3/2021

ELEMENTS

Research. Knowledge. The future.

Growth Area

Biotechnology issue

DNA

Carrier of the genetic information

DNA (deoxyribonucleic acid) is a nucleic acid composed of four different nucleotides. It carries the genetic information of living beings. It plays an important role in modern biotechnology. Analyses of genetic features are used on the one hand to identify suitable microorganisms and enzymes for biotechnological production. On the other, properties such as their metabolism can be optimized by targeted interventions in the genetic material. The fundamental structure of DNA is a double helix—like two intertwined screw threads. Every time a cell in the body divides, the double helix is first split into two single strands by the enzyme helicase. These strands are then replicated.

Nucleotide A building block of nucleic acids. A nucleotide consists of one of four nucleobases, a sugar group, and a phosphate group
Double helix Two intertwined strands of nucleotides that are linked by hydrogen bonds
Replication Duplication of the DNA

DEAR READERS,

In this issue we take a look at the voracious larva of the black soldier fly. We also report on cheese made without milk, the finest ingredients for pig feed, and bacteria that help burn victims.

Have we whetted your appetite?

We hope so, because in this issue we'll be making a deep dive into the wonderful world of biotechnology—a world that some people find incomprehensible or even scary. It's also a world that opens up endless vistas for new, sustainable products and solutions. The potential, including the market potential, for biotechnological processes is gigantic. That's why innovative companies all over the world are investing big money in these technologies—and growing together with them.

Starting on page 42, we begin an especially fascinating journey into the world of genes. Here, researchers who specialize in epigenetics are investigating the extent to which our DNA is being reprogrammed by our environment. To this end, they are evaluating huge volumes of data and arriving at surprising insights into the life history of organisms.

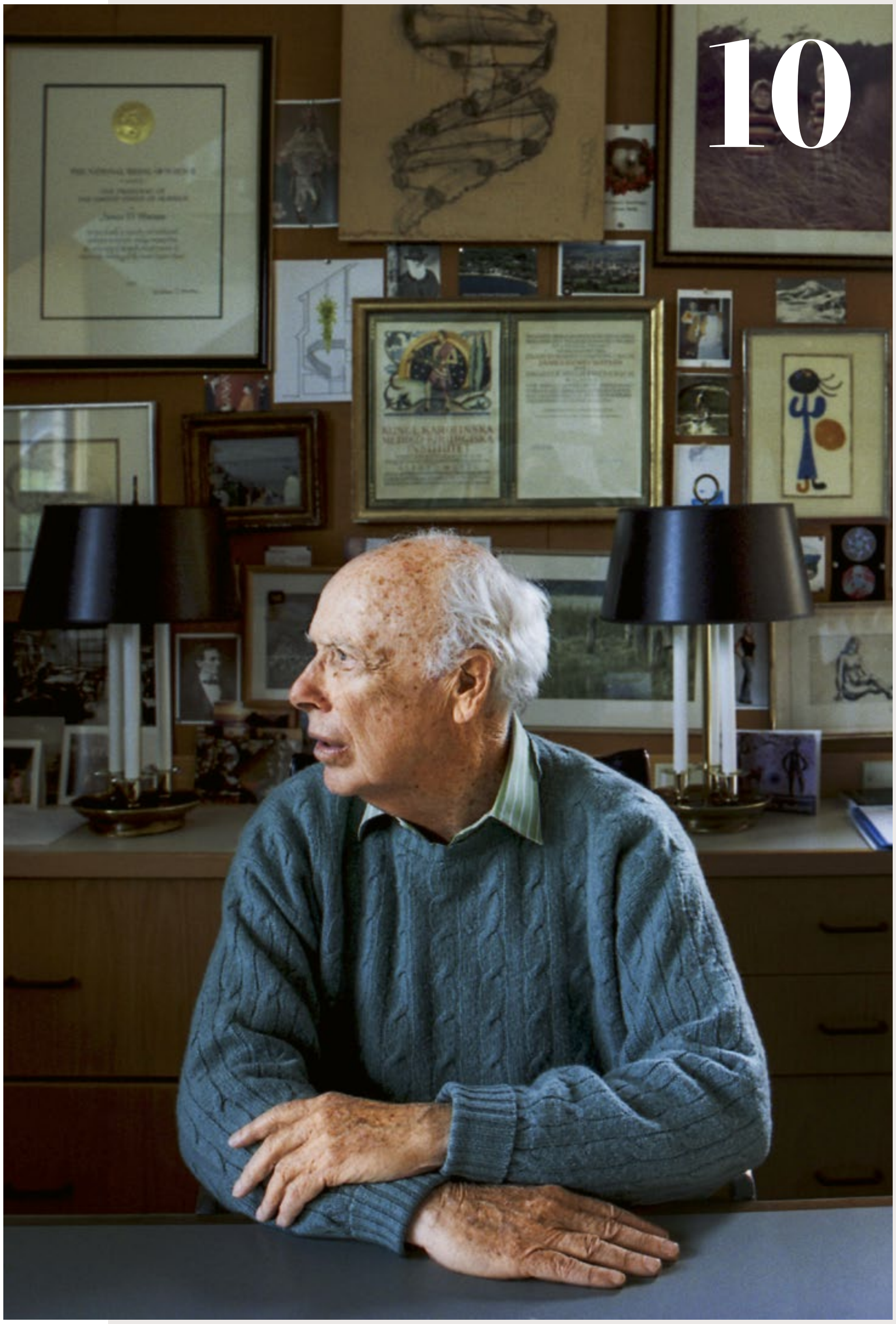
If you're one of our older readers, you might remember the first generation of digital watches. And you'll certainly remember your first computer and your very first mobile phone. These devices are the relatively simple forerunners of digitalization. Today, a few decades later, microelectronics has radically transformed our everyday lives.

And now we are once again facing similarly sweeping changes as biotechnology advances with a tremendous impact into fields such as medicine and nutrition. In the decades ahead, it will dramatically change our daily lives, but that's not all. For the chemical industry as well, it will become the driver of the great transformation leading to what we call the green economy of the future.

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 American scientist James Watson, who is now 93, is regarded as one of the founders of biotechnology. Together with his British colleague Francis Crick, he postulated the double helix model of DNA in 1953

BIOTECHNOLOGY

The epigenomes of human beings and animals can be analyzed with the help of special microchips

Longhorns on the prairie in Colorado: Cattle breeding is only one of the many areas for which Evonik offers the right products in the United States

A SKIN-DEEP MODEL

Skin protects the human body from drying out, penetration by pathogens, and ultraviolet radiation. In order to do all that, the skin sometimes requires support from pharmaceutical products and cosmetics. With the help of extensive testing, the producers of creams, lotions, and other products ensure that the ingredients are tolerated by the skin. The test procedures are expected to be quick and cost-effective and make animal testing unnecessary. Artificial tissue models are one solution that meets these requirements. For example, the Revivo startup in Singapore, in which Evonik recently acquired shares, has developed a model that simulates the reaction of skin tissue to certain substances. It imitates not only the skin's structure and functionality but also its blood flow—an important basis for efficient tests without animal subjects.

Filling up with crop waste

An especially resistant type of yeast enables ethanol to be produced from grain and corn residues

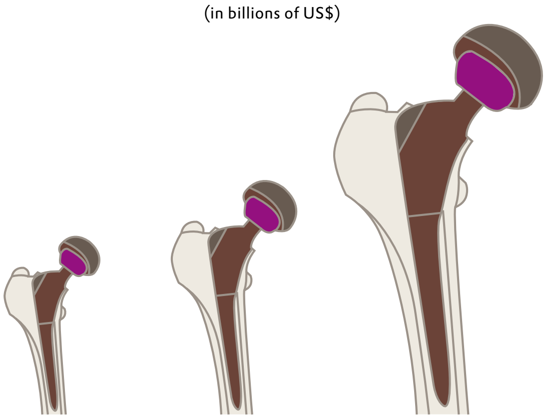
The corn waste that is left over after the harvest looks useless at first glance, but can be processed into biofuel

It's a dilemma: The wheat, corn, and rapeseed that are turned into biofuels can't serve as a source of food. In principle, using crop waste is a good alternative, because it is inedible. However, this was difficult to do until recently. Although yeast can be used to convert the sugar in the stems and leaves into ethanol, this sugar can only be dissolved by acids whose aldehydes are damaging to yeast. Now help is on the way in the form of a modified GRE20 gene. Researchers at the Massachusetts Institute of Technology have cultivated about 20,000 types of yeast, each with a differently modified GRE20 gene. After numerous tests, they found a yeast variant that is resistant to aldehyde. This yeast can turn not only corn and wheat but also straw and millet into bioethanol.

THAT'S BETTER

A big step

Global market value of biomaterials
(in billions of US$)



2016	2017	2021*
72	84	152

*Forecast

People in aging societies are becoming increasingly dependent on implants and protheses—that's why materials such as biodegradable polymers and collagen are in demand for medical technology. The market value of such biomaterials has increased greatly in recent years. It amounted to around €72 billion in 2016, but is estimated to have more than doubled by 2021, according to the market research company BIS Research.

Source: BIS Research

1,274

RESEARCH PAPERS

on CRISPR-Cas9 experiments were written in the USA in 2020. According to the online platform lens.org, China came in second, with 653 papers. With the help of the CRISPR-Cas9 genetic editing tool, for which the discoverers received the Nobel Prize in Medicine, researchers can remove or modify specific DNA components in order to combat numerous genetic diseases, cancer, and AIDS.

EXOSOMES...

...are tiny bubbles (vesicles) that can transport molecules in the human body. They are of interest to the pharmaceutical industry because they can transport pharmaceutical active ingredients. Exosomes occur naturally in many places, including cow's milk. Until recently, a complex cleaning process was needed to separate vesicles from proteins and lipids. However, researchers at the Virginia Polytechnic Institute have developed a more efficient process that makes much higher yields possible.

Tiny climate protectors

British researchers are cultivating bacteria that convert carbon dioxide into formic acid for the chemical industry

All over the world, scientists are looking for ways to convert climate-damaging carbon dioxide into basic chemical materials. The latter are then turned into useful products. Bacteria play an important role in this process. Scientists at Newcastle University have cultivated a strain of *Escherichia coli* that can capture CO_2 and convert it into formic acid with the help of hydrogen. Ants use formic acid to defend themselves against enemies. It is also an important raw material for the chemical industry. Among other things, formic acid is used to neutralize alkaline reaction mixtures and join up polymers. If the findings from Newcastle are accepted in the scientific community, the bacteria could in the future contribute considerably to the recovery of carbon dioxide and thus become tiny climate protectors.

PEOPLE & VISIONS

“The alga we investigated synthesizes hydrocarbons that have the same properties as petroleum”

THE PERSON

Because of the fresh ocean breezes and far horizons, **Naomi Harada** prefers to conduct field research out on the high seas. She already took part in an expedition to the equatorial Pacific when she was studying oceanography. On this expedition she was especially fascinated by the oceanic depths. “I found it very moving and motivating when we extracted a one-hundred-thousand-year-old sediment core from the ocean floor.” This was followed by further expeditions and a doctoral degree—research into the inner workings of the seas became the key topic of her life.

THE VISION

The history of science is full of discoveries that researchers made while they were investigating something else. This also happened to Harada. In 2013 she studied the impact that climate change was having on plankton in the Arctic Ocean. But when she took a magnifying glass to look at a species of algae known as ***Dicrateria rotunda,*** she saw something that surprised her: “The alga can synthesize special hydrocarbons that have the same properties as petroleum,” she says. This enables it to serve as a source of biofuels, which can help to reduce the emission of greenhouse gases.

GOOD QUESTION

“Will we soon be eating reactor-grown fish fillets, Dr. Rakers?”

We’ve made great progress in that direction. We’ve been working on fish cells since 2008 and have been producing cell-based fish since 2020. It is an important option for feeding the world’s growing population. In the laboratory, fish is made from adult stem cells that we only have to extract once from an animal and then multiply in a bioreactor. Our cultured product isn’t exposed to any environmental toxins and helps to protect the natural animal populations, which are greatly threatened by overfishing. Moreover, it can be produced in precisely the quantities that people actually consume and therefore reduces the amount of waste fish. However, several years of development time will still be needed before we can sell cell-based fish fillets whose appearance, taste, and cooking properties are indistinguishable from those of conventional fish.

Dr. Sebastian Rakers is the co-founder and CEO of the Berlin-based start-up Bluu Biosciences, which specializes in the production of cell-based fish.


COVID-19
Vaccine
10ml

BIOTECH BOOM

Biotechnology is one of the key sciences of the 21st century. It is enabling investments in innumerable areas, making production more efficient, and helping to conserve resources. Last but not least, it is opening up huge economic opportunities

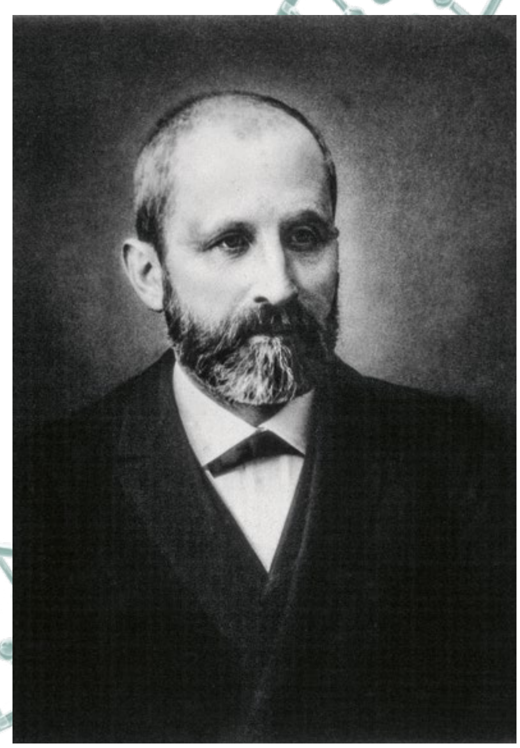
TEXT **DENIS DILBA**

In 1869 the Swiss biochemist Friedrich Miescher chose a pretty unappetizing method to obtain new findings: In the hospital of Tübingen, he gathered used dressings and rinsed out the white blood cells that were contained in the pus. He suspected that the substance in the cell nuclei plays a key role in biology. However, he couldn't have imagined that his discovery, which he called "nuklein" (nucleic acid), was the genetic material.

People repeatedly underestimated the impact that the progress of biotechnology would have. It took another 84 years until James Watson and Francis Crick discovered DNA's double helix structure. However, until the 1980s scientists thought it would be impossible to fully decode the human genome. Even after the Human Genome Project completed this mammoth task in 2003, most researchers thought that editing DNA in a targeted manner would never be possible. They were wrong →

1869

The biochemist Friedrich Miescher from Basel discovers a substance in the nuclei of white blood cells that would later be called DNA. His work lays the foundation for modern biology



1683

The Dutch naturalist Antonie van Leeuwenhoek is one of the first people to observe bacteria, which he sees with a self-constructed microscope

1857

The French scientist Louis Pasteur discovers that fermentation is caused by the activity of microorganisms. He also realizes that such microorganisms can be used to produce lactic acid, acetic acid, and alcohol again: Emmanuelle Charpentier and Jennifer Doudna presented the genome editing tool CRISPR-Cas9 in 2012, which enabled the genome to be changed with great precision.

"Throughout the history of biotechnology, every time a hurdle has been successfully taken, people thought the next one would be insurmountable, even though it was overcome just a little while later," says Professor Stefan Buchholz, head of Research at Evonik's Nutrition & Care division.

Buchholz thinks that we have plenty of additional surprises in store. "Over the past decade, new high-throughput genome sequencing techniques have dramatically improved the costs and performance of DNA analysis," he adds. The pace of development is even outstripping that of Moore's Law, which states that the number of transistors on a computer chip doubles approximately every 18 to 24 months, thus cutting the costs of computing in half (see the illustration on page 16). Although it still cost several hundred million dollars to sequence the human genome around 20 years ago, the price has now dropped to just over US$100. "The incredible dynamism of genetic research, combined with advances in automation, high-resolution imaging, artificial intelligence, and big data, is producing more and more innovations at an ever faster pace. As a result, biotechnology is increasingly moving into the business spotlight," says Buchholz.

A NEW INDUSTRIAL REVOLUTION

According to Matthias Evers, a biotech expert and senior partner at McKinsey, the importance of biotechnology cannot be overestimated. "It is a key technology of the 21st century and, like digitalization, might trigger a new industrial revolution," he says. In the report titled "The Bio Revolution," which Evers co-authored in 2020, the McKinsey business consulting firm forecast that biological technologies could generate up to

"Biotechnology is increasingly moving into the business spotlight"

STEFAN BUCHHOLZ, HEAD OF RESEARCH AT THE NUTRITION & CARE DIVISION

1915/16

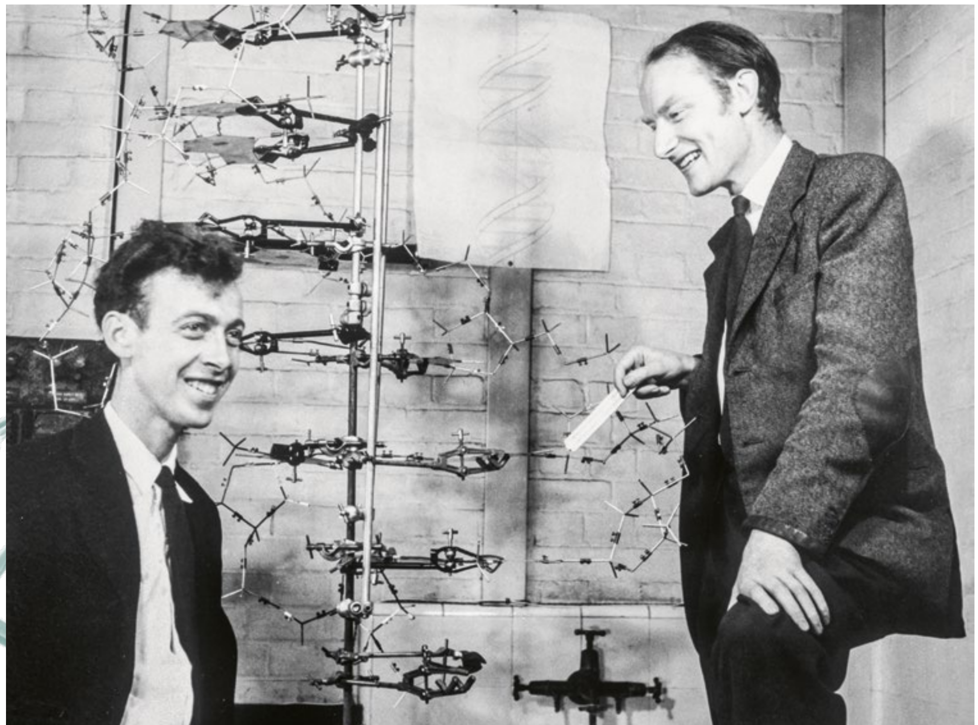
The chemist Chaim Weizmann, who would later become the first president of Israel, uses fermentation processes to make acetone and butanol

1928

Alexander Fleming, a Scottish physician and bacteriologist, discovers penicillin. This antibiotic is produced from molds

US$4 trillion of global added value annually by 2040 (see the article "Data Mining" on page 15). This enormous value added will be created by numerous processes, products, and methods that are currently still under development. Moreover, it will not be limited to the direct use of advanced genetic techniques.

Most recently, the successful development of vaccines against COVID-19 provided us with an inkling of the scientific and economic possibilities. Thanks to recent biotechnological innovations, the surfactants that have been used in detergents for decades have greatly improved in quality, enabling them to achieve the same



1977

The British biochemist Frederick Sanger develops DNA sequencing in order to determine the sequence of bases in a strand of DNA. In recognition of this achievement, he receives his second Nobel Prize in Chemistry

1953

The decoding of the double helix structure of DNA by the zoologist James Watson (left) and the physicist Francis Crick marks the birth of molecular biology. The two scientists draw on the research results of Maurice Wilkins and his colleague Rosalind Franklin. Their work paves the way for gene-based biotechnology. In 1962 Watson and Crick receive the Nobel Prize in Physiology or Medicine

washing performance at a much lower rate of energy consumption. As a result, laundry that used to be washed at 90 degrees Celsius can now be done at 30 degrees. Added to that are many pioneering innovations in the fields of nutrition, climate and environmental protection, and the production of sustainable materials. However, biotechnology does more than just enable the efficient production of active ingredients for food, animal feed, skin-compatible cosmetics, and environmentally friendly detergents and bioplastic. It also paves the way for making cultured meat, using bacteria in the mining industry, and refining bioethanol from sugar-rich plants.

A color code has been established to differentiate the various areas of application. As a result, we now have red, green, and white biotechnology. Red biotechnology deals with medical applications, while green biotechnology involves plants, and white biotechnology relates to environmentally friendly, resource-conserving industrial production processes.

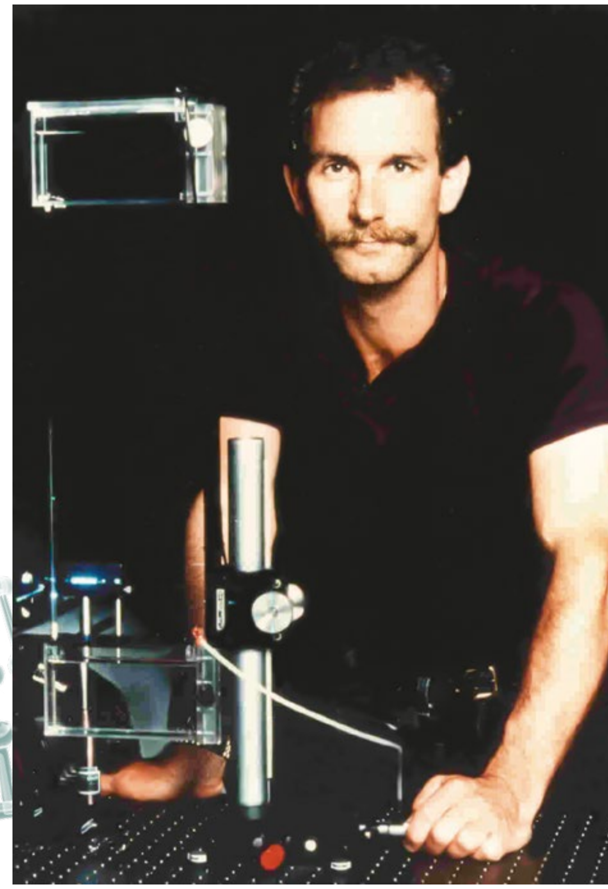
Evonik entered the field of white biotechnology all the way back in 1983, when experts at the company began to use biotechnology to produce the amino acid lysine, which is mainly used in animal feed. This production technique uses a microbiologically optimized strain of bacteria. When it is fed sugar, it produces the form of the amino acid that animals' metabolism can use (see the article on page 25). Such processes, in which microorganisms produce huge amounts of a desired functional molecule, are referred to as fermentation. The environmental benefit of these processes is that they use renewable raw materials and the products are generally biodegradable. As a result, the carbon that is required as a source of energy is recycled, and no fossil carbon is released into the atmosphere. This also makes biotechnology a key technology for a circular economy. →

1982

Insulin is the first biotechnologically produced medication to receive market approval. Prior to this, insulin was extracted from the pancreases of slaughtered pigs or cattle

1983

The US biochemist Kary B. Mullis develops the polymerase chain reaction, or PCR for short, which revolutionizes the process of copying DNA in laboratories



1986

At the California Institute of Technology, the US chemist Lloyd M. Smith develops the first automated DNA sequencer. The startup Applied Biosystems launches the device on the market, where it bears the model designation ABI Prism 370A. It eliminates the need to use radioactivity for sequencing, which was previously the case

GETTING A BETTER UNDERSTANDING OF BIOTECHNOLOGY

Evonik now uses biotechnology in the form of fermentative and biocatalytic production processes in order to make essential amino acids, probiotics, dietary supplements, and pharmaceutical active ingredients. “Our activities focus on human life,” says Johann-Caspar Gammelin, head of the Nutrition & Care division. “Biotechnology is ideal for the production of complex molecules that can be used on people, in people, or for people.”

The experts at Evonik are also using the biotechnology platform to develop sustainable system solutions for cosmetics, cleaning agents, healthcare, and animal feed. Innovation is occurring particularly at the interfaces between biology, medicine, chemistry, and engineering. The Nutrition & Care division is now generating around 20 percent of its sales with products and services based on biotechnology, and this percentage is set to increase further.

As our understanding of biotechnology grows, more and more applications will be developed. For example, researchers at Evonik have developed an epigenetic analysis technique for chickens that, among other things, reveals their state of health (see the article on page 38). This could potentially be transferred to other livestock and provide farms with better data, thus supporting more sustainable meat production. Another promising new field is that of “yellow” biotechnology, which uses insects (see the article on page 54).

“We think that insect-based animal feed has great potential,” says Buchholz. As part of the InFeed research project, Buchholz’s colleagues are working on optimizing the nutrient composition of this especially protein-rich feed. The prospects that it will create a lucrative new area of business are very good, because the global market for insect protein is forecast to grow substantially over the next decade.

A SERVICE PROVIDER FOR THE BIOTECH INDUSTRY

The latest mRNA technology breakthrough in medicine also promises to generate strong growth. That’s because the manufacturers of the active ingredients need special technologies so that their compounds can be transported unharmed to the right places in the human body. To securely transport mRNA-based active ingredients, in which a ribonucleic acid trans- Continued on page 16 →

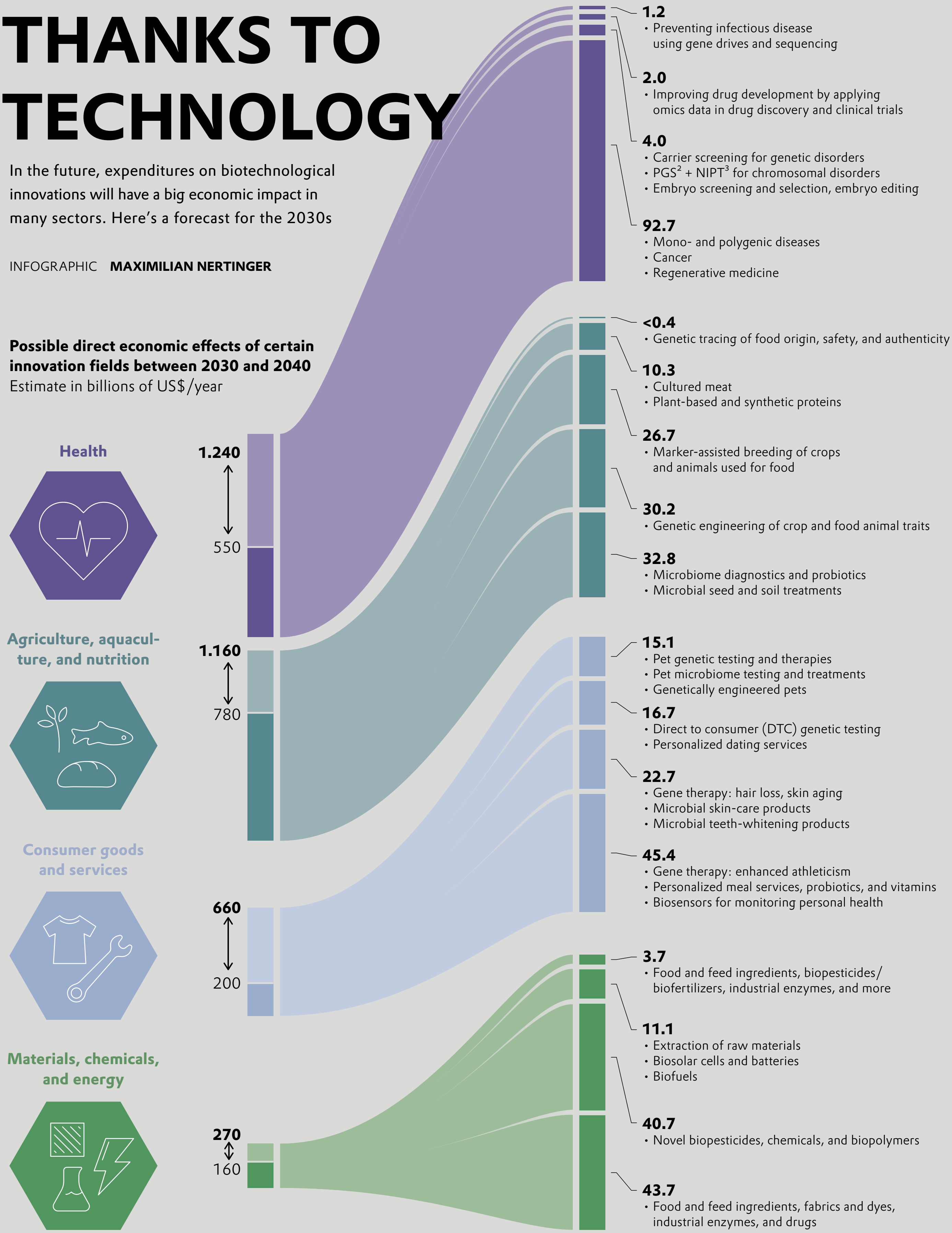
PROSPERITY THANKS TO TECHNOLOGY

In the future, expenditures on biotechnological innovations will have a big economic impact in many sectors. Here's a forecast for the 2030s

INFOGRAPHIC **MAXIMILIAN NERTINGER**

Possible direct economic effects of certain innovation fields between 2030 and 2040
Estimate in billions of US$/year

How certain areas of application contribute to these effects in percent[1]



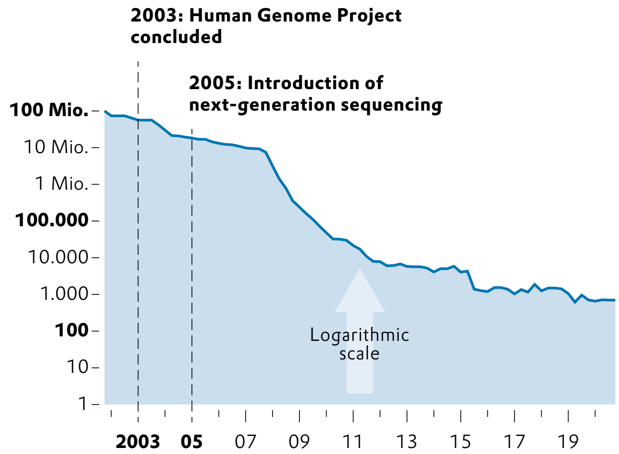
[1] Data based on estimated upper limits, deviations from 100% are caused by rounding off — [2] Preimplantation genetic screening — [3] Non-invasive prenatal testing
Source: McKinsey Global Institute, 2020

1996

Dolly, the cloned sheep, was born on July 5. Scottish researchers had cloned her by transferring genetic material from an udder cell into an egg cell with the nucleus removed and implanting the egg cell into a surrogate mother ewe. The experiment triggered a worldwide debate about the ethical boundaries of biotechnology

Cutting costs

Improved technology has dramatically reduced the cost of genome sequencing



Source: National Human Genome Research Institute

ports the genetic information for the production of a specific protein into a cell, you need lipid nanoparticles (LNPs) composed of various lipids. Evonik is one of the world's leading manufacturers of such lipids, and it is working together with scientists from Stanford University in California to create new processes that can transport the mRNA into cells with even greater precision in the future (see the article on page 30).

LESS ENVIRONMENTAL IMPACT

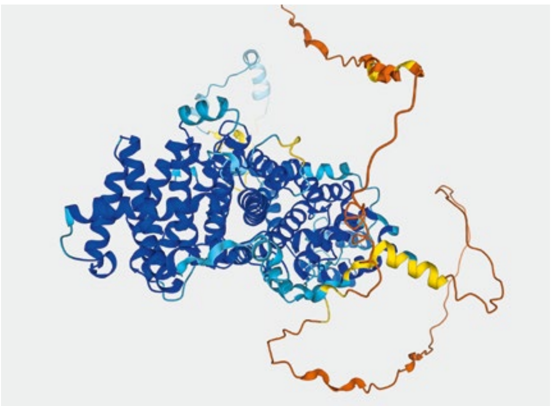
Fermentation and biocatalysis are promising options for the conservation of resources and the prevention of CO_2 emissions. However, these technologies will only be successful on the market if they are also profitable. Proof that sustainability and profitability aren't mutually exclusive is provided by the algal oil from Veramaris, a joint venture company that was founded by Evonik and the Dutch firm DSM. This product contains high concentrations of the omega-3 fatty acids EPA and DHA and it can replace the fish oil that has been used to date as a feed additive in salmon farming. This algal oil is produced in a fermenter and helps to ensure a secure supply of healthy animal protein. Moreover, it helps to protect the world's excessively overfished oceans.

Biosurfactants, which are based on rhamnolipids, also have a positive impact on the environment. They are contained in cosmetics products, detergents, and dishwashing liquids. They are completely biodegradable within a short time, eliminate dirt as reliably as very good synthetic surfactants, and are extremely skin-friendly. Researchers accomplished a great feat when they decoded the rhamnolipid production mechanism in a bacterium that is toxic for human beings and transferred this mechanism to a harmless strain of bacteria. In large fermenters, this strain is now turning dextrose into the desired lipids at room temperature. Evonik is cooperating with the British consumer goods company Unilever in order to develop and upscale the production process.

Biotechnology pioneer Doug Cameron says that rhamnolipids are a great example of the transfer of bio-

2012

The molecular biologists Emmanuelle Charpentier from France (left) and Jennifer Doudna from the USA develop the CRISPR-Cas9 technique for the quick and precise editing of DNA. This gene editing tool works in all living cells and organisms and ushers in a new era of genetic engineering. For their work, they receive the Nobel Prize in Chemistry in 2020



2020

Artificial intelligence is used to calculate protein folding and thereby accelerate the development of medications

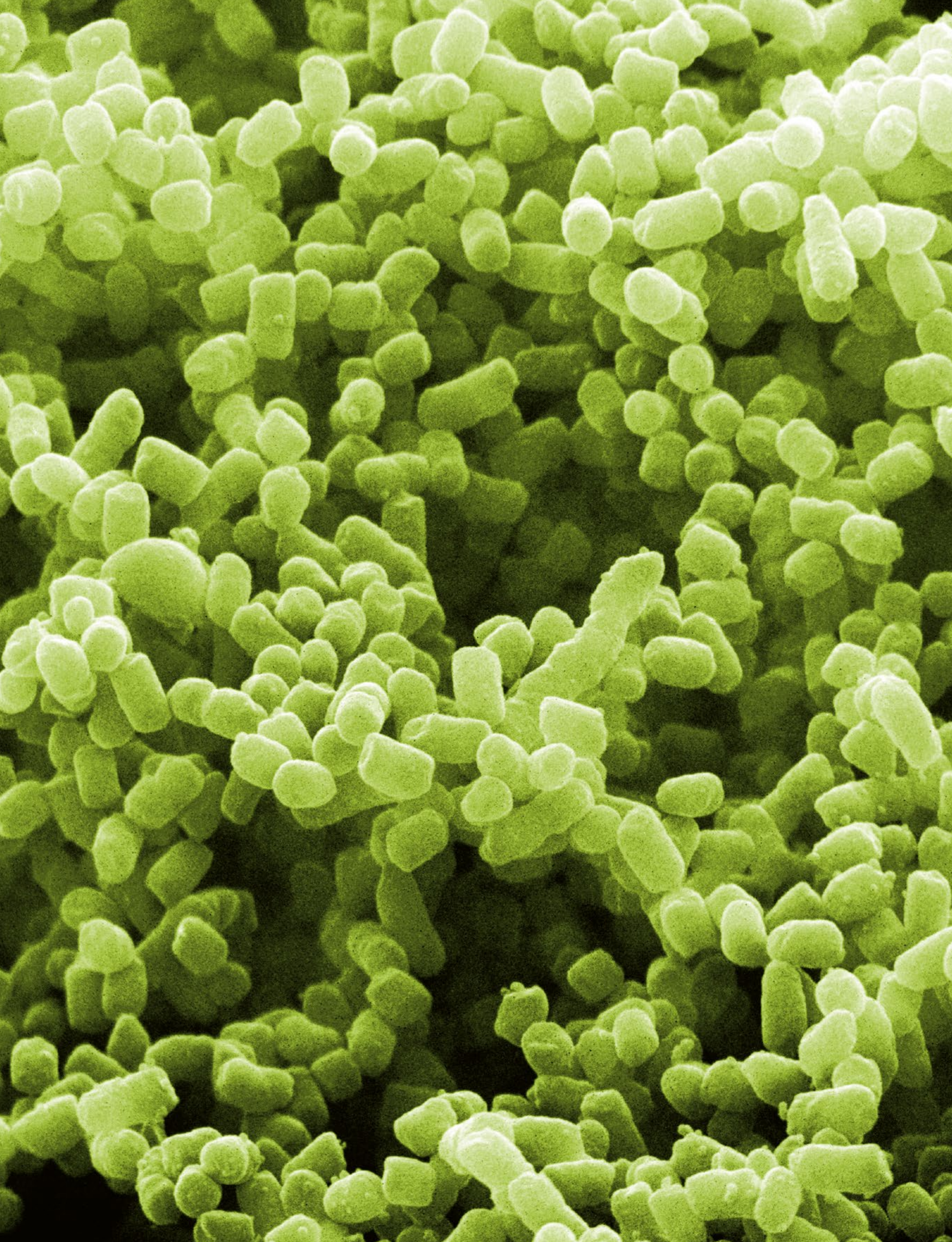
technological research results into practical applications. “This is where the strength of big companies is evident because they have a deep understanding of biotechnology as well as experience in building and operating large-scale chemical facilities, which enables them to commercialize the processes,” he says. Cameron used to be the chief scientist of the American agricultural and food corporation Cargill and is now co-president of the investment firm First Green Partners. “Although startups quickly develop exciting things in the laboratory, they often underestimate how much engineering expertise, time, and especially capital are needed to bring a production process to industrial maturity,” he adds.

But that’s not the only reason why Cameron thinks that innovative chemical companies are in a good starting position. “In the future, some of the most exciting and sustainable processes will be those that intelligently combine biotechnology and chemistry,” he explains. Matthias Evers from McKinsey thinks that biotechnology’s cross-sector potential is underestimated. “For example, our analysis shows that up to 60 percent of raw and starting materials could be produced by biological means in the future,” he states.

However, this potential can only be fully exploited if European legislation regarding genetic engineering is updated. The regulatory hurdles are especially high if techniques such as the CRISPR genome editing tool are used, irrespective of the modified organism’s properties and what dangers it might actually pose. “These questions should be at the forefront,” says Evers. “Not the question about the technique used to create it.”

Buchholz is of a similar opinion. “An updated regulation would quicken the pace of research, promote the development of innovations, and at the same time ensure a high level of safety—it would be a classic win-win situation,” he says.

Denis Dilba is an engineer and a journalist. He writes mainly about science and technology—the more complex the topic, the better



Powerful by their very nature, bacteria can easily synthesize a wide variety of substances

STRONG STRAINS

Some coveted products cannot be produced by simply using chemical processes. In many cases, microorganisms can help. Through fermentation, microorganisms can easily bring about even complicated reactions—if the right strains are used and the process know-how is correct

TEXT **ANNETTE LOCHER**

The human race has solved many of its problems with the help of chemistry. For example, the invention of ammonia-based fertilizer in the early 20th century made it possible to sufficiently feed the world's rapidly growing population. But there are some challenges for which even the best chemists cannot find technical solutions that can be implemented cost-effectively. In some of these cases, they are assisted by millions of tiny helpers riding to the rescue: bacteria that make it possible to carry out even very complex tasks by means of biotechnical processes. One of the most important such processes is fermentation.

Its effect has been utilized for centuries in areas such as winemaking. But it was not until the 19th century that Louis Pasteur, the French pioneer of microbiology, made the basic principles of fermentation the object of scientific research. Pasteur identified the mechanism by which grape juice ferments to form wine. The crucial drivers of this process are microorganisms that have no need of oxygen. Pasteur coined the term "fermentation" for this process, which takes place in the absence of air. In the field of biotechnology, fermentation is defined more extensively today. It now refers to the conversion of organic molecules by means of bacterial, fungal or cell cultures or through the addition of enzymes.

The full potential of fermentation is only being genuinely realized today. One example of that is lysine. This is an amino acid that human beings and animals need as a building block for proteins. Because their bodies cannot produce lysine on their own, they must take it in with their food. For many farm animals, lysine is indispensable for a balanced diet and optimal feed conversion.

But there's a problem: Only natural lysine, which is known as the L-form, can be used by the body, and producing it chemically is a very complex process. In the 1980s, chemists at Degussa, one of Evonik's predecessor companies, tried in vain for a long time to →

“Even the most complex molecules can be derived from sugar”

DR. TIMO MAY, HEAD OF THE FERMENTATION PROCESSES GROUP AT EVONIK’S BIOTECHNOLOGY RESEARCH PLATFORM

produce the L-form cost-effectively on an industrial scale. That’s because traditional chemical processes always produce a 50-50 mixture of the L-form and the D-form of lysine. These two forms of a molecule are like the left and right hands of a human being: They are not identical, but instead mirror each other.

The breakthrough came with the introduction of a fermentation process, because certain bacteria selectively form the desired biologically active L-form. “When the organism and the process are right, even the most complex molecules can be derived from a carbon source such as sugar,” says Dr. Timo May, an expert in fermentation processes at Evonik. Today one of the company’s most important technology platforms is derived from the process for producing L-lysine that was discovered back then (see the article starting on page 23).

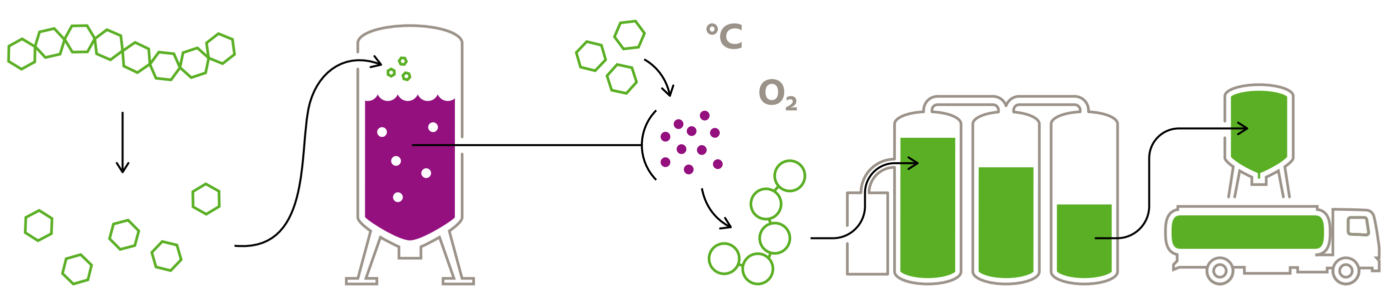
FROM ANIMAL FEED TO MEDICINE

L-lysine is only one of many products that can be manufactured cost-effectively thanks to fermentation. The areas of application of microbial processes range from animal feed to cosmetics and medicine. As a rule, fermentation processes are also more sustainable than traditional methods of production. They use renewable raw materials, are efficient, and make it possible to produce bioproducts.

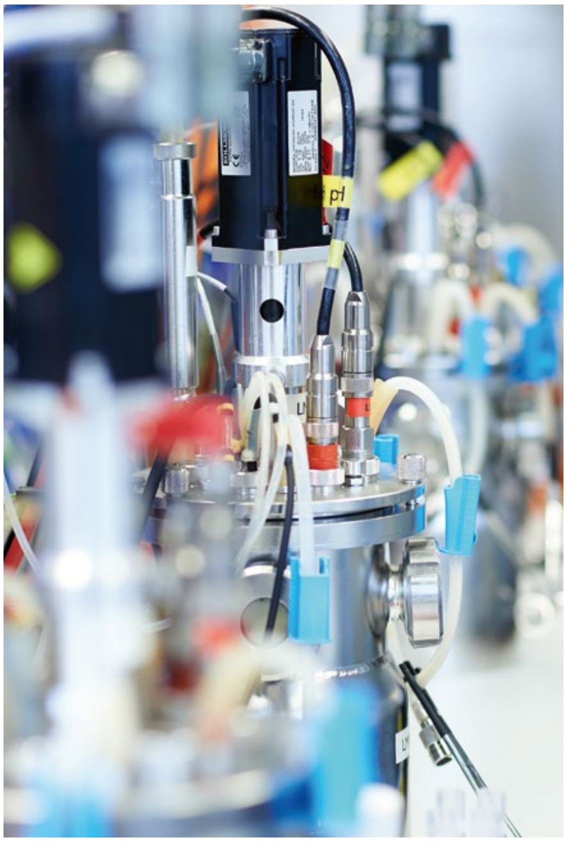
One example of the latter is the algae oil that Evonik produces by means of a fermentation process in a joint venture with Veramaris. It contains the omega-3 fatty acids DHA and EPA and also promotes environmentally friendly fish farming. Another example is rhamnolipids, the first biosurfactants in the world to be produced on an industrial scale. Thanks to fermentation processes, they are especially degradable (see the article on page 25). Customized and ultrapure collagens have also recently been produced by bacteria. These structural proteins

Small organisms with a big effect

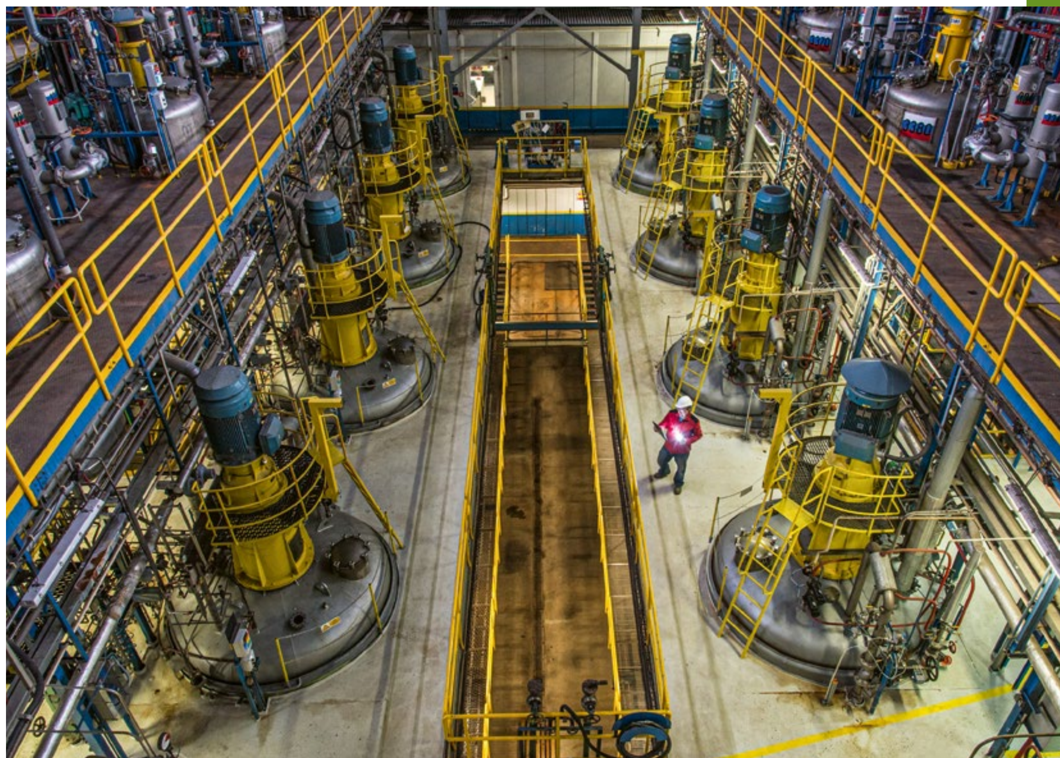
How marketable products are produced by the fermentation of starch



1. Starch from a source of carbon is processed into simple sugars.
2. Special microorganisms are grown in a fermenter and fed with sugar either in the presence of oxygen (aerobically) or without oxygen (anaerobically).
3. The microorganisms convert the sugar. Depending on their environment (temperature, oxygen etc.), they orient their metabolic processes toward the desired product.
4. Separation of cells and byproducts. In some processes (e.g. for components of animal feed) the bacterial biomass is also a component of the product.
5. Storage, filling, and transportation.



Small-scale fermenters play an important role in the development of fermentation processes



Industrial production takes place in multilevel fermenters such as these at the Evonik plant in Slovenská Ľupča

are needed in areas that include cosmetics and medical technology in order to smooth away wrinkles, heal cartilage defects, and much more. Conventional production processes use starting materials of animal origin. Production processes that use specialized bacteria eliminate the risk of variations in quality, allergic reactions, and the transmission of illnesses. As a result, they increase safety. A brand-new application is the biotechnological production of nanostructured cellulose, which is used as a dressing in modern wound treatment (see the article starting on page 26).

The biologist Timo May and his colleagues are fascinated by the way that microorganisms produce highly complex molecules. "They can conduct several desired reactions simultaneously—reactions that would require consecutive steps in a chemical synthesis and would therefore require very complex equipment," he says.

This capability also makes it possible to conduct processes such as artificial photosynthesis, in which carbon dioxide and water form specialty chemicals when exposed to solar energy. Evonik has joined forces with Siemens to develop this technology. The researchers at Evonik are working to develop a type of fermentation in which bacteria produce specialty chemicals. A pilot plant is now operating at the Evonik location in Marl.

SEARCHING FOR THE BEST STRAIN

In order to conduct biotechnological production at the top level, expertise in three areas is required: the development of bacterial strains, fermentation, and the refinement of the products. "Biotechnology is much more interactive than chemistry," says Dr. Wilfried Blümke, the head of the innovation group for the refinement of biotechnologically produced substances. That's because in biotechnology three components—the organism, the reactor, and the refinement process—all interact strongly with one another. "Only by working as a team can we decide in every individual case on what level we solve a certain problem," he says. The first task of the scientists is to find a microorganism that can produce the desired product naturally. For example, the bacterial strains *Escherichia coli* and *Corynebacterium glutamicum* have proved to be dependable producers of amino acids. The microorganism is optimized during →

Before the bacteria are used in production, they are tested in the laboratory and their properties are optimized for the desired application

the process of strain development. The goal is to get the microorganism to convert as much as possible of its carbon source, usually sugar, into the desired product. If the organism that has been found is not suited for industrial production, for example because it is pathogenic to human beings, molecular biologists transfer the relevant genes into a harmless microorganism that has proved its dependability.

FROM A BROTH TO A PRODUCT

During the first phase inside the fermenter, the microorganisms are still allowed to multiply and form biomass. Then, at a certain point in time, they are expected to direct their metabolic processes toward creating the desired product. The biotechnologists control this change of direction by adding or removing certain substances, for example. After a period that may last anywhere between a few hours and several days, the microorganisms are inactivated and the fermentation broth is drained off. Finally the desired product can be extracted from this broth.

"The refinement process varies, depending on the type of product," says Blümke. That's why the bioengineers confer with the marketing experts at an early stage in order to precisely customize the process. In many cases, several consecutive separation processes, such as filtration, centrifugation, and extraction, are needed. For example, in the production of a probiotic—in other words, living bacteria in spore form—a gentle drying process is very important. As a component of a dietary supplement or feed additive, the bacteria of course need to become active once again inside the guts of people or animals so that they can deliver their valuable metabolic products.

"We are looking for the most robust and most cost-effective of all the possible solutions," says Blümke. In this case, "robust" means that the refinement process delivers a product that precisely fulfills the quality requirements even if the results of the fermentation process vary. Between approximately 20 and 30 tried and tested refinement processes are available to the biochemical engineers at Evonik. All of the steps are modeled and simulated in the laboratory, then tested and improved in a pilot plant, and finally—if everything works well and the product is successful on the market—implemented on an industrial scale.

But at that point, the experts are still not satisfied. Even in a large-scale technical installation, biotechnological processes are constantly being optimized. For example, a higher-performing microorganism makes it possible to adapt the production and refinement process. Conversely, the bacterial strains are developed further in order to make even more cost-effective processes possible. The ultimate goal is to enable the ancient cultural technique of fermentation to help solve mankind's present-day problems sustainably with the help of cutting-edge scientific efficiency.

TOWARD CLIMATE NEUTRALITY

The use of fermentation methods at Evonik began with the production of BIOLYS® more than 30 years ago. Bioengineers are continuously improving the productivity and reducing the carbon footprint of this production process

TEXT **ANNETTE LOCHER**

The new head of process development in Blair, Nebraska, had an ambitious goal. "We can boost the plant's productivity by 50 percent," said Dr. Henning Kaemmerer in the fall of 2018, shortly after he had moved to the USA from Hanau. The plant, which had been producing the amino acid BIOLYS® for almost two decades, had been repeatedly optimized after its initial commissioning. But…50 percent? A productivity boost of this magnitude was hard to imagine.

BIOLYS® is added to animal feed—primarily feed for pigs. The animals need L-lysine, an important component of proteins. However, like human beings, they cannot produce this amino acid on their own, so they have to take it in with their feed. The amounts of the amino acid L-lysine in the plant-based components of pig feed are very low. If BIOLYS® is added to the feed as a source of lysine, the volume of the feed can be significantly reduced. That relieves the animals' metabolic processes, conserves natural resources, and reduces feed costs and emissions.

FRUGAL PRODUCERS

BIOLYS® is produced by means of fermentation. In gigantic stainless steel boilers, each with a volume of several hundred cubic meters, bacteria convert dextrose, a sugar, into L-lysine—much more of it than they need for themselves. The BIOLYS® process at Evonik uses a strain of *Corynebacterium*. The process engineers provide the ideal conditions for its growth and production processes: an aqueous medium, the right temperature, a plentiful supply of oxygen, and some mineral substances. After several days in the fermenter, the organisms are inactivated and the fermentation broth is drawn off and then vaporized. The mixture of lysine and bacterial biomass is the basis of the product, which is subsequently processed into a granular form that is easy to handle as animal feed.

Far more than 20 generations of this bacterial strain have been used since 2000. Each strain was a bit more frugal than its predecessor; in other words, it converted more sugar into lysine. But a real production boost resulted from an innovation that was promoted by the ambitious engineer Henning Kaemmerer. Within a few months, the Evonik engineers in Blair succeeded in switching the BIOLYS® process to "semi-continu- →

BIOLYS® helps to make the use of feed in pig fattening more efficient and sustainable

“We can boost the plant’s productivity by 50 percent”

DR. HENNING KAEMMERER,
HEAD OF PROCESS DEVELOPMENT IN BLAIR,
NEBRASKA, IN THE FALL OF 2018

ous” operation. Several times during the cultivation phase, part of the fermentation broth was removed and replaced with water, sugar, and the other ingredients. As a result, the product volume per fermentation could immediately be substantially increased—as predicted. The promised 50 percent increase was reached in 2019.

INTERNATIONAL KNOWLEDGE TRANSFER

Kaemmerer feels that his approach has been validated. “This shows what is possible when experts from the areas of research, process development, and production cooperate closely and pool their decades of experience regarding the microorganisms and the processes,” he says. That’s because the bacterial strain and the process must be repeatedly adapted to each other. The only unchanging element is the plant itself. As Kaemmerer explains, “The plant defines the limits within which we work.” This has enabled the product quantity per fermenter to be more than tripled since 2000. Simultaneously, the amino acid content of the initial product has increased significantly from BIOLYS®55 to BIOLYS®77.

Other Evonik locations are making good use of the experiences of their colleagues in the USA. “Of course we’ve benefited from the know-how in Blair,” says Miguel Menezes, who is responsible for BIOLYS® production in Castro, Brazil. The plant in Castro was commissioned in 2015. Since that time, the engineers in Castro have also been tinkering with improvements. Among other things, they have focused on making the production process more sustainable. They have continuously reduced not only the relatively high water requirement of the gigantic fermenters but also the consumption of steam and electricity. Energy is needed to cool the fermenters, operate the stirrers that ensure optimally uniform conditions inside the fermenters, and evaporate the water at the end of the process.

Castro is committed to renewable resources. Hydropower covers a large proportion of the plant’s energy needs, all of the necessary steam is produced with the help of eucalyptus woodchips, and the raw material dextrose is provided by a nearby corn mill. The plant is located in the midst of a corn-producing region that has been used for agriculture for more than 20 years.

Three quarters of the total production is sold in regional markets. That also reduces transportation routes and improves the carbon footprint. A recently conducted life cycle assessment confirms that only 0.1 kilogram of CO_2 equivalent is generated per kilogram of BIOLYS®77. Miguel Menezes is proud of this achievement, and Henning Kaemmerer is equally proud of his productivity increase. “We’re very close to achieving a completely climate-neutral production process,” he says. “In that case, the plant in Castro would be Evonik’s first industrial-scale production plant with a neutral carbon footprint.”

SWEET AND CLEAN

Biosurfactants that are produced by the fermentation of sugar are in demand for the manufacture of cosmetics and detergents

TEXT **CHRISTOPH BAUER**

Biosurfactants made from rhamnolipids are high-performance materials that are also environmentally friendly and gentle to the skin. They are found in hand dishwashing liquids and in care products

Five years ago, the laboratory's first attempts to produce biosurfactants by means of fermentation created huge mounds of foam, recalls Dr. Hans Henning Wenk, the head of Research and Development at Evonik Care Solutions. However, the experts in Slovenská Ľupča (Slovakia) now have the process firmly under control, and are using rhamnolipids produced by bacteria to manufacture biosurfactants.

Surfactants are contained in dishwashing detergents, shower gels, and bath additives, where they ensure that dirt doesn't collect again on dishes or skin. In the European Union, surfactants have to largely break down during wastewater treatment, which is why the consumer goods industry is increasingly using biosurfactants. However, the demand is also growing in regions where sewage treatment plants are rare but people are becoming increasingly environmentally conscious.

After its start in the cosmetics sector, Evonik and its partner Unilever developed a hand dishwashing liquid based on such biosurfactants. The product is already on the market in Chile and Vietnam, where dishes are generally washed by hand. Thanks to rhamnolipids, hand dishwashing liquids that are based on biosurfactants are on a par with very good products based on synthetic surfactants.

The demand for these sustainable raw materials is rapidly increasing. For example, Unilever wants to stop using fossil carbon in its household and textile care formulations by 2030. Rhamnolipids are now also found in toothpaste, facial cleansers, and shampoos. Evonik is therefore continuing to invest in this production technique in order to strengthen its leading position in this globally growing market.

DOWN THE DRAIN

The biosurfactants that Evonik produces consist of a sugar component and a fatty acid component. For the fermentation process, the company uses a strain of bacteria that produces both components from plant-based sugars. Evonik uses dextrose as a substrate, which is made from plants such as European corn.

Not only are the raw materials and the production process environmentally friendly, the product itself also has a low environmental impact. Says Wenk: "In the end, it goes down the drain and to the sewage treatment plant. In some regions, it is even released directly into the environment." However, the environmental impact is vastly reduced because rhamnolipids are much less toxic than conventional surfactants and very easily biodegradable.

The main feature of Evonik's fermentation process is its scalability. Although many natural bacteria convert fats into rhamnolipids, they only do so in microscopic amounts. At Evonik, this task is performed by *Pseudomonas putida*, a well-researched "safety strain." "After we gave it the genetic tools to produce rhamnolipids in large amounts, we continuously optimized it further," says Wenk.

The process ultimately created a strain of bacteria that produces biosurfactants in industrial amounts. "To achieve this, we got bioengineers together with process experts, chemists, and engineers," reports Wenk. "We benefited here from our experience with the development of surfactants." The expertise of a physical chemist proved to be crucial because he was able to explain why a surfactant that had some of its parameters modified suddenly behaved completely differently than before. This knowledge enabled the researchers to get the foam under control so that it now only goes into action in sinks and bathtubs.

FROM JENA TO THE WORLD

In the laboratories of JeNaCell, bacteria are producing the material for a dressing that enables wounds to heal quickly and gently. This area of application is scheduled to grow further following the company's acquisition by Evonik

TEXT **NICOLAS GARZ**

The dressings made of biotechnologically produced cellulose can be formed into any desired shape and they optimally protect wounds

Everything in Uwe Beekmann's daily work has to do with a soft and relatively slippery membrane. This gelatinous substance is produced by bacteria in a fermentation process. Beekmann, who has a doctorate in pharmacology, is creating the conditions in which the microbes feel at home as they work. To feed the bacteria, Beekmann pours a glucose solution into a square glass dish. "The bacteria initially use the nutrient solution to survive and multiply," says Beekmann, who works at the research and development department of the biotech company JeNaCell in Jena, Germany. "They then combine glucose components into fine fibers in order to protect themselves against dehydration and environmental factors such as ultraviolet radiation." These spider silk-like objects of nanostructured cellulose eventually form a thin fleece that Beekmann carefully separates from the nutrient solution. It is afterwards cleaned so that all bacteria are removed and only the cellulose and water remain. The material can then be cut into any shape desired.

BACTERIA BEAT PLANTS

However, more important than the exterior shape is the material's interior composition. "What's special about the bioengineered cellulose is its close-knit internal web structure," explains Beekmann. It gives the material its great stability and strength. "Added to that are its biocompatibility and good skin tolerance, which make it ideal for use in medical applications and cosmetics." If the material were plant-based, it would not be possible to achieve these properties in this quality. That's why the company is focusing on very productive strains of bacteria.

It all began with a few small Petri dishes full of cellulose that Dana Kralisch discovered in a lab at the Institute for Organic and Macromolecular Chemistry at the Friedrich Schiller University Jena in 2006. Although no concrete application was foreseeable at the time, the material fascinated Kralisch, who had just received a Ph.D. in chemistry, so much that she initiated a research project. In addition to conducting work in the laboratory, she and her team began to look for markets. "We spent months surveying companies from a variety of sectors and investigated the possibility of collaboration," she recalls.

It quickly became clear that the bioengineered cellulose promised to especially benefit the wound healing process. “It completely covers all open nerve ends and continuously cools and moistens the wound,” says Kralisch. The dressing particularly reduces the pain of burns because the material doesn’t stick to the wound and can therefore be easily changed.

> “JeNaCell has evolved into a technology platform”
>
> DR. ANDREAS KARAU, HEAD OF MEDICAL DEVICE SOLUTIONS

DISCOVERY AND EQUITY INVESTMENT

In 2012 the startup was spun off under the name JeNaCell and its activities really took off. “Although there were already many studies about this topic back then, there wasn’t an industrial manufacturing process,” relates Kralisch. “We therefore had to develop a biotechnological process that enables the material to be produced in large amounts.” The first production facility was soon put into operation so that the material could be supplied to the manufacturers of medical products. Kralisch vividly recalls the moment when she received the first report from a hospital that the biotech cellulose had been successfully employed. “To find out that our product really helps patients to heal faster was the best news we could get,” she says.

At this time, the company was also being monitored by Bernhard Mohr. As the head of Evonik’s venture capital unit, Mohr is always on the lookout for innovative startups. The decision in which companies Evonik invests is made according to clearly specified criteria: “The technology has to be innovative and attractive for relevant markets,” says Mohr. “Our confidence in the company’s management team also plays an important role.” JeNaCell fulfilled all of these criteria from the very start. “Because Evonik also has developed extensive expertise in fermentation, it was quickly clear that the startup would fit very well into our portfolio.”

In 2015 Mohr and his team decided to invest in JenNaCell in order to enable a research and growth offensive. The startup intensified its cooperation with Evonik until it was acquired by the latter in the summer of 2021. Since then, the company has been part of the Health Care business line. “JeNaCell has increasingly evolved from purely a manufacturer of wound dressings into a technology platform,” says Dr. Andreas Karau, the head of Medical Device Solutions. The cellulose is now also being used for the dermatological post-treatment of cosmetic surgery and laser treatments. Moreover, the researchers are working on using bacterial nanocellulose in implants.

The material might even carry medication. “It would enable pharmaceutical active ingredients to be transported via the skin precisely to their destination in the body,” says Karau. And all of that is thanks to millions upon millions of bacteria in square glass dishes.

Annette Locher has a degree in biology. She has been working at Evonik since 2012. She writes primarily about health, nutrition, and sustainability

Christoph Bauer is a journalist who works at Evonik’s Communications department

Nicolas Garz is an editor at the Hamburg-based communications agency Bissinger+. He regularly writes about topics from the areas of research, digital technologies, and sustainability

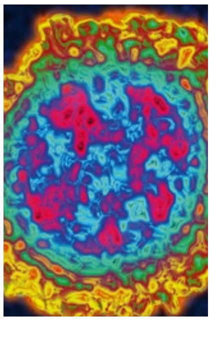
POWERFUL POLYMERS

mRNA vaccines are helping to redirect the course of the pandemic, but their potential reaches way beyond COVID-19. Now Evonik has joined forces with Stanford University to develop a new polymer-based delivery tool that could carve the path for future mRNA applications

TEXT **ELIZABETH HAWKINS**

Two years ago, who could have imagined that people waiting in line at the supermarket might talk about mRNA vaccines? Or that neighbors would compare vaccine side effects over the garden fence? There is no doubt that the world has changed since the pandemic began, but for all the sacrifices and suffering, one technological breakthrough has emerged victorious. Messenger RNA—or mRNA—has sprung to the forefront of medicine thanks to COVID-19 and is now on the path to transform the prevention and treatment of disease.

Alongside water and fat, our body is mostly made up of proteins—the large, complex molecules that are crucial for the structure, function, and regulation of tissues and organs. mRNA serves as an instruction manual for making proteins, which means it is particularly suitable for use in vaccines. An mRNA vaccine produces an immune response in the body by inducing cells to build a protein that would normally be made by a pathogen, like a virus or cancer cell. “The concept of mRNA technology is simple in a very positive way because it allows the body to turn itself into its own drug factory,” explains Stefan Randl, who is the head of research, development, and innovation at Evonik’s Health Care business line.



Influenza
Micrograph of an influenza virus. This disease, like the ones on the following pages, could possibly be tackled by mRNA-based vaccines

COVID-19 has demonstrated a key advantage of this approach: speed. mRNA vaccines can be constructed quickly using only the pathogen’s genetic code. “It takes roughly a week to generate an experimental batch of mRNA vaccine,” explains Randl. “Producing and scaling up is also relatively simple because the technology requires a standard production platform.”

High efficacy—strong therapeutic benefits—can also give mRNA vaccines an edge over others. Another positive aspect is that mRNA does not enter the nucleus of a cell, meaning that there is no risk of it being integrated into the chromosomal DNA and therefore no possibility of creating mutations in the genome.

Perhaps one of the biggest advantages of the technology is the potential to use it to tackle other diseases. BioNTech, the German biotech company that together with the American pharmaceutical corporation Pfizer introduced the first mRNA-based vaccination against COVID-19, recently announced that a cocktail of mRNAs suppressed tumors in mouse models of colon cancer and melanoma. “Our vision is to harness the power of the body’s own defense mechanisms against cancer and infectious diseases,” says Özlem Türeci, the co-founder and Chief Medical Officer at BioNTech. →

“The Stanford activities are a great opportunity for us to get hands-on experience”

PHILIPP HELLER, PROJECT MANAGER OF INNOVATION AT EVONIK

In addition to cancer immunology, scientists around the world are currently working on mRNA therapies for influenza, malaria, Zika, and rabies, as well as autoimmune diseases like multiple sclerosis and genetic diseases like cystic fibrosis.

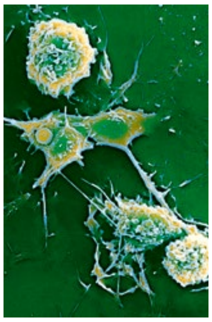
THE DELIVERY PROBLEM

Yet, delivering mRNA effectively and safely into cells to create the desired therapeutic effect is no trivial matter, and is one of the biggest challenges for expanding the use of mRNA therapeutics to promising fields such as cancer immunotherapy, protein replacement or gene editing.

Most pharmaceuticals are made up of small molecules which are more likely to be absorbed and can usually be taken orally. In contrast, mRNA is a large molecule which degrades rapidly when entering the body and cannot easily be taken up into cells. To get around this problem, mRNA needs to be enclosed in a vehicle which protects it from degradation on the way into the cell. Currently, the standard vehicle for mRNA is a protective shield made up of a mixture of lipids, the so-called lipid nanoparticles.

“Lipid nanoparticles have a strong track record of safely encapsulating genetic material including mRNA and delivering this to a target cell or organ site. They are safe, effective, simple to customize, and efficient to manufacture,” explains Andrea Engel who is a director of Research & Development at Evonik. But lipid nanoparticles—also known as LNPs—have some limitations. For example, the drug loading—the content of the active ingredient in a lipid nanoparticle—can be low, which affects the maximum drug dose to be delivered.

“If we are to harness the full potential of mRNA therapeutics, we will need a toolbox of drug delivery technologies to target an expanded range of tissues and organs,” explains Randl. As a leading integrated development and manufacturing partner for advanced drug delivery across the entire pharmaceutical chain, Evonik is ideally positioned to tackle this drug delivery challenge head on.



Multiple sclerosis
Microglial cells (round) are ingesting so-called oligodendrocytes (branched). This is the process thought to occur in multiple sclerosis

AN ALTERNATIVE VEHICLE

Around two to three years ago, a team at Evonik came across a new biodegradable material being developed by scientists at Stanford University. “We identified the importance of mRNA in drug delivery a long time ago and were looking for opportunities in mRNA therapeutics,” explains Engel.

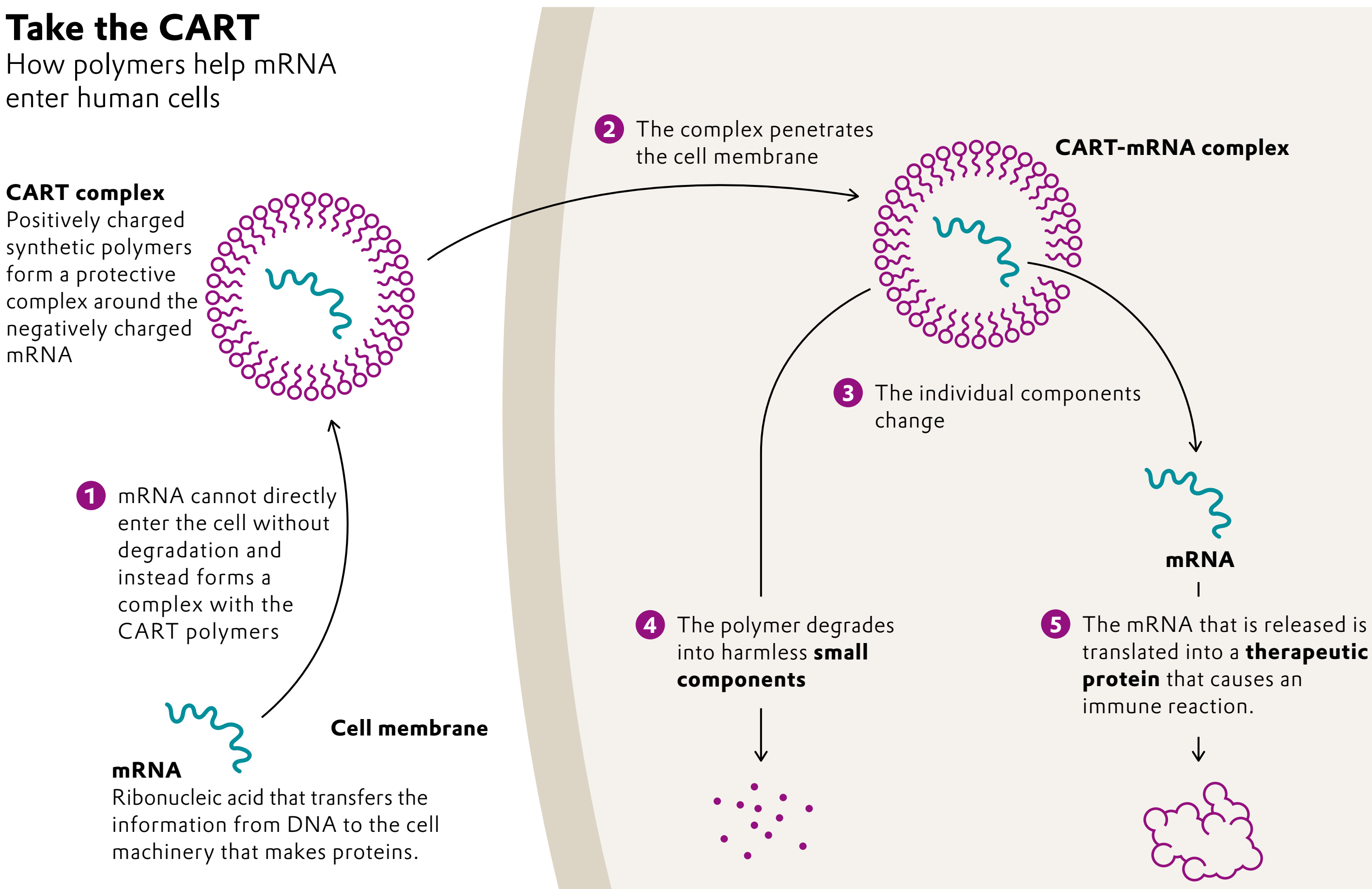
The researchers at Stanford University, led by Drs. Robert Waymouth, Paul Wender, and Ronald Levy, were working on a new class of material for the delivery of mRNA. These materials are synthetic polymers that are positively charged and form a protective complex around the negatively charged mRNA. After delivery to the cell, the polymers then lose their positive charge through a degradation process and degrade into small molecules. “These are a completely new type of polymer. They can be easily synthesized, are stable, and are designed to protect, deliver, and release mRNA,” explains Daniel Crommelin, Professor Emeritus at the Department of Pharmaceutics at Utrecht University in The Netherlands. Crommelin serves on the Scientific Advisory Board for Evonik and was involved in assessing the potential of the new technology before the collaboration began. “Although there are a number of other systems out there, this is an interesting alternative approach to lipid nanoparticles,” explains Crommelin, “Charge-altering releasable transporters” is the name the Stanford scientists chose to give to the new material. The name was shortened to just CART, which, importantly, has nothing to do with the CAR T cells that are used in cancer therapy.

PROMISING SCIENTIFIC PROPERTIES

Evonik scientists began a thorough evaluation of the material to assess its potential as part of the company’s comprehensive drug delivery platform, which includes pharmaceutical excipients such as lipids, formulation development, and the manufacturing of clinical samples and commercial drug products.

Take the CART

How polymers help mRNA enter human cells

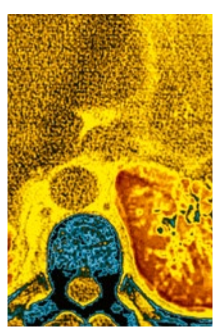


Philipp Heller, who is a project manager of innovation at Evonik, was part of the team that evaluated the technology. First, they examined how efficiently the polymers can encapsulate mRNA, deliver it to the cell, and release it there. “When we did the lab experiments, we got a very high efficiency that was comparable or even better than benchmarks like LNPs,” explains Heller. “This convinced us that these polymers are able to transport mRNA into the cells.” A second important aspect is toxicity. “If you are thinking about future applications in vivo, the polymers should have an acceptable safety profile.” And a third factor is whether a patient will have an allergic reaction against the delivery vehicle—its immunogenicity.

The thorough evaluation process convinced Evonik and Stanford that the collaboration would be fruitful. “A lot of technologies we looked at didn’t meet all three criteria. But with CARTs all three criteria looked promising,” says Engel.

MANUFACTURING CAPABILITIES

Aside from the properties of CARTs themselves, the Evonik team looked at how feasible it would be to manufacture the polymers at a reasonable scale. “In order for the polymers to be attractive to customers as a material, you have to be able to provide a certain amount of material which is sufficient for use in clinical trials,” says Heller. “The first challenge is to get to the scale of several hundred grams instead of just one gram or milligrams.” How well the new technology would fit into Evonik’s existing synthesis capabilities was another important factor. CARTs have a fully biodegradable backbone: as soon as they are injected into biological media they degrade to smaller molecules and are eventually excreted. “From this point of view CARTs fit very well alongside Evonik’s RESOMER® and LACTEL® family of bioabsorbable polymers,” the project manager points out.



Cystic fibrosis
CT scan of the thorax showing respiratory diseases due to cystic fibrosis. This genetic disease affects the glandular epithelium of many organs

Evonik is moving away from focusing on individual products and is increasing its portfolio of system solutions. These are offerings of differentiated products, advanced technologies, and formulation and manufacturing services that are tailored to unique customer needs and often have a strong focus on sustainability.

Indeed, Evonik already provides system solutions at all levels of the value chain including excipients, formulation technologies and services, and clinical and commercial manufacturing services for the advanced drug delivery parenteral market. Adding the CART platform was, therefore, an excellent opportunity to expand Evonik’s portfolio of system solutions. In June of this →

What makes a good collaboration?

Andrea Engel coordinates a diverse team of scientists, technical and business experts working on the partnership with Stanford University. This is her view on cooperations in the field of R&D

INTERVIEW **ELIZABETH HAWKINS**

Ms. Engel, how do you look for promising partnerships?
First of all, we examine the technical potential of a technology and then we look at how it could be commercialized. Of course, the team and culture of our partners also play a critical role. In the example of our collaboration with Stanford University, we were very fortunate to have an open culture early on where we could share ideas. Right from the beginning it was a fruitful relationship where both sides are interested in making great progress. In general we evaluate a lot of technologies and sometimes it can be challenging to find common ground with a potential partner. It is important that everyone is committed and willing to dedicate time. Collaborations don't work if you run them on the side.

What are the main benefits of such collaborations?
At Evonik it is not possible for us to do everything on our own. Although we do R&D, we concentrate our efforts on development and are not usually involved in academic basic research. Collaborating with partners is an opportunity for us to take technologies that are at a certain level of maturity and develop them for commercialization.

And what are the challenges?
Building a trustful relationship between the teams can be a challenge. When working on research it is important not to just share successes, but also talk about failures. There must be a good understanding of roles and responsibilities between the partners and everyone must be aware of the common goals. In the case of our collaboration with Stanford, we have actually never met in person. Due to pandemic restrictions we weren't able to travel, and now we are working virtually. Despite these difficult circumstances we have continued to develop a good virtual team spirit and I have the feeling that we have an excellent team in place and a good relationship.

How important are partnerships like this for innovation?
They are very important for innovation. By working together with partners we can help accelerate research and bring to market what otherwise might have remained in a university. We need to know where the market is heading and which competencies we need to develop to meet our customers' needs in the future. Through partnerships we can bring know-how from a lab into clinics much faster than if we did the whole process ourselves.

year, Evonik entered into a broad agreement with Stanford University to commercialize the technology to include development and scale-up for the CART platform.

PREPARING FOR PRODUCTION

While the Stanford scientists continue to develop new polymers and improve the properties of existing CARTs, Evonik is pushing ahead with manufacturing efforts. "The Stanford activities will focus on further improving the technology or the underlying chemistry and maybe bringing up new candidates in the future, perhaps with other properties or higher efficiency," explains Heller.

"What we plan to do is pick out a model candidate that already has promising properties and start establishing particle formulation and stable processes," he says. "This is a great opportunity for us to get hands-on experience so that when other candidates are available, Evonik will be ready. By having both Stanford and Evonik working in parallel, it will be possible to bring candidates into clinics faster."

Evonik already has the production capacities to start right away. The monomers, which are starting molecules needed to make the polymers, are produced by Evonik's own laboratories or through a network of Contract Manufacturing Organizations (CMOs). In the next step, polymers are then synthesized from the monomers at Evonik's site in Birmingham in the USA, after which the polymers are mixed with mRNA in a controlled manner and filled into vials at Evonik's facilities in Vancouver, Canada.

For clinical trials and commercial products, all these steps must be carried out under Good Manufacturing Practice (cGMP) guidelines and regulations to ensure their safety for use in humans. "You can start with a technical material but in the end if you want to improve people's lives, the product and processes must meet the highest pharmaceutical standards," Heller points out. "Evonik is one of the leading advanced drug

“mRNA technology allows the body to turn itself into its own drug factory”

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

delivery CDMOs with years of experience behind it, and the advantage here is that all these steps will be available within one company.” This view is also supported by a McKinsey survey of 100 organizations from global biotech, pharma, academia, and venture capital, where 70 percent of the respondents said they would prefer support from an end-to-end partner.

RISING TO THE CHALLENGE

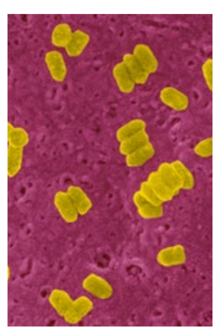
Of course the scale-up will not come without its challenges, but Evonik has successfully taken on such projects in the field of bioabsorbable polymers since the 1990s. One demanding area is related to the polymer specifications. Polymers are molecules that can come in many different lengths. For applications in pharmaceutical products, the specifications must be well defined and represent a reproducible and scalable process. “We have to look at how well the synthesis works and how narrowly defined the polymers are that we get out of it,” explains Heller. Other important challenges include the material purity.

“We also have to think about storage and stability conditions—do we have to freeze it? Is it a liquid or a powder? And how stable is it?” explains Heller. “To establish these polymers as a product we have to look at these factors more broadly than if we were just to synthesize them for R&D purposes,” Heller adds.

LOOKING TO THE FUTURE

Evonik’s collaboration with Stanford is set to run for three years and it has already got off to a good start. Stanford has developed a number of CART molecules that have been published and are suitable for translation into the clinic from a technical perspective.

“In three years, in an ideal world we would like to have fully developed the material along with the manufacturing process,” explains Engel. “We are at the stage where customers see the value of the technology and utilize it in their drug development programs.”



Rabies
Colored micrograph of rhabdovirus particles on the surface of a dying astroglial cell. Rabies is a viral disease that causes acute encephalitis

Although CARTs may have clear advantages over existing LNPs, they are not intended to replace LNP technology. “It’s not an either/or,” she adds. “It is complementary because it opens up new areas in the future.” Engel and Heller both agree that there will be further improvements on the lipids side going forward too.

Crommelin agrees: “There is definitely a need for more effective and active systems to complement the present LNPs. The CART polymers could be a great example of how science works. You see a technology that works and then try to come up with one that is even better.”

In terms of wider application, other classes of nucleic acids such as small interfering RNA (siRNA) or DNA have great potential for tackling diseases. These active ingredients all have the same phosphate backbone and thus comparable chemical and physico-chemical properties. “A material suitable for delivering one type of nucleic acid is most likely suitable for other types of this class of therapeutics,” explains Heller.

For the collaboration with Stanford, the plan is not to stay with one molecule or one candidate, but eventually to offer a library of candidates. “A portfolio of different polymers for different purposes with properties specialized for different nucleic acids” is how Heller sees it. Supplying a toolbox of drug delivery options would be a big step towards fulfilling the promise of mRNA vaccines and therapeutics as the next medical revolution.

Elizabeth Hawkins has a background in chemistry and journalism and joined Evonik in 2021 as a senior scientific editor

“Discuss first, then regulate!”

The molecular biologist and science theorist Martina Schraudner on the need for society to reevaluate the meaning of biotechnology

Martina Schraudner, who has a Ph.D. in biology, heads the Fraunhofer Center for Responsible Research and Innovation, teaches at Berlin Technical University, and has been on the Management Board of acatech – National Academy of Science and Engineering since 2018

The development of mRNA vaccines against COVID-19 has opened the door—it’s time for a revaluation of biotechnology. The fact that bioengineering was used to quickly produce very effective vaccines against the global threat posed by the coronavirus has triggered a rethink among many people, including those in the capital market and in large swathes of the political arena. People are not just debating the benefits and the obligation of vaccination—the label “biotech” is now suddenly seen as the option on fantastic profits, and governments are vying for companies from this sector who are looking to establish facilities in new locations. In these circles, biotechnology firms are, in some cases, even more in vogue than the previous favorites from the IT sector—perhaps, in part, because they combine digitalization with life sciences.

BIOTECHNOLOGY AS A JOINT EFFORT

Ideally, biotechnology can become a joint effort between society and the scientific community—provided its benefits are properly communicated. This could be done, for example, by sharing medical and genetic data so that this knowledge can be used as the basis for customized diagnoses and therapies. Promising steps have already been taken in this direction: the UK Biobank, for example, and its Finnish counterpart FinnGen. These independent digital databases provide researchers with medical information about around 500,000 people. In addition to information about the participants’ size, weight, and blood pressure, they also contain data about genetic sequences. In both systems, the data is supplied voluntarily and is anonymized. These databases have met with a great response. The resulting treasure trove of data has already enabled numerous medical discoveries.

However, as with all innovations, biotechnological progress doesn’t mean that innovations are automatically a good thing. They have to be placed in context and evaluated by society and eventually also regulated. The question is: Which applications do people want and are willing to support? For which ones is there a broad consensus regarding their utility and additional benefits compared to their potential risks? Are there any ethically motivated “red lines”? What should be the background, environment, and goal for the development and use of biotechnologies?

Many people would like to delegate the answering of these questions to governments and regulatory authorities. However, it would be vastly inadequate if the first step were to be regulation.

Every regulation must be developed on the basis of a public discussion process. This is vital if a broad consensus is to be achieved on the key issues. And only such a consensus can provide all of the players in the biotechnology sector with the reliable framework that they need to orient their research and investment activities.

There are numerous current examples that show how necessary such a discussion is. For example, we are still in the very early stages of this discussion when it comes to the methods of high-precision genome editing. Two years ago, the European Court of Justice ruled that genome-edited plants are subject in the EU to the regulations that were previously made for conventional genetic engineering. However, from a scientific point of view, the targeted genetic modification of plants is both more efficient and safer than undirected techniques such as mutagenesis and selective breeding. Although the justices clarified a legal matter within the existing political framework, the scientific basis has since then evolved further so that the legal framework might also have to be reassessed. What our society wants can only be clarified by means of broad-based discussions.

Such necessary debates can only be initiated if there is better communication about biotechnology and, above all, if two classic mistakes are avoided: first, the cultivation of boredom with the subject in order to prevent possible resistance and, second, the attempt to influence people by means of sensationalism, exaggeration, and reduction. Such dead ends are very common in today's communication of technology. Sometimes people will be rather embarrassed and shift uncomfortably from one foot to another as they wish to avoid saying anything that might be unpalatable. They will make use of catchphrases and vague imagery. At other times, they will overdo it with expressions such as "fourth industrial revolution," "technological singularity," and "nanorobots," causing the initially thrilling shudder to turn into a concerned frown. The cloned sheep Dolly and subsequent exaggerations of cloning research are vivid examples of this from the field of biotechnology.

Biotechnology-related communication currently focuses on safety. This was the case, for example, at an event staged by the German government concerning bioeconomics. To address the topic, the responsible PR agency came up with a wide range of colorful communication formats. However, one word was completely missing: biotechnology. "Why is that?" I asked one of the agency's employees. He replied that "the word"—which he avoided saying—"was hard to communicate." As a result, common European buzzwords such as "bioeconomics," "Green Deal," and "farm-2fork" quickly become elusive substitutes for the matter at hand.

BUT WHAT ABOUT "LAB-GROWN MEAT" OR "MEAT ALTERNATIVES"?

Admittedly, the combination of "bio" and "technology" in one word bears connotations. It's therefore not surprising that PR agencies prefer to use images of algae, spider webs, dandelions or sustainable clothing. Many studies and surveys have shown that much depends on the framing, i.e. the use of certain formulations in order to achieve a specific effect. In Germany, for example, this is demonstrated by our representative TechnikRadar study concerning all aspects of bioeconomics. According to the survey, two out of three Germans stated that "lab-grown meat" wasn't a good thing. However, the results are different if you ask people about "meat alternatives."

But you should not think that I'm trying to encourage the excessive blurring of terminology. In the end, such an approach is often more detrimental than beneficial because it distorts people's perceptions of reality. In the TechnikRadar study, many respondents expressed a deep-seated concern about a supposed "alienation from the production of their food." Due in part to the terminology used, a decoupling is taking place between people's perceptions of agricultural production and reality. For example, it is a cultured prejudice that organically grown products are by their nature sustainable, while conventionally grown ones are not. Actually, science and (bio)technology should help to further develop the best features of organic and conventional farming in order to secure humanity's food supply.

NEW WAYS OF COMMUNICATION

Not every biotech innovation can be as important and significant as mRNA technology. However, even every minor innovative success opens up a new opportunity for intelligent and frank communication, even if it's a bit bumpy and unrefined. If the drivers of innovation manage to become approachable and make biotechnology a joint effort, this would clear the way for society's reevaluation of this topic and consequently provide biotechnology with an innovation-promoting regulatory framework. This would benefit mankind as well as the environment.

The communication about new technologies should perhaps not—or no longer—focus only on risk assessment, i.e. the question of the benefits and the possible risks. Perhaps it should rather be asking against what background, in what context, and with what goals the technologies will be used. In view of this, the time is ripe for society to reevaluate biotechnology. The development of mRNA vaccines made its benefits publicly obvious. But change will only be possible if it is communicated more courageously and openly. Statements and clarifications become necessary—without, however, avoiding the discussion about risks.

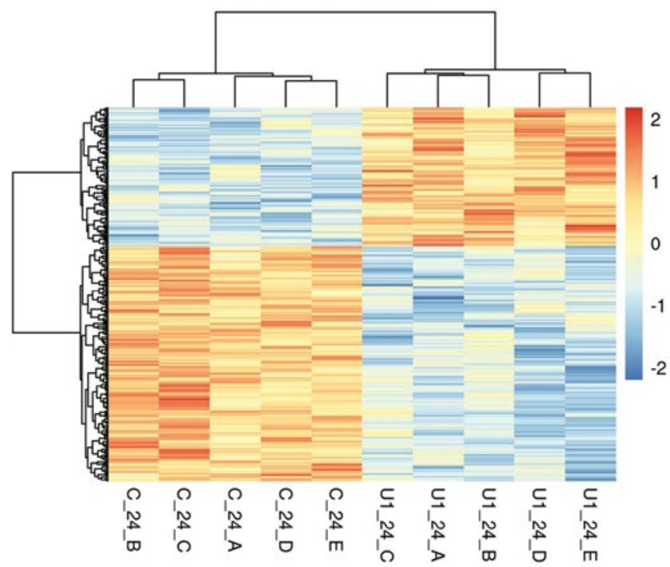
The increasing decentralization of the sector, which is being shaped by exciting startups, is creating a new opportunity for the communication of biotechnology. This structural transformation is being caused by the availability of venture capital, the declining cost of modeling and synthesis of nucleic acids, and the combination of methods from the areas of chemistry, biotech, AI, and Industry 4.0. A flourishing ecosystem of innovative startups has arisen in the food sector in particular. The startups for fermentation, new craft beers, and vegan specialties can be the ambassadors of a biotechnology that promotes diversity and sustainability.

Florian Böhl's research work at Creavis focuses on methylation patterns on DNA that point toward the origin of an individual living organism

THE PATTERN ON THE GENES

How do environmental factors influence genes? The science of epigenetics addresses this question. At Evonik, a team led by Florian Böhl has developed a process that can precisely determine the biological age of chickens

TEXT **SINA HORSTHEMKE**



Environmental influences cause methylgroups to bond to or uncouple from the DNA strand. Depending on their number and distribution, this creates a very characteristic pattern

With its multitude of colored fields juxtaposed in a seemingly chaotic arrangement, the computer monitor of Dr. Florian Böhl looks like a patchwork quilt. In fact, the colored fields on a white background show millions of measurement results obtained from the DNA strand of a chicken. "I used to think that in the field of animal diagnostics everything had already been discovered," says Böhl, who holds degrees in biology and business management and worked in Sweden, Germany, England, and Switzerland before joining Creavis six years ago. At this unit, Evonik is transforming future-oriented technologies into new business activities. "However, after I took a closer look, I discovered the uncharted territories on the map. That activated my natural affinity for scientific research."

The decoding of the human genome 20 years ago was a sensational achievement. It seemed as though every aspect of genes was now known. But that was a mistake. Today it's clear that DNA is not the only factor that determines what a living organism looks like and how it behaves. The organism's environment has an influence on its genes—and thus on its appearance and behavior, as well as the speed at which it ages. This influence is so strong that these changes are passed down to subsequent generations. Scientists call this phenomenon epigenetics.

Some researchers are investigating the epigenetics of human beings, while others are decoding the DNA of crayfish or wild animals. Florian Böhl was intrigued by chickens. Together with his team and colleagues at various locations, Böhl, who is now 49, is decoding the epigenetic patterns of this species. His goal is to develop new technologies at Creavis that help to improve an- →

Evonik uses the infrastructure of the German Cancer Research Center in Heidelberg for some of its methylome analyses. This device reads out chips containing DNA samples

“The way that the environment interacts with the epigenome is a significant element of our understanding of cancer”

PROFESSOR FRANK LYKO,
HEAD OF THE DIVISION OF EPIGENETICS OF THE GERMAN CANCER RESEARCH CENTER

imal welfare, make agriculture more sustainable, and optimize meat production. “Healthy chickens give better meat,” says Böhl. “For that reason alone, the animals should live as well as possible before they are slaughtered.”

IN THE BEGINNING WAS THE CHICKEN

There’s a good reason why Böhl is focusing on chickens: Poultry and pork are the two most popular varieties of meat worldwide. On average, every human being consumes 15.6 kilograms of poultry and of pork annually, but only 9.1 kilograms of beef. In 2019, 25.9 billion chickens were kept as livestock, 80 percent more than in 2000. “People all over the world eat chicken,” says Böhl. “By contrast, it’s hard to sell a pig in predominantly Muslim regions or to sell a cow in India.” An additional factor is efficient feed conversion: A chicken needs much less feed than a cow, for example, to produce the same volume of meat. “Besides, chicken meat is low in fat and healthier than the meat of many other animals,” Böhl adds.

Healthy nutrition is a current trend. And Böhl was already wondering years ago how it could be possible to help shape this trend in livestock farming. But how can we find out how well a chicken is doing at any given moment? By measuring the level of stress hormones in its blood? Böhl believed that would not be sufficiently precise. He thought back to his time at Cambridge University, and suddenly he had an idea. “As a cell biologist, I was investigating how genes could be shut down or activated,” he says. Böhl, who had originally conducted research with yeast and fruit flies, decided to apply the knowledge he had gained to broiler chickens—in the special field of epigenetics.

As early as the 19th century, the French biologist Jean-Baptiste de Lamarck realized that living organisms obviously transmit acquired characteristics to their descendants. Back then, no one took him seriously; this idea contradicted the recently discovered science of heredity, and Lamarck himself could not explain his theory with sufficient plausibility. The concept only picked up speed shortly after the turn of the millennium, when researchers were suddenly able to analyze DNA. Initial studies revealed that the experiences of forebears had an effect on the genes of their descendants. Elizabeth Blackburn, who received the Nobel Prize for Medicine in 2009, was one of the first researchers to investigate the hypothesis that stress alters the genome.

The monitor shows the methylation patterns that provide information about the biological age of an organism

SWITCHES ON THE DNA

Today it's a recognized fact that experiences such as famine, illness, and trauma really do have an influence on the genes. They cause either the attachment or the uncoupling of chemical markers on the DNA strand (see the diagram on pages 44/45). These markers, which are called methyl groups, switch genes on and off, because they provide orientation for the enzymes that are responsible for reading the information in the genome and turning it into physical reality. Depending on whether methyl groups are adhering to the DNA strand or not, the enzymes receive the message "Read this!" or "Don't read this!" The environment does not change the genes themselves, but it does alter the way they are interpreted and thus their activity.

In the field of epigenetics, the aim is not to influence DNA. On the contrary, epigenetics is an observational discipline. Epigeneticists look very closely at the methylation pattern on the DNA—in other words, the number and the distribution of the attached methyl groups. The pattern enables them to infer how environmental influences have changed the genes' activity in the course of a lifetime. Only a few years ago it became clear that the process is dynamic and that it plays a role in the genesis of illnesses such as cancer, for example. Researchers have also realized that there are temporary as well as lasting epigenetic changes. Because the methylation pattern reveals so much about a living organism, scientists call it the methylome or the epigenome, analogously to the genome.

THE ANCESTORS' FAMINE

Epigenetics is known as the link between the environment and the genes. It is the field of biology that deals with a living organism's physical appearance. "We look different at various points of time during our lives—depending on how old we are," says Böhl. "But this cannot be explained in terms of the genes, because they always remain the same. It can only be explained via epigenetics." Epigenetics reveals the biological age of a human being, which depends, among other things, on whether the person has had lifelong healthy nutrition, smoked heavily, practiced sports or frequently drunk alcohol.

Epigenetics also helps to explain why overweight and diabetes are strongly increasing in many countries that used to be underdeveloped. In phases of famine, the individuals who can store energy effectively have the best chances of survival. If sufficient food then suddenly becomes available, their descendants gain weight faster than the average. In animal experiments, the descendants of underweight mice had a higher risk of diabetes even two generations later.

AS CHEAP AS A T-SHIRT

In order to run comparisons of the epigenome of chickens, Böhl's team at Evonik reads out 26 million points from each set of chicken DNA. It sounds complicat- →

Evonik researcher Florian Böhl (left) with his one-time fellow student Frank Lyko from the German Cancer Research Center

ed, but it's not only simpler than previous methods but also much more precise and cost-efficient. "The analysis costs no more than a T-shirt," says Böhl. Nonetheless, the volumes of data are gigantic—they can only be evaluated by an algorithm supported by artificial intelligence. "We derive knowledge from this data and make it possible to gain insights that previously did not exist," he adds. Because DNA cannot be seen by the naked eye, the researchers visualize the chaotic mass of data as a "heat map"—the diagram that looks like a patchwork quilt.

The initial conclusion that Böhl's team reached after analyzing the chicken methylome was only an incidental finding, but it was a scientific sensation. The methylome of the sperm cells showed that in terms of their evolution birds are more closely related to platypuses and echidnas than to reptiles, fishes, and mammals. Conversely, primitive mammals such as the echidna are not as closely related epigenetically with the mammals of today as was previously believed. "We were totally fascinated by this discovery," says Böhl. "It explains why raising chickens is more difficult than raising mammals. It's because the DNA methylation in the germ cells—that is, the sperm and egg cells—functions differently."

AN EPIGENETIC CLOCK

Most importantly, however, the epigenome researchers used the data they had gained from chicken tissue to develop an "epigenetic clock" for chickens. This is how it works: An intelligent algorithm analyzes the methylation pattern on a chicken's DNA, learns related information such as its age or the conditions under which it is kept, and then becomes smarter with every additional data set. If the algorithm is fed with new DNA, it compares this DNA with the knowledge it already has and thus enables reliable statements about aspects such as the origin of the meat. That's because every type of farming leaves behind a characteristic pattern that can be created only in a certain environment.

In addition, the methylome makes it possible to pinpoint the biological age of the chickens. "Nobody has ever been able to do that before with such precision," says Böhl in praise of his team's results. For human beings, with their average lifespan of about 80 years, exact predictions can be made to within three or four years, but Böhl can precisely define what the methylome of his chickens will look like a day and a half from now. That enables him to make precise statements about the condition of the animals. In large populations of animals, this is important information. After all, the health of broiler chickens is crucial for their well-being and ultimately for the quality of their meat.

“It’s important to transform ideas into reality so that they can provide benefits”

DR. FLORIAN BÖHL, HEAD OF DIAGNOSTICS AND NEW BUSINESS DEVELOPMENT AT EVONIK

To make sure that the “chicken clock” could be used as a health check, Böhl’s team analyzed the methylome of chickens with a gut infection. “It showed that the immune system correlated with our measurements,” he says. The inflammatory reaction changes the methylation—and that too is a new discovery. Its main advantage is that this molecular biology tool can be used for every kind of tissue. “We can make the measurement in the animal’s loin, its leg or a part of its gut—on principle, it doesn’t matter where,” Böhl says.

One of the most important partners in Böhl’s far-flung network is Professor Frank Lyko, a former fellow student of his at Heidelberg University, who is now the head of the Division of Epigenetics of the university’s German Cancer Research Center (DKFZ). At some point, Böhl told his former fellow student about the chicken epigenome. Even though at first sight this topic has little to do with research on human cancer, Lyko was interested. The two scientists’ initial joint experiments eventually grew into close cooperation. Böhl uses the infrastructure of the DKFZ, and Lyko benefits from Böhl’s findings.

Today, unlike a few years ago, we know that cancer is triggered not only by mutations in DNA but also by other factors, says Lyko. Now, he explains, it’s clear that “epigenetic mutations on the DNA, which are known as epimutations, also play a role.” Lyko adds that authorization has been received for initial cancer tests based on epigenetic markers, and even for the first medications that work by means of epigenetic mechanisms. “The way that the environment interacts with the epigenome is a significant element of our understanding of cancer, but it’s not easy to investigate it in human beings,” he says. As a result, animal models are playing a major role—especially models of animals that are genetically homogeneous and grow up under standardized conditions, but are nonetheless subject to a variety of environmental factors. Chickens fulfill these requirements.

WHEN DREAMS BECOME REALITY

What Lyko appreciates about his former fellow student Böhl is that he is equally attentive to science and business. “He can conduct scientific discussions at a very high level, and at the same time he’s capable of developing a business idea out of it,” he says. Böhl admits that “something’s always at work” inside his head. He says he’s constantly thinking about possible applications for his areas of work. “It’s important to transform ideas into reality so that they can provide benefits,” says the researcher. And even though it will take some time for the epigenetic clock to be used in the meat industry, he envisions huge opportunities. He says that the long-term goal is to work together with livestock farmers to keep a closer eye on their animals’ health and thus take meat production to a new and more sustainable level. That applies to chicken farming as well as cattle breeders and aquacultures.

Moreover, consumers would be able to receive even better information about fish and meat in the future. Where did this salmon live before it landed on my grill? Was this pig healthy before it was slaughtered? And were these chicken wings really produced as sustainably as the packaging claims? The epigenome reveals something that is more important today than ever before for enlightened consumers: transparency about the food on their plates.

Sina Horsthemke is a science journalist based in Munich. She has a degree in biology and writes primarily about health-related topics

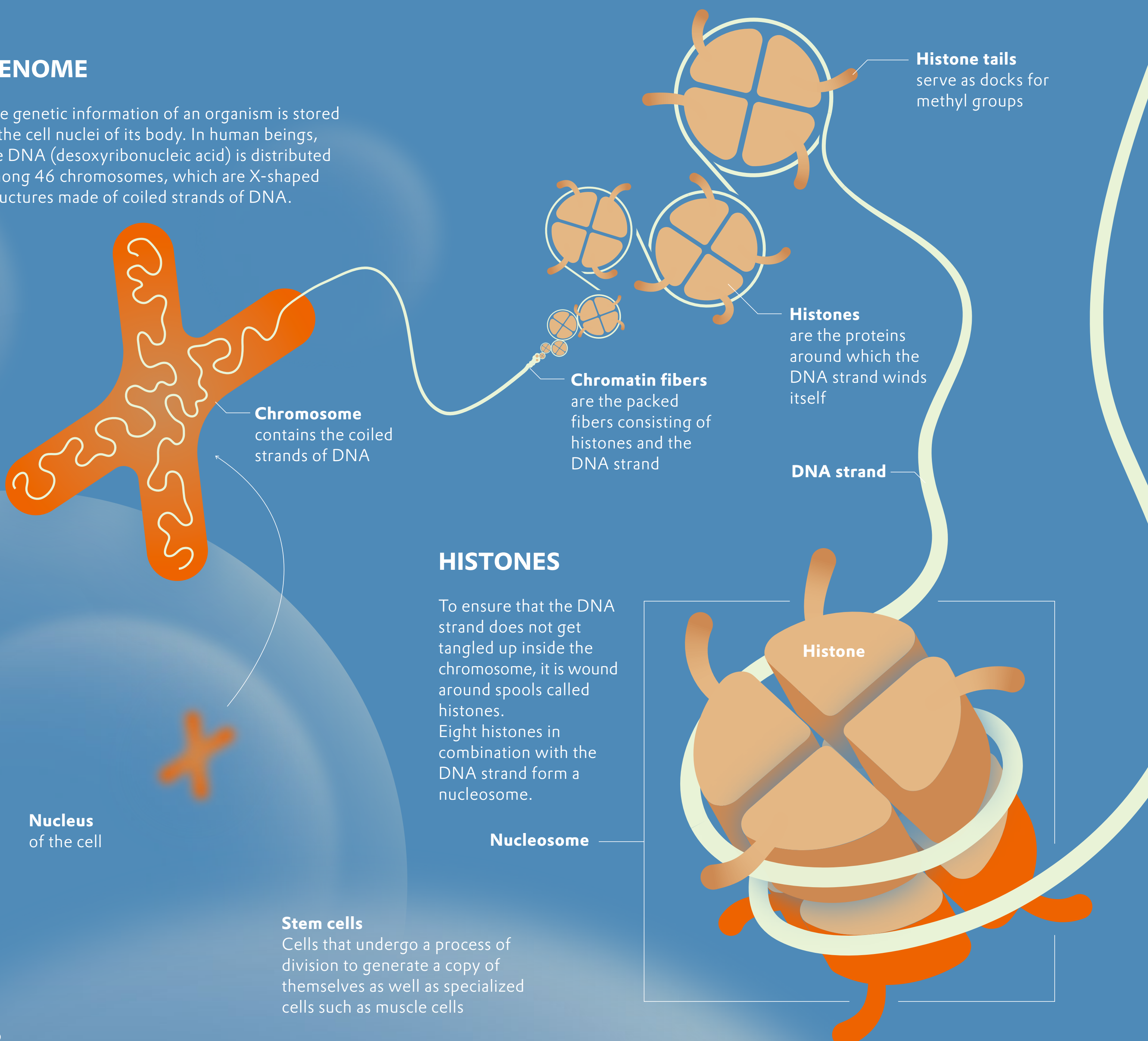
Regulating life

Classical genetics explains how genetic material is transmitted from one generation to the next. However, the environment also has a demonstrable influence on genetic information. Methyl groups that activate or repress individual genes play an important role in these epigenetic mechanisms

INFOGRAPHIC **MAXIMILIAN NERTINGER**

GENOME

The genetic information of an organism is stored in the cell nuclei of its body. In human beings, the DNA (desoxyribonucleic acid) is distributed among 46 chromosomes, which are X-shaped structures made of coiled strands of DNA.

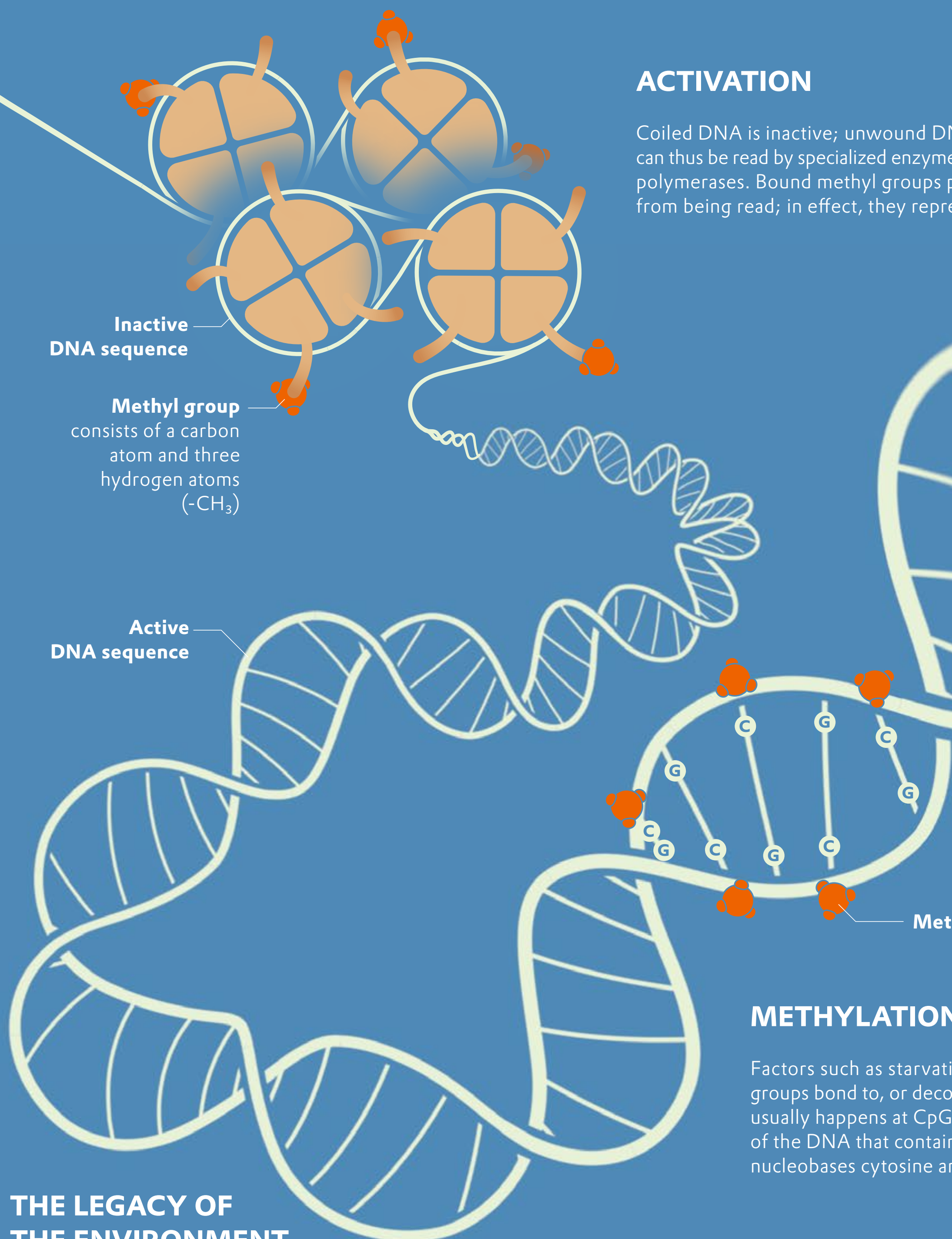


HISTONES

To ensure that the DNA strand does not get tangled up inside the chromosome, it is wound around spools called histones.
Eight histones in combination with the DNA strand form a nucleosome.

ACTIVATION

Coiled DNA is inactive; unwound DNA is active and can thus be read by specialized enzymes called RNA polymerases. Bound methyl groups prevent a gene from being read; in effect, they repress the gene.



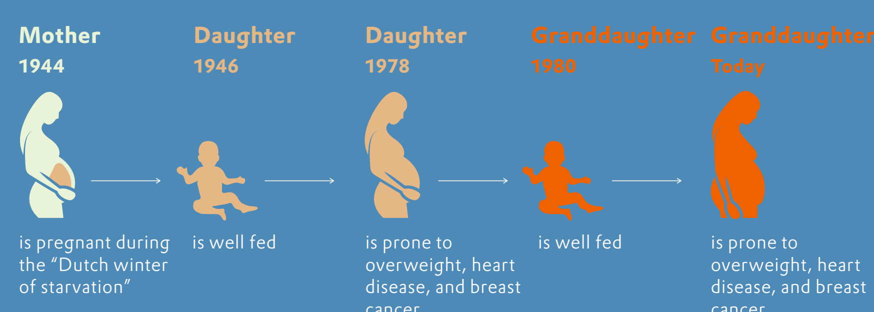
METHYLATION

Factors such as starvation or illness make methyl groups bond to, or decouple from, the DNA. This usually happens at CpG islands, which are regions of the DNA that contain high proportions of the nucleobases cytosine and guanine.

THE LEGACY OF THE ENVIRONMENT

Depending on living conditions as well as the number and distribution of the methyl groups, a very characteristic methylation pattern—the epigenome or methylome—is generated. From this pattern, epigeneticists derive precise information about an organism's biological age, health condition or origin.

The epigenetic imprinting can be transferred to the organism's descendants. If human beings suffer from starvation and their bodies therefore metabolize food with particular efficiency, their following generations may have an increased rate of obesity. This was documented for the descendants of women who had suffered through the "Dutch winter of starvation" in 1944.



Endless Opportunities

The United States of America is a pioneer regarding the major technologies of the future. It's a country that thrives on its innovative power, coupled with the will to reinvent itself again and again. Evonik participates in shaping this continuous process of renewal at many locations

TEXT **NICOLAS GARZ**

New York is a metropolis of superlatives. One World Trade Center and the Empire State Building in Manhattan are among the most famous skyscrapers. New construction is not only going skywards: Little Island at Pier 55, a park on piles that rises above the Hudson River, was opened last May. Its foundation is shielded by PROTECTOSIL®. This Evonik product prevents water from penetrating the concrete piles, thus safeguarding the stability of this unusual public park.

Firefighters sometimes put their lives on the line in order to put out forest fires—such as the Bobcat Fire in Angeles National Forest in California, photographed here in the fall of 2020. The dryness resulting from climate change is causing the increasing frequency of forest fires. Last year alone, 4.2 million hectares of land in California were devastated by forest fires—that's more than four percent of the state's total area. In their battle against the flames, firefighters depend on good protective clothing. High-performance polyimide fibers from Evonik ensure strong resistance. They form a barrier layer that protects against heat, while allowing the skin to breathe.


L.A.Co.F.D.
125

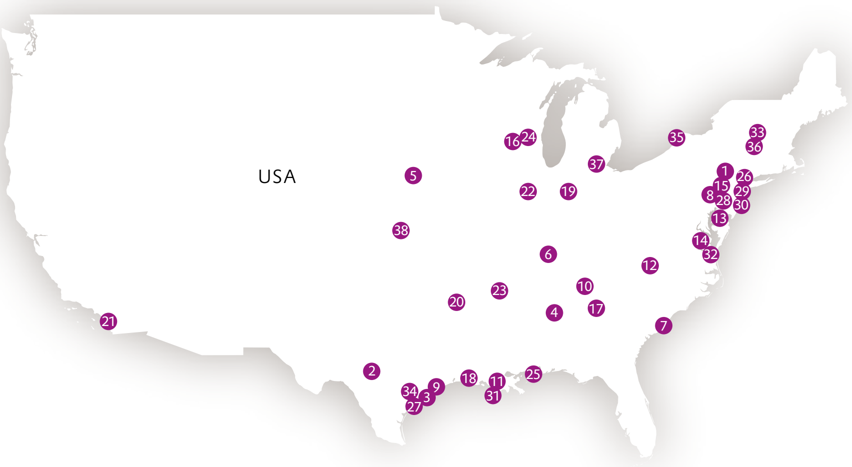
For combating a pandemic, resolute action is required. When the first vaccines against COVID-19 became available in early 2021, the rallying cry in the USA was “Vaccinate as fast as possible—and wherever possible!” So Americans received the lifesaving jabs in supermarkets and football stadiums or directly in their own cars—for example, at this drive-through vaccination center in Orlando, Florida. In addition to vaccines based on traditional methods, mRNA vaccines are also being used. Evonik supplies essential lipid nanoparticles for transporting these vaccines into human cells.

In communities throughout the country's southern states, especially Louisiana, the start of the crawfish season is celebrated with a traditional shared meal known as a "crawfish boil." The crawfish are cooked in a broth based on fresh vegetables and seasoned with a tangy combination of Cajun spices. To make sure the recipe is a success, it's essential that the spices that are used can be stored for a long time. Silicas from Evonik guarantee a long shelf life, and even in small amounts they make sure the spices remain free-flowing instead of clumping together.

Continuing an old Western tradition, cowboys drive their cattle across the dry prairie in Colorado. Neither people nor animals feel bothered by the new wind turbines. Facilities such as these already supply many US households with sustainable electricity. At the same time, the expansion of renewable energy sources is being pushed forward throughout the entire country. Evonik is a supporter of this energy transition “made in the USA.” Adhesion promoters such as DYNASYLAN® improve the rotor blades’ mechanical properties, and the crosslinker VESTAMIN® keeps them robust for a long time. They won’t break even in strong autumn storms.

TOP RANKING

Evonik has more locations in the United States of America than in any other country in the world. For good reason: It supplies products to diverse sectors in the US market, ranging from the pharmaceutical industry to automakers, electrical goods manufacturers, and the agricultural industry. Evonik's US headquarters are in Parsippany, New Jersey, and its biggest plant is in Mobile, Alabama, where the company has operated since the 1970s.



Evonik locations

1 Allentown, PA
2 Austin, TX
3 Bayport, TX
4 Birmingham, AL
5 Blair, NE
6 Calvert City, KY
7 Charleston, SC
8 Chester, PA
9 Deer Park, TX
10 Etowah, TN
11 Garyville, LA
12 Greensboro, NC
13 Havre de Grace, MD
14 Hopewell, VA
15 Horsham, PA
16 Janesville, WI
17 Kennesaw, GA
18 Lafayette, LA
19 Lafayette, IN
20 Little Rock, AR
21 Los Angeles, CA
22 Mapleton, IL
23 Memphis, TN
24 Milton, WI
25 Mobile, AL
26 Parsippany, NJ
27 Pasadena, TX
28 Philadelphia, PA
29 Piscataway, NJ
30 Princeton, NJ
31 Reserve, LA
32 Richmond, VA
33 Saratoga Springs, NY
34 The Woodlands, TX
35 Tonawanda, NY
36 Waterford, NY
37 Weston, MI
38 Wichita, KS

38

locations have

4,600

employees.

Packed with calories: The larvae of the black soldier fly eat almost anything and thus produce lots of valuable protein

ON THE FLY

Can maggots help to save the climate? A growing number of pioneering thinkers around the world are convinced that they can—and are working to develop sustainable products based on insects

TEXT **TOM RADEMACHER**

Four million creatures, densely packed together in dark metal boxes. “Yes, we carry out factory farming,” says Heinrich Katz with pride. In fact, the conditions inside the box are heavenly for the larvae of the black soldier fly that grow here. “They only feel well if they swarm around each other. They need warmth, darkness, and plenty of food,” says Katz. His company, Hermetia Baruth, is based in Baruth south of Berlin. The firm is Germany’s largest breeder of black soldier flies.

These fingernail-size insects have elongated, slim-waisted bodies that make them look more like wasps than house flies. The creatures have become a beacon of hope for protecting the climate and the environment. From nutrition and cosmetics to mobility, the flies and the substances that are made from them are potential sources of benefits in innumerable areas. Another person who is enthusiastic about the black soldier fly is Thomas Häußner. “It turns residues that would otherwise be hardly usable into valuable protein that is ideal for use as animal feed,” he says. Häußner works at Evonik, where, among other things, he is responsible for strategic research and development projects related to animal feed. Since the summer of 2020, Evonik has been working together with the Bioresources division of the Fraunhofer IME in the INFeed research project, which receives funding from the German government and the state of Hesse.

Experts think that there is a bright future for animal feed made from insects fed on leftover food. “The black soldier fly larvae are very quickly growing omnivores,” says Dr. Martin Rühl at the Fraunhofer Institute’s branch facility in Gießen. This makes them interesting as feed for pigs and chickens—and for fish, where they could substitute for fish meal and soybeans.

The use of insects for economic purposes is by no means a new idea. “The silkworm has been cultivated for the past 5,000 years,” says Professor Andreas Vilcinskas, Head of the LOEWE Center for Insect Biotechnology & Bioresources, to which Rühl’s Fraunhofer team belongs. Completely new possibilities are opening up as genomes become more and more decoded. Vilcinskas sees himself as an ambassador for “yellow” biotechnology, which employs insects. He coined the term himself. “There is red biotechnology in medicine, green in agriculture, and white in industry. ‘Yellow’ was still up for grabs.”

Insects have far more species than any other class within the animal kingdom. In fact, around 90 percent of all species on earth are insects. “They have an evolutionary head start of hundreds of millions of years and provide us with an unparalleled library of materials that we are now beginning to access,” says Vilcinskas. Among other things, he is investigating whether insect cells might be used to produce improved antibiotics. One of his studies is titled “Drugs from Bugs.”

Another big topic he is addressing is nutrition. The black soldier fly, or BSF for short, is an inconspicuous critter, which inhabits subtropical regions. It doesn’t sting, bite, pester, or transmit diseases. Moreover, it doesn’t even eat. The adult fly only exists to procreate; it doesn’t even have mandibles. Before the larvae pupate, they therefore store up enough energy for the fly’s two-week existence. That makes them real eating machines—packed with calories. Leftover food, biowaste, excrement, cadavers—they aren’t choosy in their tastes. The larvae can consume almost any organic material except for wood.

INSECT FARMING IS BOOMING

Maggots get fat especially quickly if their feed has an optimal composition. This is where the researchers from Evonik can contribute their expertise because the company has, for almost 70 years now, been producing amino acids for offsetting nutrient fluctuations in animal feed. These amino acids enable chickens, pigs, salmon, and prawns to optimally utilize their feed. “Within the INFeed project, we are responsible for analyzing and optimizing the feed,” says Häußner. These measures are improving not only the feed for the →

Short and nutritious: The male flies are around 14 millimeters long, while the female ones measure 17 millimeters. BSFs are a non-invasive species and do not transmit any diseases larvae, but also the feed that is produced from the larvae for the feeding of other animals.

To this end, samples and experts regularly commute between the laboratory in Gießen and the Hanau Industrial Park, where Evonik has pooled its animal feed expertise. "The right amino acid profile lets us exploit more of the leftover material for the larvae as well as reduce costs and thus produce a competitive protein," says Häußner. This is the only way that the insect feed idea can make insect farming into a successful business.

The market is promising, and insect startups are currently getting hundreds of millions in funding every year from investors. The global market for insect proteins is forecast to grow dramatically between now and 2030: by 5,000 percent to half a million tons of proteins per year. It will still have room for growth even then, because almost five million tons of fish meal and more than 380 million tons of soybeans are produced every year. Overfishing, deforestation, and huge climate-related effects are the result. "Just like our amino acids, insect proteins could help to feed the world's growing population much more sustainably," says Häußner.

"Insects provide us with an unparalleled library of materials that we are now beginning to access"

ANDREAS VILCINSKAS, HEAD OF THE LOEWE CENTER

BIODIESEL FROM INSECT FAT

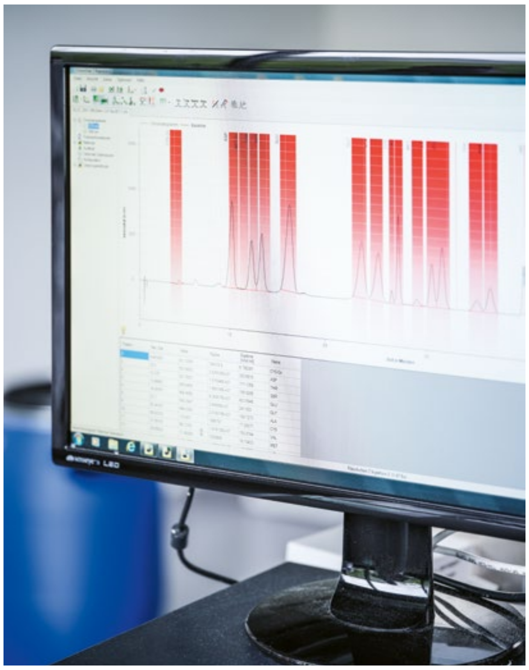
The larvae begin their lives in net-covered "love cages," where thousands upon thousands of flies mate if the conditions are right. The incidence of the light, the temperature, and the humidity all have to be the same as those in the flies' home, the tropics. In Gießen, the love cages are located in a hothouse; they fill a well-heated hall at Heinrich Katz's company in Baruth.

After mating, every female fly lays around 500 eggs, from which larvae hatch two days later and immediately begin to eat. If put on the right substrate, they will grow to 15,000 times their original size within two weeks. As a result, the larvae easily reach a "dressed weight" of 300 milligrams.

A small percentage of the larvae are allowed to pupate so that they turn into flies that can create the next generation. Most are used for production. In the laboratory, the larvae are flash-frozen, after which they are ground into a powder that can be dosed directly into animal feed or broken down into its constituent elements: protein, fat, and chitin. In addition to being used in feed, proteins are also in demand by the chemical and pharmaceutical industries. The same is true of the chitin from the carapace, which can be used to make biodegradable polymers. The fats, meanwhile, can be used by industry to make biodiesel or plastics.

Even the muck from the "maggot stable" is useful. Known as "frass" (a term derived from a German word for "feed"), this contains excrement, cast-off skin and the remains of feed. "Experiments in India have shown that this material can double rice yields when it is used as a fertilizer," reports Vilcinskas.

The final act: The adult flies die after mating in the "love cages" (right). Each female lays around 500 eggs before she perishes



Martin Rühl (left) from the Fraunhofer Institute in Gießen and Thomas Häußner (center) from Evonik check the feed's nutrient profile

So, is everything set for a big revolution in animal nutrition? Not quite, because the feeding of larvae to pigs and chickens has only been permitted in the EU since this summer and only to a limited extent. The ban was a relic from the BSE crisis of the 1980s and '90s. The disease had been caused by the use of processed animal cadavers in cattle feed. After that incident, farmers were no longer permitted to use animal-based proteins in feed. The only exception was the use of fish meal in aquacultures. For decades, experts tried to get the ban lifted because pigs, chickens, and fish like to eat insects when they are outdoors. "Insect protein contains many essential amino acids," says Häußner. "In addition, the soldier fly produces around 50 antimicrobial peptides, which strengthen the animals' immune systems and might thus reduce the use of antibiotics."

LOOKING FOR FOOD IN THE LABORATORY

The researchers are correspondingly pleased that the ban has been partially lifted. However, there is still one obstacle in Europe: Livestock may not be fed waste and the black soldier fly is defined by law as livestock. The situation is different in other countries. The Kenyan startup Insectipro, for example, feeds larvae with 20 to 30 tons of waste per day from the capital city of Nairobi. It sells the larvae to pig and chicken farmers in the surrounding region. Similar projects are also under way in Asia. In some places, the BSFs also consume manure, slurry, and human feces.

The researchers in Gießen are striking out in new directions and trying to exploit food channels that might be approved by the EU. For example, the INFeed project also involves a sweets manufacturer that is looking for ways to use cocoa bean shells. The researchers have also garnered interest in Indonesia, where huge amounts of material from the fruiting heads is left over at palm oil mills. "To date, the fibrous plant material has been either used to generate energy for the mill or simply burned out on the fields," says Rühl. The researchers in Gießen have developed a fermentation process that makes this material edible for the BSF larvae. These larvae would be an almost climate-neutral feedstuff for fish and prawn farmers in Southeast Asia. The frass would be spread on the fields. "The antimicrobial peptides in the feed might also make the shrimps more resistant to disease and reduce the need for antibiotics."

The researchers in Gießen want to demonstrate this benefit, so a shrimp farm is to be built next to the Fraunhofer Institute this year. Located far from the sea, this farm will contain big tanks, where black tiger prawns will eat sustainably produced larvae—the insatiable waste consumers from the dark boxes.

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

THE PRICE OF CHEESE

TEXT **BJÖRN THEIS**

Whether it's Gouda, Emmentaler, mozzarella or Parmesan, cheese is a food that has been eaten daily by many people for thousands of years. It's versatile, durable, delicious, and rich in nutrients. But the way it is produced could change in the future

The world loves cheese—and pays a high price for it. Not only at the market stall or the delicatessen counter, but also in terms of the environment. More than 210 million tons of cheese are consumed annually all over the world. Global milk production accounts for an estimated 2.7 percent of all anthropogenic greenhouse emissions. Besides, for the production of cheese more acreage is needed per kilo of end product than for most other kinds of food. Lots of water—about 5,000 liters—is needed as well. Apart from that, just over a third of all people are able to enjoy eating cheese. The rest of the global population suffers from lactose intolerance. It's high time to find new ways of producing this food more sustainably.

A GIFT OF THE GODS

Human beings' preference for cheese is immemorial. According to one legend, people were offering fresh milk as a sacrifice to the gods of Mesopotamia as early as 3000 BC. This milk remained on the gods' altars for days and was slowly transformed into sour milk cheese. A priest sampled this white mass, was astonished, and concluded that this food must be a gift of the gods. It's probable that cheese was already known during the Neolithic period, about 5500 BC. In what is today Poland, archaeologists have found fragments of a strainer made of clay with traces of fatty acids from milk sticking to it. These residues prove that this household utensil was used to drain off whey for cheese production.

Cheese has been mass-produced at least since the nineteenth century. Back then, the basic research done by scientists such as Louis Pasteur and Justus Liebig revealed the roles played by microorganisms in cheese production and laid the foundation for the industrialization of the process. The basic material of every kind of cheese is casein, a specific mix of proteins that is found in milk. This substance exists in every kind of milk, whether it comes from a cow, a reindeer, a sheep or a goat. With the help of microorganisms, the casein is separated from the watery whey and then processed further to make the various kinds of cheese.

NO MORE MILK

As long as cows are used for casein production, it will be nearly impossible to come to grips with the CO_2 problem. But the good news is that in the future casein could be produced by a different method that is much more compatible with the environment. For example, the US startup New Culture has developed a process for producing casein by means of fermentation—that is, with microorganisms but without any milk whatsoever. The company plans to launch its first product on the market—the first genuine mozzarella that is free of animal products and lactose—in 2023.

The Israeli company Remilk is going one step further in an effort to produce milk without involving cows—also by means of fermentation. The results achieved so far are promising and have even convinced the cheese producer Hochland to invest in the enterprise. The company owners believe that vegan milk is a sustainable alternative to today's raw material. Their production process requires only one percent of the acreage, four percent of the raw materials, and ten percent of the water that is needed for traditional milk production. What's more, in culinary terms their product is superior to "analog cheese," which has for many decades made the expensive ripening process unnecessary due to additives such as palm oil, starch, emulsifiers, and aromatic substances.

SUSTAINABLE NUTRITION

It will be quite a while before the world no longer needs any more cows in order to produce the millions of tons of cheese and billions of liters of milk that we consume. Nonetheless, the market for lactose-free and plant-based milk substitutes is growing by leaps and bounds. According to estimates, the market volume of alternatives to milk will be worth almost US$41 billion in 2026. That's a good reason for the Foresight team at Creavis to conduct deeper analyses of man-made milk and casein within the framework of this year's focus theme, "Sustainable Food Futures 2040." And who knows? Perhaps one day we'll have a plant-based cheese that would even delight the gods of Mesopotamia.

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

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"Carbon is the foundation of life"

Dr. Bernhard Schmid is a professor of plant science at the University of Zurich. In his research he investigates the biodiversity of forests. The photograph was taken in the Sihlwald Nature Discovery Park near Zurich

LOG **KAROLINA FÖST**
PHOTOGRAPHY **SEBASTIAN MAGNANI**

Even when I was a schoolboy, I was fascinated by carbon—an element that can exist as a lump of coal but also as a diamond. A particular feature of carbon is the fact that it has a valence of four. That enables it to form an incredibly large number of compounds, including some that include other elements. That's why carbon is rightly regarded as the element that makes life on our planet possible, in spite of the fact that it's a simple element with a low atomic weight.

In my research I investigate how plants extract carbon from the air in the form of carbon dioxide and transform it into biomass. This process, which is called photosynthesis, is extremely important. It has played a role in the process by which the carbon dioxide content of the atmosphere has decreased from more than 90 percent to less than 0.04 percent in the course of the earth's history, whereas the percentage of oxygen has greatly increased. This caused the protective layer of ozone to form, thus making human life possible.

Carbon accounts for about half of the dry mass of plants—or almost exactly 47.4 percent. In addition, plants account for a larger volume of biomass than any other living things on earth: 450 gigatons out of a total of 550 gigatons. All of the animals on earth put together would weigh only about two gigatons. That's why it's especially instructive to take a look at plants.

The prevailing opinion is still that biodiversity and productivity are mutually exclusive. Yet the opposite is the case. An experiment in China confirmed this for forests. In this experiment we measured how much carbon newly planted trees store in their aboveground biomass over a period of eight years. For a monoculture, it was twelve tons. For a forest with 16 different tree species, it was 32 tons per hectare—far more than twice as much. If a forest stores more carbon, it improves its productivity and stability, but that's not all. At the same time, it helps to reduce the greenhouse gases in the atmosphere.

Interrupting the carbon cycle is simultaneously the greatest problem and the greatest opportunity facing us in the Anthropocene era. By increasing biodiversity, the human race can solve many global problems at the same time: climate change, food scarcity, and environmental pollution.

Masthead

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“The role of the infinitely small…

…in nature is infinitely large,” declared Louis Pasteur, who in the mid-19th century made an important discovery in a contaminated wine barrel: tiny bacteria that produced lactic acid from sugar by means of fermentation. It soon became obvious that microorganisms have a significant impact on natural processes, not only in wine barrels but also in areas far beyond them.

Today Pasteur’s successors all over the world are working to overcome the challenges of our time by means of modern biotechnological processes. *ELEMENTS* presents some of these processes and tells the stories behind biotech innovations.

3/2021 **Biotechnology**