A PRECISE PLATFORM

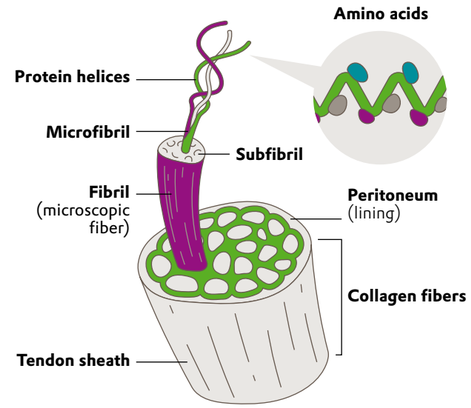
TEXT **JULIA BORN**

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

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

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

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



COLLAGEN STRUCTURE

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

HIGH BIOCOMPATIBILITY

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

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

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

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

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

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

AN INNOVATIVE PRODUCTION PROCESS

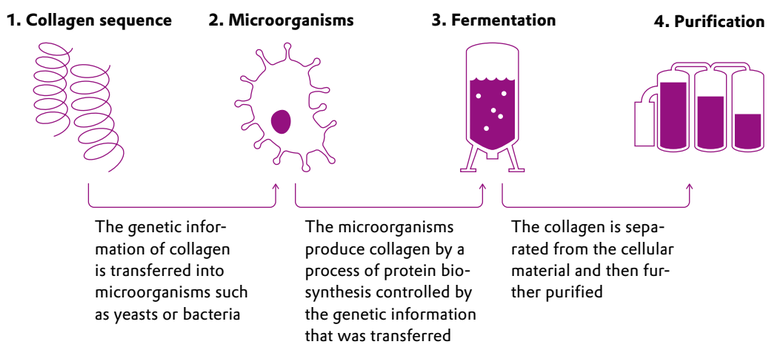
The extraction of animal collagen is being increasingly criticized because it is linked to high emissions of climate-damaging gases and extensive land use. For vegetarians, vegans, and members of a diverse array of religions such as Hinduism, Buddhism, Islam, and Judaism, products from cattle or pigs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

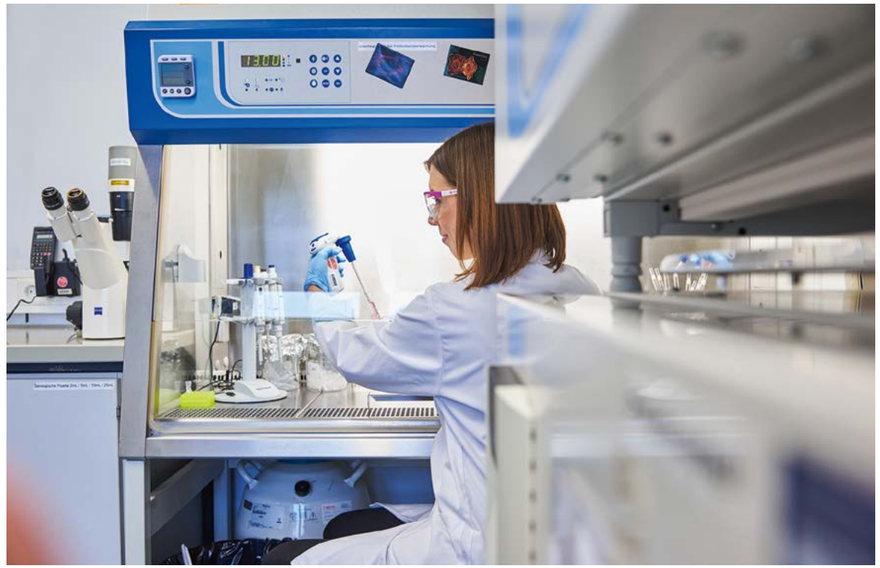
Evonik is meeting these challenges by means of an innovative production process. “Our process completely dispenses with animal starting material and makes it possible to produce an easily soluble and ultra-pure form of collagen that is safe and sustainable,” says Andreas Karau, who heads the Biomaterials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

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

Fermentation is one of the Nutrition & Care division’s core competencies, and one of its growth drivers. Many biotech innovations of the past few years have been based on microbial conversion, and have initiated disruptive developments in their respective market segments. Evonik is a market leader in the area of fermentatively produced biosurfactants, and it is now collaborating with the consumer goods producer Unilever to develop the next generation of completely biodegradable cleaning agents. Another product of fermentation is the algae oil rich in omega-3 fatty acids that was developed by Evonik together with its Dutch partner DSM in the joint venture Veramaris. This oil makes it possible, for the first time, to raise salmon in aquaculture without feeding them with fish oil. This is making fish farming more sustainable and protecting the biodiversity of the oceans.

How collagen is produced by means of fermentation





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

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

IDEAL FOR MEDICAL APPLICATIONS

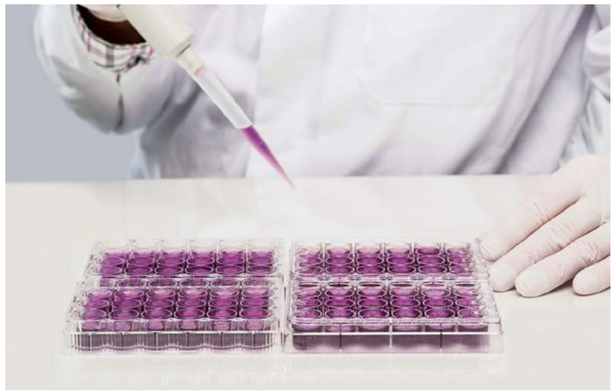
“Biotechnology enables us to develop new products very quickly and produce them on a commercial scale,” says Riermeier. “At the moment, we’re seeing a very dynamic development in the market for fermentatively produced products, and we expect that in the future proteins made via fermentation in particular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

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

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

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

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



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

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

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

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