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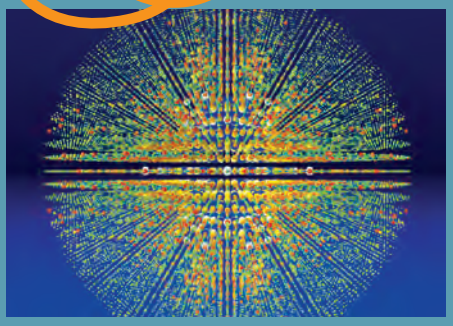

From Still Lifes to Action Movies
How technological advances have transformed structural biology

Projects and Results
New PhD projects and completed theses by BIF fellows

A BIF Fellow's Guide
Discover the secrets of Tel Aviv, Israel's vibrant nightlife capital

Protein structures such as the one shown in the cover illustration can be resolved using X-ray crystallography and other techniques discussed at the 110th International Titisee Conference in October 2014. Advances in imaging are unlocking the secrets of molecules in motion. Read more in the interview with the two ITC chairs on page 8.

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WALKING THE GREEN OR THE GOLDEN ROAD

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PAPERS IN THE SPOTLIGHT

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WORLD CHAMPIONS IN SCIENCE

»Transporting science into the public arena is no easy task.«

Rosetta and its lander Philae had travelled through space for more than 10 years before finally reaching their destination; a rendezvous with a comet just less than five kilometres wide but some 510,000,000 kilometres away. Millions of people all over the world followed Philae's historic touchdown in November. Viewers were fascinated by space exploration, its high-tech devices, and "the very big questions about the history of our solar system", as one of the scientists involved put it.

Rosetta's mission – with its heroic dimensions – was able to reach and touch so many people all over the world because it was published online, covered in local and national newspapers, and featured in the prime time programmes of major TV stations. An important point: it was discussed in local languages. English has become the undisputable lingua franca of the natural sciences, which is an invaluable advantage for its multinational scientific communities. It often seems to be forgotten that, in the overwhelming majority of countries, English remains a foreign language easily understood only by a fraction of the population. If science and researchers are to have a share of the public's (and politicians') attention equal to their findings' importance and impact, their discoveries must (also) be presented and discussed in the respective country's language(s). This premise is a particularly important point for democracies, as it touches on their fundamental concepts of participation and decision-making.

Transporting science into the public arena is no easy task. It requires more than just translation from one language to another. Research is usually abstract and complicated and most results would require, as a journalist once said, "a Nobel Prize to make it into the news". Without such a widely understood distinction – and its considerable public relations effort – the media and the public alike often overlook a result's relevance. In addition, even major news outlets seem to have largely given up their meaningful role as reporters of important developments when it comes to basic science. Stories dominate that promise "benefits" and "closeness to the reader". They often focus on topics such as advances in medical research that raise hopes for new or better cures. The space dedicated to pure "knowledge pieces" has become very limited indeed.

The Rosetta mission is a one-off. But every year, the world's most prestigious science awards, the Nobel Prizes, shine the spotlight on outstanding scientists. Journalists and news stations around the world report on them because the prize itself is newsworthy, even if they would normally reject the research it honours as not suitable for the media. In addition, the award-winning scientists can become inspiring role models similar to actors and world champion athletes.

Dr Claudia Walther, Managing Director

COILED FOR REPRODUCTION

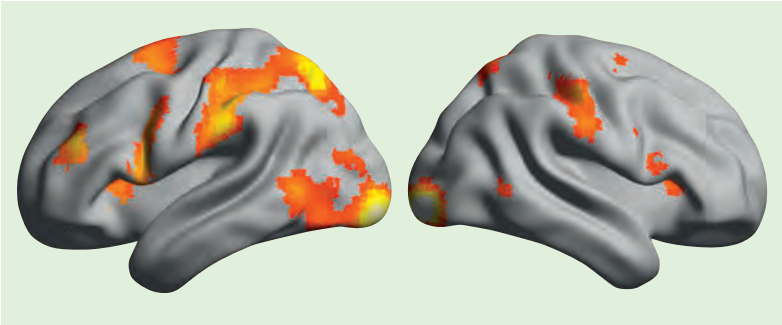
By Stefanie Gerstberger, Rockefeller University, New York, USA

This snail shell-like structure is an immunofluorescence image of a fruit fly testis taken by confocal microscopy. It shows germ stem cells (in blue) at the apical tip (located at the bottom) and daughter cells that develop into elongated spermatids (green dots and strangs). Fruit fly testis are a model system for the reshaping of cells, germline development, and stem cell renewal, enabling the relatively rapid analysis of developmental pathways, many of which are highly conserved in animals up to humans.

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.

TOOLS IN THE BRAIN

Tool use is an essential human skill – so essential that there is a specific network for it in the brain. This is the finding of a study that set out to examine tool use with functional magnetic resonance imaging (fMRI). Once inside the MRI device, participants were given ten everyday objects, including a hammer, a bottle opener, a key, a lighter, and a pair of scissors. They were asked either to use the objects or simply lift them up and put them back down again – first with the left hand and then with the right. It turned out that the left brain was activated when the subjects were planning the use of a tool – regardless of which hand they were holding it in. In addition, the researchers identified an extensive network in the brain that controlled not only the planning of an action but also the use of the tool. This "tool network" consists of regions in the parietal and frontal lobes, the posterior temporal lobe, and the lateral occipital lobe. The researchers also discovered a neural activation pattern that covered all elements of a complex action. This includes recognizing the objects as tools, understanding how they are used, and the motor action required to actually use the tool.



Planning how to use a tool requires a lot of brain activity. An entire "tool network" is devoted to the process. Our picture shows the enhanced activity in the left and right brain prior to the actual use of a tool.

REFERENCE

Brandi ML, Wohlschläger A, Sorg C, Hermsdörfer J (2014) The neural correlates of planning and executing actual tool use. *J Neurosci* **34:** 13183-13194

DNA CAN TAKE THE HEAT

In space movies, re-entry into the atmosphere is the last and often greatest challenge the protagonist has to survive in a battered space ship. Researchers at the University of Zurich, Switzerland, found that plasmid DNA is able to survive a 13-minute suborbital flight through space as well as re-entry, even if attached unprotected to the outside of a rocket. The DNA was applied to three sites on the TEXUS-49 rocket launched from Kiruna, Sweden – under and on the outside of the payload section and in the grooves of screw heads. Afterwards, researchers found functional DNA in all three areas. The results surprised them, since even in the cargo bay temperatures reached 130° C and external gas temperatures up to 1,000° C. They see their experiment as proof that DNA survival in outer space is possible, but also caution against overstating its implications for the transfer of DNA or even life across space. In any case, it raises the question of contamination in our own search for extraterrestrial life.

REFERENCE

Thiel CS, Tauber S, Schütte A, Schmitz B, Nuesse H, Möller R *et al* (2014) Functional activity of plasmid DNA after entry into the atmosphere of earth investigated by a new biomarker stability assay for ballistic spaceflight experiments. *PLoS ONE* **9:** e112979

Photos: M-L. Brandi, MRI (top); 3DSculptor/iStock (bottom)

BACTERIAL COMPETITION

One explanation for the ever growing number of bacteria resistant against antibiotics is the excessive and incorrect use of these important drugs. But researchers in Würzburg have now discovered another one. Biofilm conditions – often found in hospitals and surgeries – can suffice to promote the development of resistance in bacteria. In a biofilm, large numbers of bacteria compete for a limited amount of nutrients in a small space. The researchers grew *Staphylococcus aureus* bacteria under biofilm conditions. In this environment, the bacteria underwent evolution on a miniature scale. Some produced antibiotics due to spontaneous mutations, which gave them a clear advantage. They were able to keep competitors at bay and multiply. Through the same process, other bacteria evolved resistance against the antibiotics. Since many of the antibiotics on the market today are based on bacterial antibiotics, these could lose their usefulness, even when fighting bacteria that have never come into contact with the man-made drugs.

REFERENCE

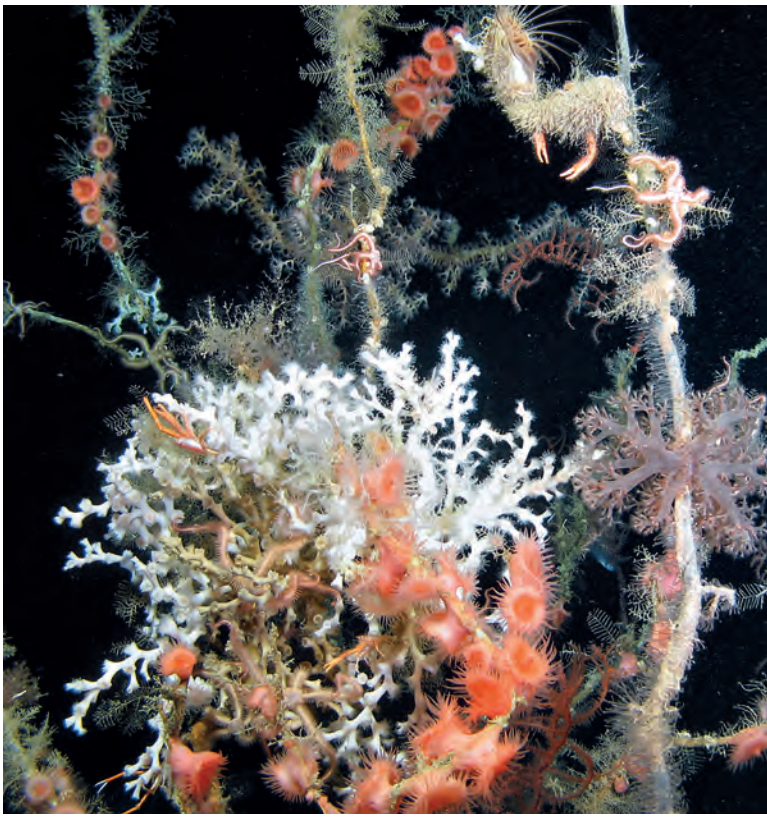
Koch G, Yepes A, Förstner KU, Wermser C, Stengel ST, Modamio J *et al* (2014) Evolution of resistance to a last-resort antibiotic in *Staphylococcus aureus* via bacterial competition. *Cell* **158:** 1060-1070

24.5

MILLION

This is the number of Christmas trees purchased in the United States each year. In Europe the figure is even higher, with an estimated 50 to 80 million trees sold during the holiday season. The most popular Christmas tree in the USA is the Balsam Fir. About 11 million customers prefer plastic over nature, though, opting for a fake tree.

Source: The National Christmas Tree Association/The National Gardening Association

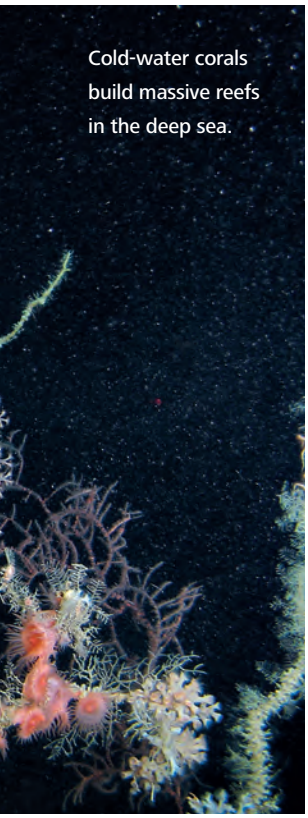


COLD FUSION

For most people, coral reefs call to mind sunny tropical waters, but they can also be found in the deep sea. In the tropics, the individual corals are cemented together by encrusting coralline algae. With their help, reefs grow to massive sizes. How deep-sea corals build reefs without the light-loving algae has now been clarified by Scottish and German researchers. Corals of the cold water species *Lophelia pertusa* fuse their skeletons together. Contrary to previous assumptions, this also happens in older and unrelated individuals. It is literally as if the bones of two strangers sitting next to each other joined without their immune systems fighting the foreign tissue. This requires the ability of cold-water corals to recognize "self" at a species level. *Lophelia pertusa* probably developed this ability as a way to save energy and stabilize its habitat. In contrast, tropical corals are not so tolerant and spend a much higher percentage of their energy fighting with all their neighbours.

REFERENCE

Hennigen SJ, Morrison CL, Form AU, Büscher J, Kamenos NA, Roberts JM (2014) Self-recognition in corals facilitates deep-sea habitat engineering *Scientific Reports* **4**: 6782



Cold-water corals build massive reefs in the deep sea.

WAR DRIVES LANGUAGE EVOLUTION

Do you know what a "succedaneum"* is? Or what "to supererogate"* means? If not, don't worry because you're not alone. These are just two examples of words that have fallen into disuse. This is a natural thing to happen since languages evolve constantly, with new words being invented and others forgotten. Yet little is known about the dynamics of such lexical change across languages. Researchers have now studied the lexical evolution of English in comparison to Russian, German, French, Spanish, and Italian using the Google Books Ngram Corpus. They focused on single words, so-called 1-grams, from six different languages and looked specifically at how frequently these words were used in print texts year by year. They found that major societal transformations such as the October Revolution in Russia or the two World Wars cause faster changes in word frequency distributions, while lexical evolution is dampened during times of stability, such as the Victorian Era. They also compared British and American English. These two drifted apart between 1850 and 1950, but afterwards started to become more similar again, probably due to the advent of mass media like TV and radio, which obliterate the barriers raised by geographical distance. Interestingly, British English lags behind by about 20 years.

* Succadaneum = something used as a substitute; to supererogate = to do or perform more than is required

REFERENCE

Bochkarev V, Solovyev V, Wichmann S (2014) Universals versus historical contingencies in lexical evolution. *J R Soc Interface* **11:** 20140841

SOFTWARE SPOTS HIDDEN TALENTS

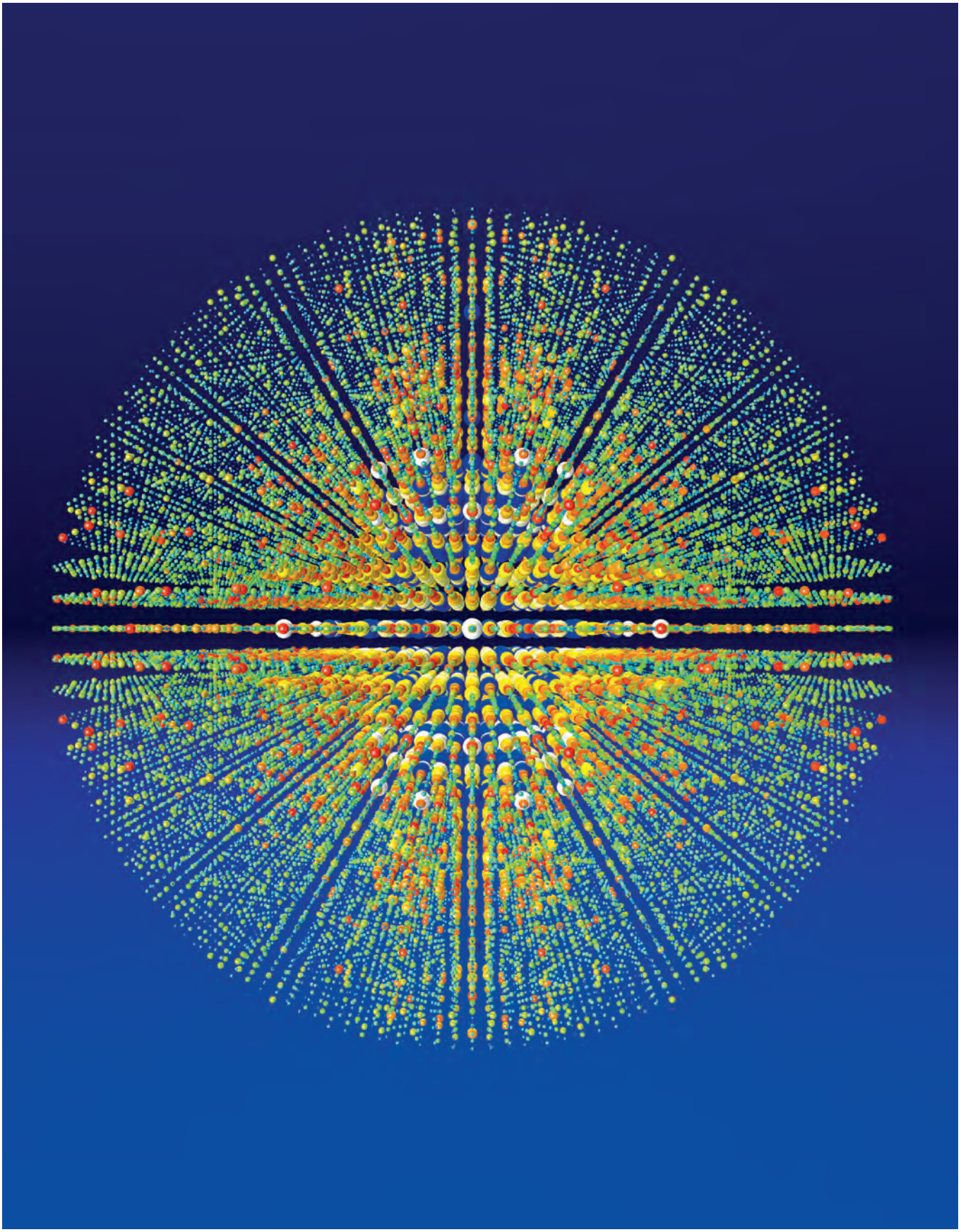
Many drugs help not only against the disease they are approved for, but also against others. German scientists have now developed a computer programme to find existing drugs that can be used to treat metastatic colorectal cancer. For their analysis they drew on a database containing information on how cell metabolism responds to more than 1,000 different compounds. According to their computations, citalopram, which is normally prescribed for depression, appears to be a particularly promising candidate. In addition, computations and initial tests on cell cultures and mouse models have shown that the substances troglitazon and enilconazol – used to treat diabetes and fungal infections – also have the potential to combat the spread and survival of colorectal cancer cells. Because the safety of these compounds has already been studied, it may be possible to introduce them for cancer treatment more quickly than newly developed drugs, even though additional research is needed to settle a number of open questions, including optimal dosage.

REFERENCE

Van Noort V, Schölch S, Iskar M, Zeller G, Ostertag K, Schweitzer C *et al* (2014) Novel drug candidates for the treatment of metastatic colorectal cancer through global inverse gene expression profiling. *Cancer Research* **74**: 5690-5699

Citalopram, an anti-depressant, could be used to treat metastatic colorectal cancer.

Photos: MARUM – Center for Marine Environmental Sciences, University of Bremen (top middle); blackred/iStock (top right); robynmac/iStock (bottom)



Serial femtosecond crystallography uses powerful and ultrashort X-ray pulses to measure diffraction patterns just before the rays vaporize the sample – here you see the result of 15,000 averaged snapshots of the membrane protein complex photosystem I.

TURNING STILL LIFES INTO ACTION MOVIES

By Michael Simm

A vast arsenal of tools and tricks has enabled structural biologists to overcome the limits of conventional microscopy and to observe the basic processes of life at the nanoscale. These technological and methodological advances – and their consequences – were the focus of the 110th International Titisee Conference "Structure, Forces and Dynamics of Macromolecular Complexes" in October 2014. Here we present an interview with its chairs.

Thanks to major advances in technology and methodology, electron microscopy allows us to study objects a few nanometres in size at near-atomic resolution – this is still two to three orders of magnitude beyond current super resolution light microscopy. With the advent of cryo-EM, biological samples can be observed in their almost native environment. Advanced computational image processing then allows us to glean stunning information on 3D structures and their dynamics. At the four-day meeting organized by the Boehringer Ingelheim Fonds, some 50 participants discussed more than two dozen presentations given by leaders in the field. The ensuing debates were as stimulating as the setting of this very special series of meetings in the heart of the southern Germany's Black Forest.

One of your colleagues – Stefan W. Hell – has just been awarded the Nobel Prize for Chemistry, together with Eric Betzig and William E. Moerner, "for the development of super-resolved fluorescence microscopy". Yet it is rather rare to hear about developments and findings in your field of study. How would you explain to a lay audience what structural biology is all about?

Holger Stark: That is a difficult task indeed. I usually try by telling laypeople that there are little machines working inside the cells of our bodies. It then quickly becomes apparent that there must be a lot of movement, too. We, as structural biologists, are the people who study these molecular machines.

Matthias Rief: The scale of things is hard to imagine. We are working on structures that cannot be seen with the naked eye and not even with conventional microscopes. The Nobel Prize highlights the ingenious achievement of surpassing the limits of light microscopy and bringing us into the nanodimension. As the Nobel Prize Committee elaborated: we can see how molecules create synapses between nerve cells in the brain; we can track proteins involved in Parkinson's, Alzheimer's and Huntington's diseases as they aggregate; and we can follow individual proteins in fertilized eggs as these divide into embryos. As a physicist, I find it fascinating to see all these things happen at constant temperatures – totally unlike the type of combustion reactions in a car's engine.

Judging from many of the presentations given here at the 110th International Titisee Conference (ITC), "still lifes" of molecular complexes are increasingly being supplemented by precise descriptions of their dynamics in the form of "action movies".

Holger Stark: Yes, this is quite an exciting development. In lectures, I often compare this advancement to the insights that we owe to one of the pioneers of motion pictures, Eadweard Muybridge. By inventing special equipment and producing over 100,000 images of animals and humans in motion, Muybridge was able to capture what the human eye could not distinguish as separate movements. People didn't know then if galloping horses ever touched the ground or if there were moments where they were actually "flying". Thanks to →

Photo: Tom White, CFEL DESY

Muybridge, we now know that horses can "fly" indeed. We know how they do it, and we also know that even the best painters of their time got it quite wrong. Théodore Géricault, one of the pioneers of the Romantic Movement and a great talent, spent a lot of his time in the stables of Versailles Palace. Yet even he pictured galloping horses with wrong leg positions, namely, hind and front legs stretched vertically at the same time. This shows that you can be totally wrong about the workings of a system, even if you can determine snapshots with great accuracy. You cannot understand function if you don't know the movements and the intermediates.

Is that why the "still lifes" of biomolecules derived from X-ray crystallography featured less prominently at this meeting?

Holger Stark: There are many changes in X-ray crystallography, but probably even more advances in electron microscopy (EM). It seems like we're entering a new age of structural biology. We have reached the next level in respect to resolution. With cryo-EM, even though we're looking at frozen molecules, we can derive information about dynamics from those images. That will lead to another boost for structural biology and our understanding of dynamics in particular.

Matthias Rief: We will probably not see *the* one method that dominates or replaces everything else. Instead, we have a constant interplay of different approaches. People select the ones that are suited best, depending on their objects and the kind of questions that they are asking. Kai Tittmann from Göttingen University has shown us in his talk that X-ray crystallography can still be improved and used to study the details of enzyme catalysis at true atomic resolution. We use highly focused laser beams to measure minuscule forces and we find these "optical tweezers" to be an ideal tool to study the mechanics of individual motor molecules. For the larger macromolecular complexes, it's probably EM that will dominate in the immediate future, because their size gives you good contrast and crystals are usually hard to get. But there will always be a grey area and it's simply impossible to predict whether an object can be crystallized.

The 132 m long undulator is part of the world's currently most powerful X-ray laser at the SLAC National Accelerator Laboratory in California.

How do you handle the massive amounts of data generated by methods such as cryo-EM?

Holger Stark: In many areas, software and computing power are crucial. Electron microscopy, for instance, is not just about the camera. In cryo-EM, developments in image processing have led to improvements in the resolution of single particle structures from 20–30 Å to near atomic resolution (~3 Å). We have just set up a computer that ranks among the 250 fastest machines worldwide – and we need that exclusively to calculate 3D structures from EM images of macromolecular complexes. The increase in computing power since I did my PhD in 1995 has been enormous. And while you needed supercomputers for X-ray crystallography at the time, these tasks can now be solved by any decent desktop PC.

Please tell us about the highlights at this conference.

Matthias Rief: It's great to witness all these advances, but they are too many to count. I enjoyed seeing how you can now elaborate the complete thermodynamics from a single molecule. I was impressed by the potential of acoustic force spectroscopy. Then I also liked a lot Jan Pieter Abrahams talk about how to solve 3D structures by electron diffraction from nano-crystals. He has been working on this for 12 years and the data just came in a few weeks ago. We feel very happy for him.

What are the mayor gaps in our knowledge?

Holger Stark: The methods are currently applied to a relatively small number of selected molecules that "behave well". But we are limited by biochemistry. It is incredibly difficult to isolate and control all these biomolecular complexes in such a way that we can apply our methods to study them. For instance, it is difficult to get a hand on complexes that are very short-lived and change or degrade very quickly. They come into play, for instance, during the assembly of proteins and protein complexes. Likewise, in catalysis, weak interactions between molecules are often crucial but very hard to catch. And we urgently need good biochemists to help us here.

Give us your vision for the future. Will structural biology merge with synthetic biology? Will we see "nanomachines" that clean our arteries and ward off infections – or will these toys remain science fiction?

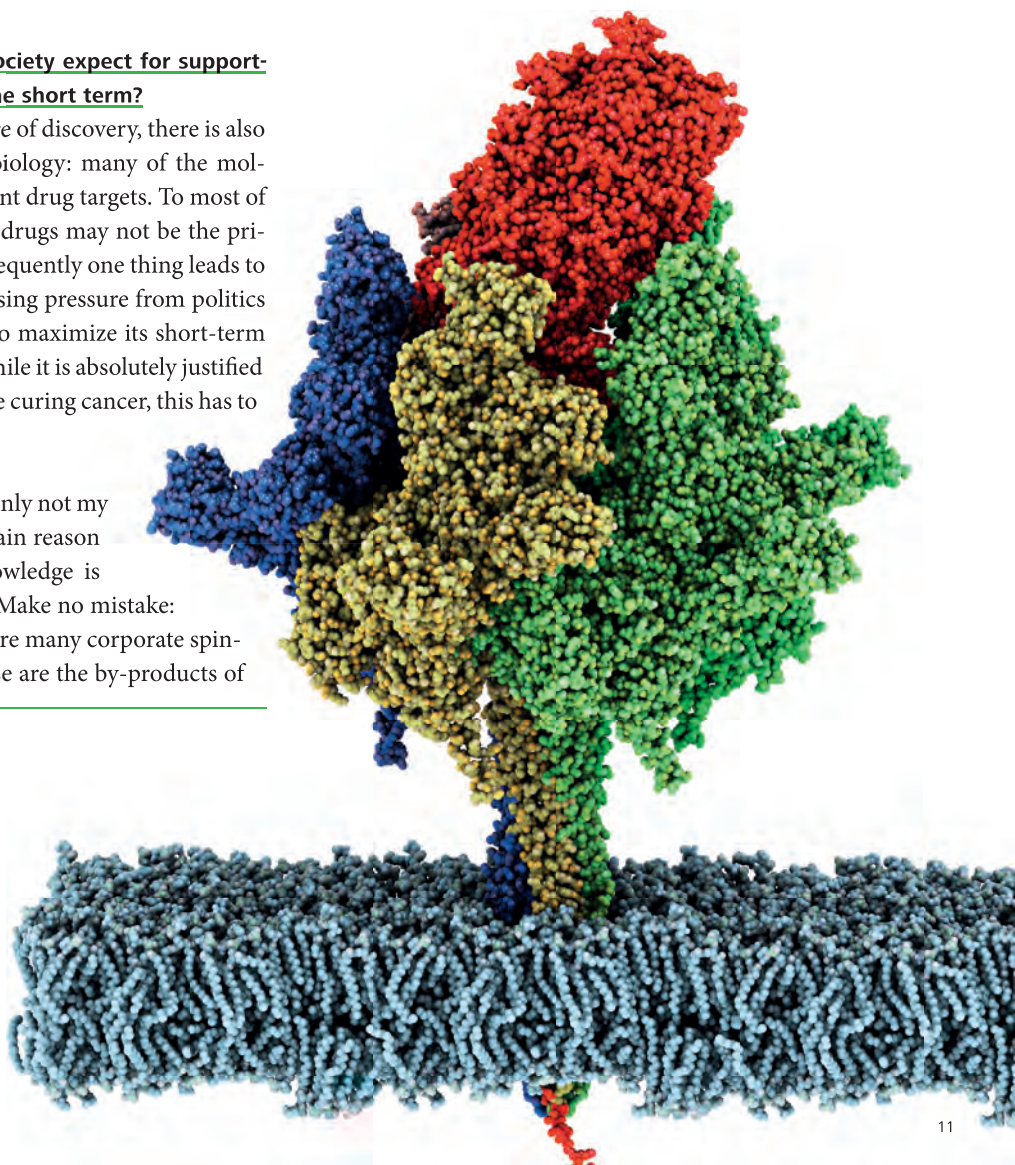
Matthias Rief: Some of these things were actually being discussed at this conference. We do have scientists that practice "DNA origami". They use DNA nanostructures as building blocks for molecular biophysics and future therapeutics. Others get inspiration from biological models, but try to improve on them by introducing modifications. It will be a long way to build biomolecules with new functions that achieve the precision and speed of the natural archetypes, but eventually, I expect this to happen.

Dr Holger Stark (left) leads a research group on 3D electron cryomicroscopy at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. His co-chair Dr Matthias Rief heads a research group on protein folding and molecular motors at Munich Technical University's Department of Molecular and Cellular Biophysics.

Apart from these visions, what can society expect for supporting research in structural biology in the short term?

Matthias Rief: In addition to the pleasure of discovery, there is also a more practical aspect to structural biology: many of the molecules that we are studying are important drug targets. To most of the attendants here at ITC, developing drugs may not be the primary goal of their research. But quite frequently one thing leads to another. As scientists, we feel an increasing pressure from politics to plan our research in such a way as to maximize its short-term returns for society and the economy. While it is absolutely justified to propose and follow a grand vision like curing cancer, this has to be driven by an urge to understand.

Holger Stark: Developing drugs is certainly not my primary motivation. Curiosity is the main reason to be in this field and advancing knowledge is what institutes like mine are made for. Make no mistake: we constantly create patents and there are many corporate spin-offs from this type of research. But these are the by-products of our curiosity.



With X-ray crystallography and cryo-EM, researchers found this cross-membrane injection mechanism in the toxin complex of *Photorhabdus luminescens*.

Photos: SLAC (bottom left), Michael Simm (top right), max-planck-gesellschaft (bottom right)

Opening doors: scholarly literature should be freely available to everyone. That is the goal of the open access movement.

WALKING THE **GREEN** OR THE **GOLDEN** ROAD

By Abby Clobridge

Over the past few years, open access – or the process of making research output free to access, free to use, and free to re-use – has been steadily gaining steam. According to a Science-Metrix study commissioned by the European Commission and published at the end of October, a milestone has been passed: more than half of all research articles published between 2007 and the present are now freely accessible on the Internet.

Open access – often just called OA – means increased access to scholarly literature without expensive paywalls or subscriptions. But it can also benefit authors by boosting the uptake of their research and thereby citations. Furthermore, researchers can re-use articles for purposes such as text mining, translations, or incorporation into anthologies. The open access movement was "born" in 2002 when its principles were first codified in the Budapest Open Access Initiative (BOAI), carried by the belief that the power of the Internet could be harnessed to disseminate scholarship. Since then, the research communication ecosystem has dramatically evolved, turning those principles into reality.

This radically different type of publishing is made possible through Creative Commons and other open licenses, which provide an alternative to traditional copyright. They start out by allowing all rights and then specify any exceptions, for example, restricting re-use to non-commercial purposes.

More and more major research funding organizations such as the European Commission, the Wellcome Trust, and the National Institutes of Health (USA) have open access provisions in their funding guidelines. Some even require researchers to provide open access to the underlying data – unless, of course, if it is of a sensitive nature. Increasingly, funders are also reviewing whether scientists are indeed complying with these policies. The Wellcome Trust is beginning to enforce this by withholding funding if criteria are not met. It is expected that other organizations will follow suit.

The different roads to open access are color-coded: taking the green road means depositing an article into a freely accessible repository. Most research institutions host and administer their own repositories. Some repositories are open to all, such as CERN's Zenodo, which covers all fields, or arXiv, which is hosted at Cornell University and specializes in physics, math, computer sciences, statistics, quantitative biology, and related sciences. Since last year there has also been BioRxiv, sponsored by Cold Spring Harbour Laboratories, which is so far mostly a pre-print server for the life sciences.

The green road allows researchers to publish in the journal of their choice, regardless of whether it is open or not. However, the author has to have the permission to do so. Many journals grant it automatically. Authors wanting to take this route should confirm whether the journal allows self-archiving. If so, they need to find out which version of the manuscript can be deposited and the length of the journal's embargo period (if any) which delays accessibility. The SHERPA/RoMEO database is a useful tool to review publishers' default policies concerning these areas.

The second route is to publish in an open access journal, which is often referred to as the "gold" road, as all articles are immediately accessible. In the past decade, many such journals have been launched: PLOS, eLife, PeerJ. , BioMed Central, Hindawi, University presses, societies, and a mix of large and small publishers also offer "golden" journals. Since funders are pushing and →

Photo: laif

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even demanding open access, most subscription access journals are increasingly offering to make their articles freely available for a fee paid by the author. Journals that offer open access on such an article-by-article basis are referred to as hybrid journals.

In the past, journals charged readers for access, either per issue or per subscription. With open access, it is the authors that are charged for publishing. Much of the controversy surrounding open access relates to this. Since publishers set their own "article-processing charges" (APCs), prices range tremendously. Solomon and Björk conducted a large-scale study, analysing data from 1,370 journals worldwide that published over 100,000 articles in 2010. They found APCs from 8 to 3,900 euros, with most ranging between a few hundred and 3,000 euros. The average was about 680 euros. They found higher APCs for professionally published journals by both commercial and not-for-profit publishers compared to journals published by societies and universities. The same is true for hybrid journals. High ISI impact factors also drove up APCs. Costs also varied by discipline, with natural sciences, especially biomedical research, tending to have higher APCs than humanities and social science journals. Funding agencies, particularly those with open access policies, and universities are often willing to help cover these costs.

One of the darker sides has been a proliferation of so-called "predatory" or "black" open access journals that try to generate fees without providing an adequate service in terms of reputable publishing. Their practices often include fake impact factors and/or reviewers. Furthermore, some journals claim that they are open access", but don't meet the criteria specified in the Budapest Open Access Initiative's definition, including not only free access, but also free re-use. Demanding that authors sign over all of their rights, including ownership of copyright, generally does not meet the commonly accepted criteria or funders' specifications.

As is the case with all types of publishing, authors should be careful about where they submit their manuscripts. Check for the following: physical address, contact information, type of licenses, prices, and conditions of payment. Best practices suggest fees should be issued for accepted articles before publication. And of course: How are articles solicited? Are they peer-reviewed? How are reviewers selected? Do members of the editorial board have expertise in the subject matter of the journal itself? A good starting point for checking is the Directory of Open Access Journals (DOAJ), which started in 2003 with just 300 journals. It lists around 10,000 journals and, according to its founder Lars Bjørnhauge, will now award a "seal" of best practice while at the same time striving to cull low-quality publications from its list in order to create an "open access whitelist".

Even though the picture of the state of open access painted by the recent Science-Metrix study is encouraging, the speed at which articles become freely accessible is still an issue. Of all the articles published in 2012, only about 13% were available instantly. Many others only became available on journal websites once the publishers' embargo ended (after 6–12 months or more) or when researchers filed them in repositories, also often delayed by an embargo. These delays, however, drastically reduce the usefulness of open access, particularly for ongoing or cutting-edge research.

The proportion of "free" papers is also dependent on country and field. In terms of country output, the study found that between 2008 and 2013, the worldwide average of open access papers was 54%. Brazil and the Netherlands topped the list with around 75%. In biomedical research, an estimated 71% of papers published between 2011 and 2013 are freely accessible. For chemistry, that number does not even reach 40%.

However, studying the growth of open access is hampered by the backfilling of repositories with older papers. According to the Science-Metrix study, last year alone 14,000 papers from 1996 were made available and 700,000 papers from 1996 to 2011 were "freed" between April 2013 and April 2014. Not only open access in general needs to be evaluated, but also the success of the papers published this way. Altmetrics have developed as the open access version of journal impact factors and citation indices. They include downloads, page views, and mentions of articles found in social media. As the different measurement tools are becoming more mature, altmetrics is becoming more widely accepted by researchers wishing to learn how their research is being disseminated and discussed. This method can also show the relevance of one's own research to peers, funders, and potential employers, similar to impact factors for traditionally published papers.

Breaking news: As Macmillan publishers announced on 2 December, subscribers to Nature as well as 48 other journals are now able to share articles with anybody for free. The papers can be read and annotated online on ReadCube, but not downloaded or printed. Not yet full open access, but a step towards it.

Photo: openaccessbutton.org

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.

PLASTICITY IN THE ANTERIOR CINGULATE CORTEX OF MICE WITH CHRONIC PAIN

cf. BIF FUTURA, VOL. 25 | 3.2010

SIGRID BLOM
Discipline: Neuroscientist, MSc
Institute: Department of Physiology, University of Bern, Bern, Switzerland
Supervisor: Prof. Thomas Nevian

The human brain is not hard-wired – its billions of neurons can undergo so-called plastic changes in order to adapt to a changing environment. Mechanisms of neuronal plasticity include alterations of excitability, i.e. how much input is needed for a neuron to fire an action potential; structural reorganizations of neuronal connectivity patterns; and modifications of the strength of the synapse between two neurons. Neuronal plasticity is thought to be the reason why we can learn and remember, but may also be the basis for pathological conditions such as chronic pain. Plasticity in the spinal cord is known to contribute to elevated pain sensitivity, but little is known about plasticity in the cortex during chronic pain. The goal of my PhD studies was, therefore, to study plasticity in the anterior cingulate cortex (ACC), a brain region important for the interpretation of pain as unpleasant. I induced chronic neuropathic pain in mice by tying three knots around the left sciatic nerve, a method known as chronic constriction injury (CCI). One to two weeks after the surgery, I performed multiple patch-clamp recordings from neurons in the ACC of CCI-operated mice and mice that had undergone sham surgery. I observed that there were fewer synaptic connections between excitatory and inhibitory neurons in CCI-operated mice than in sham-operated mice. Such structural plasticity could result in disinhibition of the local microcircuit. CCI surgery also caused excitatory neurons to fire more easily and resulted in impairment of long-term depression (LTD), a neurophysiological process that normally weakens the synapse between two neurons. A loss of the ability to undergo LTD may render the synapses unable to "unlearn" a painful experience. My data indicate that chronic neuropathic pain induces long-term neuronal changes in the ACC that could keep neuronal activity at an elevated level. These changes may be involved in turning pain from an occasional nuisance to an ongoing agony. Restoring normal activity in the ACC could remove the unpleasantness of pain. This new insight into ACC plasticity in response to CCI surgery may therefore pave the way for new strategies to relieve chronic pain.

PUBLICATIONS

Blom SM, Pfister J-P, Santello M, Senn W, Nevian T (2014) Nerve-injury induced neuropathic pain causes disinhibition of the anterior cingulate cortex. *J Neurosci* **34:** 5754–5764

SPECIES-SPECIFIC DIFFERENCES OF STING INFLUENCE ITS LIGAND INTERACTION

cf. BIF FUTURA, VOL. 25 | 3.2010

TANER CAVLAR
Discipline: Molecular Biomedic, Diploma
Institute: University of Bonn, Bonn, Germany
Supervisor: Prof. Veit Hornung

Vertebrates detect microbial invaders through their innate immune system. Germline-encoded pattern recognition receptors can recognize a limited number of well-conserved structures, such as bacterial second messenger molecules or 5′ triphosphorylated, double-stranded RNA, that are both unique to and vitally important for microorganisms. When these structures are detected, antimicrobial defense mechanisms are invoked to initiate immediate effector functions and induce adaptive immune responses, thus containing and eradicating the infection. Cytokines of the type I interferon (IFN) family play an important role in regulating this type of immune response. Discovered in the early 1970s, 10-carboxymethyl-9-acridanone (CMA) triggers type I IFN. The goal of my PhD studies was to identify the mechanism of action of CMA. I found that a protein called stimulator of IFN genes (STING) acts as a receptor for CMA, and that loss of STING leads to complete abrogation of CMA-triggered immune mechanisms in mice. However, the same activity is absent in human cells. By performing reconstitution assays using chimeric proteins in cells devoid of STING and measuring ligand interaction by differential scanning fluorimetry, I found that this species-specific phenomenon originates from the inability of CMA to bind to the C-terminal domain of human STING. My collaborators and I crystallized CMA bound to murine STING and saw an interaction similar to that between STING and its other ligands. Based on its novel ligand-sensing ability and its species-specific differences, we identified an endogenous STING ligand that limits microbial infections in a cross-species manner – suggesting that STING might constitute a reasonable pharmacological target in the treatment of microbial infections.

PUBLICATIONS

Ablasser A, Goldeck M, Cavlar T, Deimling T, Witte G, Röhl I *et al* (2013) cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING. *Nature* **498:** 380–384

Cavlar T, Deimling T, Ablasser A, Hopfner KP, Hornung V (2013) Species-specific detection of the antiviral small-molecule compound CMA by STING. *EMBO J* **32:** 1440–1450

Cavlar T, Ablasser A, Hornung V (2012) Induction of type I IFNs by intracellular DNA-sensing pathways. *Immunol Cell Biol* **90:** 474–482

KINETIC FRAMEWORK OF SPINDLE ASSEMBLY CHECKPOINT SIGNALLING

cf. BIF FUTURA, VOL. 26 | 1.2011

AMALIE ELISABETH DICK
Discipline: Life Scientist, MSc
Institute: Swiss Federal Institute of Technology, Zurich, Switzerland
Supervisor: Dr Daniel Wolfram Gerlich

The overall goal of mitosis is to distribute one copy of the duplicated genome to each of the emerging daughter cells. This process relies on faithful chromosome segregation, which is monitored by the spindle assembly checkpoint (SAC). The SAC acts as a control mechanism by delaying anaphase onset until all chromosomes are correctly attached to spindle microtubules via their kinetochores. Although a single unattached kinetochore is sufficient to delay anaphase onset, the kinetics and strength of the SAC in response to individual unattached chromosomes has been poorly characterized. Using time-lapse microscopy and fluorescently labelled human reporter cell lines, I established a laser microsurgery assay to acutely detach single chromosomes from metaphase spindles. I found that all laser-displaced chromosomes accumulated a checkpoint signal. Consistent with this, I also showed that in the majority of cells, laser-displaced chromosomes delayed anaphase onset until they had re-congressed to the metaphase plate. However, an unexpectedly high fraction of cells entered anaphase in the presence of unaligned chromosomes. My subsequent studies revealed several constraints of SAC signalling. First, it takes about five minutes after laser microsurgery to generate an effective SAC response that delays anaphase onset. Second, the strength of the SAC correlates inversely with the number of unaligned chromosomes. Third, SAC functionality depends on cyclin-dependent kinase 1 (CDK1) activity, which drops during metaphase so that the SAC becomes inactive when cells enter anaphase. My observations define a point of no return several minutes before anaphase onset, after which cells irreversibly commit to exiting mitosis. In contrast to the prevailing view of the SAC as a bistable on-off switch, my data indicate that the signal is graded. Limitations in SAC signalling, as uncovered by my study, may explain how cancer cells can develop resistance to chemotherapeutics targeting the mitotic spindle.

PUBLICATIONS

Vázquez-Novelle MD, Sansregret L, Dick AE, Smith CA, McAinsh AD, Gerlich DW, Petronczki M (2014) Cdk1 inactivation terminates mitotic checkpoint surveillance and stabilizes kinetochore attachments in anaphase. *Curr Biol* **24:** 638–645

Dick AE, Gerlich DW (2013) Kinetic framework of spindle assembly checkpoint signalling. *Nat Cell Biol* **15:** 1370–1377

HYPERACTIVE MAST CELLS EXACERBATE INFLAMMATORY RESPONSES *IN VIVO*

cf. BIF FUTURA, VOL. 25 | 2.2010

KLAUS-DIETER HEGER
Discipline: Biochemist, MSc
Institute: Max Planck Institute of Biochemistry, Martinsried, Germany
Supervisor: Dr Marc Schmidt-Supprian

Mast cells are innate immune cells that localize preferentially to vascularized tissues at the host–environment barrier. They are important players in allergic and anaphylactic reactions and have been implicated in inflammatory and auto-immune diseases in humans. However, loss-of-function studies using mast cell-deficient mice have yielded contradictory results in the latter context. To investigate the contribution of mast cells to inflammatory and auto-immune diseases, I established the first *in-vivo* mouse model for hyperactive mast cells by specifically ablating tumour necrosis factor alpha-induced protein 3 (Tnfaip3). Tnfaip3 is a ubiquitin-editing enzyme and a negative feedback regulator of inflammatory responses. Although Tnfaip3 deficiency did not affect the immediate release of preformed mediators stored in mast cell granules, a process termed degranulation, it resulted in amplified pro-inflammatory responses downstream of three activating receptor types: antigen, innate pattern recognition and alarmin receptors. Tnfaip3 loss caused profound mast cell hyperactivation, resulting in exacerbated allergic lung and skin inflammation and collagen-induced arthritis. In contrast, anaphylaxis reactions and experimental auto-immune encephalomyelitis were unaffected by the presence of Tnfaip3-deficient mast cells in mouse models mimicking these conditions. My results provide *in-vivo* evidence that hyperactive mast cells can worsen inflammatory disorders by amplifying local inflammatory reactions driven by innate stimuli and/or tissue damage that leads to the release of alarmins. Moreover, my results define diseases that might benefit from therapeutic intervention, based on the manipulation of mast cell functions.

PUBLICATIONS

Heger K, Fierens K, Vahl JC, Aszodi A, Peschke K, Schenten D *et al* (2014) A20-deficient mast cells exacerbate inflammatory responses *in vivo*. *PLoS Biol* **12:** e1001762

Heger K, Seidler B, Vahl JC, Schwartz C, Kober M, Klein S *et al* (2014) CreERT2 expression from within the c-Kit gene locus allows efficient inducible gene targeting in and ablation of mast cells. *Eur J Immunol* **44:** 296–306

Chu Y, Vahl JC, Kumar D, Heger K, Bertossi A, Wójtowicz E *et al* (2011) B cells lacking the tumor suppressor TNFAIP3/A20 display impaired differentiation and hyperactivation and cause inflammation and autoimmunity in aged mice. *Blood* **117:** 2227–2236

CDC48-REGULATED CHROMATIN UBIQUITYLATION HOTSPOTS IN *S. CEREVISIAE*

cf. BIF FUTURA, VOL. 25 | 3.2010

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Discipline: Biochemist, MSc
Institute: Max Planck Institute of Biochemistry, Martinsried, Germany
Supervisor: Prof. Stefan Jentsch

For DNA-associated pathways such as transcription, replication, and DNA repair to function properly, the binding of proteins to chromatin must be tightly controlled in time and space. In eukaryotes, the ubiquitin proteasome system and, in particular, the ubiquitin-targeted AAA-ATPase Cdc48 (p97 in mammals) are thought to play an important role in dislodging proteins from chromatin. To study the global importance of Cdc48 in extracting ubiquitylated proteins from chromatin, I analysed the genome-wide chromatin distribution of ubiquitylated proteins in wild-type and Cdc48-deficient *Saccharomyces cerevisiae* cells, using ubiquitin-directed chromatin immunoprecipitation. My work provided the first evidence that Cdc48 might indeed be of global importance for the extraction of ubiquitylated proteins from chromatin. I also identified nine genomic loci at which ubiquitylated proteins accumulated at unexpectedly high levels in Cdc48-deficient cells – referred to as Cdc48-regulated chromatin ubiquitylation hotspots. In systematic analyses of *S. cerevisiae* mutants in which single Cdc48-associated co-factors were impaired, I showed that Ufd1-Npl4, Ubx4, and Ubx5 are required to efficiently dislodge ubiquitylated proteins from these hotspots, indicating their key role in the chromatin extraction by Cdc48. A series of additional experiments revealed that seven of the nine identified hotspots share a short DNA sequence motif, bind to the same, previously uncharacterized yeast protein, and are ubiquitylated in a two-step mechanism involving the ubiquitin-like modifier SUMO and a SUMO-targeted E3 ubiquitin ligase. This novel pathway seems to be one of the most prominent functions of Cdc48 on chromatin in yeast, and exemplifies for the first time a link between the SUMO and ubiquitin pathways in the chromatin extraction by Cdc48. It is very tempting to assume that a number of chromatin proteins in higher eukaryotes are dislodged from chromatin by a similar mechanism involving a SUMO-targeted E3 ubiquitin ligase and Cdc48, thereby ensuring proper dynamics and function of DNA-associated pathways such as transcription, replication, and DNA repair.

PUBLICATIONS

Bergink S, Ammon T, Kern M, Schermelleh L, Leonhardt H, Jentsch S (2013) Role of Cdc48 (p97) as a SUMO-targeted segregase curbing Rad51-Rad52 interaction. *Nat Cell Biol* **15:** 526–532

MECHANISMS OF CIRCUIT PLASTICITY IN THE DEVELOPING RETINA

cf. BIF FUTURA, VOL. 25 | 3.2010

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Discipline: Biophysicist, MPhys
Institute: University of California, Berkeley, CA, USA
Supervisor: Prof. Marla Feller

Across the developing nervous system, immature networks spontaneously generate activity that is highly correlated amongst neighbouring cells. This correlated activity is necessary for the normal development of adult neural circuits and persists even when the underlying circuits are disrupted, indicating that degenerate mechanisms exist to maintain functional output. We examined this phenomenon in the developing mouse retina, in which correlated activity is normally mediated by cholinergic signalling and propagates across the retina as a wave. Blocking cholinergic signalling leads to the generation of "recovered" waves that propagate through a distinct, electrically coupled gap junction circuit. Surprisingly, we found that wave recovery is facilitated by light stimulation, which was not thought to influence retinal waves because of the immaturity of rod and cone photoreceptors during retinal development. Using multi-electrode array recordings of isolated retinas, we showed that light-sensitivity of recovered waves occurs via intrinsically photosensitive retinal ganglion cells (ipRGCs) – a class of retinal photoreceptor that controls non-image-forming vision, such as the pupillary light reflex. Our results suggest that light activation of ipRGCs stimulates dopamine release, which in turn increases the strength of gap junction coupling required for the propagation of recovered waves. We determined that this light-sensitive wave circuit is present but latent in wild-type retina, where it is usually suppressed by a combination of cholinergic and dopaminergic signalling. The wiring diagram of the developing retina therefore includes several over-connected circuits in which some are closed and others activated, depending on the internal state of the system. This provides a means to rapidly switch between functional circuits and rescue network activity in the event of perturbation.

PUBLICATIONS

Lee H, Brott K, Kirkby LA, Adelson JD, Cheng S, Feller MB *et al* (2014) Retinogeniculate synapse elimination requires MHC Class I proteins and can be rescued by MHC1 H2-Db. *Nature* **509:** 195–200

Kirkby LA, Feller MB (2013) Intrinsically photosensitive ganglion cells contribute to plasticity in retinal wave circuits. *Proc Natl Acad Sci USA* **110:** 12090–12095

Kirkby LA, Sack GS, Firl A, Feller MB (2013) A role for correlated, spontaneous activity in the development of neural circuits. *Neuron* **80:** 1129–1144

INORGANIC JANUS PARTICLES: MENACE OR OPPORTUNITY?

cf. BIF FUTURA, VOL. 26 | 2.2011

JAN ROTHER
Discipline: Chemist, Diploma
Institute: Institute of Physical Chemistry, Georg-August University, Göttingen, Germany
Supervisor: Prof. Andreas Janshoff

Janus nanoparticles are anisotropic, meaning that they consist of at least two chemically or physically distinct domains. Consequently, they offer unique possibilities for multiple applications, including emulsification, solar-energy conversion, and e-paper displays. Computer simulations of amphiphilic Janus particles that comprise both hydrophobic and hydrophilic parts have shown that they are able to induce pore formation, tubulation, and vesiculation of lipid bilayers and thus could potentially enter cells in a self-induced endocytotic process. While this offers great opportunities for drug-delivery applications, these particles could also pose a threat to human health, as they circumvent controlled uptake into cells via conventional endocytotic routes. During my PhD research, I addressed the interaction between inorganic Janus particles and biomembranes, using artificial membrane mimics as simple model systems for the plasma membrane. I performed surface plasmon resonance spectroscopy experiments to show that Janus particles comprising a hydrophilic manganese oxide domain and a hydrophobic gold domain interact with lipids. The binding energy per particle to these lipids was on the order of 10 k_BT, which is similar to the binding energy exerted by membrane curvature-inducing protein domains. Using giant unilamellar vesicles, I showed that the particles are able to induce tubulation and vesiculation in these membrane models. In addition, I investigated their uptake into living cells by confocal microscopy and their cytotoxicity using biochemical and biophysical assays. These properties were comparable to those of spherical isotropic control particles, indicating that self-induced tubulation and vesiculation plays only a minor role in the endocytosis and processing of these Janus particles in living cells. In summary, although my studies provide experimental evidence for Janus particle-induced endocytosis as previously predicted in computer simulations, their uptake into living cells via this mechanism does not occur to a large extent. Janus particles are therefore not appropriate for drug-delivery applications that take advantage of self-induced endocytosis. However, they do not pose an additional threat to health and so their anisotropic properties may still be exploited in other ways.

PUBLICATIONS

The results of this project have not yet been published.

A MODULE SWAP IN THE TIM23 TRANSLOCASE DRIVES MITOCHONDRIAL MATRIX TRANSPORT

cf. BIF FUTURA, VOL. 25 | 3.2010

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Discipline: Biochemist, BSc
Institute: Institute of Cellular Biochemistry, University Medical Center Göttingen, Göttingen, Germany
Supervisor: Prof. Peter Rehling

Mitochondrial biogenesis relies on the import of nuclear-encoded proteins, most of which are targeted to the organelle by an N-terminal targeting signal. These precursor proteins transit through the translocase of the outer membrane (TOM) and the translocase of the inner membrane (TIM23). The latter is composed of the Tim17, Tim21, Tim23, Tim50, and Mgr2 subunits. Whereas their initial transport across the inner mitochondrial membrane is driven by the membrane potential, full matrix translocation depends on the presequence translocase-associated motor. The mitochondrial heat shock protein 70 (mtHsp70) is recruited to the TIM23 complex and provides energy for the process through ATP hydrolysis. To achieve efficient vectorial precursor movement, motor activity needs to be temporally and spatially coordinated. Tim44 recruits mtHsp70 to the translocase exit site, where its ATPase activity is stimulated by Pam18. To be bound to the translocase, this J-protein requires a specialized J-like protein partner Pam16. Despite the identification of these co-chaperones, the mechanism by which precursor progression is coupled to the motor activity remained enigmatic. During my PhD project, I established an assay that allowed us to analyse the integration of free subunits into the active translocase in isolated yeast mitochondria. In this assay, half of the TIM23 complexes were occupied by an arrested precursor that spanned both the TOM and TIM23 complex. Radio-labelled translocase subunits were subsequently imported into these mitochondria using the vacant TIM23 complexes, and their integration into the active translocases was monitored by affinity isolations of the TOM complex. Surprisingly, I found that Pam18, Pam16, Tim44, and Tim21 integrated into the active translocase. I further performed a detailed analysis of the J-protein that revealed that Mgr2 modulates the cycling of Pam18. Taken together, the results of my PhD show that the recharging of the translocase with these co-chaperones at the TIM23 complex is required to maintain import motor function and, concomitantly, protein translocation into the matrix.

PUBLICATIONS

Schulz C, Rehling P (2014) Remodelling of the active presequence translocase drives motor-dependent mitochondrial protein translocation. *Nat Commun* **5:** 4349

ANALYSIS OF COMPONENTS OF THE REPLICATION AND REPAIR MACHINERY IN EMBRYONIC STEM CELLS

cf. BIF FUTURA, VOL. 25 | 3.2010

NADIA SELLAMI
Discipline: Biological Chemist, Diploma
Institute: University of California, Los Angeles (UCLA), Los Angeles, CA, USA
Supervisor: Prof. Kathrin Plath

The timing of DNA replication and the chromatin state of a genomic locus are tightly correlated and developmentally controlled. Genetically active euchromatic regions tend to be replicated early in S-phase, whereas heterochromatic regions are replicated late. However, the molecular mechanism underlying this correlation is unknown. Proliferating cell nuclear antigen (PCNA) forms the clamp at the replication fork and has a plethora of interaction partners, including chromatin-modifying enzymes. We therefore speculated that PCNA might mediate the replication of the different chromatin states by recruiting chromatin modifiers to the fork at the appropriate time during S-phase. To provide evidence for this model, we determined the PCNA interactome using the multi-dimensional protein identification technique (MudPIT) and mass spectrometry in embryonic stem cells (ESCs) and identified a number of chromatin modifiers, some of which indeed interacted specifically in early or late S-phase. Interestingly, among these PCNA interaction partners was the annealing helicase AH2 (also known as zinc finger ran-binding protein 3, Zranb3), which we found to be particularly highly expressed in ESCs. To understand the molecular function of AH2, we determined its interactome in ESCs and identified components of the DNA mismatch repair (MMR) machinery as novel binding partners. As ESCs potentially give rise to the whole organism, repair mechanisms and especially MMR are crucial and are upregulated to faithfully replicate the genome without the accumulation of mutations. We therefore suggest a model in which PCNA is recruited to sites of MMR and is then bound by AH2 to repair DNA lesions. Taken together, my results provide evidence for the functional linkage of DNA replication timing and the establishment or maintenance of chromatin modifications. Furthermore, they emphasize the power of comprehensive mass spectrometric approaches in ESC research, as this work also led to the discovery of a novel factor linking MMR to the replication machinery.

PUBLICATIONS

The results of this project have not yet been published.

THE INFLUENCE OF SIP1 IN ESTABLISHING NEOCORTICAL PROJECTIONS

cf. BIF FUTURA, VOL. 26 | 2.2011

SWATHI SRIVATSA
Discipline: Neuroscientist, MSc
Institute: Institute for Cell and Neurobiology, Charité, Berlin, Germany
Supervisor: Prof. Victor Tarabykin

Axonal connections between neocortical neurons in the brain and their targets form the basis of our higher cognitive abilities, such as speech, language, and imagination. Studying how these axonal projections are formed and how they are directed towards their correct target is therefore of utmost importance. Using the mouse as a model organism, we have studied the role of the transcription factor Smad-interacting protein 1 (Sip1) in establishing neocortical projections. We performed axonal tract tracing in the Sip1 mutant by placing crystals of a lipophilic dye called DiI within the cortex or within various regions of the white matter and tracing the axonal connections formed. We were able to show that Sip1 deficiency leads to the absence of many principal axonal tracts, such as the corpus callosum that lies between the two hemispheres of the brain, the anterior commissure, and the corticospinal tract. Through histological techniques such as immunohistochemistry and *in-situ* hybridization, we showed that in the absence of Sip1, accessory glial and neuronal populations of cells present at the midline are not formed. These cell groups secrete chemicals that help direct callosal axons across the midline into the contralateral hemisphere. Sip1 therefore has a cell extrinsic effect on axonal projections, as without these guidance molecules, the callosal axons terminate prematurely within the same hemisphere. Sip1 also has cell intrinsic effects, as its deletion led to stunted axonal growth, as well as a lack of formation of interstitial axonal branches called axon collaterals. We investigated the underlying mechanism behind these effects and found that Sip1 transcriptionally activates the expression of a microtubule-binding protein called ninein. Furthermore, by performing microtubule stability assays and using live imaging techniques to visualize microtubule growth, we could show that ninein, in turn, modulates the growth as well as the stability of microtubules. These changes in microtubular properties influence axonal growth rate and branching. The results of my PhD therefore provide new insights into the molecular mechanisms governing the formation of axonal projections in the brain and further our understanding of cytoskeletal modifications that underlie phenomena such as axonal growth and branch formation.

PUBLICATIONS

The results of this project have not yet been published.

NOVEL NEXT-GENERATION SEQUENCING APPROACHES TO DECIPHER A GENE NETWORK IN *TRIBOLIUM*

cf. BIF FUTURA, VOL. 25 | 3.2010

DOMINIK STAPPERT
Discipline: Biologist, Diploma
Institute: Cologne Biocentre, Institute of Developmental Biology, Cologne, Germany
Supervisor: Prof. Siegfried Roth

To understand the evolution of gene regulatory networks (GRNs), they need to be elucidated and compared in closely related species. The GRN that specifies the dorso-ventral (DV) axis in *Drosophila melanogaster* has been particularly well studied. This network changed during insect evolution: Toll signalling governs DV patterning in the fly, whereas bone morphogenetic protein (BMP) signalling dominates in most animals. Thus, investigating the DV GRN in different insects promises insights into GRN evolution. A current challenge in evolutionary developmental biology is to overcome the candidate approach by identifying genes not only by virtue of their homology to *Drosophila*, but also in an unbiased manner. We therefore used two novel, complementary next-generation sequencing approaches to find components of the DV GRN of the beetle *Tribolium castaneum*. First, we used RNA interference followed by differential expression analysis to identify those genes whose expression levels change upon knockdown of the key DV transcription factors Tc-dorsal and Tc-twist. Second, we established chromatin immunoprecipitation followed by sequencing (ChIP-seq) in *Tribolium* to identify enhancers bound by Tc-Dorsal. This approach represents the first successful ChIP-seq for a transcription factor in a non-model species outside of mammals. In total, we identified several hundred enhancers and genes as potential parts of the DV GRN. Expression analysis by *in-situ* hybridization and matching of the data sets enabled us to establish 40 of these as bona fide *Tribolium* DV-patterning genes, including the five that were already known. Initial contextualization of the data suggests a dynamic, regulative GRN downstream of Tc-Dorsal, the output of which is more dependent on interactions between Dorsal target genes rather than on Tc-Dorsal itself when compared to the fly. The results of my PhD constitute an essential foundation for future functional studies, including defined mis-expression of genes, and for developing a thorough understanding of the enhancers comprising the core of the *Tribolium* DV GRN. Furthermore, our approach offers a novel strategy for the study of GRNs in non-model species in an unbiased manner and so should facilitate future evolutionary comparisons.

PUBLICATIONS

Buchta T, Ozüak O, Stappert D, Roth S, Lynch JA (2013) Patterning the dorsal-ventral axis of the wasp *Nasonia vitripennis*. *Dev Biol* **381:** 189–202

ELUCIDATING THE MECHANISMS OF CYTOKINESIS IN BUDDING YEAST AND MAMMALIAN CELLS

cf. BIF FUTURA, VOL. 27 | 1.2012

CARSTEN WLOKA
Discipline: Biochemist, Diploma
Institute: University of Pennsylvania, Philadelphia, PA, USA
Supervisor: Prof. Erfei Bi

Cytokinesis is a complex process requiring the successful execution and coupling of many cellular events. Crucial for the physical separation of both the cytoplasm and its cellular constituents are actin filaments and myosin-II motors, which form an evolutionary conserved contractile actomyosin ring (AMR) in fungi and animal cells. The AMR powers the ingression of the plasma membrane during cell division and is spatiotemporally coupled with targeted membrane deposition. The heavy chains of type-II myosins comprise two globular heads and a long rod tail, and these form the basic structure of the ring. Despite the importance of the AMR, how it is assembled remains poorly understood. Using live cell time-lapse microscopy in combination with fluorescence recovery after photobleaching (FRAP) and fluorescence loss in photobleaching (FLIP), I demonstrated that myosin-II shows cell cycle-dependent changes in dynamics in the budding yeast *Saccharomyces cerevisiae*. Myosin-II is highly mobile early in the cell cycle and transitions through a less mobile state in G2/M to an immobile state during cytokinesis. I showed that the immobile state does not depend on actin or the motor domain of myosin-II but instead on a small region in the tail of myosin-II that is thought to mediate higher-order assembly. Other cytokinetic proteins display myosin-II-dependent immobility but not vice versa, suggesting a scaffolding role for myosin-II during cytokinesis. By chemical and dominant-negative inhibition, I could further show that myosin-II may be involved in the maturation of the midbody of mammalian cells, which is essential for the completion of cell division. The results of my studies have therefore furthered our understanding of AMR assembly and have revealed an unprecedented scaffolding role for myosin-II during cytokinesis. They may also help us to understand other cellular processes that utilize a contractile AMR, such as cell-wound repair.

PUBLICATIONS

Oh Y, Schreiter J, Nishihama R, Wloka C, Bi E (2013) Targeting and functional mechanisms of the cytokinesis-related F-BAR protein Hof1 during the cell cycle. *Mol Biol Cell* **24:** 1305–1320

Wloka C, Vallen EA, The L, Fang X, Oh Y, Bi E (2013) Immobile myosin-II plays a scaffolding role during cytokinesis in budding yeast. *J Cell Biol* **200:** 271–286

Wloka C, Bi E (2012) Mechanisms of cytokinesis in budding yeast. *Cytoskeleton (Hoboken)* **69:** 710–726

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.

PERSPECTIVES

FROM SCIENTIST TO CONSUMER MARKETING INTELLIGENCE MANAGER

Microbiologist Shane Hanson has chosen an unusual career path: after moving from her native India to Europe, she swapped the lab for the office and is now a consumer marketing intelligence manager at Royal Philipps. FUTURA talked to the BIF alumna about professional choices, challenges, and her love for German bratwurst.

INTERVIEW WITH DR SHANE HANSON, GUILDFORD, UK

Shane Hanson enjoys making connections between innovations and consumers.

After her MSc in microbiology, Shane Hanson from India worked in pharmaceutical manufacturing as well as in a biotechnology research organization. When her husband received a Humboldt fellowship she accompanied him to Germany, intent on furthering her own scientific career. She developed her PhD project on gene regulation through RNA aptamers in the lab of Prof. Wolfgang Hillen at the University of Erlangen-Nuremberg, Germany, and secured a BIF PhD fellowship from 2000 to 2002. After her PhD, she joined Procter & Gamble Technical Centres Ltd. in the UK as a research and development manager, working on developing consumer insights-driven innovations in the field of personal beauty care. In 2012, she moved to KP Snacks Ltd (part of Intersnack Group, Germany) as a marketing innovation manager leading the programme "Health & Nutrition Strategy and Innovation". She is now with Royal Philips in the Consumer Lifestyle Business Group, working on personal care as a consumer marketing intelligence manager. She lives in Bracknell, Berkshire, UK, with her husband and her four-year-old son.

What were the most important choices in your career?

One: Taking the leap out of my comfortable life in India to experience a very different culture. I have fond memories of my four years in Germany and have embraced some finer points of the German cuisine such as *Vollkornbrot*, Nuremberg bratwurst, and apple streusel cake.

Two: Applying for a BIF fellowship: It provided me with a solid financial basis for living expenses, funding cross-collaborations with other labs, and building my network at international conventions. BIF's support opened a world of opportunities that got me where I am today.

Three: Moving to England to work for Procter & Gamble. Joining P&G, I realized that there is still a lot more to learn – I enjoyed my nine years understanding how people around the world use and experience different personal care products. And now with Philips, I'm still learning about consumers' grooming and beauty needs and habits …

What excites you most about your work and what do you like least?

Commercializing innovation excites me … it is all about being able to make a connection between consumer or market insights and technology solutions. I least like the routine tasks that are present in most industry roles. I deal with them as accurately as possible so that I can move on to the more exciting elements of my role.

What do you think are qualities companies in your sector are looking for?

Three things, I would say: first, a good balance of analysis and synthesis, i.e. doing deep analysis while being able to crystallize the key message to generate a clear recommendation; second, problem-solving ability; and third, being a team player.

What lessons did you learn in your career?

Being a constant learner keeps you on top of your profession. Never let up on networking both inside and outside your organization. Having my son made me focus more on getting the right work-life balance. Redundancies and job cuts are the harsh reality of today's economic environment.

WHO'S WHO AT BIF?

DR ANJA HOFFMANN

Anja Hoffmann was born in 1977 in Landshut, Germany. She studied biology at the Universities of Regensburg, Würzburg (both Germany), and Boulder, CO, USA. For her PhD on protein quality control in Heidelberg she received a BIF fellowship. After a postdoc, she joined the BIF team in July 2010. Anja heads BIF's MD programme, supports PhD and MD fellows personally, and is in charge of the Heinrich Wieland Prize of the Boehringer Ingelheim Foundation. She loves music, the outdoors, photography and was Bavarian junior chess master in 1992.

What do you like most about your work at BIF?
Meeting our fellows. I cherish the variety of tasks and feel privileged to be able to promote such excellent people and to help them to succeed – be it in science or other areas.

What is your most remarkable experience connected with BIF?
The spirit at BIF. Having experienced different elite scholarships, I was immediately inspired by its warm, open-minded, and intimate atmosphere.

What is your favourite activity?
I love travelling, hiking, playing music or volleyball, spending time with my family …

Where would you like to live?
In Germany but with longer stays in other cultures all over the world.

What is your remedy for stressful situations?
I try to welcome the challenge, do things step by step, not forget to laugh, and enjoy relaxing hours afterwards.

What is your motto?
To make the best of everything and also cherish the little everyday things.

What fault in others can you tolerate best?
In Germany, there is a saying: never judge others until you've walked in their shoes. I can easily accept "faults" that seem less important at a second glance.

Your advice for fellowship holders?
First know what YOU want, then try to reach YOUR aims; don't give up too easily, be aware that both research and life have ups and downs and don't hesitate to contact us whenever you might need help.

What scientific achievement do you admire most?
I admire pioneers who challenge existing dogmas and open up new fields of research.

Name one thing you couldn't live without.
There are four things: the people I care about, a definite goal in mind, a job that inspires me, and at least one annual holiday trip :-).

Photos: Shane Hanson (left), BIF Carsten Costard (top), Katrin Kreft (Graphics right)

THE PORTAL IS ONLINE

Applying for BIF's travel grant programme has just become easier with our new online application portal. The grants allow PhD or MD students and postdoctoral researchers in basic biomedical research to visit another lab or a practical course for up to three months. However, anybody currently funded in the PhD or MD programmes (which have separate travel allowances) is not eligible for this programme. The grants are given for two purposes: to learn new methods or to check the match between a foreign student and a prospective PhD project. Our steadily rising application numbers show the ongoing funding gap for such research. The portal seems to be working well: in the first two-and-a-half months of its existence more than 120 applicants have used it.

It is compatible with tablets and smart phones and offers drop-down lists of the most common values, shortening the time spent entering data. The more consistent data quality is also helping to streamline the processing and evaluation of applications. A win-win situation for everyone involved.

Thanks to the new portal, applying for a travel grant has become much easier.

PAPERS IN THE SPOTLIGHT

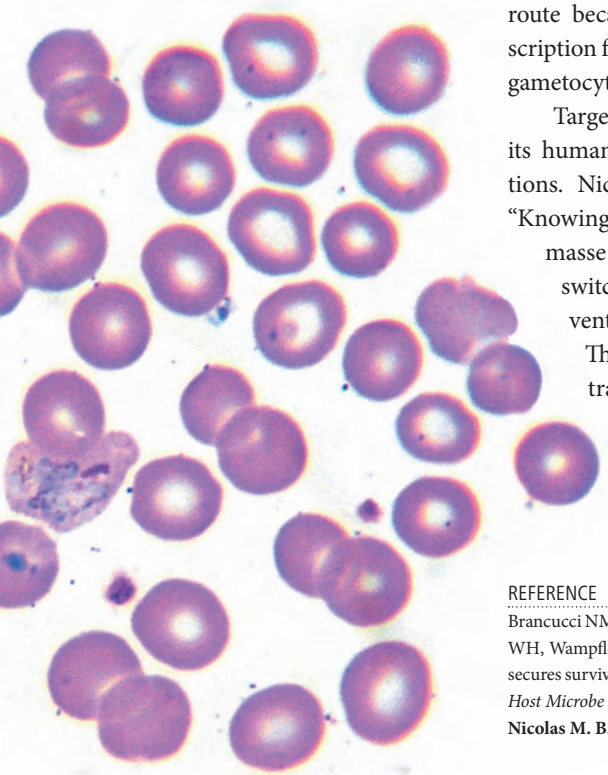
In "Papers in the Spotlight" we present papers from current or recent BIF fellows. The selection criteria are based not only on scientific merit, but also on the general interest of the topic. If you would like to see your paper discussed here, send an e-mail to kirsten.achenbach@bifonds.de.

UNMASKING MALARIA'S MANY FACES

Malaria kills about 630,000 people a year with a further 200 million falling sick, according to the WHO. The deadliest of the five malaria-causing parasites is *Plasmodium falciparum*. Nicolas Brancucci, together with his former advisor Professor Till Voss, identified a potential new avenue to prevent malaria. During his PhD at the Swiss Tropical and Public Health Institute, he studied heterochromatin protein 1 (HP1) in *P. falciparum* and its effect on *var* genes. These code for proteins displayed on the surface of infected blood cells and can therefore serve as targets for the immune system. Usually, only one of about 60 *var* variants is active in any given parasite. Changes in the expression of *var* genes in the parasite population make it hard for the immune system to fight the disease or develop immunity.

Nicolas showed that depleting the epigenetic factor HP1 causes all *var* genes to be expressed at the same time. Surprisingly, it also prevents the parasites from copying their DNA and thus from multiplying. "Without HP1, half of our parasites entered cell-cycle arrest, while the other half differentiated into gametocytes that are required to infect mosquitoes," states Nicolas. Typically, only 1% of parasites take this route because HP1 also silences a transcription factor, AP2-G, that is essential for gametocyte development.

Targeting HP1 is no feasable cure, as its human counterparts fulfil vital functions. Nicolas sees other opportunities: "Knowing how to produce gametocytes en masse by manipulating this epigenetic switch, we might find ways to prevent their production altogether. This in turn could stop malaria transmission."



The malaria parasite under the microscope.

REFERENCE

Brancucci NMB, Bertschi NL, Zhu L, Niederwieser I, Chin WH, Wampfler R *et al* (2014) Heterochromatin protein 1 secures survival and transmission of malaria parasites, *Cell Host Microbe* **16:** 165–176

Nicolas M. B. Brancucci, fellow 2009–2012

INSATIABLE ON DEMAND

The famous scene from Monty Python's "The Meaning of Life" in which a man eats until he bursts, has become reality for the fruit flies in the lab of Kristin Scott at University of California, Berkeley, USA. BIF fellow Allan-Hermann Pool has identified four GABAergic interneurons in the *Drosophila* brain that constantly suppress feeding behaviour. If they are silenced, a fly will eat and drink everything it can get its proboscis on – even denatonium, the most bitter substance known. The fly will not stop until it regurgitates, excretes, or explodes.

Allan-Hermann and colleagues identified these neurons by genetically silencing different subsets of neurons in the fly brain and screening the resulting flies for their drinking behaviour. Silencing just four out of the 100,000 neurons in the fly nervous system was sufficient to yield indiscriminate feeding. These four neurons are constantly releasing the neurotransmitter GABA, thereby inhibiting the motor neurons re-

Photos: Stockphoto/kukhunthod (bottom left); Kristin Scott, University of California (bottom right)

sponsible for the extension of the mouthparts and the ingestion of food. Only a strong feeding-promoting signal like hunger can overcome their inhibiting influence.

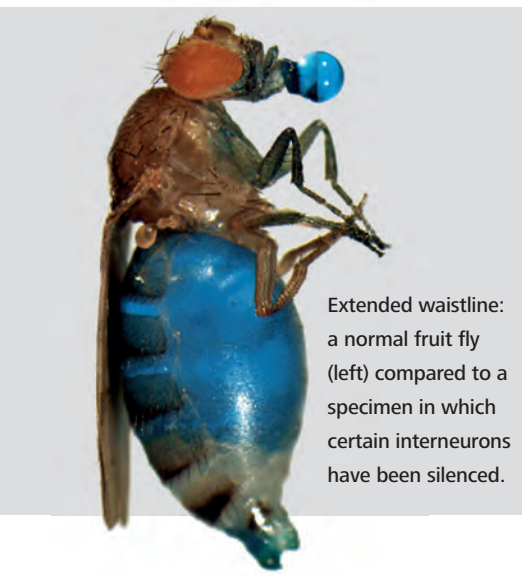
In humans, emotions like pleasure, boredom, or depression are known to be involved in eating behaviour. Finding similar neuronal circuits in mammals or even humans would help to show which triggers drive people to eat more than they want or need. Something that might just happen to some of us over the coming holidays.

REFERENCE

Pool AH, Kvello P, Mann K, Cheung SK, Gordon MD, Wang L *et al* (2014) Four GABAergic interneurons impose feeding restraint in *Drosophila*. *Neuron* **83:** 164–177

Allan-Hermann Pool, fellow 2009–2011

Photos: Christoph Thaiss, Elinav lab, Weizmann Institute (top right); Kristin Scott, University of California (bottom left)



Extended waistline: a normal fruit fly (left) compared to a specimen in which certain interneurons have been silenced.

GUT MICROBES HEAR THE CLOCK TICKING

Life on Earth is dictated by fluctuations in the environment of factors such as light, temperature, or tides, caused by the planet's rotation around its own axis. Like other organisms, humans had to find ways to adapt to these rhythms. BIF fellow Christoph Thaiss and his supervisor Eran Elinav at the Weizmann Institute of Science in Israel discovered an unexpected partner in this dance: the intestinal microbiota.

In an article published in *Cell* in October 2014, they found that the composition and function of the vast community of microorganisms living in our gut oscillates daily. Living through the ups and downs of a PhD, the study had first been hampered by a spontaneous point mutation in the mouse model the scientists had used, leading to confusing results. However, the breakthrough came when the scientists found that the bacterial oscillations are controlled by the circadian clock system of the host, indicating synchronization of day-night rhythms between the mammalian host and its bacterial community.

Christoph and colleagues also found that in individuals whose circadian clock is out of sync, such as jet-lagged travellers, this synchronization is impaired and the resultant aberrations in the microbiota predispose to obesity. Therefore, the researchers propose that gut microbes might constitute the missing link between aberrant circadian rhythms and metabolic disturbances, such as those observed in frequent flyers and shift workers.

The circadian clock system of the host controls bacterial oscillations.

REFERENCE

Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC *et al* (2014) Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* **159:** 514–529

Christoph Thaiss, fellow 2013–2015

A BIF FELLOW'S GUIDE TO ...

TEL AVIV

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 Christoph Thaiss reports from Tel Aviv, Israel, the Middle East metropolis that never sleeps.*

FACTS & FIGURES

Country: Israel
Population: 420,000
Area: 52 km²
Students: About 50,000
Famous for the "White City", the beach, a mix of Western and Middle Eastern lifestyles, and the vibrant nightlife
Websites: www.tel-aviv.gov.il/eng

WHERE TO STAY

Hayarkon Hostel: An ideal place for backpackers, two steps away from the beach and with a view of sunsets over the Mediterranean Sea that's almost too good to be true.
Crowne Plaza Tel Aviv Center 2 **:** Just a few minutes away from Tel Aviv's cultural and shopping district.

NIGHTLIFE

Diezengoff: Named after the first major of Tel Aviv, this street is lined with popular bars and cafes – and "it never sleeps".
Florentin: The young and "cool" neighborhood of Tel Aviv that attracts many artists and feels a close kinship to Berlin.
Tachana: A renovated old train station ("tachana" means train station in Hebrew) that is now filled with bars and cafes. Tel Avivians' favourite place for a date.

RESTAURANTS

Abu Hassan: For Israelis, the question which restaurant offers the best hummus in town is taken very seriously. The fact that many will name Abu Hassan as their favorite hummus place makes it a mandatory stop for every visitor.
Manta Rey: Very little food for a very high price, but the ocean view compensates for everything. People come to watch, not to eat.
Misnon: Falafel, Israel's national dish, in many new and traditional flavours. This place attracts locals and visitors alike.

ACTIVITIES

Beach 3 **:** Many miles of white sand and blue sea, with temperatures above 20° C all year … what else can you ask for?
HaCarmel Market 1 **:** Tel Aviv's most vibrant market and a unique mix of American, European, and Middle Eastern culture.

BEST SIGHTS

White City: Tel Aviv's nickname originates from this neighborhood, which is dominated by Bauhaus architecture.
Old Jaffa 4 **:** A picturesque old Arab neighborhood with unique charm and a 4,000-year history.
Namal: "Namal" means harbour in Hebrew, which in Tel Aviv means miles of restaurants, bars, and shows at the seaside.

* Please check possible travel warnings before visiting

Contributors wanted! If you would like to introduce your city to the readers of FUTURA, send an e-mail to Kirsten.Achenbach@bifonds.de

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Supervisor Dr Eran Elinav

Photos: /Wikipedia (1); borlail/iStock (4); all others: Christoph Thaiss

PROFILES

Dr Felix Halbach, from the Max Planck Institute for Biochemistry, Martinsried, Germany, was awarded the Otto Hahn Medal 2013 in June 2014. He has been honoured with this 7,500-euro prize for his PhD work on unravelling how eukaryotic cells dispose of RNA in the cytoplasm. Since 1978, the Max Planck Society honours about 30 young scientists each year with this medal for their outstanding scientific achievements. Felix was a BIF fellow from 2008 to 2010.

Prof. Hinrich Kaiser, professor of biology at Victor Valley College, Victor Valley, CA, USA, and BIF fellow from 1994 to 1996, has received an unusual distinction. His 2014 expedition to Timor Leste to assess the biodiversity of amphibians and reptiles has been nominated as a so-called Flag expedition by the Explorers Club, the world's most eminent association focused on exploration. Its flags have fluttered at both poles and atop the highest mountains; they have flown to the moon and dived to the deepest parts of the ocean. Only expeditions that further the cause of exploration and field science are selected to carry the club's flags. Currently there are 202 of these flags, many more than 50 years old, having accompanied several expeditions.

Four further BIF fellows were newly elected as EMBO members in May 2014: professors **Sebastian Bonhoeffer,** Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, **Rainer Friedrich,** Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland, **Volker Haucke,** Leibniz Institute for Molecular Pharmacology, Berlin, Germany, and **Michael Sieweke,** Center of Immunology of Marseille-Luminy, France. For its 50th anniversary EMBO decided to strategically expand its membership to encompass outstanding researchers from the fields of neuroscience and ecology & evolution. Currently, EMBO has about 1,600 members who provide suggestions and feedback on its activities, serve on programme selection committees and mentor young scientists.

Dr Alexander Tups, group leader at Marburg University, Germany, has received the 1,000-euro Ernst and Berta Scharrer-Prize 2014 of the German Endocrinological Society (DGE). Together with Christiane Koch, he showed that in mice, high fat content in the diet rather than high leptin levels produced by adipose tissue causes resistance to leptin – a hormone regulating the fat metabolism. Alexander was a BIF fellow from 2003 to 2005.

Prof. Andreas Wodarz has headed the Department for Cell Biology and Microscopical Anatomy at the University of Cologne, Germany, as W3 professor for cell biology since April 2014. The research of his group focusses on cell polarity and asymmetric division of neural stem cells, epithelial cell polarity and planar cell polarity controlled by the Wnt signalling pathway. Andreas was a BIF fellow from 1990 to 1993.

Photo: Felix Halbach, Hinrich Kaiser, Alexander Tups/Heike Pohla, Andreas Wodarz

UPCOMING EVENTS

20–25 FEBRUARY 2015

Communication training in Cold Spring Harbor, USA

Communication seminar for non German-speaking PhD fellowship holders working in Europe as well as all PhD fellowship holders working in North America. The meeting takes place in Cold Spring Harbor, New York. Participants will have the opportunity to work on their writing and presentation skills with various coaches, as well as learn more about designing graphs and figures. Further details will be sent with the invitation.

20–21 MARCH 2015

Meeting of BIF's Board of Trustees in Mainz, Germany

Our foundation's Board of Trustees consists of six internationally renowned scientists, the chairman of the Board of Managing Directors of the company Boehringer Ingelheim, and – as a permanent guest – a representative of the German Research Foundation (DFG). The trustees work in an honorary capacity. Their most crucial function is scrutinizing applications for BIF's fellowship programmes. They also review proposals for the International Titisee Conferences.

15–19 APRIL 2015

111th International Titisee Conference

"Rediscovering Warburg – the Role of Metabolism in Signalling Disease" is the title of the 111th ITC at Lake Titisee, Germany. It will be chaired by Luke O'Neill (Trinity Biomedical Science Institute, Trinity College Dublin, Ireland), Michael P. Murphy (Medical Research Council, Cambridge, UK), and Erika L. Pearce (Washington University School of Medicine, St, Louis, MO, USA). The focus of the interdisciplinary meeting will be on new insights into the Warburg effect as well as hypoxia sensing, mitochondrial ROS, and the role of metabolic changes in immune cell activation and cancer.

Participation is by invitation only.

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