Jumping from Postdoc **to Professor**

When Hendrik Dietz returned to Munich in 2009 after his postdoc period at Harvard University (USA), he became one of the youngest professors at TUM. Since then, he has built up the Chair of Experimental Biophysics there. For his work in bionanotechnology, he has received numerous grants as well as Germany's most prestigious research award.

Chair for Experimental Biophysics
www.dietzlab.org/

Picture credit: Astrid Eckert/TUM

Brigitte Röthlein

Der Sprung vom Postdoc zum Professor

Prof. Hendrik Dietz hält seit einigen Jahren die Fachwelt in Atem mit seinen Ideen und Arbeiten zum DNA-Origami. Er konzentriert sich darauf, aus DNA, Desoxyribonukleinsäure, dem Material, aus dem unsere Gene bestehen, „Dinge zu bauen, die noch nie jemand gebaut hat". Die DNA-Moleküle eignen sich gut dafür, denn sie sind kettenförmig, regelmäßig, stabil und in ihren physikalischen Eigenschaften gut verstanden.

Im Jahr 2009 entschloss sich Dietz, aus den USA zurück nach Deutschland zu gehen. An der Physik-Fakultät der TUM erhielt der junge Wissenschaftler eine Professur. „Es war eine harte Zeit", sagt der Professor für Experimentelle Biophysik in der Rückschau. „Ich musste nicht nur schnell Doktoranden finden, Forschungsgelder einwerben und eine Infrastruktur aufbauen, sondern gleichzeitig auch noch Vorlesungen halten."

Beim Aufbau seines Teams half es ihm, dass er im Rahmen zweier Exzellenzcluster Mittel und zudem im Jahr 2010 einen „Starting Grant", eine Förderung des European Research Council, erhielt. Für seine Arbeiten wurde er mehrfach mit Preisen und Stipendien ausgezeichnet, unter anderem 2015 mit dem Gottfried Wilhelm Leibniz-Preis der Deutschen Forschungsgemeinschaft (DFG), dotiert mit 2,5 Mio. Euro.

Heute verbringt der 39-Jährige seine Zeit mehr im Büro als im Labor. Er muss sie jetzt aufteilen zwischen Lehre, Management, Gutachtertätigkeit und der Betreuung seines Teams. „Wir diskutieren dann, wie man Probleme lösen und neue Ideen umsetzen könnte", sagt Dietz. In den letzten Jahren haben er und seine Forschungsgruppe ihr Verfahren weiter optimiert. Gleichzeitig fanden die Wissenschaftler wertvolle grundlegende Einsichten in Eigenschaften von Biomolekülen, etwa in die elementaren Kräfte, die zwischen ihnen wirken.

Neben Anwendungen seiner Nano-Objekte für die Mikroskopie oder die Grundlagenforschung verfolgt Dietz das Ziel, Werkzeuge zum Beispiel für die Medizin zu bauen. Sie sollen bestimmte Aufgaben in Zellen erledigen – etwa pharmazeutische Stoffe zielgerichtet im Organismus verteilen. Kürzlich ist Dietz gemeinsam mit Bioverfahrenstechnikern der TUM die Massenproduktion von DNA-Abschnitten in einem Bioreaktor mithilfe von Kolibakterien gelungen. Damit wird der Weg für breitere medizinische Anwendungen geebnet. □

DNA origami and molecular machines
In 2009, Hendrik Dietz and his colleagues published a paper outlining the method for producing all kinds of nanostructures – including tiny bricks, balls, and straight and twisted ribbons – from DNA, or deoxyribonucleic acid, from which our genes are also made. This became known as 3D DNA origami. DNA chains consist of the four bases adenine (A), cytosine (C), guanine (G) and thymine (T). These can attach to each other, but only in the pairs A-T and G-C. This is the property that Dietz and his team were able to turn to their advantage.
Their technique involves "stapling" single-strand DNA extracted from viruses, referred to as the "scaffold", together with tiny, synthetically produced DNA segments – known as staple molecules – according to a pre-programmed design. Like a puzzle putting itself together, the nanostructures emerge through self-organization – several million at a time. An electron microscope can be used to identify the shape and check all has gone to plan.
With time, the researchers gained more experience manipulating their new building blocks and were able to formulate systematic DNA assembly specifications and store them as a computer program. "We now have a set of rules that can be used to program the tiniest DNA building blocks. You can put them together however you want – almost like Lego," describes Dietz.
This might initially have looked like a game, but was in fact instrumental in advancing the method. Now that this has been established, it serves as a powerful tool to enable the assembly of nanoscale structures. These can then be used as the basis for medical delivery systems or molecular machines. Recently, Hendrik Dietz and Prof. Dirk Weuster-Botz of TUM's Chair of Biochemical Engineering devised a new method to produce large quantities of the necessary DNA segments from *E. coli* bacteria, paving the way for the use of DNA origami on an industrial scale.

Faszination Forschung: When you were appointed to TUM eight years ago, you had just turned 31. What has changed for you since then?

Hendrik Dietz: It's actually hard to believe that eight years have already passed. From a personal perspective, it seems as if not that much has changed, but actually there were many developments. At the outset, I was flying solo in my own small lab with very little in the way of research funding, whereas now I am part of a well-staffed, well-equipped research lab. A lot of ideas and concepts that only existed on paper eight years ago have since become reality. Staff have come and gone – the lab already has alumni – lab traditions have evolved, and we have developed our own lab culture.

▷

Intuitive design: A computer program with a graphical user interface enables rapid and simple development of three-dimensional nanostructures. These shapes are then converted into strands of DNA base pairs.

Picture credit: Astrid Eckert/TUM

"In the past, I saw research as more of a lone wolf activity, but now we work in teams to tackle more complex challenges."

Hendrik Dietz

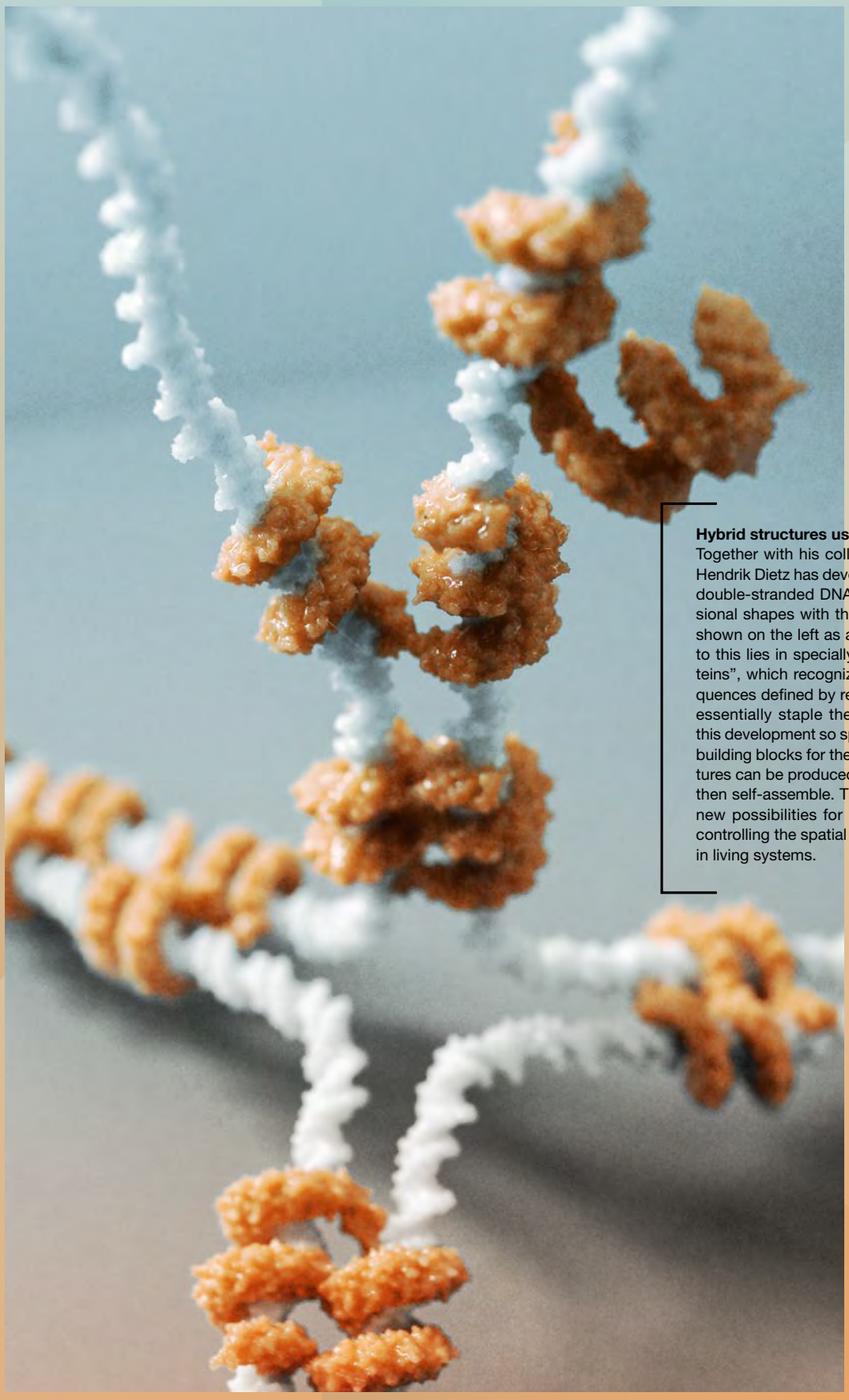
How many staff members do you have now?
We now have 25 full-time employees, as well as several young students who join us from their fourth semester onwards. This gives them very early insights into the true realities of research work. You see, it's not about reading a book and having the odd moment of illumination. You don't realize as a student that what you see on the pages of a textbook is often the product of decades of trial and error, and the huge effort that went into moving beyond those initial misconceptions or mistakes.

How has your way of working changed over the years?
My current role consists of analyzing data, discussing projects, making decisions about the direction we want to take, writing proposals and convincing funding bodies to invest in us. I was also in the lab myself for the first year or two but that quickly changed. Longer experiments requiring several consecutive days of lab work soon became impossible due to my schedule. I constantly have meetings (which is good) and need to look after my people. In the past, I saw research as more of a lone wolf activity, but now we work in teams to tackle more complex challenges.

Where do new ideas for your research come from?
The fundamental aims we are trying to achieve remain unchanged: building molecular machines with specific capabilities, such as transporting substances or producing chemical compounds. We've certainly learned a lot along the way, but haven't been able to turn these devices into reality as yet. So the vision is still there, along with plenty of ideas about how to take our research to the next level each time. The more difficult task is to filter out those ideas that have the best prospects of success and apply them in a practical context. And then it's not uncommon for everything to go wrong in the early stages. So that's when you need good and persistent people who believe in what they're doing and can cope with disappointments along the way. I'm very grateful to be working in that kind of environment.

In 2015, you were awarded the prestigious Gottfried Wilhelm Leibniz Prize, worth 2.5 million euros. What difference has that made?
Together with a series of publications in respected journals, that prize has boosted our credibility. In the early days, it was difficult when we promised to build something or other but didn't yet have anything to show for it. Now, though, I can point out that we're already halfway there. Mind you, we still regularly encounter skepticism – but there is less of it now.

You are known in scientific circles for your work on DNA origami – a method you have largely perfected at this point. What is your current research focus?
Well, to give an example: We have now used our method to build synthetic objects on the scale of viruses and cellular organelles. One of our goals is to use these DNA structures for medical treatments. We could envisage constructing ▷



Hybrid structures using DNA and proteins
Together with his colleague, Florian Praetorius, Hendrik Dietz has developed a method of folding double-stranded DNA (white) into three-dimensional shapes with the aid of proteins (orange), shown on the left as a 3D visualization. The key to this lies in specially constructed "staple proteins", which recognize two separate target sequences defined by researchers in the DNA and essentially staple them together. What makes this development so special is the fact that all the building blocks for the DNA protein hybrid structures can be produced by the cell itself and they then self-assemble. This method thus opens up new possibilities for better understanding and controlling the spatial arrangement of molecules in living systems.

("Science", 2017)

Picture credits: Hendrik Dietz

Synthetic lipid membrane channels based on DNA origami
In 2012, Hendrik Dietz and Prof. Friedrich Simmel, Chair of Physics of Synthetic Biological Systems at TUM, built synthetic membrane channels out of DNA, shown as a model above. These consist of a needle-like stem (red), which is 42 nanometers long and has an internal diameter of just two nanometers. The stem is partly sheathed by a barrel-shaped cap (white). A ring of cholesterol units (white and orange spirals) around the edge of the cap helps the device dock onto a lipid membrane, while the stem sticks through it, forming a nano-pore that appears to function just like the real thing. These synthetic membrane channels could be used as nano-needles to inject material or agents into cells.

("Science", 2012)

Reality check for DNA nanotechnology
In the same year, Hendrik Dietz and scientists from the MRC Laboratory of Molecular Biology in Cambridge (UK) were able to show that DNA objects can be assembled precisely as designed: They produced a relatively large, three-dimensional DNA-based structure, visualized on the left. This comprises more than 460,000 atoms. The researchers were able to map the object with subnanometer resolution, thus providing a crucial reality check for DNA nanotechnology.

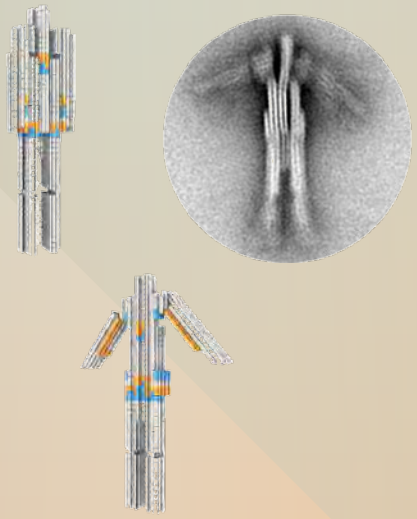
("Proceedings of the National Academy of Sciences of the USA", 2012)

a type of intelligent container, for instance, to transport active substances. Here, we would attach proteins or other molecule groups to the external coating. These would identify specific cell types, docking onto them and emptying the agent into the cells. The individual components for this type of container have all already been constructed – so the potential is definitely there. They have not yet been integrated into an overall system or tested in organisms, however.

Could you describe your most recent successes?
We now have a solution to a problem that has not been given much attention. In the past, it was much too expensive to produce DNA structures in large quantities. Using conventional origami methods, it would currently cost around 100,000 euros and take far too long to assemble a gram of DNA origami. To bring new medical applications to market, we first need to conduct experiments in animal models to observe how they respond to these types of structure – and this step alone requires quite a bit of material. That would be way too costly with the current process technologies. So to bring these costs down, we have developed new processes enabling us to produce our DNA structures in larger quantities.
Using our new method, individual strands of DNA can be produced with almost any length or sequence in cell cultures – as is already the case today for many protein-based substances, such as insulin. To this end, we harness *E. coli* bacteria, embedding our blueprints into their genetic code. When the bacteria multiply, they simultaneously multiply our DNA sequences too, which we can extract by purification at the end of the process. The difficulty here is that the DNA in cells is generally double-stranded, whereas we need single strands of DNA. Together with Prof. Dirk Weuster-Botz and his colleagues at TUM's Chair of Biochemical Engineering, we have now cleared this hurdle and produced our first actual macroscopic tablet from DNA origami powder. This symbolic gesture demonstrates that we have now reached the point of technical feasibility, while cutting costs for one gram of DNA origami from 100,000 euros down to only 100 euros. This paves the way for the development of medical applications based on this technology.

So what can we expect going forward?
Our next focus will be on medical applications. With the mass production challenge already resolved, now we need to investigate what actually happens to these structures within an organism. We have begun toxicity studies in collaboration with a partner to assess this. We also want to find out how long the biological half-life is – that is, how long such structures can survive inside the organism. Can we influence this with specific shapes or patterns? Or do we need to add on some kind of stabilizing structures? ▷

Moving nanomachines
If you change the ion concentration in the solution surrounding the "arms" of the nanorobot (below), they move up and down. To enable these synthetic DNA structures to move, Hendrik Dietz and his team turned a natural property to their advantage: nucleic acid molecules are capable of forming weak, easily reversible bonds with one another. The waving nanorobot (shown on the left and bottom as a model; on the right through the electron microscope) is based on a shape-complementary folding technique. Instead of zipping together strands of DNA base pairs, three-dimensional DNA building blocks are snapped together like pieces of a jigsaw.
("Science", 2015)



Picture credits: Hendrik Dietz

“Our next focus will be on medical applications.”

Hendrik Dietz

Prof. Hendrik Dietz

A pioneer in the field of DNA origami

Following his doctorate at TUM, physicist Hendrik Dietz moved to Harvard Medical School in Boston (USA) in 2007. There, he joined a research group led by William M. Shih, which set out to create three-dimensional objects from DNA. Together with computer scientist Shawn M. Douglas and other colleagues, Dietz then made the breakthrough that would establish his reputation as a pioneer of DNA origami.

At the outset, this entailed developing and testing the method that ultimately enabled production of all kinds of nanostructures from DNA: tiny balls, cogs and various other shapes – some of them highly intricate. Known as DNA origami, this method provides a powerful tool for assembling nanoscale structures, which can be used for example for medical applications. In 2009, Dietz took up an appointment at TUM as Professor of Experimental Biophysics. He is a Carl von Linde Senior Fellow of the TUM Institute for Advanced Study.

The 39-year-old scientist holds a Principal Investigator role in two clusters of excellence: Nanosystems Initiative Munich and the Center for Integrated Protein Science Munich (CIPSM). He received a Starting Grant from the European Research Council (ERC) in 2010, and a Consolidator Grant in 2016. In 2015, the German Research Foundation (DFG) awarded him the Gottfried Wilhelm Leibniz Prize, worth 2.5 million euros. In support of its decision, the DFG states: “Hendrik Dietz is among the world’s leading researchers in DNA nanotechnology – currently one of the most dynamic fields in basic biomolecular research.”

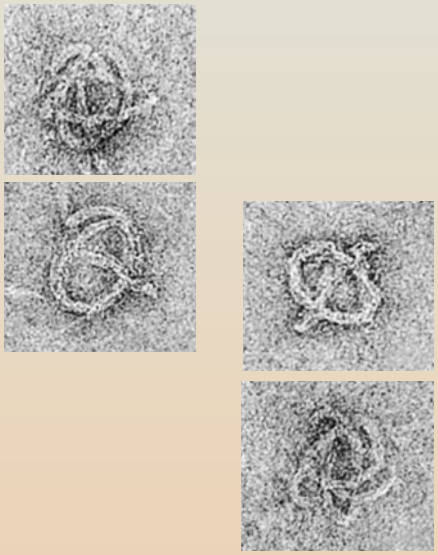
And where do you see yourself in five years' time?
I hope we'll have a string of new breakthroughs to show by then, since we still have many challenges to overcome. It would be great if our work continued as positively and productively as it has so far. Obviously, though, we are also looking to translate our research findings into practical applications. To facilitate this, we founded the company tilibit nanosystems in 2012 – where "tilibit" stands for "tiny little bit". The company distributes DNA components and shares our specialist know-how and I am delighted that we are seeing demand from all over the world. Tilibit gives us a good platform and an opportunity to gain practical experience in the business world.

What advice would you give to young people aiming for a career in research today?
In my view, a good doctoral thesis is certainly a solid and important starting point for a successful academic career. And after that, it is often worth making a break and working in another area of research as a postdoc. In this phase, too, productivity is key. It's probably better to pick a topic that inspires you personally rather than chasing trends – and ideally a topic still in its infancy, giving you room to make a significant scientific contribution. You need a certain instinct for that, and also some good luck. However, if it becomes clear that either of these two phases is proving too arduous, it might be better to pursue a different professional path. The academic world only becomes more competitive after that, while the number of positions shrinks. Of course you can also conduct research in an industrial setting. Each individual has to decide for themselves on the environment that offers them the best conditions to be happy and to develop their personal skills.

You are now a father of three – at four years old, does your oldest already understand what you do for a living?
I doubt it. I've tried to explain it to him but I think it's just too early. He's quite the little discoverer himself, though – he can spend hours watching a fly, for instance, or a spider roving about. So maybe science will appeal to him later on, too.

Brigitte Röthlein

DNA beach ball
Gears, coils and a beach ball made of DNA – in 2009, Hendrik Dietz published a method of producing curved and twisted DNA shapes. This is based on the fact that, in a DNA double helix, every seven base pairs rotate by 240 degrees. If base pairs are inserted or deleted between these segments, the structure is forced to over- or under-wind, thus bending itself. The bottom image shows a computer model of the DNA beach ball, while the top images are examples of actual objects under an electron microscope.
("Science"/"Nature", 2009)



Picture credits: Astrid Eckert/TUM; Hendrik Dietz