Protein Engineering and Design

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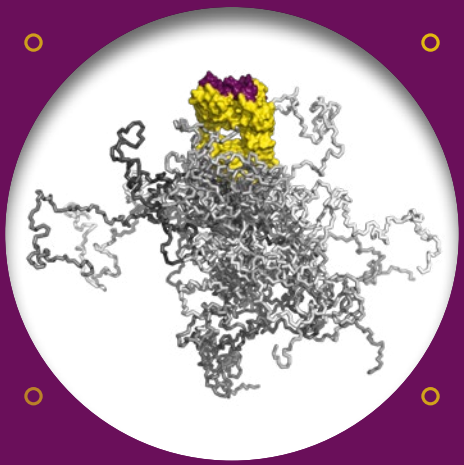
Small Molecules, Big Impact

Arne Skerra is one of TUM's most prominent entrepreneurial scientists. He knows exactly what it takes to create a company spin-off and why a winning streak can sometimes be a double-edged sword.



Graphics: ediundsepp

Prof. Arne Skerra

Pioneering protein design

Arne Skerra holds the Chair of Biological Chemistry at TUM, having been in post since 1998. He is also one of the university's most successful company founders. The protein designer originally studied chemical engineering at the Technical University of Darmstadt, Germany, and was awarded his doctorate (Dr. rer. nat.) in 1989 by Ludwig-Maximilians-Universität München (LMU). His thesis at the LMU Gene Center focused on the genetic engineering of antibodies in the laboratory bacterium *E. coli* – an important invention already at this early stage in his career, which swiftly found worldwide application. Today, Arne Skerra is (co)inventor of more than thirty international patent families.

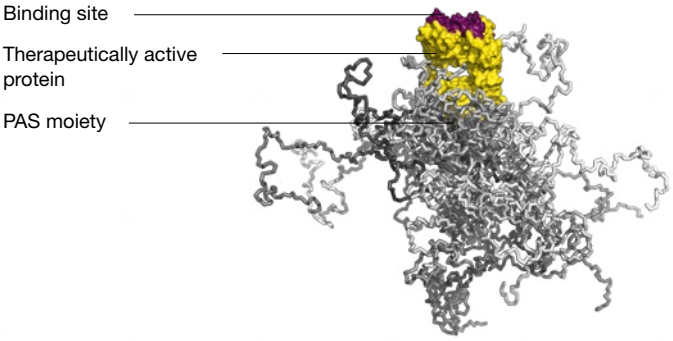
As a postdoc, his career first took him to Cambridge, UK, to the prestigious MRC Laboratory of Molecular Biology. He then returned to Germany as a group leader at the Max Planck Institute of Biophysics in Frankfurt, directed by Nobel Prize winner Dr. Hartmut Michel. He completed his qualification (Habilitation) at Goethe University Frankfurt in 1995 and held a professorship in protein chemistry at the Technical University of Darmstadt from 1994 to 1998. With his appointment at TUM, he established the new Chair of Biological Chemistry at the life science center in Weihenstephan. Thus far, his Chair has been a springboard for two well-known international spin-off companies: Pieris Pharmaceuticals, Inc. and XL-protein GmbH. Skerra is a full member of the German Academy of Science and Engineering (acatech) and a recipient of TUM's Heinz Maier-Leibnitz Medal. In 2005, he was also awarded the Karl Heinz Beckurts Prize for his achievements in applied science.

"You have to have a certain entrepreneurial spirit to steer a startup over all the hurdles on its path." *Arne Skerra*

Brigitte Röthlein

Kleine Moleküle ganz groß

Arne Skerra, Professor für Biologische Chemie an der TUM, ist einer der weltweit führenden Protein-Designer. Immer wieder entwickelten er und sein Team Innovationen auf dem Gebiet der Protein-Biotechnologie, mehrere davon wurden in Ausgründungen vermarktet.
So erfand Skerra beispielsweise ein Verfahren, um die Aufenthaltsdauer von pharmazeutischen Wirkstoffmolekülen im Körper zu verlängern. Dazu konstruierte er eine Kette aus den drei kleinen, natürlichen Aminosäuren Prolin, Alanin und Serin (PAS), die mit dem Proteinwirkstoff gekoppelt wird. Wie ein molekularer Wattebausch umgibt diese das therapeutisch aktive Protein und verhindert so, dass dieses zu schnell durch die Nieren aus dem Blutkreislauf filtriert wird. Diese Innovation wird PASylation-Technologie genannt und kann das bisher übliche Verfahren der PEGylation ersetzen, welches mit einigen Nachteilen behaftet ist. Die Entwicklung führte zur Gründung der XL-protein GmbH durch ein Team um Skerra im Jahr 2009. Bereits acht Jahre zuvor gründete Skerra zusammen mit Weggefährten die Firma Pieris. Im Jahr 2016 ging diese Firma als Pieris Pharmaceuticals, Inc. an die US-Börse Nasdaq. Sie beschäftigt sich mit der Herstellung von Anticalinen, künstlichen kleinen Bindeproteinen, die für verschiedene therapeutische Zwecke nützlich sind. Auch bei dieser Plattform-Technologie, die an seinem Lehrstuhl von den wissenschaftlichen Grundlagen bis zur Anwendung entwickelt wurde, war Skerra der Erfinder.
Eine weitere Ausgründung ist von Skerra und Mitarbeitern für die kommenden Jahre bereits geplant: Diesmal geht es um Proteine, die durch Licht schaltbar sind. □



Like a ball of cotton wool, a chain of the amino acids proline, alanine and serine (PAS) wraps around the therapeutically active protein. This voluminous structure causes delayed kidney filtration – keeping the active substance in the bloodstream for longer.

The idea struck the researcher at a conference in Berlin in 2005. The discussion revolved around ways of making active biopharmaceutical proteins, which usually get excreted quickly by the kidneys, stay longer in the human body so they could better unfold their therapeutic effect. Arne Skerra, Professor of Biological Chemistry at TUM since 1998, first became aware of this issue in connection with his groundbreaking research on Anticalin proteins. Designed by him years before, these biomolecules act like antibodies but are significantly smaller, making them both simpler to produce and easier to distribute inside the body. One option for prolonging their circulation in the blood was a process known as PEGylation. This involves coupling the active protein to polyethylene glycol (PEG), an artificially produced macromolecule (polymer). PEG can be attached to the active ingredient as a highly flexible chain, increasing the molecule's apparent size so that it no longer fits through the fine pores of the kidney and thus remains in the bloodstream for a longer period of time. ▷

Picture credit: Magdalena Jooss/TUM, graphics: ediundsepp, Arne Skerra

"At the Berlin conference, several presentations reported difficulties with production, and, also, there were observations from animal experiments that PEG can accumulate in the kidneys, liver and even the brain, because the body cannot break it down," Skerra remembers today. "Having heard about all these problems with PEGylation, I started to think there must be a more elegant way to resolve this challenge. And the first thing I thought of was replacing PEG with polyglycine." During subsequent laboratory testing, however, it turned out that this design was not ideal. So, in a second attempt, Skerra constructed a biopolymer from a sequence of three other, naturally occurring small amino acids: proline, alanine and serine (PAS). His experiments showed that this biological polymer behaves in a surprisingly similar way to PEG and, when coupled to a therapeutic protein, dramatically prolongs its in-vivo life span. This biological polymer also has the advantage that it can be genetically engineered and produced together with an active protein molecule, and, importantly, it is totally biodegradable.

Dream team – uniting business with technology

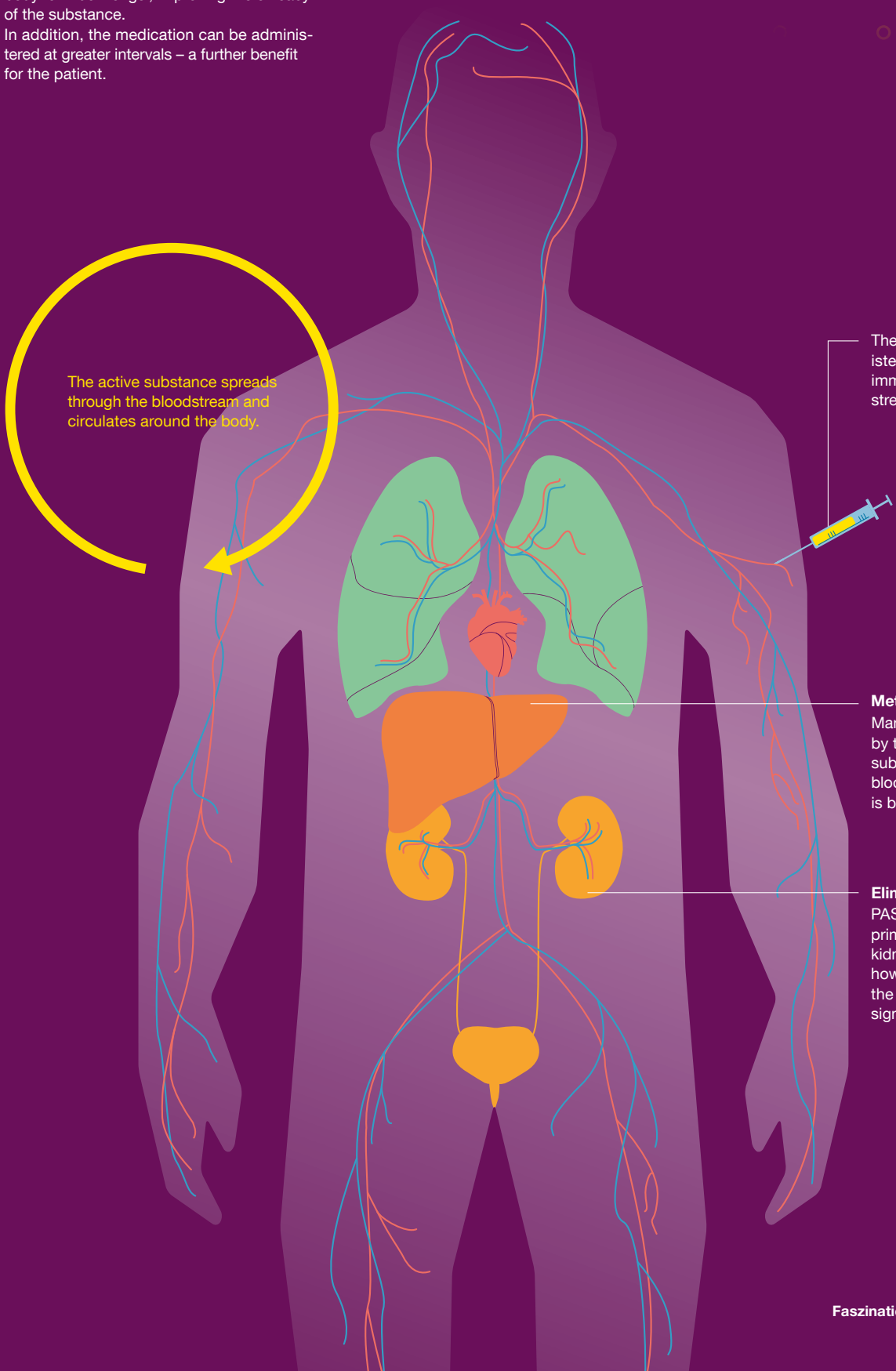
It was evident to Skerra and his co-inventors that this innovative PASylation technology, which was patented through TUM, had significant market potential. Consequently, in April 2009 they decided to start a company for its commercialization: XL-protein GmbH. The company acquired the exclusive licensing rights from Bayerische Patentallianz (BayPAT), the technology transfer office that markets TUM's patents. "XL-protein pays annual license fees, which were moderate at the start and increase over time, reflecting the fact that it takes a while for a new biotech venture to gain a strong financial footing," Skerra explains.

Entrepreneur Claus Schalper has been an important ally and business partner throughout. "The two of us make a pretty good team – as we already saw in the past when we together founded the company Pieris," confirms Skerra. "Besides the technology and finances, psychology plays a very important role when you're developing a company. You have to negotiate constantly – with licensors, investors and potential partners or customers. In our case, a visionary scientist and a business-savvy entrepreneur is a win-win combination." The duo quickly found a pharmaceutical company as a customer in a strong financial position that was interested in XL-protein and its PASylation technology, and the first business project kicked off.

Headquartered in the Innovation and Startup Center for Biotechnology (IZB) in Weihenstephan, the company now employs about ten people. It has concluded a number of cooperation agreements with prominent pharmaceutical and biotech companies keen to leverage the PASylation technology. XL-protein pursues a two-pronged business model. Initially the company constructs PASylated drugs and produces small amounts of test substances for feasibility studies. If these are successful and the partner decides to embark on advancing development, XL-protein issues a sublicense. ▷

Prolonged circulation in the bloodstream

Biopharmaceuticals often comprise small proteins that are quickly excreted from the body. Molecules enlarged with the help of PASylation technology circulate in the body for much longer, improving the efficacy of the substance.
In addition, the medication can be administered at greater intervals – a further benefit for the patient.



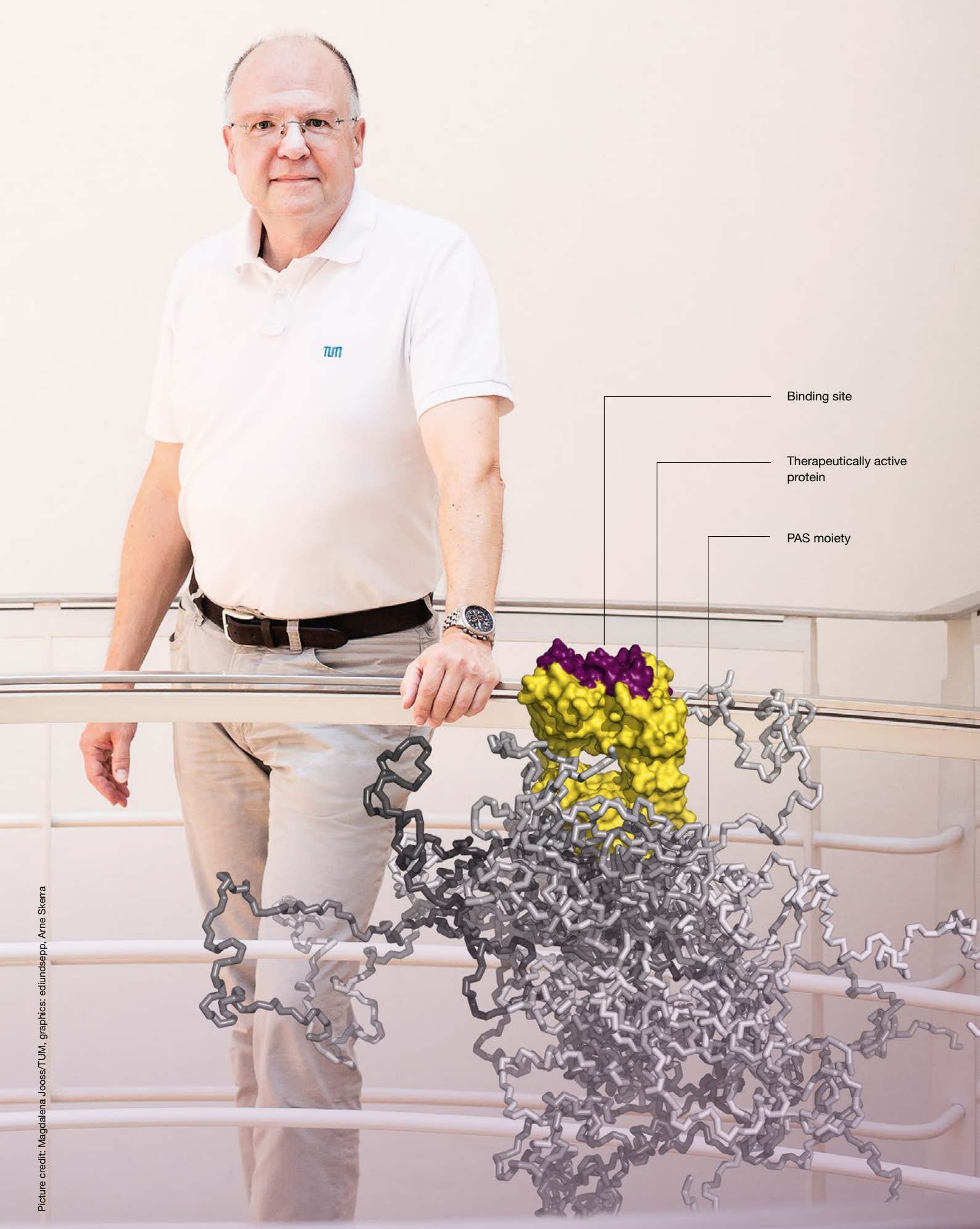
Graphics: ediundsepp (source: TUM)

Arne Skerra is one of the world's leading protein designers. With two successful startups behind him, he is currently preparing for a third.

Competitions and competitive thinking

For the spin-off XL-protein, Skerra was able to draw on experiences gained eight years before, when he founded Pieris to market his Anticalin technology. That venture capital funded company went through various stages and, meanwhile listed on the stock exchange as Pieris Pharmaceuticals, Inc. (Nasdaq: PIRS), now occupies a solid market position.

Although Skerra is passionate about his fundamental work as a researcher in protein science, he is also no stranger to business acumen. "Some find it daunting, but I have always been fascinated by the prospect of thinking research through to the real-world application. Back during my studies at the Technical University of Darmstadt, I was challenged to scale chemical processes to multi-ton quantities. And it goes without saying that cost considerations also influence the application potential," he reflects. "I always had a head for financial figures, and I credit my parents for my awareness of monetary value and sense of economy." ▷



Picture credit: Magdalena Jooss/TUM, graphics: ediundsepp, Arne Skerra

In 2000, when the Pieris spin-off was still in the planning stages, Skerra saw posters about the Munich business plan contest (MBPW) and decided to participate. “Their events offered coaching and advice and it was there that I first found out in detail what a business plan entails,” he recalls. “The MBPW also provided a variety of networking opportunities and, among other things, a bulletin board with a contact forum. That’s how I got to know my co-founder, Claus Schalper, who took responsibility for the commercial and business development side. We were on the same page right from the start.” The four-strong team, including two other scientists, won the first prize at the MBPW in July 2000.

As Skerra sees it, such competitions can certainly be supportive. XL-protein has had its fair share of success in that arena too, including at the Science4Life Venture Cup, where the startup was awarded the first prize in 2010. “That was a key learning experience,” he underscores, “allowing us to talk not only to coaches, but also to investors. At the same time however, I came to see that a winning streak can be a double-edged sword as it can fuel resentment among colleagues and jury members.”

Still, this does not deter Arne Skerra from continuing to ensure promising research results make it to market. Indeed, plans for his next spin-off are already under way. This one focuses on proteins that can be switched on and off by light. The German Federal Ministry for Economic Affairs and Energy (BMWi) is currently funding the research project as part of its EXIST initiative, with the aim of bringing it to market.

Skerra is somewhat hesitant to hand out general advice for young researchers looking to follow in his footsteps, since his position as an established professor and Chair holder means he is not the typical university-based startup entrepreneur. Yet he is quite happy to draw on his experience to help with specific issues. And for him one thing is clear: “You need to have a certain entrepreneurial spirit in order to steer a startup over all the hurdles on its path. And finding the right contacts is crucial – outside but also within the university. I recommend face-to-face conversations if at all possible. That is often the key to finding a successful compromise.” *Brigitte Röthlein*

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