EVONIK
Leading Beyond Chemistry

ELEMENTS

Research. Knowledge. The future.

Medicine for the world

3/2020

Virus

A tiny pathogen

A virus (Latin for slime or poison) is an infectious particle consisting of nucleic acids, proteins, and in some cases a viral envelope. In order to reproduce, these tiny viruses, which are between 20 and 300 nanometers in size, infect a host organism. The virus smuggles its genetic material into a host cell, where it is replicated. The virions thus created then jump into other cells. The first known virus used the tobacco plant as a host. In 1893 Adolf Mayer discovered the existence of this pathogen, which was later named the tobacco mosaic virus. Mayer categorized this pathogen as a bacterium, but in the 1930s Wendell M. Stanley demonstrated that it was an independent organism: a virus, whose physical structure was closely studied in the following decades thanks to the invention of the electron microscope.

Nucleic acids Polymers consisting of nucleotides, which store and process genetic information. We distinguish between DNA (deoxyribonucleic acid) and RNA (ribonucleic acid).
Viral envelope The outer layer of a virus, which consists of lipids and embedded proteins
Virions Virus particles that exist outside the host cell
Adolf Mayer (1843–1942) German agricultural chemist and a pioneer of virology
Wendell M. Stanley (1904–1971) US chemist, biochemist, and virologist who received the shared Nobel Prize for Chemistry in 1946 together with his research colleague John Howard Northrop

DEAR READERS,

For researchers working in the fields of biology, chemistry, and medicine, 2020 should actually be a year in which they receive the highest recognition. These scientists, who usually work in their laboratories almost unnoticed by the general public and primarily publish the results of their research in professional journals, are suddenly standing in the spotlight. The coronavirus pandemic is demonstrating to all of us every day how vitally important their research is. The development of a vaccine against Covid-19 is a unique international race against time. At stake are prestige, huge amounts of money and, above all, the lives of countless human beings.

But while scientists are finally receiving the appreciation they deserve, conspiracy theorists and self-appointed contrarians are loudly trying to turn public opinion against the experts. Climate change, Covid-19, protection by means of vaccination—according to them, it's all just alarmism and "fake news"! People who believed 2,000 years ago that the earth is flat didn't know any better, but people who still insist today that the earth is flat don't want to know any better.

When fact-based arguments clash, what's needed is a constructive argument aimed primarily at finding the best solution. Our debate starting on page 22 illustrates how this is done. But if scientific findings are simply dismissed as nonsense and lies, it's futile to engage in a discussion. The only way we can counter this mindless hostility to science is by means of comprehensible factual information.

And that's exactly what we want to offer. That's why we are responding to the current situation by devoting this entire issue to medical research, especially vaccination.

On behalf of the editorial staff, I would like to express an especially heartfelt "thank you" to the researchers who have contributed to this issue. Under the present circumstances, what could be more intriguing than to report about their work?

I wish you a thought-provoking reading experience.

Matthias Ruch
Editor in Chief

All of the articles from the printed magazine, as well as additional current content, are also available on the Internet at: elements.evonik.com

The fight against pathogens: In the Congo, a woman waits with her children to be vaccinated against the Ebola virus

VACCINATION

An Evonik employee monitors the abrasion of tablets made with the calcium silicate RXCIPIENTS®

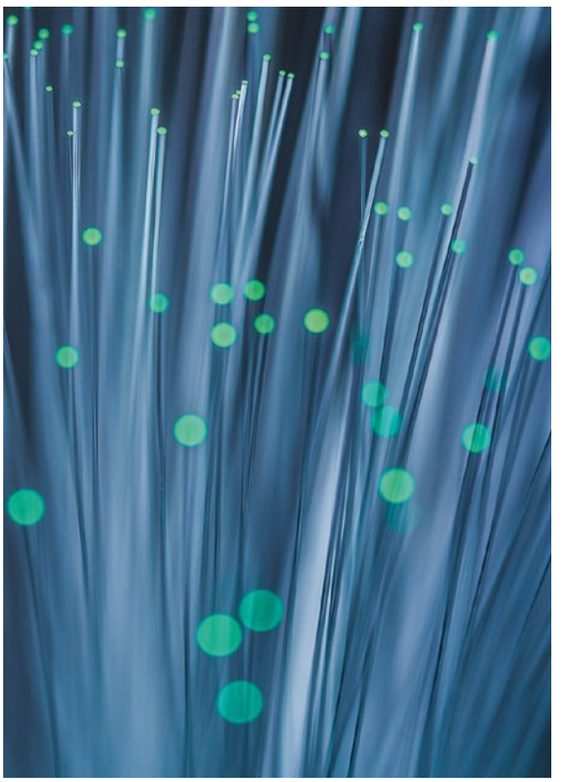
Chains of polyethylene glycol known as PEGs are produced at this laboratory in Hanau

A DROP OF LIFE

For many diabetics, the daily shot of insulin is a matter of life and death. The peptide influences the metabolism of sugar in the body. Peptides are molecules composed of amino acids, which are themselves complex and expensive to manufacture by chemical synthesis. The Düsseldorf-based startup Numaferm, in which Evonik has a holding, has developed an especially efficient biotechnological process in which bacteria play a key role. The microorganism *E. coli* converts simple nutrients into high-value peptides. This offers a sustainable way to produce more active ingredients.

Clever color choice

Throughout the world, developers are working on AI-based lab assistants. Researchers have recently achieved a breakthrough in the field of materials research



The scientists from North Carolina State University and the State University of New York at Buffalo who developed this artificial intelligence (AI) system call it the "artificial chemist." It can independently determine which reactions of which starting materials are needed in order to create substances with specific desired properties. The system's accuracy was recently demonstrated during a proof-of-concept experiment, in which the AI was tasked with finding the ideal quantum points for certain colors in LED displays. Quantum points are nanocrystals that radiate light, in TV screens, for example. The system never took more than 15 minutes to find the quantum points for a color. This success has spurred the researchers to make plans to use the artificial chemist for the development of other materials that contain liquid starting materials such as metal or metal-oxide nanoparticles.

PEOPLE & VISION

Light is the key to exploring alien worlds

THE PERSON

Lisa Kaltenegger's driving force has always been to find answers for unsolved mysteries. Kaltenegger, 42, is an astrophysicist who examines exoplanets that are many light-years away from Earth. Kaltenegger has come a long way from her home town of Salzburg, Austria: After earning her degree, she worked for the European Space Agency (ESA), from where she later switched to Harvard. She subsequently led a research team at the Max Planck Institute for Astronomy and afterwards an institute at Cornell University in Ithaca/New York, where she now conducts research. She's also written a book, titled *Sind wir allein im Universum?* (Are we alone in the universe?). Moreover, the asteroid Kaltenegger 3477 is named after her.

THE VISION

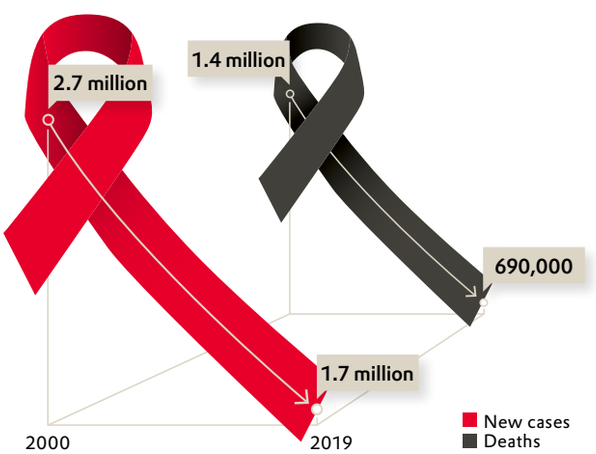
Kaltenegger is looking for alien planets so that we can better understand our own. "Earth-like planets that are in different stages of development show us how Earth has evolved and will change in the future," she says. In order to study the conditions on alien planets, Kaltenegger analyzes how starlight collides with an atmosphere. Starlight is filtered in a planet's atmosphere if chemical elements such as oxygen or hydrogen are present. "When that happens, the light our telescopes receive lacks specific wavelengths." This is proof that certain gases exist in the atmosphere and means that we might soon be able to detect life on distant planets.

Listen to the signals!

Human cells continuously communicate with one another by sending chemical signals, in the form of nitrogen monoxide, for example. If the signal paths are disrupted, this can have negative consequences for the body, such as cardiovascular diseases or muscular and retinal dystrophies. Special nanocapsules might play a mediating role between cells in the future. A research team at the chemistry department of the University of Basel and the National Centre of Competence in Research of Molecular Systems Engineering recently developed two types of capsules, each of which was filled with different enzymes that were enveloped by polymers. The researchers let the tiny containers penetrate the cells, where they latched into the signal paths. The two types of capsules cooperated: The first capsule produced nitrogen monoxide, which the second capsule received as a natural signal that it processed further. This cascade reaction boosted the signal path between the cells, thus improving their communication.

THAT'S BETTER

Less suffering



Source: UNAIDS

Don't give AIDS a chance: In the 1980s and '90s, the spread of the human immunodeficiency virus, or HIV for short, sparked a series of global educational campaigns. At the same time, medical professionals all over the world began to develop medications against the virus. Both of these measures were successful. As a result, there were around one million fewer new cases worldwide in 2019 than 19 years earlier: 1.7 million instead of 2.7 million. During the same time period, the number of AIDS-related deaths was more than cut in half—from 1.4 million to 690,000. Although there's still no cure, the drop in deaths is largely due to treatments with anti-HIV drugs. The active ingredients, which include entry and integrase inhibitors, suppress the spread of the virus in the body and thus prevent the onset of AIDS.

$630

BILLION

— that's how much *in vitro* meat is expected to generate in sales worldwide in 20 years, according to the business consulting firm A.T. Kearney. That would be four times as much as the figure forecast for 2025. The authors of the study expect vegan meat substitute products to generate sales of $450 billion in 2040.

THE DANCE OF THE ELECTRONS

Solar cells made of perovskite are considered to be especially effective. When the sun shines, ions, electrons, and the "holes" that these electrons leave behind in the mineral begin to move about. Researchers at the Max Planck Institute for Polymer Research have analyzed this "dance." The results showed that the holes move more slowly than expected. This finding might help boost the efficiency of solar cells.

GOOD QUESTION

Could 3D-printed arteries help us detect heart diseases earlier than is currently the case, Professor Wang?

Yes, that would be the case if we manage to print artificial arteries that are fully compatible with the human body. My team has successfully taken a first big step in this direction: We have developed an additively manufactured artery that consists of piezoelectric materials. These biocompatible, flexible composites emit an electrical impulse whenever the blood pressure fluctuates. These signals enable blood pressure to be monitored in real time. The cylindrical structure with its sinusoidal network also plays a key role in the detection of heart conditions. Thanks to its complex geometry, the artery can detect irregular movements, which might indicate the early stage of blood vessel blockage. This lets doctors intervene before the blockage becomes serious.

Xudong Wang is a professor at the University of Wisconsin-Madison and the co-author of a study about the uses of 3D-printed arteries

At the Sharp End

TEXT **INGA OLFEN**

High tech is coming to the fore in the struggle against viruses and bacteria. Modern vaccines transport genetic information from pathogens into target human cells in order to trigger an immune reaction there. The transportation of these "blueprints" requires tiny lipid nanoparticles of the kind that Evonik is producing in Canada

"The Covid-19 pandemic is a catalyst for the development of gene-based vaccines"

STEFAN RANDL, HEAD OF RESEARCH, DEVELOPMENT, AND INNOVATION, EVONIK HEALTH CARE BUSINESS LINE

When the country doctor Edward Jenner took a knife to his gardener's son in the English county of Gloucestershire on May 14, 1796, he could not have suspected that he was starting a medical revolution. After making an incision in the healthy eight-year-old boy's skin, Jenner rubbed into it some pus taken from a milkmaid who was sick with cowpox. One week later, the child had fever and a headache, as well as small blisters at the places that Jenner had infected. A few days later, these symptoms disappeared.

Six weeks later, the doctor repeated this procedure, this time with secretions from a patient suffering from smallpox, an illness that was killing 400,000 people a year in Europe during the 18th century. The boy developed no symptoms of illness whatsoever: Vaccination had been invented. Jenner called his process vaccination, a word derived from *vacca*, the Latin word for cow. The scientific term "vaccine" is also derived from this Latin word.

Today, a good two centuries after the invention of vaccine, scientists are researching completely new types of vaccine technology. This time, they are not working behind the doors of a country doctor's small office; instead, they are doing their work in full view of the international public. They are driven by a pandemic caused by a virus that can be deadly: the coronavirus SARS-CoV-2. They are working under tremendous time pressure. "Until just a few years ago, people estimated that it would take around 15 to 20 years to go from the analysis of a virus to the approval of a vaccine," explains Stefan Randl. As the head of research, development, and innovation at Evonik's Health Care business line, he's familiar with the challenges along the way toward new or improved medicines and vaccine serums. "Empirical data and very new technologies, such as gene-based vaccines, can significantly accelerate the process," he adds.

Evonik, as a contract development and manufacturing organization for the pharmaceutical industry, is also part of this effort. As a specialty chemicals company, it has the expertise and the technology that are needed for the development and manufacture of complex and highly specialized injectable drug products. These products can require drug delivery technologies such as lipid nanoparticles (LNPs), which are a hundred times smaller than a human blood cell and play a very important role when it's necessary to encapsulate unstable active ingredients and release them at exactly the right place in the human body. "Today, when we're discussing topics such as gene-based vaccines that have much shorter development times yet are more effective than conventional serums, lipid nanoparticles play a central role," Randl says.

By producing lipid nanoparticles, the chemical industry is making an important contribution to the development of the vaccines of the future, says Professor →

Hartmut Hengel. "The substances we call transfection reagents play a crucial role in the effectiveness of vaccines," says Hengel, who is the medical director of the Institute of Virology at the Freiburg University Medical Center and the deputy chairperson of the Scientific Advisory Board of the Paul-Ehrlich-Institut (see the complete interview starting on page 15). "These reagents determine which cells the vaccine penetrates and how effective and stable it is."

Milestones of vaccination history

Vaccines are considered the greatest achievements in the struggle against viruses and bacteria. On the following pages we present the most important challenges and successes of medicine in the past two centuries

1796 SMALLPOX

PATHOGEN *Orthopoxvirus variolae* **FIRST VACCINATION** 1796 in England (image: Edward Jenner) **VACCINATION TYPE** Injection of cowpox lymph; it was followed later on in Germany by an attenuated vaccine containing the *Vaccinia* virus, which is closely related to *Variola.* **HISTORY** Between 15 and 30 percent of infected individuals died. After a smallpox epidemic that killed 125,000 people, the German Reich passed a law in 1874 to the effect that children must be vaccinated in their first and twelfth years. Since 1980, smallpox has been considered eradicated worldwide.

The researchers have not yet determined which form of vaccination will have the best outcomes in the coronavirus pandemic. Scientific institutes, startups, and companies all over the world are working on a range of technologies. It is assumed that many different serums will be used. However, one thing is already obvious today: A vaccine is absolutely essential in order to block the virus.

FROM SMALLPOX VIA MEASLES TO THE CORONAVIRUS

Ever since Edward Jenner's pioneering work, some of the worst threats to human health have been mitigated or even eliminated through vaccination. That includes devastating diseases such as rabies, plague, diphtheria, and tuberculosis. For example, thanks to worldwide vaccination programs, smallpox has been considered eradicated since 1980. In 2002 the World Health Organization (WHO) declared that Europe was "polio-free," and a few weeks ago it extended that declaration to include the continent of Africa.

The WHO had also sought to eradicate the measles virus by 2020. Measles can lead to serious complications, including blindness or fatal meningitis, especially in children younger than five. About 2.6 million people died of measles worldwide every year before the first vaccination became available in 1964. After that, the figures rapidly decreased—until 2016. Unfortunately, since then the illness has once again been gaining ground. In 2019 the WHO sounded the alarm: The number of registered cases of measles had increased by 700 percent in Africa and by about 300 percent in Europe in a single year. Many people who live in poor regions have no access to vaccines, but the spread of measles in rich countries is primarily due to growing skepticism about vaccination. In reaction to these figures, mandatory measles vaccination was introduced in Germany in March 2020.

In the struggle against the novel coronavirus, there are no plans for mandatory vaccination, even though fears about such a mandate are being voiced by vaccination skeptics and believers in conspiracy theories. At the moment the focus is on the search for a suitable vaccine and on the associated hopes for ending the pandemic as soon as possible. "There's a lot of optimism," said Professor Klaus Cichutek, the president of the Paul-Ehrlich-Institut (PEI—the Federal Institute for

Vaccines and Biomedicines), which is responsible for approving vaccines in Germany, back in August. The initial results of ongoing studies have shown "that some vaccines can actually induce a specific immune reaction in human beings against SARS-CoV-2," he said.

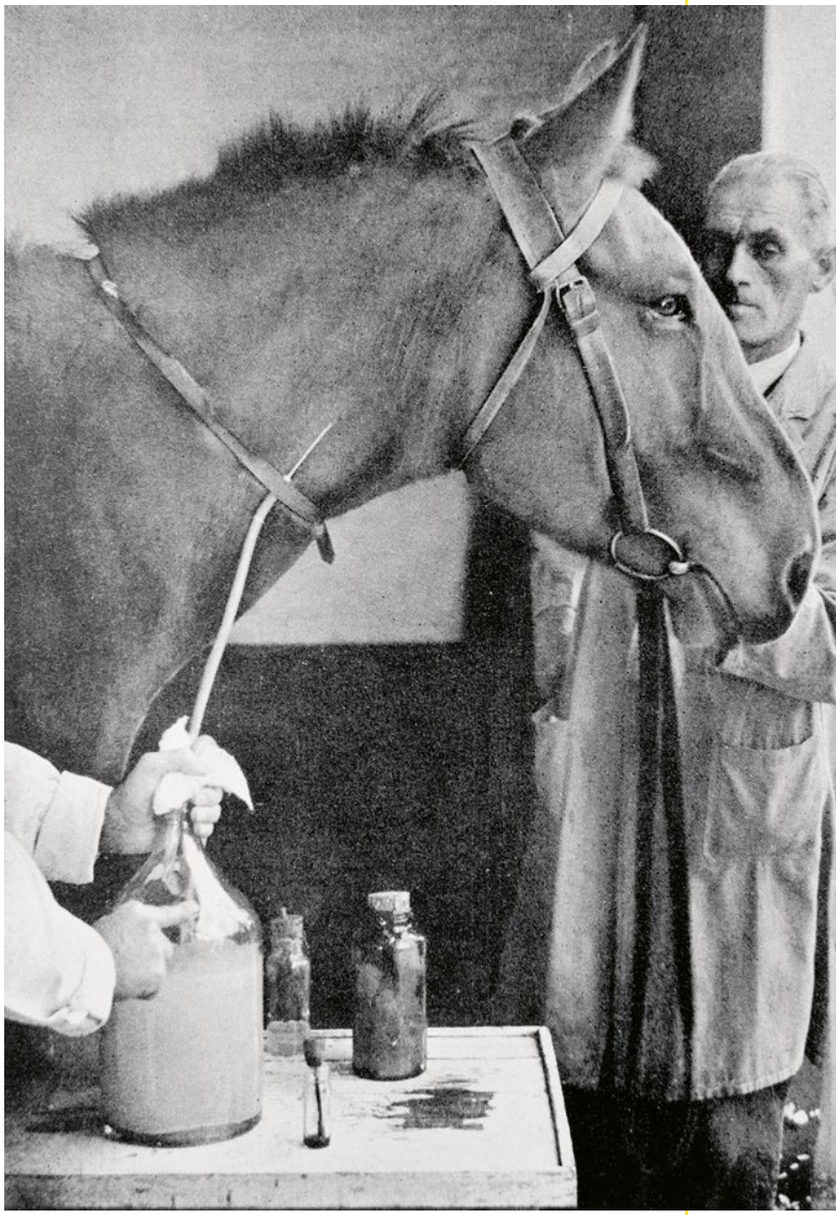
The new vaccine technologies are based on the classic processes that make use of the memory of our immune system. When it is invaded by a virus or a bacterium, the immune system reacts by forming antibodies. The information about these antibodies remains stored in special white blood cells. If there is a new infection by the same pathogen, these white blood cells can produce these antibodies very quickly and render the intruders harmless (see the diagram on pages 20/21).

As a rule, a vaccination actively introduces pathogens into the human body in order to stimulate the immune system to form antibodies. This is usually done by means of an injection into a muscle or subcutaneously. We distinguish between various classes of vaccine.

Live vaccines contain viruses or bacteria that have been attenuated to such an extent that they can still reproduce themselves but can no longer cause the disease. The protection afforded by a live vaccine lasts for many years. Examples include the live vaccines against measles, mumps, rubella, and chickenpox.

In inactivated or killed vaccines, the pathogen is first killed, so that it is unable to reproduce itself and cause the disease. In this case the protection gradually decreases and must therefore be regularly renewed with a booster shot. Vaccines of this type protect the recipients from polio, tick-borne encephalitis (TBE), and hepatitis B.

Other vaccines, such as those against tetanus, diphtheria, whooping cough, and the flu, only contain components of the pathogen, such as proteins or sugars that are recognized by our immune system. These vaccines also protect recipients for only a limited period of time. →



DIPHTHERIA 1925

PATHOGEN *Corynebacterium diphtheriae.* The symptoms are caused by a toxin made by the bacterium. **FIRST VACCINATION** In 1925 in Germany (approval: 1936), Emil von Behring (photo) and Erick Wernicke discovered a new method of immunization for treating infectious diseases. After the publication of the paper "On the Origin of Diphtheria Immunity and Tetanus Immunity in Animals," it took only four years for the industrial production of diphtheria antitoxin serum to begin. **VACCINATION TYPE** Patients were injected with blood serum from infected animals that had already formed antibodies. Today the vaccine contains inactivated diphtheria toxin. **HISTORY** Between 1881 and 1886, an average of 25,000 infants and toddlers under the age of three died annually in Prussia as a result of the infection. Diphtheria was the most frequent cause of death among children between the ages of three and five. Today 97 percent of infants and preschool children in Germany are protected, thanks to a combined vaccination during their first year of life.

1955 POLIOMYELITIS

PATHOGEN Poliovirus **FIRST VACCINATION** 1955 with inactivated vaccine, 1961 with attenuated vaccine **VACCINATION TYPE** Inactivated polio vaccine as a killed vaccine, initially usually administered orally (photo: Oral vaccination in Stuttgart, 1962), but solely as an intramuscular injection since 1998. **HISTORY** After 1880, poliomyelitis occurred as an epidemic that sickened thousands of people annually. It primarily affected children, who either died or suffered from lifelong physical disabilities ("infantile paralysis"). Starting about 1910, regional epidemics were observed in Europe and the USA at intervals of approximately five or six years. As recently as 1961, a total of 4,670 new infections were registered in Germany; in 1965, only a few years after the start of the first vaccination campaigns, that figure was less than 50, representing a decrease of 99 percent.

GENE-BASED VACCINES OFFER HOPE

The time to develop traditional vaccines can typically take several years as a general rule. For one thing, large amounts of virus material are required. For another, the large-scale production of a vaccine requires a lot of time and effort. "For example, in the case of inactivated vaccines the pathogens have to be precisely specified under strict safety conditions," explains PEI President Cichutek. "Next, the strain is produced, cultured in large amounts, and only then inactivated."

This is why the researchers who are searching for effective protection against the coronavirus as well as diseases such as AIDS and certain types of cancer have been focusing in recent years on completely new candidates: gene-based vaccines that contain not the virus itself but only a blueprint that the human body can use in order to produce exactly that part of the virus that triggers the immune response. For example, in the case of the coronavirus this part could be the "spike protein" on the virus envelope. Serums of this kind can be produced in large amounts relatively quickly, and if the pathogens should mutate the serums can be adapted as necessary.

Vector vaccines are a variant of these innovative vaccines. In vector vaccines, genetic material of the pathogen is inserted into harmless More on page 16 →

"This is a marathon, not a sprint"

The Freiburg-based virologist Professor Hartmut Hengel talks about the prospects for the rapid development of a vaccine against the coronavirus, the advantages of RNA technology, and the role of the chemical industry in new vaccination procedures

Prof. Hartmut Hengel is the medical director of the Institute of Virology at the Freiburg University Medical Center and the deputy chairman of the Scientific Advisory Board of the Paul-Ehrlich-Institut

INTERVIEW **INGA OLFEN**

Professor Hengel, in the discussion about a coronavirus vaccine, more and more skeptics are speaking up. They're saying that vaccinations have caused cancer and other diseases, overburdened the immune system, etc. Is there any truth to these assertions?
All of them can be scientifically refuted. Basically, even higher safety requirements apply to vaccines than to medications, because vaccines are administered to healthy people. Modern research is making huge efforts to offer vaccines that have a minimum of side effects. However, in the past some vaccines have in fact caused undesired effects. That's why comprehensive safety testing is so important.

That takes time, and during the battle against the coronavirus pandemic time is in especially short supply. What shortcuts could be taken so that we can administer a proven vaccine to end the pandemic as soon as possible?
Each society has to answer for itself the question of how to deal with this process at the ethical and political levels. In my opinion, we have to proceed carefully and conduct stringent testing. I think it would be not only risky but also unethical to administer a vaccine that has not been properly tested to the general population. You first have to investigate how long the protection will last and the safety aspects over time. Especially in cases where side effects occur only very rarely, these side effects might be seen only years later.

Many fears are related to gene-based vaccines, which are currently going through several approval processes. There are fears that they could alter the genetic material of the vaccinated individuals. Are these fears justified?
The vaccines that are currently being discussed in connection with SARS-CoV-2—the novel coronavirus—are primarily vaccines whose mechanism of action is based on ribonucleic acid, or RNA. The RNA converts genetic information into proteins, and—according to everything we know—it is not integrated into the genetic material of human beings. I have no fears of that.

One of the reasons why RNA-based vaccines look so attractive is that they can be produced in large quantities in a very short time. How soon will a vaccine be available?
In the case of a few vaccine candidates, we're hoping that one or more of them may still be approved in 2020. However, we can only arrive at a comprehensive safety assessment in the course of a vaccine's actual use. →

In the case of other viral diseases such as measles, it's known that 95 percent of the population must be immune in order for unvaccinated individuals to also be protected. Is that also true of the coronavirus?
We don't know. One difference between the measles virus and SARS-CoV-2 is that there are people who were infected with the coronavirus but did not produce any antibodies. It's even possible that herd immunity against SARS-CoV-2 will fail to materialize because coronaviruses are programmed for reinfection. If we succeed in developing vaccines that lack the functions of the virus that are responsible for "immune evasion," a vaccination could even protect us more effectively than a previous infection.

What role is the chemical industry playing in the development of potent vaccines?
A very important role. For example, take the lipid nanoparticles that are used in mRNA vaccines. Transfection reagents of this kind are a key determinant of the effectiveness of the vaccines, because they enable the mRNA to be transferred into the cells. They determine which cells the vaccine can penetrate, as well as how effective and stable it will be. If this method is successful against the SARS-CoV-2 virus, it would be an entry point into a new class of vaccines, and maybe even into completely new principles of vaccination.

Are you saying that this technology could solve problems for which there is no solution at present?
Absolutely! I can even imagine that in the future we will produce cocktails of messenger RNAs and thus combine multiple vaccinations. That would make it possible to generate much higher levels of immunity with far fewer individual vaccinations. It would be a big step forward.

Will there one day be vaccinations against all diseases, ranging from cancer to Parkinson's disease and all the way to diabetes?
It would be naive to believe that through vaccinations we can eliminate all diseases. However, I expect that in the future we will be able to block more infectious diseases by means of vaccinations. But we have to be patient. That's why I'm not happy at all about the current talk about a "race" to develop a vaccine against SARS-CoV-2. The winner is not necessarily the one who starts out fastest. This is a marathon, not a sprint.

"The lipid nanoparticles have to be put together out of a large number of differ-ent components"

JAY NATARAJAN, HEAD OF LIPID RESEARCH AT EVONIK IN VANCOUVER, CANADA

carrier viruses (such as the virus used for measles vaccine or attenuated adenoviruses). Initial vaccines against dengue fever and Ebola have already been approved. And Russia already dashed forward in August and produced a vector serum against Covid-19.

Scientists believe that additional opportunities are offered by vaccines based on nucleic acids, which are the carriers of genetic information inside cells in the form of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). Because the production of DNA or RNA vaccines requires not the entire virus but only its genetic material, it is much easier and faster than the production of other types of vaccine. Dozens of studies are now being conducted in this area. However, by mid-October no vaccines against Covid-19 had been approved for use on human beings.

In the case of DNA vaccines, the sequence of the desired antigen is inserted into the genetic information of a bacterium. After the bacterium has entered the target cell, this information is read in the cell's nucleus and the antigen is produced directly inside the cell. Researchers have already been working on these vaccines for many years. Pharmaceutical companies are currently working on DNA vaccines against about 20 dis-

eases including rabies, leukemia, and AIDS. So far, the possibility of foreign DNA being inserted into human genetic information, which in the worst case could lead to increased tumor formation, has not been documented in any studies. "We have spent many long decades investigating a theoretical risk that might be harbored by DNA vaccines, but in fact this risk has never materialized in animal testing or in clinical trials," said PEI President Cichutek at a press briefing in April 2020 in order to calm any fears.

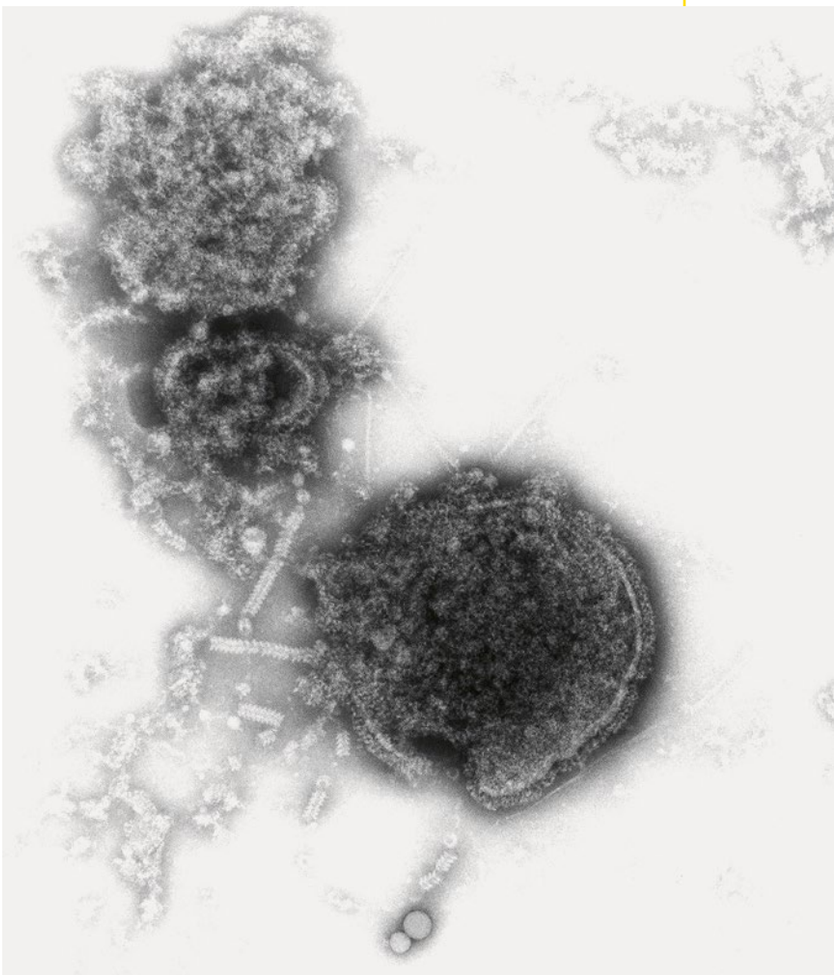
In order to completely exclude this risk, there is the option to use not the entire DNA of a protein but only its mRNA, or messenger RNA. A protein's mRNA is basically a copy of its blueprint, which is read out from the DNA. The mRNA transports this blueprint directly to those places in the cell where the desired protein is produced. In other words, it is not incorporated into the cell's nucleus, and thus it cannot be inserted into the DNA there.

THE EPICENTER FOR LIPID FORMULATIONS

However, in order to unfold its effect the mRNA must first reach the right place inside the human body. "For a long time this was a big problem for scientists, because it is a very unstable construct," explains Stefan Randl. This is where the lipid nanoparticles from Evonik—ultrafine particles of fats and waxes—once again come into play. "If I were to inject mRNA without having previously formulated it—in other words, without having packaged it inside a protective layer—it would disintegrate in the bloodstream within seconds."

Evonik produces lipid nanoparticles and complete mRNA serums at a facility in the town of Burnaby near Vancouver, Canada. In 2016 Evonik expanded its portfolio for advanced drug delivery to include the development and production of liposomal formulation technologies by acquiring the local company Transferra Nanosciences. "Vancouver is an epicenter for the development and the production of LNPs," says Randl. Research on lipid nanoparticles has been conducted there for almost 30 years. "The researchers have already developed hundreds of LNP formulations for gene-based and cell-based therapies, and they are connected with pharmaceutical and biotech companies all over the world." A whole series of the LNP-based drug products that have already been approved or are currently in development have been supported either by Evonik or, before that, by Transferra Nanosciences.

Today LNP technology is regarded as the "gold standard" for the development of complex parenteral medications—in other words, those that are admin- →



MEASLES 1963

PATHOGEN *Measles morbillivirus* **FIRST VACCINATION** 1963 in the USA **VACCINATION TYPE** Initially an inactivated vaccine, since 1968 an attenuated vaccine **HISTORY** Before a vaccine was developed, about 2.6 million people died annually worldwide; vaccination campaigns helped to reduce the number of deaths due to measles by 84 percent worldwide—from over 500,000 to around 90,000—between 2000 and 2016. Since 2018 a massive increase in cases of measles has been seen again in Europe, with more than 100 deaths between January 2018 and June 2019. Measles can be regarded as "eliminated" only after at least 95 percent of a population is immune. Vaccination against measles has been mandatory in Germany since March 2020.

istered via injection—against diseases such as cancer or amyloidosis, which is triggered by protein deposits in the body and can lead to organ dysfunction. This was the first application of an RNA-based therapy. "Certain combinations of active ingredients, as well as personalized medications, would also be unthinkable without LNPs," Randl adds. In the future, serums based on lipid nanoparticles could play an important role in the market for vaccines and many therapeutic drug products.

By means of its highly specialized and complex production processes for LNP-based medicines, Evonik develops formulations for pharmaceutical companies in Vancouver from start to finish. "For example, the customer sends us the mRNA, and we then conduct research in order to find out the proportions in which lipids must be mixed with other ingredients," says Jay Natarajan, the head of research in Burnaby. The tiny lipid particles have to protect the nucleic acids from destructive enzymes and thus enable them to pass through the cell membrane.

LAYERED LIKE AN ONION

"To make sure the mRNA safely reaches its target, the LNPs themselves have to consist of many different lipid and buffer components, so there's a long list of ingredients," explains Natarajan. The lipid ingredients are first

2015 EBOLA

PATHOGEN Ebola virus from the family *Filuviridae* **FIRST VACCINATION** 2015, approved by the EMA at the end of 2019 **VACCINATION TYPE** The vector vaccination VSV-EBOV is a combination of different variants of a viral vector that is based on the *Vesicular stomatitis virus* (VSV) (photography: Vaccination in Conakry/Guinea 2015). In order to create the vaccine, a gene from the Ebola virus is inserted into the genome of the VSV virus; this gene encodes the viral glycoprotein (GP) of the Ebola virus. **HISTORY** A large percentage of people infected with this virus die from it. Precise numbers are hard to determine. It is assumed that between 30 and 90 percent of infected individuals die, depending on the severity of the outbreak. The average mortality is estimated to be 50 percent.

dissolved using ethanol and combined with the mRNA, which has been dissolved in a buffer solution. This is done using a very rapid micromixing process that creates lipid nanoparticles encapsulating the mRNA just like the layers of an onion. These lipid nanoparticles are then subjected to a downstream purification process to form a final drug product that is ready for clinical trials on humans.

When the particles reach the target cells, they fuse with the cell membrane and release the mRNA into the cell exactly where it is needed. There the information that is required to manufacture the desired protein is read out, and the production of the antigens begins.

As soon as the right formulation for the customer's mRNA has been determined in Burnaby, serums can be produced in amounts sufficient for reaching Phase I /II of clinical testing. Looking ahead, Evonik is planning future operations that go beyond this stage. The laboratories at the company's location in Birmingham, Alabama have the capability to produce larger batches. The company has already developed and produced drugs based on bioresorbable polymer microparticles.

Incidentally, the story of the little boy in England had a good ending. Not only did the vaccination make him immune to smallpox—to show his gratitude, the country doctor Edward Jenner later on gave him a cottage to live in with his family. Eventually, this house became the first Jenner Museum.

COVID-19 2020

PATHOGEN SARS-CoV-2 **FIRST VACCINATION** The first vaccinations reportedly took place in China and Russia in the fall of 2020. A comprehensively tested vaccine is not expected to be available before the spring of 2021. **VACCINATION TYPE** Vector vaccination, inoculation with DNA or mRNA **HISTORY** The initial cases of patients infected with this "novel coronavirus" occurred at the end of 2019. Originating in China, the virus has spread throughout the world since the spring of 2020. By mid-October 2020, around 37 million people were infected and more than one million patients had died. According to the World Health Organization (WHO), more than 100 vaccines against Covid-19 are currently in development.

Inga Olfen is a science journalist based in Hamburg. She has a degree in biology and previously worked for eight years as an editor in the science department of *Stern* magazine. She founded the communications agency Kontenta in 2017.

Attack in the Body

Vaccinations train the immune defenses against dangerous pathogens. Various processes have already been established for many decades. In the future, genetically based vaccines could join them—in the fight against the coronavirus and beyond

INFOGRAPHIC **MAXIMILIAN NERTINGER**

PROVEN PROCESSES

Current vaccines use viruses or bacteria that have been killed or attenuated, or use certain components or metabolic products of the pathogens.

ATTENUATED VACCINES

These contain small quantities of pathogens that are capable of reproduction but have been so attenuated that they are not capable of causing the disease.

Examples: measles, mumps, rubella, and chickenpox

INACTIVATED VACCINES

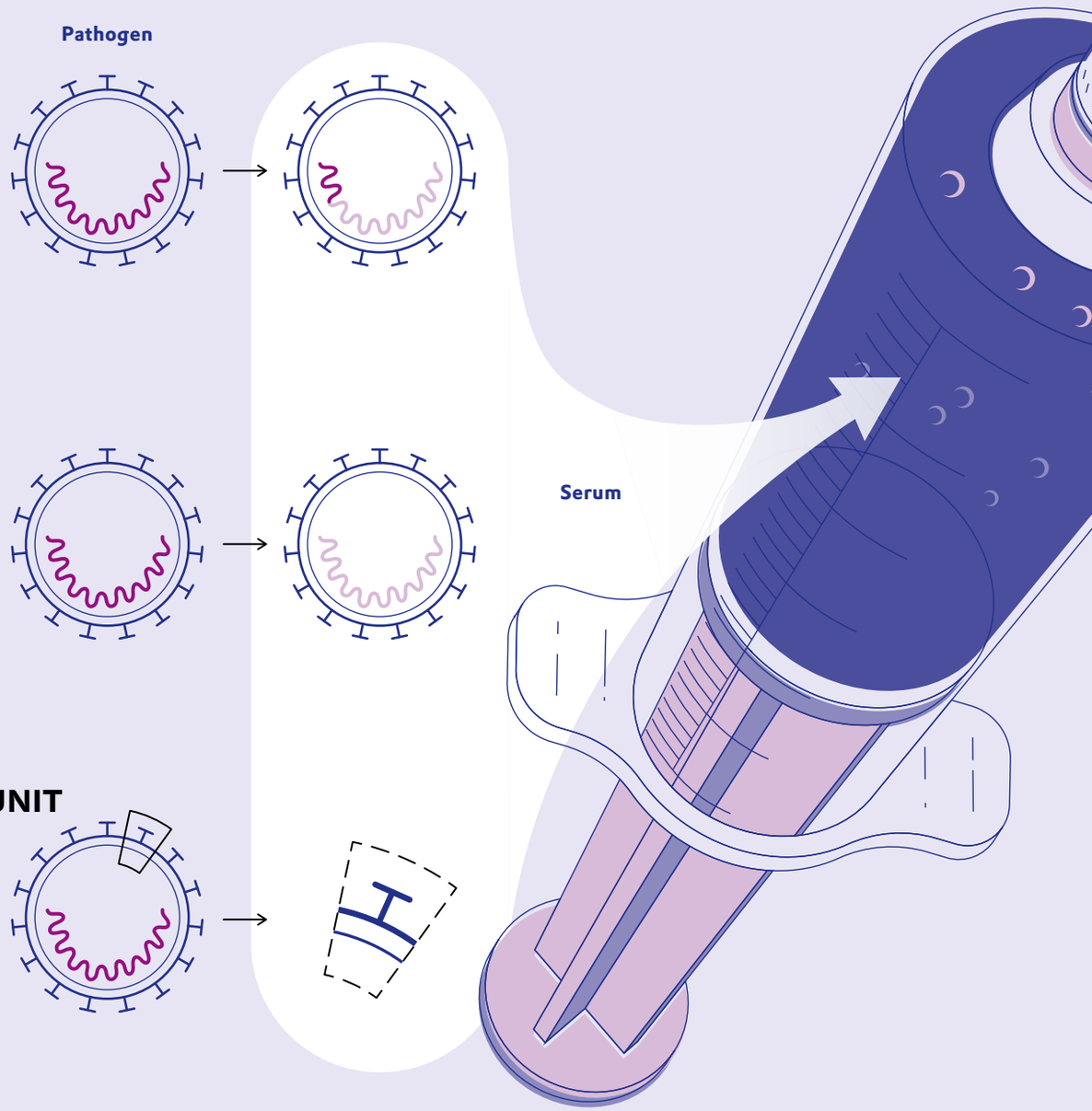
Contain killed pathogens that stimulate the body's immune system to produce antibodies, without the disease itself breaking out.

Examples: polio, TBE, hepatitis B

TOXOID AND SUBUNIT VACCINES

Contain only specific components of the pathogen such as proteins or sugars that are recognized by the immune system.

Examples: tetanus, diphtheria, pertussis, influenza, HPV



NEW PROCESSES

Gene-based vaccines contain part of the genetic information of a pathogen. The body cells of the vaccinated subject read this information and produce the proteins necessary for an immune response themselves.

VECTOR VACCINES

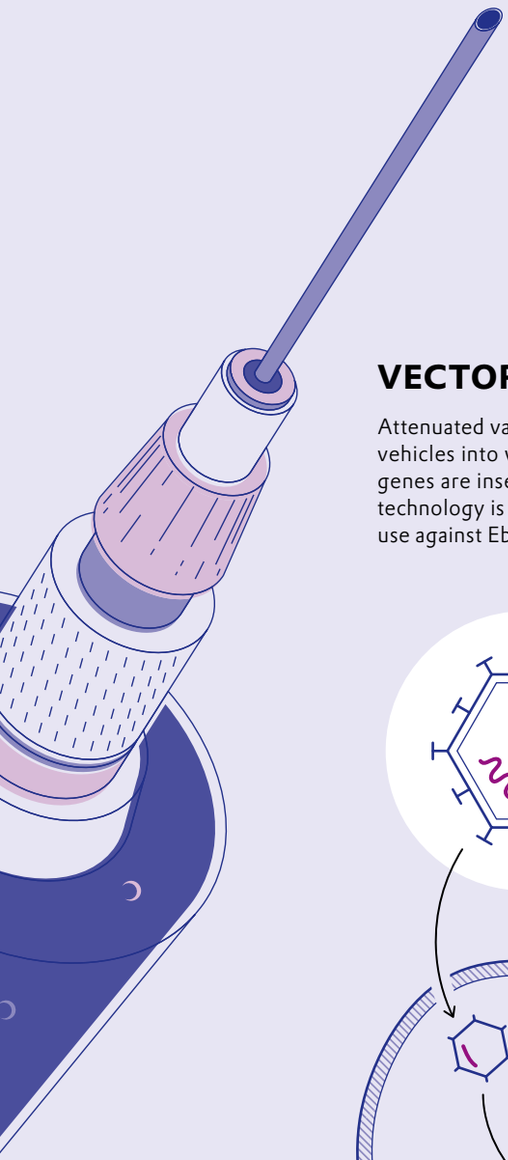
Attenuated vaccine viruses act as vehicles into which the pathogen genes are inserted. This new technology is already approved for use against Ebola and dengue fever.

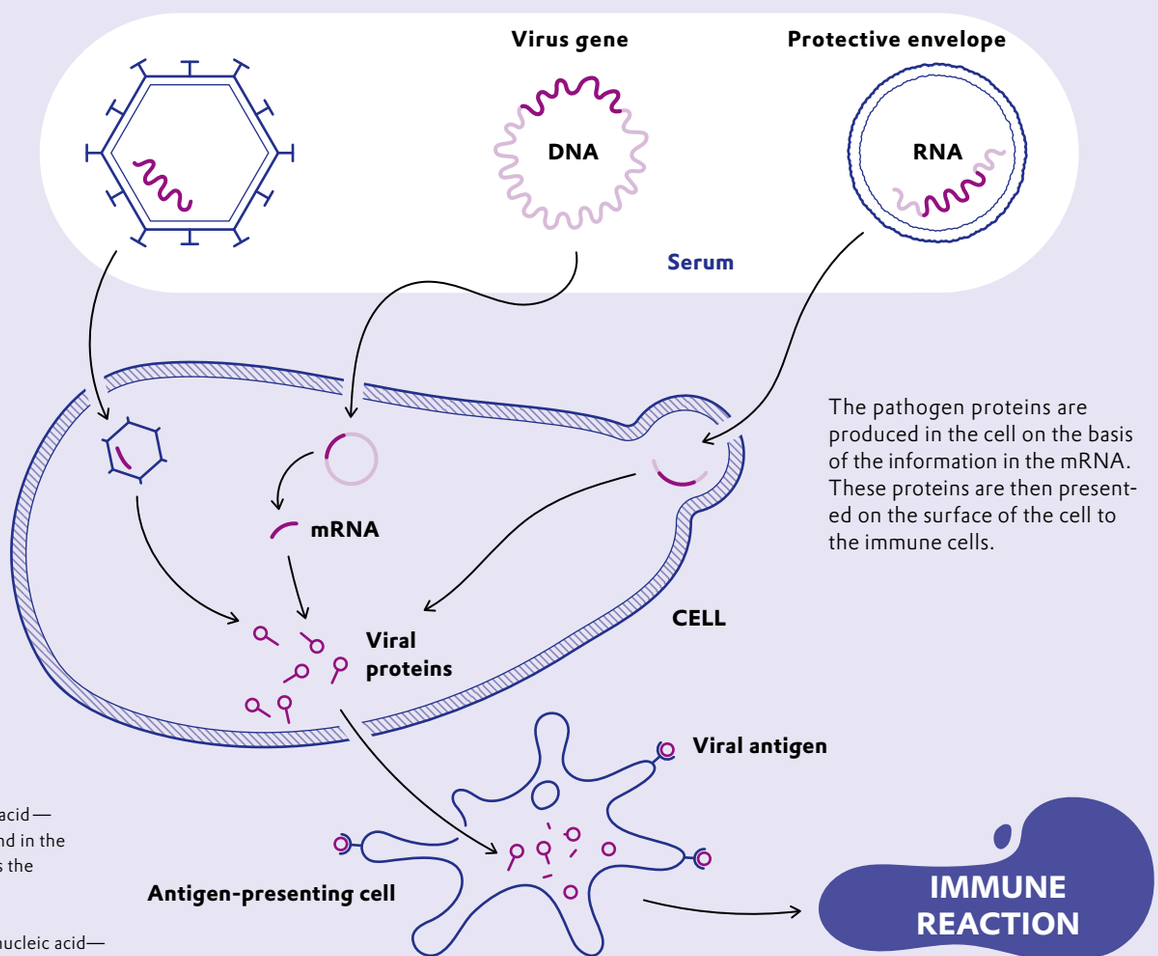
DNA VACCINES*

The DNA sequence of an antigen is inserted into bacterial DNA. The DNA is injected and is converted into mRNA in the cell nucleus. This mRNA serves as a blueprint for the antibody.

RNA VACCINES*

The mRNA is read off directly in the cytoplasm. A protective envelope consisting of LNP protects it on its journey. The mRNA is released as soon as the LNPs have fused with the cell membrane.





The pathogen proteins are produced in the cell on the basis of the information in the mRNA. These proteins are then presented on the surface of the cell to the immune cells.

* As of 10/2020: not yet approved

DNA Deoxyribonucleic acid—a biomolecule that is found in the chromosomes and carries the genetic information

mRNA Messenger ribonucleic acid—a transcript of a section of the DNA that carries the genetic information for the assembly of a protein inside a cell

LNP Lipid nanoparticles—particles composed of lipids. These are used to transport substances.

When pathogens enter the body, special cells absorb them and present parts of the pathogens—known as antigens—on their surfaces. Other immune cells form antibodies against these antigens, and further immune cells destroy infected cells. In the event of a later contact with the same pathogen, memory cells ensure its rapid elimination.

“The price for innovative medication should focus on the value for the patient”

NATHALIE MOLL, DIRECTOR GENERAL OF THE EUROPEAN FEDERATION OF PHARMACEUTICAL INDUSTRIES AND ASSOCIATIONS (EFPIA)

What is high-tech medicine worth? And what’s a proper orientation mark for its price? A debate between the Brussels-based biotech lobbyist Nathalie Moll and Dr. Carlos Correa, head of a think tank in Geneva that represents the interests of developing countries

MODERATION **MATTHIAS RUCH, JÜRGEN KRAUTER**

Ms. Moll, Dr. Correa, what is your most important lesson of the Covid-19 pandemic?

MOLL The biggest learning from this pandemic is that we couldn’t contain it. It also taught us the value of collaboration and innovation as well. Imagine if we hadn’t had anything to start from.

CORREA The pandemic has shown to us that the global community was not ready to handle it. Health systems were not well prepared.

What were the biggest challenges for your industry when Covid-19 hit our planet?

MOLL At the beginning we focused on three key areas. The first was support on the ground to countries to keep their systems running, for example giving personal protective equipment that

“If we follow that way we have to ask: What is the cost of a life?”

DR. CARLOS MARÍA CORREA, EXECUTIVE DIRECTOR OF THE SOUTH CENTRE

we have in our companies. Secondly, we had to ensure supply. And then we had, of course, to do research for treatments, vaccines, and diagnostics that serve to fight Covid-19. Our companies are working non-stop to make sure they can supply whatever happens. In some cases that means increasing production by 400 percent.

Dr. Correa, with regard to Covid-19, do we take the problems of developing countries sufficiently into account?

CORREA The European Commission has provided some funding for an international facility to ensure distribution of vaccines also to developing countries that don’t have access to either treatment or prevention. Many of these countries are facing a major crisis because of foreign debt and lockdowns. This pandemic requires a global response. But there is another conclusion that you can draw from this crisis. And this is about the innovation model. The current model is based on intellectual property rights and legal monopolies that are granted by patents. They are used in order to charge prices that are often completely unaffordable both to governments and individual patients—even in developed countries. But innovation without access doesn’t make sense.

MOLL Innovation is pointless without access, that’s true. If we only have access to vaccines in one part of the world this pandemic will never end. That’s why at the beginning of April our industry published twelve commitments spanning all stages—from research collaboration to access. The current discussion about vaccines on a European level shows this commitment in action on the part of the industry that is focused on ensuring available and accessible products.

Why are patents and intellectual property (IP) so important for innovation?

MOLL If we hadn’t had incentives like IP rights in Europe we would have had nothing to start from to research the treatments, diagnostics, and vaccines we are working on for Covid-19. Patents, apart from IP, ensure the publication of science. Thanks to patents, we share science quickly and can thus advance overall research faster. Thanks to patents, we have a base of innovation on the European level and we have the investment needed to move forward. →

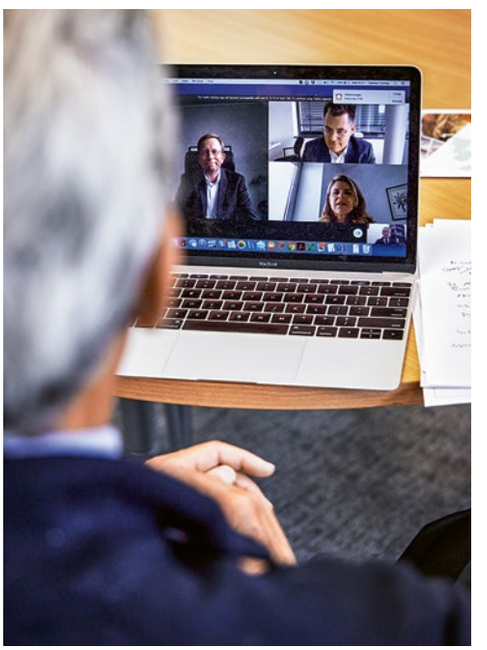
We're now facing a crisis arising from an infectious disease. But we also have bacterial infections which cannot be treated with conventional antibiotics. Is the pharmaceutical industry doing research on the most relevant diseases?

CORREA Incentive systems based on patents don't necessarily lead to an ideal outcome from a public health perspective. With regard to antibiotics we clearly have a case of underinvestment. The same applies for neglected diseases in developing countries like tuberculosis. The current model of innovation leads to doing innovation for markets with a certain profitability and not for markets with huge demand but people who are unable to pay high prices.

You are referring to expensive drugs for example against rare diseases?

CORREA Yes, and I would also like to highlight that high prices pose a problem to the public health system not only in developing countries. These drugs are useful only for a very limited number of people. But they are very profitable because of the monopoly that can be obtained. The main point is that patents grant legal monopolies. They allow the owners to set a price which is far beyond the marginal cost. Patents should be used in a manner that the society's objectives are reached. For Ritonavir, an AIDS-related medicine, the World Intellectual Property Organization found 800 patents. Some companies want to prevent generic competition and delay it as long as possible through so-called evergreening strategies.

Dr. Carlos María Correa, 71, is Executive Director of the South Centre, an intergovernmental organization of 54 developing nations with its headquarters in Geneva. It serves as an independent policy think tank and holds Observer Status at the United Nations. Correa is a renowned international authority on intellectual property and technology issues. He was member of several commissions and has advised several governments on intellectual property, innovation policy, and public health. He is both a lawyer and an economist and holds a Ph.D. in law from the University of Buenos Aires.



"Thanks to patents we have the investment needed to move forward"

NATHALIE MOLL

Nathalie Moll, 47, is Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA). This trade association, based in Brussels, represents the research-based pharmaceutical industry operating in Europe with 33 national associations and 40 leading pharmaceutical companies as members. Moll has spent over 20 years working for the biotech industry at the EU and national levels in associations and corporations. In 2017, she was named one of the 15 leading women in biotech in Europe. Moll holds an Honours Degree in Biochemistry and Biotechnology from St Andrews University, Scotland.

MOLL Dr. Correa, the reason why antibiotics are not being researched is because there are no incentives to do so. Antibiotics do not follow the normal market logic since they should be sold and used sparingly to avoid resistance. It's the perfect example of unmet medical need where the incentive system is missing—worldwide. We have to look at new systems to ensure that the industry can invest in research and survive at the end of the day. At the moment we are witnessing the downfall of biotech companies involved in antibiotic research and development (R&D). In July our industry launched a €1 billion fund to support clinical research of innovative new antibiotics that would address the most resistant bacteria. It's an artificial incentive while we wait for governments to implement the right structures to support the development of antibiotics.

CORREA I think you're wrong. The market for antibiotics is there. It is just not as profitable as other markets. And this is the point: A company's research agenda is led by profitability. This is why there is no investment in antibiotics. It's not about the patent system. The patent system is there. Patents will be granted on antibiotics if they are new, inventive, and industrially applicable. However, if a vaccine against Covid-19 were developed one additional problem is that there is not enough production capacity. Without licensing and transfer of technology sufficient supply will not be possible.

MOLL Very recently the World Intellectual Property Organization came out with a statement noting that there is no evidence that IP is a barrier to access to Covid-19 preventive measures, treatments, and cure. In our commitment from April 1, our industry declared we would be expanding our manufacturing capabilities once a successful vaccine is developed. The current productivity of the world is 5 to 7 billion doses a year of all vaccines together. In the case of Covid-19 we need about 14 billion doses if we have to vaccinate everybody twice. From the very beginning we've been working on changing and adapting our lines and sharing and seeing the legal implications of producing one another's products. I think we're turning the world upside down and with it our ways of working to respond to the crisis.

What is a fair price for medications that make such a difference to both patients and healthcare systems?

CORREA In some cases the pricing is exorbitant. Recently, there was the approval of the US Food and Drug Administration for Zolgensma, a life-saving medication to treat young children with spinal muscular atrophy. The price for one dose is $2.1 million. In the United States, the cost for a treatment with Sofosbuvir that provides a cure for hepatitis C is $84,000 which means that each pill costs $1,000. →

Business as usual

Eight months after the breakout of the coronavirus pandemic, videoconferencing has long been part of everyday life. The discussion between Nathalie Moll (in Brussels) and Carlos Correa (in Geneva) at the beginning of October also took place via Internet. The moderators were Matthias Ruch (Essen), the head of external communication at Evonik and Editor in Chief of *Elements*, and Jürgen Krauter (Frankfurt), the head of market communication. And even in these days of our participants—and millions of other professional people—mostly working from home, all four participants went in to their offices for the discussion—because of the better Internet connections.

This pill can be produced for about one dollar. In the past the pharmaceutical industry said these prices were needed to recover the costs of research and development . The problem is: Nobody knows these costs. The new theory seems to be that it is not relevant any more what the company has invested in R&D. Now they value the medicine in terms of solving a health problem. If we follow that way we have to ask: What is the cost of a life? What is a person willing to pay to save his or her life or the life of a family member? I think this is not an acceptable approach.

"Patents should be used in a manner that the society's objectives are reached"

CARLOS CORREA

MOLL Unfortunately, Dr Correa, we are an industry and we need to make money that we can reinvest in innovation. The question is: What do you want to incentivize? Whatever you base the price on will define what you are incentivizing. If you based the price on R&D you would incentivize spending on R&D. I don't think we want companies simply to spend a lot of money on R&D. We want them to give the best outcomes to patients.

How can you measure these outcomes?

MOLL It's hard to measure today because we don't have complete data sets for all diseases. For example, take patients who suffer from a chronic disease—how do you put a price on restoring their health to the extent that they can re-enter the labor market and get a job? We are in need of a paradigm change. There are new technologies that are revolutionizing our healthcare system so we have to change the way we pay for healthcare. And as with all change, that is hard.

CORREA Nathalie, what you are saying is really a matter of concern. Because you are not talking about reasonable logical profits for the companies. You are just saying you will put a price that will depend on the value for the patient, so this may have no relation, no proportionality with the cost of R&D and production. You say the companies should make any extraordinary profit they can. I think the only outcome you will get following this doctrine is that the governments will come and regulate.

MOLL Focusing on the cost for R&D doesn't help us. Think of Alzheimer's disease: 400 research projects have failed. What are you going to charge for the one that doesn't fail? A price that offsets the cost for all the ones that failed? I would argue that the price should focus on the value for the patient, for the healthcare system, and for society as a whole.

CORREA This paradigm doesn't take into account that most medicines are based on inputs from the scientific field. But in the end the companies appropriate the whole benefit of that.

MOLL As you likely know, we don't define our own prices, we negotiate these with governments. We are not like company X, who can charge a chosen price for their product Y. We have always said that the price of a product in a country should depend on the prevalence of the disease, on what the healthcare system needs, the value for patients, and other country-specific

factors. I'm surprised when you say that's not going to work, because that's exactly what we've always been doing.

CORREA You are negotiating prices with governments in Europe, but this is not the case elsewhere. If this trend continues and prices are rising further without any proportionality there will be no other option for governments than to go into the regulatory framework. When a government negotiates with a company that holds a legal monopoly as a patent it hasn't got too many options. One is to issue compulsory licenses in order to lower prices.

Will the Covid-19 pandemic change our view on the global health system?

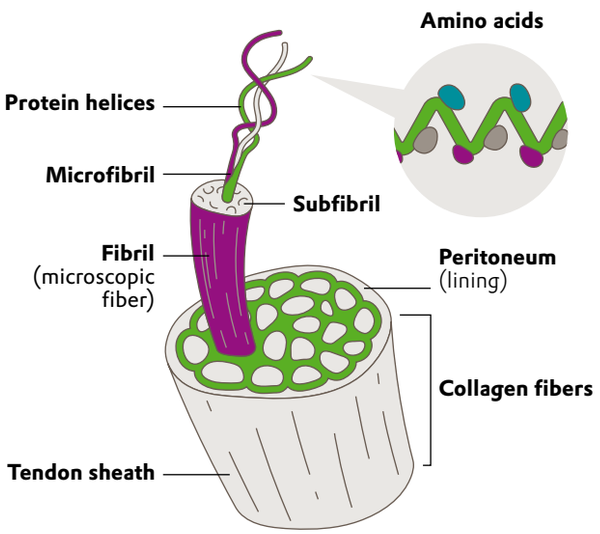
MOLL It already has. It is really impressive to see the European Union taking global leadership when the Commission's President Ursula von der Leyen launched a global pledging conference at the beginning of May. She raised €7.4 billion within two hours and at the end of June this was supplemented so the amount came up to €15.9 billion. It really gave me a shiver when I watched that. It was the opportunity to do things in a completely different way and together. I don't think we have ever had a pledging event like this—except, maybe, for the Live Aid concert back in the eighties. That's encouraging.

CORREA We need to move forward to reach universal health care also in countries that have not reached this level right now. This is not an easy thing, because it requires enormous investment by the governments. And we need to make sure medicines are priced in a sensible manner. This has all to be taken into account to build a system that is resilient and is able to face this and other pandemics.

A PRECISE PLATFORM

TEXT **JULIA BORN**

Collagen is playing an increasingly important role in medicine. However, the use of this structural protein is increasingly subject to criticism due to its animal origin. Evonik's successful development of a collagen platform based on fermentation is a biotechnology breakthrough that is setting new benchmarks for quality



COLLAGEN STRUCTURE

Collagen molecules are fiber-forming proteins that are composed of three amino acids—glycine, proline, and hydroxyproline. They arrange themselves into a tightly wound triple helix. Aggregation of several collagen molecules gives rise to the next higher organizational unit, the collagen fibrils. The formation of the collagen fibrils takes place spontaneously in the extracellular space. Collagen fibrils in different tissues have very different diameters, ranging from 20 nm to around 500 nm. This is how the fibers adapt to the demands of the respective type of tissue.

In shampoos, collagen strengthens damaged hair. In lipsticks and face creams, it has a plumping and smoothing effect. In cosmetic capsules and drinking ampules, it helps to reduce wrinkles. And even gummy bears are nothing other than collagen.

For many decades, food and cosmetics producers have been the main consumers of collagen, with more than 65 million tons of this structural protein used every year. However, collagen is also very useful for a variety of pharmaceutical and medical technology applications. That's no wonder, because collagen is the most important fibrous component of human skin, bones, sinews, blood vessels, and teeth. "We've been using it for years in orthopedic sports medicine as part of therapies for damage to cartilage in joints," says Prof. Stephan Vogt, a specialist for orthopedics and trauma surgery at the Hessing Kliniken in Augsburg and an internationally recognized expert in the field of chondrocyte (cartilage cell) transplantation. "Collagen helps the body to cure itself," he says.

In the past five years, the demand for collagen for medical applications has grown strongly. In particular, regenerative medicine using tissue engineering is expanding rapidly—and the demand for proteins is growing along with it. Evonik's Health Care business line is focusing intensely on this area. It has developed an innovative platform that makes it possible to produce collagen through fermentation—and requires no animal ingredients at all. "The platform is a biotechnological breakthrough," says Thomas Riermeier, head of the business line. It enables the widespread use of cartilage in very different medical applications ranging from orthopedics to tissue engineering."

HIGH BIOCOMPATIBILITY

Collagens account for about a third of the proteins in the human body. In total, 28 different types of this protein support a variety of bodily functions. Our connective tissue consists of collagen. The tensile strength of ligaments and tendons, the flexibility of bones, and the pressure resistance of joint cartilage are also largely due to collagen.

Thanks to its high degree of biocompatibility, collagen is ideally suited for orthopedic applications and tissue repair. It can be rebuilt by the body's own cells, and it also stimulates the body's production of its own collagen. For example, burn injuries heal better if they are covered with dressings made of collagen, which supports cell regeneration. After a tooth has been extracted, collagen promotes bone regrowth. Stents for blood vessels and implants are coated with collagen so that the body does not reject them as foreign objects. →

“The collagen platform shows that with the help of biotechnology, we’re going beyond chemistry”

THOMAS RIERMEIER, HEAD OF THE HEALTH CARE BUSINESS LINE AT EVONIK

To date, this beneficial protein has been almost exclusively derived from starting materials of animal origin—traditionally cattle and pigs, and more recently marine animals such as fish and jellyfish. Around 95 percent of the collagen used in the pharmaceutical and medical technology industry comes from these sources. A small percentage is extracted from human placentas and cells from umbilical cords and used for research (see Data Mining on page 33).

However, collagens derived from animal materials can sometimes be problematic. They can transmit illnesses such as bovine spongiform encephalopathy (BSE), which is more commonly known as mad cow disease. For many consumers and patients, that’s enough reason alone to reject the use of collagen. Moreover, between two and four percent of people are allergic to collagen from cattle or pigs. A similar percentage of people are allergic to fish and marine animals. Studies have shown that contact with animal collagen can cause an immune reaction in three to ten percent of people.

AN INNOVATIVE PRODUCTION PROCESS

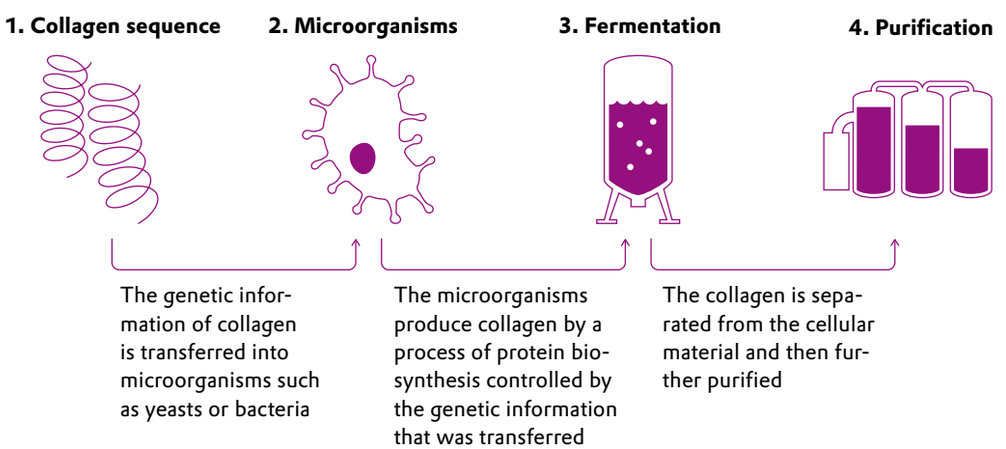
The extraction of animal collagen is being increasingly criticized because it is linked to high emissions of climate-damaging gases and extensive land use. For vegetarians, vegans, and members of a diverse array of religions such as Hinduism, Buddhism, Islam, and Judaism, products from cattle or pigs are taboo in any case.

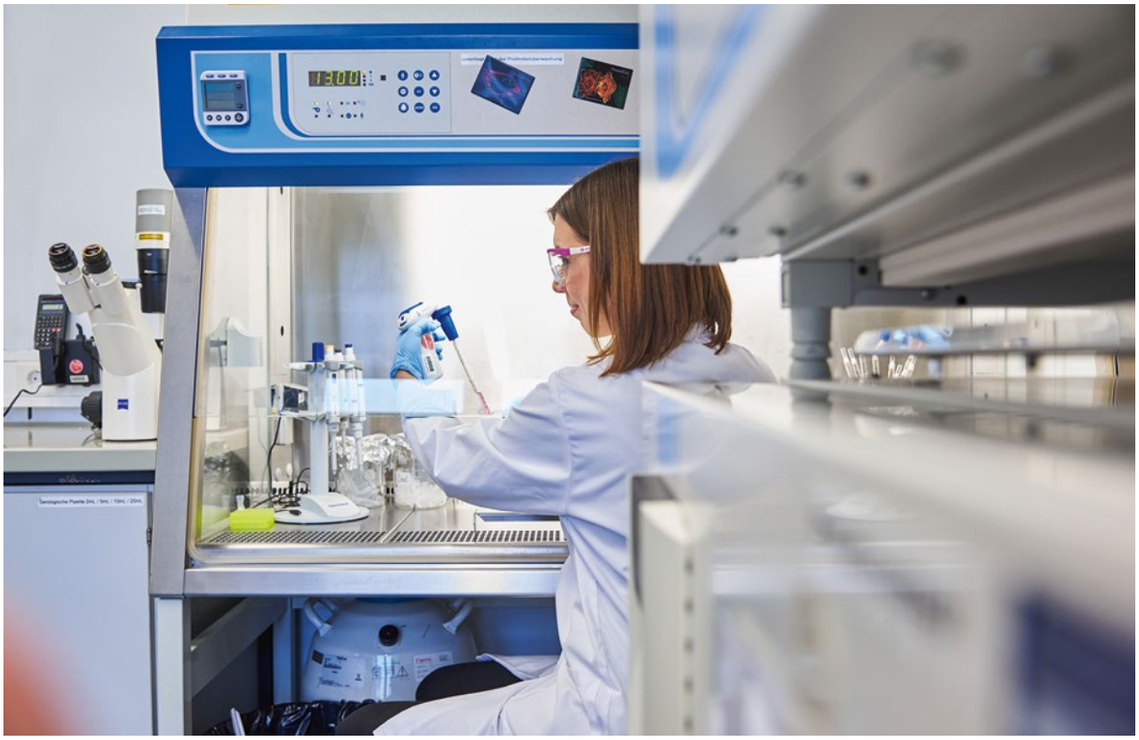
Evonik is meeting these challenges by means of an innovative production process. “Our process completely dispenses with animal starting material and makes it possible to produce an easily soluble and ultra-pure form of collagen that is safe and sustainable,” says Andreas Karau, who heads the Biomaterials product line. The special feature of this technology is that it can produce different types of collagen with little effort. In other words, it serves as a technology platform. “Thanks to this collagen platform, we are satisfying numerous market requirements that were previously unmet,” says Karau.

Evonik is using microbial fermentation processes to produce collagen. In these processes, the genetic information of a specific collagen structure is implanted into microorganisms. The collagen is then produced by the microorganisms in a few days. During this period, the collagen is transferred to ever larger fermentation vessels until the desired volume has been reached. Today this Evonik platform can already produce four different types of collagen. “The process is always the same, but depending on the customer’s needs we use different microorganisms that have specific genetic information and we adapt certain process parameters,” Karau explains. “Thus, we can generate exactly the right collagen required for a specific area of application.”

Fermentation is one of the Nutrition & Care division’s core competencies, and one of its growth drivers. Many biotech innovations of the past few years have been based on microbial conversion, and have initiated disruptive developments in their respective market segments. Evonik is a market leader in the area of fermentatively produced biosurfactants, and it is now col-

How collagen is produced by means of fermentation





Researchers in the laboratory of the Evonik location in Darmstadt check the quality of the collagen (left, below)

The collagen is stored deep-frozen in the lab. At low temperatures it forms structures similar to ice crystals

laborating with the consumer goods producer Unilever to develop the next generation of completely biodegradable cleaning agents. Another product of fermentation is the algae oil rich in omega-3 fatty acids that was developed by Evonik together with its Dutch partner DSM in the joint venture Veramaris. This oil makes it possible, for the first time, to raise salmon in aquaculture without feeding them with fish oil. This is making fish farming more sustainable and protecting the biodiversity of the oceans.

IDEAL FOR MEDICAL APPLICATIONS

"Biotechnology enables us to develop new products very quickly and produce them on a commercial scale," says Riermeier. "At the moment, we're seeing a very dynamic development in the market for fermentatively produced products, and we expect that in the future proteins made via fermentation in particular will make up a significant part of our biotechnology portfolio.

"The new process for collagen production is also enabling a quantum leap in terms of quality. "Because the fermentation takes place under precisely defined conditions, the product's high quality always remains the same. For medical applications especially, it's important to make sure that every batch has the same characteristics."

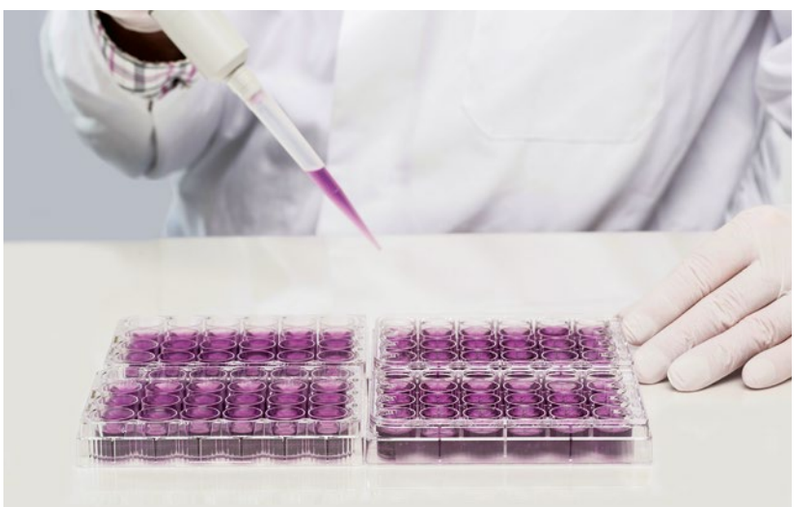
The demand for such ultra-pure collagens in the pharmaceutical and medical technology sector is growing by about six percent annually. In 2023, this business is expected to amount to US$1.5 billion. Tissue engineering is one important driver of this development. "For the regeneration of tissue such as skin, bones or organs that have been damaged or even destroyed, collagen is often used as the matrix material within which the new cells form," says Andreas Karau. Living cells are cultivated on the matrix, using it as a scaffold that contains not only nutrients but also other additives that promote growth. The collagen ensures →

that the cells grow in the right shape and develop their biological function. That's especially important for the imitation of organs in the laboratory.

Evonik is currently conducting more than ten *in vitro* studies in order to investigate the biofunctionality of the new fermentative collagen. These studies are expected to highlight under which conditions the biomaterial can initiate collagen synthesis inside the human body—for example, in order to promote the healing process after operations. In addition, the studies are testing processes for developing hydrogels containing collagen for aesthetic and regenerative medicine—in other words, for treatments such as wrinkle injection and tissue repair.

Maria Montero Mirabet, a biotechnologist at the Health Care business line, heads these studies. She helped to develop the new collagen and coordinated the collaboration between the project teams at the various Evonik locations and with research partners such as the University Hospital and the Translational Center for Regenerative Therapies of the Fraunhofer Institute in Würzburg. "The production processes were mainly developed by teams in Hanau and at other biotechnology centers in Europe. The application tests were conducted at Innovation Management in Darmstadt, the Medical Device Competence Center in Birmingham (USA), and the Tissue Engineering Project House in Singapore," says Montero Mirabet.

Initial customers are already testing the recombinant collagen from Evonik—as a coating for implants, as a dermal filler for smoothing the skin, and in several blood vessel applications. They can rely on Evonik's know-how regarding the formulation, application, and production of biomaterials and drugs, as well as the company's proficiency in tissue engineering. As a result, in the future collagen will not only make people fit and wrinkle-free but also healthy. —



Julia Born studied philosophy and has been working in Evonik's market communications department since 2017. She is head of Communications at Health Care

Ann-Katrin Kuhn, Senior Scientist in Evonik's Darmstadt Laboratory, tests the use of collagen in cell cultures

STRUCTURALLY SUCCESSFUL

Human life would be unimaginable without collagen. Demand, mostly for use in medical applications, is growing tremendously. An overview of the facts and data

1

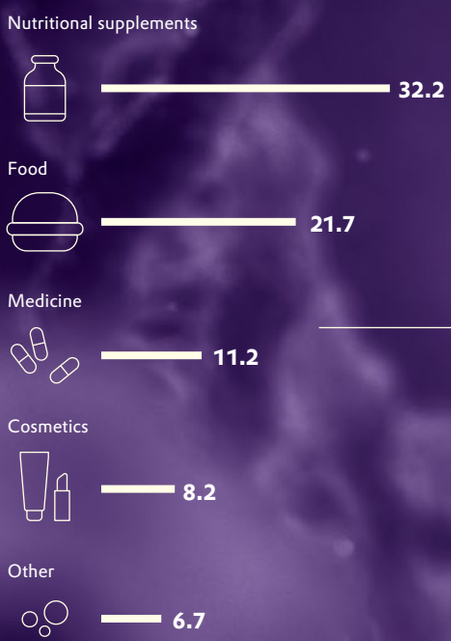
Collagen is the most important structural protein in the body
The proportion of the total protein mass in the human body is

25–35 %

2

Demand is growing continuously
Global sales of collagen in billion US$

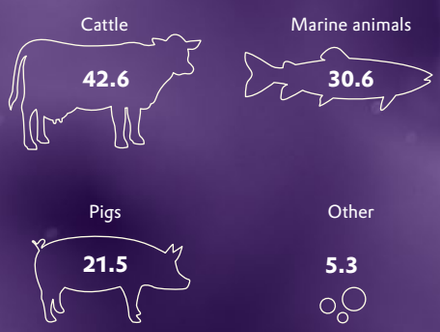
Most of it is used for nutritional supplements and food, but the highest prices are commanded by collagen for medical applications.



3

4

Most of the collagen used today comes from animals,…
Worldwide sales volumes in percent, 2017



…but this is a problem for some people

2–4 percent are allergic to collagen from pigs or cattle

3–10 percent develop an immune reaction due to animal collagen

8 percent of the world's people are vegetarian or vegan

Sources: Greenleaf, QY Research

As builders of the future, we work all day to make your daily life better. **By thinking beyond chemistry.**

Whether it's biotechnology, physics or materials science – we connect disciplines, areas of expertise and perspectives to create sustainable solutions that add value in partnership with our customers. That means we play a leading role in our markets as well as in driving our industry's development. We are passionate about giving our customers'

products outstanding properties. And that answers the question of why we exist: to make people's lives better day in, day out. **Leading beyond chemistry to improve life, today and tomorrow.**

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Tablet Solution

Orally disintegrating tablets (ODTs) make many patients' lives easier. Innovative auxiliary materials made of calcium silicate are improving the everyday practicality of these medications—and making them even more versatile

TEXT **TOM RADEMACHER**

The German name is actually absurd, but it's too late to change it," says Professor Jörg Breitkreutz, who heads the Institute of Pharmaceutics and Biopharmaceutics at Heinrich Heine University Düsseldorf. He's talking about the "melting tablets" referred to in German scientific literature, which he has been working with for almost two decades. "They don't melt at all, either during production or when they are taken," he says. Nor do they have a smooth melted glaze—on the contrary. ODTs are uncoated and brittle. The special thing about them is that they break up or dissolve quickly in the mouth. That's why they're called orally dissolving or orally disintegrating tablets—ODTs for short.

QUICKLY SOLUBLE

Even though Breitkreutz is frustrated by the misleading German name, he's enthusiastic about this invention itself. "About half of all the new tablets that are currently being developed in the USA are ODTs," he says.

There are good reasons why the developers are increasingly relying on this method for administering medications. It combines the advantages of a tablet with those of an active ingredient solution: ODTs can be dosed easily and precisely and taken without water. "Most of the new variants dissolve in less than ten seconds, and many even need less than five seconds," says Breitkreutz. As a result, the active ingredient is quickly available to the body, because when it reaches the stomach it's already dissolved.

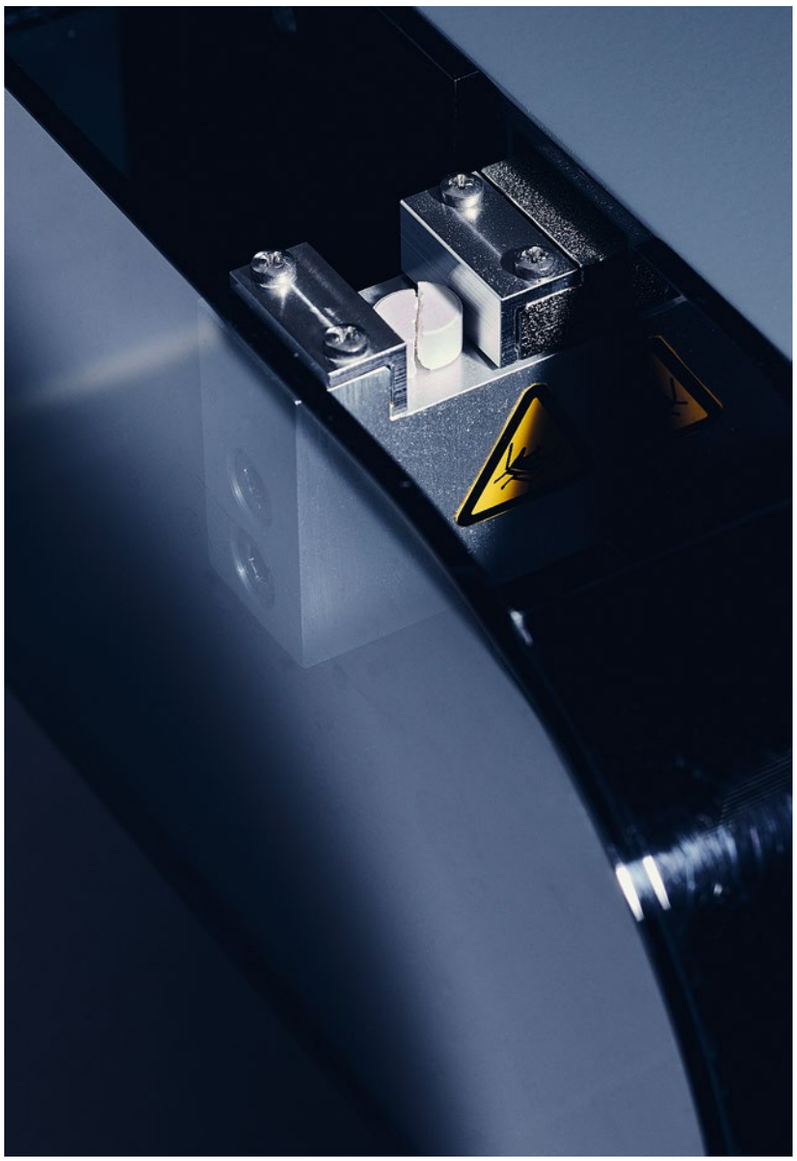
ODTs have clear advantages for patients who find it difficult to swallow conventional tablets. "For example, during an acute attack of migraine patients are often physically incapable of swallowing palliative medications," he explains. In such cases the stomach literally closes down.

Until now, physicians would often administer muscle relaxants such as diazepam rectally in the form of a gel in order to interrupt epileptic attacks in children. This was a difficult procedure that was unpleasant for the young patients. Breitkreutz has helped to develop ODTs the size of a pinhead, which pose no risk of choking even for babies and toddlers. What's more, they already transport some of the active ingredient into →

Testing new formulations: Dr. Falk Rohrbach in Hanau is developing ODTs that dissolve faster, yet are more robust

“RXCIPIENTS® has what it takes to improve many more ODT applications”

JOSEPH ZELEZNIK, A TECHNICAL PRODUCT MANAGER AT THE SPECIALTY CHEMICALS DISTRIBUTOR IMCD



the body very quickly via the oral mucous membrane. “You put a tablet inside the child’s cheek, stroke the cheek once, and the tablet is gone,” he says.

SUSCEPTIBLE TO MOISTURE

Breitkreutz wrote about medicinal preparations suitable for children in his postdoctoral qualification dissertation back in 2004. “At that time there were hardly any dosage forms that had been specially developed for children,” he recalls. The few that existed were often liquid formulations that were supposed to resemble child-friendly juice. However, these formulations raised problems of their own. For example, the World Health Organization (WHO) criticizes the fact that liquid formulations often require auxiliary substances such as solvents and preservatives or surfactants that are not problematic for adults but could be harmful to children. Besides, juices are more expensive and usually need to be kept refrigerated, because they are less stable than other types of medicine. These are two huge obstacles, especially if the medicine is destined for children in developing and emerging countries. “The WHO and the EU initiative Better Medicines for Children have been key drivers in the development of new ODTs,” says Breitkreutz. This development is still going on.

That’s because many common ODTs still have a crucial disadvantage: There are not very robust, and they are susceptible to moisture. As a result, they have to be packed individually with great care so that they don’t crumble before they can be administered. But the experts at Evonik have come up with a solution based on fumed silica: RXCIPIENTS®.

Evonik took over competence in this area when it acquired the silica division of the US company J.M. Huber three years ago. In Havre de Grace, Maryland, the company produces silicas as ingredients in many types of tablets, including RXCIPIENTS® for ODTs.

J.M. Huber began to work with ODTs at the turn of the millennium. At that time, a US pharmaceutical company was looking for an auxiliary substance for a new tablet for treating schizophrenia. ODTs are very helpful in the treatment of such mental illnesses, because they make it easier to administer medicines reliably. When they are administered under supervision, they cannot be simply spit out.

One of the researchers who followed this development was Dr. Duenwu Hua, a native of Taiwan who had come to the USA in the mid-1980s to gain a doctorate in chemistry. He was hired by J.M. Huber early in the new millennium. “It was actually unusual for our company to receive this inquiry,” Hua recalls. Silica and silicates had been used in tablet production for a long time, for example during the production process in order to →

create a homogeneous distribution of active ingredients that would make it possible to ensure a precise dosage in each tablet. However, back then they were hardly used at all in ODTs.

Even today, disintegrating aids are the key ingredients that make ODTs dissolve in the mouth within seconds. One commonly used disintegrating aid is an indigestible polymer called crospovidone. When it comes into contact with water or saliva, it swells up and bursts the tablet.

Such disintegrating aids work optimally only if the tablets themselves are not too stable. As a result, many ODTs cannot be sold in conventional blister packaging. They would simply crumble as they were being pressed out. The loose packaging in orange plastic containers with covers that is commonly used in the USA is especially problematic, because if the container is shaken the tablets simply shatter. Besides, regular opening of the container repeatedly lets moisture in, so the tablets disintegrate while they're still inside the packaging. That's why ODTs are often packaged in peel-off blisters with a foil that the patient has to remove with care. However, this is not always easy, particularly for older patients.

Thus the challenge was clearly defined: The researchers had to find an additive that would make the tablets harder and more resistant while accelerating the effect of the disintegrating agent after the tablet is in the patient's mouth. "This is actually a contradiction," Hua explains. However, a fired calcium silicate finally delivered exactly these desired effects. J.M. Huber named this development RXCIPIENTS® FM 1000 and patented it in 2002. The name is derived from the term "excipients," meaning auxiliary materials, and the abbreviation "Rx," which signifies prescriptions in the USA.

A WATER-REPELLENT EFFECT

Dr. Falk Rohrbach, the head of silica application technology at the Health Care business line in Hanau, calls RXCIPIENTS® a small but excellent product with many applications. "The special twist is the firing of the calcium silicate," he says. This makes the surface of the particles water-repellent, so that it keeps the moisture in the air away from the tablet. By contrast, inside the mouth the combination of the disintegrating agent and RXCIPIENTS® in the tablet creates a kind of water pressure that quickly breaks the tablet open.

Joseph Zeleznik, a technical product manager at the specialty chemicals distributor IMCD, has a high opinion of this auxiliary excipient. "RXCIPIENTS® has what it takes to enhance many ODT applications—for manufacturers as well as for patients," he says. Robust orally disintegrating tablets (ODTs) are in demand almost everywhere, whether it's for allergy medicines, psychopharmaceuticals, trending dietary supplements, or where water is inaccessible or unsafe. They are valued by producers of branded pharmaceuticals and generic drugs alike to meet patient needs ranging from pediatric to geriatric.

Knowing what counts: In the laboratories at Evonik, new tablets are subjected to stress tests and repeatedly measured by means of standardized methods

SHAKE, SWIRL, AND MEASURE

Zeleznik should know. In his function at IMCD he supports many pharmaceutical companies in the US market, and he has 25 years of experience with producers and suppliers in the sector. At the Pharmaceutical Technical Center in Rochelle Park, NJ, the IMCD technical team explores solutions for the formulation challenges facing ODT producers. "In many cases, the objective is to find the right balance between the greatest possible robustness and the fastest possible disintegration," he says. This challenge is compounded by cost. "In the past, many ODTs could not be produced on conventional tablet presses. Instead, some required specialized equipment and processes, such as freeze-drying, which further required special packaging." Now, with RXCIPIENTS® ODTs can be manufactured using standard manufacturing equipment and processes. "This expands packaging options as well. In all, costs are reduced and product quality and performance are enhanced," Zeleznik says.

However, the researchers are not satisfied with the status quo. Rohrbach and his team want to continue improving ODTs. Accordingly, they are producing tablets in line with customer specifications and under conditions that are as close to those of real production lines as possible. These test tablets subsequently undergo a veritable series of tortures: Special machines tirelessly shake, press, swirl, weigh, and measure the ODTs in order to find out which mechanical stresses they can withstand. The tablets are then dissolved in water in an industrially standardized process in order to determine exactly how long it takes them to disintegrate.

"Our data provide crucial selling points in order to make RXCIPIENTS® a standard ingredient of ODTs," says Rohrbach. "There is also tremendous potential for additional applications." Zeleznik is convinced that this technology will prevail on the market. "If we can now produce and package such ODTs, which are quick to dissolve and especially practical for daily use, even more cost-efficiently, this type of tablet will be on the threshold of a real breakthrough," he says.

Tom Rademacher is a translator and a freelance journalist based in Cologne. He writes about scientific and industrial topics, among others.

An Island Nation of Superlatives

Indonesia has the world's fourth-largest population—almost 270 million, and growing rapidly. This country, which is characterized by its many volcanoes, encompasses more than 17,000 islands and has the highest biodiversity worldwide. Some insights into the world's biggest island nation and its path to the future

TEXT **ANNA SCHRIEVER**

Between rain forests and the open ocean: Indonesia's natural environment is characterized by a humid climate, extensive mountains, and the ever-present Indian Ocean. Idyllic beaches such as this one on the island of Lombok are normally popular tourist destinations—but this year's restrictions on travel mean they are populated exclusively by locals. Evonik has operated in Indonesia for more than 20 years. Through its sustainable products and solutions, the company wants to help maintain a balance between the rising consumer demands of the country's growing population and its sensitive ecosystems.

Traditions and rituals are fixed components of the multifaceted cultures of Indonesia. One example is the Legong dance on the island of Bali. At the moment the opportunities to stage such performances have been greatly limited by the pandemic—but the hope remains that they can soon be resumed. Under normal conditions, the dancers perform in venerable temples and palaces, decked in colorful costumes and elaborate makeup. Even robust cosmetics like these can be removed with products that are gentle to the skin. Evonik produces high-quality surfactants for applications such as skin cleansers right here in Indonesia, at the plant in Bekasi near the country's capital, Jakarta.

How to safeguard reliable, sustainable, and affordable nutrition for Indonesia's rapidly growing population? A strong agricultural sector is necessary in order to supply food for all of the 300 million people who are expected to be living in Indonesia in 2030. Indonesia has more Muslims than any other country on earth. One reason why chicken farming is very important in Indonesia is that its Muslim inhabitants do not eat pork. In poultry barns like this one in Sukabumi, great care is taken to keep the birds healthy. It's essential to provide the chickens with good nutrition. For example, amino acids from Evonik help them optimally metabolize their feed. As a result, less protein has to be added to the feed. In this way, Evonik products and expertise in precision livestock farming help to considerably reduce the ecological footprint of feed production.

In the Mitsubishi production hall in Cikarang, workers assemble vehicles that will soon transport people from A to B, even at the outer edges of this island nation. For international automakers, Indonesia is not only a production location but also an interesting consumer market. In megacities that are struggling with severe air pollution, such as Jakarta, electric vehicles could be a major source of relief in the future. The heart of an electric vehicle is its battery. Metal oxides from Evonik make batteries more efficient, longer-lasting, and safer because they help to prevent short circuits.

A sea of brightly colored containers: The harbor of Jakarta, Tanjung Priok Port, is a hub for the shipping trade. About half of Indonesia's cargo handling takes place here. A new terminal covering 32 hectares was built for the harbor in 2016. The terminal's warehouses are protected from the weather with Protectosil® BHN from Evonik. This product offers many advantages: Even under tropical climatic conditions, it prevents water from penetrating concrete and offers optimal protection from corrosion. However, a huge problem still remains: The entire city of Jakarta has been subsiding for years.

FROM SURFACTANTS TO HYDROGEN PEROXIDE

Evonik's predecessor companies established footholds in Indonesia over 20 years ago. Since then, high-quality surfactants and esters for manufacturers of household cleansers and body care products have been produced in Bekasi. The plant was expanded in 2013. Evonik also operates a sales office in Jakarta, the capital, and a production plant in Cikarang, where it produces hydrogen peroxide for the cellulose, paper, and textile industry. Cikarang and Bekasi are both located in the Jakarta metropolitan region.

The

3

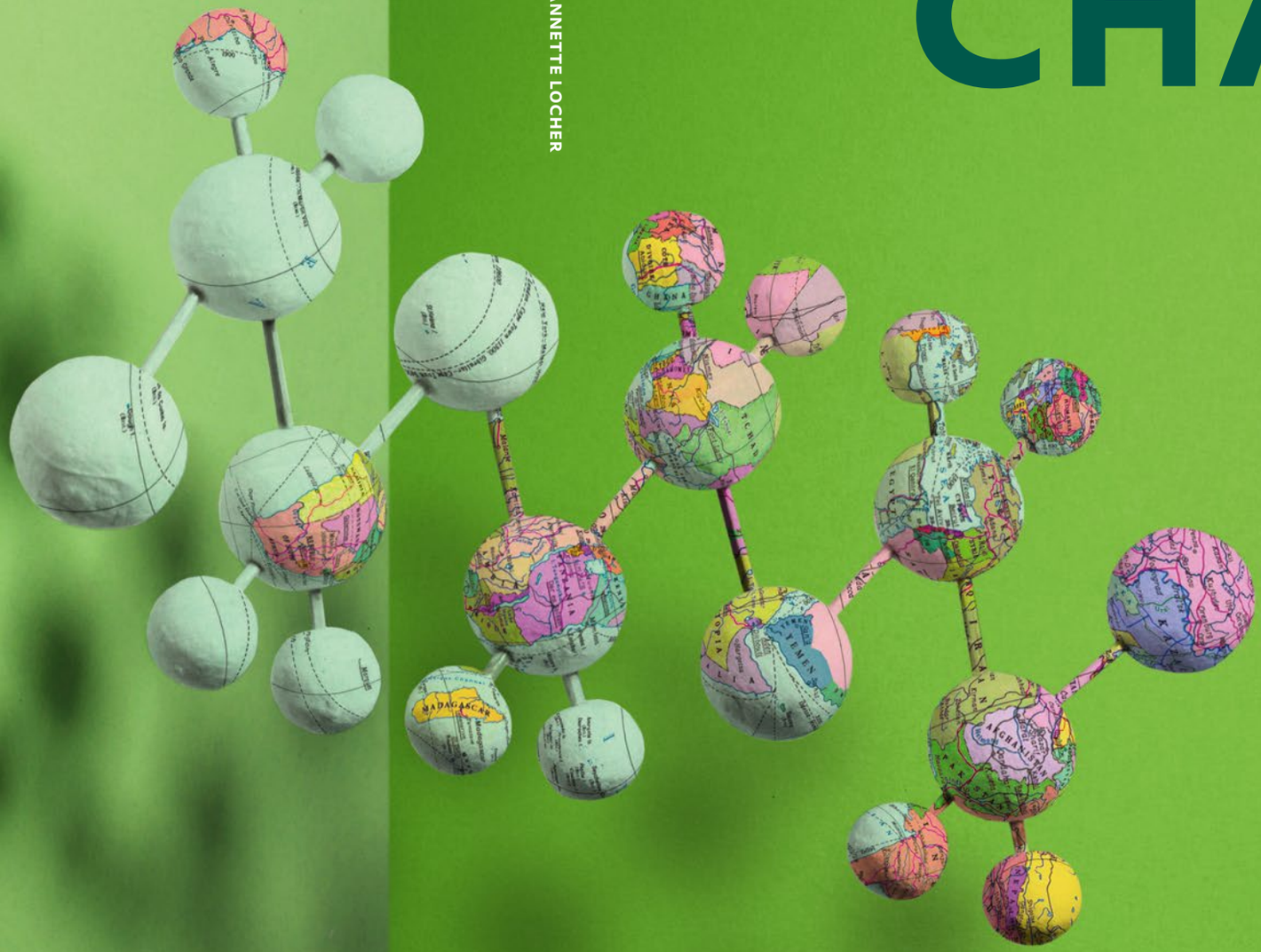
locations have

129

employees.

DEFENSIVE CHAIN

TEXT **ANNETTE LOCHER**



The use of therapeutic proteins is spreading worldwide. While these active ingredients promise to bring about major medical advances, some have the problem that they are quickly broken down in the human body before they can release their full therapeutic effect. This might be offset by chains of polyethylene glycol, which Evonik manufactures at pharmaceutical quality

All in green: Protective clothing that is impermeable to gases is obligatory for Evonik chemist Marius Mewald whenever he works with the raw material ethylene oxide

Marius Mewald loves to solve difficult tasks. He has a doctorate in chemistry, and his job at one of Evonik's research departments is to fulfill customers' wishes. Mewald, 36, has been working at the Exclusive Synthesis unit of Evonik's Health Care business line since 2015. The pharmaceutical customers that he serves, from startups to major corporations, all have very individual needs. In most cases, they want to launch a new drug on the market and are looking for a partner who can reliably produce the active pharmaceutical ingredient or a precursor of it, at the highest possible quality.

This desire often results in a research assignment for project managers like Mewald. "We have the know-how for advanced technologies that can synthesize certain classes of molecules," he says. "But each molecule needs its own process." It's Mewald's job—and his passion—to devise this process and later hand it over to his colleagues in the production department.

However, Mewald's daily work has changed considerably lately: His laboratory has evolved into a production facility. That's because a large-scale plant for the innovative technology that was tested and developed here doesn't yet exist. "Instead of trying out new things, we now have to do the same things the same way each and every day," says Mewald. "And we have to do this for months on end." It's clear that he doesn't really like this state of affairs, but he nevertheless seems satisfied and even proud. After all, this project enabled the team under his leadership to make it to the final round of the Evonik Innovation Award competition in 2019.

What was especially notable about the team's achievement is that the experts took just a few years to develop a technology for the production of polyethylene glycol (PEG) for pharmaceutical applications, to set up a pilot plant, and to land its first major contract from a customer. These long-chain molecules, which are made up of ethylene oxide building blocks, can be used to modify delicate active ingredients in such a way that they remain intact in the body long enough to achieve the desired therapeutic effect.

"Although many companies can manufacture PEGs, only a handful of them worldwide can produce PEGs for pharmaceutical use," says Mewald. Among other things, the trick is to create chains of molecules—polymers—with lengths that hardly vary and that always have specific chemical groups at both of their ends. "Any deviation can reduce the effectiveness of a →

drug," says Mewald. At the moment, his main task is to ensure continuity within the process and thus guarantee that product quality is always consistent.

The pharmaceutical industry's demand for PEGs is steadily growing, because more and more active ingredients are now being produced with the help of biotechnology. Therapeutic proteins such as small peptides, enzymes, and antibodies have, in recent years, filled the development pipelines of pharmaceutical and biotech companies. These proteins make up a big part of what are referred to as the "biologicals." In 2001, one out of five candidate active ingredients was such a biological. This figure has now risen to about one out of three.

Biologicals have the advantage that they mostly have a very specific action and are highly effective. In many cases, they are designed to treat severe illnesses such as cancer, infections, and autoimmune disorders. However, the human body tries to make foreign proteins "harmless" as quickly as possible, because they might be a poison or a harmful decomposition product. That's why the immune system often reacts to the therapeutic protein and renders it ineffective. In other cases, the protein is attacked by enzymes that take it apart. Moreover, small proteins are fairly quickly broken down by the kidneys.

As a result, modern pharmaceutical active ingredients of this type require assistance. One means of extending their retention time in the body is called PEGylation. In this process, long PEG chains are attached to the active ingredient. They make the molecule more voluminous as a whole, and thus prevent it from being filtered out of the blood plasma and later broken down in the kidneys. In addition, they shield the protein component against enzymes and the immune system.

This effect can be especially beneficial to patients. In 2000, for example, interferons for the treatment of chronic hepatitis C still had to be injected daily, because half of the administered interferon was broken down by the kidneys within around four hours. Daily injections were the only way to achieve the desired effect—the stimulation of the immune system against the hepatitis virus. The daily visit to the doctor was a big strain for the patients as well as for the healthcare system.

ESSENTIAL MEDICINES

This changed in 2000 and 2002 when the first PEGylated interferons were launched on the market: peginterferon alfa-2b and peginterferon alfa-2a. Their concentration in the blood drops off ten times slower. Since then, patients have only had to go to the doctor once a week. Peginterferons quickly dominated the market. Since 2013, they have been on the Model List of Essential Medicines published by the World Health Organization (WHO).

Pegfilgrastim, which helps to prevent life-threatening infections from occurring during chemotherapy, was the first PEGylated drug to achieve blockbuster status, generating sales of over US$1 billion. By 2019, sales had already risen to over US$3 billion. This therapeutic agent had also originally existed only in an unPEGylated form that had to be administered daily for ten days after each chemotherapy cycle. Thanks to PEGylation, only a single injection is now needed on the first day after chemotherapy.

The one-liter glass reactor at the Evonik lab in Hanau is used for tests

Markus Mewald (right) and Michael Reuter, an employee from active ingredient production, check the water content of the reaction solution

According to scientists such as the pharmacologist Dr. Bernd Meibohm, PEG modification is a real breakthrough for transporting active ingredients within the body. "What's special about PEGylation is that it changes the physical-chemical properties of therapeutic molecules without diminishing their effectiveness," says Meibohm, who is a professor at the College of Pharmacy of the University of Tennessee Health Science Center. Meibohm specializes in pharmacokinetics and pharmacodynamics, which study the chronological behavior of active ingredients in the body, and in the development of therapeutic proteins.

Meibohm, a German pharmacologist, is also familiar with other methods for modifying active ingredients, such as by combining them with an albumin protein. However, PEGylation opens up more possibilities for fine tuning. "There's an optimal PEG for every active ingredient," says Meibohm. It's possible to modify the chain length, for example, or the branching of a molecule. "And the careful identification of this PEG pays off," he adds.

Once the right PEG has been determined for a specific active ingredient, a manufacturer has to be found for the product. For supply security, in many cases at least two manufacturers are desired, preferably on different continents. "It would be much too risky if a crucial medication was dependent on a single production site," explains Mewald, the research scientist from Evonik. The coronavirus pandemic has shown how easily global supply chains can be disrupted. →

"We're one of the top three contract manufacturing organizations in the pharmaceutical sector"

Three questions for Dr. Andreas Meudt, head of the Exclusive Synthesis product line at Evonik

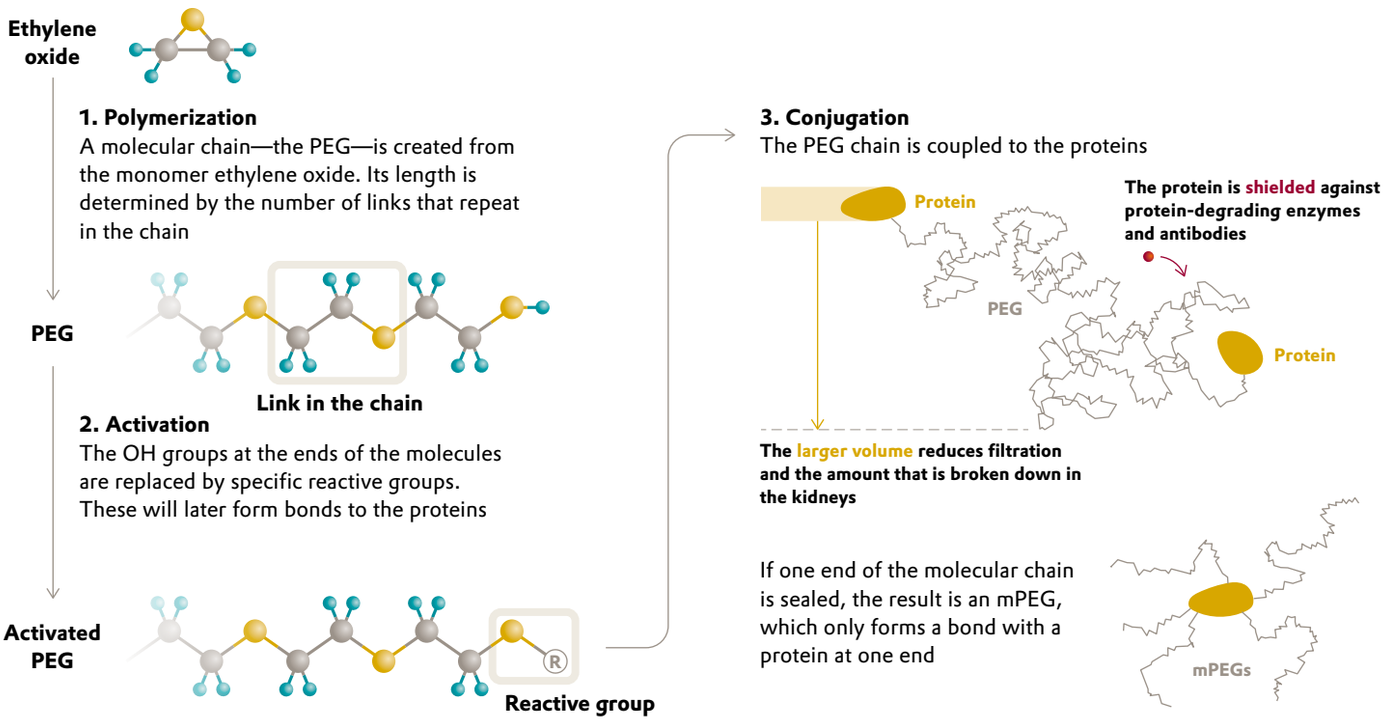
Why do even big pharmaceutical firms have active ingredients produced by third parties?
Until around ten years ago, major pharmaceutical firms in particular produced their own active ingredients and drugs. Many are now focusing on their core competencies: the development of new active ingredients and marketing. In addition, more and more specialized technologies are now needed to manufacture these actives and not every company has these capabilities.

How big is the base of potential customers?
Worldwide, over 4,000 companies work on the development of new drugs. Many of these companies are university spinoffs that don't have their own production capacities. In terms of value, almost half of the active ingredients produced worldwide are now made by contract manufacturing organizations (CMOs).

What is Evonik's role in this market?
We've been a CMO for the pharmaceutical industry for about 25 years and are now among the top three companies in this field worldwide. What differentiates us is our command of very challenging technologies. These include active ingredients known as HPAPIs that have a huge effect in the body, even in small amounts. Many anti-cancer drugs belong to this class. Handling such ingredients requires special safety precautions. We are set up for this work and have the world's biggest production capacity for HPAPIs.

Supersizing

How PEGylation gives proteins more volume



Evonik began to investigate pharmaceutical PEGs in 2015. Back then, the PEGylation of active ingredients was beginning to turn into an attractive growth market and the company had all of the required skills, although they were distributed among a variety of business units.

The specialty chemicals company had, for decades, been producing PEGs and other polyethers on an industrial scale for a variety of applications. Among other things, they are used as components of foam stabilizers and emulsifiers. That's why Evonik is familiar with the extremely reactive, toxic starting material: ethylene oxide. "Once ten ethylene oxide building blocks are connected into a chain, they are no longer hazardous," says Mewald. However, a manufacturer of PEGs also has to know how to handle the individual molecules of the monomer—and has to make sure that the finished product doesn't contain even the slightest trace of ethylene oxide.

KNOW-HOW FROM A VARIETY OF AREAS

In addition, Evonik's Exclusive Synthesis product line has long been working successfully as a contract manufacturing organization (CMO) for the pharmaceutical industry and is one of the world's leading suppliers in this field (see the short interview on page 51). Dr. Dietmar Reichert, who is responsible for technical marketing at the Exclusive Synthesis product line of the Health Care business line, says that there are two reasons for this: "We support our customers as a strategic partner and we set ourselves apart with technologies that only a few companies in the world are proficient in."

Some of these technologies require extremely specialized knowledge and experience—sometimes from completely different units. "In the case of PEGs, you have to master the entire chain: the safe handling of ethylene oxide, the development of a specific PEG, and its reproducible production in pharmaceutical quality," says Reichert.

As welcome as the first customer inquiry was, it posed a considerable challenge for Mewald's research team. "It propelled us directly into the champions league," Mewald says. The customer wanted a very big PEG. "However, the longer it is, the more difficult it becomes," says Mewald. That's because the longer a chain is, the greater the possible variability, which is extremely undesirable.

The PEG from Evonik is designed for an active ingredient that will be used against several illnesses that cannot be treated yet. It is still in the clinical development phase. It took the team a number of months to create

The 50-liter reactor is being filled with starting material. Michael Reuter checks the contents

the first acceptable sample, Mewald recalls. Although it wasn't perfect yet, the customer agreed to take part in a joint learning process. The facility was modified several times until the process and the setup were correct.

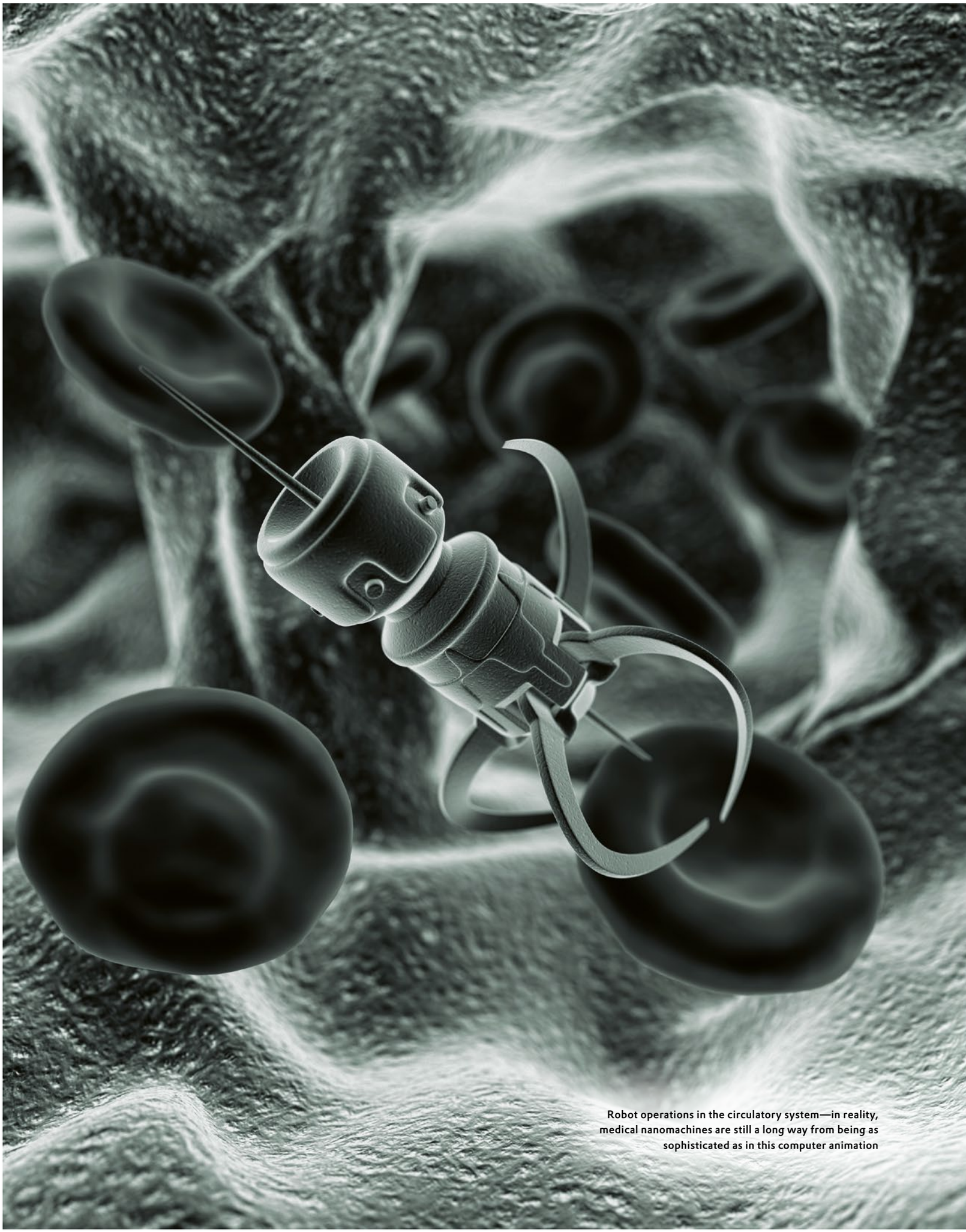
The second production series is now being manufactured in the pilot plant in Mewald's laboratory. The 50-liter reactor is located in a fume hood. All of the ingredients are automatically measured out through closed lines so that any contact with the ethylene oxide is prevented. Nothing can be seen but stainless steel and lots of sensors. "You're not even allowed to get a marker pen too close to the sensors, because they would react to the solvent," says Mewald. The process developers are now also being supported by colleagues from active ingredient production. This enables production to run in two shifts on six days of the week.

The PEG is subsequently processed further in an active ingredient production facility. This processing is done in accordance with the conditions of good manufacturing practice (GMP) required by the pharmaceutical industry. Finally, an activation step is required so that the molecule can react with the drug's active ingredient. The molecule should bond to a specific place on the active ingredient. To do this, the ends of the PEG molecule are modified. "You can compare the activation step to fitting a trailer coupling to a car," explains Mewald. Other PEGs—called mPEGs (methoxypolyethylene glycols)—are basically sealed at one end and can only be activated at the other end.

The final step, the connection of the PEG to the active ingredient, is carried out in this case by the manufacturer of the active ingredient. The activated PEG can be easily shipped in powder form—to the other side of the world, if necessary. In the future, Evonik may produce not only PEGs and activated PEGs but also PEGylated active ingredients. "We want to extend our product range in this direction," says Reichert.

The company is currently planning a commercial facility in order to expand its PEG production capacity. Once that is done, the reactor and the lab will again be free for what Marius Mewald loves and can only do on the side at the moment—developing processes for other PEG variants, of which there are many.

Annette Locher has a degree in biology and has worked for Evonik's communications department since 2012. She mainly writes about healthcare, nutrition, and sustainability



Robot operations in the circulatory system—in reality, medical nanomachines are still a long way from being as sophisticated as in this computer animation

A SMALL INTERVENTION

Making motors from an atom? Tiny particles that carry out transportation tasks? Nanorobotics will make tremendous technical progress possible in medicine and other fields

TEXT **BJÖRN THEIS**

The Czech scientist Dr. Jan Beneš defects to the West in 1965. After his flight is discovered, his pursuers lie in wait and attack him, causing severe injuries. Beneš manages to escape, but a blood clot in his brain threatens to gradually kill him. His rescuers quickly decide to run a risky experiment: They miniaturize a submarine manned by a crew of physicians and CIA agents and inject it into the scientist's body, with the mission of dissolving the blood clot.

The science fiction film *Fantastic Voyage* made in 1966 has inspired generations of researchers. One of them was Eric Drexler, who wrote *Engines of Creation*, a visionary basic work on nanotechnology, in 1986. In this book he describes numerous possible designs and applications of machines on a nanometer scale. By way of comparison, a sheet of paper is about 100,000 nanometers thick. According to Drexler, in the future we will be able to use molecular technologies to, among other things, diagnose illnesses, transport medications directly to diseased cells in the body, and carry out surgical operations as needed.

MOLECULAR MACHINES

Today we have already come much closer to making this vision a reality. In 2016 Jean-Pierre Sauvage, James Fraser Stoddart, and Bernard Lucas Feringa received the Nobel Prize in Chemistry for their design and synthesis of molecular machines. These three researchers were able to successfully combine molecules into units such as nanocars, muscles, and molecular motors that can execute controllable movements and perform certain tasks. "The 2016 Nobel Laureates in Chemistry have miniaturized machines and taken chemistry to a new dimension," wrote the Nobel Committee for Chemistry. In the same year, a research group from the Universities of Mainz, Kassel, and Erlangen-Nuremberg unveiled the world's smallest motor. This heat engine, which consists of a calcium atom, could be used as a driver of nanoobjects in the future.

A TRANSPORT VEHICLE INSIDE THE BODY

In the years since then, this development has accelerated. In 2018 the research group Micro, Nano, and Molecular Systems at the Max Planck Institute for Intelligent Systems presented a nanomachine that can move through an eye. This propeller-shaped minirobot is only 500 nanometers in size. A test using a pig's eye demonstrated that a swarm of thousands of these robots can move through the meshes of the collagen network in the vitreous body of the eye without causing any damage. The team is now aiming to get this nanopropeller ready to transport active ingredients. Their visionary goal is to use it as a tool for minimally invasive treatments of all illnesses in which the problem area is surrounded by dense tissue that makes it hard to reach.

Even though we probably won't be navigating through the human body in nanosubmarines in the future, nanomedicine is nonetheless experiencing dynamic development. We can expect to see the creation of new and effective applications and methods of treatment here, for example with the help of nanodrones. That's a good reason for the Foresight team at Creavis to keep an eye on this area. After all, more than 20 years ago the first project house at Creavis was already doing research on nanomaterials and their possible applications in electronics, cosmetics, and the coatings and pharmaceutical industries. This area still plays an important role at Evonik today. Creavis is now researching the nanomaterial graphene and identifying potential fields of application—in the area of medical devices, for example.

Björn Theis heads the Corporate Foresight department at Evonik's innovation unit Creavis. His ELEMENTS column appears regularly at elements.evonik.com

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Cl
Chlorine

“I love and hate chlorine”

The diver **Tina Punzel** (24) participated in the Olympic Games in Rio. Her next goal is the Olympic Games in Tokyo next year. That’s why she’s training more than four hours per day, half of them at an indoor pool.

LOG **ANNA SCHRIEVER**
PHOTOGRAPHY **ROBERT EIKELPOTH**

When I smell chlorine, I instantly imagine myself standing on the diving board. Just before the jump, my body is full of adrenaline, my knees are shaking, my heart is racing. Then I try to block everything out and focus completely on this dive. I’ve got only a few seconds to demonstrate what I’ve been practicing for weeks. I’ve dived off the ten-meter board thousands of times, but I still feel keyed up. The anxiety never goes away completely.

The smell of chlorine usually conjures up positive associations for me, and yet I have a love-hate relationship with this element. On the one hand, chlorine dries out the skin and can trigger allergies. In some countries, the concentration of chlorine in swimming pools is so high that the skin reacts violently and itches. On the other hand, chlorine is a good disinfectant that we can’t do without.

Ever since I was a kid, I’ve felt at home in the indoor swimming pool of the Dresden Sports Club. This is where my father, Rainer Punzel, competed as a member of the national diving team. I started learning to swim and do gymnastics when I was five years old. We still go to the sports hall often. There we practice dives, improve our strength, and do acrobatics. I train for at least 30 hours a week, half of them at the sports hall. In addition, I’m studying economics at the Technische Universität Dresden (TUD).

My international breakthrough came in 2013, when I won the European championship at the age of 17. Three years later, a dream came true when I was permitted to participate in the Olympic Games in Rio de Janeiro. The one thing I’ll never forget is the family atmosphere at the Olympic Village. Athletes from all over the world and from every discipline form a gigantic community there. In terms of sports, it was also a success for me: I reached the semifinals in my favorite discipline, the single dive from the three-meter board. And I placed seventh in the synchronized swimming competition. Even though many competitions have been canceled because of the coronavirus crisis, I’m practically certain I will qualify for the Olympic Games in Tokyo in 2021. My goal is to reach the finals!

Masthead

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“Nine tenths of our happiness…

…depends on our health alone. With health, everything is a source of pleasure; without it, nothing else, whatever it may be, is enjoyable,” wrote Arthur Schopenhauer. As a philosopher of pessimism, he did not have a very positive worldview, but he regarded health as the key source of an individual’s sense of well-being.

Current events are making these truths especially clear. Health is the foundation of an independent, carefree, and secure life—and medicine is its guarantee. In this issue we present innovations from the field of chemistry that make state-of-the-art medicine and a healthy future possible.