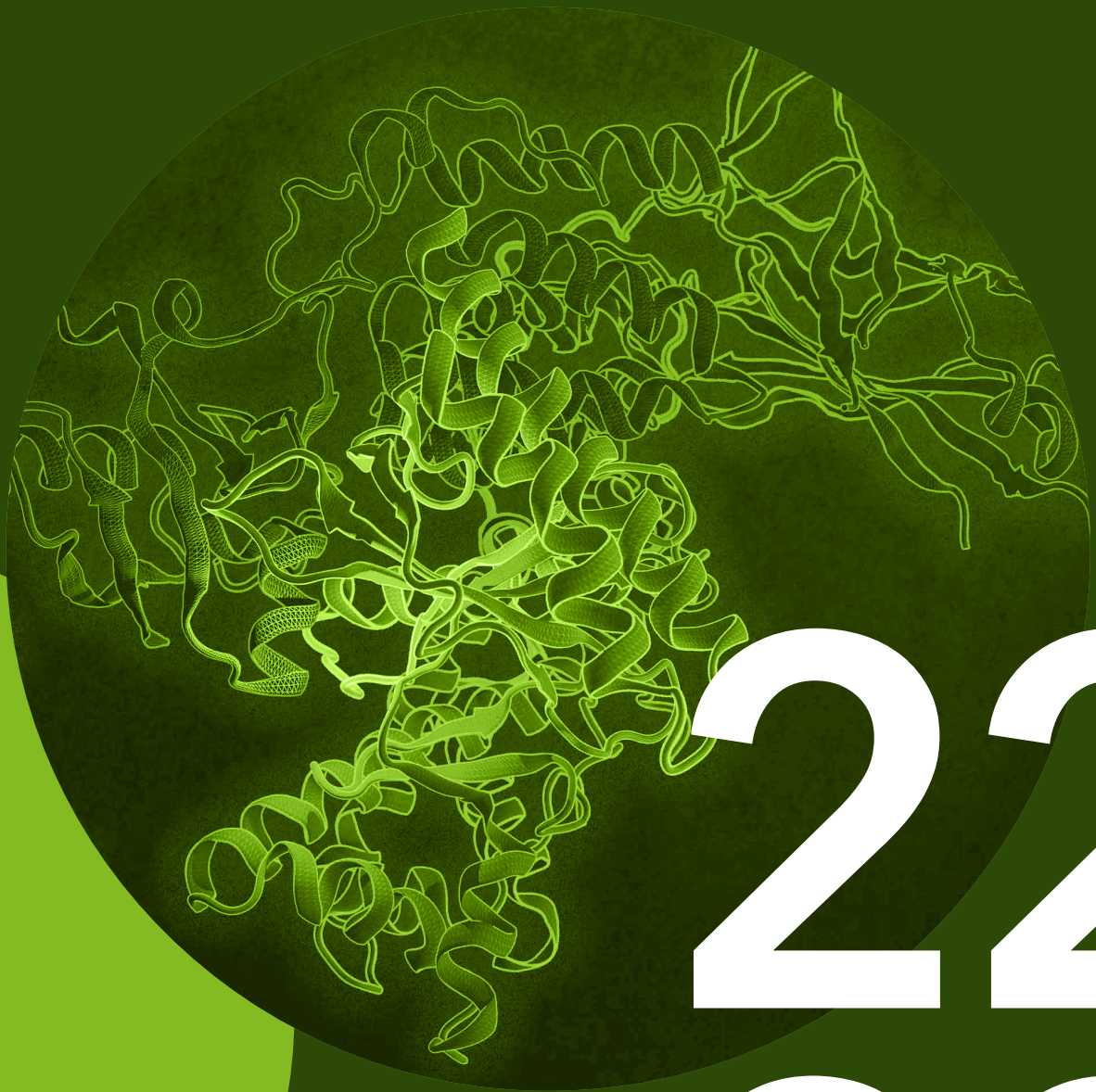
RESEARCH HIGHLIGHTS



2022
2023

LEIBNIZ
FORSCHUNGSINSTITUT
FÜR MOLEKULARE
PHARMAKOLOGIE

A look at the world of membrane proteins: Yellow represents a potassium channel, pink a claudin, blue a sodium–potassium pump, and green an ion channel. Read about the different roles and functions of these proteins in this issue.

Image: Barth van Rossum

Dear Reader,

In this first issue of our new “Research Highlights” series, I would like to present a selection of projects currently underway at the FMP.

Our goal is to show in an appealing and accessible way how groundbreaking interdisciplinary research is conducted at the FMP and how it can be consistent with sustainability.

Join us on an exciting journey through our scientific discoveries. I hope you enjoy reading this brochure and come away with new insights.

All the best,
Dorothea Fiedler

Professor Dr. Dorothea Fiedler
is Managing Director of the FMP.

WHAT RESEARCH IS BEING CONDUCTED AT THE FMP?

What keeps us healthy, what makes us sick? How does a drug reach the right target in the body without causing side effects? Conversely, how can viruses and bacteria be prevented from entering cells?

Researchers at the FMP address these questions by investigating biochemical processes in the body and by studying the molecular causes of disease. Based on these findings, our scientists can also conduct targeted drug research, developing the basis of tomorrow's medicines. Interdisciplinary teams from the fields of biochemistry, chemistry, physics, and medicine work together in a unique environment on Campus Berlin-Buch.

CONTENTS

1

NOVEL THERAPEUTIC APPROACHES

2

UNDERSTANDING THE BODY AT THE MOLECULAR LEVEL

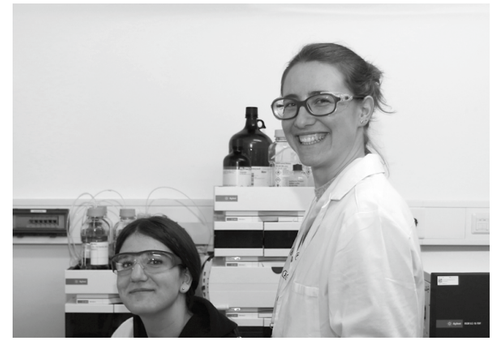
3

NEW RESEARCH METHODS

1

Novel therapeutic approaches

We are researching new substances to develop tomorrow’s medicines



Why do we constantly need new drugs, Dr. Nazaré?

SCHOOL INTERN SARAH SCHÜLEIN INTERVIEWS GROUP LEADER DR. MARC NAZARÉ

Nazaré: New drugs are needed for a number of reasons, the most important of which are medical and scientific advances, the reduction of side effects, and the constant battle against resistance.

Schülein: Could you please start by talking a little bit more about medical advances?

Nazaré: Of course. Medical advances refer to progress in the continuous development and improvement of medical technologies, procedures, and scientific knowledge. For instance, emerging insights from pharmacology or cell biology are used to describe new target proteins, which in turn pave the way for novel therapeutic approaches and new drugs. A good example of this is the now available medication for severe coronavirus infections, which has saved the lives of many people.

Dr. Marc Nazaré, leads the Medicinal Chemistry Research Group.

↑ Sarah Schülein (left) during her internship at the FMP, together with doctoral student Victoria Zeitz (right).

Schülein: And how do side effects relate to the need for new drugs?

Nazaré: The goal is to improve the safety and tolerability of a drug. All medicines can have side effects. Through research and development, we strive to develop new, more effective drugs with fewer or more manageable side effects. People who are allergic to a drug or who respond poorly to a particular treatment may also benefit from new drugs.

Schülein: You also mentioned drug resistance. Could you elaborate on that?

Nazaré: Yes, resistance to antibacterial and antiviral drugs is a particularly pressing global problem. Bacteria and viruses can become resistant to drugs over time, meaning that the substances in the drugs no longer work against them. This is a natural evolutionary process, but it can be accelerated, especially by the excessive and inappropriate use of antibiotics. The development of new antibiotics is therefore a race against time.

2

Understanding the body at the molecular level

What keeps the body healthy, what makes it sick?

Modern techniques provide new insights into the development of diseases

AN INTERVIEW WITH PROFESSOR DR. FAN LIU AND DR. SIGRID MILLES

How is the FMP using new techniques such as NMR and mass spectrometry to help understand how disease develops?

Milles: NMR, which stands for nuclear magnetic resonance spectroscopy, and single-molecule fluorescence spectroscopy are both incredibly powerful tools in biomedical research. They allow us to explore the molecular and atomic details of biological samples. NMR spectroscopy enables us to study the structure and dynamics of proteins, nucleic acids, and other biological molecules in detail. This is particularly useful in the case of diseases caused by defective molecules or molecules with altered structures, such as genetic diseases and cancer.

Liu: In contrast, we use mass spectrometry to determine the mass and chemical composition of molecules in a sample. This technique is used in proteomics, for example, to identify differences in the composition of proteins in healthy and diseased samples. The findings can later be used to develop biomarkers.

Professor Dr. Fan Liu leads the Mass Spectrometry Core Facility.

Dr. Sigrid Milles leads the Integrated Structural Dynamics Junior Group.

That sounds really exciting. Can you give an example of a disease where these techniques have been particularly beneficial?

Milles: There are several examples, such as the measles virus infection. NMR and fluorescence spectroscopy have revealed how the measles virus packages its genome. In addition, NMR spectroscopy has enabled the discovery of a dynamic interaction between two viral proteins that is key to the replication of the virus.

Liu: Mass spectrometry, on the other hand, allows us to study the composition of pathogens such as viruses. This can give us clues as to which proteins might be good targets for antiviral therapeutics.

And what opportunities do you see for these technologies in the future?

Milles: The future is very bright. We can expect the resolution and sensitivity of these techniques to continue to improve, giving us even more detailed insights into the molecular biology of diseases. In this context, we are looking forward to the new NMR spectrometer with a very high magnetic field of 28.2 Tesla that will soon be installed on our campus. This instrument will allow us to study particularly large and dynamic proteins at high resolution. It will not only help us to better understand diseases, but will also give us completely new insights into fundamental biomedical processes.

The interview was conducted by Silke Oßwald

3

New research methods

Sophisticated new techniques allow us to expand our core facilities and thus our knowledge

FMP Green Initiative

Remarkably sustainable!

BY DR. AGATA WITKOWSKA AND SILKE OSSWALD

Four years ago, something special happened at the FMP: A group of dedicated young researchers launched an initiative with the mission of promoting a culture of sustainability and introducing environmentally friendly practices in the laboratory. In 2021, Professor Volker Haucke's laboratory was certified as Germany's first "green lab" by the non-profit organization My Green Lab. But what does it mean to be a "green lab"?

Given that biomedical research is responsible for producing 5.5 million tons of plastic waste annually [1] and consumes on average 3 to 5 times more energy than offices [2], there is an urgent need for sustainable practices. Our goal is to raise awareness of this challenge and promote sustainable solutions. We have taken a number of steps to achieve this. One of the first steps was to build sustainability awareness in our team through education and training. Many small changes, such as turning off lights and other appliances when not in use, reducing water use, and making more conscious consumption decisions, add up to a significant impact on lowering resource usage. We have also introduced a more efficient waste separation system and increased the temperature of our ultra-low temperature freezers to save energy. After all, raising the temperature by just 10 degrees Celsius (from -80 °C to -70 °C) can reduce energy consumption by 30 to 40 percent. On top of that, we have largely implemented the 3Rs of sustainability – reduce, reuse, and recycle – to minimize laboratory waste. We now use glassware whenever possible and try to limit the use of single-use plastics also by reusing them, and additionally participate in many manufacturers' take-back programs. Our efforts have paid off: As of July 2023, four labs at the FMP had already been certified by My Green Lab – including the Fiedler laboratory, the Hackenberger laboratory, the Haucke laboratory (recertified at the highest green level in 2023), and the Broichhagen laboratory. In addition, several members of the initiative have been involved in various outreach activities to promote a culture of sustainability in research groups across Europe.

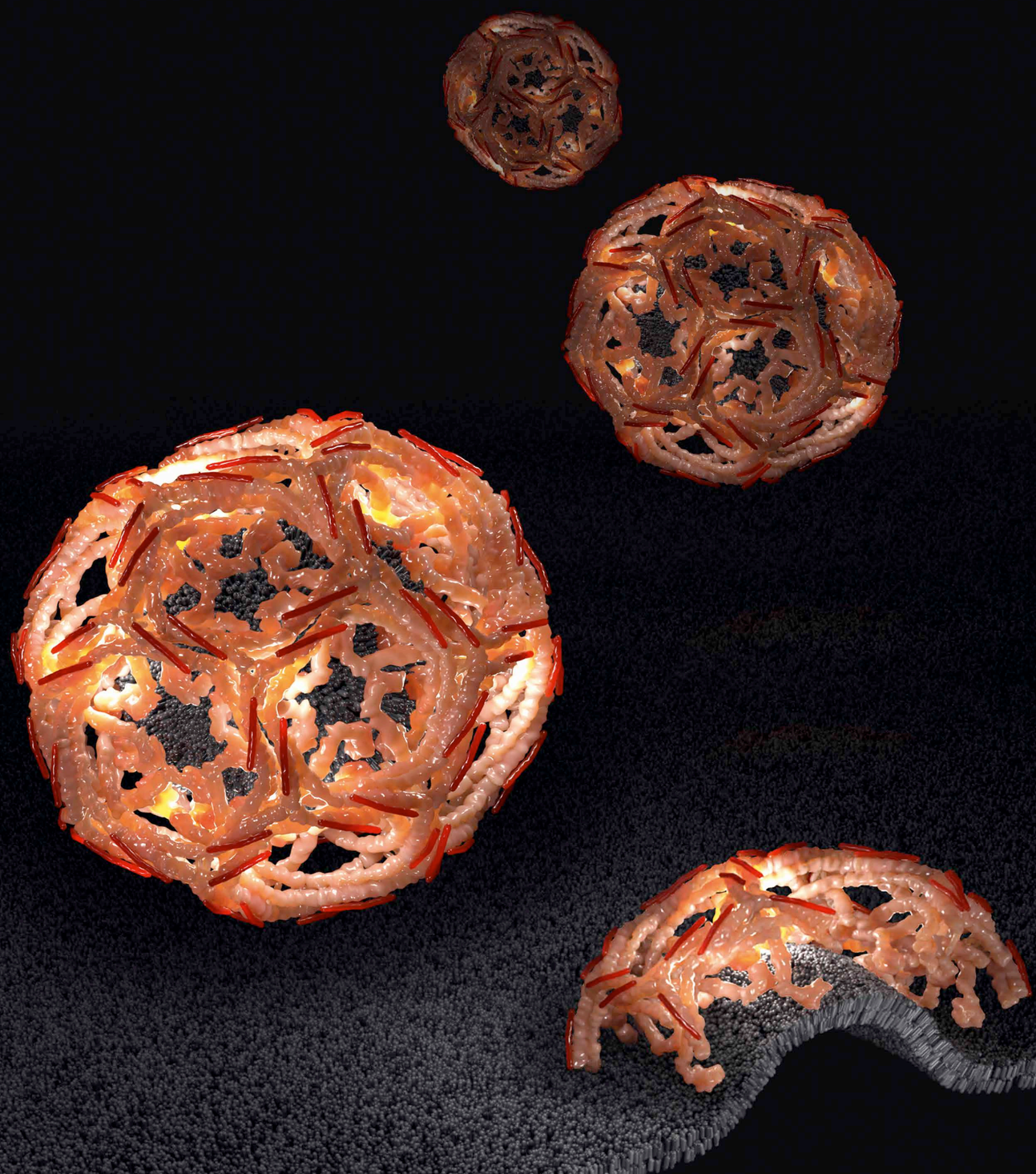
↑ Scientist Dr. Agata Witkowska has been part of the Green Initiative from day one.

1

The image shows vesicles in which cells internalize substances through their cell membranes (endocytosis). This process can be exploited in drug development to target drug delivery to specific cell types or tissues.

The newly discovered compound PITCOIN affects the membrane structure of platelets (blood components). Turn the page to learn about its effects.

Image: Barth van Rossum



NOVEL THERAPEUTIC APPROACHES

Hard to pronounce, but full of promise!

PI3KC2α – a complicated name for a novel therapeutic target for the treatment of thrombosis. The approach also has potential for cancer treatment.

↑ Marta Diceglie and Dr. Davide Cirillo work in Marc Nazaré's Medicinal Chemistry Research Group, where PITCOIN was developed. Based on the first hit, the group obtained the PITCOINs through chemical optimization, i.e., the design of more than 150 derivatives and their profiling.

↑ Dr. Wen-Ting Lo has been investigating the kinase PI3KC2α for several years.

Professor Dr. Volker Haucke leads the Molecular Pharmacology and Cell Biology Research Unit. He is also Director of the FMP.

"It is the years of persistent work in basic research that ultimately pave the way for innovation. This project is a prime example."

Dr. Jens von Kries leads the Screening Unit. Screening yielded the hit which led to the PITCOINs, the chemical structure of which is shown.on the left side.

Thromboses such as venous thrombosis and pulmonary embolism, which occur with an annual incidence of about 1 per 1,000 adults, pose a threat to human health, particularly in the elderly. Patients take blood thinners to prevent blood clots, but these medications can have serious side effects such as bleeding.

The lipid kinase PI3KC2α is known to play an important role in blood coagulation by regulating the function of platelets, which in turn play a key role in initiating blood clotting. This difficult-to-pronounce kinase – PI3KC2α – is therefore a prime target for the development of new antithrombotic drugs. Researchers at the FMP have had their eye on this target for a long time and have studied its structure intensively. Now, for the first time, they have succeeded in developing and characterizing PI3KC2α inhibitors.

After an extended search in the Screening Unit and further chemical optimization studies, the researchers were able to identify a compound that binds particularly well to PI3KC2α: PITCOIN3 has a remarkable selectivity for PI3KC2α and has been shown to impair platelet membrane remodeling and thrombus formation. "The antithrombotic effect of PITCOIN inhibitors counteracts thrombosis through effects on the internal membrane structure of platelets rather than by blocking their activation, thus providing an improved therapeutic window," stated Professor Volker Haucke, explaining the findings.

The new PITCOIN inhibitors represent a promising new approach for the development of related drug candidates. In addition, PITCOINs may be important tools for other researchers to investigate and uncover unknown functions of PI3KC2α.

The most important news, however, is that the results presented could open up new possibilities for the treatment of thrombosis, according to the researchers involved. Not only that: PITCOINS also inhibit the migration of breast cancer cells in the laboratory. This drug may therefore thus be a promising candidate for cancer therapy.

▶ VIDEO

Science Clip:
The Molecule that Loved Me

Less invasive cancer treatment

Antibody-drug conjugates are considered a new generation of biopharmaceuticals that deliver drugs where they are needed in the body to fight disease. A new cancer therapy technology developed at the FMP delivers more drugs directly to tumor cells – with fewer side effects. This makes chemotherapy more effective and better tolerated.

↑ Targeted molecular transporters reduce side effects, shown here by the pink tires.

When cancer is treated with conventional chemotherapy, healthy cells are also affected. To reduce the often severe side effects, the FMP is working with the company Tubulis to develop a new generation of antibody-drug conjugates. The strength of this class of drugs lies in the combination of the precision with which the antibody targets the tumor cell and the high potency with which the targeted cell is attacked by the associated chemotherapeutic agent. This is achieved by the antibody recognizing specific surface proteins on cancer cells and delivering the drug directly to the tumor cell. This allows highly potent cytotoxins to be delivered directly into cancer cells where they can exert their toxic effects. Healthy cells and organs are spared.

Each antibody must deliver as much drug into the cell as possible to effectively kill the targeted cancer cells. Therefore, one goal in the development of new antibody-drug conjugates is to increase the number of drugs per antibody. One problem that arises is that conventional and effective drugs that are well suited for antibody conjugates are often molecules with large hydrophobic (water-repelling) structures. These structures, which are poorly soluble in aqueous systems, can cause the antibody-drug conjugates to aggregate, or stick together, in the blood. As a result, they are quickly removed from the bloodstream and often do not reach their target, the tumor.

Christian Hackenberger and his team have developed a smart solution to this problem: water-soluble anchors can now be used to easily attach hydrophobic drugs to the antibody. Figuratively speaking, this means that the drugs are given a water-loving “buoyancy aid” based on polyethylene glycol chains.

As a result, the conjugates are more water soluble and circulate longer in the body, allowing them to reach the tumor with a high degree of precision to deliver their deadly cargo. In the future, the new technology will help in the development and commercialization of new antibody-drug conjugates that enable effective – and therefore well-tolerated – cancer therapies.

Professor Dr. Christian Hackenberger leads the Research Unit Biomolecule Modification and Delivery at the FMP. Research projects in the laboratory combine techniques and approaches from organic chemistry, biochemistry, and biophysics, with a major emphasis on synthetic methodology development for natural protein modifications.

A major success for the group was the development of new conjugation techniques, which enabled the spin-off of the company Tubulis.

!

Tubulis was founded as a spin-off of the FMP and the Ludwig-Maximilians-Universität (LMU) München in 2019.

Molecules inhibit the formation of metastases

Cancer cells in the bloodstream are a major challenge in cancer therapy. The FMP spin-off PROSION Therapeutics is addressing this challenge by developing a novel method to inhibit the migration of these cells.

Dr. Matthias Müller and Juliana Rojas Pión in the Biochemistry Laboratory at Prosion's Berlin site.

Cancer is an insidious disease that can return even after a tumor appears to have been completely removed because dormant cancer cells often remain in the bloodstream. Researchers at the FMP have developed a novel method to stop these dangerous cancer cells from migrating and thus prevent the formation of metastases.

The point of attack is the Ena/VASP family of proteins, which play an important role in cell movement and shape change and are significantly overexpressed in highly invasive cancer cells. Targeted inhibitors aim to limit the ability of cancer cells to move and prevent them from metastasizing.

As early as 2015, the team of researchers developed a molecule that binds to the Ena/VASP protein family, but it was not sufficiently effective. After further chemical modification, a set of molecules has now been successfully modified to have an impact in a living organism in small quantities. Experiments have demonstrated that cancer cells treated with the substances lose their ability to migrate towards attractants.

Seeking to thwart dormant tumor cells. Team meeting at PROSION's Cologne site.

Tests on zebrafish embryos implanted with breast cancer cells confirmed that this method also works in the living organism. Keeping the fish in a solution containing the modified molecules significantly reduced the number of metastasizing cancer cells.

Subsequent studies in mice further substantiated the pharmacological potential: studies in triple-negative breast cancer and pancreatic cancer models showed that treatment with the inhibitors significantly inhibited cancer progression.

The researchers are confident that these results could pave the way for new therapies that prevent or slow down metastasis in parallel with chemotherapy. The next step is to further optimize the pharmacological properties of the molecules to achieve maximum efficacy with minimum toxicity. Despite the challenges that lie ahead, this development represents an important first step toward a potential new cancer therapy.

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PROSION is a biotech startup spun out of the FMP and the University of Cologne.

2

UNDERSTANDING THE BODY AT THE MOLECULAR LEVEL

The lethality of tiny amounts of poison

Bacteria are masters of manipulation, playing with our cells and wreaking havoc on the body. Researchers at the FMP have unraveled the mechanism of bacterial Tc toxins and shown how they attack the skeleton of our cells, the cytoskeleton.

Dr. Daniel Roderer leads the Research Group Structure and Mechanism of Microbiome-Driven Diseases.

"Using cryo-electron microscopy and single particle analysis, we determine the structures of protein complexes that facilitate host-microbiome interaction, a prerequisite for the structure-based development of personalized drugs."

Professor Dr. Hartmut Oschkinat leads the NMR-Supported Structural Biology Research Unit.

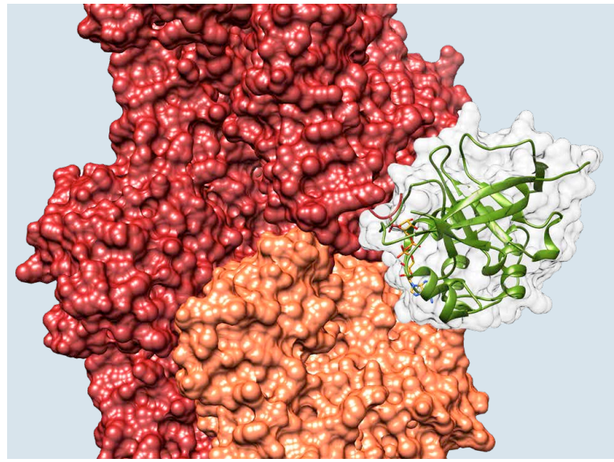
"For a long time, we struggled with obtaining a complete picture of the intoxication process. We now know the mechanism of action of Tc toxins and can say that nature did quite a good job."

Many bacteria produce deadly toxins, from which a few thousandths of a milligram can be enough to kill a living organism. Examples include anthrax toxin and Tc toxins, which translocate toxic enzymes into the cells of target organisms in a complex, multi-step process. The intoxication process caused by Tc toxins, which are produced in many bacteria, can harm insects and humans.

Researchers at the FMP, together with colleagues from the Max Planck Institute of Molecular Physiology in Dortmund, have now learned more about how the toxic enzymes Tc toxins work. First, they wanted to know how the toxins were assembled. They were able to visualize their structure and transport mechanism using two techniques: Cryo-electron microscopy (cryo-EM) and nuclear magnetic resonance (NMR). While cryo-EM analyzes high-resolution images of vitrified samples, NMR uses very strong magnetic fields to provide atomically precise insights into molecular structures. For this purpose, the FMP has a special facility with powerful magnets that are more than 300,000 times stronger than the Earth's magnetic field.

In their investigations, the researchers discovered that Tc toxins act in distinct steps. First, several subunits of the complex work together to transport the toxic molecule to its target, which is the cell. The protective cell membrane is penetrated with a molecular syringe and the actual toxic molecule, i.e., the toxic enzyme, is injected. In the process described, this toxic enzyme only accounts for 2 percent of the total Tc toxin's mass, so the bacteria devote significantly more effort to syringe formation than to toxin production. Once it reaches its target, the toxin causes the cytoskeleton to collapse.

Unlike the human (bone) skeleton, cells must be able to respond and adapt to their environment. The cytoskeleton is therefore not comparable to human bones, but rather to flexible steel ropes that can be attached and detached depending on the situation. One important molecule that forms these rope-like filaments is actin. This is precisely where the injected toxin takes effect: It changes the molecule through a chemical reaction that prevents the filaments from breaking down properly. As the cytoskeleton continues to build up in an uncontrolled manner, the cell dies from the unregulated expansion of actin filaments, which eventually leads to their aggregation.



↑ The toxin of the toxin complex (green) binds to actin (red/orange). The chemical reaction takes place at the point of contact, permanently altering the actin and damaging the cytoskeleton.

The methods used for this research – cryo-EM and NMR – complemented each other: While the electron microscopy images provided a detailed picture of the entire Tc toxin and the actin filaments, NMR provided insights into the small toxin molecule and its effect.

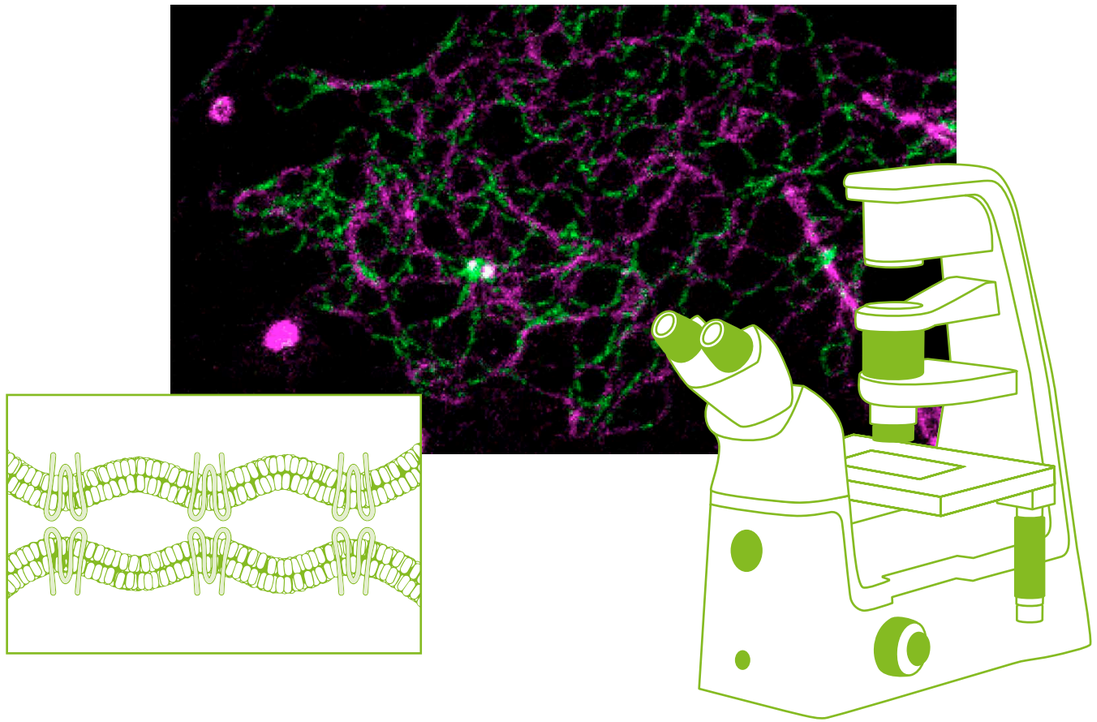
The researchers plan to continue working on this project in the future. The latest evidence is that toxic enzymes can be exchanged within Tc toxins without loss of function. This allows other molecules to be injected, offering the prospect of targeted treatment of infections.

PODCAST

WSR058 The Dark Side of the Microbiome & Cryo-Electron Microscopy – An interview with Dr. Daniel Roderer (conducted in German)

Tissue barriers in the body

Tight junctions decide what is allowed to enter the body, almost like a VIP club. Researchers have now cracked the gatekeepers' code. Let's take a look behind the velvet curtain!



↑ Claudins interlock like zippers to seal spaces between epithelial cells. There are five different organization principles for how the 26 proteins intermix and segregate.

↑ Let only what is necessary pass, otherwise form a tight barrier: STED microscopy reveals for the first time the nanoscale organization of tight junction claudins.

Dr. Martin Lehmann leads the Cellular Imaging Facility, a microscopy core facility at the FMP.

Tight junctions (TJ) play a key role in the human body. They act like highly specialized gatekeepers, selectively letting in what is allowed to enter, while protecting the inside of the body from bacteria and their toxins. These biological barriers are made up of claudins that come in 26 variants in humans. They are found wherever different cells form epithelial sheets in tissues and organs, like intestine, kidney and lung. Claudins can assemble in different combinations to form barriers with variable permeabilities. But until now, it was unclear exactly how they did this.

A team of researchers at the FMP has solved this mystery. Using super-resolution stimulated emission depletion (STED) fluorescence microscopy, a technology with much higher resolution than previous fluorescence microscopy, it was possible to study the exact structure and organization of claudins at the nanometer scale.

The results of this study are revealing – they show that claudins interlock like zippers to seal intercellular spaces. However, some claudins are unable to polymerize into strands independently, which means that they are reliant on the cooperation of other claudins to form functional tight junctions. In addition, there are five different ways in which claudins can intermix and segregate. These findings may have implications for future medical research. After all, mutations in claudins are involved in a number of hereditary diseases, such as the HELIX syndrome, a rare condition causing reduced sweat production.

The researchers caution that they are still a long way from translating this research into clinical practice. However, the new fundamental understanding of the structure of these networks can serve as a basis for the future search for small molecules that could affect tight junction function. In other words, the FMP researchers have created a kind of blueprint for claudins that could help us better understand and treat diseases in the future.

↑ Using super-resolution microscopy, doctoral student Rozemarijn van der Veen resolves claudin polymers.

Ions keep things moving

Researchers unravel an important aspect of cellular processing of extracellular material.

Large vesicles, called macropinosomes, take up extracellular material in a non-specific manner and transport it either deeper into the cell for further processing or back to the cell surface ("recycling"). Vesicle shrinkage plays a critical role in this process. The chloride channel ASOR, which is essential for shrinkage, may be important for the function of immune and cancer cells.

Professor Dr. Dr. Thomas Jentsch has already discovered many ion channels and described their biological functions, identifying some of them as being involved in genetic diseases. The chloride channel ASOR is one of his greatest discoveries. At the FMP, Jentsch leads the Physiology and Pathology of Ion Transport Research Unit.

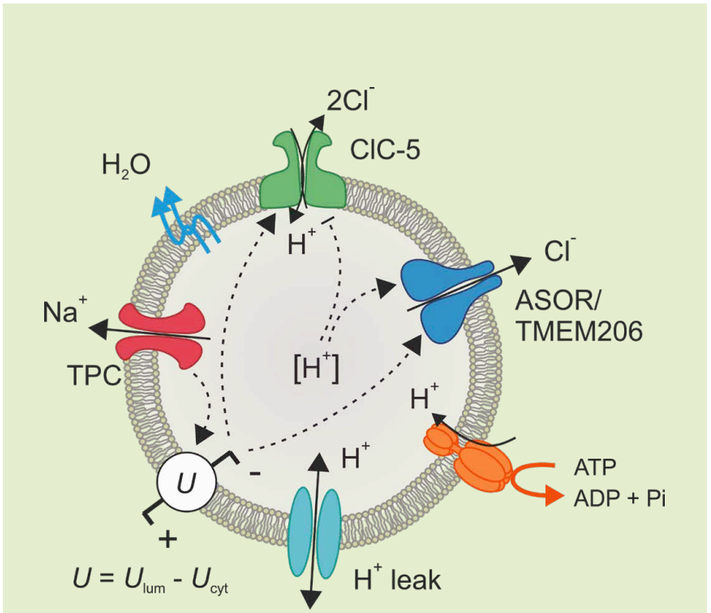
In the human body, cells continuously absorb water, salts, and nutrients to perform their functions. One of the ways they do this is through vesicles, which are small bubbles enclosed by lipid membranes. Macropinosomes, which are especially large vesicles, play a particularly important role in immune cells and cancer cells.

The processing of enclosed materials requires vesicle shrinkage. This process is achieved by the release of water, which is indirectly driven out of the vesicles by salt transport through specific ion channels.

The team of researchers identified the acid-sensitive chloride channel ASOR as a key factor in vesicle shrinkage. In the absence of ASOR, vesicles take longer to shrink. This shrinkage is central to the functioning of cells. It enables the transport of ingested substances back to the outside of the cell and prevents their premature degradation. Interestingly, the researchers observed that cancer cells without the ASOR channel can grow faster because they can absorb more nutrients from their environment.

Future studies will investigate the role of ASOR in further steps of vesicle processing. This will provide a basis for understanding and treating various disease processes.

UNDERSTANDING THE BODY AT THE MOLECULAR LEVEL



Shrinkage of macropinosomes – large vesicles that take up extracellular material for further processing in the cell, in a non-specific manner – is mediated by salt (NaCl) efflux through parallel TPC Na^+ channels and the ASOR Cl- channel. Recently, in 2019, Jentsch's group molecularly identified the acid-sensitive ASOR channel as Tmem206. The voltage and acid sensitivity of the channels are critical to this process, as the group has shown experimentally and through mathematical modeling.

"Degradation and recycling of protein fragments are balanced in healthy cells. Tumor cells grow faster when the ASOR channel is absent."

Doctoral student Mariia Zeziulia in the laboratory.

3

The gate (in blue) is closed with an M2M cross-link, preventing substrates from accessing the active center.
The rhomboid protease shown here is an enzyme involved in several diseases. Turn the page for the latest results.

Image: Barth van Rossum

NEW RESEARCH METHODS

Keeping an eye on harmful enzymes

At first glance, Parkinson's disease and malaria have little in common. But a certain enzyme is involved in both diseases. And this is the subject of intensive research at the FMP.

↑ Doctoral student Leonie Kurz prepares a sample.

↑ NMR (nuclear magnetic resonance) spectroscopy allows visualization of the enzyme structure at the atomic level. Samples are analyzed in an extremely strong magnetic field. In the large inner section, the solenoid coil must be cooled to just above absolute zero (approximately -269 °C / 4 K).

NEW RESEARCH METHODS

Professor Dr. Adam Lange leads the Molecular Biophysics Research Unit. The group uses solid-state NMR spectroscopy and a variety of other biophysical methods to study membrane protein structure and dynamics.

Parkinson's disease, malaria, cancer and diabetes: All are thought to be linked to a small enzyme – one that we cannot live without. After all, rhomboid proteases are involved in almost all biological (metabolic) processes. But because the enzymes also maintain pathological processes in the worst case, they are an important therapeutic target that is literally "under scrutiny" at the FMP.

However, rhomboid proteases are difficult to study because they are located in the cell membrane (cell envelope). In 2019, FMP researchers succeeded in producing dynamic images of these proteases for the first time – using solid-state NMR spectroscopy.

The three-dimensional, dynamic image indirectly revealed how they perform their primary task of cleaving other membrane proteins, triggering a signaling cascade in the cell. It also came to light that, for the cleaving process to happen, a gate opens briefly, enabling substrates to move from the otherwise anhydrous cell membrane to the hydrous active site of the enzyme.

In another study in 2023, the FMP researchers were able to show that this enzyme activity is dependent on gate dynamics. If the gate was easier to open (due to mutations), enzyme activity increased; if the gate was closed, activity came to a standstill. This time, the results obtained by solid-state NMR spectroscopy were corroborated by other biophysical and biochemical methods, as well as by computer simulations.

This work has helped researchers better understand how these enzymes function in healthy and diseased organisms. This insight is important for the development of new drugs. The search for new compounds is already well underway at the FMP.

Professor Dr. Han Sun leads the Structural Chemistry and Computational Biophysics Research Unit. The group specializes in the structure of drug-like molecules and their interactions with proteins.

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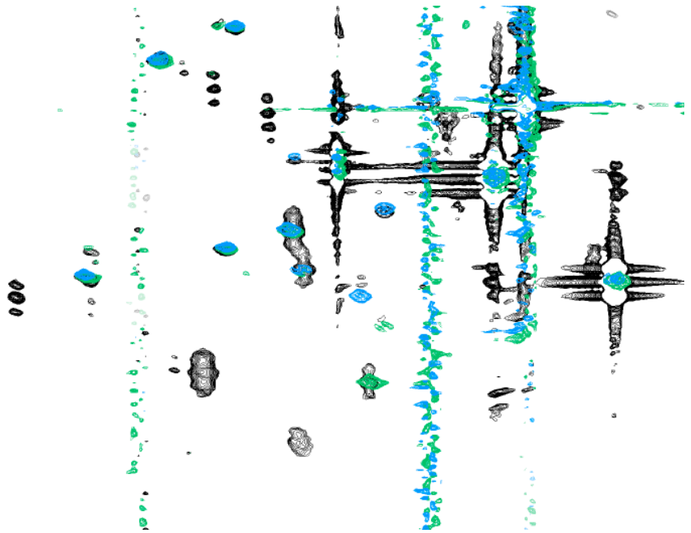
Rhomboid proteases are a clinically important target. The new findings represent important groundwork for the development of novel drugs.

Where basic research meets avant-garde art

Signaling molecules tell the body what biological processes need to occur, when, and how. A new way of looking at the metabolism of these important molecules was developed at the FMP. The results are not unlike Pollock paintings.



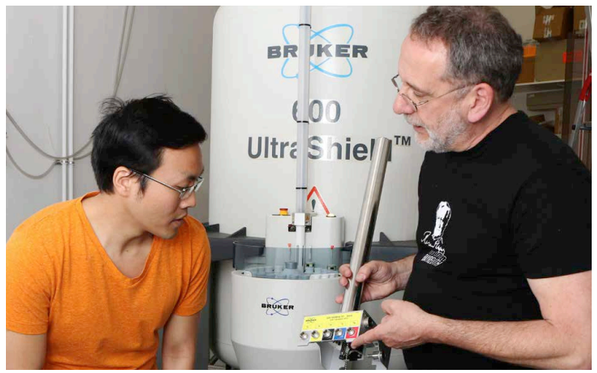
Our cells must constantly communicate with each other for the body to function properly. Signaling molecules are an important part of this communication process. They also coordinate processes within the cell, communicating which biological processes should occur, when, and how. Inositol polyphosphates (InsPs) are one such group of signaling molecules. InsPs have many faces – they consist of a myo-inositol backbone with up to eight uniquely arranged phosphate groups.

↑ NMR helps us to understand the structure of molecules and determine their quantity. And sometimes the resulting spectra resemble art.

NEW RESEARCH METHODS

Professor Dr. Dorothea Fiedler leads the Chemical Biology of Signal Transduction Research Unit.

Dr. Peter Schmieder leads the Nuclear Magnetic Resonance Spectroscopy Core Facility.



↑ Minh Nguyen Trung from Dorothea Fiedler's group and Peter Schmieder in front of an NMR spectrometer. This is where samples are analyzed with atomic resolution.

Different InsPs activate specific cellular processes. To avoid permanent overactivation, the cell must regulate how InsPs are metabolized. However, this metabolism is only partially understood because InsPs are difficult to detect.

For analysis mixtures of InsPs from biological samples usually need to be physically separated. This works well for InsPs with many phosphate groups, but has weaknesses in the case of less phosphorylated InsPs. Another major challenge is the differentiation of InsPs with mirror-image arrangements of phosphate groups, called enantiomers.

FMP researchers have therefore taken a completely new approach to looking at the metabolism of the difficult-to-detect InsPs. The core idea is to separate mixtures of InsPs spectroscopically, rather than physically, using two-dimensional nuclear magnetic resonance (2D NMR) spectroscopy.

The resulting spectra resemble Pollock paintings, with each cluster of spots containing structural information about the InsPs.

To detect InsPs that are present only in small amounts, the team combined 2D NMR with a method called isotope labeling, which makes the signals in the NMR more intense. This approach allowed the study of complex mixtures of highly and lowly phosphorylated InsP, including the elusive enantiomers, in human cell lines. The method also revealed a previously unknown degradation pathway for $InsP_6$, the most abundant InsP, in human cells.

The researchers not only gained important new insights into signaling molecules, but also demonstrated that 2D NMR in combination with isotope labeling is a new, useful tool for studying InsPs metabolism in humans.

A molecular color box

New techniques reveal previously hidden details about receptors that play a key role in the treatment of diabetes and obesity. Using fluorescent dyes and gene editing, researchers are gaining new insights into the localization and dynamics of these important proteins.

Dr. Johannes Broichhagen, leads the ChemBioProbes Research Group.

"Through our research, we contribute to a deeper understanding of how to improve approaches for treating diabetes and obesity."

Using a new technique and lots of bright colors, researchers at the FMP have shed light on a little-studied protein at the endogenous level: the glucagon-like peptide-1 receptor (GLP1R). GLP1R plays a critical role in blood glucose regulation and satiety. Consequently, this protein or receptor is found in both the pancreas and the brain. GLP1R has been a therapeutic target for several years: Modern GLP1R agonists are drugs used to treat diabetes and obesity.

The molecular mechanism is well understood: The GLP1R agonist binds specifically to its receptor and activates it, triggering a signaling cascade in the cell that causes the body to release more insulin. This helps regulate blood glucose levels and bring them down to a healthy level.

Until now, it has been difficult to understand where this particular protein naturally occurs in the body, how it is grouped, and how it behaves or moves.

A clear case for the FMP: By combining several techniques from different disciplines, more precise research can now be carried out. The researchers, in collaboration with Professor Dr. David J. Hodson, University of Oxford, developed a genetic mouse model using the Nobel Prize-winning CRISPR/Cas9 genetic scissors to fuse a special enzyme into the natural Glp1r gene. This enzyme, or more precisely the SNAP tag, can then be labeled with chemical dyes that have also been newly developed at the FMP.

Ramona Birke observes a solution under the microscope. The technician has been part of the ChemBioProbes group, which was established as a junior research group at the FMP in early 2020, from day one.

The use of fluorophores: Fluorophores are molecules that can absorb and emit light. They are used to label proteins so that they can be visualized under a fluorescence microscope.

The label color is freely selectable, allowing a wide range of other wavelengths to be used to better study the position and movement of GLP1R. By studying GLP1Rs at the nanoscopic level – i.e., at the extremely small molecular scale – the researchers discovered that GLP1Rs are highly organized. Therefore, it can be hypothesized that their function is related to the arrangement of specific structures or patterns. Another indication is treatment with GLP1R agonists, bringing the movement and distribution of these receptors on the cell surface to a standstill.

The combination of genome editing and fluorescent dyes made it possible to study the GLP1R receptor in its natural environment for the first time. The researchers were able to show how this receptor changes its behavior in the cell in native and complex tissues. Thanks to a molecular color box.

The FMP in figures

BUDGET IN 2022*

19.1 m
IN TOTAL

EXTERNAL FUNDING IN 2022*

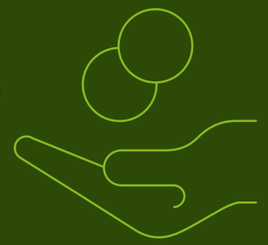
DFG
3.6 m

EU/INTERNATIONAL
2.9 m

OTHER (INDUSTRY, FOUNDATIONS, ETC.)
1.4 m

OTHER PUBLIC SOURCES (SAW, UNIS, ETC.)
1.2 m

GERMAN FEDERATION
0.4 m



9.5 m
IN TOTAL

*IN EUROS

PUBLICATIONS IN 2022

108
IN TOTAL

89
OF WHICH
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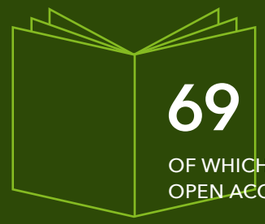

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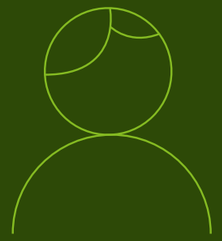
OF WHICH
OPEN ACCESS

FMP STAFF



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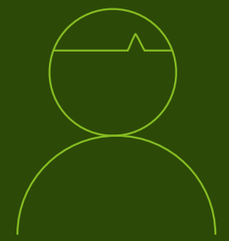
WOMEN

+19 VISITING SCIENTISTS



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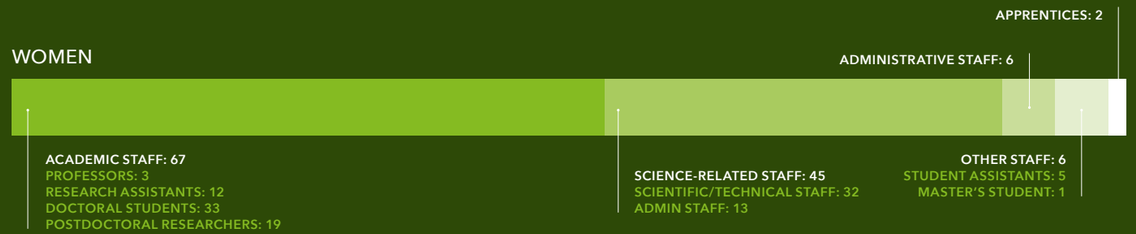
MEN

+19 VISITING SCIENTISTS

STAFF STRUCTURE IN 2022



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35
NATIONALITIES

5
CONTINENTS

Research groups

At the FMP, research is conducted in independent research groups in one of three sections: Molecular Physiology & Cell Biology, Structural Biology, and Chemical Biology. The overview shows the research groups and examples of their research topics.

Research section MOLECULAR PHYSIOLOGY AND CELL BIOLOGY

Name of group
MOLECULAR PHARMACOLOGY AND CELL BIOLOGY

Leader: Professor Dr. Volker Haucke
Type of group: Research Unit
Topics: From stem cells to nerve cells · Neurotransmission in the brain · Brain diseases (from Alzheimer's to stroke) · Aging research

Name of group
PHYSIOLOGY AND PATHOLOGY OF ION TRANSPORT

Leader: Professor emeritus Dr. Dr. Thomas Jentsch
Type of group: Research Unit
Topics: Signal transduction between and within cells · Intracellular vesicle transport · Ion transport-related diseases (e.g., neurodegeneration, epilepsy, kidney disease, hypertension) · Structure and function of ion transport proteins · Identification of novel channels and their interaction partners

Name of group
SYNAPSE BIOLOGY

Leader: Dr. Noa Lipstein
Type of group: Junior Research Group
Topics: Information transfer in the brain · Neurodevelopmental disorders · Neurodegenerative diseases

Name of group
CELLULAR IMAGING FACILITY

Leader: Dr. Martin Lehmann
Type of group: Core Facility
Topics: Super-resolution STED fluorescence microscopy (STED = stimulated emission depletion) · Ultrastructure of organelles, cells, and tissues · Development of correlative light and electron microscopy · Quantitative image analysis · Nanostructure & function of paracellular barriers

Name of group
CELL ENGINEERING FACILITY

Leader: Professor Dr. Ralf Schülein
Type of group: Core Facility
Topics: CRISPR/Cas · Gene knock-out · Gene knock-in · Genetic engineering tools

Name of group
ANIMAL FACILITY

Leader: Dr. Natali Wisbrun
Type of group: Core Facility
Topics: Animal welfare · Alternatives to animal testing · 3R research

Research section STRUCTURAL BIOLOGY

Name of group
MOLECULAR BIOPHYSICS

Leader: Professor Dr. Adam Lange
Type of group: Research Unit
Topics: Biomolecular nuclear magnetic resonance (NMR) spectroscopy · Protein structure and dynamics · Membrane proteins in their natural environment · Bactofilin filaments in Helicobacter pylori · Bacteriophages as an alternative to antibiotics

Name of group
STRUCTURAL INTERACTOMICS

Leader: Professor Dr. Fan Liu
Type of group: Research Unit
Topics: Mass spectrometry and proteomics · Protein structure dynamics and interactions · Spatially resolved proteomics · Virus–host interactions

Name of group
NMR-SUPPORTED STRUCTURAL BIOLOGY

Leader: Professor emeritus Dr. Hartmut Oschkinat
Type of group: Research Unit
Topics: Protein NMR in solution and in the solid state · Development of DNP methods · Studies of biofilm protein structure and function · Studies of protein–protein interactions · Structure determination of membrane proteins

Name of group
INTEGRATED STRUCTURAL DYNAMICS

Leader: Dr. Sigrid Milles
Type of group: Junior Research Group
Topics: Nuclear magnetic resonance spectroscopy · Single molecule fluorescence spectroscopy · Proteins without a stable three-dimensional structure · Protein dynamics · Interaction networks

Name of group
STRUCTURE AND MECHANISM OF MICROBIOME-DRIVEN DISEASES

Leader: Dr. Daniel Roderer
Type of group: Junior Research Group
Topics: Bacterial adhesion to human cells · Structural analysis of membrane proteins · Protein–protein interactions · Microbiome-associated carcinogenesis · Cryo-electron microscopy

Name of group
NMR SPECTROSCOPY FACILITY

Leader: Dr. Peter Schmieder
Type of group: Core Facility
Topics: NMR method development · Structural elucidation of natural products · NMR analysis of small molecules · Studies of protein structure and dynamics · Studies of protein–molecule interactions

Research section
CHEMICAL BIOLOGY

Name of group
CHEMICAL BIOLOGY OF SIGNAL TRANSDUCTION

Leader: Professor Dr. Dorothea Fiedler
Type of group: Research Unit
Topics: Cellular signal transduction · Protein modification · Cellular phosphate balance · Hyperphosphorylated messenger molecules · Chemical tools

Name of group
BIOMOLECULE MODIFICATION AND DELIVERY

Leader: Professor Dr. Christian Hackenberger
Type of group: Research Unit
Topics: Biopharmaceuticals · Post-translational Protein Modifications (PTMs) · Targeted Drug Delivery · Antibody-Conjugates · Cell-Permeable Proteins · Chemical Tools

Name of group
STRUCTURAL CHEMISTRY AND COMPUTATIONAL BIOPHYSICS

Leader: Professor Dr. Han Sun
Type of group: Research Unit
Topics: Ion channels and membrane proteins · Mechanisms of membrane transport · Computer-aided drug design · Structural chemistry and chirality

Name of group
CHEMBIOPROBES

Leader: Dr. Johannes Broichhagen
Type of group: Junior Research Group
Topics: Chemical synthesis · Fluorescent dyes · (High-resolution) microscopy · Receptors in diabetes research · Endogenous protein labeling

Name of group
MEDICINAL CHEMISTRY

Leader: Dr. Marc Nazaré
Type of group: Research Group
Topics: Chemical tools · DOTAM-based diagnostics · Fluorescent tools for the endocannabinoid system · Infection and tumor visualization · Phosphatase and kinase inhibitors

Name of group
SCREENING UNIT

Leader: Dr. Jens Peter von Kries
Type of group: Core Facility
Topics: Genome-wide analysis of gene functions · Drug discovery for disease diagnosis/inhibition · Cellular pathology: pattern recognition for targeted disruption of cell functions based on variations in cell structure · Identification of drugs to inhibit enzymes / protein interactions for disease treatment

Name of group
COMPOUND MANAGEMENT

Leader: Dr. Edgar Specker
Type of group: Core Facility
Topics: Automated storage of substance libraries · Provision of screening plates

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The FMP hosts research groups and core facilities. See below for more information and a brief description of each group.

!

We believe it is important to share our knowledge. From apprenticeships to academic careers, we welcome you. Simply drop us a line!

!

Any questions? Visit us at the Long Night of the Sciences (Lange Nacht der Wissenschaften) on June 22, 2024.

!

In the FMP ChemLab, high school students take on the role of chemists and, working in small teams and guided by scientists, solve problems relating to natural and active substances, polymers, and dyes. All courses take place in the Life Science Learning Lab.

COURSES
Indigo & Co. – What a colorful array
Caffeine – Compound or drug?
Plastics – Materials for (almost) everything!?
Follow your nose! – Perfume distillation
Carbohydrates: From glucose to glycoproteins

Listening in on Wirkstoffradio

Since September 2018, Wirkstoffradio has provided a platform for engaging conversations about the broad and fascinating field of compounds and drug discovery. The host, Bernd Rupp, invites his interviewees to explain their research projects in an understandable and simple way. In addition to providing their listeners with factual information, the researchers are able to convey their enthusiasm and fascination for their particular topic.

↑ Wirkstoffradio: Dr. Bernd Rupp and Professor Hans-Dieter Höltje talking to Professor Ralf Schülein about the topic of drugs and their side effects.

The episodes broadcast on Wirkstoffradio cover a wide range of topics. Fundamental aspects such as “What are drugs?”, “The role of the membrane in cellular signal transduction”, and “Natural killer cells and the immune system at work” are covered as well as topics of direct relevance to everyday life. Examples include “Stroke, stroke units and research responsibility”, “Drugs for depression, migraine, and vomiting”, and “Ibuprofen, ASA, acetaminophen, and the trinity of weak analgesics”.

Subscribe to Wirkstoffradio for free and listen wherever you are – all you need are earbuds and a podcast app.

Wirkstoffradio is a science communication project initiated by the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) and supported by the Leibniz Research Alliance “Bioactive Compounds and Biotechnology”. The science podcast is a unique resource designed to help people understand the fascinating relevance of drugs and their research to everyday life.

PODCAST

WSR007 Studying molecules atom by atom with NMR spectroscopy – an interview with Dr. Peter Schmieder (Conducted in German)

PODCAST

WSR052 The role of the membrane in cellular signal transduction – an interview with Professor Dr. Volker Haucke (Conducted in German)

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Masthead

RESEARCH HIGHLIGHTS 2022/2023
provides insight into our institute's research. For more information, please visit our website www.leibniz-fmp.de

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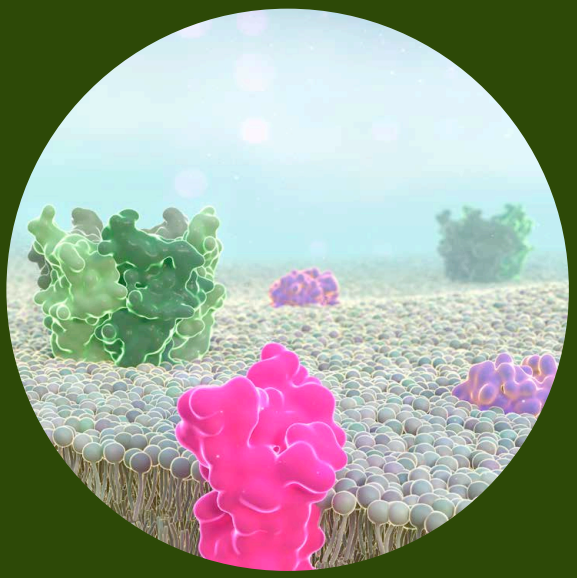

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