LDC, how often does an idea lead to a start-up?
We have undertaken around 80 projects since 2008. Nearly half of these have yet to be completed, so we can't yet say if they're going to be successful. From the remaining 40 projects that have already been completed, we have generated licenses, joint development programs with biotech and pharma companies and/or start-ups. All in all, we have successfully completed 19 projects, giving a success rate of about 50 percent. Of course we have had our failures – these are unavoidable in drug development. As soon as it becomes clear that the original hypothesis can't be fulfilled, we have to respond accordingly.

By ditching the project?
Not necessarily. When one door closes, another sometimes opens. For example, we were investigating a mechanism involved in a metabolic disease at the LDC, and developed a drug candidate for it. But the project hit a dead end. During our experiments, however, we noticed that this mechanism plays a much greater role in neurodegenerative disorders. So we revised the hypothesis, came up with another strategy, and followed this new approach. Pharma concerns don't usually have this degree of flexibility because their therapeutic focus is often very narrow and they are under greater pressure to generate money.

Apropos money: how is the LDC financed?
In the first ten years, many projects from the Max Planck Society were financed within a cooperation framework: the Society provided EUR 6 million per annum for project-related activities at the LDC until the middle of 2018, with a total turnover of just over EUR 11 million that same year. This sum for project financing has now been reduced to EUR 3 million per annum. However a new, fund-like structure provides a further stable source of financing. This KHAN-I fund delivers EUR 3 million in reciprocal financing per annum, in addition to completely new drug research approaches, so that we still have EUR 6 million available for project ideas from the Max Planck Society. In addition we have always created other sources of income at the LDC. These include grant funding, collaboration contracts with industry, and licensing revenues.

Does money also flow back to the Max Planck Society?
Yes, it's a very dynamic system. The licensing agreements with our cooperation partners stipulate payments coupled to particular milestones. And as soon as a product is launched on the market, the Max Planck Society and the LDC receive a percentage share of revenue. The latter is a relatively new phenomenon for us – due to the long lead times in drug development, we are only just beginning to see the fruits of our labor.

LEAD DISCOVERY CENTER (LDC)

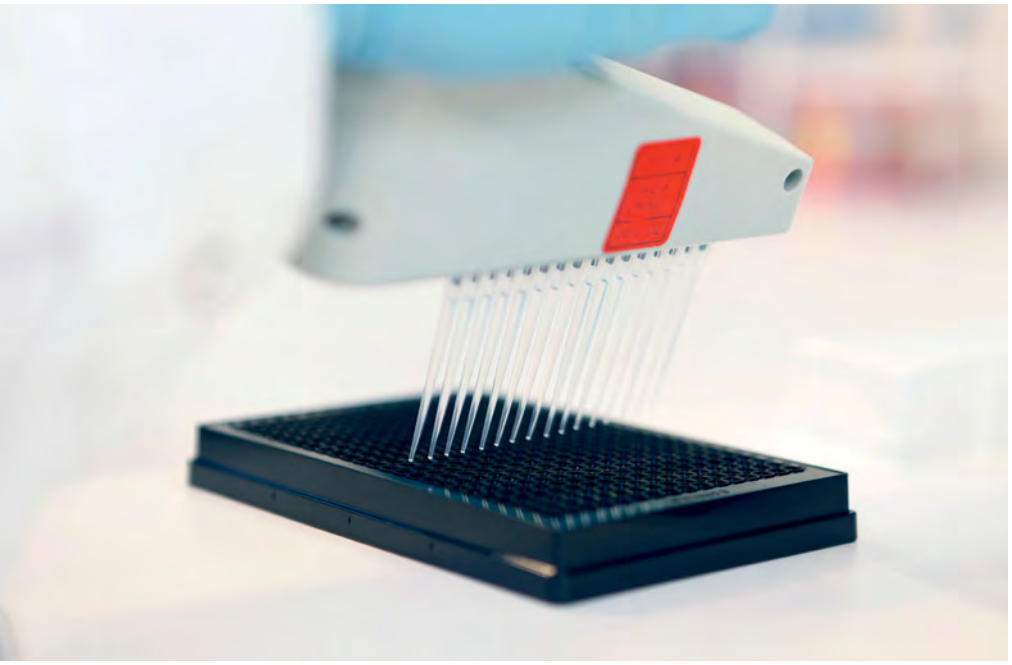
The Lead Discovery Center (LDC) was founded in 2008 as a spin-off of Max Planck Innovation. The aim of the organization, which is based at the BioMedizinZentrum in Dortmund, is to translate research projects into novel drugs, developing them for the market. Scientists in basic research are supported by an interdisciplinary team of around 80 molecular biologists, pharmacologists and project managers. To date, 20 patents have been registered and 20 projects partnered.

Do you work exclusively on Max Planck projects?
Up until 2018, most original ideas came from the Max Planck Institutes. In future, as a result of the new fund-like structure, the portfolio will grow synergistically. Apart from the Max Planck Foundation, the investors in the KHAN-I fund include the promotional bank of the Austrian federal government – and in return they naturally expect support for Austrian research projects. In addition, because we receive funding from various other sources, we have always pursued third-party projects. But to be perfectly clear: our focus will definitely remain on the Max Planck Institutes.

When the LDC was founded in 2008, there were 30 members of staff. Now there are 80. Do you want to expand further? And do you have the space?
In view of our steadily rising turnover, we expect to hit the 100 staff mark within the next few years. And yes, it's getting a bit cramped, but we can upgrade. The BioMedizinZentrum in Dortmund where we are based is continually being expanded, and a new building is planned there for the end of 2021. We certainly want to continue on our current road to success. >

Many processes at the LDC are automated. This analyzer can measure the binding of small molecules to proteins with a high degree of sensitivity.

Photo: Lead Discovery Center



Pipetting robots can transfer a large number of minute liquid portions at once.

And then there's your Munich branch…
Correct. In 2016 we opened a branch in Munich – in Planegg, to be precise – which specializes in the development of therapeutic antibodies. LDC Biologics is situated at the heart of the Munich biotech cluster, which is considered the center of German drug research. We will also be expanding at this location in the years to come.

Is this enough to cope with the increasing demand?
Our growth is not limitless. We are already in a position to initiate more projects than our capacity allows. I would be delighted if more institutes follow the LDC's example. The demand is certainly there, and pharmaceutical basic research everywhere is just waiting to be transferred into applications. The Max Planck Society recognized this need early on, and created the LDC as an effective instrument to bridge the "valley of death" – i.e. the usual funding gap between basic research and commercial application.

Do you miss having state support?
In my opinion, the LDC fulfills a kind of political mandate. There is huge political pressure for sustainable start-ups and spin-offs. I believe we can adequately fulfill this requirement – our success rate to date speaks for itself. As far as I know, the federal government is currently planning a translation fund. This would be a good first step that we at the LDC would certainly welcome. Otherwise, I can only appeal to every decision maker to follow our lead. We at the LDC would be happy to advise!

SMOTHERING CANCER CELLS IN REFUSE

In mid-January 2020, a joint venture between the LDC, the South Korean pharma company Qurient and Nobel Prize winner Robert Huber founded QLi5 Therapeutics – the most recent success story at the LDC. Robert Huber is the originator of the idea, and his research forms the basis for the project. Specifically, QLi5 is engaged in the search for proteasome inhibitors. These prevent cells from breaking down proteins that are no longer required. Cells are "smothered" by the accumulated protein "refuse" and die. In this way, cancer cells can be effectively destroyed.

Huber, now Director Emeritus at the Max Planck Institute of Biochemistry, has been pursuing this therapeutic approach with the support of the LDC for some time. A few years ago, Merck came on board as strategic partner, although the Darmstadt company does not hold shares in QLi5. Instead, the Seoul-based biotech company Qurient is cooperation partner and primary investor. "The fact that QLi5 Headquarters are nevertheless in Dortmund, shows the high level of trust that Qurient has in the LDC," says Robert Huber. "The LDC has truly deserved this trust, as Qurient's success is based primarily on two LDC-supported products." It is therefore logical that the South Koreans want to extend their cooperation with the LDC. A further indication of the close collaboration is the appointment of Michael Hamacher, who has worked at the LDC since 2008, as the CEO of QLi5.

Photo: Lead Discovery Center

High-Tech Gründerfonds

WE INVEST IN PEOPLE.

VENTURE CAPITAL FOR HIGH-TECH FOUNDERS.
MADE IN GERMANY.

+++ The High-Tech Gründerfonds is THE seed investor for innovative technologies and business models.

+++ We successfully support the best founders, whose ideas can revolutionize entire industries and improve people's lives.

+++ From the foundation to the exit.

50 YEARS OF
MAX-PLANCK-INNOVATION
CONGRATULATIONS
& THANK YOU!
FOR THE GOOD COOPERATION

Our fund investors

7

NUMBER OF
LISTED COMPANIES

26

NUMBER OF
COMPANY SALES

NUMBER OF **JOBS**

approx.
6000

Facts & Figures

"Insight must precede application" – according to the motto of the Max Planck Society, Max Planck Innovation has made a decisive contribution to turning scientific findings into products.

TOTAL REVENUES

approx. €
490
million

approx.
4450

NUMBER OF **INVENTIONS**

NUMBER OF
LICENSE AGREEMENTS

approx.
2680

156

NUMBER OF **SPIN-OFFS**

Research Establishments

- Institute / research center
- Sub-institute / external branch
- Other research establishments
- Associated research organizations

The Netherlands
- Nijmegen

Italy
- Rome
- Florence

USA
- Jupiter, Florida

Brazil
- Manaus

Luxembourg
- Luxembourg

MAX PLANCK GESELLSCHAFT

Publisher's Information

MaxPlanckResearch is published by the Science and Corporate Communication Office of the Max Planck Society for the Advancement of Science. Legal headquarters of the Association: Berlin.
ISSN 1616-4172

Publisher's mailing address
Hofgartenstraße 8, D-80539 Munich
Tel. +49 89 2108-1719 / -1276 (in the mornings)
e-mail: mpf@gv.mpg.de
The magazine as ePaper: www.mpg.de/mpresearch
App for free download: www.mpg.de/mpr-mobile

Content Authority
Dr. Christina Beck (-1276)

Editors-in-Chief
Peter Hergersberg (Chemistry, Physics, Technology; -1536)
Helmut Hornung (Astronomy; -1404)

Editorial Staff
Dr. Elke Maier (Biology, Medicine; -1064)
Dr. Harald Rösch (Biology, Medicine; -1756)
Mechthild Zimmermann (Culture, Society; -1720)

Photo Editor
Susanne Schauer (-1562)
Annabell Kopp

Translation
Proverb oHG
Marktplatz 12
70173 Stuttgart
Tel. +49 711 164090-0
e-mail: proverb@proverb.de

Art Direction
Julia Kessler, Sandra Koch
Voßstraße 9, 81543 Munich
Tel. +49 89 27818770
e-mail: projekte@designergold.de

Lithography
KSA Media GmbH
Zeuggasse 7, 86150 Augsburg

Printing & Distribution
Vogel Druck- & Medienservice GmbH
Leibnizstraße 5, 97204 Höchberg

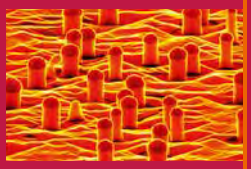
Advertising
Beatrice Rieck
Vogel Druck und Medienservice GmbH
Leibnizstraße 5, 97204 Höchberg
Tel.: +49 931 4600-2721
e-mail: beatrice.rieck@vogel-druck.de

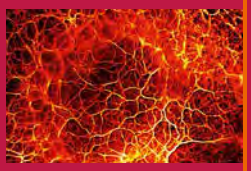
MaxPlanckResearch seeks to keep partners and friends of the **Max Planck Society** up to date on the latest research conducted at the Max Planck Institutes. Four editions of the magazine are published in German each year, all of which are translated into English. At present, the English version has a circulation of 10,000 copies (**MaxPlanckForschung**: 85,000 copies). It is free of charge. None of the views and opinions expressed in **MaxPlanckResearch** may be interpreted as representing the official views of the **Max Planck Society** and its associated bodies. Reprint of texts is permitted only with the prior approval of the publisher. Photographic rights may be granted by agreement. Circulation of the special edition: 10,000 copies.

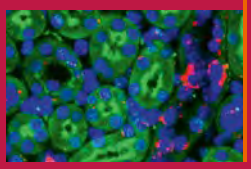
The Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V. (**Max Planck Society**) comprises 86 institutes and research facilities where around 23,400 employees, including some 6,700 employed scientists, work and conduct research. The annual budget for 2018 is 1.8 billion euros. Research activities of the **Max Planck Society** focus on basic research in natural sciences and the humanities. The **Max Planck Society** is a non-profit organization registered under private law as an incorporated association. Its central decision-making body is the Senate, with members from the world of politics, the scientific comunity, and the professional public, providing for a well-balanced partnership.

Max-Planck-**Innovation**

Connecting **Science and Business.**

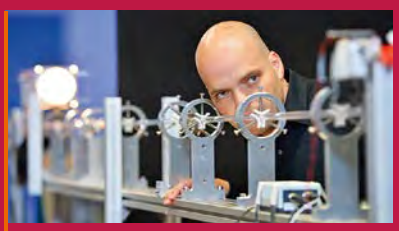






Max Planck Innovation is responsible for the technology transfer of the Max Planck Society and, as such, the link between industry and basic research. With our inter-disciplinary team we advise and support scientists in evaluating their inventions, filing patents and founding companies. We offer industry a unique access to the innovations of the Max Planck Institutes. Thus we perform an important task: the transfer of basic research results into products, which contribute to the economic and social progress.

Connecting Science and Business



www.max-planck-innovation.de