«The greater the obstacles, the more I am fascinated by them»

Everything is interrelated on multiple levels

Andreas Plückthun designs synthetic proteins as therapeutics, for example against cancer. The current European project now supports his important high-risk basic research.

Andreas Plückthun is a designer and a creator. He creates synthetic proteins. To create something new, to build new substances, has fascinated him ever since his adolescent days. Therefore, he went on to study chemistry in Heidelberg. «I wanted to understand how life works and comprehend the chemical and physical processes behind it all,» he says. However, Andreas Plückthun did not merely wish to understand the processes. Instead, he wanted to use the findings for the creation of something new. During his studies, he specialised in proteins and spent seven years in the US, at Harvard University among other institutions, in order to acquire the skills and knowledge of genetic engineering. This field became popular in the early 1980s in the United States, and Plückthun remembers those days clearly: «I worked in an intellectually highly inspiring environment among many visionary researchers.»

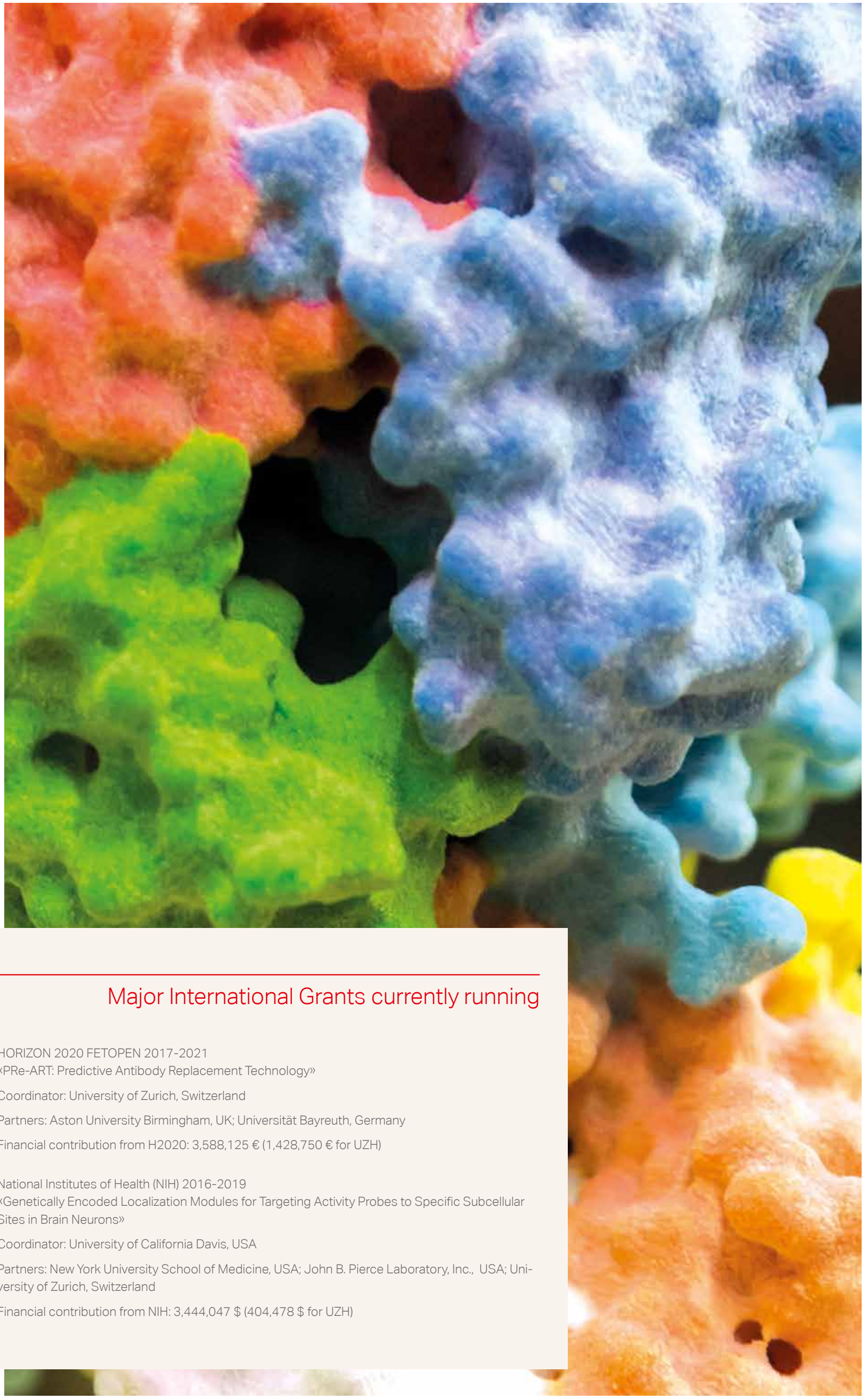
For many years now, Plückthun has been a visionary researcher himself. He is a Professor at the Department of Biochemistry at the University of Zurich, creating synthetic proteins to great success. He has received numerous awards and prizes and has helped to found three spin-off companies over the course of three decades, all three of them developing therapies against diseases on the basis of synthetic proteins. The German biotechnology company MorphoSys, the oldest of the three companies, currently employs 430 members of staff.

Synthetic antibodies and synthetic proteins

Proteins are macromolecules. They are part of the basic building blocks of every cell. In our bodies, there are several hundred thousand different proteins. They are responsible for the cell's structure, but they also serve as molecular machines. They transport substances, such as the blood's iron, they accelerate chemical reactions in the body or slow them down, and, finally, they act as antibodies to fight infections and other diseases.

> Nature is by far a much better creator than myself.

Andreas Plückthun and his team are specialised in the development of synthetic proteins. Creating new protein molecules is done by computer design and by means of the so-called «directed evolution». With this method, the Zurich researchers create simultaneously 100 billion variants of the protein molecules, all of them with small changes (mutations). A few of them then bind tighter to the target molecule - they are enriched, the procedure is repeated and the protein functions increasingly better. «It is our goal to create



Major International Grants currently running

- HORIZON 2020 FETOPEN 2017-2021
  «PRe-ART: Predictive Antibody Replacement Technology»

  Coordinator: University of Zurich, Switzerland

  Partners: Aston University Birmingham, UK; Universität Bayreuth, Germany

  Financial contribution from H2020: 3,588,125 € (1,428,750 € for UZH)

- National Institutes of Health (NIH) 2016-2019
  «Genetically Encoded Localization Modules for Targeting Activity Probes to Specific Subcellular Sites in Brain Neurons»

  Coordinator: University of California Davis, USA

  Partners: New York University School of Medicine, USA; John B. Pierce Laboratory, Inc., USA; University of Zurich, Switzerland

  Financial contribution from NIH: 3,444,047 $ (404,478 $ for UZH)

antibodies and other proteins that exceed the natural properties and may therefore be used as therapeutics,» the biochemist explains. This revolutionary search strategy was developed by Plückthun some 20 years ago and has been the foundation of his research ever since.

Therapeutics against cancer and retinal disease

Synthetically produced antibodies and other therapeutic proteins, developed according to the procedures from the Plückthun Lab, are currently in clinical trials. One antibody (by the name of Guselkumab), developed by MorphoSys against severe psoriasis, was recently approved by the US Food and Drug Administration as a drug. It is administered by injection every eight weeks. Another class of synthetically created proteins, the so-called DARPins, also show great promise in the clinic. One DARPin for curing macular degeneration, a disease of the eye's retina common in old age, was developed by Plückthun's second company - Molecular Partners - and is currently in the late-stage clinical trial phase. Additional cancer treatment drugs are in clinical trials at both companies.

Plückthun and his team practise their research on the Irchel campus of the University of Zurich in a well equipped laboratory, divided into various special rooms on two floors. In one laboratory, for example, human tumour cells are merged with synthetic proteins to test which of the many variants trigger the desired effect on the cells. The labs are equipped with robots; they analyse thousands of proteins within a few minutes.

So, is Plückthun a creator? He laughs and agrees. «Yes, but a poor one. Nature is by far a much better creator than myself,» he adds. «The closer I get to the core of life, the more humble I have become. The interrelationships and interdependencies are becoming increasingly complex the closer you look.» The perfection of nature's interplay will probably never be reached.

Numerous international research projects

Not that he is frustrated about that. «The greater the obstacles, the more I am fascinated by them. The magnificent aspect of my field is that you can, at least in principle, develop agents for all diseases, for instance, that could fight tumour cells or activate the body's own immune system. All you have to do is find out what the rules are and the effects of each agent.»

> Our research is highly complex and we are therefore dependent on the collaboration with other partners with complementary knowledge.

Plückthun is among those professors at the University of Zurich and ETH Zurich who have raised the most European and other international research project funds. One of the reasons for this success is that he regularly participates in open calls - and that he is persistent: If the first attempt fails, he is not discouraged but focuses on the second try. Together with his team, he participated in the grand total of ten projects of the EU's Seventh Framework Programme for Research FP7, the predecessor of Horizon 2020. He explains his commitment by stating that each project generates research funds, important research findings and new contacts. Being persistent is rewarding: At the end of 2017, he was among only eight out of 190 researchers whose project proposals were accepted by one particular call of the Swiss National Science Foundation.

Coordinator of a FET Open project

His persistence also paid off in view of the current EU funding programme Horizon 2020: In his third attempt, Plückthun received a FET Open project as coordinator. These projects are fiercely contested as well; several hundreds of researchers from all across Europe are participating and only four to five percent of them are awarded. There is a reason for the FET Open's popularity: support is given to research projects with a radical vision, with a pioneering technological goal and with ambitious interdisciplinary research. Already in the early stages, FET Open funds these high-risk projects that might well not ever result in social or economic innovations. Plückthun is delighted that it all worked out. The project is a collaboration between himself, his team and the UK's Aston University as well as the German University of Bayreuth; their goal is to develop a new fundamental platform which replaces the conventional antibody technology. Very simply put, the project team plans to create «Lego® bricks» that improve the diagnosis of diseases in the first place and that, afterwards, may be implemented in therapies, depending on the disease. The project is based on an interdisciplinary approach. The researchers of the three universities combine computer design, the experience from cell experiments, X-ray structural analyses, protein engineering and much more. The Zurich lab is responsible, among other things, for designing proteins, for analysing them and for their synthesis. The partner universities, in turn,

will be in charge of other, complementary tasks. «Our research is highly complex and we are therefore dependent on the collaboration with other universities and partners with complementary knowledge,» Plückthun says. This kind of research projects, according to him, has great potential, as all parties involved work intensively on the same questions within a relatively short period of time. «They all have a common goal, are greatly motivated and committed.» Plückthun has acted several times as a project coordinator of consortia; however, it is a first as EU project coordinator. It is yet uncertain whether the researchers will reach their goal in this visionary project. «We know what we want, but nothing similar has ever been attempted before; we therefore do not know whether the molecules that we design and create will eventually function as desired. We do know, though, that if they will - it would have a great impact.»

Participation requests from the United States

The protein specialist has also participated in three projects sponsored by the renowned American National Institutes of Health (NIH), one of them is still running. He did not even apply for this NIH brain research project; the University of California had asked for his expertise in protein engineering and his support. The great reputation of the «Plückthun Lab», as his laboratory at the Department of Biochemistry is called, has been noted in the USA.

He also appreciates the explorative characteristics of these projects. Plückthun considers it crucial that researchers dare to «do without the familiar glow of the lamp» and embark on a journey into darkness, trying something new without having to deliver a predefined product. «Unfortunately, most funds are allocated to research projects with predictable results that are quickly achieved, even though the progress itself is only incremental. The high-risk basic research, by contrast, falls behind.» The unthinkable may only be achieved by explorative research, with much patience and the willingness to take risks.

He believes that the hope placed on genetic engineering for the development of new therapies is great and justified. The development of drugs by means of programmed micro-organisms or cell reactors he deems necessary; however, he considers genome modifications on humans completely irresponsible at this point in time. «We simply do not know enough about the possible consequences, about the interactions and relationships.» During the course of his research, he has become increasingly aware of the fact that everything is interrelated on multiple levels. At first glance, it seems surprising that such a complex organism like a human being is directed by a mere 20,000 genes. «But that is because it is not only the 20,000 genes piloting the organism; they are supported by an inconceivably large number of interactions.»

> If the molecules that we design and create will function as desired - it would have a great impact.

A small mutation to a gene can trigger different effects at completely different locations and levels. «Instead of concentrating on the optimisation of the genome, we should step back and admit in all modesty that we simply know far too little at this stage - all we see is the tip of the iceberg, the major parts are still under water.» Editing the tip of the iceberg irrevocably is a complete taboo for him, but not the continuous research of the entire iceberg. And, as we have seen before: Plückthun is fascinated by the unknown, he is motivated by challenges.

● Denise Battaglia

Interview clip:
www.grantsaccess.ethz.ch/en/sciencestories

Andreas Plückthun

Andreas Plückthun studied Chemistry at the University of Heidelberg and received his graduate education at the University of California at San Diego, where he obtained a PhD. He was a postdoctoral fellow at the Chemistry Department of Harvard University (1982 to 85). From 1985 until 1993, he was group leader at the Gene Center Munich and the Max Planck Institute of Biochemistry in Martinsried, Germany. He was appointed as a Full Professor of Biochemistry at the University of Zurich in 1993. His research achievements include fundamental contributions enabling the emergence of antibody engineering, studies on synthetic antibodies which led to the first fully synthetic antibody library, the development of ribosome display and the development of the Designed Ankyrin Repeat Protein (DARPin) technology. His research remains centred on protein engineering, combining protein design, directed evolution, biophysical basic research and biotechnological applications. In 1992, he co-founded the Munich biotech company MorphoSys AG, in 2004 the Biotech Company Molecular Partners AG in Zurich-Schlieren, and in 2014 the Biotech Company G7 Therapeutics in Zurich-Schlieren (now Heptares Zurich).