FUTURA

THE JOURNAL OF THE BOEHRINGER INGELHEIM FONDS

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Fighting an ever-changing enemy
Using new strategies to curb the danger of malaria

Projects and results
Thirty-four new PhD projects and fourteen completed theses

A BIF fellow's guide to Dresden
Historical, cultural, and culinary highlights of Dresden

The cover illustration shows a simplified model of *Anopheles*, a genus of mosquito containing 460 species. Thirty to forty of them transmit parasites of the genus *Plasmodium* that cause malaria in humans. The most dangerous malaria parasite to humans is *Plasmodium falciparum*, transmitted by *Anopheles gambiae*.

FACTS

FAVOURITE PAPERS

PROFILE OF *ESCHERICHIA COLI*

FIGHTING A SHIFTY ENEMY

FELLOWS

NEW PHD PROJECTS, FIRST ROUND 2021

NEW PHD PROJECTS, SECOND ROUND 2021

NEW PHD RESULTS

FOUNDATION

TAKING THINGS IN STRIDE AND ON THE FLY

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BIF'S DNA

»We cannot thank our trustees enough for their generosity!«

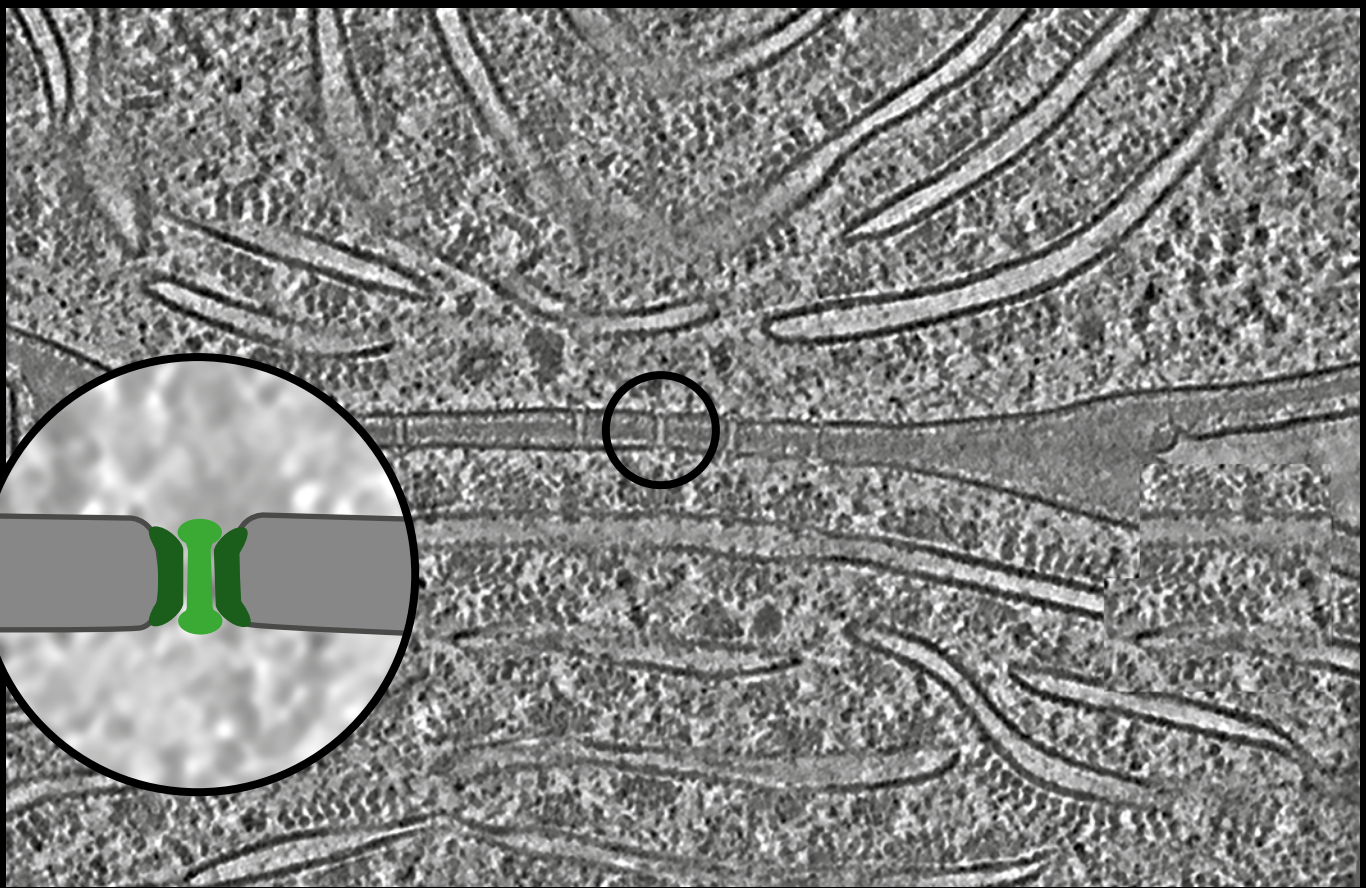
The BIF has always put people first. From the very start, we have believed that selecting the most talented junior researchers and providing them with just a monthly check is not enough. That's why BIF invites its fellows to a variety of tailor-made seminars and supports them comprehensively: we meet and listen to them, encourage them during the thorny stretches of a PhD, and offer advice whenever needed. We aim to create an atmosphere in which trust can develop and talents thrive. What is more rewarding than seeing such gifted young people from all over the world develop their talents to the fullest and find their place in the world?

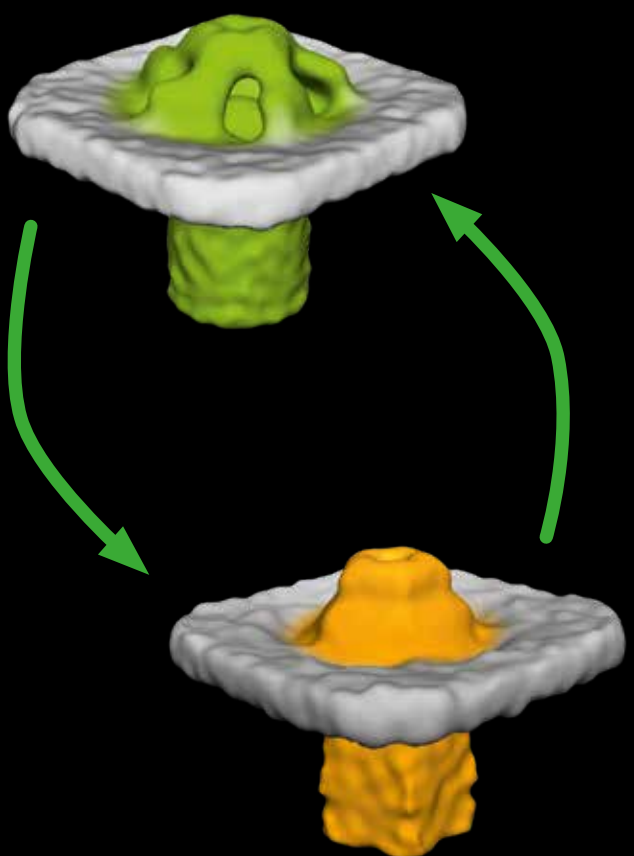
Fostering junior researchers and funding blue sky research are investments in our society's future. Both require stamina, a long-term perspective, and courage. Who knows when and in which seemingly exotic field the next ground-breaking discovery will arise? For this reason we welcome all topics and approaches – as long as they aim to elucidate the basic phenomena of human life through experimental research.

The difficult task of deciding who and what to fund out of the plethora of candidates and proposals falls to our Board of Trustees. In times in which there are growing demands on the time of experts, we are very happy that we have been able to welcome distinguished new board members in 2021 and 2022 (see page 65 of this issue). Under our articles of association, the trustees decide on all fundamental matters at the BIF. Supported by external peer review evaluations, they also select the fellows and projects we fund. When recruiting new scientists for the board, we need to answer a long list of questions. First of all, are they internationally renowned for their own research? Is their scientific expertise broad and are their quality standards uncompromising? Further questions include: What field of research is needed to supplement the board's expertise and to account for new developments? Does their expertise cover the most important model organisms, approaches, and methods? Is there a good balance between researchers from universities and other academic institutions? Do they allow us to address other aspects of diversity, such as the international makeup of the board? Fairness and integrity are also pivotal. Board members must be prepared to approve a proposal even if it challenges their own hypotheses – provided it is well thought out and conceptualized and profoundly argued. In short, board members must enjoy the confidence of their peers – a particularly important point when applications are rejected.

Board members must also be prepared to take risks and, finally, to give the benefit of the doubt to all our applicants, particularly to those pursuing high-risk, high-gain projects. And they must be willing to reach a decision on several hundred applications a year, since every application must be scrutinized by two board members. On top of this, they perform their truly formidable tasks in an honorary capacity.

We therefore cannot thank our trustees enough for their generosity! Without them and their dedication, the BIF could not be what it is today.





BACTERIAL GAP JUNCTION ANALOG

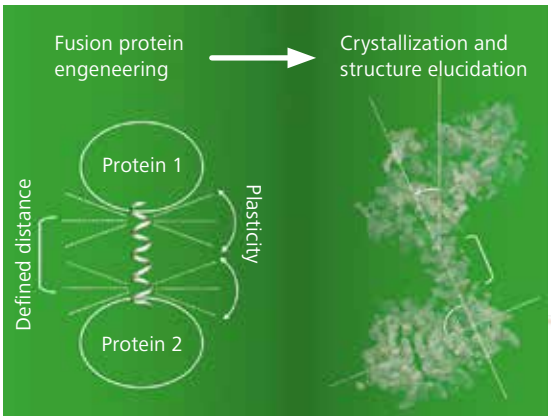
By Piotr Tokarz, Swiss Federal Institute of Technology (ETH Zurich), Zurich, Switzerland; cryotomogram collected by Gregor Weiss.

The upper panel shows a 13.5 nm-thick slice of a cryotomogram of two cyanobacteria from the species *Nostoc* sp. PCC 7120. The cells of this filament-building species are connected via several septal junctions (insert). The cells use these junctions to communicate and exchange metabolites with each other for proper growth and differentiation. To the left are 3D representations of septal junctions in open (green) and closed (orange) states. They can switch between these states within seconds. They always consist of three modules: a plug in the inner membrane, a cap in the cytosol on top of the plug, and a septum-spanning tube, which connects the plug with the caps of the neighbouring cells. Using light microscopy, electron microscopy, mass spectrometry, and biochemical assays, Piotr and colleagues want to identify the proteins building these structures and to understand their mechanism of gating.

We are always looking for exciting scientific photos and illustrations! If you would like to have your image published, contact Kirsten at kirsten.achenbach@bifonds.de.

STIFF HELIX KEEPS YOUR PROTEINS APART

Nature has had millions of years to hone the shape and position of all the parts of a protein. Molecular biologists are rather new to this craft, which promises to open up myriad applications. One of the challenges is to keep proteins apart in order to avoid unwanted interactions; another is to give the parts of a protein complex enough room to move and function. So far, though, it has been difficult to design proteins that keep suitable distances, as most of the designed linkers have been too flexible. This aspect can be optimized by trial and error, but that takes a lot of time and effort. Researchers at the Swiss Paul Scherrer Institute have now identified a stiff helical motif in a protein involved in wound healing that can solve this problem. With this motif they were able to join two proteins while keeping them at a defined distance and positioning them at a defined fixed angle. Their experiments also showed that the motif is easily incorporated and stable. One application of this motif could be virus-like particles used to develop vaccines. These particles are made up of several virus proteins that need to be far enough apart to allow room for interaction with the antibodies of the immune system. The researchers also hope that their helix will make it possible to build protein scaffolds for artificial bones or, when knitted together, to produce biodegradable silk-like textiles. In basic research, these helixes can help to unravel the precise structure and dynamics of complex proteins. They can also enable the crystallized parts of proteins to retain their natural freedom of movement relative to each other. With the new tools of protein crystal structural analysis, such as X-ray free-electron lasers, such proteins can even be observed in action – for example, when membrane pumps transport substances out of a cell.

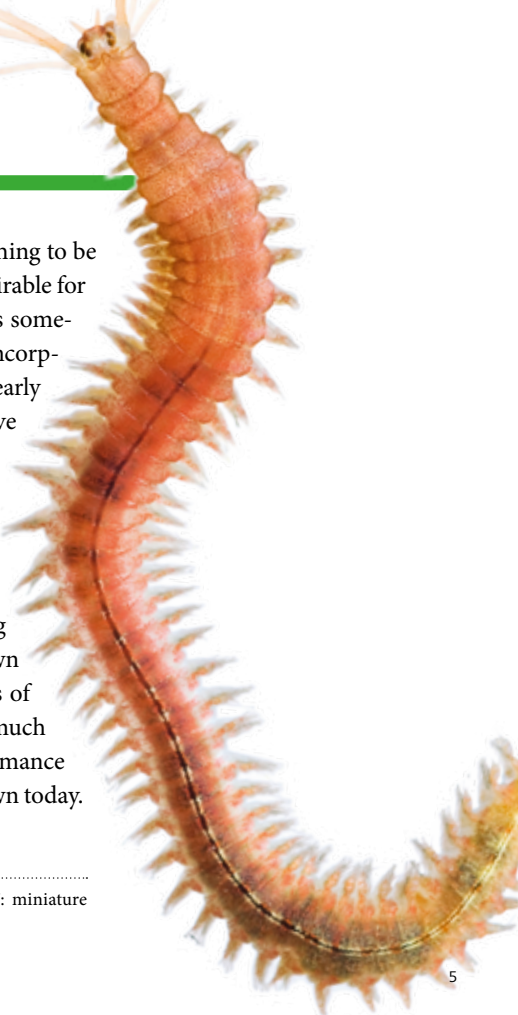


REFERENCE

Gao X, Bender F, Soh H, Chen C, Altafi M, Schütze S *et al* (2021) Place fields of single spikes in hippocampus involve Kcnq3 channel-dependent entrainment of complex spike bursts. *Nat Com* **12**: 4801, doi: 10.1038/s41467-021-24805-2

NATURE'S CYBORGS CHEW WITH METAL JAWS

Ever since the Terminator films, the metallic sheen of cyborg extremities is seen as something to be feared. However, metal has the advantage of extreme durability and flexibility, which is desirable for the skeleton of organisms, especially for those under extreme stress, such as jaws. This is something marine worms seem to have realized 500 million years ago, when they started to incorporate metal ions such as magnesium and zinc into the proteins of their jaw, making them nearly indestructible. In Vienna, researchers from the TU Wien and the Max Perutz Labs have analysed the tiny jaws of the bristle worm *Platynereis dumerilii* and found that in tests of durability and flexibility, the jaws perform similarly to metals. They also found out why they do so, despite being organic in nature: "The metal ions are incorporated directly into the protein chains and ensure that different protein chains are held together," says Professor Florian Raible of the Max Perutz Labs. This creates a very strong material. The trick, however, lies in the interaction of the proteins: under stress, they create sliding surfaces along which the atoms can move against each other, creating the flexibility known from metals. They bend before they break. To work metal, one needs immense amounts of energy. Bristle worms have found a way to create materials with similar properties in a much more efficient way. The authors hope that their studies can help us to create high-performance materials in a biological way – more efficient and environmentally friendly than those known today.



REFERENCE

Zelaya-Lainez L, Balduzzi G, Lahayne O, Ikeda KN, Raible F, Herzig C *et al* (2021) Jaws of *Platynereis dumerilii*: miniature biogenic structures with hardness properties similar to those of crystalline metals. *JOM* **73**: 2390–2402

BALANCING INFECTION RISK AND WOUND HEALING

If the barrier of our skin is breached, there are two priorities: closing the wound and preventing infection. Researchers from the University of Zurich, Switzerland, have now found that natural killer cells are also involved in wound healing, although this impairs their ability to prevent infections. The main job of natural killer cells – as their name implies – is to kill virus-infected or otherwise abnormal body cells, including cancer cells and invaders such as bacteria. In this capacity they are also called to skin wounds, which are usually low on oxygen due to cut blood vessels. The killer cells adapt to these conditions with the help of hypoxia-inducible transcription factors (HIFs). To study this adaptation, the researchers looked at killer cells without the oxygen-activated HIF-1α isoform in mice and found that the cells release fewer cytokines such as interferon γ. This blunts the immune response, and the killer cells are less able to fight off bacteria directly or indirectly. But the drop in cytokines also leads to faster growth of new blood vessels and wound healing. When the researchers forcibly activated the HIF pathway, more cytokines were released and the killer cells became better at fending off infection, but wound healing was slowed. They concluded that HIF-1α in killer cells is important to balance antimicrobial defence against skin repair.

REFERENCE

Sobecki M, Krzywinska E, Nagarajan S, Audigé A, Huỳnh K, Zacharjasz J *et al* (2021) NK cells in hypoxic skin mediate a trade-off between wound healing and antibacterial defence. *Nat Com* **12**: 4700, doi: 10.1038/s41467-021-25065-w

LOSING YOUR RHYTHM, LOSING YOUR PLACE

To go someplace else, you first need to know where you are. To help in the process, your brain has so-called place fields made up of place cells. These cells fire only in a specific rhythm when you are in the particular place they represent, forming a map of your surroundings in your brain. Scientists from Germany and the United States have now learned how a specific potassium channel in the brain is instrumental in maintaining the firing rhythm of place fields. The authors found that healthy mice show a specific temporal and spatial pattern of firing in single action potential and burst signals to help them navigate. Single signals are more precise, while burst signals are more likely to arouse a downstream neuron and therefore to pass on the information. The authors discovered that the specific pattern of single and burst signals is lost in mice without the potassium channel KCNQ3. This helps us to better understand how our brain navigates, but it also has medical implications. We know that as Alzheimer's patients gradually lose control of potassium flow in their brain, they also often lose their orientation. We need to study the role of the KCNQ3 channel in this process. What is already well known is that several mutations that change the function of this channel – as well as others from the KCNQ family – cause different forms of epilepsy in humans. Some of these forms can be treated with potent drugs targeting this channel.

REFERENCE

Gao X, Bender F, Soh H, Chen C, Altafi M, Schütze S *et al* (2021) Place fields of single spikes in hippocampus involve Kcnq3 channel-dependent entrainment of complex spike bursts. *Nat Com* **12**: 4801, doi: 10.1038/s41467-021-24805-2

120°

CELSIUS

is the new limit for life, as shown by microbes living more than a kilometre below the seafloor in the Japanese Nankai trench. They can only do so because their fast metabolism can repair the heat damage in their DNA.

Source: Beulig F, Schubert F, Adhikari RR, Glombitza C, Heuer VB, Hinrichs K-U *et al* (2022) Rapid metabolism fosters microbial survival in the deep, hot subseafloor biosphere. *Nat Commun* **13**: 312 doi: 10.1038/s41467-021-27802-7

Photos: sciencedirect.com/Elsevier Ltd. (left); GettyImages/Cultura RM Exclusive/Albert Lleal Moya (bottom/middle); iStock/Ivan Pantic (top)

FAVOURITE PAPERS

"Favourite Papers" is a new series in which we invite renowned scientists to introduce a paper that has impressed them, influenced their career or thinking, or driven their field forward.

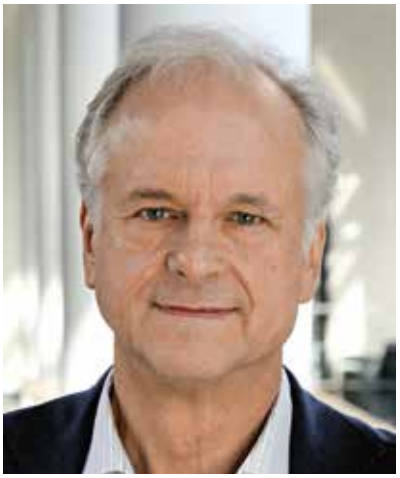


Photo: H. Buttler

The series is kicked off by BIF's former trustee **Prof. U. Benjamin Kaupp**, founding director of the Center of Advanced European Studies and Research (caesar) in Bonn, Germany, and now director emeritus at the MPI for Neurobiology of Behavior – caesar. He discusses the paper "Physics of Chemoreception" by Howard Berg and Edward Purcell (1977), *Biophysical Journal* **20**: 193–219.

In a nutshell, what's the paper about?

Berg and Purcell examine the physical and chemical parameters that determine how accurately a cell can measure the concentration of molecules in the surrounding fluid and how many receptors it needs on its surface to do so. If you study the "chemical senses" of cells or organisms, you need to know this paper!

This publication is about 50 years old, but most of the many papers that cite it stem from the last 15 years. Why do you think this is so?

Because it is such a fundamental paper. The concepts its authors developed and cast into mathematical formulas are still valid today. The arguments are simple and compelling. The theory can be tested – and has been confirmed on several organisms. The topic – how cells measure ligands on their surface – is still hot. However, it's only now that new technologies are enabling us to apply and verify some of its theoretical aspects. Even though the paper is not very accessible due to its many formulas and length, it is written clearly and elegantly. It's a very important paper, but too long for *Nature* or *Science*. Berg wanted to explain his work in depth rather than have a publication in a high-impact journal. In *Biophysical Journal* he got the space and found the audience willing to follow him through all the equations and analogies.

When did you come across this paper?

That must have been at the end of the 1990s, when I started to work with sperm and became familiar with chemotaxis. I read it several times to understand the implications of the formulas and did a lot of mulling over. I thought we could test the concept and do experiments to show that it also holds true for sperm! It was like a how-to for the next morning in the lab. Which we followed!

How did it influence your work?

The authors' approach, which entails looking at the precision of an organism counting molecules, fascinated me and has deeply influenced my thinking. Throughout my career, I've followed up on several ideas generated by this paper. I started to think not only in terms of ion channels – my topic at that time. I also looked at adjacent topics, such as how sperm measure gradients to find the egg. More directly, we used Berg's formulas to calculate how many receptors a single sea urchin sperm needs to be able to detect the molecules released by the egg in pico- or even femtomolar concentrations. The answer: 400,000–600,000! At first we didn't believe it. Later we finally managed to count the receptors, and indeed, these cells are absolutely paved with receptors. By contrast, bacteria have about 10,000 to 15,000 receptors and work at micromolar concentrations of ligands. To do their job, sperm need a much higher density of receptors, and if you read Berg's paper, this basically falls at your feet.

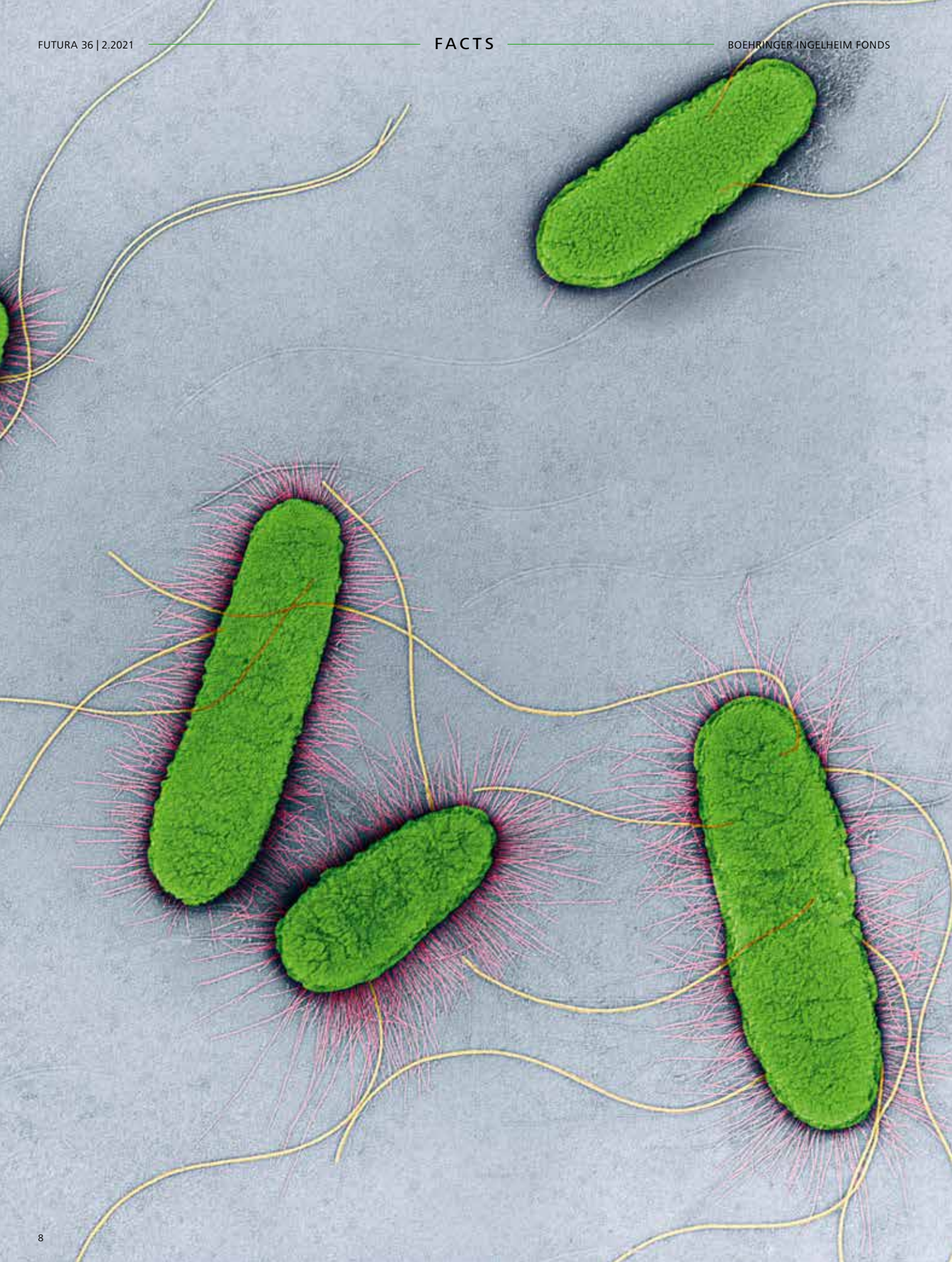
Berg is a master of the so-called back-of-the-envelope calculations often done by biophysicists. His calculations have been scrutinized several times and proven to be correct within a factor 2 – quite amazing. I love back-of-the envelope calculations and find them tremendously helpful.

It's fair to say that without this paper, my career would have taken a different path.

What do you think it takes to write a good paper?

Understand your subject as deeply as possible. Work quantitatively, even if it takes twice as long. When I evaluate a publication list and see someone works quantitatively and has just a small number of papers, that's fine. But if one semi-qualitative paper follows another, I get sceptical. But I know that today the pressure on young people to publish is insane.

And: clarity, clarity, clarity. When I read papers today, even in areas that I am deeply involved in, often enough I just don't want to read on. Unfortunately, for many scientists, writing concisely and clearly is not part of their education. I believe that if you can put things simply, you have understood them. If you need a lot of jargon to explain things, you aren't there yet. That was true 50 years ago for Howard Berg and it still is true today.



PROFILE OF ESCHERICHIA COLI

By Mitch Leslie, PhD

When the biologists Jacques Monod and François Jacob began their pioneering work to uncover how cells control gene activity, they chose to experiment on the bacterium *Escherichia coli*.

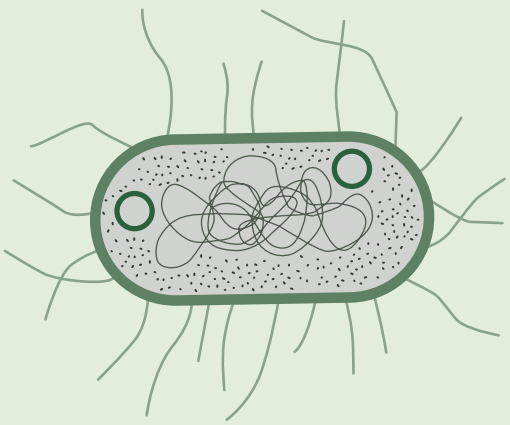
The microbe also enabled Arthur Kornberg to discover the first DNA-duplicating enzyme in 1955. It was instrumental for Marshall Nirenberg's work to decipher the genetic code. Tomas Lindahl, Paul Modrich, and Aziz Sancar relied on the bacterium for their research, which revealed how cells repair damaged DNA. These – and more – advances made possible by *E. coli* were honoured with the Nobel Prize.

Discovered by German paediatrician Theodore Escherich in 1885, *E. coli* dwells in the intestines of humans and other mammals. Scientists were initially attracted to the bacterium as a research subject because it was easy to obtain and grow. Its reproductive feats – it can divide every 20 to 60 minutes – accelerated their experiments. Its relative simplicity – it lacks a nucleus and has only one-fifth as many genes as human cells – made it easier to study. Over the years, the bacterium's merits have made it the most-studied and best-understood organism.

E. coli has been indispensable for understanding many basic cellular functions. And researchers have used it to delve into other topics as diverse as the repeatability of evolution, interactions among predators and prey, the effects of radiation, and cooperation among cells. In 1973 the microbe became the first organism to be genetically modified by researchers. Today, altered *E. coli* cells are working hard in factories around the world, producing biofuels, chemicals, and a variety of drugs, including much of the insulin for diabetes treatment.

Although *E. coli* is usually harmless, some strains, especially the notorious 0157:H7, can kill if they contaminate food. An important area of *E. coli* research concerns what makes these varieties dangerous, how they spread, and how to stop them. Scientists are also probing how the beneficial *E. coli* cells in our intestines interact with other microbes and our immune system to keep us healthy.

WHO AM I? A FEW FACTS



- I am about 1–2 µm long.
- I can reproduce as often as once every 20 minutes.
- I eat sugars and other organic molecules.
- I work mainly in molecular biology, microbiology, and biotechnology.
- I have helped scientists to win 12 Nobel Prizes.

Like other model organisms, *E. coli* has its limitations. For example, it lacks the complexity of eukaryotic cells and cannot express all mammalian proteins. Recently, some researchers advocated switching to another bacterial species that divides even faster. However, *E. coli* remains the go-to model organism for many scientists.

Photo: eye of science

When it comes to change-ability, the parasites that cause malaria are in the same league as chameleons.

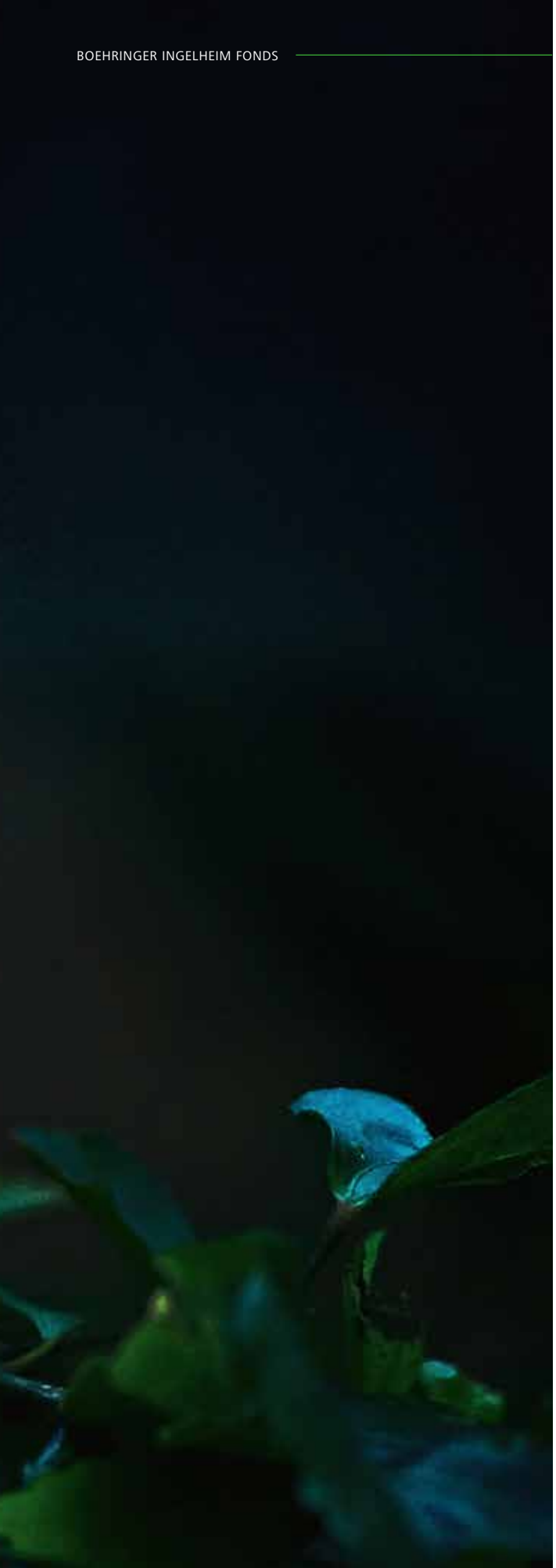


Photo: gettyimages/Gerhard Troester/EyeEm

FIGHTING A SHIFTY ENEMY

By Liam Drew, PhD

In the fight against malaria, exciting new strategies are being developed. Do they have what it takes to reduce malaria mortality significantly by 2030? Liam Drew has taken a close look.

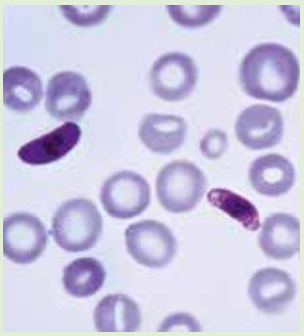
The 37-year-old man who volunteered for a study at the University of Maryland School of Medicine, Baltimore, in 1971 probably did not realize that he was about to make history. Over the next few months, he and two other men who were also taking part in the study would permit swarms of mosquitoes to pierce their skin and inject them with *Plasmodium falciparum parasites*, a species that usually causes malaria. However, these parasites had previously been crippled by radiation.

The three research subjects endured the insects' attacks as part of the first clinical trial to attempt to vaccinate people against malaria. The scientists hoped that the disabled parasites would stimulate the immune system to produce antimalarial defences.

To find out whether the procedure worked, the researchers exposed the men to mosquitoes that were loaded with vigorous parasites that could still provoke the disease. Two of the subjects came down with malaria after being bitten, but the 37-year-old did not. He became the first person to develop at least temporary immunity to malaria through vaccination. Results from this study and other similar projects in the early 1970s provided "proof of principle that we can develop a vaccine", says Matthew Laurens, vaccinologist at the University of Maryland Medical School.

Malaria vaccines have come a long way since these early efforts and could soon start saving lives. In October 2021, the World Health Organization (WHO) for the first time endorsed a vaccine for the disease, known as RTS,S. Other vaccines that →

PLASMODIUM'S DANGEROUS DIVERSITY



Plasmodium falciparum is one of the species of *Plasmodium* that cause malaria in humans.

P. falciparum parasites use a devious strategy to stay one step ahead of an infected person's immune system. During the red blood cell stage of their life cycle, the parasites dwell in and eventually destroy red blood cells. One of their proteins, known as PfEMP1, slips into the plasma membrane of infected cells and can betray the parasites' presence to the immune system. However, *P. falciparum* carries about 60 versions of the var genes that code for PfEMP1, each of which yields a different variety of the protein. The parasites regularly change which var gene they switch on, thus altering which PfEMP1 version they produce and presenting a different look to the immune system.

Infected people can produce antibodies against PfEMP1 that provide some protection against the disease, making it a possible target for vaccines. But the diversity of the var genes is an obstacle. The genes' sequences differ from place to place, and parasites can swap sections of DNA, further increasing their genetic variability. However, researchers think they may be able to target one version of PfEMP1 that allows the parasites to attack the placenta. Two vaccines that may protect pregnant women are already in clinical trials.

could be even more powerful are in the works. And vaccines are just one of the novel approaches to fighting malaria. Some scientists are using powerful screening methods to identify new drugs, while others are investigating genetic engineering techniques that could slash mosquitoes' populations or prevent them from spreading the disease. Researchers and global health experts hope that these new strategies can boost the efforts to reduce malaria mortality.

MALARIA GAINS AND SETBACKS

The world has made remarkable progress against malaria in the last two decades. According to the WHO, about 558,000 people – almost all of them children in sub-Saharan Africa – died from the disease in 2019. That is still a large number, but it was down nearly 50% from 2000. The annual number of cases has also fallen, from around 242 million in 2000 to about 227 million in 2019.

The WHO ascribes these reductions to several factors. One of the most important was the increased use of insecticide-treated bed nets that fend off mosquitoes at night, when the *Anopheles* species that spread malaria typically bite. By 2015, about 68% of children in sub-Saharan Africa were sleeping under these nets, according to WHO figures. Insecticide spraying inside homes was another factor. For people who develop malaria, new rapid blood tests have accelerated diagnosis, and potent treatments – including derivatives of the compound artemisinin – have increased survival.

Hoping to build on these accomplishments, the WHO in 2015 proposed ambitious new goals that include cutting malaria cases and mortality by an additional 90% by 2030. Although there have been some notable advances since then – in 2021, for instance, the WHO for the first time declared China malaria-free – the pace of improvement has slowed. Most of the decrease in death rates occurred between 2000 and 2015, and malaria mortality fell only 18% in the next four years, much less than the 40% necessary to meet the WHO's 2030 goal. COVID-19 has erased some of the progress against malaria. Laurens notes that the virus has already forced researchers to delay or cancel some clinical trials for malaria vaccines. In its most recent World Malaria Report, released December 2021, the WHO estimates that the pandemic has led to an increase in malaria cases and almost 50,000 additional deaths in 2020 alone.

One reason that new approaches to combat malaria are necessary is that *Plasmodium* parasites are so adaptable. In some regions, *P. falciparum*, the most dangerous of the five parasite species that cause malaria, has evolved at least partial resistance to the most important drug combinations. The parasites are even becoming "resistant" to the most widely used rapid tests, losing a protein that these tests detect. Mosquitoes are also beating current control strategies. Resistance to insecticides in bed nets is now widespread in Africa. In addition, mosquitoes in some areas have changed their feeding time, notes molecular geneticist Anthony James of the University of California, Irvine. "If people put up bed nets and spray indoors," he says, "pretty soon they are getting bitten outdoors during the day" – instead of at night.

TAKING A SHOT AT *PLASMODIUM*

To reach the WHO's goal of a 90% reduction in malaria mortality by 2030, "a vaccine is necessary", Laurens emphasizes. However, he adds, developing one has proven difficult for two reasons. Because of their rapid evolution, malaria parasites are extremely variable genetically, and devising vaccines that provide protection against multiple strains has been challenging [see inset box]. According to Laurens, researchers are still trying to determine the most effective immune response against the parasites. They are not sure whether they should design a vaccine that stimulates the production of antibodies, T cells, B cells, or some combination of these defences.

Photo: CDC/Dr. Mae Melvin Transwiki

Despite these obstacles, more than a dozen vaccines are under development or in clinical trials. The vaccine RTS,S is produced by genetic engineering and contains fragments of the circumsporozoite surface protein (CSP), which coats one life stage of the parasite. The vaccine also includes pieces of a surface protein from the hepatitis B virus, which help the CSP fragments stimulate the immune system.

After several trials found that the vaccine reduced malaria infections in young children, an international pilot project was launched to gather further data on its effectiveness and safety and to test procedures for delivering it. This project, which included 800,000 children from three African countries and wrapped up in 2021, provided key evidence that convinced the WHO to endorse RTS,S. Now, says Laurens, individual countries can begin considering whether to license RTS,S for their populations.

RTS,S only provides modest protection, preventing about 50% of recipients from developing malaria in the first year after vaccination, Laurens notes. The WHO's goal is a vaccine that is 75% effective. Still, he says, "with nearly half a million kids dying every year, a partially efficacious vaccine could put a huge dent in the number of deaths." And researchers are exploring new ways to make RTS,S more potent. In one study reported in 2021, scientists gave children in West Africa the vaccine along with a mixture of drugs that prevent malaria infections. The combination boosted the vaccine's efficacy to 71%.

RTS,S prepares the immune system to attack sporozoites, the parasite life stage that a mosquito injects when it bites. Another vaccine that targets the sporozoite stage, known as R21, "is very promising", says Laurens. Like RTS,S, the vaccine contains portions of CSP and the hepatitis B virus surface protein, but it provides a relatively larger dose of CSP fragments. A clinical trial conducted in the West African country of Burkina Faso found that R21 kept 77% of children from developing malaria within one year. This study included only 450 subjects, and larger clinical trials are necessary to confirm the findings, but R21 "could be as good as, if not better than, RTS,S", notes Laurens.

Researchers have also resurrected the approach known as whole sporozoite vaccination. This was used in the original trials in the 1970s but proved impractical, as it required about 1,000 mosquito bites per person for immunization using disabled parasites. Injecting weakened whole sporozoites into the bloodstream has so far had a mixed record in clinical trials, but researchers are working to improve the performance of this method.

One problem could be that the crippled sporozoites cannot reproduce inside a recipient's body, which may limit their ability to incite the immune system. To overcome this problem, researchers injected 42 volunteers with sporozoites that were able to reproduce. The subjects also received antimalarial drugs to prevent them from developing the disease. The scientists reported in 2021 that when they subsequently injected the subjects with either of two strains of sporozoites, the vaccine-drug regimen produced 78% to 88% protection, depending on the strain.

Vaccines that target other stages of the parasites' life cycle are also under development. If RTS,S receives clearance from individual countries, its success could pave the way for the approval of more vaccines, Laurens says. Within five to ten years, several could be in use, he predicts.

RESTOCKING THE MEDICINE CABINET

In the mid-1990s, a new class of drugs based on artemisinin revolutionized malaria treatment. Phytochemist Tu Youyou of the China Academy of Traditional Chinese Medicine, Beijing, isolated artemisinin from the sweet wormwood plant *Artemisia annua*, which had long been an ingredient in a traditional remedy for malaria. For the discovery, Tu shared the 2015 Nobel Prize in Physiology or Medicine. Today, patients receive a regimen called ACT, which combines an artemisinin derivative such as artesunate with a second unrelated drug like amodiaquine or piperaquine. ACT can banish malaria parasites from the blood in less than three days.

However, mutations that confer resistance to ACT therapy have been detected in *P. falciparum* parasites in Africa, Asia, and South America. The latest WHO report on the subject, released in 2020, notes that in more and more patients, parasites remain in the blood longer than three days, a sign that ACT's potency is declining in some areas. Drug resistance has not become a crisis, the WHO report emphasizes. Even in areas where resistance to some ACT mixtures has cropped up, at least two combinations remain effective, and most patients are eventually cured. And so far, resistance has not increased deaths from malaria.

Nonetheless, researchers are doing more than develop new drugs against resistant strains. Improved drugs might be active for longer periods, require fewer doses, be better at preventing infection, or be safer for pregnant women.

"There has been a lot of progress recently," says microbiologist Elizabeth Winzeler of the University of California, San Diego. One major effort that has begun to pay off is the Medicines for Malaria Venture, launched in 1999, which unites academic and →

In some regions, *P. falciparum*, the most dangerous of the five parasite species that cause malaria, has evolved at least partial resistance to the most important drug combinations.

pharmaceutical industry labs to pursue new treatments for the disease. Over the last two decades, scientists have screened more than seven million compounds to determine whether they kill malaria parasites in the lab. Two promising molecules that emerged from these searches, cipargamin and ganaplacide, are in phase II clinical trials, and more than 20 others are at some stage of development.

Winzeler, who took part in the screening that uncovered cipargamin and ganaplacide, says this work was important because many of the compounds had never been tested against malaria. But she notes that screening is becoming less and less productive. For one thing, it cannot reveal the targets of potential drugs. If researchers can identify the protein that a promising compound thwarts, they may be able to design a more effective and safer version of that compound.

That is why Winzeler and other researchers have adopted another approach called target-based discovery. Scientists typically start by dosing malaria parasites in the lab with a molecule uncovered through screening. Over time, some parasites will evolve resistance to the compound. Researchers then sequence the genomes of these parasites to determine which gene accumulated mutations, thus revealing a potential new drug target.

Winzeler is the director of the Malaria Drug Accelerator, a nine-year-old consortium of academic and industry labs that used target-based discovery to pinpoint 23 new potential drug targets and is evaluating more than 200 compounds that might block them. For some compounds, animal tests have been started.

TURNING MOSQUITOES' GENES AGAINST THEM

One of oldest strategies for preventing malaria targets the mosquitoes that spread the disease. Researchers are now giving it a new twist, developing an approach that "could be a game changer in some situations", says James.

Measures such as insecticide spraying and draining mosquito breeding sites eliminated malaria from many areas where it was once common, including parts of North America and Europe. But these approaches have limitations. Insecticides require repeated applications or mosquito populations rebound. The toxins can also harm other species and become less effective as mosquitoes evolve resistance.

To improve on those methods, scientists are working to harness genetic engineering to reduce mosquito populations or stop the insects from transmitting the disease. Merely altering a mosquito gene and then letting the novel version spread through normal reproduction would be too slow, says molecular biologist Tony Nolan of the Liverpool School of Tropical Medicine, UK. Instead, he and other researchers have turned to gene drives, an approach that relies on selfish segments of DNA to speed up the process. "You can rapidly change a population to modify its genetic makeup," he explains.

The selfish DNA chunks that researchers insert into organisms often contain sequences that code for the Cas9 editing enzyme and the guide RNA that determines where it cuts. Each segment slips into a specific chromosome location and then induces cells to make copies of it that replace the DNA that used to reside at that spot. This step occurs as a mosquito is producing eggs or sperm, allowing the selfish DNA to spread swiftly among the insect's offspring.

Nolan and colleagues at Imperial College London crafted such a gene drive system that places the selfish DNA into a gene that controls the mosquitoes' sex. It has no effect on males, but it makes females sterile. James and his co-workers took a slightly different tack, creating DNA inserts that carry genes for anti-parasite antibodies, which mosquitoes start producing.

Nolan's and James' groups have independently shown that these selfish segments rapidly take over mosquito populations in small indoor cages. And in the most realistic trial of the approach for malaria yet, Nolan and his collaborators raised thousands of *Anopheles* mosquitoes in indoor cages large enough for a person to stand in. The mosquitoes thrived in the enclosures. But when the researchers introduced mosquitoes that carried the selfish DNA, the insects died out in less than a year because females were not producing eggs, as the team reported in 2021. "It's quite an encouraging finding," says Nolan.

The two approaches would have different effects on wild mosquito populations. The female sterility strategy would reduce mosquito numbers so much that malaria transmission would plummet, Nolan says. In contrast, James and colleagues engineer mosquitoes to make antibodies that "cure" them of malaria parasites, thus curbing transmission without eliminating the insects, which do not need the parasites to survive. "We do not believe this is a standalone solution," says James. "This is a complementary technology to be used in conjunction with drugs and hopefully the new vaccine."

Although the lab results for gene drives are promising, the approach faces significant regulatory and safety hurdles. "This is a new technology and we want to be good citizens with it," says James. Regulators and communities where the insects will be released will have to give their approval, he cautions. To gauge whether the strategy will work and to test attitudes towards use of the organisms, the Target Malaria organization in 2019 released and tracked 6,400 genetically altered male mosquitoes in Burkina Faso. However, these mosquitoes did not carry the selfish gene drive DNA segments, and no organism created with this technology has yet been introduced into the wild. Nolan says that devising safety rules and gaining local acceptance for such a release will be "as challenging or even more challenging than the actual science".

A global vaccination programme eliminated smallpox, and polio is on the verge of eradication, with the number of cases down by 99% since 1988. Scientists and public health workers have long hoped to eliminate malaria as well. The new vaccines, drugs, and gene drive approaches that researchers are developing may not achieve that goal, but they could bring us closer to a malaria-free world. The most hopeful candidate is the new mRNA technology, which has proved so successful in vaccine development against SARS-CoV19. In 2021, one of the pioneers in this field already announced that they will tackle malaria vaccines.

Please understand that in the interest of our fellows, we publish only results online, not descriptions of ongoing projects.

Therefore, this pdf continues with the section Results.

RESULTS The Boehringer Ingelheim Fonds funds excellent PhD students who are selected as much for their academic record as for their ambitious projects. Here, they present a synopsis of their findings, which aim to push the boundaries of our knowledge of the fundamental phenomena of human life.

Shared first authorship is indicated with an *.

INTERACTIONS OF PROXIMAL NASCENT PROTEINS DRIVE CO-TRANSLATIONAL COMPLEX ASSEMBLY

cf. BIF FUTURA, VOL. 32 | 2.2017

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Most proteins in the cellular proteome function as part of multi-subunit complexes. To limit the exposure of aggregation-prone intermediates and secure the efficient biogenesis of complexes, many proteins assemble co-translationally. In a process known as co-post assembly, fully synthesized, diffusing proteins can interact with their nascent partner subunits. In my PhD project, I considered co-co assembly: an alternative mode of assembly that relies on the interaction of two proximal nascent subunits and hence uncouples assembly from diffusion. To characterize this putative assembly mode, I developed disome selective profiling (DiSP), a technique that allows the conversion of single ribosomes to nascent chain–connected ribosome pairs to be monitored across the proteome at high resolution. Using DiSP on two human cell lines, I showed that co-co assembly is a general strategy to guide assembly of thousands of candidate proteins. It is used mainly to form homomeric complexes primarily via interactions between N-terminal assembly interfaces as soon as they are exposed on the ribosome surface. Interactions are driven by five major dimerization domains, which can be completely or partially exposed at the onset of assembly, suggesting that nascent chains can simultaneously fold and assemble as translation progresses. By reconstituting co-co assembly of human lamin C in bacteria, I showed that this process does not require eukaryotic-specific assembly factors but instead relies on the intrinsic assembly propensity of nascent chains. Biochemical analysis suggested that lamin dimerization occurs on one polysome, which enhances the fidelity of homodimer formation by preventing isoforms with identical dimerization domains from mixing. My results show that translation, folding, and assembly are highly intertwined in driving efficient protein complex biogenesis. My findings also raise a number of questions regarding the implications of co-co assembly on polysome structure; the interdependence of co-co assembly, folding, and translation kinetics; and the consequences of co-co assembly failure. These questions must be answered to understand assembly errors and related diseases.

PUBLICATION

Bertolini M*, Fenzl K*, Kats I, Wruck F, Tippmann F, Schmitt J *et al* (2021) Interactions between nascent proteins translated by adjacent ribosomes drive homomer assembly. *Science* **371**(6524): 57–64

HEADS OR TAILS: HOW DO PLANARIAN FLATWORMS "DECIDE" WHAT TO REGENERATE?

cf. BIF FUTURA, VOL. 31 | 2.2016

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Supervisor: Dr Jochen Rink

Many animals have the extraordinary ability to replace lost body parts, yet how they 'sense' what is missing and thus needs to be regenerated remains an open question. The goal of my PhD was to address this question in planarian flatworms, which regenerate a head at the anterior end of tissue fragments and a tail at the posterior end. Their regeneration polarity involves a canonical Wnt signalling 'switch' that is driven by the preferential expression of the Wnt signalling antagonist *notum* at anterior but not posterior wounds. However, the cue that triggers asymmetric *notum* expression – and thus the mechanistic basis of regeneration polarity in general – remains unknown. I took a comparative approach to identify the elements of planarian regeneration polarity. First, I observed that the planarian flatworm *Girardia tigrina,* unlike the model species *Schmidtea mediterranea,* is highly prone to regenerating bipolar heads from narrow tissue pieces. Specifically, by systematically amputating planarians in different ways and following the resultant pieces over time, I identified piece length, body size, and axial position of the wound as system-level determinants of regeneration polarity. Second, using RNA fluorescence *in situ* hybridization and quantitative image analysis, I found that interspecies differences in asymmetric *notum* activity likely contribute to the species-dependence of regeneration polarity. Third, I developed a novel pharmacological approach to precisely control Wnt signalling in planarians. Using this approach, I demonstrated that an organism-wide gradient of Wnt signalling likely underlies the dependence of regeneration polarity on piece length, body size, and axial position in *G. tigrina*. My findings indicate that pieces of planarian flatworm establish regeneration polarity through deployment of species-specific Wnt signalling mechanisms – polarized *notum* activation in *S. mediterranea* and the Wnt signalling gradient in *G. tigrina* – and, in doing so, provide new mechanistic insights into the more general question of how animals tailor the regenerative response to precisely what is missing.

PUBLICATION

Stückemann T*, Cleland JP*, Werner S*, Thi-Kim Vu H, Bayersdorf R, Liu S-Y *et al* (2017) Antagonistic self-organizing patterning systems control maintenance and regeneration of the anteroposterior axis in planarians. *Dev Cell* **40**: 248–263.e4

DEVELOPMENT OF AN ORGANOID SYSTEM FOR KRAS-DRIVEN LUNG ADENOCARCINOMA

cf. BIF FUTURA, VOL. 32 | 2.2017

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Lung cancer is the leading cause of cancer-related death worldwide. Kirsten rat sarcoma viral oncogene homologue (KRAS) is the most frequently altered oncogene in epithelial cancers. Despite the high incidence of KRAS-driven lung adenocarcinoma (LUAD), the mechanisms that cause the early stages of tumorigenesis are not well understood. To investigate these mechanisms, I developed an organoid system to model LUAD *in vitro*. I showed that *in vitro* KRAS-transformed primary alveolar stem-cell-derived cancer organoids recapitulated LUAD progression histologically. When transplanted orthotopically, the cancer organoids gave rise to tumours *in vivo*. By analysing the transcriptional landscape of oncogenic KRAS-expressing cells early after transformation, I found that KRAS alone was sufficient to reprogram the cells to a more de-differentiated phenotype that had a higher level of expression of developmental genes. Using transcriptional data, I identified an ephrin receptor tyrosine kinase as a potential target to treat early-stage LUAD. To further characterize the molecular changes that occur during tumour progression, I performed a time-course analysis of the transcriptional landscape of alveolar organoids and cancer organoids at single-cell resolution. I found that the alveolar organoids followed a regeneration response similar to that found *in vivo*. In contrast, cancer organoid cells lost the alveolar differentiation trajectories and instead expressed factors early after oncogene initiation that are connected to pluripotency and development. Even though the cancer cells partially recovered markers of alveolar cells at a later time point, they remained in a de-differentiated state. Overall, I developed a new organoid tool that can be used for an array of applications. I characterized the system and explored the transcriptional changes that followed oncogenic KRAS expression, most notably a lasting de-differentiation response early after initiation. Delineating the molecular mechanisms that lead to this response will help us understand KRAS biology and provide new avenues for targeted cancer treatments.

PUBLICATION

Dost AFM*, Moye AL*, Vedaie M, Tran LM, Fung E, Heinze D *et al* (2020) Organoids model transcriptional hallmarks of oncogenic KRAS activation in lung epithelial progenitor cells. *Cell Stem Cell* **27**: 663–678.e8

CHEMICAL DISSECTION OF HUMAN MEDIATOR COMPLEX FUNCTION

cf. BIF FUTURA, VOL. 32 | 2.2017

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DNA-binding transcription factors (TFs) recruit RNA polymerase II (Pol II) to activate their target genes. Pol II recruitment occurs indirectly via an intermediary factor, the multi-subunit transcriptional Mediator complex. Due to difficulties in perturbing this essential transcriptional co-activator with sufficient speed and precision, the direct roles of Mediator in human transcriptional control were not known. In my PhD project, I characterized the direct transcriptional consequences of acute Mediator disruption. I used a ligand-inducible protein degradation system to ablate eight endogenously tagged Mediator subunits in human cells within minutes of compound treatment. High-throughput mRNA sequencing after subunit degradation revealed that Mediator disruption had an unexpectedly mild impact on overall mRNA levels compared to known inhibitors of transcription. Degradation of the Mediator subunit MED14 induced the strongest response, so I focused my efforts on characterizing the primary phenotypic consequences, which are evident within 1–2 hours of degradation. MED14 loss biochemically disrupted the Mediator complex and destabilized nuclear Mediator and Pol II clusters, while minimally impacting chromatin conformation. Nascent transcriptional profiling revealed severe defects in Pol II initiation dynamics at super-enhancer-driven TF genes, which specify the cell type via gene regulatory networks. An unexpected feedback mechanism partially compensated for these initiation defects by decreasing the duration of promoter-proximal pausing of Pol II via CDK9 activation. This mechanism mitigated transcriptional defects at most genes, but fell short of rescuing the fast-paced expression of these super-enhancer-driven TF genes. My results position Mediator as a globally acting co-activator that selectively safeguards the kinetics of cell-type-specifying transcription.

PUBLICATIONS

Jaeger MG, Winter GE (2021) Fast-acting chemical tools to delineate causality in transcriptional control. *Mol Cell* **81**: 1617–1630

Jaeger MG, Schwalb B, Mackowiak SD, Velychko T, Hanzl A, Imrichova H *et al* (2020) Selective Mediator dependence of cell-type-specifying transcription. *Nat Genet* **52**: 719–727

Mayor-Ruiz C*, Jaeger MG*, Bauer S, Brand M, Sin C, Hanzl A *et al* (2019) Plasticity of the Cullin-RING ligase repertoire shapes sensitivity to ligand-induced protein degradation. *Mol Cell* **75**: 849–858.e8

PROTEIN CONDENSATION IN THE HEAT OF EVOLUTION

cf. BIF FUTURA, VOL. 32 | 2.2017

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Cells frequently face large changes in temperature, so they require an adaptive response to survive. This response involves the assembly of translation factors into stress granules (SGs), which promotes a translational switch towards the production of stress-protective proteins. How proteins assemble into SGs and how assembly is controlled at the molecular level are not known. Using the SG model protein Ded1p from budding yeast, I studied the molecular events that enable Ded1p to detect stress and assemble into condensates. Through targeted mutagenesis and *in vitro* reconstitution, I found that Ded1p autonomously detects temperature changes and that its mode of assembly depends on the stress intensity. Upon mild heat stress, Ded1p assembly is mediated by RNA, but upon severe physiological heat stress, Ded1p assembly is determined by the structural stability of the helicase domain and is modulated by the protein's intrinsically disordered regions. In addition to Ded1p from the mesophile *Saccharomyces cerevisiae*, I studied the assembly behaviour of Ded1p orthologues from fungi living in different climates. Although all Ded1p orthologues assemble upon exposure to heat, the assembly temperature is adapted to the thermal niche of the species. This suggests that Ded1p assembly might also be important for the heat stress survival of other fungi. Consistent with my discovery of what drives Ded1p assembly, my data revealed that adapting the assembly temperature of Ded1p across evolutionary time scales involves adapting the structural stability of the helicase domain, which co-evolved with the intrinsically disordered regions. Thus, heat-induced Ded1p assembly is determined by a complex interplay of domains, which is subject to evolutionary pressures that adapt the assembly temperature to physiological conditions. Overall, these data provide a molecular understanding of a critical aspect of heat stress response, which has important implications for understanding temperature adaptation in light of climate change.

PUBLICATION

Iserman C, Altamirano CD, Jegers C, Friedrich U, Zarin T, Fritsch A *et al* (2020) Condensation of Ded1p promotes a translational switch from housekeeping to stress protein production. *Cell* **181**: 818–831

MOLECULAR ARCHITECTURE OF THE HUMAN tRNA LIGASE COMPLEX

cf. BIF FUTURA, VOL. 31 | 1.2016

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In all three domains of life, some transfer RNA (tRNA) molecules are transcribed as precursors containing introns. To form functional tRNAs, the introns must be removed by tRNA splicing. In eukaryotes, this two-step process involves endonuclease-catalysed intron excision followed by exon ligation. In human cells, the ligase RTCB mediates direct 3′-5′ ligation of tRNA exons. RTCB is part of the tRNA ligase complex (tRLC), along with the DEAD-box helicase DDX1 and three proteins of unknown function, FAM98B, CGI-99, and Ashwin. In addition to its essential role in tRNA splicing, tRLC is responsible for unconventional mRNA splicing in the unfolded protein response. It has also been associated with other functions, such as the shuttling of cellular mRNAs between nucleus and cytoplasm. To obtain insights into the molecular architecture and mechanism of tRLC, I used biochemical analysis and cross-linking/mass spectrometry to map the inter-subunit interactions within the complex. I found that the structural core of tRLC is composed of RTCB together with the C-terminal alpha-helical regions of DDX1, CGI-99, and FAM98B. Structural analysis of the individual subunits revealed a calponin-homology (CH) domain fold for the N-terminal domain of CGI-99, along with insights into the active site coordination of RTCB bound to the reaction product GMP and divalent cations. Although the CH domain of CGI-99 interacts with the N-terminal domain of FAM98B, the mechanistic role of the CH domain or this interaction is not known. In addition, I discovered and characterized a novel *in vitro* microtubule-binding activity of tRLC. In collaboration with the Martinez group at the Max Perutz Labs, I also characterized the *in vitro* interaction of RTCB with the reductase PYROXD1, which protects RTCB from oxidative inactivation. My results help us to understand human tRLC assembly and the catalytic activity of its ligase subunit, as well as providing a framework for ongoing functional and structural investigations of the tRLC holocomplex.

PUBLICATION

Asanović I, Strandback E, Kroupova A, Pasajlic D, Meinhart A, Tsung-Pin P *et al* (2021) The oxidoreductase PYROXD1 uses NAD(P)+ as an antioxidant to sustain tRNA ligase activity in pre-tRNA splicing and unfolded protein response. *Mol Cell* **81**: 2520–2532

Further results of this project can be discussed on *BioRxiv*: doi: 10.1101/2021.07.11.451954

NEURONAL DNA BREAKS AT THE CENTRE OF NEUROINFLAMMATION-INDUCED NEUROLOGICAL DISORDERS

cf. BIF FUTURA, VOL. 33 | 1.2018

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Chronic systemic inflammation often accompanies neuropsychiatric disorders. Unlike in acute sickness behaviour syndrome, where proinflammatory cytokines contribute to a patient's hypoactivity, the impact of chronic cytokine exposure on cognitive behaviour and the underlying mechanisms remain largely unknown. DNA double-strand breaks (DSBs) induced by neuronal stimulation are a key epigenetic factor in neuronal function. In my PhD project, I studied the role of cytokine-induced DSB dysregulation during neuroinflammation in related behavioural impairment. After showing that the cytokine interleukin-1β (IL-1β) can cause DSBs in primary neurons, I used osmotic mini-pumps to chronically expose mice to systemic IL-1β levels. After three weeks of treatment, I analysed the memory capacity of the mice using behavioural tests. I found that chronic IL-1β exposure impaired spatial memory, which relies on the hippocampus. Memory impairment was not accompanied by overt microgliosis or astrocytosis (both of which have previously been linked to high levels of neuroinflammation), hypoactivity or reduced neurogenesis, leading me to conclude that the impact of chronic IL-1β exposure on behaviour is different from the effects of cytokines in sickness behaviour syndrome. I also showed that chronic IL-1β increased the number of neurons with DSBs in the hippocampus, suggesting a role for these DSBs in the observed memory impairment. To understand the mechanisms underlying this impairment, I bred an original transgenic mouse model in which the IL-1β receptor (IL-1R1) can be deleted in excitatory neurons of the hippocampus. With this model, I showed that the lack of IL-1R1 was sufficient to prevent IL-1β-induced memory impairment. To decipher the role of the signalling pathways induced by the generation of DSBs in IL-1β-induced memory impairment, I genetically ablated histone H2A.X in excitatory neurons. H2A.X is phosphorylated early in the detection of DSBs to recruit DNA repair factors. I found that the absence of phosphorylation prevented IL-1β-induced memory impairment. Hence, I unravelled novel molecular mechanisms underlying the impact of chronic IL-1β exposure on memory. Since IL-1β has been found in many people with neuropsychiatric and neurodegenerative diseases, understanding these mechanisms may help combat these diseases.

PUBLICATION

Marty FH, Bettamin L, Thouard A, Bourgade K, Allart S, Larrieu G *et al* (2021) Borna disease virus docks on neuronal DNA double-strand breaks to replicate and dampens neuronal activity. *iScience* **25:** 103621, doi: 10.1016/j.isci.2021.103621

DISSECTION OF NEURAL CIRCUITS INVOLVED IN NEUROPSYCHIATRIC AND METABOLIC DISEASES

cf. BIF FUTURA, VOL. 31 | 1.2016

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Supervisor: Prof. Jeffrey Friedman

The subthalamic nucleus (STN), part of the basal ganglia, has a key role in controlling movement and limbic-associative functions. Whereas STN functionality is well understood, the role of specific cell types is less clear. Modulating the STN with deep brain stimulation improves the symptoms of Parkinson's disease (PD) and obsessive-compulsive disorder (OCD). However, deep brain stimulation does not allow for cell-type-specific modulation. In the first part of my PhD project, I performed an anatomical characterization of molecular markers of specific STN neurons. I found that all STN neurons express paired-like homeodomain 2 (*Pitx2*), while overlapping subsets express gamma-aminobutyric acid (GABA) receptor subunit rho-3 (*Gabrr3*), neuron-derived neurotrophic factor (*Ndnf*) or nitric oxide synthase 1 (*Nos1*). I showed that optogenetic activation of STN^{Pitx2} and STN^{Gabrr3} neurons modulates motor functions and improves locomotion in a PD mouse model. Photoactivation of STN^{Pitx2} and STN^{Gabrr3} neurons also induced repetitive grooming in mice, which is linked to OCD. Repeated stimulation led to a persistent increase in grooming that could be reversed by fluoxetine, a first-line treatment for OCD. Conversely, repeated inhibition of STN^{Gabrr3} neurons suppressed grooming in an OCD mouse model. Finally, circuit and functional mapping of STN^{Gabrr3} neurons showed that these effects are mediated via neural projections to the globus pallidus/entopeduncular nucleus and substantia nigra reticulata. Together, these data identify STN^{Gabrr3} neurons as important in mediating the beneficial effects of STN modulation, thus providing potential cellular targets for PD and OCD drug discovery. In the second part of my project, I identified GABA-expressing neurons in the brain stem that are necessary for controlling core body temperature in mice. This discovery could provide a new target for treating diseases characterized by imbalances in energy homeostasis, such as obesity.

PUBLICATIONS

Parolari L, Schneeberger M, Heintz N, Friedman JM (2021) Functional analysis of distinct populations of subthalamic nucleus neurons on Parkinson's disease and OCD-like behaviors in mice. *Mol Psychiatry,* doi: 10.1038/s41380-021-01162-6

Schneeberger M*, Parolari L*, Das Banerjee T*, Bhave V, Wang P, Patel B *et al* (2019) Regulation of energy expenditure by brainstem GABA neurons. *Cell* **178**(3): 672–685.e12

THE GAPDH REDOX SWITCH PROMOTES TUMOUR GROWTH BY SAFEGUARDING REDUCTIVE CAPACITY

cf. BIF FUTURA, VOL. 31 | 2.2016

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Institute: German Cancer Research Center (DKFZ), Heidelberg, Germany
Supervisor: Prof. Tobias P. Dick

The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is catalytically inactivated by oxidation in response to increased levels of hydrogen peroxide (H_2O_2). GAPDH oxidation has been linked to oxidant detoxification and cellular survival, which suggests a causal role for this redox switch in oxidative stress resistance. Functional investigation of the GAPDH redox switch had not been possible, however, because the same cysteine residue is the target of both the glycolytic reaction and oxidation by H_2O_2 – thus preventing its function from being studied using classical mutagenesis approaches. Investigating the (patho)physiological relevance of this redox switch is only feasible following the elucidation of the specific mechanism that selectively facilitates oxidation without affecting glycolysis. In my PhD project, I studied the function of the GAPDH redox switch using several biochemical approaches. With metabolomics analyses, I showed that GAPDH oxidation blocks glycolytic flux, allowing glucose to enter the pentose phosphate pathway (PPP) to maximize the production of nicotinamide adenine dinucleotide phosphate (NADPH). Using fluorescent biosensors, I showed that GAPDH oxidation is critical for human cells to maintain the levels of reduced NADPH required for oxidant metabolization. Importantly, GAPDH oxidation is vital not only in response to artificially high levels of H_2O_2 but also under conditions that increase the production of endogenous oxidants, such as the growth of human cells in 3D culture. Taking this observation one step further, I showed that GAPDH oxidation sensitivity promoted the growth of xenografted human tumours *in vivo*, and that loss of GAPDH oxidation sensitivity correlated with decreased PPP flux and increased oxidant levels in tumour cells. Finally, I found that GAPDH oxidation sensitivity conferred resistance in human tumours against clinically relevant treatments. My results could be useful for developing novel cancer treatments that are not counteracted by GAPDH oxidation.

PUBLICATION

The results of this project have not yet been published.

INVESTIGATING SPINDLE ASSEMBLY IN MAMMALIAN ZYGOTES USING LIGHT-SHEET MICROSCOPY

cf. BIF FUTURA, VOL. 33 | 1.2018

ISABELL SCHNEIDER
Discipline: Chemical Biologist, MSc
Institute: European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
Supervisor: Dr Jan Ellenberg

In the first mitotic divisions of the mammalian embryo after fertilization, chromosomes are frequently mis-distributed into daughter cells. These chromosome abnormalities are a major cause of early pregnancy loss in humans. The goal of my PhD project was to investigate how the mitotic spindle apparatus in early embryos differs from the spindle in somatic cells and how it provokes incorrect chromosome distribution. Using light-sheet and confocal microscopy of the spindle apparatus in mouse zygotes, my colleagues and I found that two spindles assemble separately around the two parental genomes. The spindles initially organize the chromosome sets separately and then align them in parallel late in pro-metaphase, before finally segregating them in a concerted fashion. Even though I imaged spindle assembly at low resolution, I was able to show that the two spindles maintain distinguishable poles, even in metaphase. The discovery that two spindles form was unexpected, but the early mouse embryo is exceptional as it contains many acentriolar microtubule organizing centres instead of two centrosomes. By using light-sheet imaging of live bovine zygotes, I showed that dual spindles also assemble despite the presence of only two centrosomes. When the two pronuclei failed to approach each other in early mitosis, the two spindles assembled far from each other, leading to the erroneous distribution of chromosomes into more than two nuclei. I thus discovered how mammalian zygotes assemble the first spindle apparatus and found an explanation for multinucleated embryonic phenotypes.

PUBLICATIONS

Schneider I*, de Ruijter-Villani M*, Hossain MJ, Stout TAE, Ellenberg J (2021) Dual spindles assemble in bovine zygotes despite the presence of paternal centrosomes. *J Cell Biol* **220**(11): e202010106

Schneider I, Ellenberg J (2019) Mysteries in embryonic development: how can errors arise so frequently at the beginning of mammalian life? *PLOS Biol* **17**: e3000173

Reichmann J*, Eguren M*, Lin Y*, Schneider I*, Ellenberg J (2018) Live imaging of cell division in preimplantation mouse embryos using inverted light-sheet microscopy. *Methods Cell Biol* **145**: 279–292

Reichmann J, Nijmeijer B, Hossain MJ, Eguren M, Schneider I, Politi AZ *et al* (2018) Dual-spindle formation in zygotes keeps parental genomes apart in early mammalian embryos. *Science* **361**: 189–193

ELUCIDATING THE FUNCTION OF ADAM17 AND ITS REGULATOR iRHOM1 IN THE BRAIN

cf. BIF FUTURA, VOL. 31 | 2.2016

JOHANNA TÜSHAUS
Discipline: Biochemist, MSc
Institute: German Center for Neurodegenerative Diseases (DZNE) Munich and Technical University of Munich (TUM), Germany
Supervisor: Prof. Stefan F. Lichtenthaler

The secretome is a key driver of intercellular communication. It includes all proteins actively released by the cell, which mainly comprise soluble secreted proteins and ectodomains of transmembrane proteins that are released by proteolytic cleavage. Quantitative analysis of the secretome remains technically challenging due to its low protein concentration. The first step of my PhD project was to develop the high-performance secretome protein enrichment with click sugars (hiSPECS) method. This mass spectrometry-based workflow enables the secretome to be determined in a highly efficient and robust manner. I used hiSPECS to elucidate the secretome of the four major types of brain cells – neurons, astrocytes, oligodendrocytes, and microglia. Using this resource, I could then determine the cellular origin of proteins in cerebrospinal fluid, including biomarkers for neurodegenerative diseases. The transmembrane metalloprotease ADAM17 (a disintegrin and metalloprotease 17) has key roles in development and inflammatory diseases such as lupus and rheumatoid arthritis, but little is known about its function in the brain. To advance knowledge of ADAM17 and inactive rhomboid 1 (iRHOM1) – a regulator that guides ADAM17 to the cell surface – I used hiSPECS to determine their substrate repertoires in primary neurons *in vitro*. To find the *in vivo* secretome of all the cell types, I performed proteomic analysis of cerebrospinal fluid from mice in which iRHOM was inactivated and the active form of ADAM17 was lacking. With this work, I not only established an optimized proteomic workflow to study the secretome of primary cells, but also gained fundamental insights into the function of ADAM17 and iRHOM1 in the brain by establishing their substrate repertoires.

PUBLICATIONS

Tüshaus J, Müller SA, Shrouder J, Arends M, Simons M, Plesnila N *et al* (2021) The pseudoprotease iRhom1 controls ectodomain shedding of membrane proteins in the nervous system. *FASEB J* **35**: e21962

Hsia HE, Tushaus J, Brummer T, Zheng Y, Scilabra SD, Lichtenthaler SF (2020) Functions of 'A disintegrin and metalloproteases (ADAMs)' in the mammalian nervous system. *Cell Mol Life Sci* **76**: 3055–3081

Tüshaus J, Müller SA, Kataka ES, Zaucha J, Sebastian Monasor L, Su M *et al* (2020) An optimized quantitative proteomics method establishes the cell type-resolved mouse brain secretome. *EMBO J* **39**: e105693

CONFORMATION SWITCHING UNDERPINS DYNAMIC PROTEIN FILAMENT FUNCTION

cf. BIF FUTURA, VOL. 31 | 2.2016

JAMES WAGSTAFF
Discipline: Structural Biochemist, MSc
Institute: MRC Laboratory of Molecular Biology, Cambridge, UK
Supervisor: Prof. Jan Löwe

Inside the cell, molecules are organized in space and time by protein filaments. Cytomotive filaments power the directed movement of other molecules by coupling the free energy released by nucleotide hydrolysis to a (de)polymerization cycle. Only homologues of actin and tubulin proteins are known to form cytomotive filaments. Despite decades of research, mostly on eukaryotic actins and tubulins, we lack a mechanistic understanding of their filament dynamics. The protein FtsZ, a tubulin homologue that is present in almost all bacteria and many archaea, forms cytomotive filaments that organize cell division. Using X-ray crystallography and cryo-electron microscopy (cryo-EM), I demonstrated that FtsZ switches conformation when polymerizing to form filaments. I also showed using cryo-EM that this conformational switch is likely needed for filament recognition during division by the protein ZapA. This conserved cross-linking protein promotes FtsZ filament bundling and alignment, thereby ensuring the robustness of cell division. Using further cryo-EM experiments and structural bioinformatics tools, I found that the FtsZ conformational switch is conserved within the tubulin superfamily and that members of the actin superfamily also exhibit a conserved conformational switch upon polymerization. My colleagues and I developed models showing that such a switch explains the coupling of kinetic and structural polarities required for cytomotivity. This insight unifies a number of observations and theories about how protein filaments perform useful work in cells. My results demonstrate the value of studying members of protein families from across the tree of life for better understanding basic principles underpinning eukaryotic, and human, biology.

PUBLICATIONS

Szewczak-Harris A, Wagstaff J, Löwe J (2019) Cryo-EM structure of the minCD copolymeric filament from *Pseudomonas aeruginosa* at 3.1 Å resolution. *FEBS Lett* **593**: 1915–1926

Wagstaff J, Löwe J (2018) Prokaryotic cytoskeletons: protein filaments organizing small cells. *Nat Rev Microbiol* **16**: 187–201

Wagstaff JM, Tsim M, Oliva MA, Garcia-Sanchez A, Kureisaite-Ciziene D, Andreu JM, Löwe J (2017) A polymerization-associated structural switch in FtsZ that enables treadmilling of model filaments. *mBio* **8**: e00254-17

STRUCTURE OF A THYLAKOID MEMBRANE-ANCHORED CONTRACTILE INJECTION SYSTEM

cf. BIF FUTURA, VOL. 32 | 1.2017

GREGOR WEISS
Discipline: Biochemist, MSc
Institute: Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
Supervisor: Prof. Martin Pilhofer

Most bacteria need to interact with surrounding cells to survive. A common mediator of bacterial cell–cell interactions are contractile injection systems (CISs), which use a phage tail-like structure to inject effector molecules into a target cell. CISs show two modes of action: extracellular CISs are released through cell lysis and act on their target cell's surface, while type 6 secretion systems (T6SSs) are attached to the inner membrane and function upon cell–cell contact. Although many CIS gene clusters have been discovered, their mode of action was unknown. In my PhD project, I studied a cyanobacterial CIS using an integrative imaging approach. *Cyanobacteria* are abundant organisms that play key roles in geochemical cycles. Using cryo-electron tomography of focused ion beam-milled cells of the model organism *Anabaena* PCC 7120, I revealed that the *in situ* architecture of cyanobacterial CISs is unique, as they are embedded in a pore of the thylakoid membrane stack. I found the CISs predominantly in the outermost thylakoid membrane, facing the outside, with membrane anchoring achieved by 12 proteinaceous connectors. Single-particle cryo-electron microscopy of purified CISs showed that these connectors are composed of extensions to tail fibre and baseplate components. Since this anchoring of a CIS in the thylakoid membrane stack is incompatible with an extracellular CIS-like or T6SS-like mode of action, I investigated how CISs in *Anabaena* could interact with a potential target cell. Using light microscopy, I showed that upon stress, *Anabaena* filaments fragment and induce the formation of ghost cells. These ghost cells are no longer viable, but cryo-electron tomography revealed that many CISs were still anchored in the remaining thylakoid sacculus and exposed to the environment. In this state, CISs could potentially interact with a target cell. My results show that CISs in *Anabaena* use a mode of action that is fundamentally different to that of extracellular CISs or T6SSs. This project further provides a framework for understanding the evolutionary re-engineering of CISs to accommodate a new mode of action.

PUBLICATION

Weiss GL, Eisenstein F, Kieninger AK, Xu, J, Minas, HA, Gerber M et al (2022) Structure of a thylakoid-anchored contractile injection system in multicellular cyanobacteria. Nat Microbiol 7: 386–396

Weiss GL*, Kieninger A-K*, Maldener I, Forchhammer K, Pilhofer M (2019) Structure and function of a bacterial gap junction analog. *Cell* **178**(2): 374–384

MICOS-DEPENDENT CRISTAE REMODELLING AND METABOLIC ADAPTATION

cf. BIF FUTURA, VOL. 31 | 2.2016

FLORIAN WOLLWEBER
Discipline: Biomedical Scientist, MScR
Institute: Medical Biochemistry & Molecular Biology, Saarland University Medical Centre, Homburg, Germany
Supervisor: Prof. Martin van der Laan

The mitochondrial inner membrane forms large invaginations, or cristae, for ATP production. The mitochondrial contact site and cristae organizing system (MICOS) complex stabilizes the junctions between cristae and the inner boundary membrane and mediates contacts with the outer membrane. The dynamin-like GTPase Mgm1 mediates mitochondrial fusion and the adaptation of cristae shape to metabolic demands. In my PhD project, I hypothesized that the MICOS complex is required for metabolic adaptation processes in yeast and human cells. By screening yeast MICOS mutants, I found that MICOS-independent functions of core subunits, rather than the integrity of the crista junctions or MICOS complex, are required for efficient metabolic adaptation. These functions include highly conserved interactions with cristae-shaping proteins and a direct role in spatially organizing mitochondrial protein biogenesis. An analysis of MICOS complex stability showed that the assembly of core subunits is regulated by accessory subunits. As the integrity of the MICOS complex and the crista junctions seems to be dispensable during metabolic adaptation, I extended my analysis to Mgm1. Structural data from my collaborators suggested that Mgm1 can assemble into dimers, tetramers, and filaments on curved membranes. I validated the structural model *in vivo*, showing that defective assembly leads to aberrant cristae shape and drastically reduces mitochondrial function. The proposed assembly mechanism could allow for dynamic cristae remodelling, e.g. during metabolic adaptation.

PUBLICATIONS

Rampelt H, Wollweber F, Licheva M, Kraft C, van der Laan, M, Pfanner N (2022) Dual arole of Mic10 in mitochondrial cristae organization and ATP synthase-linked metabolic adaptation and respiratory growth. *Cell reports* **38:** 110290

Faelber K*, Dietrich L*, Noel JK, Wollweber F, Pfitzner A-K, Mühleip A *et al* (2019) Structure and assembly of the mitochondrial membrane remodelling GTPase Mgm1. *Nature* **571**: 429–433

Rampelt H*, Wollweber F*, Gerke C, de Boer R, van der Klei IJ, Bohnert M *et al* (2018) Assembly of the mitochondrial cristae organizer Mic10 is regulated by Mic26–Mic27 antagonism and cardiolipin. *J Mol Biol* **430**: 1883–1890

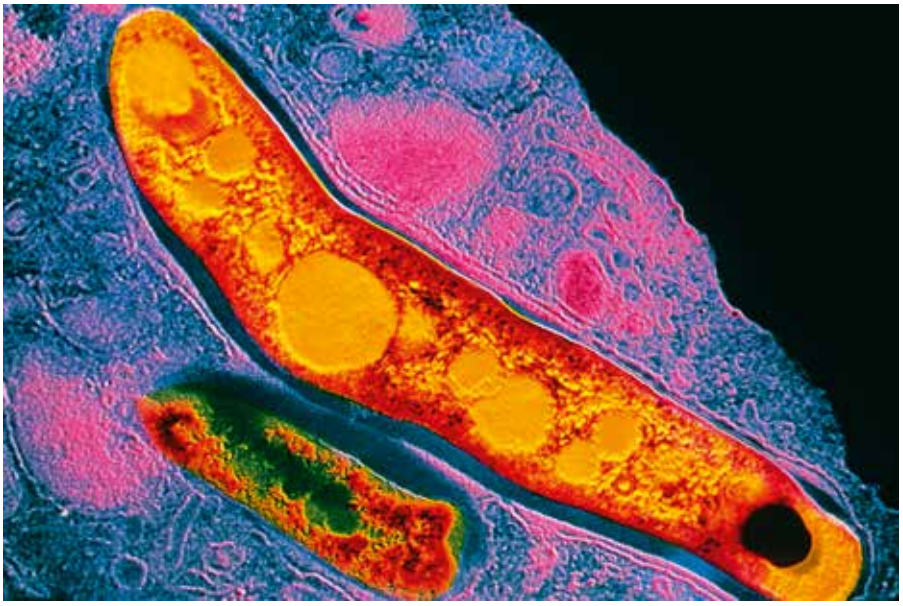
Wollweber F, von der Malsburg K, van der Laan M (2017) Mitochondrial contact site and cristae organizing system: a central player in membrane shaping and crosstalk. *Biochim Biophys Acta Mol Cell Res* **1864**: 1481–1489

THE FOUNDATION The Boehringer Ingelheim Fonds (BIF) is a public foundation – an independent, non-profit organization for the exclusive and direct promotion of basic research in biomedicine. The foundation pays particular attention to fostering junior scientists. From the start, it has provided its fellowship holders with more than just monthly bank transfers: seminars, events, and personal support have nurtured the development of a worldwide network of current and former fellows.

PAPERS IN THE SPOTLIGHT

In "Papers in the spotlight", we present papers from current fellows and recent BIF alumni. The selection criteria are based not only on scientific merit but also on the general interest of the topic. If you would like to see your paper discussed here, send an email to kirsten.achenbach@bifonds.de.

HOW TO FIND THE SOFT SPOT OF KILLERS



False-colour TEM of the bacterium *Mycobacterium tuberculosis* (gold) within a macrophage.

Mycobacterium tuberculosis is still one of the biggest threats in the world. According to the WHO, it killed 1.5 million in 2020 alone, despite years of intense search for antibiotics against it. Many hopeful drugs have failed, even though they target gene products essential for the bacteria's survival. Barbara Bosch and colleagues from the laboratory of Jeremy Rock at the Rockefeller University in New York City have now analysed *Mycobacterium's* genes, asking for each gene: how important is it for the cell's fitness and how much does its activity need to be reduced to kill the bacterium? To this end, they developed a CRISPR interference system with which they were able to tune the level of inhibition for a gene *in vitro* from 0 to almost 100%. This allowed them to identify the bacteria's soft spots: essential genes that need to operate at full throttle for the bacterium to survive. They also found invulnerable ones: essential genes that need to be knocked out almost completely to kill the bacterium. They thus make a compelling argument for redefining the concept of essential genes from a yes/no model to include a measure of their vulnerability. While soft spots are likely very good drug targets, invulnerable genes are likely not, as even the best drugs almost never block a gene product completely. Bosch and her colleagues compiled the first vulnerability index of *Mycobacterium*'s gene products: at the top of the list are the most vulnerable ones, including two targets of the most potent TB drugs on the market. Only a small decrease in their activity kills the pathogen. At the bottom of the list are the hardiest ones, including two targets of hopeful TB drugs that failed to deliver. Such failure has often been attributed to a drug not reaching its target, but perhaps it was simply unable to hit it hard enough. The team also found further soft spots, important for folding and secretion, which have not been explored as drug targets. With new and more potent antibiotics urgently needed, this work is highly welcome news, especially as the method can be used for other pathogens as well.

REFERENCE

Bosch B, DeJesus MA, Poulton NC, Zhang W, Engelhart, CA, Zaveri A *et al* (2021) Genome-wide gene expression tuning reveals diverse vulnerabilities of *M. tuberculosis*. *Cell* **184**: 1–14

Barbara Bosch, fellow 2017–2020

Photo: CNRI

SUPERKILLER 7 KEEPS FISH EGGS HEALTHY

The transition from mature egg to embryo is a time of fast development, driven by massive changes in RNA and protein content. But as no new RNA is produced and all new proteins are derived from the existing maternal RNAs, RNA levels can only be controlled by degradation. While we understand RNA degradation in yeast quite well, we still do not understand fully how this process is accomplished in animals. Luis Cabrera-Quio, a recent PhD in the laboratory of Andrea Pauli, Institute of Molecular Pathology (IMP), Vienna, Austria, and colleagues have finally found the hiding place in the zebrafish genome of an important protein in RNA degradation in yeast. Further, they learned that *ski7* indeed also plays an important role during the transition from egg to embryo in vertebrates.

In yeast, it was known that two protein complexes work in tandem to degrade RNA: the exosome and superkiller (ski) which, however, only act when linked via the protein Ski7. In animals, RNA degradation was thought to operate differently, because the gene for Ski7 had not been found in animal genomes due to its intricate splicing pattern – although recent studies hinted at its presence.

Luis Cabrera-Quio and colleagues have finally found *ski7* in zebrafish, characterized it, and analysed its role in animals *in vivo* for the first time. They learned that *ski7* is highly expressed during the transition from egg to embryo, indicating an important role. When they studied zebrafish lacking Ski7, they found that while some of the eggs did not develop at all, those fish that did develop were fine once they had passed the one-cell stage.

Next, the authors compared gene expression patterns at different stages of the egg-to-embryo transition of wild-type fish and *ski7* mutants. The mutants had different levels for hundreds of RNAs, most of them higher than in wild-type embryos. Many of these RNAs were involved in the cell's response to redox stress. Yeast without Ski7 was already known to deal less well with stress. However, the surviving fish without Ski7 actually dealt better with redox stress than the wild-type animals.

The authors concluded that, just as in yeast, Ski7 is necessary for regulating the balance of reduction and oxidation in the embryo. Further, they speculate that without it, only embryos with the right level of maternal RNA to protect them from cellular stress survive and are then equipped to deal better with stress – an idea that remains to be tested.

REFERENCE
Cabrera-Quio LE, Schleiffer A, Mechtler K, Pauli A, (2021) Zebrafish Ski7 tunes RNA levels during the oocyte-to-embryo transition. *PLoS Genet 17 (2)*: e1009390

Luis Cabrera-Quio fellow 2016–2018

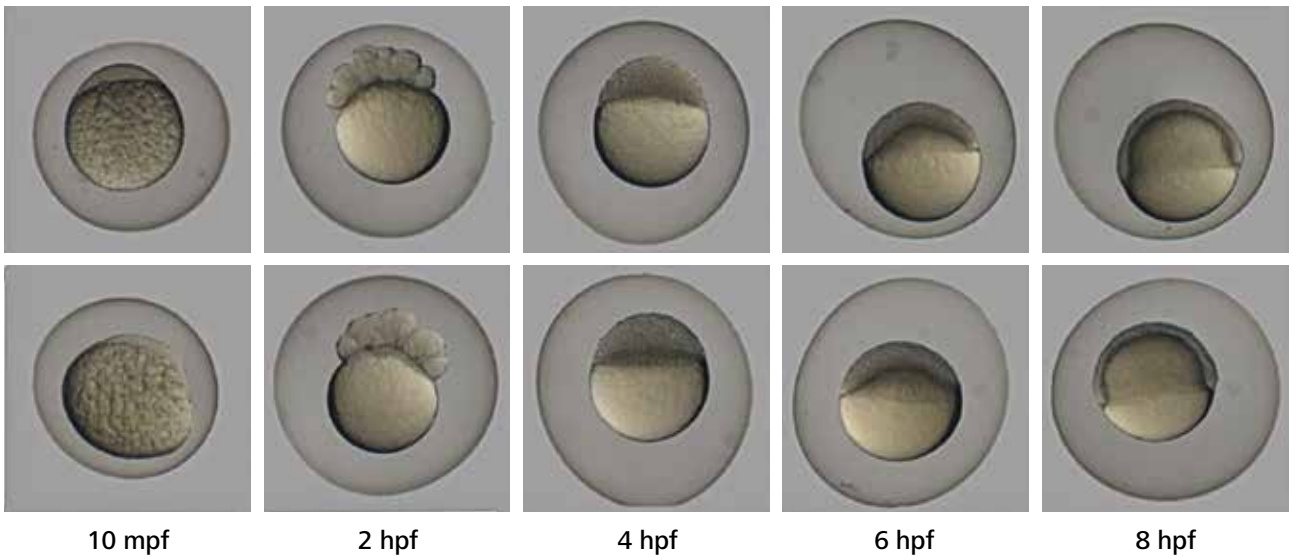


Photo: L. Cabrera Quio/PLOS Genetics

Both types of embryos – those with (above) and without Ski7 – develop normally once they have passed the one-cell stage.

PROFILES

PROFESSOR KRISTIN TESSMAR-RAIBLE,
Institute: University of Vienna, Austria
Fellowship: 2001–2003

PROFESSOR KARSTEN WEIS
Institute: ETH Zurich, Switzerland
Fellowship: 1993–1995

Kristin Tessmar-Raible and Karsten Weis have been elected members of the European Organization for Molecular Biology (EMBO). **Kristin** intends to shed light on the molecular calendars that control how the behaviour and physiology of animals react to cues other than sunlight, including seasons, tides, and phases of the moon. **Karsten** is studying how the nucleus is organized and how material is transported across its membrane. He also focuses on mRNA transport, degradation, and phase separation. In 2021, 64 outstanding life scientists working in 21 different countries were elected to the EMBO, joining a community of more than 1,800 leading life scientists.

MATILDE GALLI
Institute: Hubrecht Institute, Utrecht, The Netherlands
Fellowship: 2008–2010

Matilde Galli has received an ERC Starting Grant for her project "Timing Cell Cycles in Multicellular Development". She will study nematodes to determine how their cells change their division patterns during development. She intends to map changes in gene activity, identify the molecules driving the changes, and implement a new imaging platform to visualize and manipulate cell divisions in the gut in real time.

YOHANNS BELLAÏCHE
Institute: Institut Curie, Paris, France
Fellowship: 1985–1989

Yohanns Bellaïche has received an ERC Advanced Grant for his project "Scaling Sensitivity", which will study the developmental scaling of cell mechanosensitivity in epithelial tissues. All biological systems need to scale their organization and processes to their size, including physiology, gene expression, and cell cycles. Yohanns will draw on recent developments in mechanical detection to elucidate how cells regulate and sense cell size in epithelial tissues. He will look at different scales, from the cytoskeleton to tissues, and examine their changes over time, from seconds to hours.

PROFESSOR ANDREAS BERGTHALER
Institute: Medical University of Vienna, Austria
Fellowship: 2004–2006

In early 2022, Andreas Bergthaler was appointed professor of molecular immunology at MedUni Vienna. He also heads the Institute for Hygiene and Applied Immunology at the Center for Pathophysiology, Infectiology and Immunology. He and his team are investigating how inflammatory processes are regulated and how the immune system reacts to viral infections.

MOHAMED EL-BROLOSY
Institute: Whitehead Institute for Biomedical Research, Boston, MA, USA
Fellowship: 2017–2019

Mohamed El-Brolosy has received two honours for his outstanding PhD thesis: the Otto Hahn Medal of the Max Planck Society, and the Hans Peter Hofschneider Award, presented every two years for outstanding research in molecular biology.

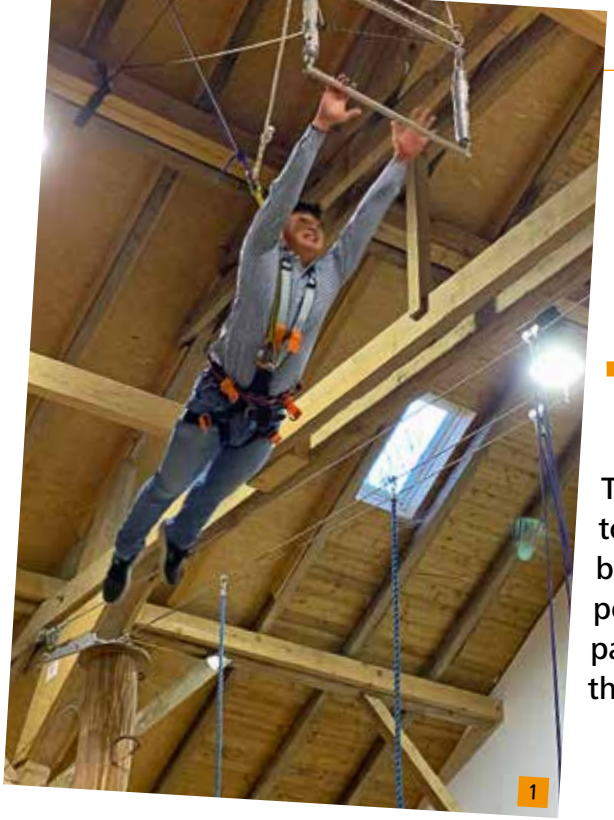
MICHAEL BRECKWOLDT
Institute: Heidelberg University Hospital, Heidelberg, Germany
Fellowship: 2006–2007

MAGDALENE SCHLESIGER
Institute: Heidelberg University, Germany
Fellowship: 2011–2014

The German Research Foundation (DFG) has accepted the BIF fellows Michael Breckwoldt and Magdalene Schlesiger into its prestigious Emmy Noether Programme for Group Leaders. **Michael** aims to develop imaging methods and corresponding biomarkers to visualize and understand how invasive gliomas infiltrate the brain and how they react to different treatments. His project is titled "Translational Multimodality Imaging of Glioma Hallmarks to Assess the Dynamics of the Immune Cell Landscape and Tumor Cell Invasion during Targeted Therapy". **Magdalene** wants to characterize the neuronal signature of long-term memory formation in the lateral entorhinal cortex and to examine how the hippocampus and the ventral tegmental area interact to build long-term memory traces.

Photos: Tessmar-Raible: BarbaraMair; Weiss: ETH Zurich; Galli: private; Bellaïche: private; Bergthaler: MedUni Vienna; El-Brolosy: private; Breckwoldt: Heidelberg University Hospital; Schlesiger: private

TAKING THINGS IN STRIDE AND ON THE FLY


1

The BIF's seminars have been evaluated as "highly beneficial to academic careers" in a study by the University of Heidelberg. We therefore very much regretted having to cancel, postpone, or go virtual with many of our seminars over the past two years. However, we stepped up to the challenge in the usual BIF manner.


3

Our first foray into the virtual seminar world took place in September 2020 with a one-day remote meeting attended by nearly 130 participants – as a substitute for our biennial North America conference in Woods Hole. Four more intimate onboarding seminars for new fellows followed immediately. They gave about 70 fellows from different selection rounds the first chance to meet one another. The newbies were also warmly welcomed to the BIF community by current and former fellows via short video clips.

In spring 2021, we went full out, holding two five-day communication seminars within three weeks. Although the training schedule was demanding, we still found time for networking and many fun activities – e.g. a pub quiz, an escape room game, one-on-one breakout rooms, and socializing via a more informal platform. Preparing these seminars was intense (and our learning curve steep), but most importantly, feedback from the participants was very positive.

In summer 2021 – finally! – we were able to hold our first in-person seminars in almost two years, which of course included stringent hygiene measures based on the 2G+ concept* and daily testing. The progress seminar for current fellows in Hirschegg, Austria, was followed by an alumni seminar in Glashütten, Germany. For many participants, it was the first in-person scientific event in two years. Their desire to exchange ideas was all the greater – as was the pleasure they took in the discussions. The North America meeting shortly afterwards, however, had to be online once again, as we could not travel to the United States. We built a virtual bridge across the continents and also invited current fellows from Europe who had been unable to go to Hirschegg. We once again combined science with as much networking as possible.


2

As we were unable to hold any communication seminars in 2020, we scheduled two seminars in Lautrach, Germany 1, 2, 3 – one in English, the other in German – in order to give all current fellows a chance to participate. While the English seminar took place as planned, circumstances made it necessary to switch to an online format for the German seminar, landing us in the now all too familiar tiles of the digital world.

We wish to thank all the fellows who made these seminars successful and safe, whether online or in person.

At the time of writing, we are planning additional in-person seminars for 2022. Let's hope for the best. Our takeaway from the last two years: while the online seminars worked much better than we had hoped, nothing beats meeting face to face.

* 2G = German for vaccinated or recovered + a negative test

UNRAVELLING THE IMMUNE SYSTEM – 2021 HEINRICH WIELAND PRIZE FOR THOMAS BOEHM

As one of the world's foremost immunologists, Professor Thomas Boehm, director at the MPI of Immunobiology and Epigenetics in Freiburg, Germany, has made groundbreaking contributions to our understanding of how the immune system of vertebrates develops, works, and has evolved over time. His outside-the-box thinking and original approaches have enabled surprising, even paradigm-shifting, insights into the function of the immune system, which reach beyond immunology. For his many achievements, the Boehringer Ingelheim Foundation awarded him the 2021 Heinrich Wieland Prize, endowed with 100,000 euros.

Prof. Thomas Boehm

BIF's SISTER FOUNDATIONS

"Applying his scientific acumen and unconventional approaches to such diverse systems as human cells, mice, zebrafish, and even deep sea anglerfish, Thomas Boehm has given us a detailed understanding of the immune system, especially of the role played by the thymus," says Christoph Boehringer, chair of the Executive Committee of the Boehringer Ingelheim Foundation. Boehm received the prize at a festive award ceremony that included last year's awardee, Professor Craig M. Crews of Yale University, New Haven, CT, USA. On 21 November, a hybrid symposium was held in honour of both scientists at Nymphenburg Palace in Munich, Germany. On 2 November, as part of the Berlin Science Week, Boehm and renowned philosopher Professor Markus Gabriel of the University of Bonn, Germany, discussed human vulnerability in the context of disease and society.

PROFILES

ALEXANDER BATES
Institute: Harvard Medical School, Boston, MA, USA
Fellowship: 2016–2018

LISA TRAUNMÜLLER
Institute: Harvard Medical School, Boston, MA, USA
Fellowship: 2016–2018

PROFESSOR MICHAEL LENHARD
Institute: University of Potsdam, Germany
Fellowship: 1998–2000

Three fellows have received grants from the International Human Frontier Science Program Organization (HFSP). In both of its programmes, fewer than 10% of applicants were successful. **Alexander Bates** and **Lisa Traunmüller** each received an HSFP Long-Term Fellowship for their innovative, ground-breaking projects. The funds will enable them to take a new research approach and obtain training in a new area of research in an outstanding laboratory of their choice in another country. Both have decided to pursue their 3-year fellowship at Harvard Medical School. **Alexander's** project is titled "A Cartesian Coordinate System for Generating Flexible Internal Goals". The title of **Lisa's** is "Contribution of Activity-Regulated Neuropeptide Function to Synaptic Plasticity and Memory". **Michael Lenhard** has received an HFSP Research Grant as principal investigator for the project "The Biology of Left-Right Asymmetry – Linking Structural Determinants to Ecology and Evolution". Together with colleagues from Canada, the Netherlands, and South Africa, **Michael** will investigate mirror symmetry in flowers. The collaborative HFSP research grants fund risky, cutting-edge projects and are the only ones that support teams located in different countries. The interdisciplinary groups are expected to create novel approaches to problems in fundamental biology.

Photos: Bates: private; Traunmüller: private; Lenhard: private; Boehm: MPI-IE Rockoff

BIF'S BOARD OF TRUSTEES

Our Board of Trustees decides on all matters of fundamental importance for the BIF. As an independent committee of experts, it appoints the chairs of the International Titisee Conferences. Through its selection of fellows, it ensures that we fund the most talented applicants working on cutting-edge and well-designed projects in top-notch laboratories. The board includes six internationally renowned scientists, a representative of our founders, and, as a permanent guest, a representative of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG).

Effective January 2022, we are very happy to welcome two new board members: Prof. Michael Häusser of University College London, UK, and Dr Michel Pairet, member of the Board of Managing Directors of Boehringer Ingelheim and representative of our founders.

We would also like to take this opportunity to introduce two not so new trustees: Prof. Marina Rodnina of the newly renamed MPI for Multidisciplinary Sciences in Göttingen, Germany, and Prof. Andrea Schietinger of Memorial Sloan Kettering Cancer Center in New York, USA. The two joined the Board in 2020 and 2021, respectively. In times in which there is a growing demand for peer review, we are particularly grateful that they have agreed to assume on the responsibility associated with their new positions.

They were preceded by Prof. Reinhard Jahn, also of the MPI for Multidisciplinary Natural Sciences, Prof. Andreas Barner, member of the Shareholders' Committee of Boehringer Ingelheim, and Prof. Benjamin U. Kaupp of the MPI for Neurobiology of Behavior – caesar in Bonn, Germany. We extend our deepest gratitude to all of them for their many years of service to the BIF, outstanding expertise, and dedication. They are now "honorary BIFlers".

The new members join Prof. Thomas Braun, MPI for Heart and Lung Research, Bad Nauheim, Germany, Prof. Christian Klämbt, University of Münster, Germany, and Prof. Jan-Michael Peters, Research Institute of Molecular Pathology (IMP), Vienna, Austria. All will work to ensure the continuity of BIF's essence while embracing change, keeping abreast of the times, and reacting to new developments.

PROF. MARINA RODNINA
Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany

DR DR MICHEL PAIRET
Board of Managing Directors of Boehringer Ingelheim, Ingelheim am Rhein, Germany

PROF. DR JAN-MICHAEL PETERS
Research Institute of Molecular Pathology, Vienna, Austria (Deputy Chairman)

PROF. MICHAEL HÄUSSER
PhD, University College London, UK

PROF. DR ANDREA SCHIETINGER
Memorial Sloan Kettering Cancer Center, New York, USA

PROF. DR DR THOMAS BRAUN
Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

DR INGRID OHLERT
Deutsche Forschungsgemeinschaft, Bonn, Germany (permanent guest)

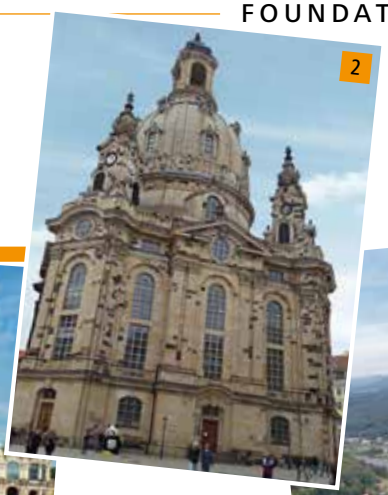
PROF. DR CHRISTIAN KLÄMBT
University of Münster, Germany

Photos: Barner: BI; Braun: MPI for Heart and Lung Research; Klämbt: WWU/Peter Grewer; Pairet: CHBS; Peters: IMP/Lukas Beck; Ohlert: private; Rodnina: MPI; Schietinger: Memorial Sloan Kettering Cancer Center

A BIF FELLOW'S GUIDE TO ...

DRESDEN


1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Travelling is fun – especially if you get insider tips from locals! In each edition of FUTURA, one fellow shows you around his or her city. In this edition your guide is Laura Meißner. She reports from Dresden, Germany, the city best known for its delicious *Weihnachtsstollen*.

FACTS & FIGURES

Country: Germany
Population: about 560,000
Area: 330 km²
Students: about 45,000
Famous for its baroque old town, cultural life, pub district, and the Elbe
Website: www.dresden.de

RESTAURANTS

Pulverturm: located in an old vault, service and entertainment by staff in baroque costumes.
Bautzner Tor: hearty, traditional German and Saxon fare with regional beers and beer tastings.
Altes Wettbüro: a former casino that now serves Mediterranean and Asian cuisine on a large terrace.
Lila Soße: modern German cuisine with appetizers served in glass jars.

WHERE TO STAY

Backstage: has just 12 rooms, decorated by artists from Dresden.
Mondpalast: hostel with zodiac-themed rooms.
Innside: designer hotel with spa in the city centre.

BEST SIGHTS

Explore the baroque **old town (Altstadt)**, visit the **Zwinger** 1 and the **Residenzschloss**, view the **Fürstenzug** mural, climb up the cupola of the **Frauenkirche** 2. Cross the **Elbe** (**Carola Bridge** offers the best view, **Waldschlösschen Bridge** is the most impressive) and take in the **Neustadt** district. Walk through the **Kunsthofpassage** and enjoy the food and drinks. Visit the **Elbe castles** 4, stroll through the park at **Lingnerschloss,** and walk down to the river along the path through the vineyards.

NIGHTLIFE

Bottoms Up: popular bar with a nice beer garden.
Katy's Garage: a beer garden, bar, and music venue with furniture made of car parts.
El Cubanito: rustic bar with Cuban cocktails and cigars.

ACTIVITIES

Spring: take a bike tour along the Elbe or a hike in "Saxon Switzerland", visiting the Bastei Bridge, the Schrammsteine, or Königstein Fortress. 3
Summer: attend one of the festivals on the river bank (e.g. Bunte Republik or Movie Nights).
Fall: view a winery and take part in a wine tasting at Lingerschloss or Radebeul.
Winter: eat stollen and check out the Striezelmarkt, Germany's oldest Christmas market.

Contributors wanted! If you would like to introduce your city, send an email to kirsten.achenbach@bifonds.de

Laura Meißner, Center for Molecular and Cellular Bioengineering (CMCB), Dresden
Supervisor: Prof. Stefan Diez
Age: 26

Photos: Laura Meißner

WHO'S WHO AT BIF?

Photo: BIF/C. Costard

VERA SCHLICK

Vera Schlick was born in Rhineland-Palatinate, Germany, in 1966. She studied foreign languages in Mainz and Saarbrücken and worked as a bilingual secretary in the pharmaceutical industry before joining the BIF. Here she handles all incoming inquiries regarding PhD and MD fellowships and travel grants and is responsible for the initial formal check of applications, preparing them for the decision process. In addition to her many other tasks, she organizes the interviews with PhD candidates and the meetings of BIF's Board of Trustees.

What's your most remarkable BIF experience?
The nicely written emails I sometimes receive from applicants whose applications were rejected. I'm always touched when I read their kind and thankful words despite the disappointment they must feel.

What's your favourite activity?
Retreating to the mountains for long hiking excursions, combined with a meal and a beer at a hut. For me, this is a guarantee for highly content and happy moments.

What's your remedy for stressful situations?
Putting on my shoes and going for a run or a walk in the fresh air.

What fault in others can you tolerate best?
The desire to eat more than one should.

Your advice for fellowship holders?
Never give up. Be focused, but not too focused. Don't become desperate and get paralyzed if something doesn't work out right away. Be patient. Go out for a walk and let your mind wander to make room for new ideas. And don't forget: you also have a life beyond your project.

What scientific achievement do you admire?
Bionics and engineering solutions for which nature has served as a model, like shark skin for aircraft hulls, the structure of bones for timber-framing, and animal movement for robotics.

Name one thing you couldn't live without.
My garden. When I come home from the "big" city of Mainz and enter my tranquil green garden, I immediately feel as if I'm on vacation.

UPCOMING EVENTS

25–29 MARCH 2022
Communication training, Lautrach, Germany
Communication seminar for non-German-speaking PhD and MD fellowship holders working in Europe. The meeting will take place in Lautrach, Germany. Participants will have the opportunity to work on their writing and presentation skills with various coaches, as well as to learn more about designing graphs and figures. Further details will be sent with the invitation.

27 APRIL–1 MAY 2022
123rd International Titisee Conference, Titisee, Germany
The 123rd ITC, titled "RNA as a Driving Force in Cellular Organization and Function", will be chaired by Karla Neugebauer (New Haven, USA) and Christine Mair (New York, USA). Addressing the fundamentals of RNA in cells – including sequences, dynamics, activity, and localization patterns – the meeting will envision new ways of thinking about RNA. Also on the agenda: cutting-edge methods and emerging data.

5–9 MAY 2022
North America meeting, Woods Hole, USA
Seminar for alumni and current PhD and MD fellows working in North America. Participants will present their scientific results. The programme is complemented by keynote presentations and talks on career opportunities and other topics. It includes tours of the scenic surroundings in Cape Cod.

24–26 JUNE 2022
European alumni seminar, Glashütten, Germany
Annual meeting of former BIF PhD and MD fellows based in Europe.

Need an update on upcoming events? Check our website at www.bifonds.de

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