# **Drug evolution** riding high

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

TEXT **DIRK BÖTTCHER**

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

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

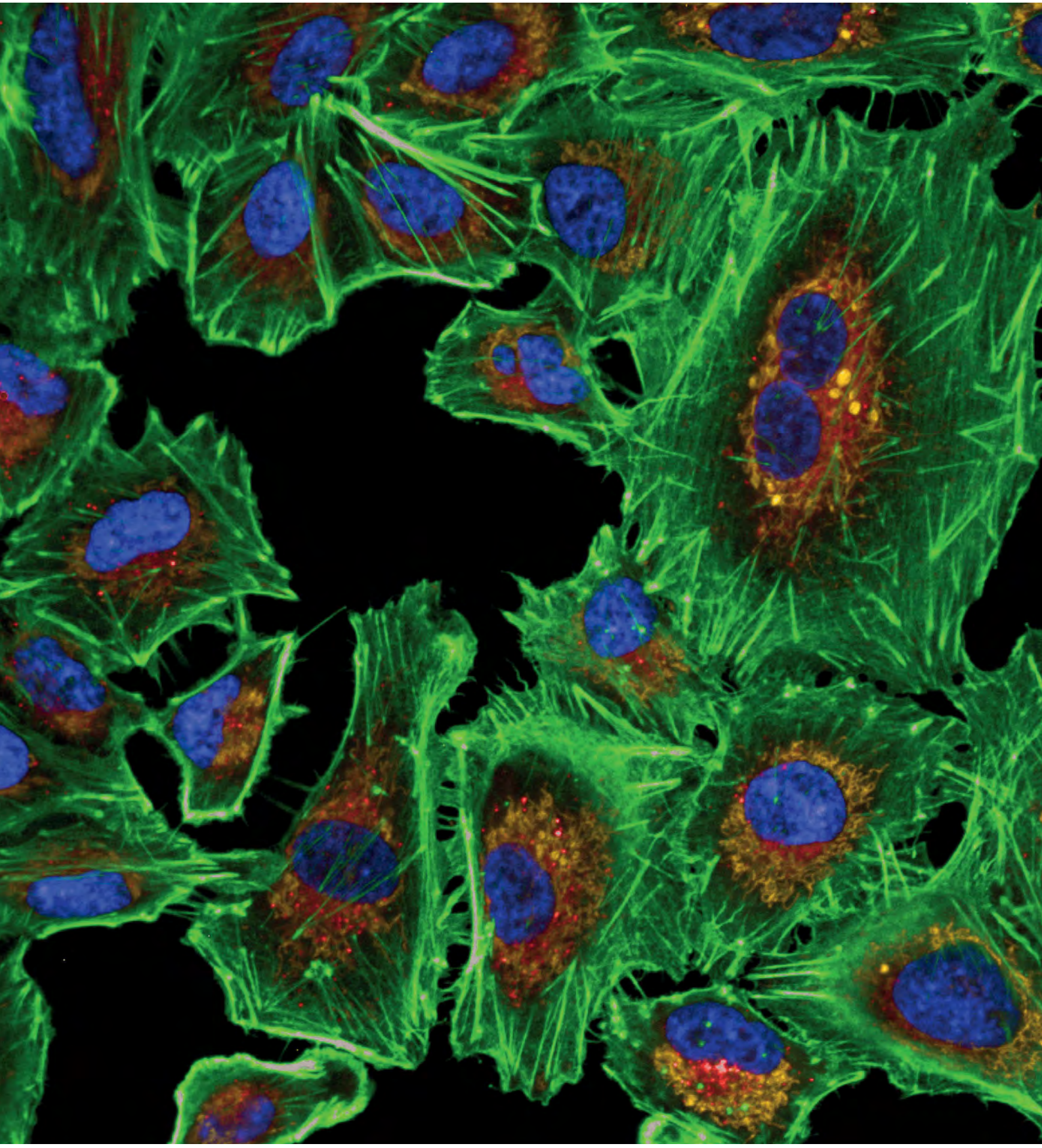
## FOURTEEN SITES, SIX COUNTRIES, 3,000 EMPLOYEES

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

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

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

Photo: Evotec



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

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

## DRUG SCREENING ON AN INDUSTRIAL SCALE

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

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

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

## LOOKING FOR MARKETABLE INNOVATIONS

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

Photo: Inge von Kruse


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

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

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

## FOURTEEN MILLION COMPOUNDS SCREENED IN 2019

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

Photo: Evotec

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

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

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

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


Photo: Evotec

## TESTING ELECTRICAL CURRENTS FOR ANTI-ALZHEIMER DRUGS

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

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

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

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

Werner Lanthaler

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

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

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

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

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

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

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

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

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

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

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

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

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

Interview: Dirk Böttcher

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

Photo: Evotec