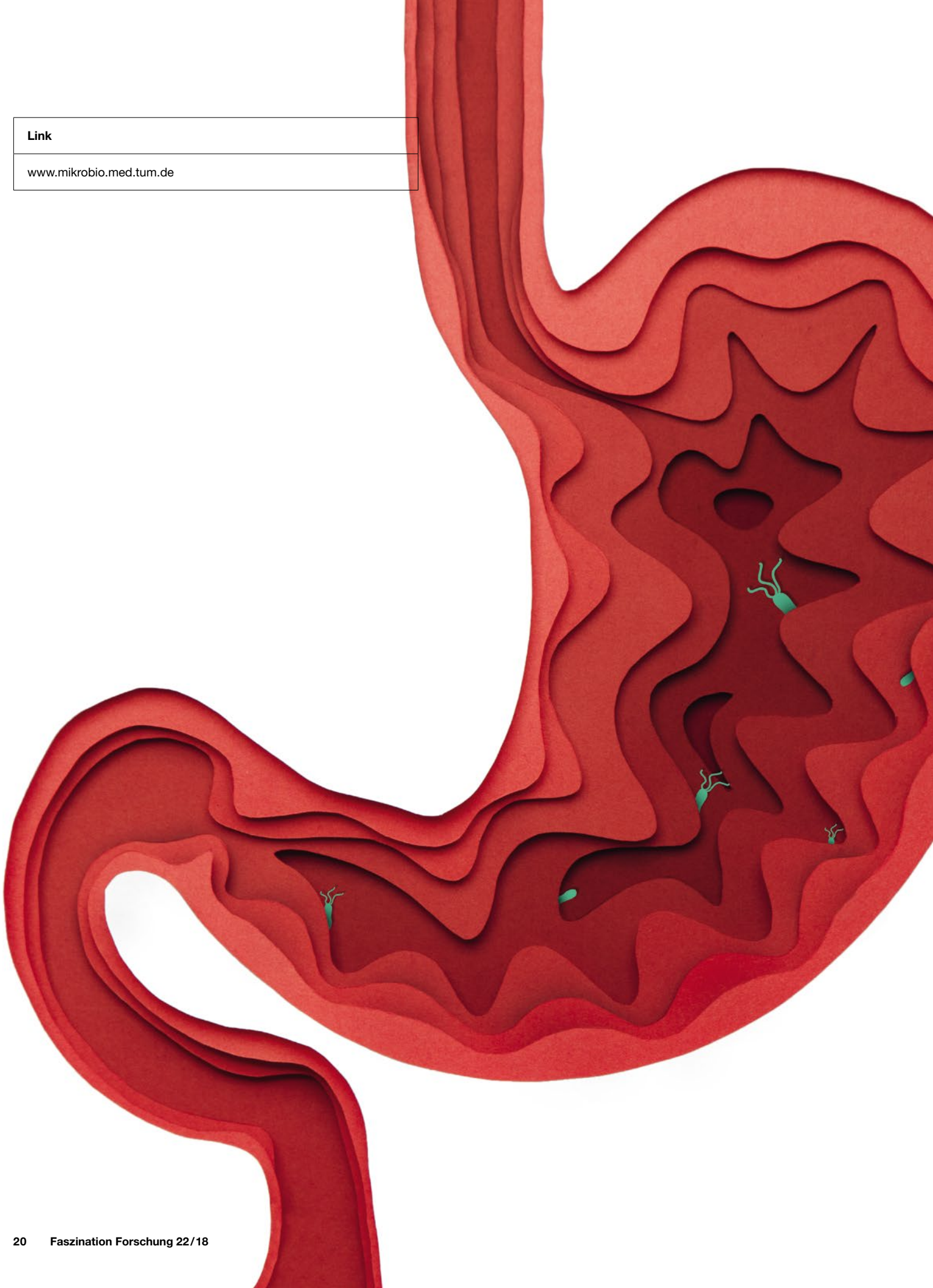


Link

www.mikrobio.med.tum.de





Vaccine against Stomach Cancer

In 2005, when the Nobel Prize was awarded to Barry J. Marshall and J. Robin Warren for the discovery of the stomach bacterium *Helicobacter pylori*, TUM medic Markus Gerhard published an exciting scientific finding. This was intended to pave the way for the development of what would likely be the first vaccine against *Helicobacter pylori*, which causes peptic ulcers and stomach cancer. Nine years later, Gerhard – by then Professor of Medical Microbiology and Immunology at TUM – founded ImevaX. The company is currently running clinical trials (phase I) to test the tolerability of its vaccine. Prof. Gerhard's discovery makes this potential vaccine unique: It disrupts a mechanism used by the pathogen to inhibit the human immune system.

Markus Bernards

Impfen gegen Magenkrebs

Seit Beginn seiner Karriere in der Gastroenterologie beschäftigt sich Prof. Markus Gerhard mit dem weit verbreiteten Magenkeim *Helicobacter pylori*. Das Bakterium kann Magengeschwüre und Magenkrebs auslösen. Zwar gibt es wirksame Antibiotika gegen *H. pylori*, doch zunehmend erschweren Antibiotika-Resistenzen die Behandlung.

Markus Gerhard und sein Team fanden heraus, dass das Bakterium ein Protein absondert, das die menschliche Immunabwehr lahmlegt: Die gamma-Glutamyltranspeptidase, kurz gGT. Diese Arbeiten führten zu einem neuen Ansatz bei der Entwicklung eines Impfstoffs. Markus Gerhard ließ die Zielstruktur patentieren und gründete die Firma ImevaX, die nun den Impfstoff klinisch testet. □



“I wanted to get to the bottom of it!” After a great deal of lab work, Markus Gerhard (left) was finally able to determine why the human immune system is unable to combat *H. pylori* stomach bacteria effectively.

Half of the world’s population is infected with *Helicobacter pylori* – a type of bacteria that was only discovered in the early 1980s. Infection usually takes place during childhood, and the microbes then remain in the stomach lining for a lifetime. While this often goes unnoticed, the bacteria can also cause stomach inflammation (gastritis), peptic ulcers and even stomach cancer. Worldwide, 950,000 people are diagnosed with this type of cancer each year – and in almost 80 percent of cases, *H. pylori* is responsible. The only treatment for infection with this pathogen is a complex combination therapy consisting of two antibiotics and an acid blocker. But even this is problematic: The bacteria are becoming increasingly resistant, so treatment is failing more and more frequently.

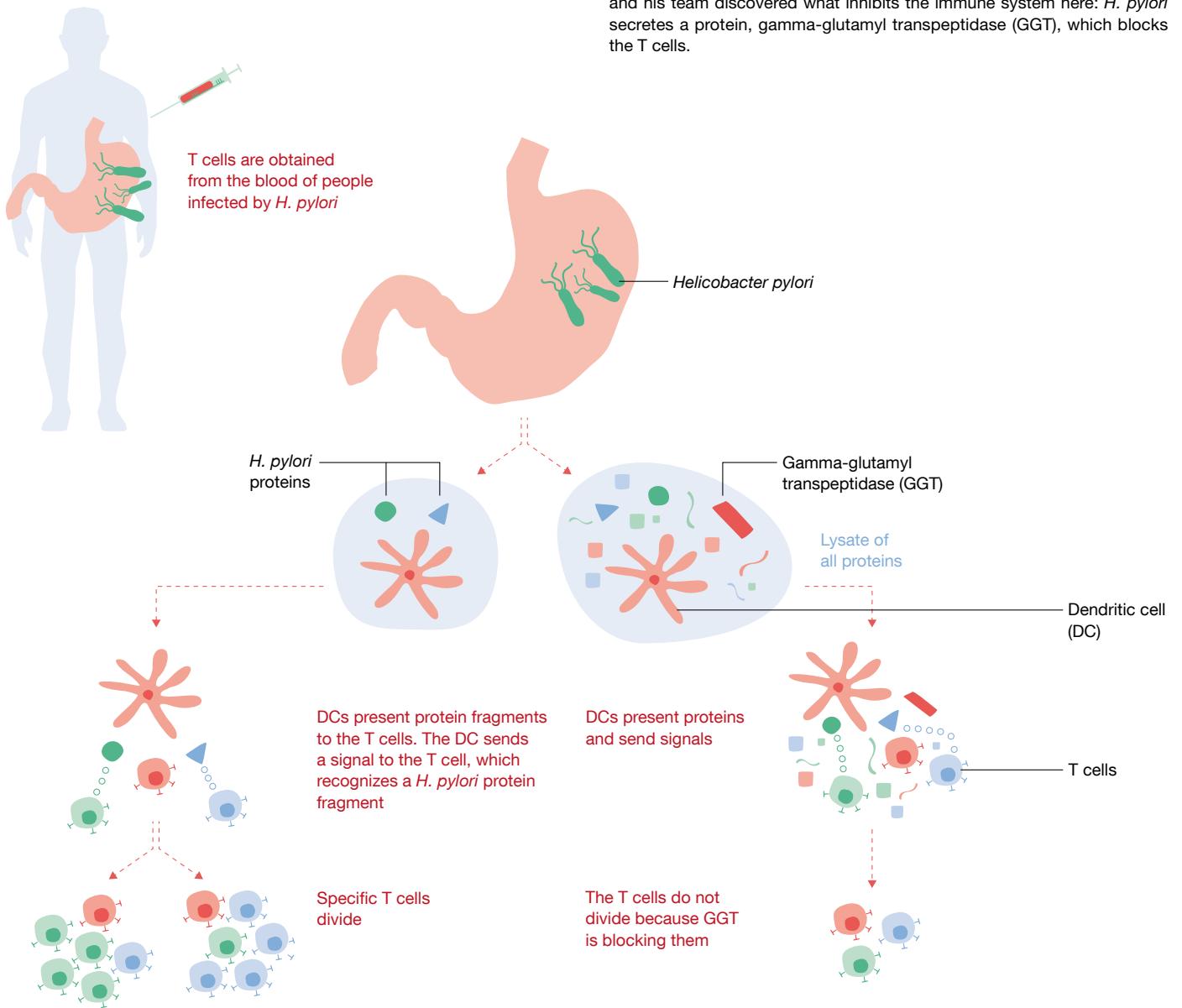
As a doctor, Markus Gerhard became interested in *H. pylori* early on in his scientific career. He was keen to find out how these bacteria trigger inflammation of the stomach lining. Although the human immune system does respond to the pathogen, it is not able to combat it effectively. So Gerhard and his team wanted to see how they could give the immune system a helping hand. How could they vaccinate against this bacteria?

The scientists began by systematically adding single *H. pylori* proteins to specific immune cells, which they obtained from the blood of people infected by *H. pylori*. As it turned out, a whole series of these proteins clearly activated the immune cells. The idea was to intensify this immune response by adding an adjuvant (or boosting substance) to the vaccination. What failed to work, however, was one of the controls, consisting of broken-down *Helicobacter* bacteria (a lysate). This protein mixture was supposed to induce rapid division in specific immune cells, known as T cells. Strangely, the T cells did not react at all – although all the other control experiments worked as expected.

“I want to know what’s up”

“At some point I just thought: this is getting on my nerves; I want to know what’s up,” declares Gerhard. It took four years, but then the scientists had their answer: The bacteria secrete a protein, gamma-glutamyl transpeptidase (GGT), which blocks T cells. “This protein was so effective that the T cells didn’t even react to substances like interleukins, which normally cause them to start dividing like crazy,” recalls Gerhard, clearly still impressed with this discovery.

T cells blocked by protein



Individual *H. pylori* proteins stimulate the T cells to divide, but a lysate of broken-down *Helicobacter* bacteria fails to have this effect. Markus Gerhard and his team discovered what inhibits the immune system here: *H. pylori* secretes a protein, gamma-glutamyl transpeptidase (GGT), which blocks the T cells.

Gerhard and his team worked out just how important the secreted protein is to the bacteria in tests using mice: Bacteria lacking the protein were essentially unable to colonize the stomach lining of the rodents. The professor had thus found a promising candidate for the treatment of *H. pylori* infection: a protein essential to the pathogen. “If we could deactivate this protein either chemically, using an inhibitor, or immunologically through vaccination, we could enable the immune system to respond to the microbe. So that’s how the two application scenarios were born.” Gerhard patented the target structure and published the results in scientific journals. But he had yet to work out how to turn the idea into a vaccine... In theory, he could have granted

a license for the patent or entered into a strategic partnership with a company. But there was a hitch. “Nowadays, you can’t sell a patent that still requires that much development work. The pharma industry wants to see data that will enable it to transition directly to a clinical application.” Additionally, there was no real interest in a *H. pylori* vaccine back then, since the assumption was that the infection could be treated effectively with antibiotics. So Gerhard made up his mind to develop his discovery independently and start a company to secure the necessary funds. The physician was certainly passionate about his project: “I wanted to be in the driving seat myself. This was our baby – we’d figured out the underlying mechanism and I just wanted to take it as far as possible.” ▶

Graphics: edlundsepp (source TUM), picture credit: Jull Eberle/TUM



Researchers in the laboratory were able to identify gamma-glutamyl transpeptidase as the target structure in combating *H. pylori*. This was the starting point for the vaccine, which is now undergoing clinical trials.



Markus Gerhard thus drew up a plan of action and – with the help of a friend from business studies – wrote his first business plan in 2007, which he then took to the Munich business plan competition (MBPW). Not only did he win that competition, he also gained a jury member as a freelance startup coach.

Nevertheless, there was still a long, hard road ahead to get the company up and running. “I had no idea what I was letting myself in for,” Gerhard recollects. “I think I made almost every mistake in the book. Above all, there were many things I underestimated – development effort, timelines and financial requirements.” His initial patent was already a major hurdle:

the newly founded Bayerische Patentallianz (BayPAT) patent agency rejected the application that had the backing of TUM. So Gerhard went on to file the patent privately. “Financially, that was almost the end of me,” he states. “I don’t know if I would ever do that again.” Still, supported by friends and family, it worked out in the end and he subsequently signed the patent over to the newly founded ImevaX, which now holds the rights.

For three years, Gerhard benefited from the Bavarian Science Ministry’s pre-seed funding program. In 2009, he applied for the GO-Bio program run by the German Federal Ministry of Education and Research (BMBF) – and was rejected. “They

“We’d figured out the underlying mechanism and I just wanted to take this discovery as far as possible.”

Markus Gerhard

told us that two parallel approaches – the chemical GGT inhibitor and the vaccine – was too much; we wouldn’t manage this,” he reports. So Gerhard and his team limited their second application to vaccine development only and ultimately received three years of support from GO-Bio, starting in 2011. The next setback could easily have marked the downfall of the project: Gerhard’s team had placed an order with a small biotech company for large-scale production of the vaccine proteins – and that company failed to produce the goods. The money was gone. But Gerhard persevered, reallocating funds with the support of the BMBF to commission a more experienced company. Finally, in 2014, it all came together: ImevaX was launched and, with venture capital and additional funding from the GO-Bio program, the company was able to undertake its first clinical trial (phase 1) to test the tolerability of its potential vaccine in humans.

The company is on the right track

Markus Gerhard was then holding down two “part-time” jobs, working mornings and afternoons as a university professor at TUM, then late into the evening as the scientific director of ImevaX. Or the other way around. “That was certainly a challenging time – and hard on my family too,” he acknowledges. Two years later, with the company on the right track and the phase 1 trial under way, Gerhard’s job there was done and he returned to TUM full time. Despite all the challenges, it was a role he enjoyed – but he also values the freedom that comes with basic science. Building on his experience as a company founder, he now channels the clinical application perspective into his basic research at a very early stage. He is still involved with ImevaX in an advisory capacity and is very eager to see how *Helicobacter pylori* will respond to “his” potential vaccine in humans.

Markus Bernards



Prof. Markus Gerhard

Basic research and clinical application

Markus Gerhard began studying medicine in the German cities of Heidelberg and Hamburg. After receiving his doctorate in 1996, he embarked on his medical career at TUM’s Klinikum rechts der Isar university hospital. From 2004 to 2006, he worked at the Netherlands Institute for Developmental Biology in the research group led by Prof. Hans Clevers. Then, in 2010, he was appointed Associate Professor of Medical Microbiology and Immunology at the Institute for Medical Microbiology, Immunology and Hygiene at TUM.

Gerhard has received several awards in recognition of his scientific and entrepreneurial achievements. In 2007, for instance, he won first prize at the Munich business plan competition (MBPW). He then went on to win the DZIF Prize for outstanding translational research awarded by the German Center for Infection Research (DZIF) in 2015. As the DZIF’s own commendation states: “The development of a *Helicobacter pylori* vaccine is a particularly good example of a successful translational project resulting from closer collaboration between basic researchers and clinicians.”

“The ability to bridge both worlds is what makes this institute so special”

Prof. Dirk Busch, Director of TUM's Institute of Medical Microbiology, Immunology and Hygiene, has founded two companies: STAGE cell therapeutics GmbH and T-Cell Factory B.V. The launch of STAGE Cell Therapeutics was supported by IBA GmbH, which holds a license for the Strep-tag system developed by TUM professor Arne Skerra (see page 62). The products STAGE offers are based on Streptamer technology.



Prof. Busch, you yourself founded two biotech ventures that were bought by major pharmaceutical companies in 2015. What prompted you to start your own companies in the first place?

I still find it fantastic that both of those companies are now “big pharma”. Essentially, the startup route was the only realistic path forward. In terms of the Streptamer technology, it was clear from the outset that our development work was pointing toward the production of a clinical product. And that's a long road, involving cost-intensive manufacturing processes that would be beyond the reach of normal university resources. But with a small company as a partner, you can access additional funds from third parties – for instance the EU or Germany's Federal Research Ministry – which helped us a great deal. In the end, we were able to demonstrate that our concept was clinically feasible and thus pave the way for the acquisition.

What advice would you give prospective company founders?

I would push out the venture capital step as far as possible, because most investors immediately seek a majority stake in the company and can then call the shots. This can jeopardize the flexibility and creativity of startups, since ultimately it's the founders who are passionate about the invention. STAGE spent a long time applying for third-party funding in collaboration with strategic partners (such as TUM) and this meant we were able to stay in control throughout the entire development process, sometimes making decisions over the phone within just a few hours. However, in many cases, it simply isn't possible to do without venture capital – sometimes it's the key success factor. But it is certainly a step to consider very carefully.

Would you start another company yourself?

Yes, of course. At the moment, though, our focus is on the major research programs we are working on with Juno Therapeutics, the company that took over STAGE Cell Therapeutics. But with Markus Gerhard's experience and my own background, we have a very strong startup culture here at the institute. There is a grass-roots awareness that the startup path is always an option. In our daily work, we often come across research findings where we say: “That has product potential.”

With all these product developments, do you still enjoy basic research?

What I especially like is the connection between basic and applied research. At this institute, we leave no stone unturned in the pursuit of basic knowledge – covering everything from crystal structures through complex mouse models to genetic models. At the same time, we are a medical institute, and the basic curiosity that drives us is always linked to a medical or clinical context. This ability to bridge both worlds is what makes this institute so special. We think clinically, but can also take a strong application back to the basic research bench or launch a new company to transition innovative research to clinical practice.

Markus Bernards