FUTURA

THE JOURNAL OF THE BOEHRINGER INGELHEIM FONDS

VOL. 34 | 2.2019

RNAs on the move
Discovery of RNA localization and distribution patterns

Projects and results
Twenty-nine new PhD projects and fourteen completed theses

Collegium Glashütten
New venue for the European alumni seminar

The cover illustration shows a simplified model of a tadpole. In this issue, we spotlight the African clawed frog, which was originally used in human pregnancy testing and the modelling of human diseases. Today, it plays an important role in studies of kidney disease, the development of the spinal cord, the toxicity of agricultural chemicals, eye tumour growth, and other subjects.

FACTS

PROFILE OF *XENOPUS LAEVIS*

RNAs ON THE MOVE

FELLOWS

NEW PHD PROJECTS, FIRST ROUND 2019

NEW PHD PROJECTS, SECOND ROUND 2019

PHD RESULTS

FOUNDATION

LIFE IN MOTION

PUBLISHING INFORMATION

Published by Boehringer Ingelheim Fonds (BIF)
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Printed by LUC GmbH,
Hansaring 118, 48268 Greven, Germany

Images Boehringer Ingelheim Fonds, unless stated otherwise

Cover photos gettyimages/anucha sirivisansuwan (bottom left); Istock/sturti (bottom middle); all others BIF

Publication date of current issue April 2020

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STANDING TOGETHER

»This may be the time to reconsider approaches and results and discuss them anew (ideally, remotely).«

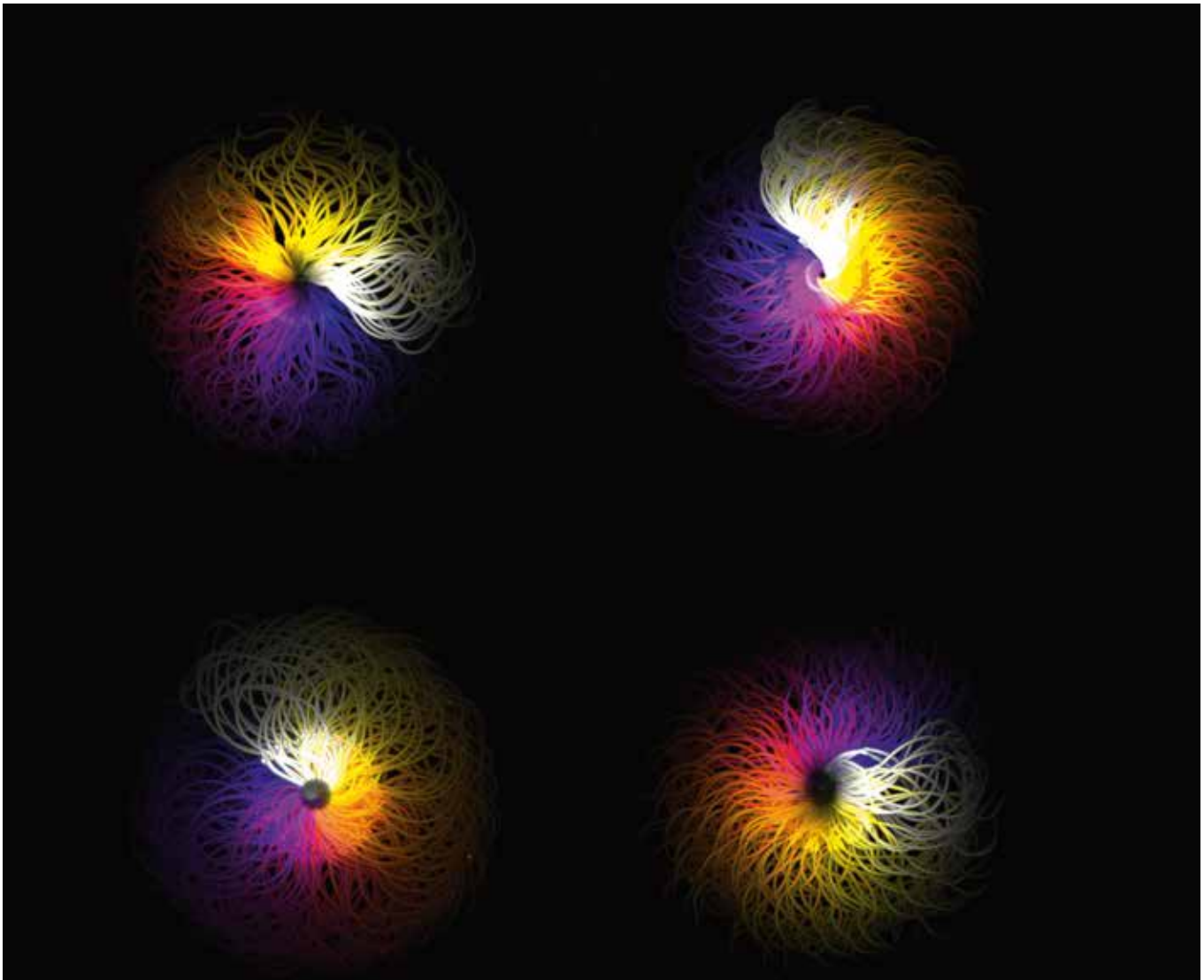
The COVID-19 pandemic requires unusual measures from every one of us – among them, staying at home and keeping our distance from others. But we also need to stand together to lessen the virus's impact while continuing our necessary work as best as possible. Of course, at BIF, we have also changed procedures to protect everyone involved in our work. At the same time, we are ensuring that our fellows and grantees continue to receive their stipends and funding and that the selection of fellowship holders can proceed as planned. No deadline needs to be changed.

At present, we are receiving many calls and emails asking what to do about flights and hotels that have been booked with BIF's support to attend now-cancelled conferences and courses. COVID-19 is also leading to fellowships and research stays abroad being cancelled or interrupted so that participants must return home. Depending on the region and the country, research institutes and universities have shut down for a few weeks or the next few months. In many cases, these measures have ruined complex experiments and left students wondering whether they can complete their PhDs. But what alternatives do these organizations have to slow down the virus's spread and protect people? This may be the time to step back and take stock of what has been achieved in a research project so far – to reconsider approaches and results and discuss them anew (ideally, remotely). Without the daily bustle of the lab, students may discover at an early stage that an important control is missing or that not all of the data support a pet hypothesis. It may also be the time to write a draft of a paper or thesis.

To protect our fellows and do our share in containing the virus, we have also postponed or cancelled all of our events through the end of June: the International Titisee Conference in spring, seminars, communication trainings, and our alumni meeting. We will inform fellows by email and on our (relaunched) website www.bifonds.de if further changes are necessary. The decision about these events was taken with a heavy heart, since it touches one of the cornerstones of BIF's work: personal exchange and support. But there was no choice. One of the appeals of our network is that it brings together people working on different biomedical research topics in many different cities and countries. However, this has a large potential to turn a BIF event into a hotspot for the spread of the new coronavirus.

Despite not being able to meet you in person right now, we will continue to be there for you – via phone and email. We will closely monitor the development of the pandemic, and we hope that in due course we can again send out invitations for BIF events – although, admittedly, this may not be very soon.

Until then: stay healthy and in good spirits and help out where you can.



LIGHT MAKES THE SPERM GO ROUND

by Jan Niklas Hansen, University Hospital Bonn, Germany

This image is a time projection (colour represents time) of four head-tethered transgenic mouse sperm. In mouse sperm, the symmetry and frequency of the beating of the flagella is regulated by cyclic adenosine monophosphate (cAMP). The sperm in this experiment were engineered to express the photo-activated adenylate cyclase bPAC, which is stimulated by blue light. Manipulating the cAMP levels in mouse sperm using bPAC makes the sperm flagellum beat faster and more asymmetrically. As a result, the head-tethered sperm start to rotate.

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.

Photo: Niklas Hansen

NO ANT LEFT BEHIND

Veromessor pergandei foraging columns are a bonanza for false widow spiders (*Steatoda sp.*), which construct simple webs over the ants' paths.

Researchers at Arizona State University, USA, have found some surprisingly selfless behaviour in one species of harvester ants.

Veromessor pergandei ants live in colonies of tens of thousands, which means a lot of mouths to feed. Worker ants spend most of the day roaming outside the nest in search of food and can often get entangled in spider webs. Luckily, they have their own rescue services to call upon for help.

An entangled ant releases a chemical alarm signal attracting passing ants to come to its aid. They rescue the trapped insect and carry it back to the nest, where they carefully clean the spider silk from its body.

Other ants risk their lives to destroy the spider's web by pulling at it with their legs. It is a dangerous mission with one in sixteen becoming ensnared or captured by spiders themselves. Such rescue behaviour is rare in the animal kingdom, particularly for species that live in large groups, where each individual member may be considered disposable.

The researchers suspect that because all the ants from the colony forage along the same route, the destruction of dangerous spider webs blocking the way helps to maintain a steady stream of food back to the nest.

REFERENCE

Kwapich C and Hölldobler B (2019) Destruction of spider webs and rescue of ensnared nestmates by a granivorous desert ant (*Veromessor pergandei*). *The American Naturalist* DOI: 10.1086/704338

Photos: C. L. Kwapich (top); Adobe Stock (bottom)

TAKING MOULD TO MARS? SPORES MAY SURVIVE THE JOURNEY THROUGH SPACE

Mould is an unwelcome guest in any household or workplace as it can make people sick. Unfortunately, mould is also very resilient and hard to get rid of, so it can be a persistent problem in many places. Mould is even an issue on the International Space Station, where astronauts spend hours cleaning it from the walls inside the station.

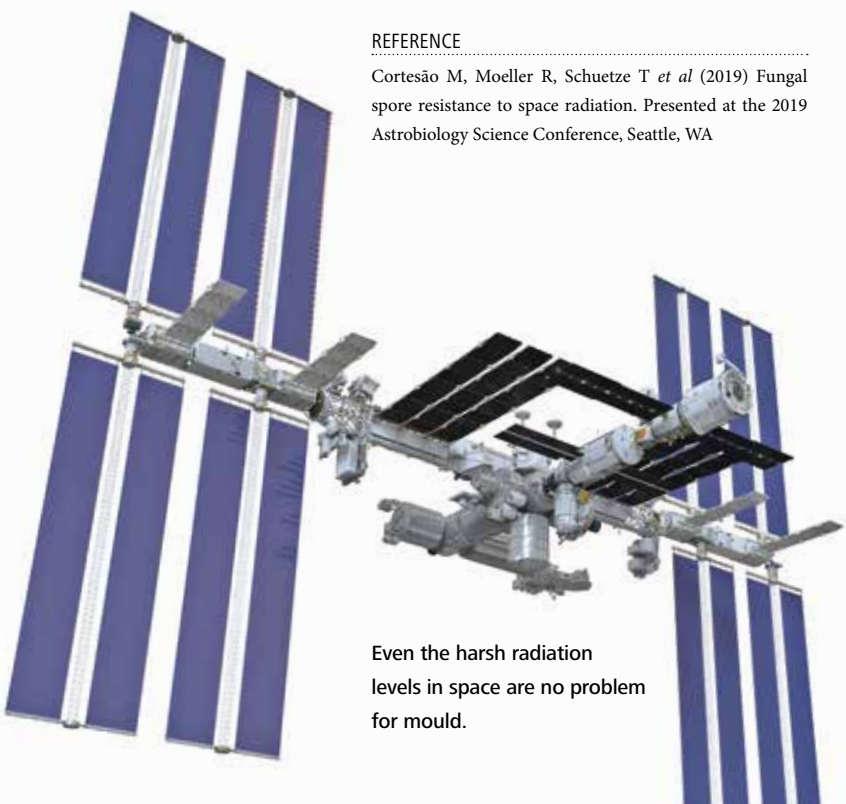
New research now suggests that mould may even be able to survive on the outside walls of a spacecraft, where it is exposed to the hostile conditions of space – a finding that has major implications for space exploration.

Researchers from the German Aerospace Center (DLR) in Cologne have discovered that mould spores commonly found on the International Space Station, such as *Aspergillus* and *Penicillium*, can survive doses of radiation 200 times higher than the lethal dose for humans. This means that they can easily withstand the radiation levels they would experience on the six-month journey to Mars on the outside of a spacecraft.

However, radiation is not the only challenge that mould may encounter in space. The DLR team's next mission is to investigate whether spores can survive the lack of gravity, extreme temperatures, and other harsh conditions they will experience on their space expedition. Their results will help us to avoid bringing our mouldy problems with us as we begin to explore new planets.

REFERENCE

Cortesão M, Moeller R, Schuetze T *et al* (2019) Fungal spore resistance to space radiation. Presented at the 2019 Astrobiology Science Conference, Seattle, WA



Even the harsh radiation levels in space are no problem for mould.

Changing weather conditions may have enabled the first RNA molecules to come into being.

LIFE ON EARTH? BLAME IT ON THE WEATHER

The origin of life is a subject that has long mystified biologists. One idea is that the nucleic acid RNA, which can store genetic information, existed before the first organisms evolved. This theory suggests that RNA began to replicate itself, eventually leading to the evolution of life in the form of bacteria.

RNA molecules are made up of four building blocks called nucleotide bases. Each base is made from a sugar molecule, ribose, and a ring of carbon and nitrogen atoms. For two of the bases, the carbon and nitrogen atoms make up a single ring, known as a pyrimidine, while the other two bases have a double ring called a purine. These distinct chemical structures suggest that purine and pyrimidine bases would have required different conditions to form on the early earth.

For decades, scientists have been searching for plausible conditions that would have allowed both types of bases to appear at the same time and in the same place, so RNA could eventually assemble. Now, a team of researchers from Germany, the UK, and Japan has come up with a theory for how all the RNA bases could have formed together, and it is all about the weather.

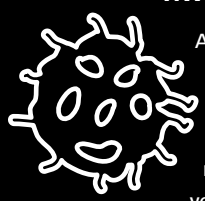
The scientists suggest that changing environmental conditions caused wet and dry cycles, which were able to drive all the necessary reaction steps required to make all the components of RNA in the chemical "soup" present on early earth. The team then proved their theory's credibility by recreating the same reactions to produce RNA in the laboratory.

REFERENCE

Becker S, Feldmann J, Wiedemann S *et al* (2019) Unified prebiotically plausible synthesis of pyrimidine and purine RNA ribonucleotides. *Science* DOI: 10.1126/science.aax2747

8.7

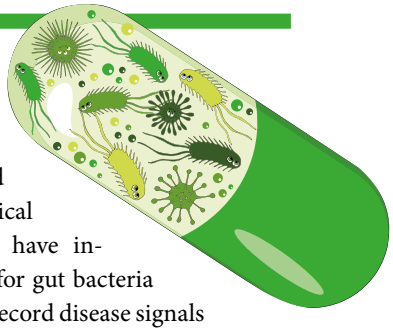
MILLION YEARS



A new study by the American Cancer Society estimates that cancer took more than 8.7 million years of life from adults in the United States in 2015. Researchers used the number of cancer deaths and life-expectancy data to project how much longer people would have lived if they had not died of the disease.

Source: Islami F, Miller KD, Sigel RL *et al* (2019) Lost earnings from cancer deaths in the United States: national and state estimates. *JAMA Oncology* DOI: 10.1001/jamaoncol.2019.1460

BACTERIAL BIOSENSORS SPOT THE SIGNS OF DISEASE IN THE GUT



Researchers from Harvard University and Harvard Medical School, USA, have invented a way for gut bacteria to detect and record disease signals inside the body to help diagnosis.

The team created a genetic circuit that detects "trigger" molecules, which may indicate the presence of disease, such as chemicals associated with inflammation. In the presence of a trigger, a genetic switch flips, activating a gene for resistance to an antibiotic called spectinomycin.

The scientists engineered the circuit into bacteria and fed them to mice. They then extracted the bacteria from the animals' droppings and tested if they could survive in the presence of spectinomycin. If they grew in the presence of the antibiotic, the team knew that the bacteria must have encountered a trigger molecule on the journey through the mouse's gut.

The team created a library of bacteria containing circuits responding to a wide range of triggers produced by specific health conditions in the gut, identifying bacterial biosensors that respond to a variety of disease-relevant molecules at differing sensitivities.

The work represents a step towards being able to detect multiple conditions using probiotic pills containing a sophisticated mixture of genetically engineered bacteria.

REFERENCE

Naydich, AD *et al* (2019) Synthetic gene circuits enable systems-level biosensor trigger discovery at the host-microbe interface. *mSystems* DOI: 10.1128/mSystems.00125-19

THE BACTERIA THAT SWIM ALONG THE EARTH'S MAGNETIC FIELD

Some animals seem to have a sixth sense when it comes to navigating. Many of these creatures use the earth's magnetic field to tell them which way to go, but how most of them do this remains a mystery. This question has now been answered for one species – *Magnetospirillum gryphiswaldense* – as scientists from the University of Bayreuth, Germany, have discovered how these bacteria align themselves with the earth's magnetic field.

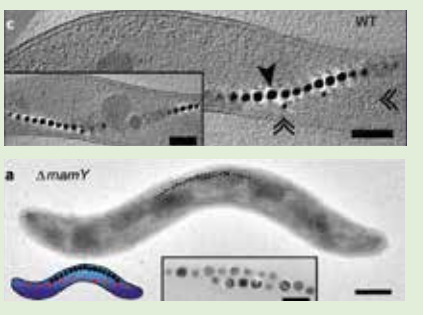
It was already known that each spiral-shaped *Magnetospirillum* cell contains around 50 compartments known as magnetosomes, each of which holds a tiny crystal made of the magnetic mineral magnetite. The magnetosomes form a straight line, like the needle of a compass, which aligns with a magnetic field and tells the bacteria which way to go.

But until recently, scientists were not able to explain how the magnetosomes formed such an orderly line within the cell. They knew that thread-like filaments connected the magnetosomes, but it was still a mystery how the chain of crystals got into line.

The researchers used high-resolution microscopes to observe the tiny magnetic crystals inside the bacteria. They discovered that a structural protein called MamY is responsible for organizing the magnetosomes into a chain and holding them in a rigid linear position. Cells lacking MamY still form crystal chains, but their internal compass is bent so the bacteria cannot navigate effectively.

REFERENCE

Toro-Nahuelpan M, Giacomelli G, Raschdorf O *et al* (2019) MamY is a membrane-bound protein that aligns magnetosomes and the motility axis of helical magnetotactic bacteria. *Nature Microbiology* DOI: 10.1038/s41564-019-0512-8x



MamY determines the localization of the magnetosome chain at the geodetic axis of *M. gryphiswaldense*.

Photo: Adobe Stock/valdezrl (left);shutterstock (right); www.nature.com/articles/s41564-019-0512-8 (bottom)

The African clawed frog, or *Xenopus laevis*, is common throughout Sub-Saharan Africa.

PROFILE OF **XENOPUS**

By Mitch Leslie

A frog from Sub-Saharan Africa has made its way to biological laboratories worldwide and even to space on the space shuttle *Endeavour* in 1992, showing that frog eggs fertilized in zero gravity develop into normal tadpoles.

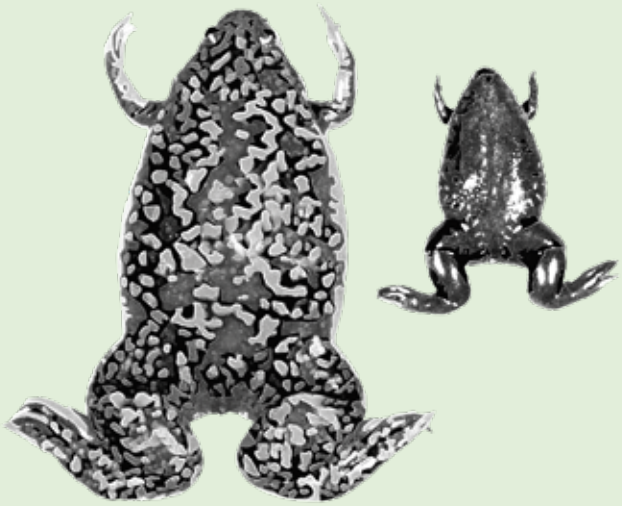
Today you will find the African frogs *Xenopus laevis* and *X. tropicalis* in labs that study kidney disease, the development of the spinal cord, the toxicity of agricultural chemicals, eye tumour growth, and a variety of other subjects. *X. laevis* first made a scientific splash in the 1930s because it was crucial for one of the early pregnancy tests. A British researcher working in South Africa, where *X. laevis* lives, discovered that injections of hormone-rich extracts from cattle pituitary glands spurred female frogs to lay eggs. Injecting the frogs with urine from pregnant women that contains the hormone chorionic gonadotropin had the same effect, providing one of the first reliable indicators of pregnancy.

Developmental biologists were quick to see the frog's potential. To probe how the animal body takes shape, they had been scrutinizing the eggs of other amphibian species such as newts. But to perform experiments, researchers typically had to wait for the animals to lay eggs naturally in the spring. By contrast, they could obtain eggs at any time from *Xenopus* frogs by stimulating females with commercially available hormones.

Xenopus was convenient to study for further reasons. Females lay numerous eggs that are large – more than 1 mm in diameter – which makes them easier to observe and manipulate than mammalian eggs. Embryonic development is rapid, with tadpoles appearing only 36 hours after the first cell division. The adults are resistant to diseases and easy to raise.

In the 1950s and early 1960s, *Xenopus* allowed researchers to tackle one of the biggest questions of the time – whether cells jettison or permanently shut down some of their genes as they specialize during development. To find out, John Gurdon, a graduate student at Oxford University in the United Kingdom, inserted nuclei from the intestines of *Xenopus* tadpoles into eggs that lacked chromosomes. Some of the eggs eventually grew into fertile adults, showing that specialized cells did not lose or irreversibly close down certain genes and that, with the right stimulation, they could revert to an earlier stage of differentiation. Gurdon's results paved the way for research on embryonic stem cells and mammalian cloning, and he shared the 2012 Nobel Prize in Physiology or Medicine for his discoveries.

CV OF *XENOPUS LAEVIS* AND *X. TROPICALIS*



- We usually grow to between 4 and 10 cm long.
- We live up to 30 years.
- We eat aquatic arthropods.
- We work in many areas of biology, including developmental biology, cell biology, and toxicology.
- We have helped researchers win four Nobel Prizes

Researchers in a variety of other fields have capitalized on the frog's qualities. Centrifuging large numbers of *Xenopus* eggs yields cell-free extracts that have proven invaluable for probing topics such as control of the cell cycle, DNA replication, and formation of the nuclear membrane. The frog's eggs have also been important for studying the channels that allow ions and water to move into and out of cells. By modifying the eggs to make the channels, researchers can study their functions.

Photos: eye of science (left); Thomas Splettstoesser/Wikimedia Commons (right)

Within the cell, mRNAs are shipped to where they are needed. They are packaged in such a way as to prevent translation before they reach their destination.

Photo: gettyimages/anucha sirivisansuwan

RNAs ON THE MOVE

By Mitch Leslie

Cellular tranport is not limited to finished goods – as it turns out, mRNAs, the blueprints for protein synthesis, are also shuttled to where they are needed and are not evenly distributed within the cell.

In the early 1980s, molecular cell biologist Robert Singer, then at the University of Massachusetts Medical School in Worcester, thought he had come up with a way to answer a question that was vexing researchers: when do certain genes switch on during muscle formation in the embryo? Instead, the discovery he and his postdoc Jeanne Bentley Lawrence reported in 1986 helped transform how scientists think about RNA and protein synthesis.

The technique they and a colleague had invented involved tagging mRNAs with radioactive DNA probes. In the images the researchers generated with this method, individual RNA molecules showed up as tiny dots within cells. The technique was slow, requiring three months to generate a single image, but it produced surprising results. The scientists expected that mRNAs would be scattered around cells. But when they tagged the mRNA for actin, a protein necessary for muscle contraction and cell movement, up to 80% of the molecules clustered in the projections the cells extend as they crawl. "We did not anticipate that the RNA would be localized," says Singer, who is now at the Albert Einstein College of Medicine in New York City. →

When the scientists used the same method to pinpoint mRNAs of other proteins, they saw different arrangements. mRNA that encodes the cytoskeletal protein vimentin, for instance, concentrated near the nucleus. "Each RNA had its own distribution pattern," Singer says. Those differences, the researchers concluded, suggested that the cells were sending their mRNAs to certain locations, presumably where the corresponding proteins were being synthesized. The results of this work were so intriguing, Singer says, that he gave up studying muscle cell development to focus on RNA localization.

Further research suggests that RNA localization may have key roles in memory and learning, embryonic development, cell adhesion, mitosis, and a variety of other processes. And it does not just occur in the chicken cells that Singer and his colleague studied. Organisms as different as mammals, yeast, and bacteria rely on RNA localization to customize different parts of their cells.

Now, new techniques are allowing researchers to investigate the process in even greater detail. With more powerful imaging methods, researchers can follow the journeys of individual RNA molecules in real time and observe them in the brains of living animals. Next-generation sequencing techniques have enabled researchers to census the RNAs in different parts of cells. Scientists are also probing how RNA localization can go wrong and whether it malfunctions in neurological diseases like amyotrophic lateral sclerosis and fragile X syndrome.

Researchers have long known that different parts of cells harbour different protein repertoires. However, scientists assumed that this local specialization arose because proteins travelled. Translation of mRNAs into proteins could occur anywhere in the cytoplasm, researchers thought. The newly formed proteins would then make their way to the part of the cell where they performed their tasks. Günter Blobel of Rockefeller University in New York City received the Nobel Prize in Physiology or Medicine in 1999 for showing that this process was not haphazard. He discovered that some proteins carry zip codes that direct the molecules to particular sites, such as the endoplasmic reticulum.

Cells of many different types localize a large fraction of their RNAs, a mechanism that allows on-site protein synthesis and permits different parts of a cell to specialize.

Singer's work suggested that cells have another mechanism to steer certain proteins to the right locations. He was not the only scientist to find signs of RNA redistribution. Research by 1995 Nobel Prize winner Christiane Nüsslein-Volhard of the Max Planck Institute for Developmental Biology in Tubingen, Germany, and other scientists revealed that some RNA molecules were unevenly apportioned in eggs of some animals. However, for years researchers thought that RNA localization only occurred in certain cases, says molecular cell biologist Ralf-Peter Jansen of the University of Tübingen. "The idea was that this is an odd phenomenon that few mRNAs undergo."

Studies by Singer and other scientists have since confirmed that cells of many different types localize a large fraction of their RNAs, a mechanism that allows on-site protein synthesis and permits different parts of a cell to specialize. "It turns out that RNA localization is a major factor in gene expression," says Singer. "Where an mRNA is translated is as important as why it is translated or even whether it is made or not."

One 2007 study, for example, revealed that 71% of mRNAs are unequally distributed in *Drosophila* embryos. And around 1,000 mRNAs may be on the move in neurons of mammals. Although researchers cannot say exactly what percentage of mRNAs are localized, the evidence suggests that "this might be the rule rather than the exception", says Jansen.

Cells go to all this trouble because relocating RNAs provides numerous benefits. For one thing, cells do not have to wait for proteins made elsewhere to diffuse or be transported to the right locations. The cytoplasm is dense and in a neuron proteins might have to travel a metre or more. With RNA localization, cells can synthesize proteins when and where they are required, saving time and energy.

In addition, once mRNAs have arrived at their destinations, cells can use them over and over to produce proteins. It is more efficient for a cell to make 40 copies of a protein from one localized mRNA than to ship 40 individual proteins to the site, Jansen says. RNA localization can also help cells coordinate the activity of proteins that function in concert, says Singer. "A whole cohort of RNAs involved with a particular aspect of physiology are localized together and produce proteins that are synergistic."

But to reap these benefits, the cell has to solve some engineering challenges. RNAs need a way to get around, along with an accurate navigation system to direct them to specific sites. As mRNAs move, the cell has to prevent them from being translated before they get to their destinations. The cell also has to position the translation machinery, including ribosomes, so it is ready to begin making the proteins.

Although researchers do not fully understand the logistics of RNA localization, they have unraveled some steps of the process. They have found that RNAs do not travel solo. RNA-binding proteins, or RBPs, attach to newly made mRNAs and shepherd them to their destinations. RBPs also perform another important job by preventing premature translation. RNAs and their RBP companions journey to their destinations in style, chauffeured by motor proteins such as myosin, dynein, and kinesin, which travel along microtubules or actin fibres. RNAs also carry sequences that serve as address labels, telling the cell where to send the molecules.

Scientists know the most about how RNA localization works in yeast. When a mother yeast cell starts to divide, it sends mRNAs that code for the protein Ash1 into the daughter cell – the protein determines which cells the daughter can later mate with. Singer, Jansen, and other researchers have dissected how this translocation occurs, revealing that a team of proteins is necessary to ship the mRNA into the daughter cell, including five proteins in the SHE family. Two of the SHE proteins help link the RNA to the motor protein. Other unrelated proteins clamp onto the RNA and stop it from being translated during its journey. Researchers have discovered that the mRNA for Ash1 contains four sequences known as zip-code elements that specify its destination. However, yeast "is the only example where we understand [localization] at all these levels," says Jansen.

Researchers have also delved into the mechanics of localization in the eggs of some animals. "RNA localization is very important for specifying cell fate later in development, including the fate of future germ cells," says Douglas Houston, a developmental biologist at the University of Iowa in Iowa City. The process helps to polarize the egg so that divisions produce distinctive cells that give rise to different structures in the body. The egg uses a passive mechanism to sort some of its RNAs. About 400 of its 10,000 mRNAs shift to the vegetal pole, which gives rise to the gut. A little understood structure known as the Balbiani body traps these molecules and carries them along as it moves to the vegetal pole. The egg also transports some mRNAs actively, ferrying them along microtubules. Houston notes that RNA localization is more significant for animals such as zebrafish, *Drosophila*, and *Xenopus*, in which the fertilized egg divides rapidly. In mammals, however, the egg divides more slowly and has time to synthesize new RNAs rather than moving them around.

RNA localization in yeast and eggs is simple compared to the complex choreography in neurons. When one neuron transmits a message to another across a synapse, for instance, the cell that receives the signal may boost protein synthesis in one of its dendritic spines, which means that spine requires a supply of mRNAs posthaste. "RNA goes to the right one," Singer notes, even though "in a neuron, there are thousands of dendritic spines."

Using techniques such as fluorescence microscopy, Singer and his team have been trying to determine how neurons organize these movements. In a 2016 study, the scientists labelled individual RNAs that code for the protein β-actin with a fluorescent probe. Stimulated dendritic spines need to build more β-actin so they can reorganize their cytoskeleton – this overhaul helps bolster synapses and fosters learning and memory. Singer and colleagues followed the labelled RNAs in real time in the dendrites of isolated, living mouse brain neurons. When the researchers stimulated a particular dendritic spine on a neuron, β-actin mRNA zipped to that spine – in about half the cases, at least one molecule arrived within 15 minutes. The mRNA then parked at the base of the spine, where it could remain for hours. The neurons were translating the stationary mRNAs to produce β-actin, the team showed.

The scientists also tracked mRNA movements in unstimulated dendrites. Researchers had assumed that RNAs went to a →

specific location and waited there until they were needed. But the RNAs Singer and colleagues observed were continually on the move, riding for short distances on the cytoskeleton and then stopping. An RNA molecule only travels "for about 10 seconds, then it falls off and looks for action", says Singer. A dendritic spine can capture the mRNAs it requires, although researchers are still working out how it traps the molecules. But if an mRNA is not snared by a dendritic spine, it moves again. Jansen says that researchers describe this mechanism as the sushi belt model. Like dishes of sushi in a restaurant, which circulate on a conveyor belt until a diner removes them, mRNAs cruise around the cell until they are "chosen".

Researchers still need to work out many of the details of RNA localization. "The major part that we do not know is what the RNA localization signal generally looks like," says Jansen. Scientists have identified specific sequences in a few mRNAs, such as those for Ash1 and β-actin, which steer the molecules to certain sites. Unlike the four zip codes in Ash1, the address sequence for β-actin mRNA is a 54-nucleotide stretch in the 3′ untranslated tail of the molecule, which binds to an RBP.

However, scientists have not been able to deduce any general rules to pinpoint the addresses in other mRNAs. As a result, they cannot predict these molecular zip codes, says Singer. Research on the zip codes that scientists have uncovered suggests that they form complex three-dimensional structures that interact with RBPs, Singer notes. "It is not just the sequence" of nucleotides that is important for localization, "but also the structure of the mRNA that often is recognized by the proteins that complex with it."

Where an mRNA – and its corresponding protein – ends up in a cell may also depend on whether and how the molecule has undergone splicing. Different portions of a cell can carry different versions of a particular protein, produced from alternatively spliced RNAs. Molecular biologist Matthew Taliaferro of the University of Colorado School of Medicine in Aurora and colleagues have discovered that the mRNA's tail may help cells sort these versions. In a 2016 study of neurons, they found that whether a protein variant localizes to the cell body or to dendrites and axons depends on whether splicing has removed the final coding segment of its mRNA, known as the alternative last exon.

With RNA localization, cells can synthesize proteins when and where they are required, saving time and energy.

Other questions researchers are trying to answer include how cells move the protein-making machinery to the mRNA localization sites. Some studies suggest that ribosomes cluster at spots where mRNAs will stop. But how cells guide them to these locations is unclear, Jansen says. Another issue is how cells coordinate the movements of different mRNAs. If thousands of mRNAs are zipping back and forth in a neuron, it needs a traffic control mechanism to prevent crashes and jams, says Taliaferro. Researchers are also investigating whether faulty RNA localization promotes certain diseases. Some patients with fragile X syndrome, amyotrophic lateral sclerosis, and spinal muscular atrophy carry mutations in genes for RNA-binding proteins, suggesting that RNA transport may be defective in these illnesses. However, Taliaferro cautions that so far "no one has been able to prove that the mislocalization of a specific mRNA directly contributes to disease phenotypes".

The significance of RNA localization for human health may be unclear. But Singer says that the evidence shows that the process has a bigger role in the lives of cells than he imagined in 1986. "This is an extremely important process," he says. "It has been around for a long time and is present in bacteria and yeast, so this is not some sort of mammalian cell luxury."

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 *.

UNDERSTANDING SMALL RNA-GUIDED NUCLEAR GENE SILENCING OF TRANSPOSABLE ELEMENTS

cf. BIF FUTURA, VOL. 30 | 2.2015

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Discipline: Molecular Biologist, MSc
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Supervisor: Dr Julius Brennecke

Transposable elements (TEs) are selfish genetic elements whose uncontrolled activity in the animal germline destabilizes the genome, thus leading to sterility. The PIWI-interacting RNAs (piRNAs), which are small non-coding RNAs, protect the germline genome by establishing repressive heterochromatin at TE loci. This transcriptional repression requires piRNA-guided targeting of nuclear PIWI proteins to newly transcribed, or nascent, TE RNAs. The goal of my PhD project was to better understand the molecular mechanism underlying nuclear TE repression by identifying and functionally characterizing proteins that are essential for this process in *Drosophila melanogaster*. By combining co-immunoprecipitation, mass spectrometry, and biochemical approaches, I uncovered a novel protein complex, SFiNX (silencing factor interacting nuclear export variant), consisting of three proteins: Panoramix, a previously uncharacterized fly-specific protein; Nxf2, a member of the highly conserved nuclear RNA export factor (NXF) family; and Nxt1, a general NXF co-factor. Using genetics and next-generation sequencing-coupled techniques, I showed that SFiNX is required for maintaining fertility, repressing TEs, and establishing heterochromatin downstream of Piwi – the sole nuclear PIWI protein in *D. melanogaster*. Furthermore, I generated a cell culture-based silencing reporter assay to show that SFiNX can induce repression when experimentally targeted to a nascent RNA, independently of piRNAs and Piwi. This assay, combined with a systematic protein domain analysis, revealed that Nxf2 binds RNA, while Panoramix recruits chromatin effector proteins. Together with my colleagues, I found that one of these effectors is Setdb1, a histone-modifying enzyme that trimethylates H3K9 to generate repressive chromatin at TE loci. My findings reveal key players and provide new insights into the mechanism of small RNA-guided gene silencing, a process conserved in animals.

PUBLICATIONS

Batki J*, Schnabl J*, Wang J*, Handler D, Andreev VI, Stieger CE *et al* (2019) The nascent RNA binding complex SFiNX licenses piNA-guided heterochromatin formation. *Nat Struct Mol Biol* **26**: 720–731

Sienski G*, Batki J*, Senti K*, Dönertas D, Tirian L, Meixner K *et al* (2015) Silencio/CG9754 connects the Piwi-piRNA complex to the cellular heterochromatin machinery. *Genes Dev* **29**: 2258–2271

GENOME-LAMINA INTERACTIONS ARE ESTABLISHED *DE NOVO* IN THE EARLY MOUSE EMBRYO

cf. BIF FUTURA, VOL. 30 | 2.2015

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Supervisor: Prof. Maria Elena Torres Padilla

Upon fertilization, the two parental genomes are epigenetically reprogrammed to give rise to a totipotent state. In the mammalian embryo, this process involves an extensive three-dimensional rearrangement of nuclear organization. Genomic loci in contact with the nuclear lamina at the nuclear periphery, termed lamina associated domains (LADs), have a low rate of transcription, are gene-poor, and provide a scaffold for proper genome function. The aims of my PhD project were to determine when LADs are first established in embryo development, whether they are inherited from the germline, and what molecular mechanisms regulate their formation. I created genome-wide maps of LADs from mouse preimplantation embryos and oocytes at the single-cell level. I found that LADs are absent in oocytes, but are established *de novo* in zygotes. Embryonic LADs are dynamically rearranged during the two- and eight-cell stages, with little heterogeneity between individual cells. Single nucleotide polymorphisms in hybrid embryos allowed the maternal and paternal alleles to be distinguished. I found that the two alleles of certain loci localize differently relative to the periphery, which likely reflect each allele's germline history. Moreover, I determined that LAD formation precedes the maturation of topologically associated domains (TADs) in a DNA replication-independent manner, suggesting that LADs form the very first scaffold of genome organization after fertilization. I found that H3K4 methylation on LADs is asymmetric between the paternal and maternal genomes in zygotes. Reducing the H3K4me3 histone mark by overexpressing the lysine demethylase KDM5B resulted in a loss of LAD structure, specifically in the paternal zygotic genome, suggesting a novel mechanism of allele-specific LAD formation through histone methylation. My work contributes a genome-wide resource on mouse preimplantation nuclear organization for further epigenetic studies of early embryos.

PUBLICATIONS

Borsos M*, Perricone SM*, Schauer T, Pontabry J, de Luca KL, de Vries SS *et al* (2019) *De novo* establishment of spatial genome organization in the mouse embryo. *Nature* **569**: 729–733

Borsos M, Torres-Padilla ME (2016) Building up the nucleus: nuclear organization in the establishment of totipotency and pluripotency during mammalian development. *Genes Dev* **30**: 611–621

STRUCTURAL STUDIES OF CO-TRANSLATIONAL MEMBRANE INSERTION AND N-GLYCOSYLATION

cf. BIF FUTURA, VOL. 31 | 1.2016

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Discipline: Biochemist, MSc
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Supervisor: Prof. Roland Beckmann

Approximately 30% of eukaryotic genes encode alpha-helical transmembrane proteins. Most of these proteins carry covalently linked oligosaccharide modifications that are critical for their folding, stability, and function. In mammals, nascent protein chains undergo co-translational membrane insertion and asparagine-linked glycosylation (N-glycosylation) at the endoplasmic reticulum membrane. Both events are crucial for membrane protein topogenesis, trafficking of proteins to their final intra- or extracellular destination, and protein functionality. Glycan transfer is catalysed by the oligosaccharyltransferase (OST). This complex of at least eight protein subunits exists in two isoforms in higher eukaryotes: STT3A-OST and STT3B-OST. The transient and highly dynamic nature of OST-containing ribosome-translocon complexes had limited their structural characterization to moderate-resolution cryo-electron tomography structures. The goal of my PhD project was to elucidate the mechanisms of co-translational membrane protein insertion and characterize its coupling to N-glycosylation. I successfully designed a protocol to generate and isolate intermediates of these two processes. Using cryo-electron microscopy, I determined the first high-resolution structure of a mammalian OST-containing ribosome-translocon complex, a very early biogenesis intermediate of bovine opsin. My work revealed the spatial arrangement of mammalian STT3A-OST subunits and explained how only STT3A-OST can associate with the ribosome and the membrane insertion machinery. Cryo-electron tomography studies of microsomes from human wild-type and STT3A- or STT3B-knockout cells, performed by collaborators, verified previous reports that co-translational modification by mammalian OST is driven specifically by the STT3A-OST isoform. Comparison of my structure with structures of yeast OST confirmed that the complexes have a conserved architecture but also potential differences. My results contribute significantly to our understanding of the complex mechanisms involved in the biogenesis of eukaryotic transmembrane proteins.

PUBLICATIONS

Braunger K*, Pfeffer S*, Shrimal S, Gilmore R, Berninghausen O, Mandon EC *et al* (2018) Structural basis for coupling protein transport and N-glycosylation at the mammalian endoplasmic reticulum. *Science* **360**: 215–219

THE MOLECULAR DETAILS OF MEMBRANE-MEDIATED PROTEIN KINASE D ACTIVATION

cf. BIF FUTURA, VOL. 30 | 2.2015

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Supervisor: Assoc. Prof. Thomas A. Leonard

Protein kinase D (PRKD), an essential serine threonine kinase in animals, is required for cellular processes such as vesicle trafficking, cytokine secretion, and actin remodelling. In addition to a catalytic domain and a PH domain, PRKD contains two C1 domains, which bind the lipid second messenger diacylglycerol (DAG). DAG is produced in cells in response to various extracellular cues, such as neurotransmitters, growth factors, and peptide hormones. When DAG allosterically binds to the C1 domains, it activates PRKD, which is accompanied by phosphorylation of the so-called activation loop in the PRKD catalytic domain. Phosphorylation of PRKD is reportedly carried out by kinases from the novel protein kinase C (nPKC) family, which would place PRKD in a signalling pathway downstream of nPKCs and DAG. Because a thorough *in vitro* biochemical and structural characterization of PRKD is lacking, the molecular details of its activation are poorly understood. In my PhD project, I discovered a region at the N-terminus of PRKD that was unannotated and uncharacterized. Using X-ray crystallography, I found that this region forms a distinct domain with an ubiquitin-like fold that assembles into a dimer. I validated the dimerization interface for this isolated ubiquitin-like domain using static light scattering and fluorescence anisotropy measurements *in vitro*. Using co-immunoprecipitation, I demonstrated that this interface is the primary site for full-length PRKD dimerization in cells. I showed that dimerization of this domain is required for PRKD activation, both under resting conditions and when PRKD is activated by a neurotransmitter. I also demonstrated that the isolated catalytic domain of PRKD can undergo autophosphorylation in its activation loop *in vitro*. In contrast to the current view of PRKD activation by upstream kinases, my work suggests a mechanism that relies instead on dimerization-mediated trans-autophosphorylation. This observation is important because it gives a mechanistic explanation for why PRKD-specific processes can be independent of PKC activity. Furthermore, my findings show how nature has repurposed a generic three-dimensional fold to encode a new function, namely dimerization, to control kinase activation.

PUBLICATIONS

Elsner DJ, Siess KM, Gossenreiter T, Hartl M, Leonard TA (2019) A ubiquitin-like domain controls protein kinase D dimerization and activation by trans-autophosphorylation. *J Biol Chem* **294**: 14422–14441

STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF HUMAN NUCLEOTIDE EXCISION DNA REPAIR

cf. BIF FUTURA, VOL. 31 | 1.2016

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Supervisor: Prof. Patrick Cramer

Nucleotide excision repair (NER) is a major DNA repair pathway that removes UV-induced and bulky DNA lesions. The NER machinery assembles around transcription factor IIH (TFIIH), which unwinds the DNA, scans for the lesion, and organizes the excision of the damaged DNA fragment. TFIIH has ten subunits that comprise the kinase module and the core module, the latter of which contains two ATPases: xeroderma pigmentosum group B and D proteins (XPB and XPD, respectively). Biochemical studies have identified NER factors and the main events leading to lesion removal, but the lack of structural knowledge about NER intermediates hinders our mechanistic understanding of this process. In my PhD project, I purified and biochemically characterized seven human NER factors, including the TFIIH complex. I used a reconstituted NER system to show that NER factors XPA and XPG regulate TFIIH function by stimulating XPB's double-stranded DNA translocase activity and XPD's helicase activity, respectively. To gain structural insight into this stimulation, I assembled the core TFIIH-XPA-XPG complex on a bifurcated DNA scaffold and analysed it using single-particle electron cryo-microscopy. The high-resolution structure revealed that the core module contains both TFIIH ATPases in a DNA-bound state: XPB binds the DNA duplex and XPD binds the 5′ single-strand extension. I also found that XPA wraps around the junction between the duplex and the single-stranded DNA and forms a bridge between XPB and XPD. The extended helix in XPA traps the DNA in the XPB active site, thereby anchoring the NER machinery to DNA and increasing its capacity to scan for lesions. Moreover, for DNA repair to proceed, the TFIIH kinase module needs to dissociate from the core module. A comparison of the structures of the XPA-bound and kinase-bound core module shows that XPA dramatically rearranges the core module to release the inhibitory kinase module, removes a newly identified plug element from the DNA-binding pore in XPD, and allows XPD to move by 80 Å to initiate lesion scanning. Overall, my work provides the basis for a mechanistic understanding of the NER pathway and aids the structure-based design of novel anti-cancer drugs.

PUBLICATIONS

Kokic G, Chernev A, Tegunov D, Dienemann C, Urlaub H, Cramer P (2019) Structural basis of TFIIH activation for nucleotide excision repair. *Nat Commun* **10**: 2885

RECODING OF VIRAL GENES BY PROGRAMMED RIBOSOME FRAMESHIFTING

cf. BIF FUTURA, VOL. 31 | 1.2016

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Supervisor: Prof. Marina V. Rodnina

Viruses use a translation phenomenon called –1 programmed ribosome frameshifting (–1PRF) to produce buildings blocks for viral particles and reinforce their infectivity. The goal of my PhD project was to study –1PRF in two phylogenetically distant human pathogenic viruses: human immunodeficiency virus type 1 (HIV-1) and Semliki Forest virus (SFV). To identify –1PRF timing and location, I used an *in vitro* reconstituted translation system and a chromatographic peptide analysis system that were developed in my lab. Based on my data and published reports, I concluded that –1PRF is highly evolutionarily conserved and operates via two distinct kinetic pathways. The first pathway takes place in the late stage of translocation via dual transfer RNA (tRNA) slippage under optimal translation conditions and requires additional stimulatory elements (e.g. mRNA secondary structures). The second pathway proceeds via a single tRNA slippage stimulated by a long translation pause, which in turn is caused by a limiting concentration of tRNA. Pathway choice is modulated by the availability of tRNAs necessary for the translation of the frameshifting motif. I showed that HIV-1 contains a second, normally silent, motif that could potentially support efficient –1PRF if altered in response to antiviral treatment. Using mutational analysis and chemical probing, I found that the HIV-1 and SFV frameshifting motifs have specific nucleotide sequences and mRNA secondary structures, respectively, that provide an extra level of frameshifting modulation. My work deepens our understanding of –1PRF in pathogenic viruses and reveals virus-host interactions at the level of tRNA profiles and protein synthesis. Frameshifting modulation by specific tRNAs might lay the foundation for virus-specific antiviral therapy that minimizes side effects.

PUBLICATIONS

Korniy N, Samatova E, Anokhina MM, Peske F, Rodnina MV (2019) Mechanisms and biomedical implications of –1 programmed ribosome frameshifting on viral and bacterial mRNAs. *FEBS Lett* **593**: 1468–1482

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Caliskan N, Wohlgemuth I, Korniy N, Pearson M, Peske F, Rodnina MV (2017) Conditional switch between frameshifting regimes upon translation of dnaX mRNA. *Mol Cell* **66**: 558–567

EPITHELIAL-MESENCHYMAL PLASTICITY IN PANCREATIC CANCER METASTASIS

cf. BIF FUTURA, VOL. 30 | 1.2016

LAURA MAIORINO
Discipline: Molecular Biologist, MSc
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Supervisor: Prof. Mikala Egeblad

Most patients with pancreatic cancer present with metastatic disease, a dismal diagnosis with a median overall survival of six months. For metastasis to occur, cancer cells must leave the primary tumour, invade distant tissues, colonize those sites by resuming proliferation, and avoid elimination by the immune system. Throughout this sequence of events, cancer cells undergo transitions in their phenotypes. For instance, cancerous epithelial cells from a primary tumour can spread more easily by gaining mesenchymal traits, like invasiveness, through a process called epithelial-to-mesenchymal transition (EMT). While EMT is well known to promote the spread of cancer cells to distant tissues, the reverse process – known as mesenchymal-to-epithelial transition (MET) – has been proposed to be an obligatory step before the cells can resume proliferation. The dynamics of these changes and their impact on pancreatic cancer metastasis are, however, not well understood. In my PhD project, I used distinct strategies to model two stages of metastasis – invasion and colonization – using cancer cells derived from a genetically engineered mouse model of pancreatic cancer. By imaging pancreatic tumours directly in anesthetized animals, I observed that actively disseminating pancreatic cancer cells were single, elongated, slow-moving cells – consistent with EMT. To visualize the dynamics of EMT and MET *in vivo*, I engineered a fluorescent reporter of EMT using CRISPR-Cas9 genome editing. With this strategy, I showed that pancreatic cancer cells that had disseminated to the liver after undergoing EMT transitioned back to the epithelial phenotype spontaneously as they formed metastases. Lastly, I found that failure to initiate the second phenotypic switch – MET – curtailed metastasis, because disseminated mesenchymal cancer cells were eliminated by the immune system in the liver, specifically by natural killer cells. My results provide evidence of a link between epithelial-mesenchymal plasticity and anti-cancer immunity in pancreatic cancer metastasis. Importantly, I describe a critical role for natural killer cells in controlling pancreatic cancer metastasis in the liver.

PUBLICATIONS

The results of this project have not yet been published.

SPECIFIC RECOGNITION OF ATYPICAL UBIQUITIN MODIFICATIONS

cf. BIF FUTURA, VOL. 29 | 2.2014

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Discipline: Biochemist, MSc
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Supervisor: Dr David Komander

The attachment of ubiquitin (Ub) to substrates is one of the most abundant post-translational modifications and is essential in eukaryotes. Ub can also attach to itself on any of its primary amines (M1, K6, K11, K27, K29, K33, K48, and K63), leading to the formation of eight distinct polyUb chains. Ubiquitination is thus an incredibly versatile modification that can regulate almost all aspects of signalling. However, how the cell distinguishes these chain types and therefore achieves specific signalling is poorly understood. The broad aim of my PhD project was to investigate how these linkage types are differentiated. In the first part, I aimed to identify endogenous proteins capable of linkage-specific recognition of Ub chains. I discovered that a small zinc finger domain in the enzyme ZRANB1 (zinc finger RANBP2-type containing 1) specifically binds to K29- and K33-linked Ub chains – the first protein known to do so. Biochemical experiments together with my crystal structure of ZRANB1 bound to a K33-linked Ub dimer revealed the molecular determinants of this specificity. In the second part of my project, I developed affimers – engineered non-antibody protein scaffolds that bind to a specific target – for studying K6- and K33-linkages. Research tools that recognize particular Ub linkages do not exist for most linkages, but are crucial for investigating their biological roles. I characterized the affimers, which were selected in collaboration with biotechnology company Avacta, using a combination of biophysical, structural, and biochemical techniques, and validated their use in numerous applications. My work has identified novel linkage-specific components of the Ub system and has contributed tools that facilitate targeted investigations into these remarkable Ub signals for the first time.

PUBLICATIONS

Michel MA, Swatek KN, Hospenthal MK, Komander D (2017) Ubiquitin linkage-specific affimers reveal insights into K6-linked ubiquitin signaling. *Mol Cell* **68**: 233–246.e5

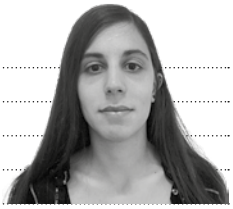
Noad J, Malsburg von der A, Pathe C, Michel MA, Komander D, Randow F (2017) LUBAC-synthesized linear ubiquitin chains restrict cytosol-invading bacteria by activating autophagy and NF-κB. *Nat Microbiol* **2**: 17063

Michel MA*, Elliott PR*, Swatek KN, Simicek M, Pruneda JN, Wagstaff JL *et al* (2015) Assembly and specific recognition of K29- and K33-linked polyubiquitin. *Mol Cell* **58**: 95–109

REGULATION OF CENTRIOLE *DE NOVO* BIOGENESIS

cf. BIF FUTURA, VOL. 30 | 2.2015

CATARINA ANTUNES ANGÉLICO PINTO NABAIS
Discipline: Cell Biologist, MSc
Institute: Instituto Gulbenkian de Ciência, Oeiras, Portugal
Supervisor: Dr Mónica Bettencourt-Dias



Centrosomes, the major microtubule-organizing centres in animal cells, participate in cell division, organelle positioning, and polarity. In proliferating cells, centrosome formation via canonical duplication is regulated spatially, temporally, and numerically by the presence of mature centrioles. However, in several eukaryotic cell types, centrioles assemble *de novo*. Very little was known about the regulation of this process, in part because technical limitations have prevented its investigation in live samples. The goal of my PhD was to study the regulation of centriole *de novo* assembly by focusing on how Polo-like kinase 4 (Plk4) – a critical molecule for centriole biogenesis – modulates this process, using *Drosophila melanogaster* as a model organism. I started by determining the endogenous Plk4 concentration, diffusion, and oligomerization in the fly embryo. I found that the kinase undergoes limited self-association in the cytosol, a process that is critical for ensuring that centrioles form only in the right place. Then, I established an *ex vivo* assay for high-resolution live imaging of centriole assembly within small cytosolic explants from unfertilized fly eggs overexpressing Plk4. Using this system, I could trigger centriole *de novo* assembly and investigate how it is spatially and temporally regulated. I found that both canonical duplication and *de novo* pathways occur within the same cytoplasmic explant, indicating that these pathways are not mutually inhibitory, as was previously believed. I followed centriole *de novo* biogenesis in time-lapse recordings and determined where and when centrioles formed. Comparing my observations to stochastic models showed that recently formed centrioles do not affect the location of *de novo* assembly. I observed that after an initial delay, centrioles assemble at a high rate that accelerates over time. My results indicate that this burst in biogenesis is due not to a cell-cycle-dependent mechanism but rather to Plk4 concentration – and presumably its activation. Indeed, altering Plk4 concentration delayed the onset of centriole biogenesis. This means that local Plk4 concentration is critical in controlling the onset of centriole *de novo* formation and its temporal kinetics.

PUBLICATIONS

The results of this project have not yet been published.

PREDICTING ANTIBIOTIC RESISTANCE WITH SYNTHETIC BIOLOGY AND DIRECTED EVOLUTION

cf. BIF FUTURA, VOL. 31 | 1.2016

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Discipline: Molecular Biologist, MSc
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Supervisor: Dr Csaba Pál

The rapid emergence of drug resistance frequently plagues antibiotic drug development. However, assessing the susceptibility of a new drug to antibiotic resistance is difficult at the preclinical stage. Standard laboratory methods for analysing evolutionary processes explore only a small fraction of the sequence space and fail to identify exceedingly rare resistance-conferring mutations. New rapid and exhaustive methods are thus needed to accurately assess the vulnerability of drug candidates to antibiotic resistance. In my PhD project, I developed a genome engineering method for the targeted and accelerated directed evolution of a broad range of prokaryotic species. DIvERGE (directed evolution with random genomic mutations) allows an up to one million-fold increase in mutation rate along the full length of multiple user-defined genomic and episomal loci. In a single day, DIvERGE efficiently explores the sequence space and thereby reveals a species' potential for developing clinically significant resistance to a drug candidate. Using DIvERGE, I identified previously undetected mutations in enterobacteria that confer resistance to trimethoprim in a species-specific manner and thus could pave the way for the development of narrow-spectrum antibiotics. I also used DIvERGE to detect the probable emergence of resistance against gepotidacin, an antibiotic that is currently in phase III clinical trials. As DIvERGE enables the simultaneous directed evolution of multiple genes and regulatory sequences in their native genomic context, I expect that this tool will stimulate the development of the next wave of antimicrobial drugs, as well as novel enzymes and biologics.

PUBLICATIONS

Nyerges Á, Csörgő B, Draskovits G, Kintses B, Szili P, Ferenc G *et al* (2018) Directed evolution of multiple genomic loci allows the prediction of antibiotic resistance. *Proc Natl Acad Sci USA* **115**: E5726–E5735

Nyerges AJ, Pal C, Csorgo B, Kintses B (2018) Mutagenizing intracellular nucleic acids. PCT/EP2017/082574

Nyerges Á*, Csörgő B*, Nagy I, Bálint B, Bihari P, Lázár V *et al* (2016) A highly precise and portable genome engineering method allows comparison of mutational effects across bacterial species. *Proc Natl Acad Sci USA* **113**: 2502–2507

TRANSCRIPTION AND FUNCTION OF THE TELOMERIC LONG NON-CODING RNA TERRA

cf. BIF FUTURA, VOL. 30 | 1.2015

PATRICIA RENCK NUNES
Discipline: Molecular Biologist, MSc
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Supervisor: Prof. Joachim Lingner

The ends of linear chromosomes must not be recognized as double-strand breaks in DNA, as this would elicit DNA-damage responses and lead to genomic instability. Chromosome ends are protected by telomeres, which inhibit the activation of unwanted DNA-damage responses. Telomeres are transcribed into a telomeric long non-coding RNA (TERRA), which participates in the regulation of telomerase activity, the processing of uncapped telomeres, and the formation of heterochromatin. Since TERRA inhibits telomerase activity *in vitro*, it has been proposed that TERRA levels are linked to telomere length. The goal of my PhD project was to investigate this hypothesis using a cell line with short telomeres and high TERRA levels. I found that DNA methyltransferase deficiency leads to TERRA upregulation, but only at the subset of chromosome ends that contain CpG islands. By amplifying specific telomeres using a modified long-range small-pool polymerase chain reaction, I found that short telomeres were uniformly present in this cell line, independent of the differences in TERRA expression between chromosome ends. Thus, telomere length is not dictated by *cis*-acting TERRA expression. Furthermore, I quantified TERRA molecules per cell and demonstrated that chromosome ends without CpG-islands produce similar levels of TERRA as those containing CpG islands. My data revealed the existence of two types of TERRA promoters: those that contain CpG islands and those that do not. Only the latter type is regulated by DNA methyltransferases, which can methylate the CpG island-containing promoters and thus limit TERRA expression. To study the influence of TERRA on telomere structure, I developed a CRISPR system to upregulate 10q and 13q TERRAs. This led to an increase in H4K20me3 at telomeres. *In vitro* experiments further demonstrated that the enzyme responsible for H4K20me3 deposition, SUV420H2, binds TERRA. Thus, I found that TERRA may contribute to telomere protection via the formation of local heterochromatin. My results contribute to our understanding of the transcriptional regulation of TERRA and unravel the mechanism by which it could promote genomic stability.

PUBLICATIONS

Feretzaki M*, Renck Nunes P*, Linger J (2019) Expression and differential regulation of human TERRA at several chromosome ends. *RNA* **25**: 1470–1480

ANTIMALARIAL PROPERTIES OF NATURAL MOSQUITO MIDGUT BACTERIA

cf. BIF FUTURA, VOL. 30 | 1.2015

RAÚL G. SARAIVA
Discipline: Microbiologist, MSc
Institute: Johns Hopkins University, Baltimore, MD, USA
Supervisor: Prof. George Dimopoulos

Malaria is responsible for more than half a million deaths per year, a number only partially contained by current control strategies. Infection of the mosquito vector, *Anopheles gambiae*, by the malaria parasite, *Plasmodium falciparum*, is modulated by the microbiota of the mosquito midgut. In my PhD project, I set out to characterize the molecular mechanisms through which these bacterial species limit the development of the malaria parasite in the mosquito. I was able to unfold how *Kosakonia cowanii* and *Chromobacterium spp*. isolates, retrieved from Zambian and Panamanian field mosquitoes, respectively, reduce pathogen load in the insect. By measuring *Plasmodium*'s gene expression when exposed to *K. cowanii*, I showed that this bacterium induces a partial and temporary shutdown of the parasite's antioxidant response and stimulates the production of reactive oxygen species, which together likely lead to the arrest of parasite development. Using bioassay-guided fractionation of culture supernatants, I showed that the anti-*Plasmodium* activity of *Chromobacterium spp*. is mediated by romidepsin, a histone deacetylase inhibitor. I reinforced this conclusion by showing that romidepsin-null mutant *Chromobacterium spp*. did not inhibit *P. falciparum* growth in *A. gambiae in vitro* or *in vivo*. Its inhibitory effect, however, could be rescued by adding romidepsin, providing further validation for romidepsin as the causative agent. My work provides the first mechanistic descriptions of how certain members of the mosquito microbiota may control malaria transmission. I hope this knowledge will support the development of new strategies to prevent the disease, such as approaches to enrich pathogen-protective bacteria in the microbiota of field mosquitoes.

PUBLICATIONS

Saraiva RG, Huitt-Roehl CR, Tripathi A, Cheng YQ, Bosch J, Townsend CA, Dimopoulos G (2018) *Chromobacterium spp.* mediate their anti-*Plasmodium* activity through secretion of the histone deacetylase inhibitor romidepsin. *Sci Rep* **8**: 6176

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COMPLEX AND SPATIALLY SEGREGATED AUDITORY INPUTS OF THE MOUSE SUPERIOR COLLICULUS

cf. BIF FUTURA, VOL. 30 | 2.2015

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Discipline: Biologist, BSc
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Supervisor: Dr Michael Hideki Myoga

Animals integrate various sensory information to navigate their environment. In the midbrain, the superior colliculus (SC) combines auditory, somatosensory, and visual inputs and translates them into movements to orient the head towards salient objects. Recent studies have provided insights into how the SC processes visual information, but little is known about the identity of the SC neurons that receive auditory inputs or the nature of that information. In my PhD project, I investigated the connectivity between auditory-recipient SC neurons and the two structures in the brain that provide auditory information: the nucleus of the brachium of the inferior colliculus (nBIC) and the external cortex of the inferior colliculus (ECIC). First, I infected neurons in the mouse nBIC and ECIC with an adeno-associated virus expressing light-gated cation channel channelrhodopsin (ChR2). By optically activating presynaptic nBIC and ECIC axons running towards the SC while recording the resulting postsynaptic currents in SC neurons *in vitro*, I showed that this circuit comprises at least two types of inhibitory connections, in addition to previously described excitatory connectivity. Furthermore, I described a difference in the organization of the direct (conveyed by a single synaptic connection) inhibitory and excitatory connections in the circuit. Using ChR2-assisted circuit mapping, I found that the direct inhibitory axons were located medially in the ECIC but not in the nBIC, whereas the direct excitatory axons were distributed more equally between medial and lateral locations in both brain structures. Using anatomical tracing experiments, I substantiated this finding and found similar anatomical differences. As the ECIC is situated more medially in the brain than the nBIC, I propose that the direct inhibition originates mostly in the ECIC but not in the nBIC. Recent anatomical evidence suggests that auditory excitation is processed in the nBIC, while multisensory inhibition is processed in the ECIC. This functional segregation may accompany the anatomical differences that I have discovered, suggesting that sensory integration in the SC is more complex and multifaceted than previously thought.

PUBLICATIONS

Bednárová V, Grothe B, Myoga MH (2018) Complex and spatially segregated auditory inputs of the mouse superior colliculus. *J Physiol* **596**: 5281–5298

STRUCTURAL INSIGHT INTO AUTOINHIBITION AND LIPID FLIP BY A P4 ATPASE LIPID FLIPPASE

cf. BIF FUTURA, VOL. 31 | 1.2016

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Institute: Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark
Supervisor: Prof. Poul Nissen

Phospholipids constitute a major building block of cell membranes. In the late secretory pathway of eukaryotes, specific phospholipids are asymmetrically distributed between the two leaflets of the membrane. This asymmetry is important for biological processes such as signalling and vesicle formation. The P4 ATPases regulate lipid asymmetry by "lipid flipping": mediating the active import of specific phospholipids from the extracellular leaflet to the cytosolic leaflet. Also known as lipid flippases, these proteins belong to the P-type ATPase family and are thus topologically similar to ion pumps such as the sodium potassium pump. Multiple transport models have been proposed to explain how P4 ATPases transport lipids, which are much larger and chemically different than the small cations transported by ion pumps. However, no structural information was available to provide direct insights into their transport mechanism. My PhD project aimed to fill this gap by solving a structure of the heteromeric lipid flippase Drs2p/Cdc50p from *Saccharomyces cerevisiae*. Drs2p is the P4 ATPase, while Cdc50p belongs to the CDC50 family, members of which are required by many P4 ATPases for their function. Using cryo-electron microscopy, I determined the structures of three conformations, mapping the progressive activation of the complex from the autoinhibited state, via an intermediate, to a fully activated state. This was the first direct visualization of an autoinhibited conformation of a P-type ATPase. By identifying the regulatory lipid binding site and by showing how the Drs2p C-terminus binds to inhibit the complex, these structures help to explain the results of biochemical studies of Drs2p regulation. I showed that during activation, a cleft on the luminal face of Drs2p opens. This could be the entry site of a putative transport pathway, the location of which fits well with one of the proposed transport models. In this model, only the lipid headgroup is transported by the protein, while the fatty acid tails remain within the membrane. My results provide a structural basis for interpreting previous findings and are the first step towards gaining a deeper understanding of the function of P4 ATPase.

PUBLICATIONS

Timcenko M*, Lyons JA*, Januliene D*, Ulstrup JJ, Dieudonne T, Montigny C *et al* (2019) Structure and autoregulation of a P4-ATPase lipid flippase. *Nature* **571**: 366–370

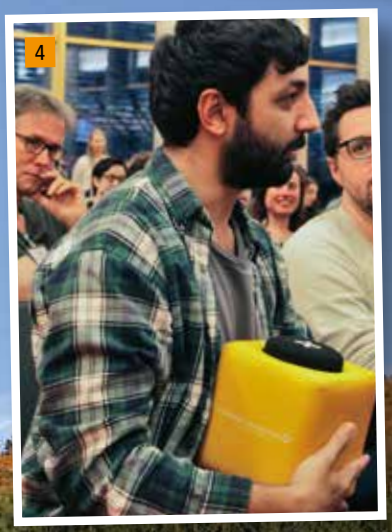
THE FOUNDATION The Boehringer Ingelheim Fonds (BIF) is a public foundation – an independent, non-profit organization for the exclusive and direct promotion of basic research in biomedicine. The foundation pays particular attention to fostering junior scientists. From the start, it has provided its fellowship 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.

LIFE IN MOTION – NEW VENUE FOR EUROPEAN ALUMNI SEMINAR


1

The theme of the 2019 alumni seminar in Europe – "life in motion" – seemed a fitting one. After all, for the first time in the 29-year history of the seminar, it moved to a new venue. After Castle Gracht was sold, the BIF sought – and found – a new and entirely different home for its yearly alumni meeting. It now takes place at Collegium Glashütten near Frankfurt.

By Kirsten Achenbach


4

Photos: Collegium Glashütten, Kirsten Achenbach

The seminar started out with a talk about the Tara Oceans expedition, a three-year round-the-world voyage on a sailing boat to collect about 15,000 seawater and marine organism samples for subsequent genetic and other analyses on land. The talk vividly described what it meant to coordinate such a project. On Saturday morning, we moved from the smallest visible things – a discussion of single-molecule sensing by BIF alumnus Frank Vollmer – to how extreme athletes do what they do. The warm October sunshine was perfect for the ensuing outdoor speed-dating session. The afternoon continued with talks on diseases on the move worldwide, cells moving in the body, and the way mobile technology, especially health apps, might change our behaviour. As usual, the evening was spent in lively discussion among the roughly 120 alumni present. Many of them connected with fellows they had never met before, also facilitated by the speed-dating. On Sunday, the seminar ended on a serious note, with a talk on human migration and the complex reasons fuelling it.

We are happy to report that the feedback on the new venue was very positive – so we will be returning.

1 **More room** – we can now accommodate a larger number of participants, and the new venue is located only 45 minutes from Frankfurt Airport by car or public transport.
2 **The venue has an airy feel** thanks to its many glass walls, which provide access to several large terraces.
3 **The building is designed** to foster communication, offering many smaller nooks and sitting areas for more tranquility.
4 + 5 **Much appreciated and used:** the throw-cube microphone (well padded) for audience questions.

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.

NUCLEUS HELPS CELLS TO SELECT THE CORRECT ROUTE

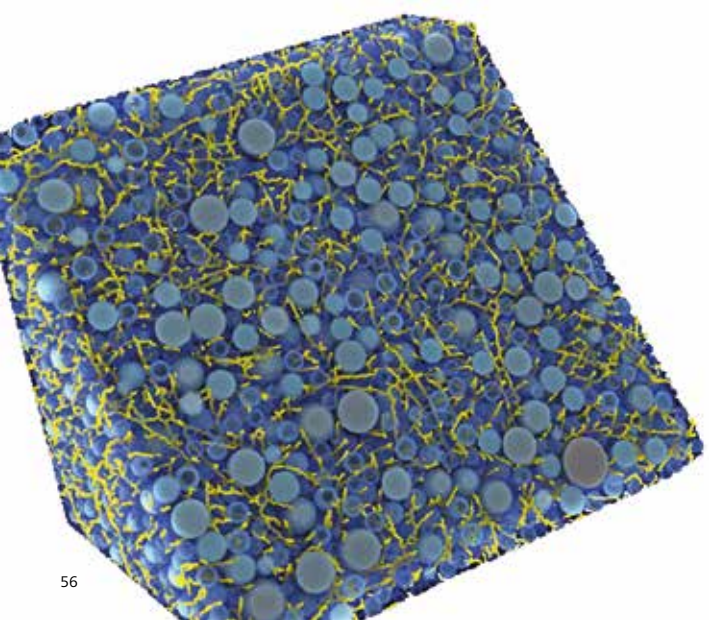
A migrating cell has to get through the tissue between it and its target, either by creating a path by dissolving tissue or by finding one using amoeboid movement – which is less destructive and up to 100 times faster. Together with colleagues, Jörg Renkawitz from the lab of Michael Sixt at the Institute of Science and Technology Austria in Klosterneuburg discovered that some cells that rely on amoeboid movement, such as leukocytes, push their nucleus forward while travelling. They use it as a gauge to detect the best path through the extracellular matrix or the maze of different-sized gaps between cells. Renkawitz and colleagues followed different types of leukocytes such as dendritic cells that migrate around obstacles and found that the cells usually chose the fastest route, even if it was not the shortest. The cells relocated their nucleus – their largest part – so that it was the foremost organelle in regard to the cell's direction of travel. This shift enabled them to gauge the size of different openings using their sensitive nucleus and then enter gaps they could fit through easily. Nevertheless, a minority of the dendritic cells the researchers studied did not push the nucleus forward. Consequently, these cells were less efficient at picking the largest pores and travelled more slowly.

The researchers hypothesize that all cells that use amoeboid cell movement probably rely on this newly discovered arrangement of cell organelles for efficient migration.

REFERENCE

Renkawitz J, Kopf A, Stopp J, de Vries I, Driscoll MK, Merrin J *et al* (2019) Nuclear positioning facilitates amoeboid migration along path of least resistance. *Nature* **568**: 546–550.

Jörg Renkawitz, fellowship 2009–2011

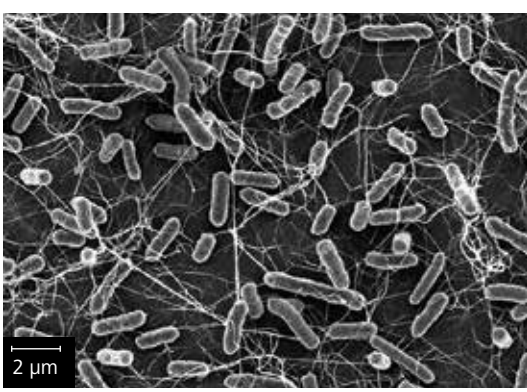


Representation of the cellular pore space within a 3D collagen matrix (yellow) filled with blue measuring beads.

PERSISTERS SPREAD ANTIBIOTIC RESISTANCE

Bacteria that survive an antibiotic without suitable resistance genes – for example, by going dormant – are called persisters. They can revive, and if they possess resistance plasmids against different kinds of antibiotics, they can transfer these to other bacteria. They can thus spread resistance to bacteria that have never encountered those antibiotics. This was discovered by Erik Bakkeren in the group of BIF alumnus Wolf-Dietrich Hardt at ETH Zurich in Switzerland and his colleagues, among them BIF alumnus Sebastian Bonhoeffer.

Bakkeren and his colleagues wanted to know if persisters confer resistance by passing on corresponding plasmids. To test that possibility, the researchers colonized the gut of mice with a strain of *Salmonella* bacteria that harbored the so-called P2 plasmid. They then gave the mice the antibiotic ciprofloxacin against which the bacteria were not resistant, killing the bacteria in the lumen of the gut. However, a few persister cells survived in the animals' tissues.



Next, the scientists gave the mice *Salmonella* bacteria that did not contain the P2 plasmid. These quickly colonized the gut. After two to three days, up to 99% of the bacteria in the animals' gut lumen harbored the P2 plasmid, even though there was no advantage to having it without the corresponding antibiotic being administered. The researchers concluded that a few persisters had emerged from their tissue refuge, moved back into the gut, and started sharing the P2 plasmids with the newly arrived *Salmonella* and even with *Escherichia coli*. The P2 recipients then shared the plasmid among themselves.

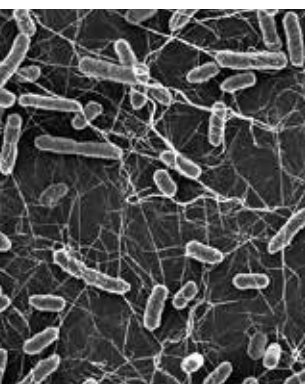
The number of persisters hiding in the tissues was crucial, the researchers found, with more of them leading to more transfer. Reducing their number, i.e. through vaccination, may therefore be needed to win the fight against antibiotic resistance.

REFERENCE

Bakkeren E, Huisman JS, Fattinger SA, Hausmann A, Furter M, Egli A *et al* (2019) *Salmonella* persisters promote the spread of antibiotic resistance plasmids in the gut. *Nature* **573**: 276–280.

Erik Bakkeren, fellowship 2018–2019
Sebastian Bonhoeffer, fellowship 1992–1994
Wolf-Dietrich Hardt, fellowship 1993–1995

Photos: Robert Hauschild, IST Austria (bottom left); S. Fattinger (bottom); Helmholtz Zentrum München (top right)

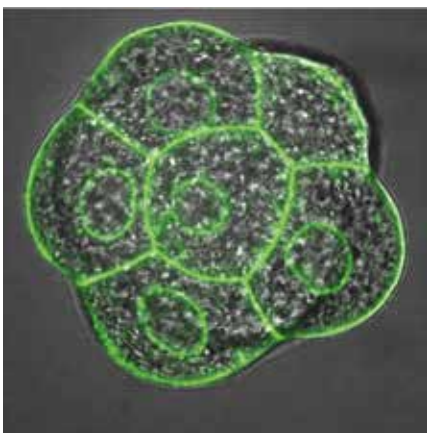


Salmonella Typhimurium causes diarrhoea in humans and farm animals such as pigs.

SPATIAL GENOME ORGANIZATION FORMS ANEW IN EMBRYOS

Every cell type in our body can develop from a fertilized oocyte. The programmes regulating gene activity depend on different levels of the 3D structure of the genome, for example, on whether a gene is located in the centre or near the periphery of the nucleus. Máté Borsos from the lab of Maria-Elena Torres-Padilla at Helmholtz Zentrum München, Germany, and colleagues discovered that certain aspects of the 3D genome structure, the so-called lamina-associated chromatin domains (LADs), are not inherited, but form anew within hours after fertilization.

LADs are regions of the genome in close contact with the lamina, the inner lining of the nuclear membrane. LADs can be found in all cell types and the genes within them are usually silenced, while genes closer to the centre of the nucleus are more often transcribed. Máté and his colleagues used a technique called DamID for the first time in mammalian embryos. With it, they could map the pattern of LADs in the genome. They looked at mouse oocytes, zygotes, and embryos at two to eight-cell and blastocyst stage. While oocytes did not show any LADs one day before fertilization, LADs were found within eight hours after sperm entry. Thus, it seems they are not inherited, but established anew. Additionally, Máté and his colleagues found that at first, the LAD patterns established by genetic material inherited from the paternal and the maternal side differed. However, by the eight-cell stage, the patterns had become similar. Surprisingly, the researchers could stop LADs from forming on genes from the paternal side by overexpressing an H3K4 histone demethylase. This suggests that epigenetic cues orchestrate LAD formation differently in maternal and paternal genes at the very beginning of mammalian development. This might offer a powerful tool for studying the early development and the epigenetic mechanisms involved.



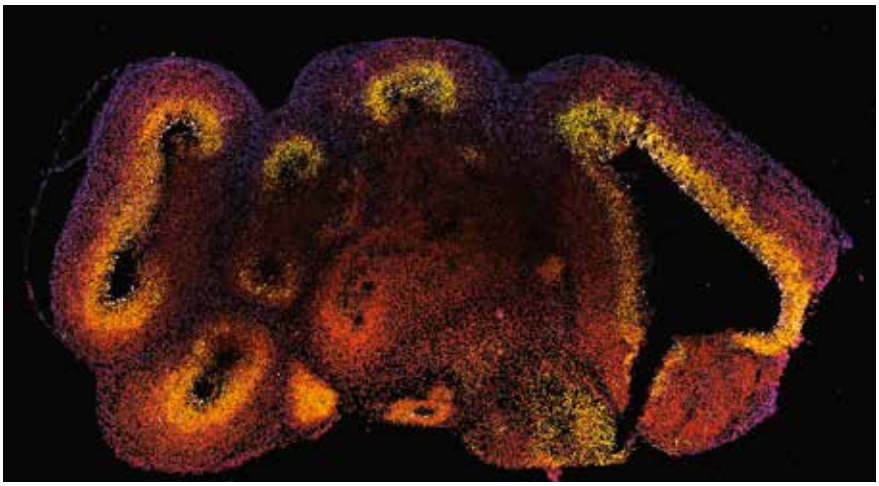
Green circles in the cells represent genetic material interacting with the nuclear membrane in an eight-cell mouse embryo.

REFERENCE

Borsos M, Perricone SM, Schauer T, Pontabry J, de Luca KL, de Vries SS *et al* (2019) Genome–lamina interactions are established de novo in the early mouse embryo. *Nature* **569**: 729–733.

Máté Borsos, fellow 2015–2018

MINI-ORGANS REVEAL DIFFERENCES BETWEEN HUMAN AND APE BRAIN DEVELOPMENT



A chimp brain organoid at 52 days (precursor cells are yellow and neurons are violet).

The human brain develops more slowly than other primate brains and shows different patterns of gene expression and chromatin accessibility. Together with colleagues, BIF fellow Sabina Kanton and her supervisor Barbara Treutlein (a BIF alumna) of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, arrived at this conclusion by studying brain-like structures they grew in the lab from stem cells. These so-called cerebral organoids replicate many aspects of early brain development.

It is still poorly understood how genetic and developmental mechanisms create the differences between the brains of humans and other primates. The researchers compared single-cell RNA sequencing data from human, chimpanzee, and macaque organoids. They found that starting at an early stage, the human brain develops more slowly. For example, the neurons of chimpanzees and macaques were more mature based on gene expression signatures. Also, in four-month-old human brain organoids, fewer astrocytes, a specialized form of glia cells, developed than in chimpanzee ones.

The scientists also identified distinctive patterns of gene expression in human brain organoids compared to the other primate species. For example, in cells from the dorsal telencephalon lineage, 98 genes showed different expression patterns. The parts of the genome accessible for expression also varied between species and some of the gene expression differences could be linked to these accessibility changes in neural progenitor cells and neurons.

We do not yet understand the implications of these findings, but they will hopefully help us to study and further decipher the molecular basis of what distinguishes the human brain from other primates during early brain development.

REFERENCE

Kanton S*, Boyle MJ*, He Z*, Santel M, Weigert A, Sanchís-Calleja F *et al* (2019) Organoid single-cell genomic atlas uncovers human-specific features of brain development. *Nature* **574**: 418–422.

Sabina Kanton, fellowship 2016–2017
Barbara Treutlein, fellowship 2009–2010

PROFILES

PROFESSOR SEBASTIAN BONHOEFFER
Institute: ETH Zurich, Institute of Integrative Biology, Zurich, Switzerland
Fellowship: 1992–1995

PROFESSOR IVAN DIKIC
Institute: Goethe University Frankfurt, Germany
Postdoctoral award: 1997

PROFESSOR DETLEF WEIGEL
Institute: Max Planck Institute for Developmental Biology, Tübingen, Germany
Fellowship: 1987–1988

Sebastian Bonhoeffer, Ivan Dikic, and Detlef Weigel have been elected to the American Academy of Arts and Sciences (AAAS). To be honoured in this way, individuals must show compelling achievements in academia, business, government, or public affairs. "With the election of these members, the academy upholds the ideals of research and scholarship, creativity and imagination, intellectual exchange and civil discourse, as well as the relentless pursuit of knowledge in all its forms," said David W. Oxtoby, AAAS president. All three inductees are members of the same discipline, the biological sciences, but will join different sections: Sebastian and Detlef were elected to Section 2 (Cellular and Developmental Biology, Microbiology, and Immunology) and Section 4 (Evolutionary and Population Biology and Ecology), respectively, while Ivan will be an intersectional member. The new members also include former First Lady Michelle Obama.

Photos: S. Kanton (top left); Bonhoeffer: ETH Zurich; Dikic: Deutsche Forschungsgemeinschaft; Weigel: c_MPI DB

PROFESSOR BERND BODENMILLER
Institute: University of Zurich, Switzerland
Fellowship: 2005–2007

MARC ERHARDT-SINGER
Institute: Humboldt University of Berlin, Germany
Fellowship: 2007–2010

Bernd Bodenmiller and Marc Erhardt-Singer have each received an ERC Consolidator Award. **Bernd** intends to develop novel approaches that comprehensively capture tumour complexity and support precision medicine. He will work on new technologies and computer-aided methods that rationalize this complexity and describe tissues akin to social networks. **Marc** is aiming to use the grant, worth up to two million euros, to reconstruct the coordinated self-assembly of a bacterial nanomachine – namely, the bacterial flagellum.

MARC LEMOINE
Institute: Universitätsklinikum Hamburg Eppendorf
MD fellow: 2010

Marc Lemoine has received the Wilhelm P. Winterstein Award of the Deutsche Herzstiftung (German Heart Foundation) for his role in discovering a molecular mechanism that causes hypertrophic cardiomyopathy and a method to treat patients who carry the specific gene variant that is responsible for it.

PROFESSOR LUDGER JOHANNES
Institute: Institut Curie, Paris, France
Fellowship: 1993–1995

Ludger Johannes has been elected to the German National Academy of Sciences Leopoldina. He has joined the Genetics/Molecular Biology and Cell Biology Section. Leopoldina is the world's oldest academy of natural sciences. Its members are distinguished scientists from all over the world.

PROFESSOR JOHANNES LE COUTRE
Institute: University of New South Wales, Sydney, Australia
Fellowship: 1992–1995

Johannes Le Coutre has gone back into academia full-time and switched continents to do so. He accepted a full professorship for Food and Health at the University of New South Wales (UNSW) School of Chemical Engineering in Sydney, Australia. Johannes is developing a broad research agenda on cellular agriculture to deliver innovation for agriculture and the food industry.

PROFESSOR REINHARD JAHN
Institute: MPI for Biophysical Chemistry and University of Göttingen, Germany
Member of BIF's Board of Trustees: 2010 to present

Starting on 1 December 2019, Reinhard Jahn was entrusted with the presidency of the University of Göttingen in an interim role. In April he was presented with the Aureus Gottingensis Medal of the University of Göttingen for "outstanding contributions to the University and Campus and support for early career researchers in particular".

ISABEL SCHELLINGER
Institute: University Clinic of Leipzig
Angiolutions
Göttingen, Germany
MD fellowship: 2013–2014

Isabel Schellinger has been elected one of the 50 members of the Junge Akademie, the world's first academy for young academics and artists. Members are elected on the basis of outstanding scholarly or artistic merit and membership is for five years only.

KATHARINA SONNEN
Institute: Hubrecht Institute, Utrecht, The Netherlands
Fellowship: 2008–2010

Katharina Sonnen has received an ERC Starting Grant for her project "Signalling Dynamics in the Control of Cell Proliferation and Differentiation during Development and Homeostasis". She and her team will use a comprehensive tool set including advanced light microscopy, perfusion chambers, and *in vitro* cultures of embryos and mini-organs in the dish to reveal how cells communicate with each other via signalling dynamics to ensure proper development and tissue homeostasis.

PROFESSOR VOLKER HAUCKE
Institute: Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany,
Fellowship: 1994–1997

Volker Hauke has been elected to the Cell and Developmental Biology Section of the Academia Europaea. He is one of 324 international scholars to receive this honour in 2019.

Photos: Bodenmiller: Wim Möllmann; Erhardt-Singer: HZI; Lemoine: private; Johannes: private; Le Coutre:Froniers Media S.A.; Jahn: Universität Göttingen; Schellinger: private; Sonnen: Hubrecht University; P. Heller; Haucke: S.OßwaldFMP

PROFESSOR MIRIAM STÖBER
Institute: University of Geneva, Switzerland
Fellowship: 2009–2011

Miriam Stoeber has been named assistant professor at the Cell Physiology and Metabolism Department of the University of Geneva. She studies how the precise subcellular location of receptor signalling defines ligand-selective effects, in particular in the G protein-coupled receptor family (GPCR) of opioid receptors. She will combine cutting-edge live-cell microscopy, novel nanobody-based biosensors, pharmacology, neurobiology, and genomic approaches to dissect clinically important GPCR signalling systems in the cellular context. Her group is funded by an Eccellenza Grant from the Swiss National Science Foundation (SNSF). It is worth up to 1.5 million Swiss francs over five years.

PROFESSOR PIOTR SZWEDZIAK
Institute: University of Warsaw, Poland
Fellowship: 2009–2011

Piotr Szwedziak has been appointed assistant professor for structural cell biology at the Centre of New Technologies at Warsaw University. In his lab, he focuses on explaining certain aspects of archaeal structural cell biology, such as liquid–liquid phase separation, membrane formation, and vesicle biogenesis. To establish his laboratory, he has been awarded an EMBO Installation Grant. He will receive 50,000 euros annually for three to five years and be a member of the EMBO Young Investigator Network.

PROFESSOR BARBARA TREUTLEIN
Institute: ETH Zurich, Zurich, Switzerland
Fellowship: 2009–2010

Barbara Treutlein has been awarded an EMBO Young investigator Award for her project "Reconstructing Organ Development Using Single-Cell Genomics", which she will carry out at the ETH Zurich in Switzerland. The award encompasses financial and practical support over four years as well as access to the network of current and former awardees. "Each of the new Young Investigators has demonstrated their ability to carry out research at the highest level," says EMBO Director Maria Leptin.

PROFESSOR NICOLE TREUSCH
Institute: University of Osnabrück
Fellowship: 1999–2002

Nicole Treusch has been appointed professor at the Department of Biomedical Sciences at the University of Osnabrück, Germany. She has also received the 10,000-euro Bionorica Award from the pharma company of the same name for her research on natural substances that inhibit the resistance-developing mechanisms of tumour cells, and on methods for making them responsive to chemotherapeutic agents once again.

PROFESSOR STEPHANIE GANAL-VONARBURG
Institute: University of Bern, Switzerland
Fellowship: 2009–2012

Stephanie has been awarded the Peter Hans Hofschneider Endowed Professorship for Molecular Medicine. With it, she has established her own group as an assistant professor at the University of Bern. She studies how the maternal or early-life microbiota influence the development of the infantile immune system. The endowment includes her salary for five years, the salary of one PhD student, and consumables for five years.

YOHANNS BELLAÏCHE
Institute: Institut Curie, Paris, France
Fellowship: 1995–1998

PROFESSOR CHRISTINE SELHUBER-UNKEL
Institute: University of Kiel, Germany
Fellowship: 2004–2006

The ERC has awarded two Proof of Concept (PoC) grants to BIF fellows. PoC grants are follow-up grants to verify the innovation potential of ideas arising from ERC-funded projects and bring the research results to a pre-demonstration stage. **Yohanns Bellaïche** will develop a computer algorithm that will teach itself to recognize when a biological phenomenon is about to occur in a sample observed via microscope. The programme can then adapt how images are taken, for example, by zooming in or taking more images in a given time. In his previous work funded by the ERC, Yohanns developed this type of "deep learning" programme to track and understand cell and tissue dynamics. The new project will widen the field of applicability to other phenomena. **Christine Selhuber-Unkel** has now been granted her third PoC grant in as many years. She will build synthetic blood vessel grafts that mimic natural vessels in the way they stiffen under pressure. They will be constructed from a material she developed with her previous PoC grant.

Photos: Stöber: private; Szwedziak: University of Warsaw; Treutlein: Ronny Barr/MPI-EVA; Treusch: private; Ganal-Vonarburg: private; Bellaïche: private; Selhuber-Unkel: Kiel University

BIF'S SISTER FOUNDATIONS

DOUBLE HONOURS FOR TRUSTEES OF THE HEINRICH WIELAND PRIZE

Two of the most valuable science awards have recently been presented to scientists on the Board of Trustees of the Heinrich Wieland Prize: Professor Franz U. Hartl, chairman of the board, has received one of four 2020 Breakthrough Prizes in Life Sciences for discovering the function of molecular chaperones in mediating protein folding and preventing protein aggregation. If this process malfunctions, misfolded proteins could set the stage for neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's. The awards are funded by the Breakthrough Prize Foundation and are worth three million dollar each, making them the most valuable science honours worldwide.

The prestigious Balzan Prize was awarded to Professor Werner Seeger and his fellow founding members of the German Center for Lung Research (DZL) in Gießen, Germany: Professors Erika von Mutius, Klaus Rabe, and Tobias Welte. It recognizes their outstanding achievements in the area of lung pathophysiology. The DLZ, founded in 2011, is a prime example of bench-to-bedside research, which translates "innovative research into new treatments to improve the quality of life for … patients, while also motivating and training the next generation of scientists", according to the Balzan Prize Foundation. The prize is endowed with 750,000 Swiss francs, and the awardees are required to allocate half to funding research in their field.

DECIPHERING HOW THE BRAIN CONTROLS OUR WEIGHT

Professor Jens Brüning, director at the Max Planck Institute for Metabolism Research in Cologne, Germany, has been honoured with the 2019 Heinrich Wieland Prize for his pioneering work on how the brain regulates the uptake, storage, and use of energy in the body. "Jens Brüning is one of the world's leading researchers of how the brain regulates the metabolism of energy in our body. Over the past 20 years, his pioneering research has laid much of the groundwork for identifying the brain as the master regulator of energy metabolism and for unveiling the brain's tight rein on blood sugar levels and its control over appetite and body weight," says Professor F.-Ulrich Hartl, chairman of the award's selection committee. Brüning received the 100,000-euro prize, which is funded by the Boehringer Ingelheim Foundation, at a scientific symposium on 7 November 2019 in Munich.

50 YEARS OF THE BOEHRINGER INGELHEIM PRIZE

Since 1969, the Boehringer Ingelheim Prize has been awarded to particularly promising and advanced members of the next generation of scientists at the University Medical Center Mainz. "Today, we gratefully look back on more than 100 awardees and their impressive achievements," says Christoph Boehringer, chair of the Executive Committee of the Boehringer Ingelheim Foundation, which has been funding the prize since 1995. In its 50th year, the 30,000-euro award was presented to Dr Timo Uphaus and Dr Neha Tiwari. It honours their research, which helps to protect patients from a renewed stroke and shows how certain brain cells mature that play an important role in neurological disease such as Parkinson's. During the anniversary symposium in Mainz, new and former awardees presented their current research, and Nobel Prize Laureate Professor Stefan Hell gave a key note lecture on the microscopy revolution, which has enabled us to see processes in living cells at the molecular level.

Photos: BIS/ A. Griesch (top); BI / Wolfgang Reuter (bottom)

A BIF FELLOW'S GUIDE TO ...

LONDON

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 George Cameron, who reports from London, United Kingdom, the city of double-deckers and Big Ben.

FACTS & FIGURES

Country: United Kingdom
Population: about 8.9 million
Area: 1,500 km²
Students: about 370,000
Famous for Buckingham Palace, black cabs, Big Ben, pubs, and the London Underground

BEST SIGHTS

Royal Botanic Gardens, Kew 4**:** find some peace in these world-famous botanical gardens.
Greenwich 1**:** visit Greenwich for the park, the Royal Observatory, and views across the Thames.
Docklands: a regenerated area with a good museum, take a trip on the Docklands Light Railway (DLR).

RESTAURANTS

Mildred's: fresh and colourful vegetarian food.
Dishoom: contemporary Indian food in a chain of beautifully designed restaurants, visit in the morning for a bacon naan roll.
Seven Dials Market: a good selection of street food in a converted banana warehouse.

NIGHTLIFE

The Lexington: good small pub venue to see live music in the Angel area.
Bussey Building: popular venue for all-night music sessions in Peckham.
Gordon's Wine Bar: 19th-century wine bar in candlelit cellars with original decor.
The Chandos: a reasonably priced, convenient, and centrally located pub near Leicester Square.

ACTIVITIES

The Globe Theatre 3**:** watch a Shakespearean play in this reconstructed open-air theatre from the 16th century.
Bermondsey Tap Rooms: a group of craft breweries with a massive selection of beers under the railway arches near London Bridge Station.
The Barbican Centre: check for plays, exhibitions, and music, also visit the indoor garden, open on Sundays.

WHERE TO STAY

Youth Hostel Association (YHA) hostels, various locations: stay in central locations on a budget.
Church Street Hotel: a quirky hotel located off the beaten track, with excellent bus connections to central London.
St Pancras Renaissance Hotel 2**:** a luxury option in an iconic building with an interesting history.

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

George Cameron is 24 years old. He is studying at the Francis Crick Institute, London, and his supervisor is Dr Hasan Yardimci.

Photos: George Cameron

WHO'S WHO AT BIF?

KIRSTEN ACHENBACH

Kirsten Achenbach was born in Bremen, Germany, in 1971. She studied marine biology in Bremen and the United States and later completed a specialized communication programme. She has worked in science communication since 2000, beginning her career at the Marine Biology Department of Bremen University. In 2008, she took charge of the press office of the Max Planck Institute for Chemistry in Mainz. Since 2013, she has been responsible for communication at the Boehringer Ingelheim Foundation. Her work involves the communication and alumni seminars, the *Futura* magazine, the foundation's website, and everything in between.

What is your most remarkable BIF experience?
The fellows' energy and thirst for knowledge during the communication seminars – starting at eight in the morning and still going strong at ten at night.

Why did you choose a science-based career?
I grew up on and around the water and have always been fascinated by marine life. I enjoy learning and sharing knowledge, so science communication is a perfect choice for me.

What is your favourite activity?
Right now, seeing the progress we make in renovating our new house. Aside from that, being outdoors, going to concerts, meeting friends, riding my bike, reading.

What is your remedy for stressful situations?
Breathing deeply and taking a hot bath with a good book and a glass of wine.

What fault in others can you tolerate best?
The faults I understand, because I can see their roots.

Your advice for fellowship holders?
Work on becoming a good communicator. It pays off in all areas of life, but is especially valuable to get the credit you deserve for your work and to avoid or resolve conflicts.

What scientific achievement do you admire most?
The ingenuity of scientists when it comes to finding ways around obstacles, whether in finding proxies for geological processes in the distant past or in making headway in imaging technology.

Name one thing you could not live without.
My own mind, with all its quirks and perks.

Photo: Carsten Costard, BIF

UPCOMING EVENTS

In view of the developments surrounding the Corona pandemic, we decided to postpone or cancel all BIF events until the end of June. Please see our website for up-to-date information.

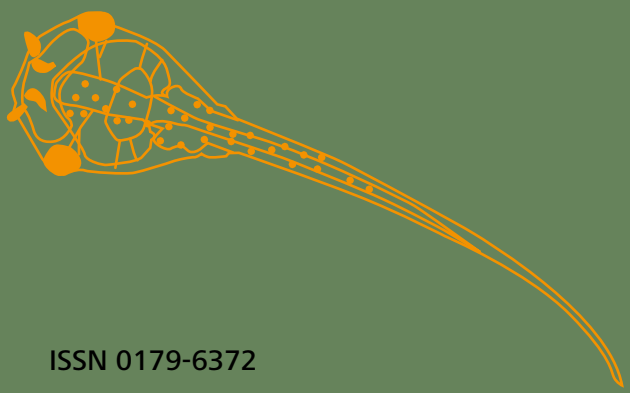
8–13 MAY 2020 – **POSTPONED** TO 2–7 DEC 2020
Communication training, Lautrach, Germany
Communication seminar for German-speaking PhD and MD fellowship holders working in Europe, held near Ulm, Germany. An effective presentation of your work and results can make the difference. During the five-day intensive communication seminar 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.

19–21 JUNE 2020 – **CANCELLED**
European alumni seminar, Glashütten, Germany
Annual meeting of former BIF PhD and MD fellows based in Europe.

3–4 JULY 2020
Meeting of BIF's Board of Trustees
The trustees decide on the allocation of fellowships, review the proposals for the International Titisee Conferences, and handle all the foundation's matters of fundamental importance.

29 AUGUST–4 SEPTEMBER 2020
Progress seminar, Hirschegg
We believe that presenting and discussing research projects in person is much more conducive to research and personal development than written interim reports. During the progess seminar in Hirschegg, Austria (yes, there is also some hiking), you will have the chance for scientific exchange and networking with around 60 other current BIF fellows working in Europe.

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



ISSN 0179-6372

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