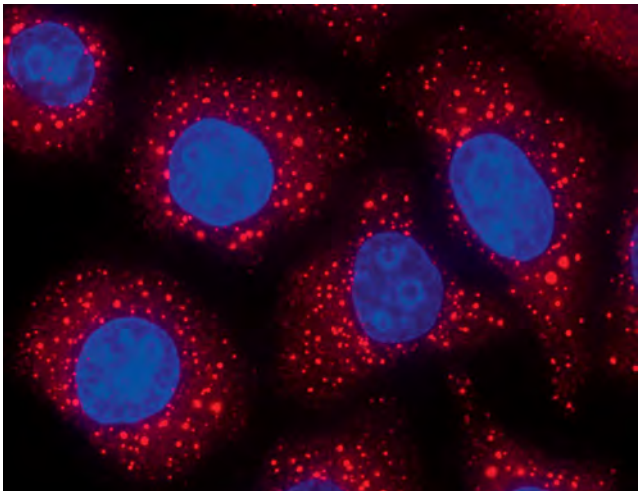
Order is half the battle

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.

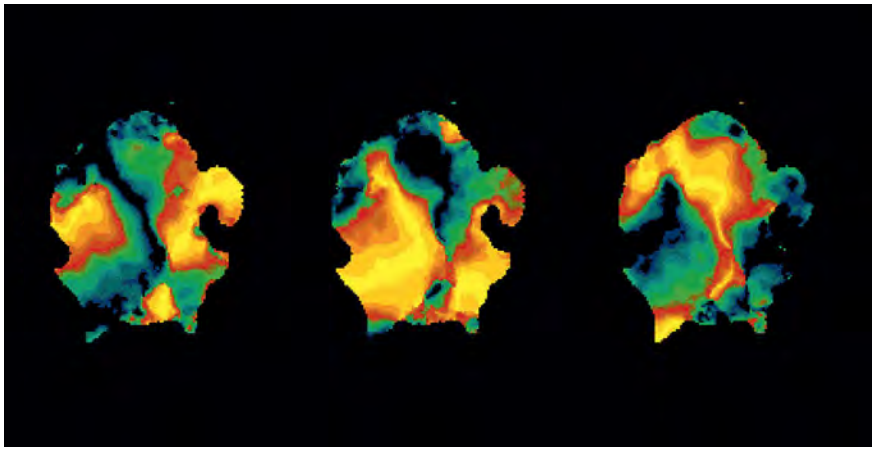
"We haven't yet finished investigating the tissue damage, but we already expect it to be significantly less due to the reduction in energy we have achieved so far," says Stefan Luther. "However, whether or not we can reduce the energy used during the fibrillation by about 90 percent and thus make the 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

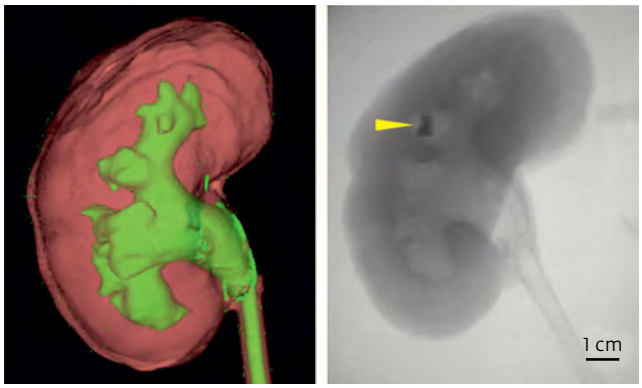
Organ models made of a hydrogel compound may improve medical training

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.

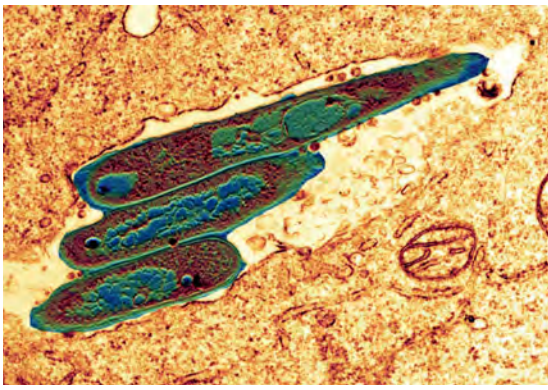


Photo: MPI for Infection Biology – CF Microscopy / Volker Brinkmann

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.

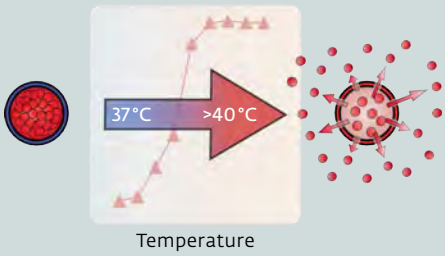
paths between the conductor and the electrode material. This accelerates the charging and discharging processes. The battery's capacity can also be increased in certain cases since the active material is utilized more efficiently. "We assume that a battery with conductors that penetrate the active material 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

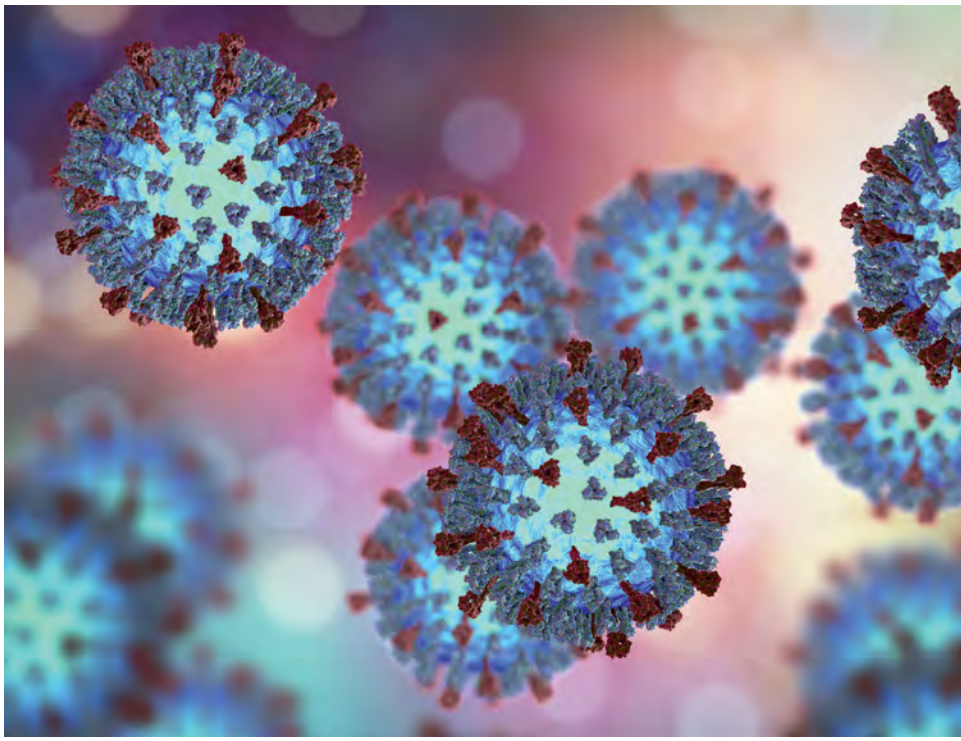
Much of the effort expended on pharmaceutical research focuses on making drugs more effective and reducing side-effects. Hansjörg Eibl, former Director of the Max Planck Institute for Biophysical Chemistry, is also pursuing this goal. It occurred to him that an active substance cannot trigger side-effects 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.

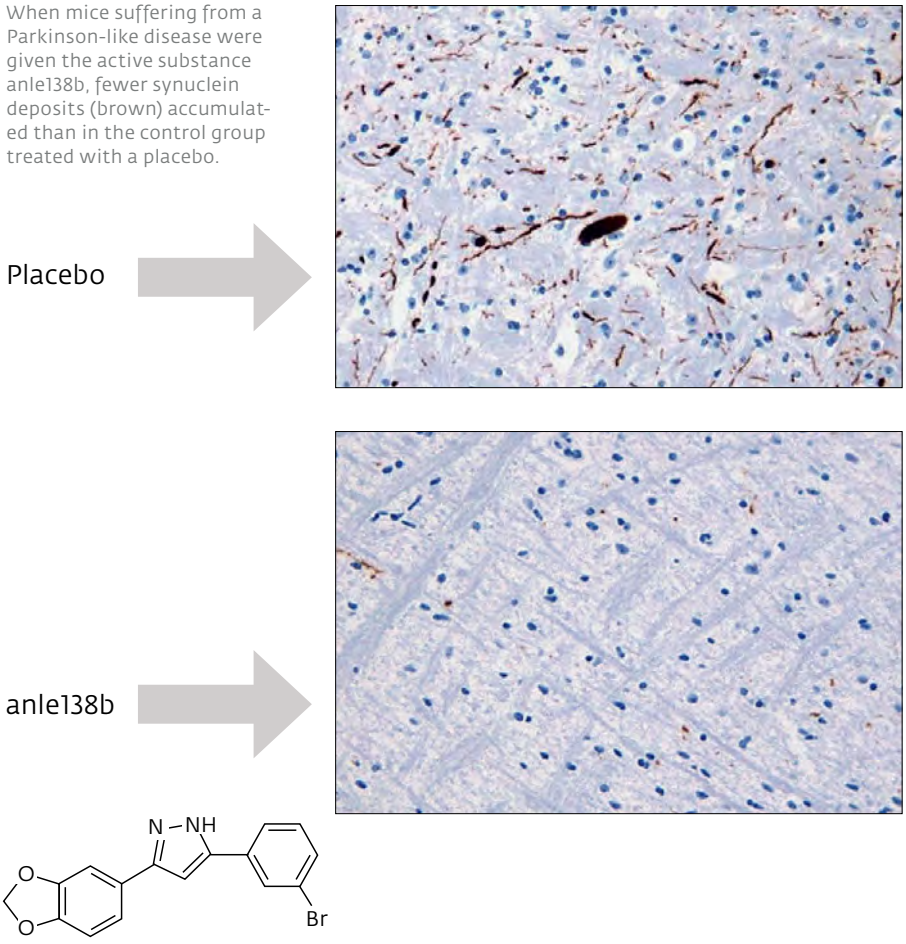
If genetically modified mice suffering from Parkinson's disease are treated with anle138b, they can coordinate their movements better and remain symptom-free for a longer period. Mice with Alzheimer's disease and so-called multiple system atrophy can be treated with similar success.

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