TECHNISCHE UNIVERSITÄT DRESDEN

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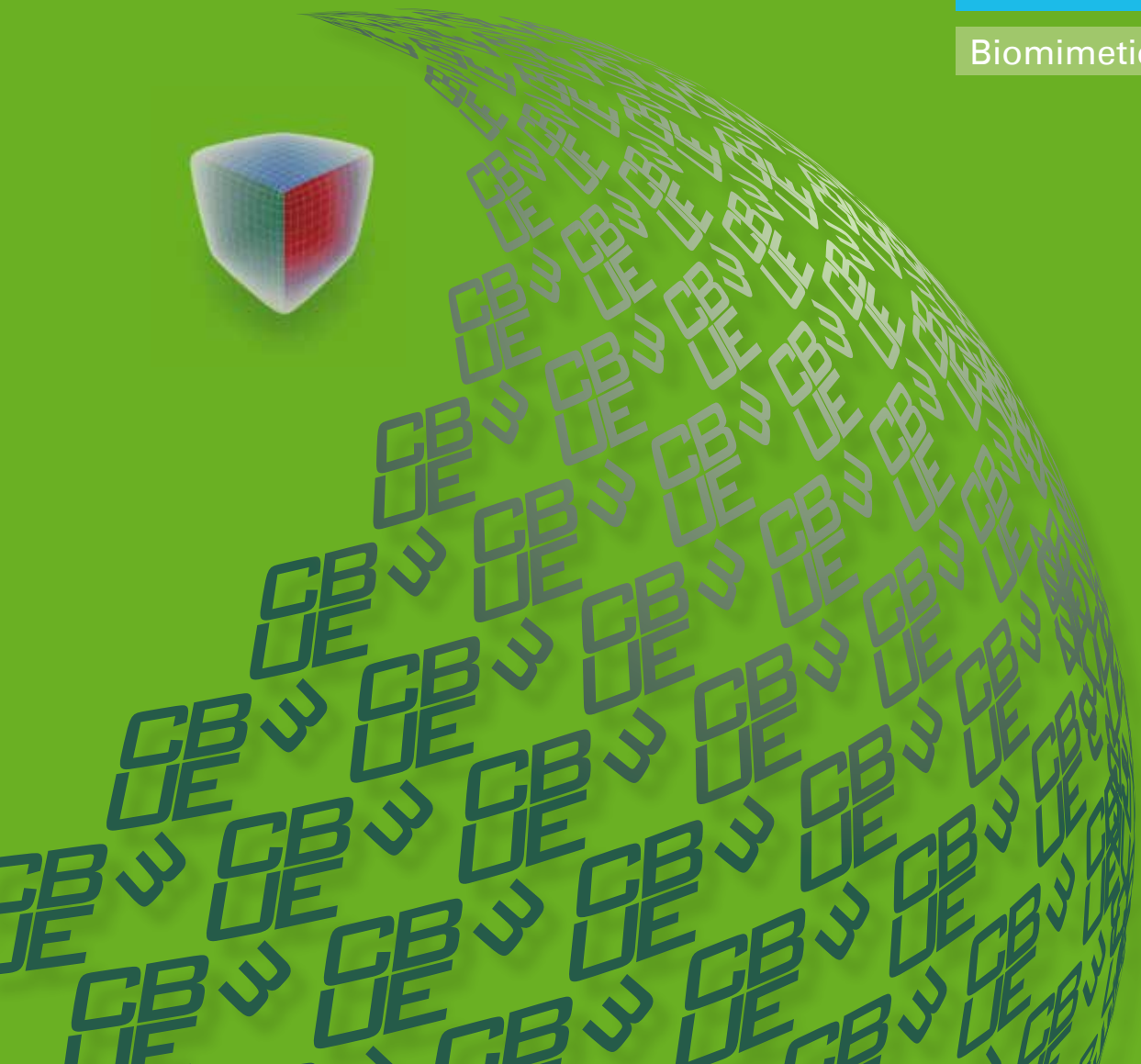
B CUBE

CENTER FOR MOLECULAR BIOENGINEERING

BioProspecting

BioNano Tools

Biomimetic Materials



B CUBE

CENTER FOR MOLECULAR BIOENGINEERING

Nanotech inspired by nature

Deep within the cells of living beings, nature still holds many secrets that we have yet to discover and performs tasks to specifications that are far beyond current technologies.

To find inspiration for new technologies and medicines, we enter the curious inner world of the cell, where single molecules are the key players and where random thermal motion is stronger than gravity. On the length scale, this realm is measured in nanometers (nm), where one nanometer is a millionth of a millimeter.

The living cell depends on molecular machines that perform to standards of precision and efficiency still far from what our technologies can do. By understanding the natural processes of the nanoworld we can learn to copy them where they provide efficient paths to our goals (e.g. manufacturing on the nanoscale, computation), and to block them where they are unwanted (e.g. disease progression, biofouling on ships).

At B CUBE we study natural phenomena and mechanisms at the nanometer scale, from small molecules to protein machines and cellular structures. We develop new methods to gain a deeper understanding of these structures. From our findings, we aim to derive innovative methods, materials and technologies. Together with the global research community, we work at the forefront of biotechnology, removing the boundaries between biological and artificial systems.

Dresden is an ideal location for our project. We can collaborate with the well-staffed science and engineering departments of the university, and

B CUBE - Center for Molecular Bioengineering at the Technische Universität Dresden is dedicated to investigate and engineer biological materials along three main axes:

BioProspecting

Identification and systematic recording of natural mechanisms that could be used for novel applications in technology. The organisms of study will be characterized with respect to their application potential and organized in a database of natural mechanisms.

BioNano Tools

Development and application of novel methods to characterize structure and function on the molecular scale. Conversely, biomolecular systems will also be investigated for their suitability as tools that can operate in a synthetic environment for nanotechnology applications.

Biomimetic Materials

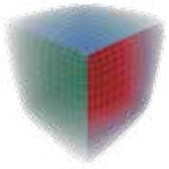
Design and synthesis of novel materials inspired by structures found in biological systems. This research field is called Molecular Bionics and utilizes as well as develops further modern techniques in Nanotechnology.

we are integrated in a diverse and tightly woven network of research institutes complementing each other. These interactions help us to develop new ideas and concepts, and provide an excellent and complementary scientific infrastructure.
Our research is bound to have significant impact in several areas of economic importance, from drug development, medical diagnostics to the production of functional materials. Nature's nanotechnology still has many secret recipes for us to learn and to apply to the benefit of all.

Our mission is to develop new approaches in molecular bioengineering rooted in the close co-operation of life sciences and engineering.

The main GOALS are:

- to develop new ways to further our understanding of natural phenomena based on their molecular components, and
- to translate the insights gained from investigation of the molecular world into innovative materials, systems and technologies of economic importance.



History of our Research Center

The idea of a novel Center for Molecular Bioengineering was conceived in 2006, and the concept for B CUBE was entered in a nationwide competition for new research initiatives. As one of the shortlisted initiatives it received an initial one-year grant to develop its strategy.

In 2008, it secured five years of funding from the federal research ministry (BMBF). The funding was utilized to set up two junior research groups, and B CUBE became a research center that operates as a scientifically independent unit of the Technische Universität Dresden. Additional funds from the state government of Saxony (partially from the European Regional Development Fund) and from the TU Dresden were instrumental in setting up the infrastructure for B CUBE.

In 2010, the research groups of Yixin Zhang, Michael Schlierf and Stefan Diez moved into the newly refurbished laboratory space in Arnoldstraße 18. In January 2012, Nils Kröger's team moved from Atlanta (USA) to complete the current line-up.

In June 2012, the TU Dresden was selected as one of the new group of "excellence" universities. B CUBE is part of two of the "excellence clusters" receiving special funding from the federal government.

Currently, plans are afoot for a new research building to house B CUBE, which should be ready by the beginning of 2017.

Research groups

Dynamic teams discover the secrets of structure formation to molecular drive

Research group

Prof. Dr. Stefan **Diez**

Biomolecular Transport Systems

Research group

Prof. Dr. Nils **Kröger**

Silica biomineralization and underwater adhesion

Junior research group

Dr. Michael **Schlierf**

Replication and repair of DNA and protein degradation

Junior research group

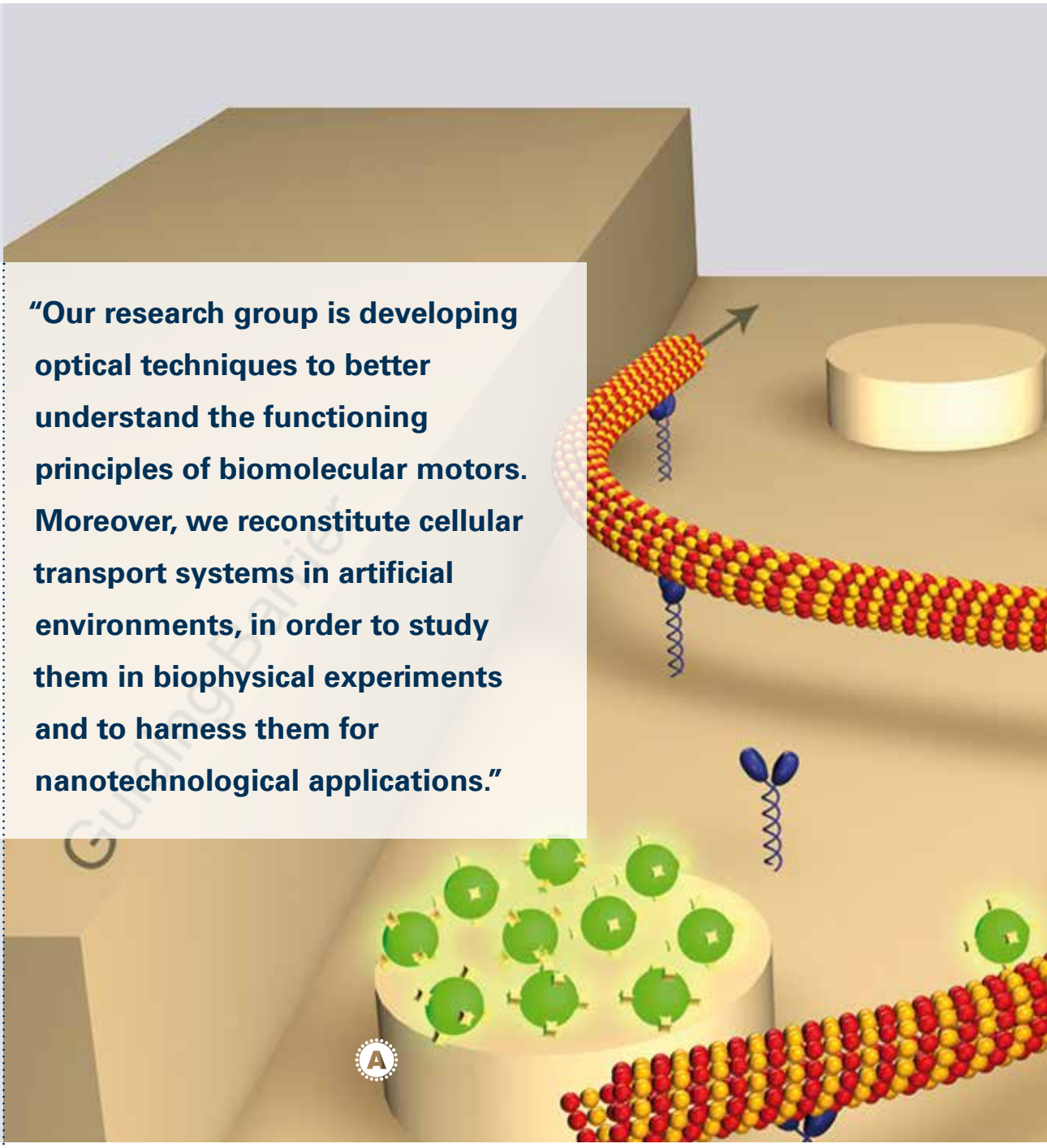
Dr. Yixin **Zhang**

Chemical methods for biological and medical research and application

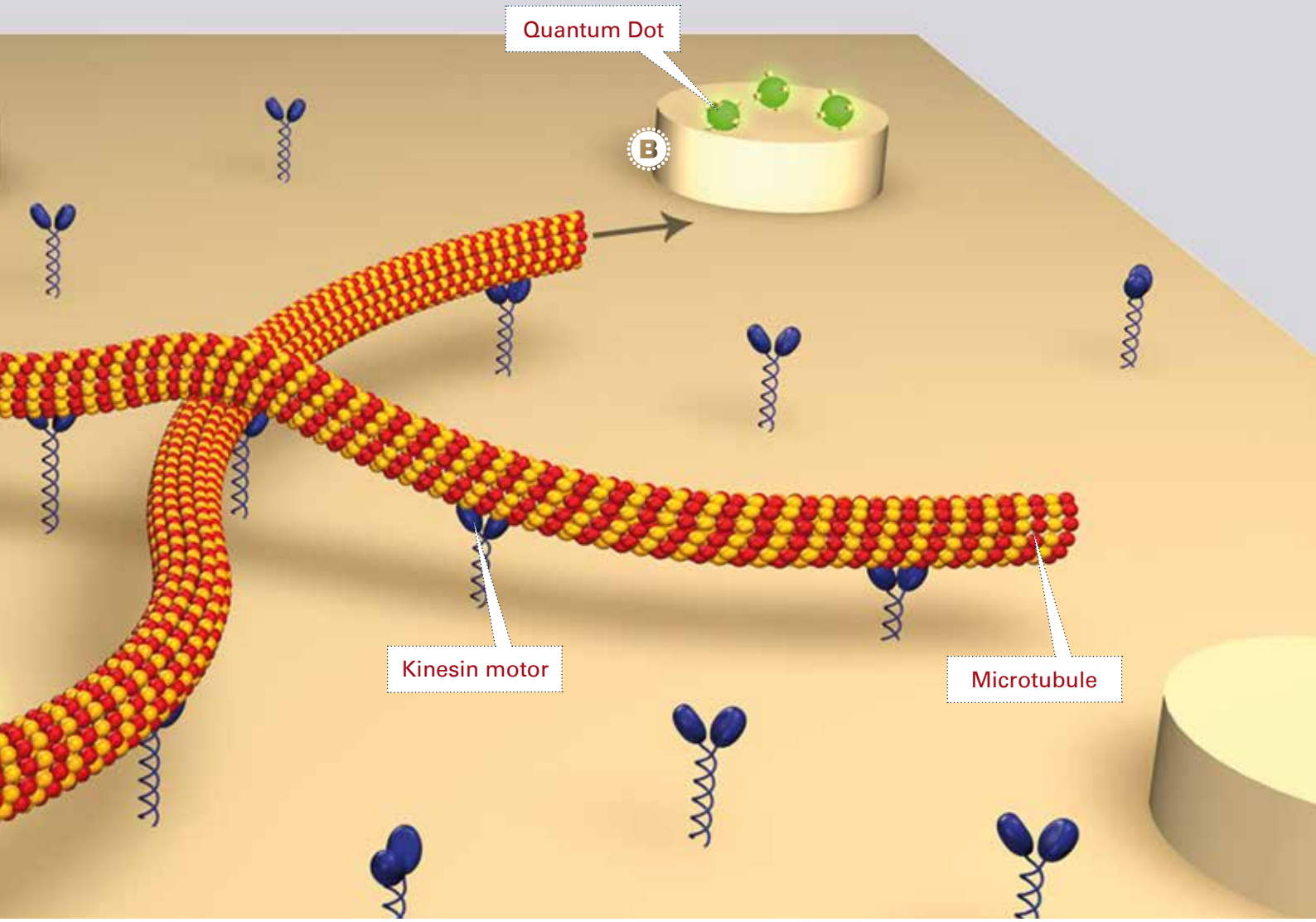
Research group Prof. Dr. Stefan Diez

Biomolecular Transport Systems

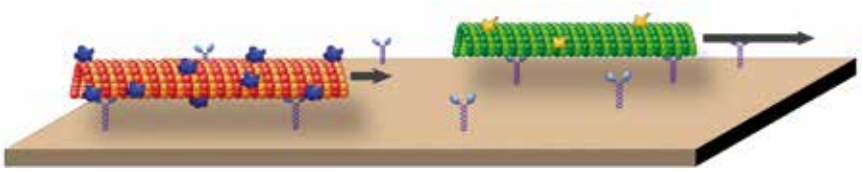
“Our research group is developing optical techniques to better understand the functioning principles of biomolecular motors. Moreover, we reconstitute cellular transport systems in artificial environments, in order to study them in biophysical experiments and to harness them for nanotechnological applications.”



Kinesin-microtubule transport system in synthetic environment: Microtubules are propelled over the surface by immobilized kinesin motors in the presence of ATP. For example, cargo (e.g. quantum dots) is to be picked up at a loading station (A) and moved to an unloading station (B).



Biomolecular motors on the nano-highway



◂ **Molecular detection system:** Macromolecules on the surface of microtubules obstruct the movement of motor proteins. The resulting slowdown of the sliding motion can be used for the quantitative and highly sensitive determination of macromolecule concentration in the surrounding solution.

We are studying the physics of biological movement and transport processes from the single molecule to the molecular systems level. We aim to improve the understanding of fundamental mechanisms in molecular motors and to use these in the construction of artificial, biologically inspired nanoscale systems.

Most cellular motors are not rotary like a car engine but linear. Typically, a motor protein will move along a molecular track like a person climbing up a rope, by alternating gripping and shifting moves. The physical challenges in both cases are very different, however. While the rope-climber has to contend with gravity, the main physical force the molecular motor has to deal with is random thermal motion. Even though molecular motors such as those of the muscle have been studied for decades, new biophysical methods can still significantly improve our understanding of how they actually work.

We focus on the kinesin motor which in the

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Full professor (W3) of BioNanoTools „Molecular Transport in Cell Biology and Nanotechnology"

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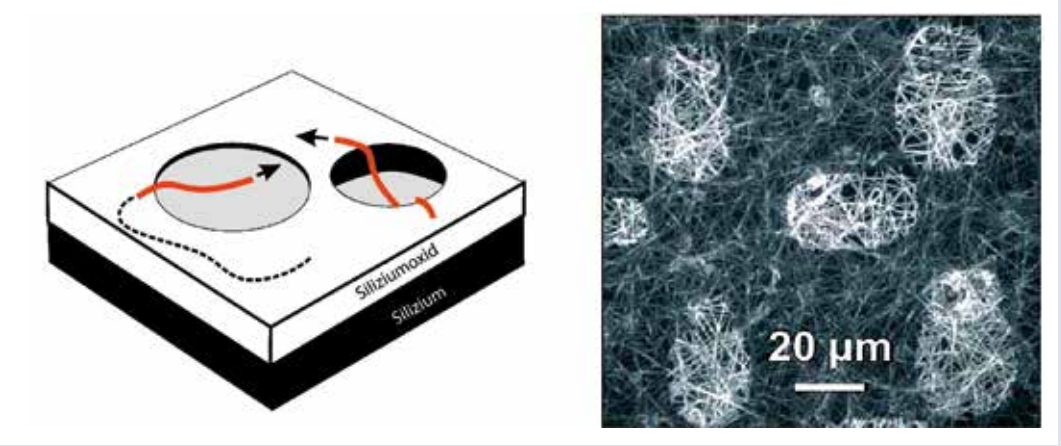
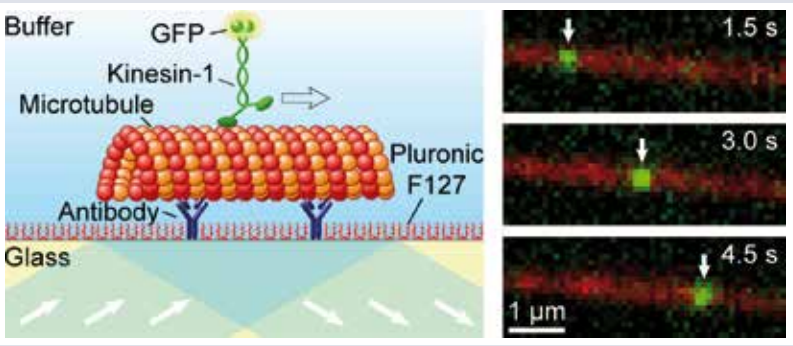


◀ **Nanometric surface measurements:** Microtubules can be used as self-propelled nanoprobes for exploring surface structures in the nanometer range. An image of the surface is obtained for example by the "maximum projection" of many bright fluorescence images that were recorded during the movement of the microtubules.

cell runs on microtubule rails, carrying cargoes which may be much larger than the motor protein itself. We aim to contribute to the understanding of this system by developing and applying optical 3D imaging methods with nanometer resolution to conduct single-molecule studies on motor proteins and by investigating co-operative effects in multi-motor transport.

Understanding nature's molecular motors brings the benefit that we will be able to use them in non-natural contexts, such as in nanoscale production lines. In a nanotechnology factory, motor proteins could serve to ferry around molecular assemblies that are being modified in various steps.

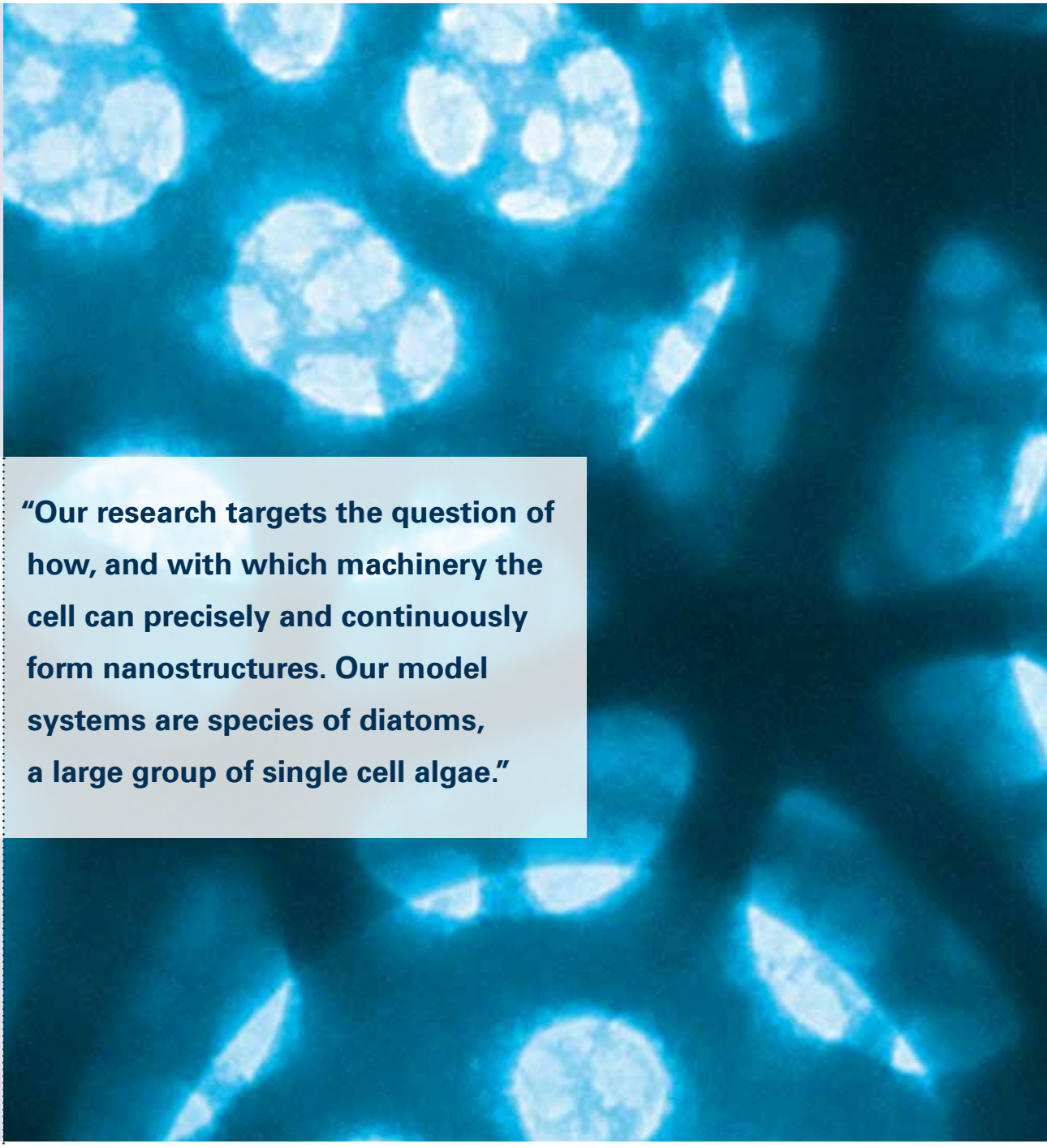
Example: **KINESIN MOTOR**



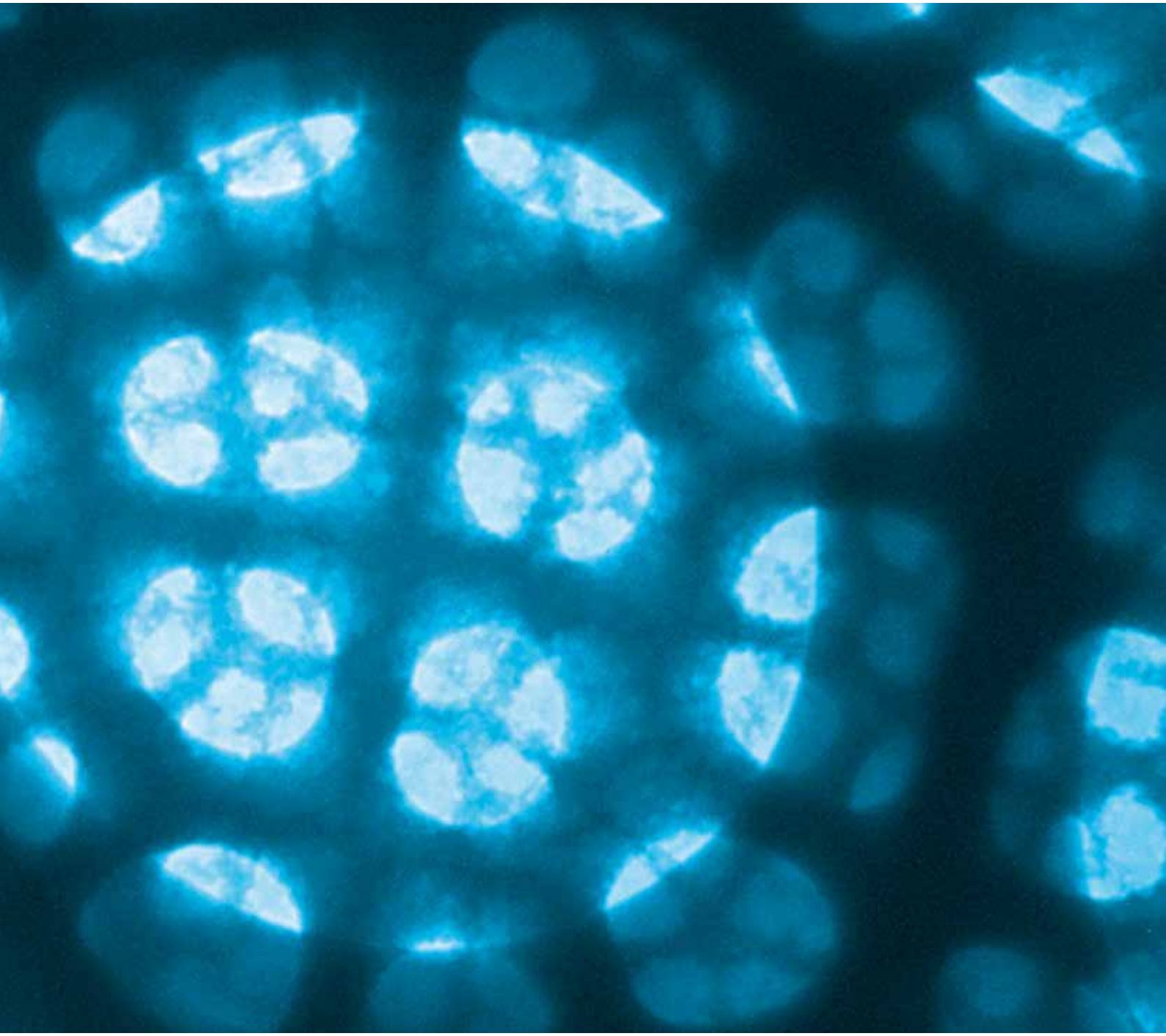
▲ **Imaging single GFP-labeled kinesin-1 molecules moving along microtubules:** Microtubules are bound to a glass surface via antibodies. Single kinesin-1 motors labeled by a green fluorescent protein (GFP) are imaged using the evanescent field generated by a totally internally reflected laser beam. The three frames of an image sequence show a single kinesin-1 molecule (green) moving along a microtubule (red).

Research group Prof. Dr. Nils Kröger

Silica biomineralization and underwater adhesion



“Our research targets the question of how, and with which machinery the cell can precisely and continuously form nanostructures. Our model systems are species of diatoms, a large group of single cell algae.”



Unlocking the design principles for biological nanoscale structures

Our research addresses the question what machinery the cell uses to fabricate three dimensional structures from the nano- to the microscale with high precision and reliability. Our model systems for this research are diatoms, single-cell algae with a shell made of silicon dioxide (silica).

There are more than 10,000 species of diatoms known, and each builds its silica shell in its own specific shape and with its own nano-scale pattern of pores. Production of such inorganic structures with similar accuracy and under mild conditions is far out of reach of current technology. Our research trying to uncover the diatoms' secrets for the biosynthesis of nanopatterned silica may make it possible to copy their achievement one day. Moreover, we can already use their silica shells as a basis to create nanotech devices by either layering other materials onto the silica or even gradually replacing it with metals or semiconductors which would then make the structure useful for use in electronic or optical devices.
Diatoms are so widespread in the oceans that they even have a substantial role in the global

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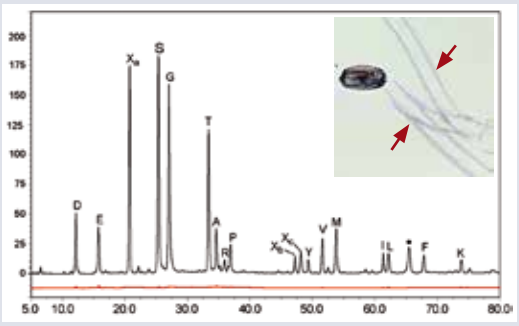
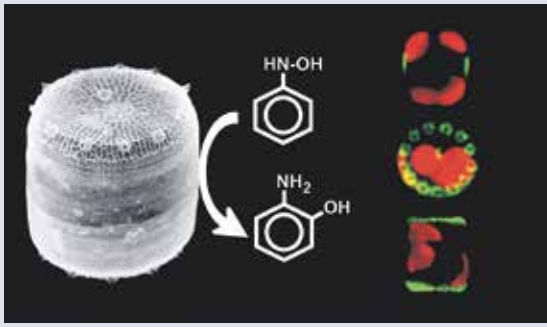


▲ Using an HPLC-coupled mass spectrometer (left), we can separate and identify the components of the underwater glue of diatoms (indicated by arrows in the small image top right).

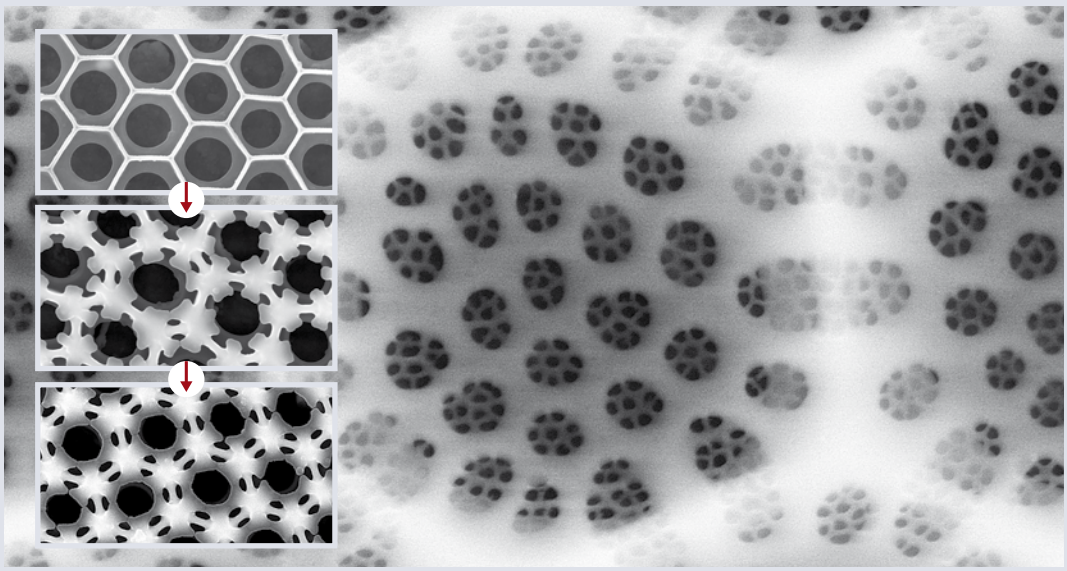


▲ Through methods of gene technology, enzymes (top left) and fluorescent proteins (top right) can be incorporated into the silica shell of living diatoms.

carbon cycle and thus help to stabilize climate. They are less welcome, however, when they settle on the hulks of ships, where they can attach themselves with a strong glue even under water. They prepare the surface for the colonization by other organisms (biofouling) which then will cause significant drag and thus economic loss.

Understanding the adhesion mechanisms of diatoms will be useful both for the prevention of biofouling on ships and for the development of similarly strong, biocompatible adhesives, for instance for surgical applications.

Example: **BIOMINERALIZATION**

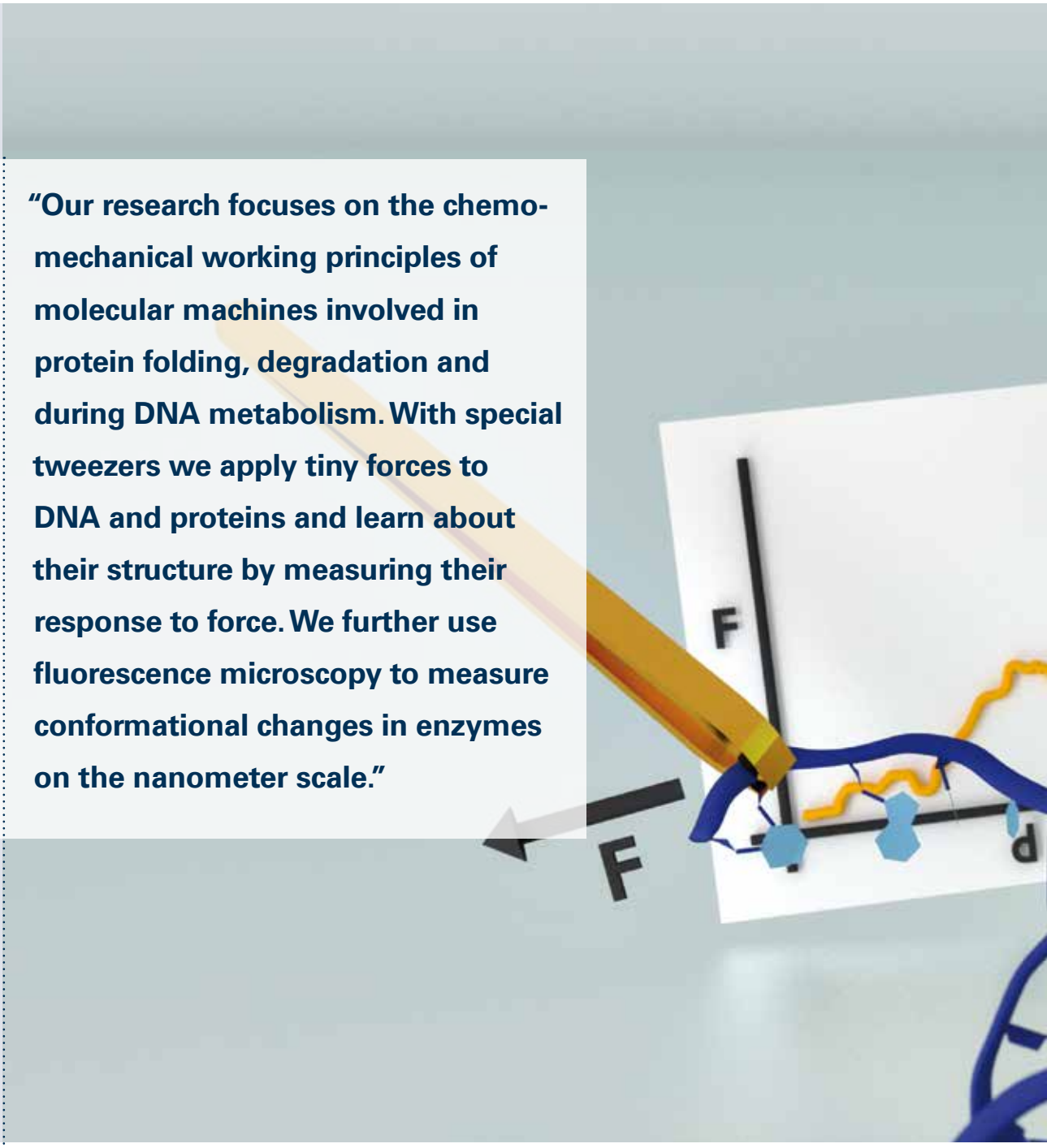


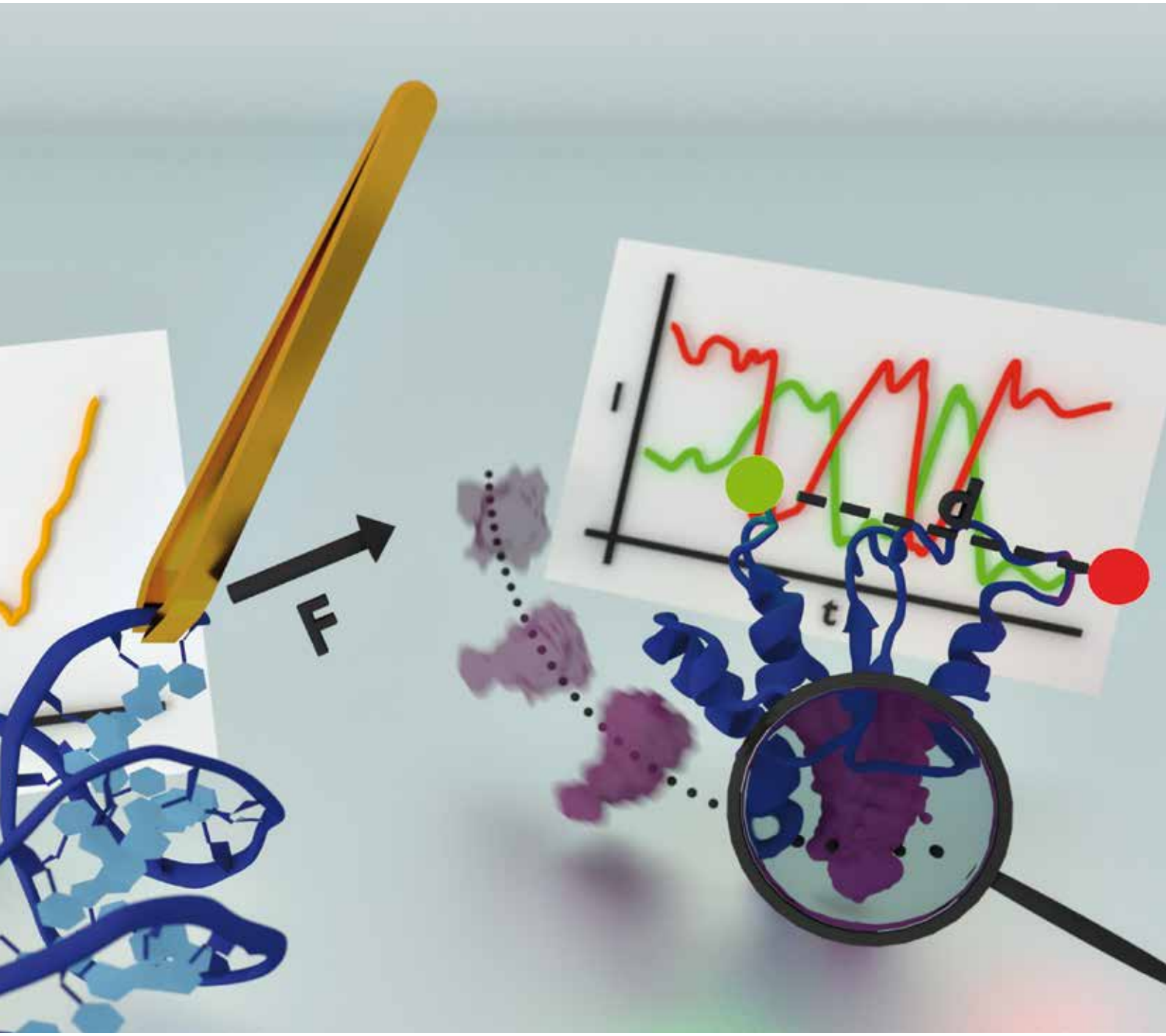
▲ Structure of the silica of a *Coscinodiscus* diatom. The three smaller images show intermediate stages in the biological processes of silica formation.

Junior research group Dr. Michael Schlierf

Replication and repair of DNA and protein degradation

"Our research focuses on the chemo-mechanical working principles of molecular machines involved in protein folding, degradation and during DNA metabolism. With special tweezers we apply tiny forces to DNA and proteins and learn about their structure by measuring their response to force. We further use fluorescence microscopy to measure conformational changes in enzymes on the nanometer scale."

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Molecular machines on the nerve of life

Much of our research focuses on enzymes that are involved with the copying of DNA, including helicases that unwind the template double helix and recombinases that insert acquired DNA sequences into specific regions in the genome.

In order to understand what is going on during the DNA metabolism, we have to be able to study the process at a single molecule level and in real time, so we can observe the sequence of events on a given DNA strand. Specifically, we use single molecule fluorescence techniques to follow the changes in the protein molecules operating on the DNA, and magnetic or optical tweezers to observe, prepare and manipulate the binding of enzymes to the DNA strands.

Applying these techniques to the action of helicases, which open the double helix and separate the strands, we hope to reveal crucial mechanisms, which could help in fighting a number of diseases. DNA replication is a key target for cancer treatment, for instance, as cancer cells divide more often than healthy cells and thus need to copy more DNA.

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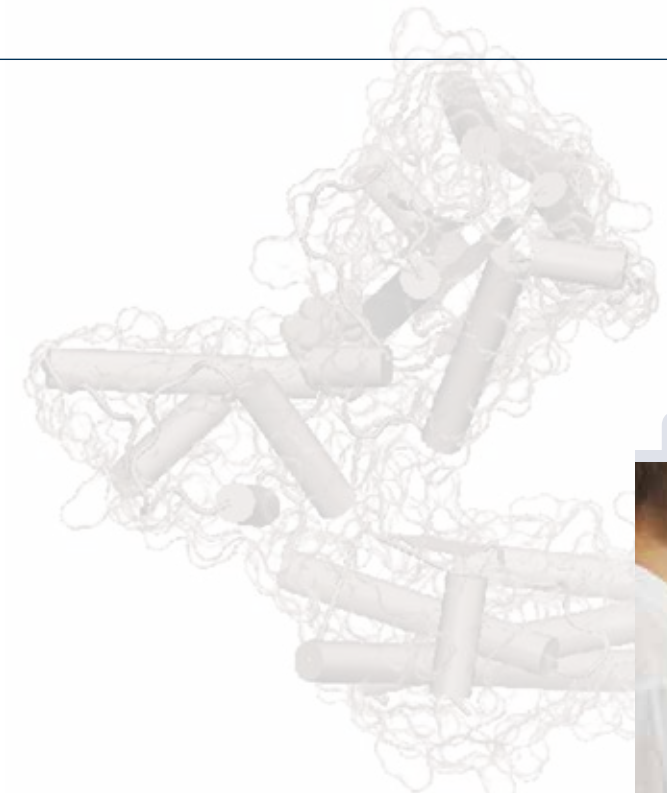
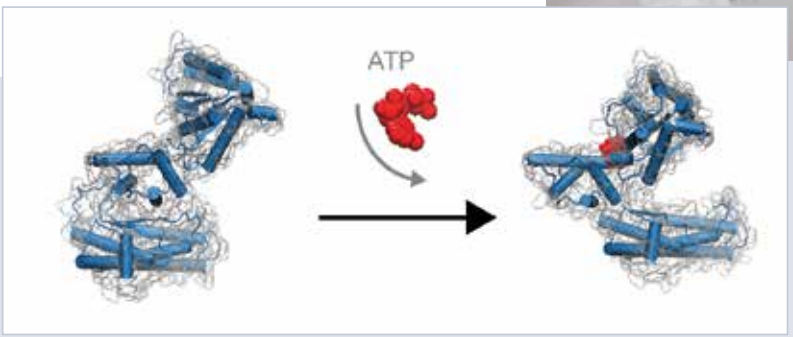
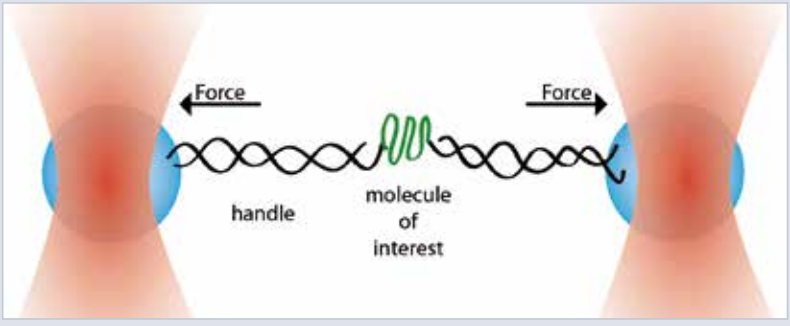


Example: **PROTEIN STRUCTURE**

Moreover, bacteria have evolved a sophisticated system for adaptation on the level of DNA, which, for instance, can be used for the transfer of antibiotic resistances. This system works extremely efficiently but is little understood on the molecular level. Our unique set of techniques enables us now, to look closer at the bacterial adaptation process.



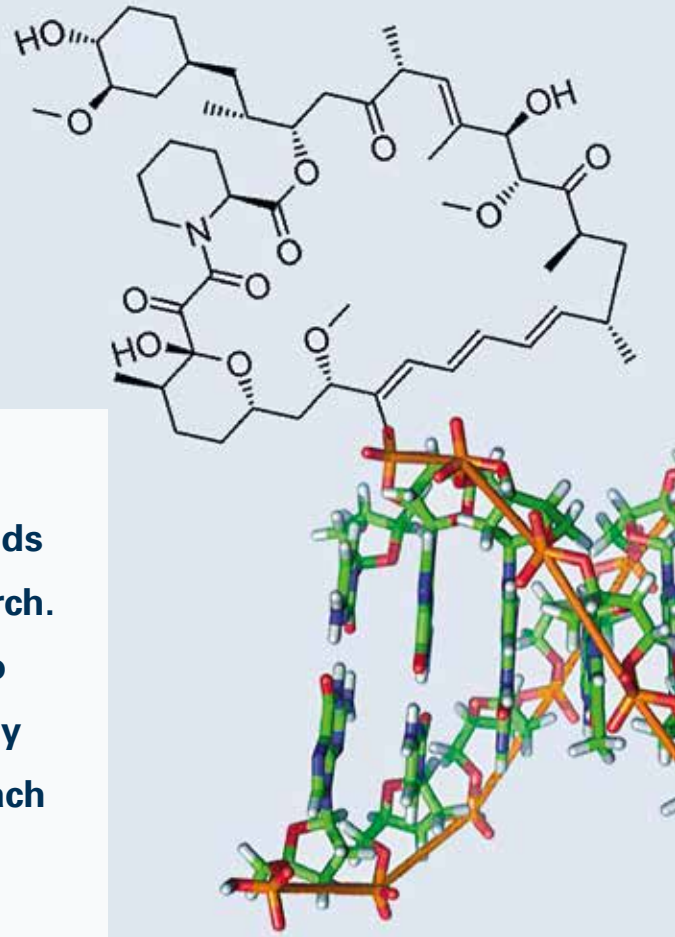
◄ Molecular Machines often use the chemical energy of ATP and transform it to a mechanical movement that can be followed in real-time in our experiments.



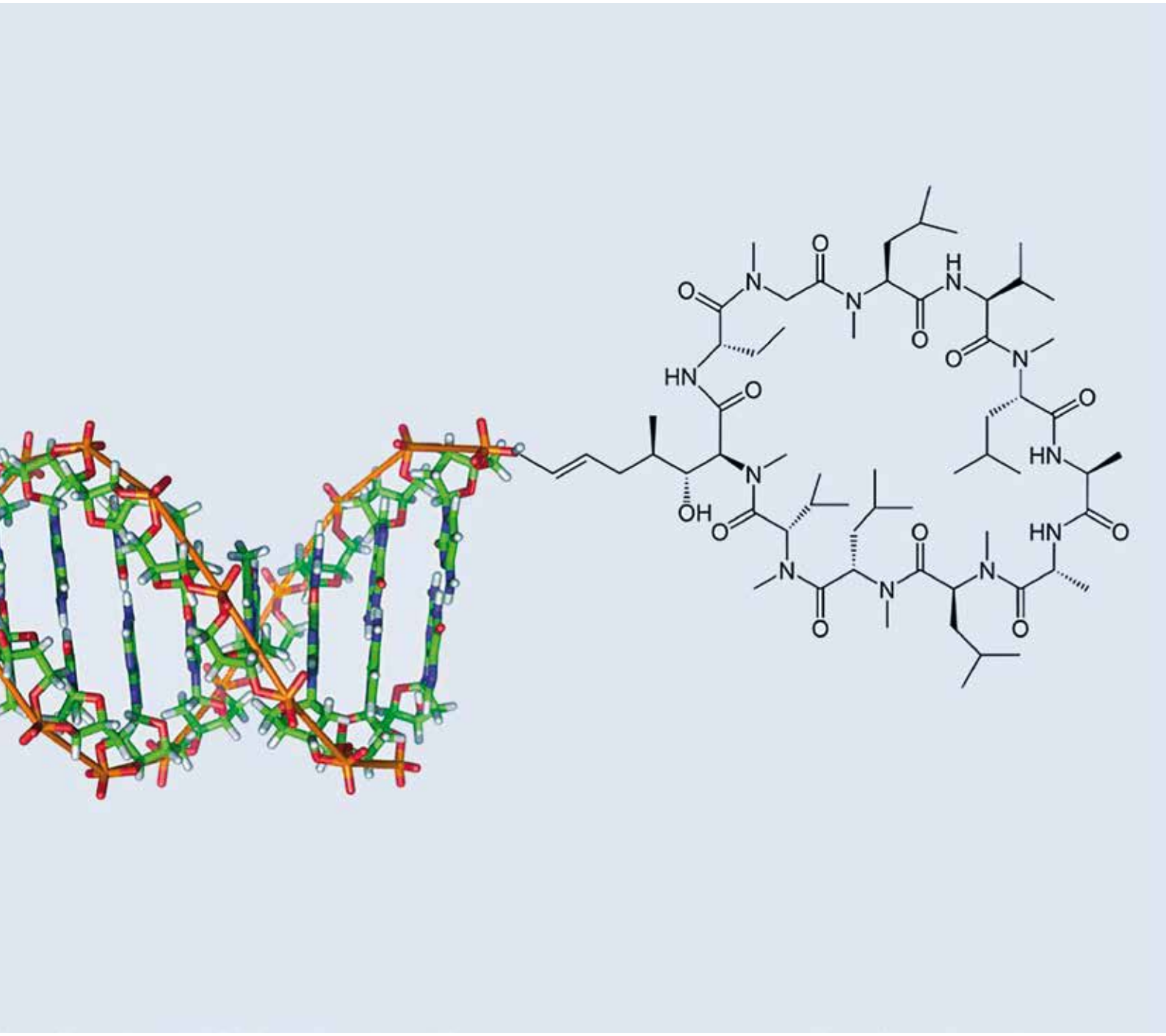
◄ We are trapping two small glass beads with a focussed laser and apply forces to molecule of interest to learn about their molecular structure and function.

Junior research group Dr. Yixin Zhang

Chemical methods for biological and medical research and application



“Our research targets the development of chemical methods for biological and medical research. Among other things, we want to develop drug molecules that only become activated when they reach the disease tissue.”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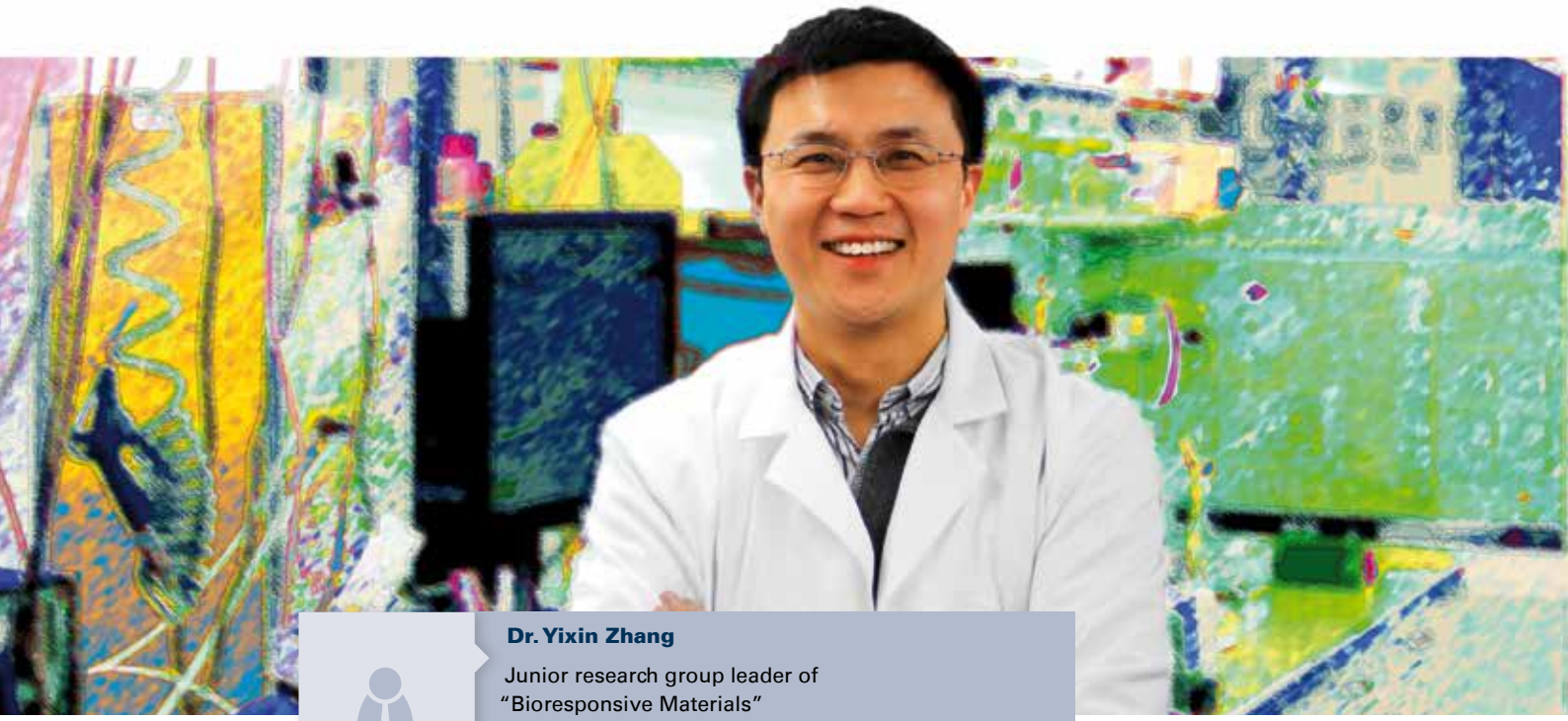
Bioactive molecular systems and research on DNA-coded compounds

We are developing several innovative technologies to facilitate the high throughput discovery of drugs, to tune their targeting to affected cells and tissues, and their activation at the target site.

For drug discovery, we focus on DNA-coded libraries of candidate molecules. This approach enables the simultaneous testing of an unlimited number of molecular species, as each molecule that binds the target can then be identified by its unique DNA label.
In the field of drug targeting and activation, our research involves the switching of drug molecules by UV light and infrared light. Specifically, we are interested in application of modulators of the immune system which can be controlled by light.
Another part of our research involves the development of artificial material to replace the extracellular matrix, into which many types of cells are embedded. Hydrogels made of the molecule heparin mimic some of the chemical properties of the matrix and enable *in vitro* studies of cell-cell interactions. Such materials could also find applications in cell replacement therapies.



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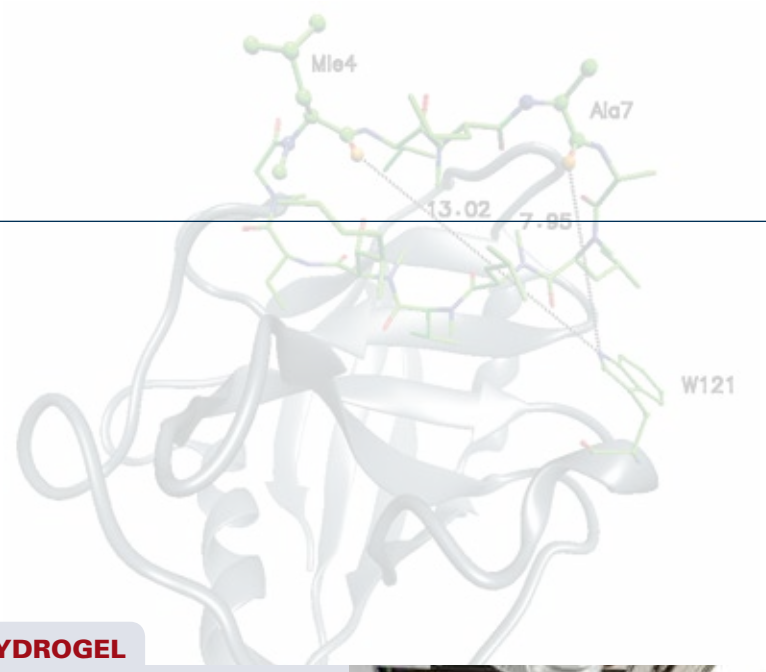
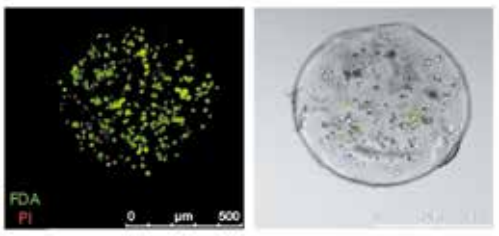
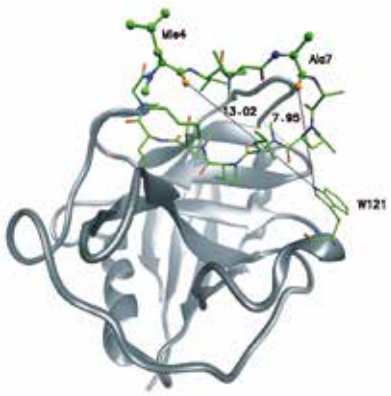


Example: **HYDROGEL**

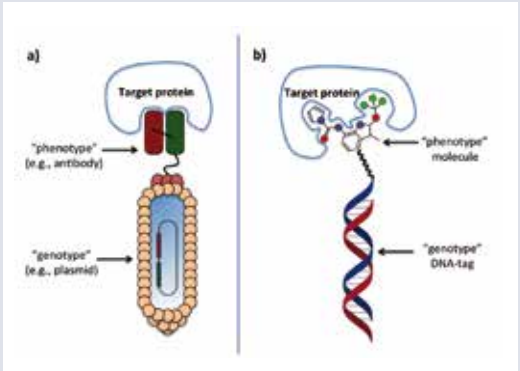


▲ Encapsulation of cells in a chemically defined biomatrix to grow and analyse cells in a 3D matrix and to manipulate them for medical applications.



▲ Rational design of improved versions of existing pharmaceuticals, e.g. anti-cancer drugs and immuno-suppressants, in order to make them more efficient and safer.

Coupling each chemical compound with a DNA molecule. This way, we can identify the compound through DNA sequencing, just like reading a barcode at a supermarket to identify the item.▼



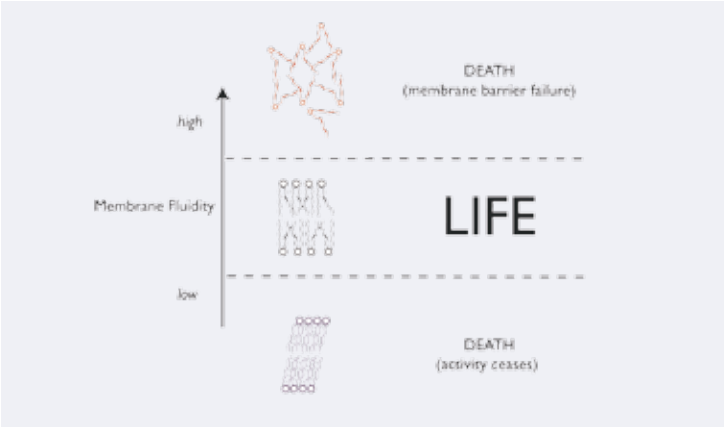
Research Group James Sáenz

Bottom-up Synthetic Biology

How cell membranes create structure in chaos

How did the first protocells on earth arise from a primordial soup? What role do lipids play in creating complex systems in nature? Which elements do we need to construct artificial cells? The work of the research group "Bottom-up Synthetic Biology" headed by James Saenz (born 1981 in New York) is motivated by these and related questions.

Our research group investigates the special role of lipids in the organization of cell membranes in bacteria. With that understanding, we want to create functional biological membranes artificially. At the same time we aim to understand how targeting bacterial membranes can prevent infections and antibiotic resistance. Our research also leads us to the origin of life: We want to explore how the first forms of life arose billions of years ago on earth.



▲ The fluidity of all cell membranes must be maintained within a narrow range. If the membrane becomes too fluid, it fails to act as a barrier. If the membrane becomes to stiff, proteins within the membrane cease to function. The cell adjusts its lipid composition in response to perturbations to maintain membrane functionality.

The line between life and death is as thin as a wafer: Only a few nanometers of membrane separate the cells of the simplest forms of life from their environment. This skin maintains the internal pressure and shape of the cell, protecting it from the outside world. Not only are membranes barriers to the outside, they also contribute to complex biological systems: They place the power plants and motors of the cell in the right place. They create structure and identity in chaos.

Lipids play a key role here. Certain types of fat molecules make the membrane particularly stable or particularly liquid. In that way lipids control the activity of proteins that are integrated into the cell membrane. These highly specialized proteins have different functions: Some are signal lines, others act as water pipes, some pump substances into and through the cell, and so on.

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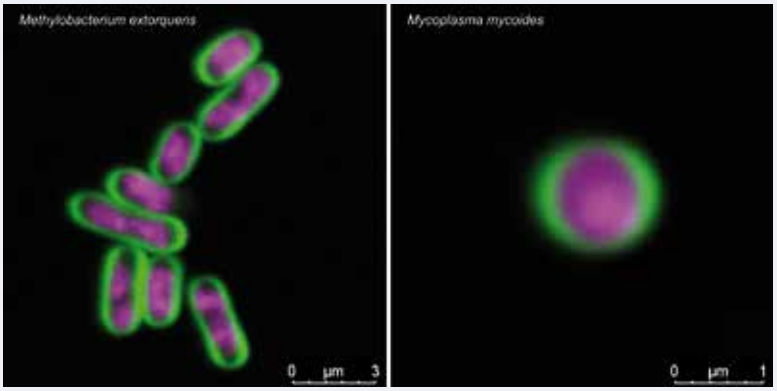
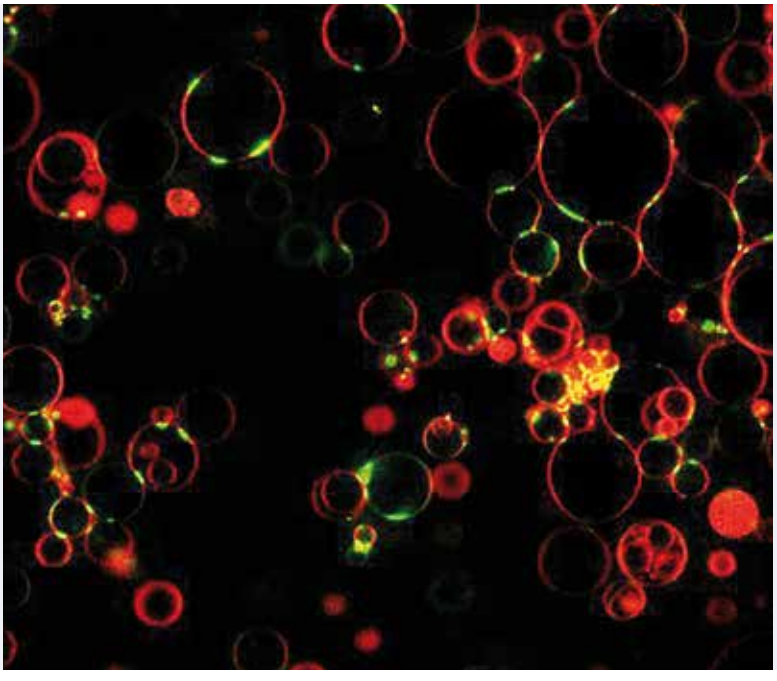


◂ All living organisms have a cell membrane made up of a lipid bilayer and proteins. The membrane serves as both a selective barrier, and as an organizational matrix. The bacteria shown in these microscopy images (DNA = purple, membrane = green) are simple organisms that we use as model systems to understand the design principles of living membranes.

Cell biologists in Dresden have already made artificial membranes from lipids. But these membranes were static. That's why our next step is to build a fully functional membrane that acts and reacts like a living organism.

This would be an important basis for constructing synthetic life in the long run. What we have in mind are not artificial humans, but technology based on biological principles, for example biological computers and sensors with a very low energy consumption.

The best example is the human brain: With the energy consumption of a light bulb it manages image recognition capabilities, which exceed even present-day supercomputers of the megawatt class.



◂ The ability for membranes to act as a scaffold to organize the parts of the cell in space and time is essential for life. This is a confocal image of a giant lipid vesicle that is demixed into two liquid phases (green and red). A fluorescently labelled RNA aptamer (green) preferentially binds to the ordered liquid phase. This shows that RNA can bind to lipid membranes and exhibit selectivity for membranes with certain properties. We are exploring how RNA-lipid interactions could have contributed to the origin of life and how these interactions can be engineered as an organizing principle in synthetic systems.

Research Group Igor Zlotnikov

Multi-Scale Analysis

Thermodynamic and Nanomechanical Aspects of Biomineralized Tissue Formation and Function

Why are molluscan shells so strong? How do marine sponges produce highly symmetric glass architectures? The process of their growth is called biomineralization – the formation of three-dimensional mineral-organic functional architectures by living organisms. The interest in biomineralization stems from the efficiency of the biochemical machinery that is responsible for bottom-up biotic mineral formation, functional capacity of the mineralized tissue as a whole and, at the same time, the elegance and even simplicity of the solution it provides to the organisms. These are the main goals of current bioinspired technology.

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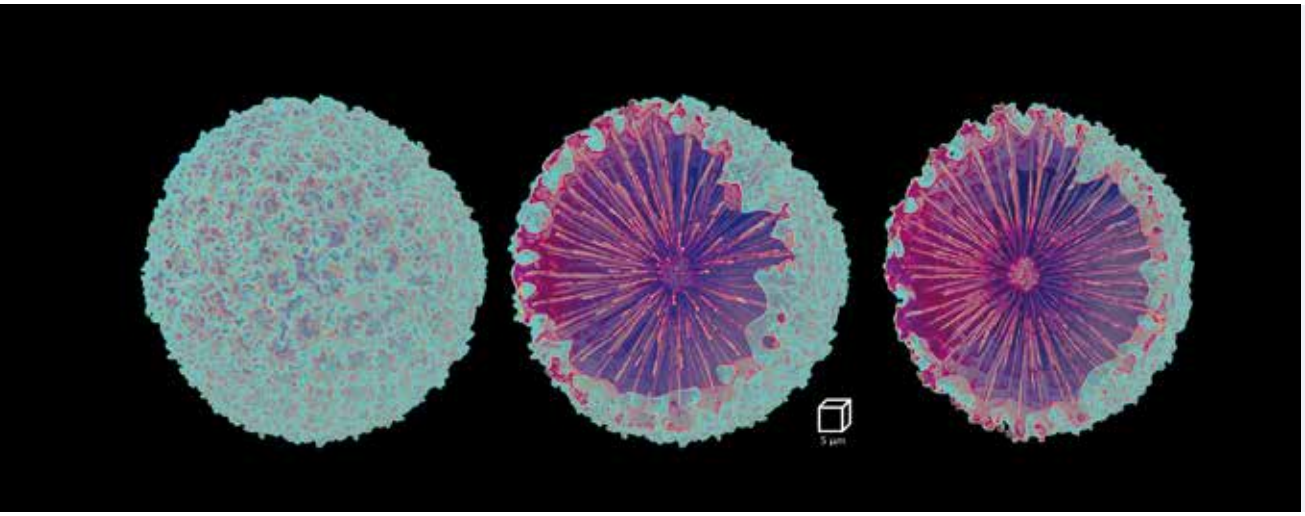
We study how molluscan shells, glass sponges, and other marine organisms incorporate minerals into biological tissue to create intricate 3D composite architectures with unique functionalities. With that knowledge, we aim to inspire the development of new technologically relevant materials.

Living organisms form complex mineralized biocomposites that perform a variety of essential functions. These biomaterials are often multifunctional, being responsible for not only structural support and mechanical strength, but also providing optical, magnetic or sensing capabilities. The remarkable diversity in functionality is accomplished from a relatively narrow range of constituent inorganic materials. Hence, a significant effort has been directed toward studying the process of biomineralization – to understand how organisms assimilate elements from the environment and incorporate them into living tissues. Many studies have emphasized the complexity of biochemical mechanisms in charge of the delicate equilibrium and interaction chemistry between inorganic precursors and macromolecular components leading to nucleation, assembly and growth of different biominerals. In contrast, thermodynamic constraints, governing the microstructure formation, growth kinetics and the morphology of the mineralized tissue leading to a specific functionality are much less understood.

Therefore, we aim to address the fundamental question of how nature takes advantage of thermodynamic principles to generate complex morphologies and



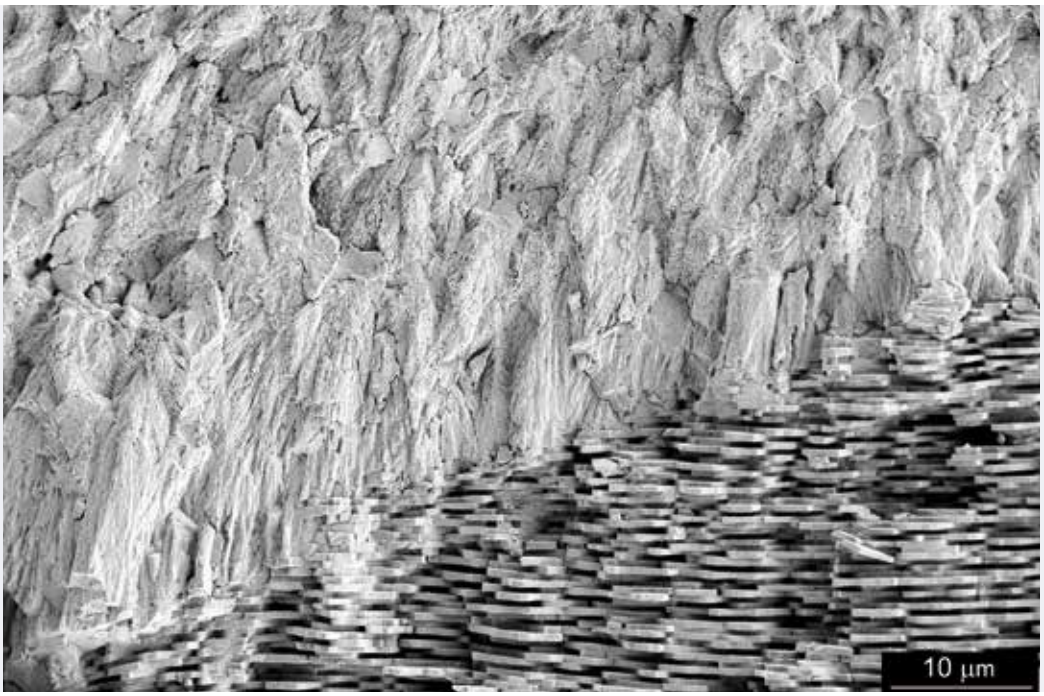
◀ 3D Tomographic reconstruction of a sphere-like spicule from the sponge *Geodia cydonium*.

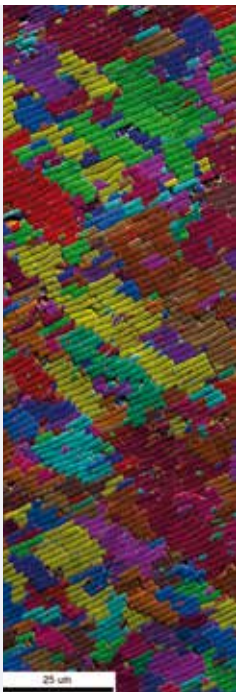
to study the interplay between physics of materials and cellular control in this process.

Structural, biochemical and functional characterization of biomaterials is a challenging task that requires implementation of state-of-the-art techniques from a large spectrum of fields in life and physical sciences. Since the primary function of biomineralized tissues is mechanical strength and structural support, the field of nanomechanical characterization of biomaterials has become a major area of research providing inspiration for the design of mechanically efficient synthetic materials. Hence, **we aim to resolve and understand the mechanisms of time, temperature and humidity dependent elastic and viscoelastic response of naturally occurring functional composite systems.**

▼ Internal structure of the shell of the gastropod *Haliotis asinine*.

▲ EBSD map of the nacreous assembly in the shell of *Unio pictorum*.





Technology platform

At B CUBE, advanced technologies and services requiring significant investment has been established as a shared platform accessible to all research groups.

This platform ensures the cost-efficient use of the instruments and provides the interdisciplinary research teams with as much diversity in specialized techniques as possible. The staff members of the platform vouch for the expertise and high quality of service.

B CUBE's technology platform is part of a local network with our partners, who use it and in turn offer access to their instruments and services, which further broadens the scope of technologies available. Technology platforms not only enable the economically responsible use of public funding, they can also generate new projects and thus become the basis for new grants from national and international agencies.

Example: **PEPTIDE SYNTHESIS**

The facility provides peptides services ranging from peptide synthesis and modifications to high throughput peptide array synthesis (SPOT method) for libraries. The service is open to B CUBE research groups and collaborators as well as other external scientists.

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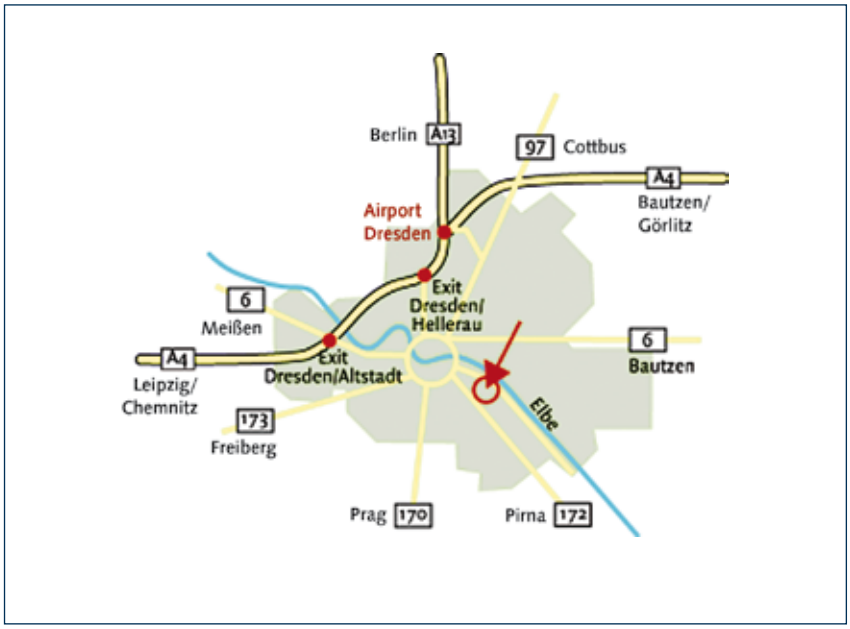

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