



Brake for breast cancer

Researcher or entrepreneur – thanks to **Axel Ullrich**, this is no longer a contradiction for the Max Planck Society: he's both. This is proven by countless publications and honors, two cutting-edge cancer drugs, six start-up companies and over 100 patents. Ullrich, a former Director of the **Max Planck Institute of Biochemistry** in Martinsried has been instrumental in promoting the combination of basic and applied research at the Max Planck Society.

TEXT **HARALD RÖSCH**

To outsiders, it didn't seem like a big deal when the Max Planck Society announced in 1988 that a scientist from California would be transferring to the Max Planck Institute of Biochemistry in Martinsried. But Axel Ullrich's appointment did cause a stir in specialist circles. While he was widely regarded as a brilliant scientist on the one hand, on the other, he had joined the biotech start-up Genentech after completing his doctoral thesis in Heidelberg and a research stay at the University of California. At that time,

Trastuzumab crystals under the microscope. The approval of this antibody against a certain form of breast cancer in 2000 marked a milestone in cancer treatment.

switching sides from academic research to the private sector was still frowned upon in Germany.

CLONING EXPERT

Genentech, which was founded in 1976, had set itself the goal of genetically modifying microorganisms in such a way that these could produce vital proteins for medical research and practice. Back then, Ullrich was regarded among his colleagues as an expert in the isolation of genes and their incorporation into bacterial genomes, a process known as cloning. In 1977 at the University of California, he developed a method that enabled him to transfer a copy of the human insulin gene to bacteria, which then went on to produce the signal substance. This made it possible to produce

human insulin on an industrial scale for the first time: a huge relief for millions of diabetics who had been dependent on animal insulin until then, which is not always tolerated so well by the human body.

As a renowned cloning expert, he was of course very welcome at Genentech where, he joined a group of talented and well-disciplined, although sometimes eccentric, young researchers who set out to revolutionize molecular biology. Anyone who reading the recollections of those involved will, to a certain extent, be reminded of the Silicon Valley computer kids who invented the PC at about the same time.

As a private investor, Ullrich, with his keen sense for a worthwhile research project, first had to lose some of the money he invested: short of cash and desperately in need of a car, he sold his Genentech shares for a few thousand dollars – too soon, as it turned out in retrospect; they would have been worth several million dollars following

the company's IPO. From then on his friends always made joking reference about his "million dollar Volkswagen".

This anecdote symbolizes the care-free spirit of the "wild youngsters" at that time. Yet, it also clearly shows their willingness to dare to do something new and not to allow themselves to be discouraged. They met with considerable resistance, because as brilliant as they were, many of these researchers were stonewalled by their scientific colleagues following their transition from the noble pursuit of academic research to industry.

MOVING INTO THE BUSINESS SECTOR

Fearing that he may no longer be able to get a job in basic research, Ullrich himself initially shied away from switching sides. But he eventually took the risk and never regretted it: he stayed with Genentech for nearly ten years. The company, which was taken over by

the Swiss pharmaceutical giant Roche in 2009, is now regarded as an "elite school" from which countless other biotech start-ups have emerged. For the American science journalist Robert Bazell, Ullrich is an example of how science works: "As so often happens in science the research that led to this breakthrough did not begin with hundreds of scientists working towards a stated goal, but a lone researcher trying to satisfy his own curiosity."

When the Max Planck Society asked Ullrich whether he would transfer to one of its Institutes in the late 1980s, he made his return to Germany conditional, an unusual demand at the time: he wanted to continue to make his research available to medical practice going forward. He had learned in the U.S. that this would only be possible with the support of private companies. Although there were no anxieties about contacts between academic and applied research, this represented a paradigm shift for the Max Planck Society. Its researchers had not been allowed to hold shares in private companies until then for fear of conflicts of interest.

From that point on, Ullrich strove to combine basic and applied science, an approach that has made him one of the ten most cited scientists worldwide throughout the past 25 years, as well as a highly successful entrepreneur whose current companies include Sugent, Axxima, U3 Pharma, Kinaxo, Blackfield and SciMab. He also still holds the record for having registered the most patents within the Max Planck Society.

His career as an entrepreneur began in 1991 when he founded Sugent, which was also the Max Planck Society's first spin-off. The name of the company evokes the names of the founders, Joseph Schlessinger from New York University and Axel Ullrich. Because there was no relevant start-up scene in Germany at that time, the company was



Axel Ullrich carried out his research at Genentech in San Francisco from 1979 to 1988. He and his colleagues transferred human genes to bacteria thus converting them into production machines for novel drugs; a revolution for the pharmaceutical industry.

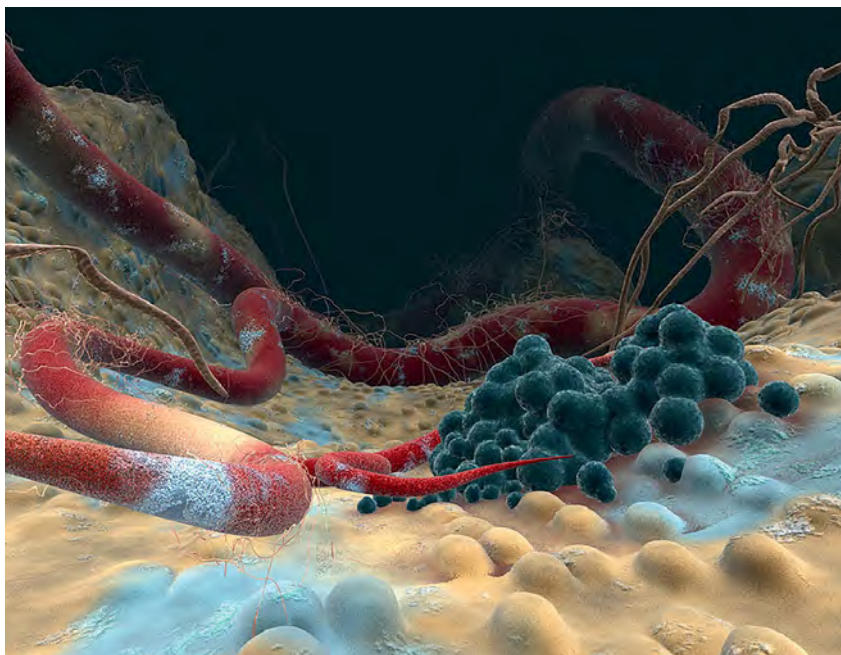
founded in the U.S. It was not until 1993 that Evotec, a company based on technologies developed by Nobel Prize winner Manfred Eigen, became the first German company in which the Max Planck Society purchased shares along with its scientific founders.

The Max Planck Society's knowledge transfer subsidiary, Max Planck Innovation, has been supporting Ullrich's spin-offs right from the start. With Sugen, Ullrich broke new ground for the Max Planck Society, as Jörn Erselius, Managing Director of Max Planck Innovation since 2005, explains: "Contract and investment negotiations, discussions with investors – none of these things had ever existed at the Max Planck Society before. At that time," he continues, "there was still a rule under which a given scientist was only allowed to hold a minor shareholding in a company up to the same number of shares held by the Max Planck Society."

SUCCESSFUL SPIN-OFF

The young Californian company continued its close collaboration with the Max Planck Institute of Biochemistry in Martinsried, which resulted in 30 joint patents, and went on to be extremely successful. The Swedish pharmaceutical giant Pharmacia bought Sugen out in 1999 for USD 650 million and the Max Planck Society received several million euros by selling its shares in the company. The income generated from the license agreement with Sugen now totals well in excess of EUR 100 million, making Sugen its most financially successful spin-off to date. "What Axel Ullrich has shown," Erselius explains, "is that there is no contradiction between excellent basic research and successful applied science."

The secret of Sugen's success was based on so-called receptor tyrosine kinases, receptor molecules that protrude

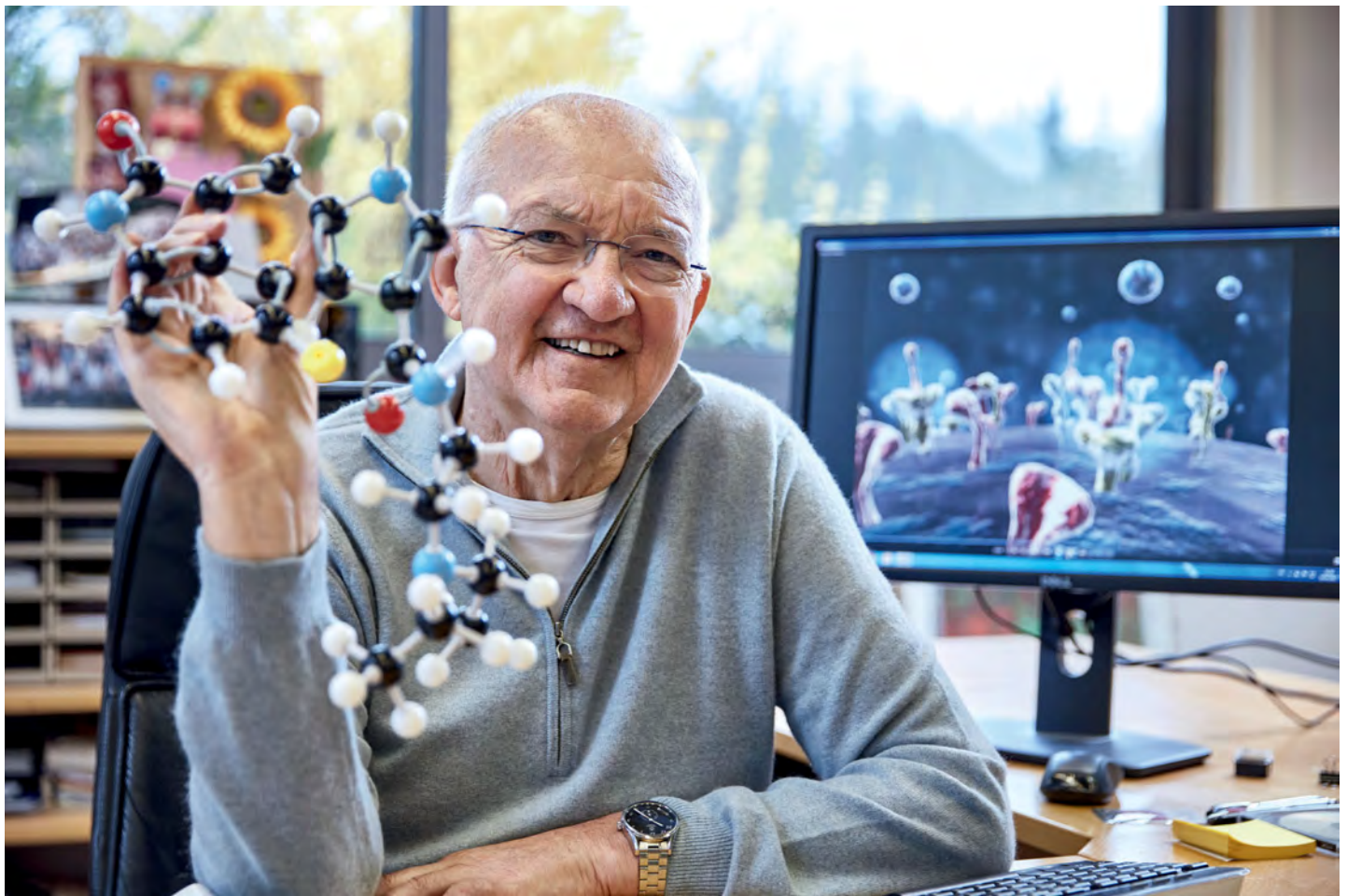


through the membrane into the cell's interior. Whenever a growth factor docks on to the receptor, it transmits phosphate molecules, which activate various signaling pathways that control gene metabolism and other gene activity. When doing this, receptor tyrosine kinases ensure, for example, that blood vessels can grow, which is a prerequisite for the supply of oxygen and nutrients to tumors.

Ever since his time at Genentech, Ullrich has been pursuing the idea that drugs that target these tyrosine kinases may be able to switch off cancer cells and cure the disease. He then went on to study several hundred types of proteins within this family.

The success of this strategy has been impressive: two cancer drugs that target receptor tyrosine kinases, so-called kinase inhibitors, have emerged from his laboratory: Trastuzumab (Herceptin) was approved in Germany for a specific type of breast cancer in 2000, followed by sunitinib, which is sold under the product name Sutent for the treatment of advanced kidney cancer in 2006. Ullrich has received countless awards for his findings. They earned him a place in the European Inventor Award finale in 2017, among other things. He was awarded the highly prestigious Lasker Prize for his discovery in 2019. >

Tumors need a food and oxygen supply via the bloodstream, to which end they release substances that stimulate the growth of blood vessels. Vascular cells can detect these signals with the aid of tyrosine kinase receptors.



Axel Ullrich in his office in Martinsried with a model of the tyrosine kinase inhibitor sunitinib, an active agent that is considered to be one of his most significant discoveries.

Yet tyrosine kinases also play a role in diseases other than cancer. In 1997, Ullrich and Heinrich Kuhn, the then Managing Director of Max Planck Innovation, decided to found another company to investigate these further. This company, Axxima, which is based in Martinsried, focused on the role played by tyrosine kinases in infectious diseases such as AIDS, hepatitis and influenza. The relevant pathogens use these receptors to infect body cells. The intention is to use kinase inhibitors to shut off this gateway. The Company was acquired by GPC Biotech in 2005.

Ullrich founded another company in 2001, his third after Sugan and Axxima, to conduct research into other tyrosine kinases that are involved in cancer. Among other things, the purpose of U3, which stands for Ullrich 3, was to study the "Fibroblast Growth Factor Receptor" (FGFR4) and its role in the development of cancer. From the outset, the company collaborated closely with Daiichi Sankyo, a Japanese pharmaceutical company that acquired U3 in 2008 for EUR 150 million.

By contrast, Kinaxo, which was founded in 2005, has been focusing on a technology developed in Ullrich's lab-

oratories to analyze the targeting accuracy of kinase inhibitors, which is an important building block for the development of cancer drugs with fewer side effects. Kinaxo collaborated with many pharmaceutical companies and was therefore able to make the relevant technology available to other development programs in the field of cancer research. The company was sold to Evotec in early 2011. Ullrich still comes up with ideas and acts as a point of contact for his most recent start-ups, Blackfield (which was sold in 2016) and SciMab, which was founded in 2017.

The turn of the millennium was a goldrush period for the biotech scene. "Back then," says Erselius, "investors were much more willing to take risks than they are today, and raising venture capital was relatively easy." But that was soon to change: when the dotcom bubble burst in 2000 and many venture capitalists lost their investments, the necessary capital also dried up in the field of biotechnology. New start-ups fell by the wayside as developers of novel active agents. Suddenly it had become almost impossible to develop new drugs from laboratory findings.

It was at that point that Max Planck Innovation came up with the idea of the Max Planck Society's Lead Discovery Center (LDC) in Dortmund, which was set up with the aid of several employees from Ullrich's laboratory. As Erselius explains: "Axel Ullrich provided significant support for the foundation of the Lead Discovery Center in 2008 both in terms of his research and his ideas. Once again, he came up with ideas and served as the driving force for knowledge transfer within the Max Planck Society."

FROM THE LABORATORY TO THE PATIENT

The LDC is now an independent company that picks up on basic research findings to develop active pharmaceutical agents, which licensed or collaboration partners test in clinical studies to determine whether they are suitable for use as therapeutic drugs. Ten years after its establishment, the LDC can look back on some impressive results: one of its research projects has managed to make the leap to the clinical stage and is currently being tested in a phase 1b study; two others will be following soon. All in all, the LDC has filed 23 patent applications and granted licenses to collaboration partners to carry out research into 15 additional substances.

One licensed project is based on a molecule called Axl that can block the tyrosine kinase, an enzyme that is overactive in most forms of highly invasive breast cancer. Ullrich had discovered that this kinase has an influence on the formation of metastases. The LDC then identified a molecule that is able to block the Axl kinase and is suitable

for use as an active therapeutic agent. Qurient, a Korean pharmaceutical company, has acquired a license from the LDC to develop the substance and is currently testing it in preclinical trials.

The initial euphoria of cancer researchers has now given way to a certain degree of disillusionment: the kinase inhibitors have not led to the anticipated big breakthrough in spite of the many different research approaches. Although many of these drugs are currently in use, their success in the battle against cancer is only partial. Ullrich was initially convinced that cancer could be defeated during his own lifetime, a prognosis that has sadly not yet been borne out.

It is possible that future cancer treatments will entail a combination of different approaches that can be tailored to individual patients, which may, in addition to kinase inhibitors, involve such treatments as drugs that target other cancer genes and those that switch on the suicide program of cancer cells. The current standard cancer treatment program also includes drugs that stimulate cancer patients' own immune systems to fight tumors.

It is possible that certain forms of cancer will never be completely curable. Rather than hoping for a cure, some cancer researchers are therefore focusing on simply slowing down the progress of the disease to such an extent that patients will no longer suffer the terminal stage of the cancer. In this case, Ullrich and his fellow frontline comrades will have succeeded in achieving something similar to what AIDS researchers had previously accomplished: transforming an acutely fatal disease into one that is chronic but controllable. ◀



Top To thrive, cancer cells need growth factors (blue), which bind to tyrosine kinase receptors (yellow, red) on their surfaces and activate signaling pathways within the cells. Herceptin (brown) blocks the receptors, thus preventing the further multiplication of cancer cells.

Bottom Sutent (orange) blocks a molecule that supplies the tyrosine kinase receptor with energy (green), thereby interrupting the intra-cellular signal transduction. Meaning that the active ingredient can prevent the cancer cells from dividing and block the formation of new blood vessels to feed the tumor.