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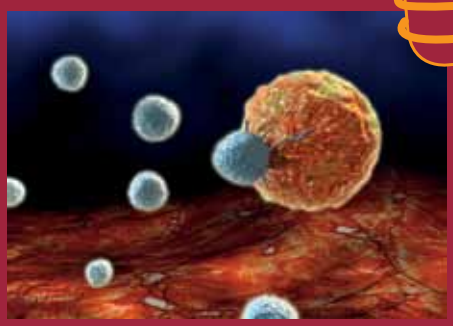

The Red Dragon's PhDs
China is rapidly gaining on the nations leading the science race

Projects, Results and MD Fellows
PhD projects, completed theses and research projects by BIF fellows

Papers in the Spotlight
Read about three papers by BIF fellows

The cover illustration shows a simplified model of the histone-DNA complex. The accessibility of genes depends on how tightly this complex is packed. If the transcription factors cannot reach the DNA, these genes are silent. Among other things, epigenetics studies how this process is regulated. Read more about this fast-moving discipline in our main story on page 8.

FACTS

FELLOWS

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Stiftung für medizinische Grundlagenforschung
Schusterstr. 46–48
55116 Mainz
Germany
Tel. +49 6131 27508-0
Fax +49 6131 27508-11
E-mail: secretariat@bifonds.de
www.bifonds.de

Editor-in-Chief Dr Claudia Walther

Editors Kirsten Achenbach (BIF, executive editor), Karsten Fiehe, Michael Mennig (muehlhausmoers corporate communications gmbh)

Authors in this issue Kirsten Achenbach, Michael Mennig, Yadan Ouyang, Michael Simm, Dr Claudia Walther

Translating, copy-editing and proofreading Adam Blauhut, Dr Caroline Hadley, Dr Caroline M. Taylor, Dr Susan Simpson

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Project management Karsten Fiehe, Michael Mennig
Art direction Britta Siebert

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THE BAZINGA FORMULA

»Despite all the accurate science, 'The Big Bang Theory' does not teach – nor does it aim to.«

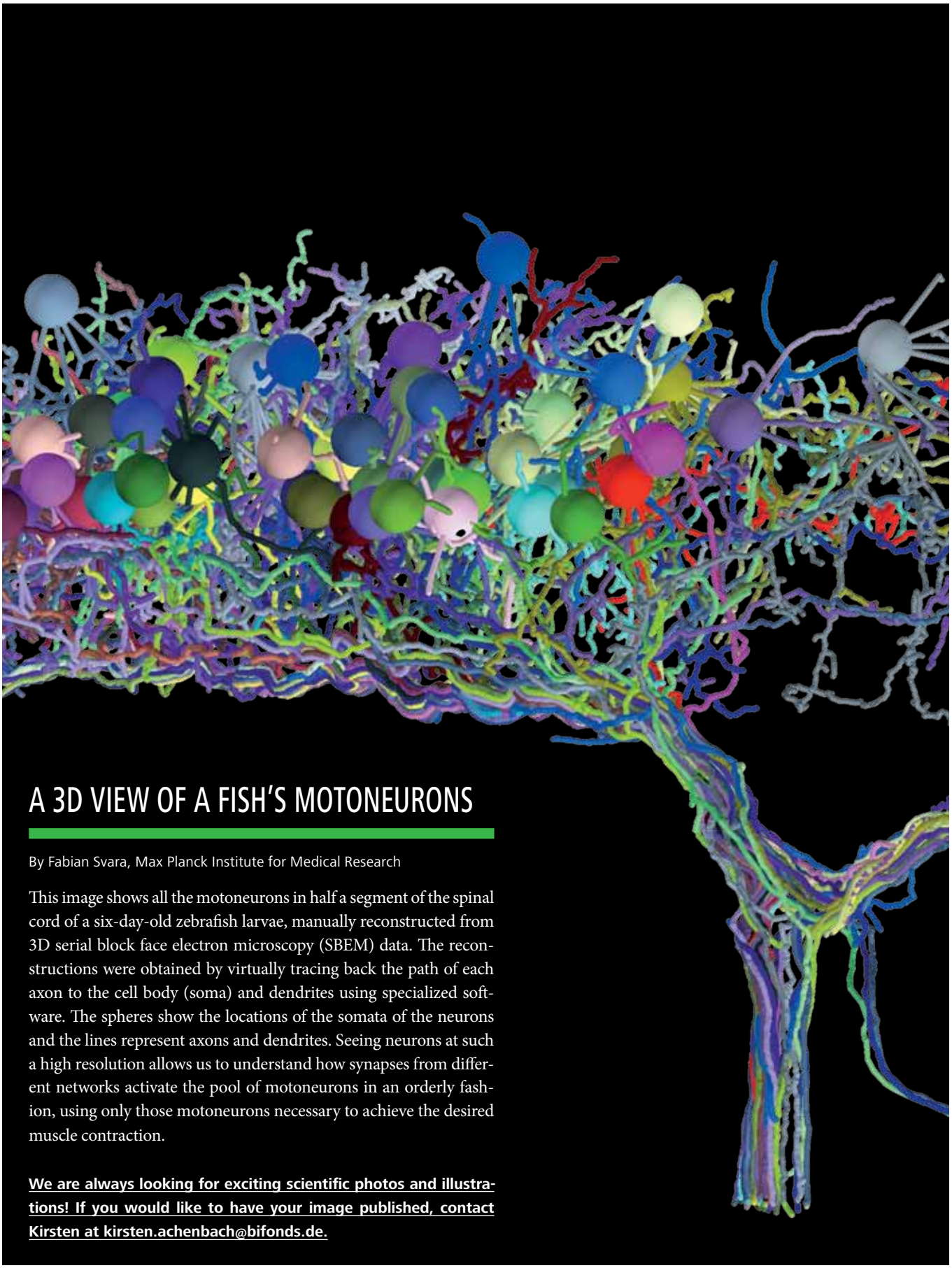
String theory, quantum mechanics and their equations – the bane of science communication – as backdrops for a successful TV comedy? It's possible. The critically acclaimed "The Big Bang Theory" with its nerdy, genius scientists (three physicists, a neurobiologist and an engineer) and socially skilled, common-sensed Penny, has become one of the most popular shows ever. Started in 2007, now 23 million people watch every episode in the USA alone. Even its slightly less sparkling German version reaches a spectacular 25% viewers in the age group below 40 and twice as many followers as Germany's famous crime series "Tatort".

Its side effects: Asteroid 246247, alias Sheldoncooper, has been named after the main character of the show; *Euglossa bazinga*, a species of orchid bee, after his catch phrase; and a dramatic rise in the popularity of physics. In 2005, physics was officially classified as a "vulnerable" subject in the UK – now it ranks among the top ten most popular A-level topics. The number of applications for physics courses at university has seen a double-digit percentage increase. Even experts at the Institute of Physics (UK) give some of the credit to "The Big Bang Theory". Though – as Sheldon surely would point out – there is no scientific evidence for a causal relationship, and other factors including physicist and popular TV presenter Brian Cox are likely to have contributed to this increase in popularity.

In a rare consensus, even scientists love the show. Physicists and the journal Nature assure us that the facts, diagrams and complicated strings of equations decorating rooms and labs in the show are accurate. And science is everywhere: The Doppler effect becomes a costume for a fancy-dress party; heartbreak is analyzed with EEG readings, dialogues are spiked with titbits ranging from rare languages and classical antiquity to social sciences. The rituals and hazards of the academic world come to life when Sheldon ruthlessly discusses with a (real) Nobel laureate about author position. Howard repeatedly becomes the target of arrogance between disciplines for being "only" an engineer, and when Raj's grant money runs out he faces the tough equation: no grant = no job = no visa for the United States.

Contrary to many science communication efforts, "The Big Bang Theory" does not convey the illusion that string theory or any of the science it portrays is easy. The fast and witty dialogues are often full of jargon, and quite a few are way beyond anyone but physicists. While this usually puts off, here it is part of the charm. Do we learn much? Nope. Despite all the accurate science, "The Big Bang Theory" does not teach – nor does it aim to. Sheldon, Leonard, Amy, Howard and Raj are utterly funny. They win our hearts with their human nerdyness and their infectious enthusiasm. They celebrate curiosity and exploration. They turn research and the quest for knowledge into something "cool". This renders "The Big Bang Theory" one of the finest and most effective pieces of science communication. Serious studying is only the second step on the road to becoming a real-life scientist.

Dr Claudia Walther, Managing Director



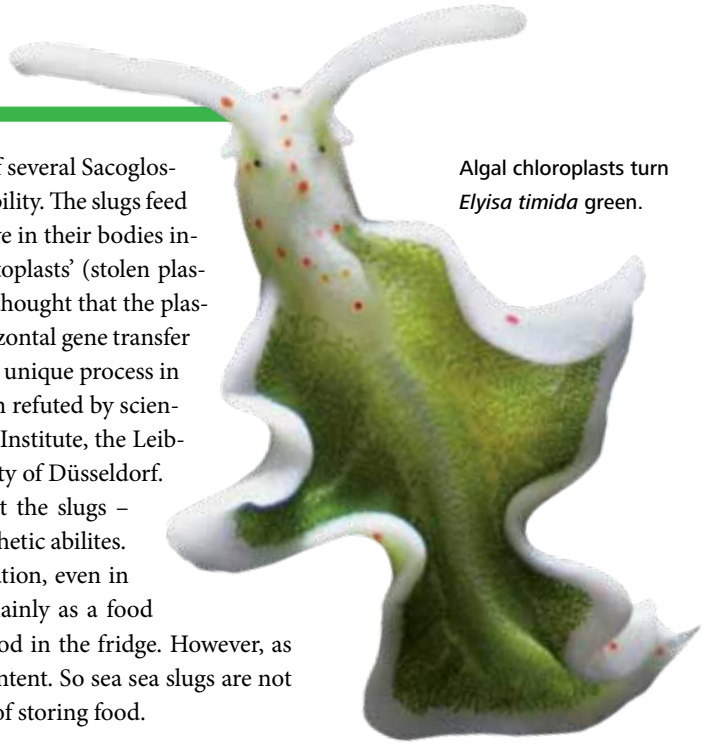
A 3D VIEW OF A FISH'S MOTONEURONS

By Fabian Svara, Max Planck Institute for Medical Research

This image shows all the motoneurons in half a segment of the spinal cord of a six-day-old zebrafish larvae, manually reconstructed from 3D serial block face electron microscopy (SBEM) data. The reconstructions were obtained by virtually tracing back the path of each axon to the cell body (soma) and dendrites using specialized software. The spheres show the locations of the somata of the neurons and the lines represent axons and dendrites. Seeing neurons at such a high resolution allows us to understand how synapses from different networks activate the pool of motoneurons in an orderly fashion, using only those motoneurons necessary to achieve the desired muscle contraction.

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.

SOLAR-POWERED SLUGS?



Algal chloroplasts turn *Elyisa timida* green.

If you can't make it, steal it! This could be the motto of several Sacoglossan sea slugs. Why? Because they have a very special ability. The slugs feed on the sap of algae and keep the algal chloroplasts alive in their bodies instead of digesting them. Inside the animals the 'kleptoplasts' (stolen plastids) continue to store solar energy. It was previously thought that the plastids could stay functional outside the algae due to horizontal gene transfer between sea slugs and algae, which would have been a unique process in the animal kingdom. But this theory has recently been refuted by scientists from the Alexander Koenig Zoological Research Institute, the Leibniz Institute for Animal Biodiversity and the University of Düsseldorf. The researchers also disproved another notion about the slugs – namely, that they keep the plastids for their photosynthetic abilites. The slugs are able to survive several months of starvation, even in the dark. This suggests that the kleptoplasts serve mainly as a food supply which stays fresh for a very long time, like food in the fridge. However, as long as there is light, this food increases its energy content. So sea sea slugs are not solar powered after all, but have evolved a clever way of storing food.

REFERENCE

Christa G *et al* (2014) Plastid-bearing sea slugs fix CO_2 in the light but do not require photosynthesis to survive. *Proc R Soc Lond B Biol Sci* **281:** 20132493

From your gut with love: Research suggest that microbes can manipulate our diet choices.

THE VOICES FROM WITHIN

Ever wondered why you crave certain foods? Scientists believe to now have found the answer. In an article published in October 2014 in *BioEssays*, researchers claim the culprit may come from deep within us – the bacteria living in our digestive tract. The multiple resident species, collectively known as the gut microbiome, are heralded as being able to make us reach for specific foods in order to ensure their survival. This goes against previous beliefs that the bacteria passively live off the nutrients we humans, as their hosts, ingest. Depending on the microbe, different nutrients are needed to thrive. Carlo Marley, Director of the San Francisco Center for Evolution and Cancer at the University of California and corresponding author on the paper labels the bacteria as manipulative. "There is a diversity of interests represented in the microbiome, some aligned with our own dietary goals, and others not," he says. Microbes apparently release molecules into our intestines that influence our eating behavior to consume those nutrients they need. The research implies that the bacteria potentially influence our eating choices via the vagus nerve and produce toxins to make us feel lousy or, contrarily, release chemical rewards that make us feel good about what we have eaten.

REFERENCE

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NEW APP MEASURES CELL PHONE USE

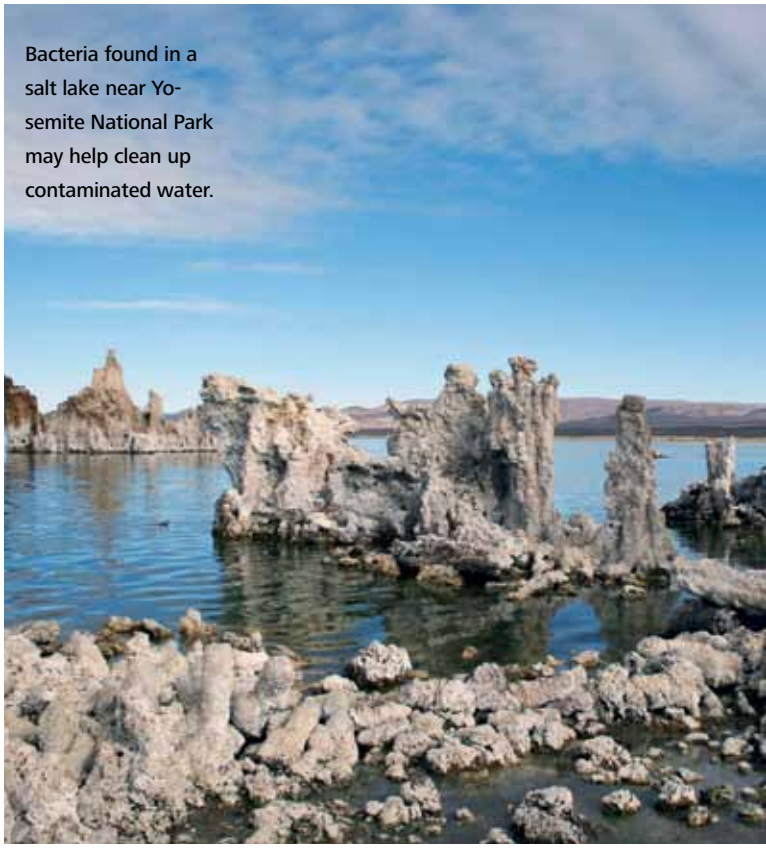
An average smartphone user activates his or her device 80 times a day – this is one of the findings of a study with 50 students conducted by Bonn University with the help of a new app called 'Menthal'. Available as a free download, the app was developed by computer scientists and psychologists at Bonn University to obtain unbiased data on cell phone use. Anyone who installs the app can use it to monitor his or her cell phone use and determine whether it is within the normal range. The app allows users to get a realistic picture of their behaviour – a big advantage over questionnaires, which often yield unreliable results. 'Interaction with cell phones can lead to addiction-like symptoms,' says Dr Christian Montag, associate professor of psychology at Bonn University. There are also plans to use the app as a depression detector in the field of psychoinformatics: 'We suspect that cell phone use changes noticeably when people are depressed,' says Professor Thomas Schläpfer from Bonn University Hospital.

70 BN

DOLLARS

This is the value of the pollination work that honey bees perform each year throughout the world. After pigs and cattle, bees are the most important animal helpers of human beings and make a huge contribution to their food security. However, bee populations are declining worldwide due primarily to pests and pesticides.

Source: German Beekeepers Association



Bacteria found in a salt lake near Yosemite National Park may help clean up contaminated water.

FROM POISON TO TREASURE

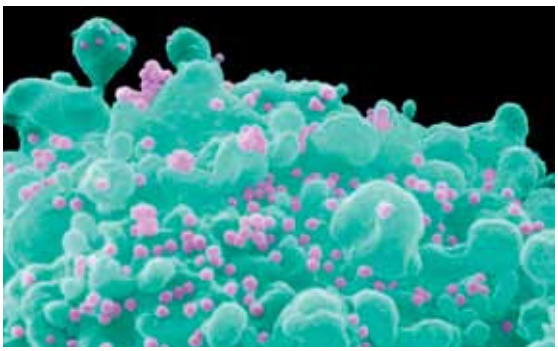
Located in California's Eastern Sierra, Mono Lake is one of the most productive ecosystems in the world and a habitat for millions of migratory and nesting birds. But the real treasure of this shallow salt lake might well be found buried in the mud along its shore. Here, researchers from the University of Georgia have found bacteria that breathe a toxic metal or even arsen instead of oxygen. The bacteria, members of the order Bacillales (phylum Firmicutes), can extract the energy needed for growth and reproduction by reducing antimonate, a salt of the metal antimony. They are able to convert antimonate into an extremely pure form of crystalline antimony trioxide, which is used in various branches of industry to produce plastics, vulcanized rubber, solar cells and LEDs. Up to now, this compound has been produced in an expensive, time-consuming process that creates dangerous by-products, meaning the discovery of the bacteria might also be of commercial significance. And that's not all: the bacteria contain enzymes that eliminate selenium and tellurium from water, contaminated e.g. by mining. Additional tests need to be undertaken to determine whether the bacteria can be used to recycle and clean up water.

REFERENCE

Abin C *et al* (2014) Dissimilatory antimonate reduction and production of antimony trioxide microcrystals by a novel microorganism. *Environ. Sci. Technol.* **48 (1):** 681–688

CELL SUICIDE CAUSES AIDS

American researchers have gained new insight into the development of AIDS. It was previously assumed that HIV directly infected immune cells and re-programmed their DNA, thus transforming it into a production site for the virus. In fact, HIV does so only in a small number of CD4 T cells. In the majority of cells the virus aborts its attempt to infect the body. However, as a result of the attack, a protein is released that activates the enzyme caspase-1 and initiates pyroptosis, an inflammatory form of programmed cell death. In this process immune cells produce cytokines, swell, burst and die. This response is devastating not only because the CD4 T cells destroy themselves in the effort to defend the body, but also because they trigger a chain reaction that leads to the self-destruction of other CD4 T cells. In experiments with anti-inflammatory drugs, researchers are attempting to find out if this disastrous cycle can be stopped by blocking the caspase-1 enzyme. Even if their tests are not successful, the study, which was published in the journals *Nature* and *Science*, is a very significant contribution to finding targets for AIDS therapy.



HI viruses (pink) attacking CD4 T cells (green) and triggering cell suicide.

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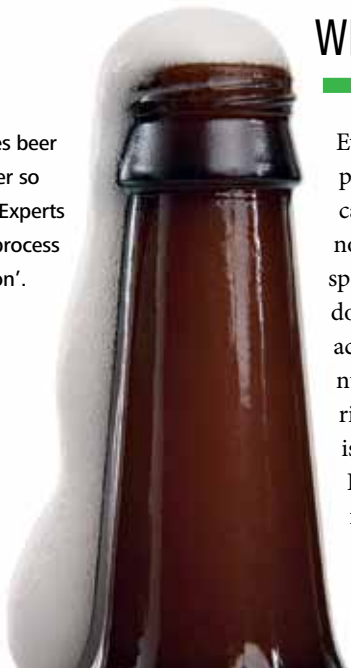
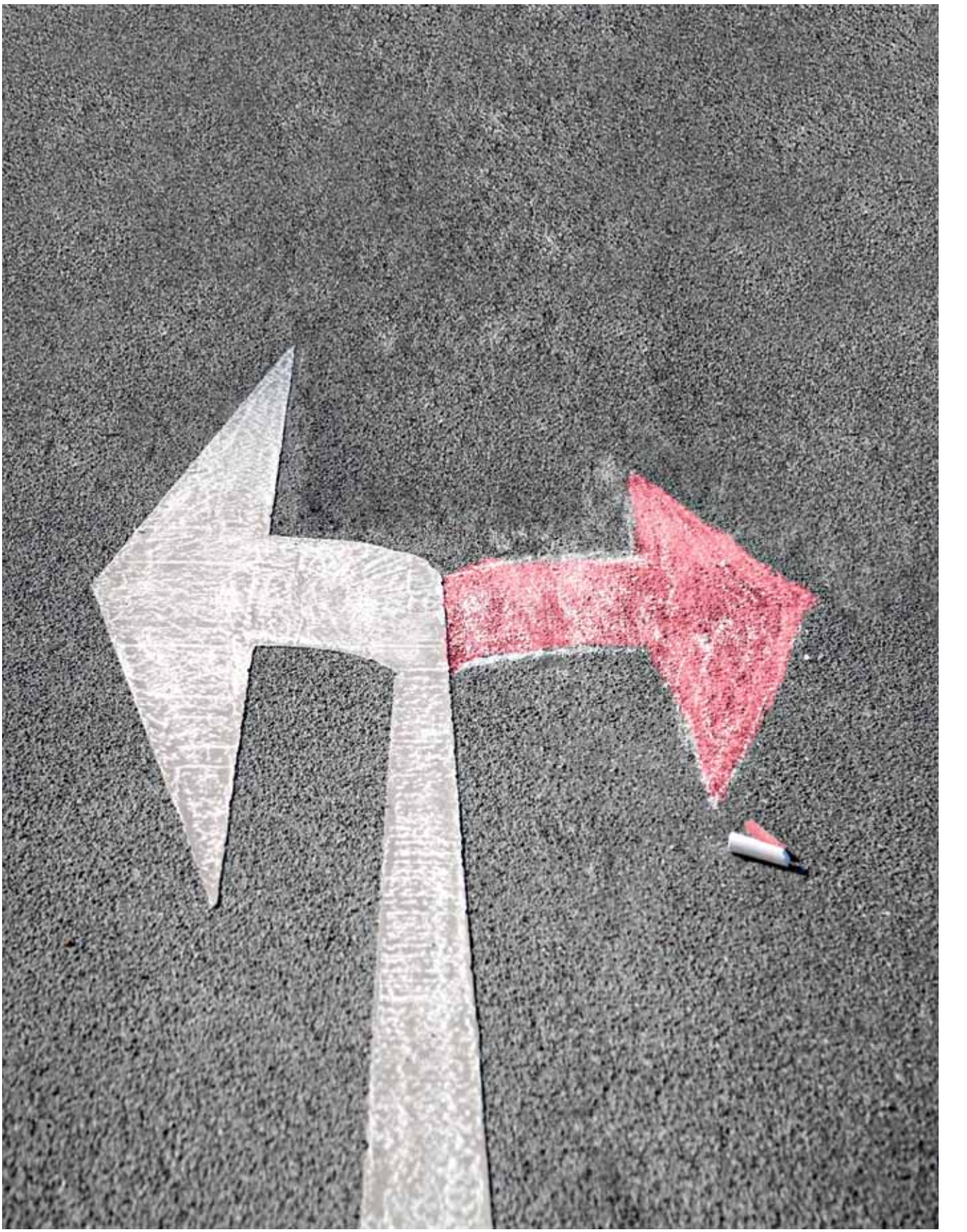


Why does beer foam over so quickly? Experts call the process 'cavitation'.

WHY BEER BOTTLES EXPLODE

Everyone is familiar with the phenomenon but hardly anyone can explain it: if you hit a bottle of beer (or other carbonated beverage), it causes the liquid inside to foam over. Spanish and French scientists have now conducted more extensive research into this matter. Using a high-speed camera capable of shooting 50,000 frames per second, they have documented the process and discovered that it is the result of a chain reaction: striking the bottle triggers a pressure wave that forms a large number of bubbles. These break into ever smaller bubbles that rapidly rise to the top of the liquid because they are of lighter weight. The effect is similar to an explosion: almost all of the beer foams out of the bottle. Incidentally, the technical term for the process is 'cavitation', which refers to the formation and collapse of gas bubbles in liquids. Cavitation also occurs when objects such as ship propellers move quickly in water, leading to costly damage and higher fuel consumption.



Genes play an important role in how our life pans out. But that's only part of the story – the environment also influences our path through life.

THE HIDDEN **SWITCHES** OF **OUR DESTINY**

By Michael Simm

Biology is a fast-moving discipline these days. If ever any proof was needed for this claim, it is epigenetics. Epigenetics literally means 'around the gene' and has been broadly defined as the study of heritable changes in gene expression that occur without a change in DNA sequence. It is a discipline that shows us surprising new ways in which environmental factors may imprint our genes – and our behaviour – not only throughout our lifetime but also for several generations to come. And by studying these mechanisms, scientists may even find new ways to treat cancer and other diseases.

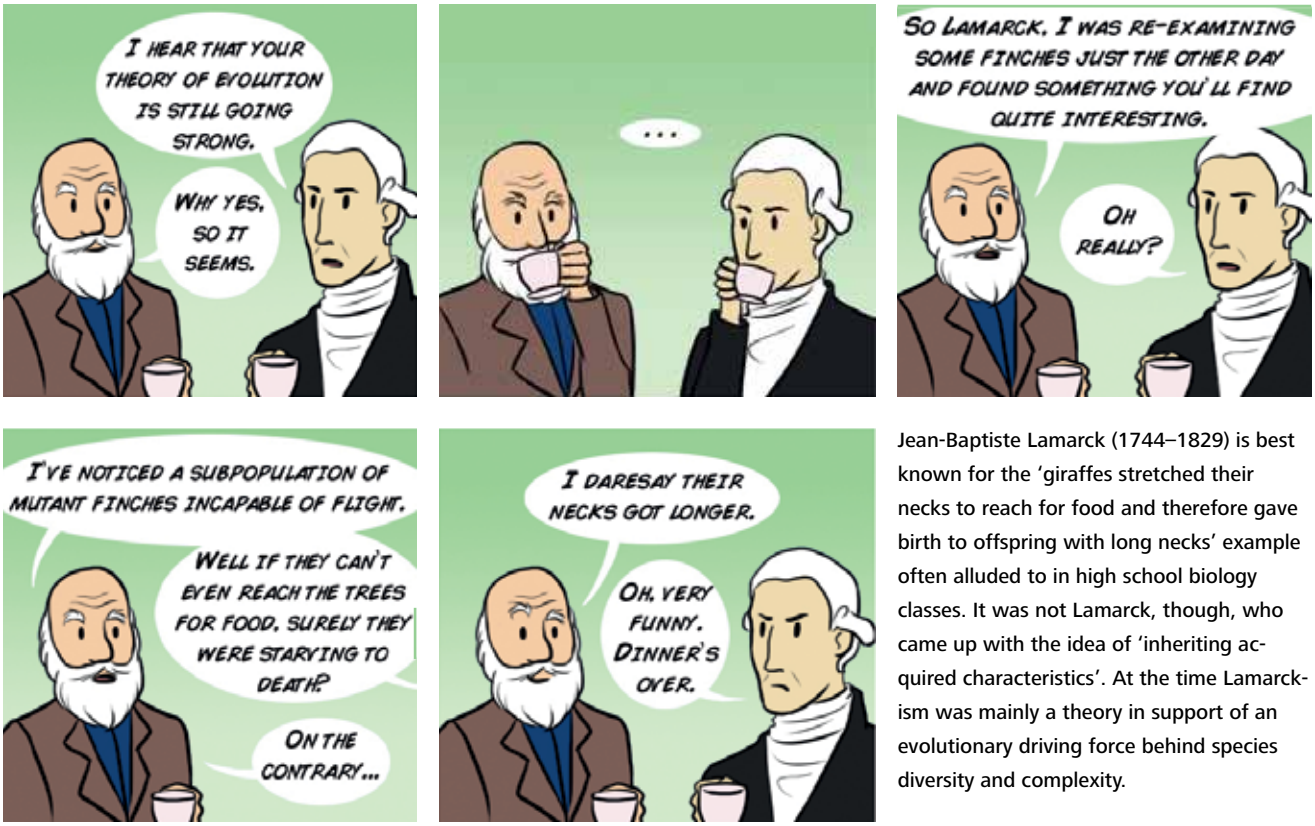
For almost two centuries the consensus in biology was that Charles Darwin was correct in his suggestion that nature selects the best-adapted individuals based on new traits that arise spontaneously. At the same time, no one doubted the theory proposed by Augustinian friar Gregor Mendel, who said that such traits were inherited according to strict innate patterns. And of course there were James Watson, Francis Crick and Rosalind Franklin, who resolved the structure of DNA – the substrate of inheritance that beautifully explains and unifies the observations of countless experiments.

None of these giants of biology, however, could have explained what happened to the children who were exposed to famine in the Dutch Hunger Winter of 1944/45 while still in the womb. While the Netherlands was under German occupation, food rationing cut daily energy intake to less than 1,000 kcal per person in Amsterdam and to 580 kcal in the west of the country by the end of February 1945. During that time, something particular happened to pregnant women and their susceptible fetuses. The babies were born into a free society that soon started to prosper, with hunger mostly unknown after the end of the war. Yet they grew up to be more susceptible to diabetes, obesity, cardiovascular disease, microalbuminuria and a host of other health problems compared with children whose mothers had not suffered through the famine.

As one would expect, the 'hunger children' were underweight at birth and smaller than those born before or after the famine. Unexpectedly, though, that effect carried over to the next generation, with the grandchildren of the starved mothers also significantly smaller than average. Transgenerational effects of environmental factors were also seen in the Swedish municipality of Överkalix. Using historical records of harvests and food prices from 1890 to 1955 and comparing them with clinical records, scientists were able to find sex-specific correlations between food supply and mortality (mainly through cardiovascular risks) that extended from grandparents to their grandchildren.

Superficially, this sounds like echoes of Lamarck's theory of the inheritance of acquired traits (see box), but what are the mechanisms behind it? Searching for biological correlates to these →

Photo: beyond/Corbis



Jean-Baptiste Lamarck (1744–1829) is best known for the 'giraffes stretched their necks to reach for food and therefore gave birth to offspring with long necks' example often alluded to in high school biology classes. It was not Lamarck, though, who came up with the idea of 'inheriting acquired characteristics'. At the time Lamarckism was mainly a theory in support of an evolutionary driving force behind species diversity and complexity.

phenomena, Bastian Heijmans from Leiden University Medical Center and colleagues found that the intrauterine deprivation during the Dutch Hunger Winter had left its mark on at least one specific metabolic gene: insulin-like growth factor 2 (*IGF2*), which is key for human growth and development. Heijmans studied 60 individuals who were conceived during the famine and compared them with their same-sex siblings to achieve partial genetic matching. After six decades, Heijmans found, individuals whose parents were malnourished around the time of their conception had significantly fewer methyl groups attached to specific cytosine-nucleotides in the so-called differentially methylated region (DMR) of *IGF2* at four out of five loci. Children who were exposed to famine only late in gestation did not show such a difference. 'Our study provides the first evidence that transient environmental conditions early in human gestation can be recorded as persistent changes in epigenetic information,' Heijmans and his colleagues concluded, adding: 'Epigenetic marks may be particularly vulnerable during the very early stage of mammalian development, which is a crucial period for establishing and maintaining epigenetic marks.'

By now, the modification of histones (see box on page 12) and changes in DNA methylation patterns have been clearly established as the basis for epigenetic regulation. Methylation – in particular at cytosine nucleotides that directly precede guanine nucleotides (CpG sites) – generally serves to silence a gene by making it harder for transcription factors to bind at regulatory sequences and do their job of facilitating the transcription of genes into messenger RNA. Histones provide a higher level of regulation, as these proteins in concert with others assemble to serve as a scaffold for the DNA in a cell's nucleus. The resulting complex of histones, DNA and other proteins is called chromatin. Histones can be modified post-translationally at specific amino acids and these changes will result in the DNA being wrapped around the histones more tightly or more loosely, changing its accessibility to the transcriptional machinery of the cells.

Both types of modifications – at the DNA and at the histone level – can be preserved through cell divisions and inherited from one generation to the next. They thus provide a 'main switch' for adjusting our metabolism – and also our behaviour – to a rapidly changing environment, as Tracey L. Bale, professor of neuroscience in psychiatry at the University of Philadelphia, recently explained at a special lecture at the Society for Neuroscience meeting in San Diego. The purpose of it all? 'The problem with conventional genetics is: it's glacially slow.'

Although the activity of a gene can change quite fast in response to external cues, giving an organism the ability to digest different kinds of food or to fight a multitude of infections, preserving these 'presets' and passing them on to the next generation could be an evolutionary advantage, Bale suggests. And albeit

Illustration: Jenny Liu and Rui Shu, the Dartmouth Undergraduate Journal of Science

slower than a change in gene activity, an epigenetic modification is much faster than the 'conventional' response via spontaneous mutations.

While this idea may be hard to prove, numerous experiments, also presented at the Neuroscience meeting, actually did find preliminary evidence for the existence of 'presets' that reflect an individuals' past experiences. Yasmin Hurd from the Icahn School of Medicine at Mount Sinai Medical School in New York reported that the postmortem brains of long-term heroin abusers showed epigenetic changes in neuronal genes compared with non-abusers. From the same institution, well-known psychiatrist Professor Eric Nestler presented evidence that cocaine abuse changes chromatin in a repeatable, predictable way in mice. Yet another experiment – this one by Mathieu Wimmer from the University of Pennsylvania – found that male rats exposed to cocaine can pass epigenetic changes on to their male offspring, thereby altering the next generation's response to the drug.

Wherever scientists look, they seem to find new evidence of epigenetic phenomena being involved in the regulation of everyday biological processes. About half of our susceptibility to pain, for example, seems to be determined by classic genetic factors. But looking at 50 pairs of identical twins, Tim Spector and Jordana Bell from King's College London noted major differences in pain thresholds between siblings. These differences, they found, were associated with the methylation patterns of nine different genes. The well-known pain-related gene *TRPA1*, in particular, conferred a higher sensitivity to pain when it had fewer methyl-groups in its promoter region, and vice versa.

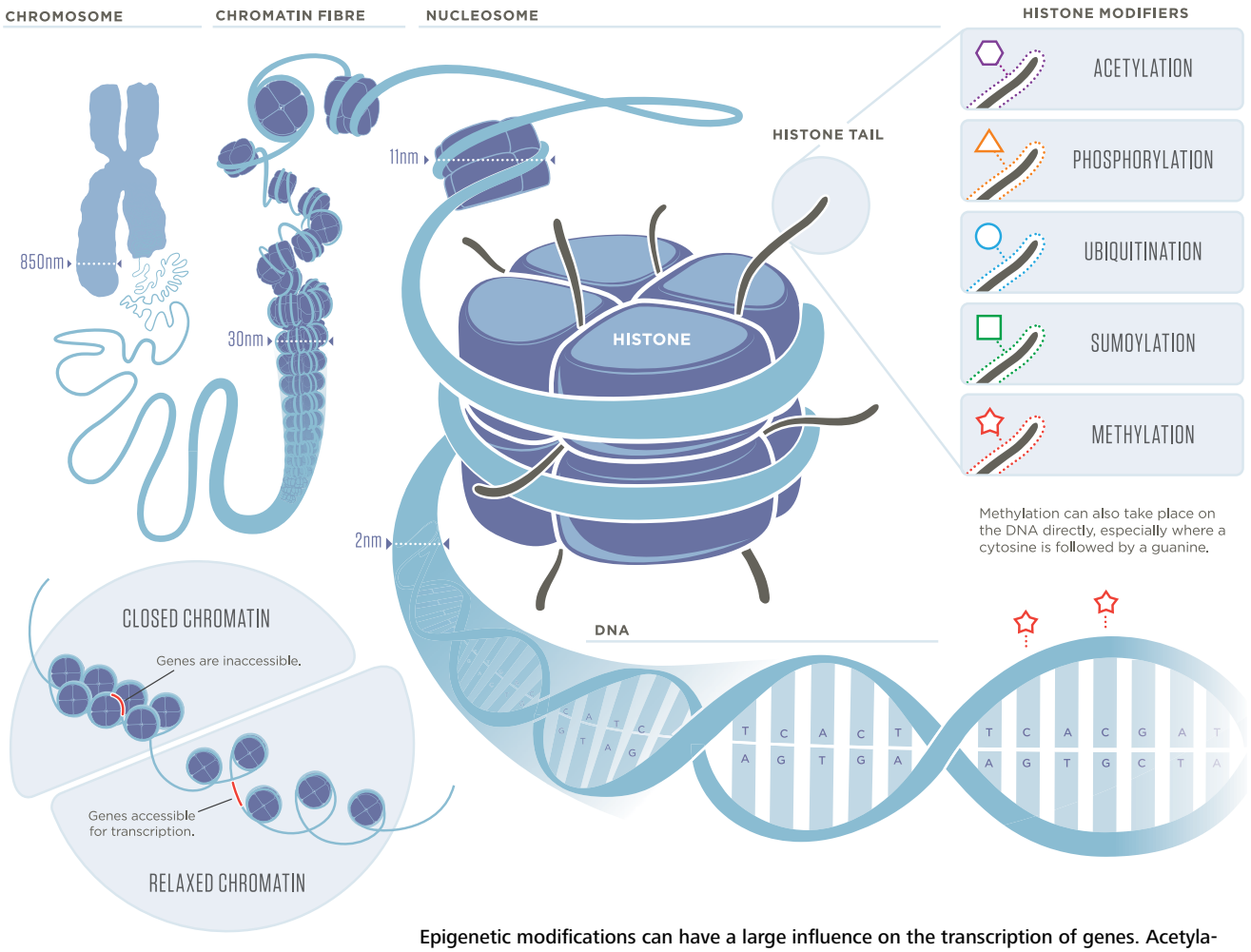
Through animal experiments – mostly on rats – the effects of particular environmental influences have been documented. For example, if mothers are prevented from licking and grooming their pups as usual, the wrappings of the DNA in the offspring are modified in a highly specific manner. The stress response of the pups is permanently altered, and when these animals reach adulthood, they are more anxious than rats who were raised normally. Again, these effects have been observed in the following generation, and the one after that as well.

Going from rats to humans, two pioneers in the field – Michael Meaney and Moshe Szyf from Montreal's McGill University – were able to show how abuse and early childhood trauma can exert their effects through epigenetic modifications. Comparing the brains of 13 suicide victims who had been abused in their childhood with brains of people who were killed in accidents, they found differences in the DNAs wrapping that were specific to the hippocampus. It is this very region of the brain that is crucial for storing and retrieving memories. More methyl groups were found in the brains of the abused children, thus shutting down the production of some key proteins that might be crucial for the normal development of the hippocampus. Despite the very small sample size, the results are interesting and suggestive.

How can this knowledge of epigenetic modifications be used to treat behavioural problems and diseases? To date, the most thoroughly investigated area is cancer. Both hypomethylation (in oncogenes) and hypermethylation (in tumour suppressor genes) have been linked to the disease. Independently of altered DNA methylation, the modification of histones H3 and H4 by hypoacetylation and hypermethylation has also been shown to play a role in oncogenesis, reports Professor Tony Kouzarides from the Gurdon Institute in Cambridge, UK.

Kouzarides, who in 2013 received the prestigious Heinrich Wieland Prize for his 'pioneering and dogma-changing discoveries in the field of epigenetics', has identified numerous proteins →

Wherever scientists look, they seem to find new evidence of epigenetic phenomena being involved in the regulation of everyday biological processes.



Epigenetic modifications can have a large influence on the transcription of genes. Acetylation/deacetylation for example changes the charge of histone tails and thus influences whether the DNA is in a relaxed or closed chromatin state.

involved in the modification of histones – the packing material of DNA – which regulate gene activity. Fifty years have passed since the discovery of acetylation as the first histone modification. Yet, new ones are still being found, as Kouzarides and his colleague Professor Thomas Jenuwein from the Max Planck Institute of Immunology and Epigenetics in Freiburg, Germany, recently reported at the First Barcelona Conference on Epigenetics and Cancer.

One of Kouzarides latest discoveries pertains to I-BET 151, a small molecule inhibitor that is of potential use for the treatment of leukaemia. In a mouse model of mixed lineage leukaemia (MLL), a hard-to-treat disease, the animals survived significantly longer when given I-BET 151, and lab-grown human leukaemia cells were also destroyed under the same treatment. MLL is the most common type of leukaemia in children under the age of two years and accounts for up to one in ten cases of leukaemia in adults. I-BET 151 sticks to specific parts of a class of proteins (BET) that would otherwise attach to certain histone modifications (known as acetylated lysines) and bring in yet another protein (MLL) that ultimately cranks up the production of cancerous blood cells.

Clinical trials with I-BET 151 have now been launched and Kouzarides is eagerly awaiting results. The treatment is currently being tested in acute myelocytic leukaemia (AML), a disorder that includes MLL leukaemia as well as a rare solid tumour (NUT midline carcinoma), caused by the translocation of a BET protein.

Four drugs targeting epigenetic changes – all anti-cancer drugs – are on the market already. Almost a dozen new ones are in various stages of clinical development by different pharmaceutical companies. 'Of course, it is never sure that any will be approved for use', says Kouzarides. 'But if all goes well some of them will be available in a couple of years. And of course: the potential is that other diseases besides cancer have an epigenetic component and therefore will also be treatable by epigenetic drugs,' he predicts.

Illustration: Richard E. Ballermann

THE **RED DRAGON'S** PHDS

By Yadan Ouyang

Only 36 years after opening up to the West, China is not only rapidly gaining on the nations leading the science race in the West, but passing them on some important indexes of research activity. Here we present an insider's look at research in China by science writer Yadan Ouyang.

Photo: Norio Sato/corbis

The scientific research landscape has transformed dramatically in China over the past 40 years. While there is much to validate the country's progress in building a modern research and education system from scratch, perhaps few could put it more intuitively than Lin Hongsheng, director of the oncology department at Guang'anmen Hospital in Beijing. 'In my day, we were sent to the countryside,' she recalls, referring to a policy initiated by Mao Zedong in the 1960s and 1970s that sent millions of Chinese urban students to villages for 're-education' through hard labour on farms. 'And now we send the students abroad.'

Each year, tens of thousands of Chinese students receive government grants to fly overseas and study at some of the world's best universities, while hundreds of thousands more are self-financing their education abroad as the country's economic boom has enabled many families to afford expensive tuitions. At home, annual enrollments in PhD programs across the country have grown more than tenfold in the past 20 years, to 69,000 in 2013. In comparison, in 1978, the first year China resumed graduate education after the Cultural Revolution, there were only 18 doctoral candidates in the entire country. Already in 2008, roughly 50,000 students graduated with doctorates in all disciplines each year, making China the largest producer of PhDs in the world. By comparison, in the same year, the number of PhDs granted was just shy of 49,000 in the US, 25,500 in Germany and 16,600 in the UK. Many people believe, however, there is still a yawning gap in quality between Chinese doctorates and their Western counterparts. Fair or not, such concerns have contributed to an increasingly prevalent phenomenon: a doctoral degree obtained abroad has become a must for many academic positions at the country's top universities.

But many students who have completed their degrees abroad – or have been 'gilded', as it is called in Chinese – never return. According to surveys, for every 10 students who left in the past few decades, only four have returned. To reverse the brain drain of scientific minds, over the past 20 years the government has taken a series of policy initiatives to lure scientists and experts back by offering them tenured positions, research funds, labs and lump-sum bonuses typically of at least one million yuan (or US$160,000) per person. Similar programs have also been set up specially for young scientists.

Those efforts are all part of China's ambitious goal of attaining the status of a world power in science and technology. By some measures, it seems underway. In 2012, China devoted 1.98% of its GDP to research and development, topping the European Union by a narrow edge, according to estimates by the Organization for Economic Co-operation and Development. China's R&D spending leapt from $10.8 billion to $168 billion between 2000 and 2012, but to put these figures into perspective, it is still about 60% lower than that of the United States, the world's biggest R&D spender. In addition, the soaring growth of China's R&D expenditure has been largely fueled by increasing investment in product development, which accounted for 83.9% of the total expenditure. Meanwhile, the share of R&D expenditure allocated to basic research actually dropped from 5.96% in 2004 to 4.84% in 2012. In contrast, world leaders in science typically spend 15% to 20% on basic research.

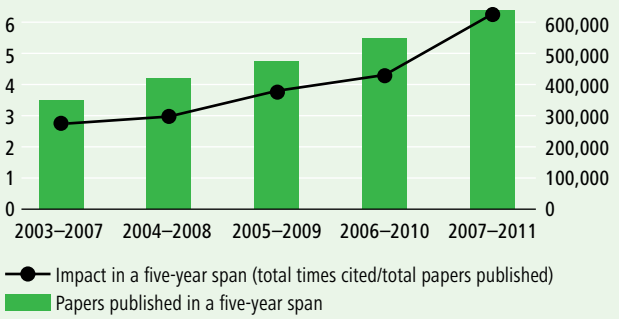
In an interview with Science last year, Yang Wei, the head of the National Natural Science Foundation of China (NSFC), pointed out that even though the foundation expected a double-digit rate of budget growth for the next five years, the size of its budget still has a long way to go to catch up with funding levels in the US. Modelled on the US National Science Foundation, the NSFC disbursed a total of $3.9 billion in 2012 in peer-reviewed grants to support basic research, young scientists and other research activities. In the same year, 38.6% of the funds of its largest category of general research grants went to finance research in medicine and life sciences, with average funding of approximately $115,000 per project. In the absence of a Chinese equivalent of the US National Institutes of Health (NIH), grants for life-science research take up a third of the foundation's total budget, according to Yang. If this is what China has to compete with the NIH, which enjoys an annual budget of $31 billion, the gap is immense.

While funding opportunities are provided by government agencies across the country, the national R&D programmes, which are managed by the Ministry of Science and Technology (MOST), are among the largest. The National Programme for Key Basic R&D (also known as the '973 Programme'), for instance, funded 191 research projects in 2011 with average funding of $3.85 million for each project, and at least 20 of those projects were devoted to biomedical research. But despite their relatively large size, the distribution of such grants managed by bureaucrats is often as opaque as the rest of the bureaucracy.

'The grants managed by MOST are in fact in a black box,' says Cong Cao at the University of Nottingham, an expert on China's science policy. No official records have been made public of who the recipients have been and how much money they have received. 'Nobody knows how the ministry has spent the money.' Such systematic loopholes have left room for misconduct. It is

CHINA IN THE SCIENCE CITATION INDEX

From 2003 to 2011, the impact of Chinese papers, measured in five-year spans, has more than doubled. On average, a Chinese paper was cited 6.2 times in 2011.



Source: China Statistical Yearbook on Science and Technology 2013

thus not surprising that more than 50 science bureaucrats in the southern province of Guangdong have been caught up in a corruption investigation last year for allegedly embezzling millions of dollars from government R&D funds. Given the central government's determination to root out corruption, Cao believes there will be reforms of how research grants are managed and distributed, and hopefully soon.

This research culture, ironically characterized by lack of respect for research itself, has prompted some scientists to speak out. In an editorial published in *Science* in 2010, two eminent Chinese biologists, Yi Rao of Peking University and Yigong Shi of Tsinghua University, offered sharp criticism of the system of allocating research grants, which they believe is smothering innovation. 'To obtain major grants in China, it is an open secret that doing good research is not as important as schmoozing with powerful bureaucrats and their favorite experts,' they wrote. As a result, 'a significant proportion of researchers' spend so much time on networking that they can hardly be found in their own labs.

SCIENCE IN SINGAPORE: PERSONAL IMPRESSIONS FROM BIF FELLOWS

Singapore, a teeming city-state in which 75% of the population is of Chinese origin, is well on its way to becoming a hub of science in Asia. Two of our alumni, Heike Wollmann, 34, and Peter Dröge, 57, have been living and working in this fascinating Asian country for several years.

Photo: Heike Wollmann

HEIKE WOLLMANN

Heike pursued her PhD in Tübingen in the lab of Detlef Weigel. She was a BIF fellow from 2006 to 2007.

1. How long have you been working in Asia?

I moved to Singapore in March 2009.

2. Where and in what positions have you worked?

I joined Temasek Lifesciences Laboratory (TLL) as a postdoc to pursue my interest in genome-wide epigenetic regulatory processes. I recently moved to the Genome Institute of Singapore (GIS) to expand my expertise in large-scale genomics and transcriptome profiling.

3. Why did you go to Singapore?

Singapore has set itself a mission to establish scientific excellence and has undertaken tremendous investments in infrastructure, attracting internationally renowned scientists and offering fantastic career opportunities for young researchers. On a personal level, I was seeking international experience after my PhD in Germany – in Singapore I was able to pursue both my primary research interests and have the adventure of living in Southeast Asia.

4. What was your greatest change when you went to Singapore?

Moving to Singapore is probably not much different from moving to any Western metropolis. Naturally, there are a lot of changes both at work and in day-to-day life. While I would count most of my new experiences as very rewarding, settling in can be a little bit frustrating. Housing prices are sky-high and the market is not tenant-friendly, but with patience and a bit of luck these problems can be overcome.

5. What do you miss most?

Obviously, I don't see my family and friends at home as often as I'd like, but after moving to Singapore about five years ago, I am willing to stay for another five! Living in Singapore and travelling in Southeast Asia are wonderful. I have spent most of my vacations so far diving on the great reefs of the Coral Triangle.

6. What is your advice to BIF fellows wishing to work in Asia?

If you feel the urge to experience life and work in Asia, give it a shot! I never looked back after moving to Singapore and none of my expat friends and colleagues regret coming here. Nevertheless, it is a good idea to visit first to make sure reality meets your expectations.

7. What fascinates you most about Singapore, outside the work environment?

In Singapore you experience the contrast between tradition and modern life like nowhere else. While the city is evolving at tremendous speed, tradition plays an important role in everyday life. The multicultural environment allows glimpses into a great variety of religions, foods and festivities.

PETER DRÖGE

Peter pursued his PhD in Konstanz in the lab of Prof. Knippers. He was a BIF fellow from 1986 to 1987.

1. How long have you been working in Asia?
I came to Singapore in 2002.

2. Where and in what positions have you worked?
I am a tenured professor in the School of Biological Sciences, Nanyang Technological University, Singapore

3. Why did you go to Singapore?
I was offered the challenge of building a faculty of life sciences from scratch. We started out with a faculty staff of six and now have more than 60. It also meant the chance to do research with human embryonic stem cells in a more vibrant research environment and with governmental support.

4. What was your greatest change when you went to Singapore?
I did not encounter any real problems.

5. What do you miss most?
I miss the different seasons.

6. What is your advice to BIF fellows wishing to work in Asia?
To embrace it as a unique opportunity. It is the fastest-growing region in the world and you should be prepared to work harder than ever before.

7. What fascinates you most about Singapore, outside the work environment?
The variety of great food.

While it is easy to point fingers at individual researchers for losing integrity, many scientists believe the system provided strong incentives for such behaviours. After the country opened up economically to the rest of the world in the late 1970s, its science system began to gradually move from a centrally planned, Soviet-inspired model to a competitive, market-oriented system. Now most scientific research in China is funded by government grants and industry. And because researchers, especially junior ones, are generally low-paid, research funding often needs to subsidize their meager salaries. Those without sufficient funding from government may have to take on more projects for industry.

Regardless of what work has been done with the money, compared to industry projects, a government grant usually comes with a sense of academic superiority. Even at institutions where most of their research money comes from corporations, government projects still matter most when it comes to how researchers are evaluated. The bias is also displayed in the academic jargon used to describe how research is funded: 'vertical' refers to government funds, while 'horizontal' means the money is from corporations or private non-profit organizations. Similarly, a grant from the central government carries more weight than a grant from a provincial one, revealing traces of the hierarchical Soviet-type scientific system that China has never completely broken away from.

Combined with an especially stressful 'publish or perish' culture, the quality of research has suffered from 'an environment that is utilitarian and impetuous', says Bingqi Xiong of the 21st Century Education Research Institute. Scholars often are not judged by the quality of their research but the quantity of it. Publications in renowned international journals such as those included in the Science Citation Index (SCI) have become one of the most important criteria for evaluating candidates for doctorates, scholarships, promotions and bonuses. An investigative report published in *Science* in November discovered a lucrative market in which shady Chinese agencies advertised SCI credits for sale. Co-first authorship on a paper that has already been accepted by an SCI journal is priced at $14,800.

In fairness, the quality of research by Chinese scientists has improved significantly over the years, though not as quickly as the quantity has increased. One indicator is the output of research papers. According to the Institute of Scientific and Technical Information of China, the country's share of research articles published in SCI journals has grown continuously to 9.5% in 2011, making the country the second-largest producer of papers, behind the US. From 2002 to 2012, more than one million SCI papers by Chinese researchers were published; however, on average each Chinese paper was cited only 6.5 times by others, which ranks the country fourteenth in the world. In comparison, an average American paper was cited 15.9 times over the same time period.

Nevertheless, China leaders seem eager to have a homegrown Nobel laureate, as no Chinese-born scientist has ever received a Nobel Prize for research conducted at home. In 2011, the announcement of the Lasker Foundation's first award to a Chinese scientist working on the mainland made waves in China's science circles. Some believe a Nobel Prize is near. But not everyone is so optimistic. Yi Rao of Peking University suggests that at least in biology, China's place in the world is not even where Japan was 30 years ago. To speed up and truly become a scientific powerhouse, China must overhaul the research system. Otherwise, Rao argues, 'not only does it waste grant money, but it leads young people astray'.

Photo: Peter Dröge

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 that aim to push the boundaries of our knowledge of the fundamental phenomena of human life.

INSIGHTS INTO THE EPIGENETIC REGULATION OF *PLASMODIUM FALCIPARUM* VIRULENCE GENES

cf. BIF FUTURA, VOL. 25 | 3.2010

NICOLAS BRANCUCCI
Discipline: Infection Biologist, MSc
Institute: Swiss Tropical and Public Health Institute, Basel, Switzerland
Supervisor: Prof. Till Voss

Plasmodium falciparum is responsible for the majority of more than 600,000 malaria deaths each year, which places a major health burden on the developing world. After an infected mosquito vector ingests blood, injected parasites replicate asexually within the human host. The intra-erythrocytic developmental cycle (IDC) causes the rupture of infected cells and the flu-like symptoms of malaria. Continuous parasite proliferation during this stage of infection also delivers a constant supply of sexual parasite forms that are essential for malaria transmission. During the IDC, variants of *P. falciparum* erythrocyte membrane protein 1 (EMP1) are exported to the surface of infected cells, causing the cells to sequester from the blood stream. This phenomenon is closely linked to severe disease and chronic infection. Switches in mutually exclusive activity of the EMP1-encoding *var* genes result in antigenic variation and allow the parasite to evade the host's immune system. The aim of my PhD studies was to understand the mechanisms used by the parasite to vary virulence gene expression. Using a promoter deletion strategy, I identified a *cis*-acting DNA-protein interaction that is essential for mutually exclusive *var* gene activity. By conditionally depleting *P. falciparum* heterochromatin protein 1 (HP1), which is conserved in eukaryotes and involved in heterochromatin formation and gene silencing, I revealed that this epigenetic regulator is required to keep inactive *var* genes in their repressed state. I found that HP1 also balances mitotic proliferation and the sexual conversion of parasites during the IDC by regulating the bi-stable expression of a phylum-specific transcription factor. My results reveal that *P. falciparum* exploits a common regulatory strategy in the epigenetic control of antigenic variation and sexual differentiation. This finding opens up new possibilities for future malaria intervention strategies.

PUBLICATIONS

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* (In press)

Brancucci NMB, Witmer K, Schmid CD, Flueck C, Voss TS (2012) Identification of a *cis*-acting DNA-protein interaction implicated in singular *var* gene choice in *Plasmodium falciparum*. *Cell Microbiol* **14:** 1836–1848

INVESTIGATION OF THE ROLE AND REGULATION OF MODIFIED DNA AND RNA NUCLEOSIDES

cf. BIF FUTURA, VOL. 25 | 3.2010

CATERINA BRANDMAYR
Discipline: Biochemist, MChem
Institute: Ludwig Maximilians University, Munich, Germany
Supervisor: Prof. Thomas Carell

Modified nucleosides are abundant in DNA and RNA. In mammals, methylcytosine (mC) is responsible for epigenetic regulation of gene expression. The mechanism of methylation that leads to gene silencing is well understood, but gene re-activation by DNA demethylation remains enigmatic. The role of the oxidized cytosine derivatives is also largely unknown. By contrast, modified transfer RNA (tRNA) nucleosides are known to modulate codon–anticodon interactions. However, despite extensive knowledge about the role and biosynthesis of specific tRNA modifications, little is known about their systemic behaviour. My PhD work aimed to elucidate putative pathways for the removal of mC in genomic DNA as well as to investigate the role and distribution of tRNA modifications in mammalian tissues. Using high-resolution mass spectrometry, I discovered a role for formylcytosine and carboxylcytosine in replication-coupled DNA demethylation but could not confirm the occurrence of demethylation via cleavage of the carbon-carbon bond at the cytosine C5 position. Furthermore, I showed that deamination of hydroxymethylcytosine to hydroxymethyluracil (hmU) in mouse embryonic stem cells has only a minor role in demethylation. Instead, steady-state levels of hmU result from Tet enzyme-dependent oxidation of thymine, pointing to thymine as a novel substrate for this class of DNA-modifying enzymes. Finally, I found that tissue-specific variations in the level of modified tRNA nucleosides in mammals correlated with *in-vitro* protein synthesis rates. My findings reveal that such variation in modification content may be regulated to accommodate for tissue-specific translational needs.

PUBLICATIONS

Pfaffeneder T, Spada F, Wagner M, Brandmayr C, Laube S, Eisen D *et al* (2014) Tet oxidizes thymine to 5-hydroxymethyluracil in mouse embryonic stem cell DNA. *Nat Chem Biol* (In press)

Steigenberger B, Schiesser S, Hackner B, Brandmayr C, Laube SK, Steinbacher J *et al* (2013) Synthesis of 5-hydroxymethyl-, 5-formyl-, and 5-carboxycytidine-triphosphates and their incorporation into oligonucleotides by polymerase chain reaction. *Org Lett* **15:** 366–369

Brandmayr C, Wagner M, Bruckl T, Globisch D, Pearson D, Kneuttinger AC *et al* (2012) Isotope-based analysis of modified tRNA nucleosides correlates modification density with translational efficiency. *Angew Chem Int Ed* **51:** 11162–11165

CONDENSIN AIDS SISTER CHROMATID DECATENATION BY TOPOISOMERASE II

cf. BIF FUTURA, VOL. 25 | 2.2010

ADRIAN CHARBIN
Discipline: Molecular Biologist, BA (Hons)
Institute: London Research Institute, Cancer Research UK, London, UK
Supervisor: Dr Frank Uhlmann

Condensin is a key determinant of chromosome architecture during mitosis. Although best known for its role in the compaction of DNA to form chromosomes, this large protein complex is also required to resolve sister chromatid linkages during chromosome segregation in anaphase. The separation of sister chromatids aids the resolution of the physically entangled, or catenated, DNA produced in S-phase. Complete resolution of this DNA requires condensin, a dependency that becomes more pronounced with increasing chromosome size. Condensin interacts directly with topoisomerase II (topo II), the main enzyme responsible for separating the topological links formed between DNA replication products after their synthesis. Cells harbouring defective condensin or inactive topo II are characterized by persistent linkages between sister chromatids, producing characteristic structures during anaphase called chromosome bridges. How condensin resolves sister chromatids, and the nature of these bridges, are not well understood. The goal of my PhD project was to understand how condensin promotes topo II's ability to resolve the catenanes holding the sister chromatids together. I developed an assay to measure the catenation status of minichromosomes that I had selectively purified from specific stages of the *Saccharomyces cerevisiae* cell cycle. Using gel electrophoresis and Southern blotting, I observed the formation and resolution of catenated DNA at different time points. By repeating this process in yeast cells in which condensin and topo II were mutated, I could quantitatively measure condensin's contribution to catenane resolution. Using purified yeast condensin and topo II, I showed that condensin stimulates the ability of topo II to decatenate DNA *in vitro*. My work explored how topo II inactivation can lead to DNA damage and malignancies, which has implications for the use of topo II inhibitors in cancer treatment. Perhaps through selectively targeting proteins that interact with topo II, less harmful oncolytic agents can be developed.

PUBLICATIONS

Charbin A, Bouchoux C, Uhlmann F (2013) Condensin aids sister chromatid decatenation by topoisomerase II. *Nucleic Acids Res* **42:** 340–348

O'Reilly N, Charbin A, Lopez-Serra L, Uhlmann F (2012) Facile synthesis of budding yeast a-factor and its use to synchronize cells of α mating type. *Yeast* **29:** 233–240

EVOLUTION AND FUNCTION OF THE CHEMOSENSORY IONOTROPIC RECEPTORS IN *DROSOPHILA*

cf. BIF FUTURA, VOL. 25 | 3.2010

VINCENT CROSET
Discipline: Biologist, MSc
Institute: Center for Integrative Genomics (CIG), University of Lausanne, Lausanne, Switzerland
Supervisor: Prof. Richard Benton

Organisms use chemical sensing to find food, recognize other members of their species and avoid toxins or predators. Insects have 3 types of chemosensory receptor: odorant receptors (ORs), which are found in the antennae and detect volatile compounds; gustatory receptors (GRs), which are present in taste organs and detect solid or liquid compounds; and ionotropic receptors (IRs), some of which are involved in olfactory sensing. Originally discovered in the fruit fly, *Drosophila melanogaster*, IRs are not related to ORs or GRs and their origin remains unclear. The goals of my PhD were to understand how IRs have evolved and to test whether non-olfactory IRs could function as taste sensors. Using a bioinformatics screen, I found IRs in all sequenced species of the protostome clade (which includes most invertebrates, such as arthropods, nematodes, molluscs and annelids). My results suggest that IRs emerged in their common ancestor ~540 million years ago and are thus one of the most ancient families of chemoreceptors. IRs involved in olfaction are generally conserved amongst insects, whereas other IRs are more species-specific. I used transgenic reporters to map the expression of all 66 IRs in the fruit fly and found that 39 of them are expressed in taste neurons, suggesting that they function as taste receptors. By using a fluorescent calcium sensor to measure the response of IR-expressing neurons to various potential tastants *in vivo*, I identified a subset that specifically detects a group of L-amino acids. The identification of neurons that can sense amino acids is an important step in the study of the mechanisms of feeding behaviour. This in turn could provide insights into the treatment of metabolic diseases such as obesity or diabetes. More generally, my results shed light on how sensory systems evolve, thereby enabling species to adapt to their environments.

PUBLICATIONS

Rytz R, Croset V, Benton R (2013) Ionotropic receptors (IRs): chemosensory ionotropic glutamate receptors in *Drosophila* and beyond. Insect *Biochem Mol Biol* **43:** 888–897

Croset V, Rytz R, Cummins SF, Budd A, Brawand D, Kaessmann H *et al* (2010) Ancient protostome origin of chemosensory ionotropic glutamate receptors and the evolution of insect taste and olfaction. *PLoS Genet* **6:** e1001064

CONTROL OF THE MITOTIC SPINDLE BY DYNEIN LIGHT CHAIN 1 (DYNLL1) COMPLEXES

cf. BIF FUTURA, VOL. 26 | 1.2011

ANJA DUNSCH
Discipline: Biochemist, Diploma
Institute: University of Oxford, Oxford, UK
Supervisor: Prof. Francis Barr

Mitosis ensures that the genetic material of a cell is duplicated and faithfully distributed by the mitotic spindle into 2 daughter cells. The goal of my PhD was to analyse how the motor protein dynein, which is found at the spindle and forms a cap at the cell cortex, contributes to the formation and orientation of the spindle by assembling discrete subcomplexes. I used mass spectrometry of complexes isolated from human cells to show that dynein light chain 1 (DYNLL1) interacts directly with 2 complexes: the astrin-kinastrin complex, which is localized to the kinetochore, a protein structure required for chromosome attachment to the spindle; and a spindle microtubule-associated complex formed by 2 poorly characterized proteins known as CHICA and HMMR. I found that the previously unknown protein kinastrin is the major interactor of the spindle-localized protein astrin in mitotic cells and is required for astrin targeting to microtubule plus ends. Fixed cell microscopy revealed that cells overexpressing or depleted of kinastrin mislocalize astrin. Depletion of the astrin-kinastrin complex causes the loss of normal spindle architecture and sister chromatid cohesion before anaphase onset. Using immunoprecipitation and microtubule binding assays, I showed that CHICA and HMMR interact with each other and target to the spindle and that CHICA interacts with DYNLL1. Fixed and live cell microscopy revealed that depletion of DYNLL1, CHICA or HMMR causes a slight increase in the proportion of cells undergoing mitosis but has little effect on spindle formation. However, this depletion causes the loss of the asymmetric distribution of cortical dynein and the failure of the spindle to orient correctly in relation to the cell culture surface. My results shed new light on the roles of these complexes and add to our understanding of the regulation of symmetric cell division.

PUBLICATIONS

Dunsch AK, Hammond D, Lloyd J, Schermelleh L, Gruneberg U, Barr F (2012) Dynein light chain 1 and a spindle-associated adaptor promote dynein asymmetry and spindle orientation. *J Cell Biol* **198:** 1039–1054

Dunsch AK, Linnane E, Barr F, Gruneberg U (2011) The astrin-kinastrin/SKAP complex localizes to microtubule plus ends and facilitates chromosome alignment. *J Cell Biol* **192:** 959–968

ROLE OF THE IMMUNORECEPTOR NKG2D IN iNKT CELL-MEDIATED IMMUNE RESPONSES

cf. BIF FUTURA, VOL. 25 | 3.2010

STEPHANIE GANAL
Discipline: Molecular Medic, Diploma
Institute: Institute for Medical Microbiology and Hygiene, University of Freiburg, Freiburg, Germany
Supervisor: Prof. Andreas Diefenbach

Natural killer T (NKT) cells are a subset of T cells that express both a T cell receptor (TCR) and markers associated with NK cells. NKT cells that bear an invariant TCR (so-called iNKT cells) recognize glycosphingolipid antigens presented on cluster of differentiation 1 (CD1d), a non-classical major histocompatibility complex molecule. iNKT cells are activated to clear certain bacterial infections and in response to autoimmune diseases and tumour rejection. In adult mice, about half of all iNKT cells express the activating immunoreceptor NKG2D (natural killer group 2, member D). In humans, the extent of NKG2D expression on iNKT cells is more variable. NKG2D binds self molecules that are upregulated upon cellular stress caused by events such as viral and bacterial infection, tumour transformation or radiation. Although NKG2D is known to have a co-stimulatory role in other immune cell populations, its function in iNKT cell biology remains elusive. The goal of my PhD project was to uncover the signals that induce NKG2D upregulation on a subset of murine iNKT cells and to evaluate the function of this receptor during iNKT cell activation. I used intrathymic fluorescein isothiocyanate labelling to show that the majority of mouse iNKT cells are $NKG2D^-$ when they first exit the thymus. After adoptive cell transfer of mature hepatic $NKG2D^-$ iNKT cells into a congenic mouse, iNKT cells upregulated NKG2D in a time- and CD1d-dependent manner. Germ-free mice had significantly fewer $NKG2D^+$ iNKT cells, which suggests that the indigenous microbiota contribute to NKG2D upregulation. Using an *in-vitro* iNKT cell stimulation assay to trigger NKG2D increased iNKT cell activation when TCR-mediated signals (such as plate-bound antibodies against the TCR or iNKT cell agonists) were limiting. I also showed that blocking NKG2D during concanavalin A-induced hepatitis, an experimental model for autoimmune hepatitis that is strictly dependent on iNKT cell activation, ameliorated the disease. My work has revealed for the first time that NKG2D-expressing iNKT cells represent a previously activated subset of iNKT cells. This suggests that interference with NKG2D signalling could comprise a new therapeutic target in iNKT cell-mediated diseases.

PUBLICATIONS

The results of this project have not yet been published.

NEW ROLES FOR SUMO-TARGETED UBIQUITIN LIGASES IN GENOME STABILITY

cf. BIF FUTURA, VOL. 24 | 1.2009

CHRISTINE JOHANNA HEIDEKER
Discipline: Molecular Biologist, Diploma
Institute: The Scripps Research Institute, La Jolla, CA, USA
Supervisor: Dr Michael N. Boddy

Many cellular activities rely on the post-translational modification (PTM) of proteins. The covalent attachment of ubiquitin and small ubiquitin-like modifier (SUMO) proteins are common types of PTM that affect protein function. The conserved SUMO-targeted ubiquitin ligases (STUbLs) recognize sumoylated proteins and subsequently ubiquitinate them, thereby providing a functional link between these 2 PTMs. STUbLs are also known to be critical for genome stability. In my PhD studies, I investigated whether STUbLs are connected to the repair of DNA damage induced by topoisomerase 1 (Top1). Top1 breaks DNA strands to facilitate DNA unwinding. Broken strands that cannot be resealed result in mutations or cell death; Top1 inhibition is thus widely exploited in anticancer therapy. My work combined the fission yeast model system, DNA damage assays, site-directed mutagenesis and a novel chromatin immunoprecipitation technique involving an inducible Top1 expression system. I found that the fission yeast STUbL Slx8-Rfp prevents Top1-induced genome instability. This activity is independent of tyrosyl-DNA phosphodiesterase 1 (Tdp1), a known repair enzyme capable of removing Top1-induced lesions in DNA. My results suggest that Slx8-Rfp may act in a repair pathway with 2 other genome stability factors: non-structural maintenance of chromosomes element 2 (Nse2), a SUMO E3 ligase; and Rad60, which is functionally connected to the SUMO pathway. These 3 proteins facilitate the repair of Top1-induced DNA damage when the damage cannot be repaired by Tdp1. My work expands our current understanding of DNA repair and uncovered a new role for STUbLs in genome maintenance.

PUBLICATIONS

Nie M, Aslanian A, Prudden J, Heideker J, Vashisht AA, Wohlschlegel JA *et al* (2012) Dual recruitment of Cdc48 (p97)-Ufd1-Npl4 ubiquitin-selective segregase by small ubiquitin-like modifier protein (SUMO) and ubiquitin in SUMO-targeted ubiquitin ligase-mediated genome stability functions. *J Biol Chem* **287:** 29610–29619

Heideker J, Prudden J, Perry JJ, Tainer JA, Boddy MN (2011) SUMO-targeted ubiquitin ligase, Rad60, and Nse2 SUMO ligase suppress spontaneous Top1-mediated DNA damage and genome instability. *PLoS Genet* **7:** e1001320

Heideker J, Perry JJ, Boddy MN (2009) Genome stability roles of SUMO-targeted ubiquitin ligases. *DNA Repair (Amst)* **8:** 517–524

THE STRUCTURE AND ARCHITECTURE OF EISOSOMES

cf. BIF FUTURA, VOL. 23 | 2.2008

LENA KAROTKI
Discipline: Biologist, Diploma
Institute: Max Planck Institute of Biochemistry, Martinsried, Germany
Supervisor: Dr Tobias Walther

The spatial organization of membranes into domains that have distinct protein and lipid compositions is a fundamental feature of biological systems. In *Saccharomyces cerevisiae*, the lateral compartmentalization of the plasma membrane (PM) is partially mediated by huge, immobile protein complexes termed eisosomes, which are stably anchored underneath the PM at the cell cortex. They are distributed in a uniform punctate pattern and are mainly composed of 2 proteins, Pil1 and Lsp1. However, the molecular architecture of eisosomes and how they segregate proteins and lipids into distinct compartments were not known. To investigate eisosome-driven PM organization, the major goal of my PhD was to characterize Pil1 and Lsp1 at several levels of resolution. Using a combination of different biochemical and electron microscopy (EM) approaches, I showed that these proteins self-assemble into higher order structures, such as thin filaments and helices. Furthermore, both proteins directly bind membranes with lipid-binding specificity and deform them into long tubules. By fitting the crystal structure of a stable core domain of Lsp1 into 3D models of eisosome proteins bound to membranes, I unveiled how these proteins self-assemble and bind to membranes and pinpointed the amino acids that are essential for this process. Furthermore, I demonstrated that the EM-derived 3D structures of Pil1 and Lsp1 assemblies resemble eisosomes *in vivo*. Collating all the data from my studies, I developed a model that explains how eisosomes are molecularly constructed and how they organize the PM by self-assembly into a protein scaffold that directly binds and deforms membranes. My research will also increase our general understanding of self-assembly systems, particularly how they organize cellular structure and how they are used to regulate PM organization and functions such as endocytosis.

PUBLICATIONS

Karotki L, Huiskonen JT, Stefan JS, Ziolkowska NE, Roth R, Surma MA *et al* (2011) Eisosome Proteins Assemble into a Membrane Scaffold. *J Cell Biol* **195:** 889–902

Ziolkowska NE, Karotki L, Rehman M, Huiskonen JT, Walther TC (2011) Eisosome-driven plasma membrane organization is mediated by BAR domains. *Nat Struct Mol Biol* **18:** 854–856

Wang H, Kakaradov B, Collins SR, Karotki L, Fiedler D, Shales M *et al* (2009) A complex-based reconstruction of the *Saccharomyces cerevisiae* interactome. *Mol Cell Proteomics* **8:** 1361–1381

INVESTIGATING THE STRUCTURE AND FUNCTION OF RNA POLYMERASE II–BYE1 COMPLEXES

cf. BIF FUTURA, VOL. 26 | 1.2011

KERSTIN KINKELIN
Discipline: Biologist, Diploma
Institute: Gene Center, Ludwig-Maximilians University (LMU), Munich, Germany
Supervisor: Prof. Patrick Cramer

In order for RNA polymerase (Pol) II to catalyse the transcription of eukaryotic protein-coding genes, it must transiently associate with a range of transcription factors. Although genetic studies had linked Pol II to Bye1 (bypass of Ess1), a transcription factor found only in yeast, how Bye1 affects Pol II structure and function was not known. In my PhD project, I obtained crystal structures of 4 complexes of *Saccharomyces cerevisiae* Pol II, each bound by different Bye1 constructs. By combining X-ray crystallography, in-vitro RNA extension assays and transcription assays using yeast nuclear extracts and chromatin-free templates, I showed that Bye1 does not affect basic Pol II mechanisms such as nucleotide incorporation and backtracking. Furthermore, I used chromatin immunoprecipitation coupled to microarray analysis to demonstrate that Bye1 is present at all actively transcribed genes. Peptide microarrays revealed that Bye1 interacts generally with histone marks of active chromatin and binds specifically to trimethylated lysine 4 on histone 3, a histone mark found at all genes transcribed by Pol II. Using a synthetic lethality screen, I identified 2 genes, involved in transcription elongation and histone modification, that functionally interact with Bye1. I performed bioinformatics analyses to look for putative Bye1 homologues in higher eukaryotes and found another 2 human proteins known to be involved in cancer development. One of these, death inducer obliterator (Dido), specifically binds to histone marks in a similar way to Bye1. Based on these results, I speculate that Bye1 binds directly to Pol II during early transcription elongation and tethers surrounding histones that contain active marks of transcription. The point of this function could be to prevent histone loss when the polymerase passes through chromatin. My identification of putative human homologues of Bye1 will allow others to study their function in chromatin loss during transcription and might hint at the underlying mechanisms of their involvement in cancer development.

PUBLICATIONS

Kinkelin K, Wozniak GG, Rothbart SB, Lidschreiber M, Strahl BD, Cramer P (2013) Structures of RNA polymerase II complexes with Bye1, a chromatin-binding PHF3/DIDO homologue. *Proc Natl Acad Sci USA* **110:** 15277–15282

MOLECULAR BASIS FOR THE RECRUITMENT OF THE CHECKPOINT PROTEIN BUB1 TO KINETOCHORES

cf. BIF FUTURA, VOL. 25 | 3.2010

VERONICA KRENN
Discipline: Biotechnologist, MSc
Institute: Max Planck Institute for Molecular Physiology, Dortmund, Germany
Supervisor: Prof. Andrea Musacchio

The spindle assembly checkpoint (SAC) is a safety mechanism required for accurate chromosome segregation in eukaryotes. Defects in the SAC cause aneuploidy, a hallmark of cancer and several congenital diseases. The protein kinase Bub1, together with other SAC components, recognizes kinetochores of unaligned chromosomes and triggers the SAC response from these sites. The goal of my PhD studies was to unravel the molecular basis for the recruitment of Bub1 to kinetochores. By combining immunoprecipitation and localization studies of Bub1 domains in human cells, I identified a minimal kinetochore-targeting region. This region comprises the Bub3-binding domain, which allows Bub1 to interact with its partner Bub3, and an additional sequence of unknown function. Using immunofluorescence of tagged Bub1 fragments, I showed that this sequence promotes the co-recruitment of Bub1-Bub3 to unaligned kinetochores. Subsequent structural and biochemical studies revealed that the sequence also enables Bub3 to interact directly with Met-Glu-Leu-Thr (MELT) repeats, phosphorylated sequences located on a kinetochore protein called cancer susceptibility candidate 5 (CASC5). By expressing an engineered version of CASC5 in human cells, I proved that co-recruitment of Bub1-Bub3 to a single MELT repeat is sufficient for a SAC response. Using immunoprecipitation of truncated versions of Bub1 and CASC5, I also discovered that another domain of Bub1, the tetratricopeptide repeat, interacts with a motif in CASC5. This interaction enhances the recruitment of Bub1-Bub3 to the most N-terminal MELT repeat, thereby boosting SAC activity. My work paves the way for a molecular understanding of how SAC signalling is generated at unaligned kinetochores. This will help clarify the molecular processes through which eukaryotic cells faithfully segregate their genetic material.

PUBLICATIONS

Krenn V, Overlack K, Primorac I, Van Gerwen S, Musacchio A (2014) KI Motifs of Human Knl1 Enhance Assembly of Comprehensive Spindle Checkpoint Complexes around MELT Repeats. *Curr Biol* **24:** 29–39

Krenn V, Wehenkel A, Li X, Santaguida S, Musacchio A (2012) Structural analysis reveals features of the spindle checkpoint kinase Bub1-kinetochore subunit Knl1 interaction. *J Cell Biol* **196:** 451–467

CHARACTERIZATION OF A NOVEL PROTEIN INVOLVED IN OXIDATIVE STRESS RESISTANCE

cf. BIF FUTURA, VOL. 25 | 3.2010

YAN LE
Discipline: Biochemist, MSc
Institute: Chair in Biotechnology, Technische Universität München, Garching, Germany
Supervisor: Dr Jeannette Winter

Reactive oxygen species (ROS) – including superoxide, hydrogen peroxide and hydroxyl radicals – are generated as byproducts of the respiratory chain in aerobic organisms and as part of the immune response against invading bacteria. ROS can modify vital cellular components and cause severe cell damage. Cells have evolved various mechanisms that enable them to withstand elevated intracellular levels of ROS, or oxidative stress. The aim of my PhD project was to explore the existence of additional stress survival pathways in the model organism *Escherichia coli*. I used a genomic library screen to identify ROS resistance-conferring proteins and discovered a novel conserved protein, YifE, whose function and structure were unknown. By implementing a phenotypic screen in a strain lacking YifE, I found that the protein confers resistance not only to ROS but also to several ribosome-disrupting antibiotics such as tetracycline, chloramphenicol and spectinomycin. In addition, an analysis of cellular growth revealed that YifE is important even under non-stress conditions as cells lacking the protein grew much more slowly than wild-type cells. To determine its *in-vivo* function, I performed pull-down assays that showed that YifE binds to both 23S and 16S ribosomal RNAs and several ribosomal proteins. By then using sucrose gradient ultracentrifugation, I could demonstrate that it is able to associate with ribosomes and that this recruitment increases under stress conditions. Furthermore, ^{35}S-methionine incorporation assays revealed that YifE can increase translation efficiency under stress conditions. My results therefore suggest that YifE is a ribosome-related protein that promotes the relief of translation inhibition. Given that ROS can attack ribosomes and cause a translational pause, it is highly likely that YifE rescues the stalled ribosome by actively promoting ROS/antibiotic-impaired translation. It is well known that cells typically activate a ROS-specific transcription factor to diminish ROS-derived damage. Now, this study has uncovered another mechanism that cells use to withstand oxidative damage and the presence of antibiotics, and has shed some light on the potential crosstalk between the cellular response to both challenges.

PUBLICATIONS

The results of this project have not yet been published.

RHOMBOID-LIKE PROTEINS AND THEIR FUNCTIONS

cf. BIF FUTURA, VOL. 25 | 3.2010

CHRISTIAN LUGINSLAND
Discipline: Biochemist, MSc
Institute: Medical Research Council (MRC) Laboratory of Molecular Biology, Cambridge, UK
Supervisor: Prof. Matthew Freeman

The rhomboid-like superfamily of proteins comprises the derlins, the rhomboids and a third group called transmembrane (Tmem) 115. Derlins, Tmem115 and a subfamily of inactive rhomboids, called iRhoms, are catalytically inactive homologues of the rhomboid proteases. In *Drosophila* and mammalian cells, iRhoms regulate growth factor signalling by feeding ligands of the epidermal growth factor receptor pathway into endoplasmic reticulum-associated degradation (ERAD). The function of the highly conserved Tmem115 group remains elusive. The goals of my PhD project were to study iRhom function using a structure–function approach and to examine the role of Tmem115 proteins. I investigated mammalian Tmem115 in human tissue culture cells and its *Drosophila melanogaster* homologue, *CG9536*, in fly and tissue culture cells. To understand better the mechanism by which the iRhom rhomboid-5 drives growth factors into ERAD, I established a gene replacement approach in *D. melanogaster*. The system revealed the importance of the N-terminal and iRhom homology domains and 4 specific amino acids for rhomboid-5 function in ERAD. Furthermore, using 2 variants of wild-type rhomboid-5 tagged with endogenously expressed green fluorescent protein, I showed that rhomboid-5 is expressed not only in the central but also in most of the peripheral nervous system in *Drosophila* embryos. To elucidate the function of *CG9536*, I generated *Drosophila* mutants and determined the expression patterns of *CG9536* and Tmem115 in human tissue culture cell lines using immunofluorescence experiments. The life spans of *Drosophila CG9536* nulls were reduced by 26–36%. By contrast, overexpression of *CG9536* caused pupal lethality. In human cells, Tmem115 overexpression led to fragmentation of the Golgi apparatus. My findings present a first step towards a better understanding of the mechanism of action of iRhoms in *Drosophila* and might provide a foundation for further research in mammalian systems. These results also point to roles for Tmem115 as a Golgi-resident protein and as a regulator of the structure of the Golgi apparatus in mammalian cells. My work thus extends the biological roles of the rhomboid superfamily.

PUBLICATIONS

The results of this project have not yet been published.

INSIGHTS INTO THE DRIVING-ION RELEASE OF THE NEUROTRANSMITTER: SODIUM SYMPORTERS

cf. BIF FUTURA, VOL. 25 | 3.2010

LINA MALINAUSKAITE
Discipline: Molecular Biologist, MSc
Institute: Aarhus University, Aarhus, Denmark
Supervisor: Prof. Poul Nissen

Signalling between neurons in the brain is achieved by the release of neurotransmitters and terminated by the neurotransmitter: sodium symporters (NSS). They actively transport neurotransmitters across the presynaptic neuron plasma membrane by exploiting the energetically favourable Na^+ electrochemical gradient. Their structure–function relationship is of particular interest as the NSS family is involved in psychological and neurological disorders and is therefore the target for several therapeutic drugs including antidepressants and psychostimulants such as cocaine and amphetamines. These transporters act according to an alternating access mechanism in which the substrate-binding site is accessible only from 1 side of the membrane at a time (outward- and inward-open) with intermediate occluded states. Several crystal structures of a bacterial NSS homologue – the amino-acid transporter LeuT from *Aquifex aeolicus* – have been solved that represent outward-open, occluded outward-facing, and inward-open states. However, these structures do not provide any insight into how intracellular Na^+ release is coupled to the vectorial transport of the substrate. During my PhD project, I studied an alternative bacterial model of the NSS family: the multihydrophobic amino-acid transporter MhsT from *Bacillus halodurans*. Using X-ray crystallography, I obtained a structure of this protein with bound L-tryptophan and Na^+ ions in the presence of lipids that revealed an occluded inward-facing state, a previously unknown conformation for the NSS. This structure shows the beginning of solvation of the driving Na^+ ion before its release and the structural changes that switch the transporter from an outward- to inward-occluded state. We observed a unique feature – an unwinding of the cytoplasmic side of the fifth transmembrane helix – that opens a solvation and plausible release passage from the cytoplasm to the driving-ion binding site. Thus, this new structure of the NSS cycle provides novel insight into NSS function and how Na^+-dependent transporters operate, and brings us closer to a complete picture of their transport mechanism.

PUBLICATIONS

The results of this project have not yet been published.

CORRELATED PLASTICITY OF SYNAPTIC STRUCTURES DURING SYNAPTIC ENLARGEMENT

cf. BIF FUTURA, VOL. 25 | 1.2010

DANIEL MEYER
Discipline: Neurobiologist, MSc
Institute: Max Planck Institute of Neurobiology, Martinsried, Germany
Supervisor: Prof. Tobias Bonhoeffer

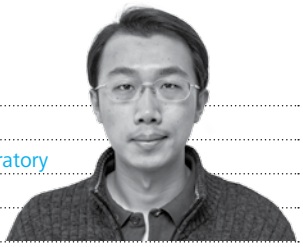
An important process underlying learning and memory is plasticity, or the modification of connections between synapses in the brain. Plasticity can occur in 2 ways: first, by remodelling synaptic connections, i.e. by the elimination of existing synapses and the generation of new ones; and second, by a change in the synaptic strength of synapses. This latter form of plasticity is specifically called "synaptic plasticity". Importantly, synaptic strength correlates with synaptic size. Most excitatory synapses consist of a postsynaptic compartment called the dendritic spine and a presynaptic compartment called the bouton. Both of these contain dense molecular structures that are important for the strength of synaptic transmission, namely the postsynaptic density (PSD) in the spine and the active zone in the bouton. Under naïve unstimulated conditions, there is a correlation between the sizes of these structures but it is not known whether or how this is maintained after synaptic plasticity. Using glutamate uncaging, which is expected to induce an increase in synaptic strength, I stimulated synapses in cultured hippocampal slices from rats, and could show that during the resulting spine enlargement, there is a coordinated change in spine, PSD and bouton size. 2-photon fluorescence imaging revealed increases in spine size as well as in the amount of the PSD marker proteins PSD-95 and Homer1c within 3 hours of plasticity induction. If the PSD proteins did not increase, the new spine volume did not stabilize. I also conducted an electron microscopy analysis of dendritic spines, which confirmed that the correlation between spine, PSD and bouton size is indeed maintained after stimulation. My results therefore support a model of plasticity in which the stabilization of synaptic changes requires a concomitant change in the size of all synaptic structures.

PUBLICATIONS

Meyer D, Scheuss V, Bonhoeffer T (2014) Balance and stability of synaptic structures during synaptic plasticity. *Neuron* **82:** 430–443

RECOMBINANT PRODUCTION OF HUMAN GENERAL TRANSCRIPTION FACTOR TFIID IN INSECT CELLS

cf. BIF FUTURA, VOL. 25 | 2.2010



YAN NIE
Discipline: Biophysicist, MSc
Institute: European Molecular Biology Laboratory (EMBL), Grenoble, France.
Supervisor: Dr Imre Berger

The transcription of eukaryotic Class II (protein-encoding) genes is initiated by the preinitiation complex (PIC), which contains RNA polymerase II and the general transcription factors (GTFs). The largest GTF, TFIID, plays a vital role in transcription initiation by recognizing promoters and recruiting the remaining PIC components. Human TFIID (hTFIID; ~1.5 MDa) comprises 14 subunits and is heterogeneous in its composition owing to, for example, cell type-specific isoforms of certain subunits. Its intracellular concentration is also low, making it very difficult to extract sufficient amounts of endogenous hTFIID with the required purity for high-resolution structural studies. Consequently, the resolution of the hTFIID cryo-electron microscopy (EM) model has been stalled at ~ 30 Å for years, and little is known about its supramolecular assembly *in vivo*. To address this bottleneck, I have used the MultiBac system to produce – for the first time to our knowledge – fully recombinant hTFIID in insect cells. Excitingly, both the quantity and quality of our recombinant hTFIID is superior to endogenously purified hTFIID samples. Furthermore, the recombinant hTFIID is active in an *in vitro* transcription assay and, using single-particle EM analysis, I have shown that it resembles the structure of native hTFIID. Therefore, my thesis work has set the stage for future high-resolution structural studies and for elucidating the function of individual subunits in the assembly and activity of hTFIID.

PUBLICATIONS

Nie Y, Bellon-Echeverria I, Trowitzsch S, Bieniossek C, Berger I (2014) Multiprotein Complex Production in Insect Cells by Using Polyproteins. *Methods Mol Biol* **1091:** 131–141

Haffke M, Viola C, Nie Y, Berger I (2013) Tandem Recombineering by SLIC Cloning and Cre-LoxP Fusion to Generate Multigene Expression Constructs for Protein Complex Research. *Methods Mol Biol* **1073:** 131–140

Trowitzsch S, Bieniossek C, Nie Y, Garzoni F, Berger I (2010) New baculovirus expression tools for recombinant protein complex production. *J Struct Biol* **172:** 45–54

ACTIVATION OF RECONSTITUTED PRE-REPLICATIVE COMPLEXES *IN VITRO*

cf. BIF FUTURA, VOL. 25 | 3.2010

KIN FAN ON
Discipline: Biochemist, MPhil
Institute: Clare Hall Laboratories, London Research Institute, Cancer Research UK, Potters Bar, UK
Supervisor: Dr John F. X. Diffley

Eukaryotic DNA replication is initiated from multiple replication origins in the genome. Each origin must fire only once per cell cycle to avoid genomic instability, which is a hallmark of cancer. Replication initiation is therefore separated into 2 biochemically discrete steps – origin licensing and origin firing – that are tightly coupled to the oscillation of cyclin-dependent kinase (CDK) activity during the cell cycle. Origin licensing involves the loading of an inactive double hexamer of the MCM2-7 helicase onto the double-stranded DNA to form the pre-replicative complex (pre-RC), which can only occur during the G1 stage of the cell cycle when CDK activity is low. Increases in CDK and Dbf4-dependent kinase (DDK) activity during S phase then activate the MCM helicase and DNA replication begins. However, little is known about this so-called origin firing step and the other factors involved. The aim of my PhD was to create an *in vitro* system in which replication initiation could be studied in detail. I partially reconstituted origin firing in *Saccharomyces cerevisiae* using pre-RCs assembled from purified proteins, purified DDK and an S-phase cell extract. I was able to show that DDK phosphorylation results in the recruitment of replication factors to the MCM helicase. Using mass spectrometry, I identified these proteins as replisome factors that had been previously isolated from replication forks *in vivo*. Importantly, the resultant MCM helicase supported semi-conservative DNA replication *in vitro*, indicating that active replisomes were assembled in the reaction. Our *in vitro* DNA replication system produced full-length, covalently closed DNA products and is thus sufficient for replication initiation, elongation and termination. The system that we have developed represents an important step forward in the complete reconstitution of DNA replication *in vitro* from purified proteins. I expect this will provide a powerful approach for studying this process and should help to increase our mechanistic understanding of DNA replication initiation.

PUBLICATIONS

On KF, Beuron F, Frith D, Snijders AP, Morris EP, Diffley JFX (2014) Prereplicative Complexes Assembled In Vitro Support Origin-Dependent and -Independent DNA Replication. *EMBO J* **33:** 605–620

SPIRE1 AND SPIRE2 CO-OPERATE WITH FORMIN-2 TO DRIVE ASYMMETRIC MAMMALIAN OOCYTE DIVISION

cf. BIF FUTURA, VOL. 25 | 3.2010

SYBILLE PFENDER
Discipline: Biochemist, MSc
Institute: Medical Research Council (MRC) Laboratory of Molecular Biology, Cambridge, UK
Supervisor: Dr Melina Schuh

Oocytes are large cells that are full of the messenger RNA and proteins required for embryo development. Before fertilization, oocytes must eliminate half of their chromosomes; the sperm contributes the other half of the complete set. To preserve most of its contents, an oocyte divides asymmetrically into a large egg and a small cell termed the polar body. Although the chromosomes are divided equally between the 2 cells, the egg receives most of the cytoplasmic contents. In mammals, the meiotic spindle initially forms close to the center of the oocyte. Because the spindle midzone determines the position of the cleavage plane, the spindle must first re-position itself to the oocyte surface before the polar body is extruded. Although spindle re-positioning and polar body extrusion are crucial steps for asymmetric oocyte division and thus fertility, little is known about their underlying mechanisms. Using RNA interference and quantitative high-resolution 4-dimensional imaging in live dividing mouse oocytes, I discovered that Spire-type actin nucleators are key factors involved in asymmetric oocyte division. First, I showed that Spire1 and Spire2 mediate spindle positioning by forming an actin network that serves as a substrate for spindle movement. Second, I showed that Spire1 and Spire2 drive polar body extrusion by promoting ingression of the cleavage furrow. My results suggest that Spire1 and Spire2 co-operate with another type of actin nucleator, Formin-2, to nucleate actin filaments. Both types of actin nucleator co-localize and show a positive, synergistic effect on actin nucleation when expressed together. Furthermore, the 2 types of actin nucleator act as a functional unit and cannot substitute for each other in loss-of-function experiments. My work not only reveals how Spire1 and Spire2 drive critical steps of asymmetric oocyte division, but also uncovers the first physiological function of Spire-type actin nucleators in vertebrates. These results represent an important step towards investigating whether defects in Spire1 or Spire2 contribute to pregnancy loss and unexplained infertility in humans.

PUBLICATIONS

Pfender S, Kuznetsov V, Pleiser S, Kerkhoff E, Schuh M (2011) Spire-type actin nucleators cooperate with Formin-2 to drive asymmetric oocyte division. *Curr Biol* **21:** 955–960

NEURONAL CONTROL OF FEEDING IN *DROSOPHILA MELANOGASTER*

cf. BIF FUTURA, VOL. 25 | 2.2010

ALLAN-HERMANN POOL
Discipline: Neuroscientist, BSc
Institute: University of California, Berkeley, CA, USA
Supervisor: Prof. Kristin Scott

Food intake in animals is essential for achieving metabolic homeostasis and is critical for survival. However, how taste detection and internal deprivation signals are converted to feeding behaviours remains poorly understood. In my PhD studies, I used the genetically tractable model organism *Drosophila melanogaster* to examine the neural mechanisms underlying feeding decisions. I implemented a molecular genetics approach to inactivate different neuronal subsets in the fruit fly brain. Screening transgenic animals in which different neuronal populations were genetically silenced yielded a number of behavioural mutants that were insatiable. These flies displayed voracious overconsumption of appetitive as well as aversive compounds. Genetic intersectional approaches enabled me to identify the causal cells for this phenotype. I showed that a cluster of 4 inhibitory neurons in the taste processing centre of the fly brain that secrete the neurotransmitter gamma-aminobutyric acid are responsible for suppressing a nonselective and unrestricted feeding state. I used a combination of electrophysiology and imaging with genetically encoded Ca^{2+} sensors to demonstrate that this brain centre constantly inhibits downstream feeding circuits and regulates food intake independently of taste and satiety signalling. I showed that the activity of these neurons prevents noxious compounds from engaging the motor neurons that execute feeding initiation and ingestion. These findings shed light on the principles underlying the organization of feeding circuits. Previous work in vertebrates as well as *Drosophila* has identified multiple neuromodulatory and inhibitory systems that shift the feeding threshold by making animals less averse to food contaminants or by reducing their sensitivity to internal satiety signals. Here I have described a brain centre that completely uncouples taste and satiety signals from feeding behaviour. Whether a similar neural mechanism for establishing feeding thresholds exists in other animals remains to be determined.

PUBLICATIONS

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

Pool AH, Scott K (2014) Feeding regulation in *Drosophila*. *Curr Opin Neurobiol* (In press)

MONITORING HOMOLOGY SEARCH DURING DNA DOUBLE-STRAND REPAIR *IN VIVO*

cf. BIF FUTURA, VOL. 25 | 2.2010

JÖRG RENKAWITZ
Discipline: Molecular Biologist, MSc
Institute: Max Planck Institute of Biochemistry, Martinsried, Germany
Supervisor: Prof. Stefan Jentsch

Homologous recombination (HR) is pivotal for genomic stability and for genetic exchange. It is a central cellular pathway for the repair of DNA double-strand breaks (DSBs) and relies on the use of intact homologous donor sequences. HR has been extensively investigated for decades; however, homology search – the imperative step of exploring the genome for a homologous donor sequence – still remained a mystery. During my PhD research, I was able to visualize homology search for the first time *in vivo*, using chromatin immunoprecipitation (ChIP) of the recombinase Rad51 in the yeast *Saccharomyces cerevisiae*. Rad51 forms a nucleoprotein filament at the DSB, which assists in the recognition of the homologous donor sequence during homology search. Due to a high ChIP efficiency and genome-wide analysis by tiling arrays (ChIP-chip), we detected Rad51 not only in the nucleoprotein filament directly at the DSB but also at distant locations. We were able to produce several lines of evidence to show that these DSB-distant Rad51 signals reflect homology search, including using a mutant Rad51 protein lacking the second DNA-binding site needed for homology probing. By taking advantage of this approach, we made several discoveries that led us to conclude that homology search is influenced by the nuclear organization: it preferentially probes on the broken chromosome with increasing efficiency towards the DSB; it can be efficiently guided to a far-distant chromosomal location by an intrachromosomal loop in the yeast mating-type system; and it can be guided to all centromeres upon the introduction of a centromere-proximal DSB. In addition, we discovered that the translocase Rad54 promotes the process of homology search and that the histone phosphorylation γH2A, which is a well-known histone mark covering large chromosomal domains around DSBs, in fact follows the pattern of homology search. My studies have therefore revealed important principles of how homology search functions in the nuclear environment. Moreover, the ability to monitor this process *in vivo* will allow the underlying mechanism to be studied in greater detail.

PUBLICATIONS

Renkawitz J, Lademann CA, Kalocsay M, Jentsch S (2013) Monitoring homology search during DNA double-strand break repair *in vivo*. *Mol Cell* **50:** 261–272

Renkawitz J, Lademann CA, Jentsch S (2013) γH2AX spreading linked to homology search. *Cell Cycle* **12:** 2526–2527

REGULATED MEMBRANE TRAFFICKING OF THE PRION-LIKE DOMAIN-CONTAINING PROTEIN Pin2p

cf. BIF FUTURA, VOL. 23 | 3.2008

ALICJA MARIA RITZ
Discipline: Biochemist, MSc
Institute: Biozentrum, University of Basel, Basel, Switzerland
Supervisor: Prof. Anne Spang

The cell surface proteome can be adjusted in response to environmental cues and to mediate polarized growth but the signals that determine this regulated trafficking of membrane proteins are not fully characterized. In *Saccharomyces cerevisiae*, the protein Pin2p localizes to the plasma membrane in a polarized, cell cycle-dependent fashion and is rapidly internalized upon environmental stress. Like several other integral membrane proteins, Pin2p contains a prion-like domain (PLD) and the aim of my PhD was to determine whether this domain has a role in Pin2p trafficking. To maintain its dynamic localization pattern, Pin2p shuttles between internal stores and the cell surface. We characterized Pin2p transport using mutants in trafficking machinery components and identified 3 distinct steps: export from the trans-Golgi network (TGN) to the plasma membrane mediated by the specialized exomer complex; ubiquitin-dependent endocytosis at the cell surface; and early endosome to TGN retrieval mediated by the clathrin adaptor, AP-1. We created several Pin2p truncations and expressed them as green fluorescent protein (GFP) fusions *in vivo* to assess their localization and as glutathione S-transferase (GST)-tagged recombinant proteins to test their binding to cellular trafficking machineries in pull-down assays. We found that the Pin2p PLD encompasses binding motifs for both exomer and AP-1 and its reversible aggregation seems to modulate motif recognition. Expansion of the Pin2p PLD through triplication of the glutamine/ aspargine (Q/N)-rich region of Pin2p or the insertion of 2 Q-rich repeats from the Sup35p prion protein enhances Pin2p retention in internal compartments under stress conditions. By contrast, when we introduced repulsive, charged residues to prevent PLD aggregation, we promoted Pin2p escape to the cell surface. Together, our results indicate a novel role for PLDs as trafficking signals in the control of polarized and stress-responsive protein localization.

PUBLICATIONS

Ritz AM, Trautwein M, Franziska G, Spang A (2014) The Prion-like Domain in the Exomer-Dependent Cargo Pin2 Serves as a trans-Golgi Retention Motif. *Cell Rep* **7:** 249–260

BUILDING SUN–KASH COMPLEXES AT THE NUCLEAR ENVELOPE

cf. BIF FUTURA, VOL. 24 | 1.2009

ANDREA ROTHBALLER
Discipline: Biochemist, MSc
Institute: Institute of Biochemistry, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland
Supervisor: Prof. Ulrike Kutay

The double membrane of the nuclear envelope (NE) separates the nucleoplasm from the cytoplasm in eukaryotic cells. SUN (Sad1/UNC-84)- and KASH (Klarsicht/ANC 1/SYNE homology)-domain proteins are transmembrane proteins of the inner and outer nuclear membrane, respectively. By forming a complex in the lumenal space, they connect the NE to nuclear and cytoskeletal structures and transduce the forces that are generated, for example, during nuclear migration or chromatin positioning. The aim of my PhD project was to study the formation and structure of these crucial SUN–KASH complexes. Together with 2 of my colleagues, I first investigated the targeting of human SUN2 to the NE. Using mutational analyses, fluorescence microscopy and interaction studies, we identified 3 components within the SUN2 protein that are important for its correct localization: a nuclear localization signal that binds to the import receptors importin α/β; a Golgi retrieval signal that recruits the vesicle-coating complex COPI for Golgi-to-ER transport and thus keeps SUN2 in the ER network, which is contiguous with the NE; and the SUN domain itself. For the second part of my project, I reconstituted SUN–KASH complexes from purified proteins and dissected the molecular basis of their interaction. In collaboration with Thomas Schwartz of the Massachusetts Institute of Technology in Cambridge, USA, we solved the first X-ray structure of a SUN–KASH complex. This revealed a hexameric structure comprising 3 molecules of each protein. SUN trimers are formed via coiled coils, and the whole complex is stabilized by extensive non-covalent contacts and a disulphide bond between SUN and KASH. Altogether, my findings have uncovered essential mechanisms of NE protein targeting, SUN–KASH interaction and nucleo-cytoskeletal coupling.

PUBLICATIONS

Rothballer A, Schwartz TU, Kutay U (2013) LINCing complex functions at the nuclear envelope: what the molecular architecture of the LINC complex can reveal about its function. *Nucleus* **4:** 29–36

Sosa BA, Rothballer A, Kutay U, Schwartz TU (2012) LINC complexes form by binding of three KASH peptides to domain interfaces of trimeric SUN proteins. *Cell* **149:** 1035–1047

Turgay Y, Ungricht R, Rothballer A, Kiss A, Csucs G, Horvath P *et al* (2010) A classical NLS and the SUN domain contribute to the targeting of SUN2 to the inner nuclear membrane. *EMBO J* **29:** 2262–2275

XRN2 FORMS A COMPLEX WITH THE NOVEL PROTEIN PAXT-1

cf. BIF FUTURA, VOL. 25 | 3.2010

STEFAN RÜEGGER
Discipline: Molecular Biologist, MSc
Institute: Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland
Supervisor: Dr Helge Grosshans

Exoribonuclease 2 (XRN2) is a conserved eukaryotic nuclease with widespread roles in RNA metabolism, including processing of ribosomal RNAs, degradation of microRNAs (miRNAs) and transcription termination. Although constitutive interaction partners of XRN2 that affect its stability and catalytic activity have been identified in yeast and the ciliate *Tetrahymena thermophila*, none has been found in metazoans. The goal of my PhD studies was to discover XRN2-binding proteins in animals, more precisely in the nematode *Caenorhabditis elegans*. I began by purifying XRN2 complexes by immunoprecipitation from worm lysates. Mass spectrometry analysis of the XRN2 immunoprecipitates identified a previously uncharacterized protein, R05D11.6, which I termed *PAXT-1* (Partner of XRN-Two 1). To characterize the function of *PAXT-1*, I generated a *paxt-1* knockout strain through transcription activator-like effector nuclease-mediated genome editing. The *paxt-1* knockout worms had lower XRN2 levels and slower miRNA turnover than wild-type worms. The only discernable domain within *PAXT-1* is a domain of unknown function, DUF3469. I confirmed that this domain, when expressed from a transgene in worms, is sufficient to bind to and stabilize XRN2. DUF3469 has been annotated in several metazoan proteins. I showed that DUF3469 in human proteins mediates interaction with XRN2, confirming this domain as a binding platform for XRN2 beyond *C. elegans*. My results pave the way to investigate the function of DUF3469-containing proteins in general.

PUBLICATIONS

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Miki TS, Richter H, Rüegger S, Grosshans H (2014) PAXT-1 promotes XRN2 activity by stabilizing it through a conserved domain. *Mol Cell* **53:** 351–360

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Rüegger S, Grosshans H (2012) MicroRNA turnover: when, how, and why. *Trends Biochem Sci* **37:** 436–446

STUDYING PROTEIN ORGANIZATION IN CELLULAR MEMBRANES BY HIGH-RESOLUTION MICROSCOPY

cf. BIF FUTURA, VOL. 26 | 3.2011

SINEM SAKA KIRLI
Discipline: Molecular Biologist, MSc
Institute: European Neuroscience Institute, Göttingen, Germany
Supervisor: Prof. Silvio O. Rizzoli

Most plasma membrane proteins are found in clusters, which show a patterned distribution rather than being randomly scattered. The aim of my PhD project was to investigate the general mechanism behind the patterning of membrane proteins. First, I indiscriminately tagged cellular proteins of cultured cells by the metabolic incorporation of modified amino acids over a period of several days. I applied click chemistry to couple small dye molecules to the tagged proteins, which allowed me to investigate all proteins in the membrane simultaneously in fixed plasma membrane sheets or living cells. Super-resolution stimulated emission depletion (STED) microscopy revealed a pattern comprising heterogeneous domains that were highly enriched in proteins, distributed on a protein-poor background. I termed these high-abundance domains 'protein clouds'. The protein cloud pattern was remarkably robust and resisted various manipulations including changes in ionic composition, decreases in protein density, disruption of cytoskeletal elements and hydrolysis of phospholipids. Among many different factors that were tested, I identified cholesterol as the key effector of cloud patterning: its depletion eliminated the clouds in a reversible manner. I also showed that the actin cytoskeleton contributes to the patterning by controlling the cloud size. Using 2-colour STED microscopy, I examined the distribution of specific proteins and found that they were enriched differentially in particular areas, such as the cloud edges or centres. Functional partners showed similar enrichment profiles, indicating a link between the sub-cloud organization and protein function. My studies suggest that the confinement of proteins into the clouds is a primary fundamental principle in the hierarchy of membrane patterning and it underlies the distribution of many membrane proteins.

PUBLICATIONS

Saka SK (2014) Light microscopy and resolution. In Super Resolution Microscopy Techniques in Neurosciences, Fornasiero EF, Rizzoli SO (eds). Springer, Berlin, Germany (in press)

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THE FUNCTION OF BASAL CILIARY STRUCTURES IN *CAENORHABDITIS ELEGANS*

cf. BIF FUTURA, VOL. 26 | 2.2011

CLEMENTINE SCHOUTEDEN
Discipline: Molecular Biologist, MSc
Institute: Max F. Perutz Laboratories, Vienna, Austria
Supervisor: : Dr Alexander Dammermann

The cilium is a slender, protruding organelle that is involved in motility, sensation and signal transduction in most eukaryotic cells. Previously considered to be vestigial – that is, a remnant of evolution – there has been a resurgence of interest in cilia due to their link to a class of developmental disorders now known as ciliopathies. These are complex diseases, characterized by a wide range of symptoms, and affect numerous tissues and organs. Whereas some ciliopathies are organ-specific, the most severe forms are more widespread and lead to prenatal mortality. In the effort to understand these diseases, 2 basal ciliary structures – the basal body and the transition zone – are of particular importance as most ciliopathy-associated proteins localize to these areas. The aim of my PhD project was to gain some insight into the function of these structures in *Caenorhabditis elegans.* Using light and electron microscopy, I showed that the basal body protein HYLS-1 is essential for the formation of cilia, whereas disruption of the transition zone does not significantly perturb this process. However, the transition zone proteins NPHP-4, MKSR-2 and CEP-290 are crucial for extending the cilia-bearing dendrite and thus positioning the cilia. I demonstrated that mutations affecting the transition zone prevent the anchorage of the dendrite tip during neurogenesis and therefore the correct positioning of cilia. This anchorage function seems to involve interactions with adhesive proteins DEX-1 and DYF-7 of the extracellular matrix. The results of my project therefore assign distinct functions to the basal body and the transition zone. They also ascribe a novel function for the latter in cellular architecture by linking cilia proteins to extracellular players, which might help us to understand the aetiology and phenotype of ciliopathies.

PUBLICATIONS

The results of this project have not yet been published.

STRUCTURAL PLASTICITY OF GABAergic AXONS

cf. BIF FUTURA, VOL. 24 | 2.2009

ANNE SCHUEMANN
Discipline: Molecular Medicine, BSc
Institute: Max Planck Institute of Neurobiology, Munich, Germany
Supervisors: Prof. Tobias Bonhoeffer and Dr Corette Wierenga

The term synaptic plasticity refers to changes in synaptic strength over time and these often coincide with structural changes in the synapse itself, such as the size of its components. Increases or decreases in the strength of excitatory synapses frequently correspond to changes in their postsynaptic compartment, the dendritic spine. For inhibitory synapses – most of which depend on the release of the neurotransmitter γ-aminobutyric acid (GABA) – the structural correlates of synaptic plasticity are, however, less well known. As most inhibitory synapses have no readily identifiable postsynaptic structure (ie. a spine), the goal of my PhD was to study the structural dynamics of the presynaptic axon terminal, or bouton. Using time-lapse 2-photon microscopy in hippocampal slice cultures, I found that about 80 % of the inhibitory boutons were stable over the course of 4 hours, showed moderate growth or shrinkage, and mainly correspond to established synapses. The remaining boutons were dynamic, appearing and disappearing along the axon, and mostly represented immature or partial synapses. This suggests that inhibitory axons are continuously probing potential locations for the formation of new synapses by assembling and disassembling boutons along the shaft. Furthermore, neuronal activity affected bouton dynamics: blocking activity reduced and enhancing activity increased the growth, shrinkage and presence of boutons. I also showed that the high-activity-induced changes in the structural dynamics of GABAergic axons critically depend on the activation of $GABA_A$ receptors, indicating that these receptors could be part of a feedback mechanism that assesses the level of GABA release in a network and adjusts structural plasticity accordingly. My study therefore suggests that activity-dependent regulation of inhibitory bouton dynamics contributes to changes in inhibitory synaptic strength and represents a system to study the molecular mechanisms of inhibitory plasticity.

PUBLICATIONS

Schuemann, A, Klawiter, A, Bonhoeffer, T, Wierenga, CJ (2013) Structural plasticity of GABAergic axons is regulated by network activity and $GABA_A$ receptor activation. *Front Neural Circuits* **7:** 113

ROLE OF LYMPH NODE FIBROBLASTS IN T CELL PRIMING

cf. BIF FUTURA, VOL. 23 | 2.2008

STEFANIE SIEGERT
Discipline: Immunologist, Diploma
Institute: Department of Biochemistry, University of Lausanne, Lausanne, Switzerland
Supervisor: Prof. Sanjiv Luther

Adaptive immune responses are generated when T cells encounter antigen-bearing dendritic cells (DCs) within the T zone of secondary lymphoid organs, such as lymph nodes. These T zones are spanned by a 3-dimensional (3D) network comprising T zone fibroblastic reticular cells (TRC). TRCs guide the incoming T cells both chemically, by the secretion of the chemokines CCL19 and CCL21, and physically, by the construction of a road system to which DCs also adhere. In this way, TRCs are thought to facilitate encounters between T cells and DCs and thereby accelerate the selection of rare antigen-specific T cells. However, the precise role of TRCs in T-cell priming is not fully understood. To reconstruct a lymphoid T zone *in vitro,* we established TRC cell lines along with a 3D cell culture system. This resulted in the formation of a network of TRCs with *in vivo*-like morphology. Surprisingly, the co-culture of these TRCs in 2D or 3D with DCs and T cells inhibited antigen-specific CD8+ T-cell proliferation via inducible nitric oxide synthase (iNOS)-dependent nitric oxide production by the TRCs. The expression of iNOS was upregulated in a subset of TRCs by both DC signals as well as interferon-γ produced by primed CD8+ T cells. In virally infected mice, we observed iNOS induction in a subset of TRC and mice lacking iNOS showed an exaggerated immune response, thus supporting a suppressive role for TRC *in vivo*. Our findings therefore suggest that in addition to their established positive roles in T-cell responses, TRCs and DCs cooperate in a negative feedback loop to attenuate potentially harmful T-cell expansion, which could endanger organ integrity.

PUBLICATIONS

Siegert S, Luther SA (2012) Positive and negative regulation of T cell responses by fibroblastic reticular cells within paracortical regions of lymph nodes. *Front Immunol* **3:** 285

Siegert S, Huang H-Y, Yang C-Y, Scarpellino L, Carrie L, Essex S *et al* (2011) Fibroblastic reticular cells from lymph nodes attenuate T cell expansion by producing nitric oxide. *PLoS One* **6:** e27618

Tomei AA, Siegert S, Britschgi MR, Luther SA, Swartz MA (2009) Fluid flow regulates stromal cell organization and CCL21 expression in a tissue-engineered lymph node microenvironment. *J Immunol* **183:** 4273–4283

STRUCTURAL BASIS OF HALLUCINOGEN SIGNALLING THROUGH SEROTONIN AND OPIOID RECEPTORS

cf. BIF FUTURA, VOL. 25 | 3.2010

DANIEL WACKER
Discipline: Biologist, MSc
Institute: The Scripps Research Institute, La Jolla, CA, USA
Supervisor: Prof. Raymond C. Stevens

The G protein-coupled serotonin (also known as 5-hydroxytryptamine [5-HT]) and opioid receptors are targets of several drugs, including antidepressants, antipsychotics and antiemetics. Besides their therapeutic use, the psychedelic drugs lysergic acid diethylamide (LSD) and salvia (Salvinorin A, SalA) also act through 5-HT and opioid receptors, respectively. However, the molecular details of drug action at these receptors remain poorly understood. Pharmacological studies indicate that LSD elicits markedly different signalling at the 13 subtypes of 5-HT receptors compared with the endogenous agonist 5-HT. For instance, LSD and its related derivatives are full agonists at the 5-HT_{1B} receptor, β-arrestin-biased agonists at the 5-HT_{2B} receptor, and antagonists at the 5-HT_{7A} receptor. To investigate this further, we used X-ray crystallography to solve the crystal structures of the 5-HT_{1B} and 5-HT_{2B} receptors bound to the LSD derivative ergotamine (ERG). These structures reveal the LSD-binding mode, important receptor–ligand interactions, and a highly conserved binding pocket core that explains promiscuous binding of LSD to all 13 5-HT receptors. Comparison of the 2 structures also reveals how ERG preferentially activates the β-arrestin signalling pathway at 5-HT_{2B}, whereas it signals through both G-protein and β-arrestin pathways at 5-HT_{1B}. In addition, we also performed structural studies of opioid receptors and showed that SalA mostly interacts with non-conserved residues in the ligand-binding pocket of the κ opioid receptor. This explains why SalA selectively acts through this receptor subtype and not the other 3 opioid receptors. Together with docking and mutagenesis studies, the structures solved during my PhD research provide comprehensive insights into the mechanism of drug action at opioid and serotonin receptors, which should ultimately facilitate the development of safer and more effective therapeutics.

PUBLICATIONS

Wacker D, Wang C, Katritch V, Han GW, Huang XP, Vardy E *et al* (2013) Structural features for functional selectivity at serotonin receptors. *Science* **340:** 615–619

Wang C, Jiang Y, Ma J, Wu H, Wacker D, Katritch V *et al* (2013) Structural basis for molecular recognition at serotonin receptors. *Science* **340:** 610–614

Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E *et al* (2012) Structure of the human κ-opioid receptor in complex with JDTic. *Nature* **485:** 327–332

INVESTIGATION OF PROTEIN TARGETING AND ITS IMPACT ON LIPID DROPLET EXPANSION

cf. BIF FUTURA, VOL. 25 | 3.2010

FLORIAN WILFLING
Discipline: Biochemist, MSc
Institute: Yale University, New Haven, CT, USA
Supervisor: Prof. Tobias Walther

Lipid droplets (LDs) are dynamic organelles that comprise a core of neutral lipids such as triacylglycerols bounded by a monolayer of phospholipid. They are found in most cell types and rather than being inert fat depots as originally thought, it is now recognized that LDs also contain proteins and have important roles in lipid metabolism. Their established link with metabolic diseases such as obesity, diabetes and atherosclerosis has led to a recent increase in interest in LDs but many aspects of their biology are still a mystery. For example, the current model for LD formation posits that they emerge from the endoplasmic reticulum (ER) but how proteins and newly synthesized neutral lipids are delivered from the ER to expanding cytosolic LDs is unclear. Using fluorescence microscopy and mass spectrometry, I investigated the mechanism of protein targeting from the ER to LDs and the importance of the targeted proteins for LD growth. I found that a subset of triacylglycerol-synthesizing enzymes localizes to LDs. Among these I focused on GPAT4, the rate-limiting enzyme in the triacylglycerol pathway, which moves from the ER along ER–LD membrane bridges to the surface of LDs. I showed that GPAT4 targeting requires the COPI machinery – which modulates the LD surface and allows the formation of connections between the ER and LDs – and that, together with other enzymes on the LD surface, GPAT4 mediates LD growth through local triacylglycerol synthesis. In addition, different subpopulations of LDs could be identified based on their capacity for LD-localized lipid synthesis. As excessive storage of neutral lipids lies at the heart of many metabolic diseases, my findings not only highlight a mechanism that enables specific triacylglycerol enzymes to relocalize from the ER to LDs for LD expansion, but they could also have an impact on the development of new approaches for treating obesity.

PUBLICATIONS

Wilfling F, Thiam AR, Olarte MJ, Wang J, Beck R, Gould TJ *et al* (2014) Arf1/COPI Machinery Acts Directly on Lipid Droplets and Enables their Connection to the ER for Protein Targeting. *eLife* **3:** e01607

Wilfling F, Wang H, Haas JT, Krahmer N, Gould TJ, Uchida A *et al* (2013) Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from the ER to lipid droplets. *Dev Cell* **24:** 384–399

INVESTIGATION OF THE STOICHIOMETRY BIOLOGY OF THE SYNAPSE

cf. BIF FUTURA, VOL. 26 | 2.2011

BENJAMIN WILHELM
Discipline: Biologist, MSc
Institute: European Neuroscience Institute, Göttingen, Germany
Supervisor: Prof. Silvio Rizzoli

Complex organisms rely on the transmission of information between cells to ensure correct motor function and sensory perception. This process is controlled by neurons, the core component of the nervous system. Synapses act as the interface between neurons, facilitating the passage of signals. Neuronal communication at chemical synapses, which comprise the majority of synapses in the brain, relies on the exocytosis and endocytosis of vesicles containing neurotransmitters. Both processes are tightly regulated and involve a number of proteins. Much is known about the nature of these proteins and their interplay during vesicle recycling. However, much remains unknown, including the precise molecular anatomy of the synapse and how its function relates to the number and distribution of these proteins. The goal of my PhD project was to address these questions using the rat as a model system. I began by determining the physical parameters of synapses – such as their size, shape and organelle composition – from the brain using 3-dimensional reconstructions of ultrathin electron microscopy sections. I performed quantitative immunoblots to determine absolute copy numbers for 59 of the most well-known synaptic proteins, and then examined their spatial distribution using super-resolution stimulated emission depletion microscopy. These data then formed the basis of a 3-dimensional model of the pre-synaptic terminal in which synaptic proteins were placed in the appropriate locations in their correct quantities. This information enables us to place the known functions of these proteins into the context of their interaction partners and of the synapse as a whole, which adds significantly to our understanding of synaptic function. My findings allow us for the first time to consider that the spatial availability of proteins could be involved in the regulation of synapse function. In other words, synaptic function could be regulated primarily by the abundance of specific proteins rather than by other control mechanisms.

PUBLICATIONS

The results of this project have not yet been published.

MD FELLOWS 2013

With its MD fellowships, the Boehringer Ingelheim Fonds helps outstanding medical students to pursue an ambitious experimental research project in basic biomedical research. Applicants for this programme must be students in Germany and change their working place (institution and city) for at least ten months to join an internationally renowned laboratory. Here, we present the 10 fellows who have been granted an MD fellowship by the BIF Board of Trustees in 2013.

CARINA DEHNER

Molecular mimicry of gut commensals in human antiphospholipid syndrome

FRANK DUBOIS

The role of TRPC5 and TRPC6 in albuminuria initiation

BENJAMIN ENGLERT

Lineage tracing of Gli1-expressing cells in pancreatic inflammation, regeneration and cancer development

DIRK KANZ

Identifying the mutation that causes hypochromic anemia in zinfandel zebrafish using the CRISPR/Cas system

TIMO KUSCHMA

Investigating the role of the EZH2 methyltransferase in Rb-deficient tumours

JAN LANZER

Adenosine receptor signalling-mediated modulation of tissue non-specific alkaline phosphatase in vascular calcification

NORA LAVANDIER

Mechanisms of HLA-mediated control in HIV infection

JOHANNES REINER

Screening for novel binding partners of occludin and their impact on tight junction dynamics

ISABEL SCHELLINGER

The role of miRNA-146 in vascular inflammation and abdominal aortic aneurysm disease development

TOBIAS WERTHEIMER

Organ-specific endothelial cells in graft-versus-host-disease (GvHD) and post-BMT regeneration

MOLECULAR MIMICRY OF GUT COMMENSALS IN HUMAN ANTI-PHOSPHOLIPID SYNDROME

CARINA DEHNER

Duration: 5/2014–2/2015

Host Institute: Institute of Immunobiology, Yale University, New Haven, CT, USA

Supervisor: Prof. Martin Kriegel

Home university: University of Munich

THE ROLE OF TRPC5 AND TRPC6 IN ALBUMINURIA INITIATION

FRANK DUBOIS

Duration: 8/2013–7/2014

Host institute: Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

Supervisor: Prof. Anna Greka

Home university: University of Heidelberg

LINEAGE TRACING OF GLI1-EXPRESSING CELLS IN PANCREATIC INFLAMMATION, REGENERATION AND CANCER DEVELOPMENT

BENJAMIN ENGLERT

Duration: 4/2013–3/2014

Host institute: Karolinska Institute, Center for Biosciences, Huddinge, Sweden

Supervisor: Prof. Rune Toftgard

Home university: Charité University Hospital, Berlin

IDENTIFYING THE MUTATION THAT CAUSES HYPOCHROMIC ANEMIA IN ZINFANDEL ZEBRAFISH USING THE CRISPR/CAS SYSTEM

DIRK KANZ

Duration: 11/2013–10/2014

Host institute: Harvard Medical School, Children's Hospital Boston, Boston, MA, USA

Supervisor: Prof. Leonard Zon

Home university: Freiburg University Hospital

INVESTIGATING THE ROLE OF THE EZH2 METHYLTRANSFERASE IN RB-DEFICIENT TUMOURS

TIMO KUSCHMA

Duration: 1/2014–11/2014

Host institute: Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, CA, USA

Supervisor: Prof. Julien Sage

Home university: University of Heidelberg

ADENOSINE RECEPTOR SIGNALLING-MEDIATED MODULATION OF TISSUE NON-SPECIFIC ALKALINE PHOSPHATASE IN VASCULAR CALCIFICATION

JAN LANZER

Duration: 9/2013–8/2014

Host institute: National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Bethesda, MD, USA

Supervisor: Manfred Boehm

Home university: University of Heidelberg

MECHANISMS OF HLA-MEDIATED CONTROL IN HIV INFECTION

NORA LAVANDIER

Duration: 9/2013–7/2014

Host institute: Nuffield Department of Medicine, University of Oxford, Oxford, UK

Supervisor: Prof. Philip Goulder

Home university: University of Heidelberg

SCREENING FOR NOVEL BINDING PARTNERS OF OCCLUDIN AND THEIR IMPACT ON TIGHT JUNCTION DYNAMICS

JOHANNES REINER

Duration: 5/2013–3/2014

Host institute: Department of Pathology, University of Chicago, Chicago, IL, USA

Supervisor: Prof. Jerrold R. Turner

Home university: University of Rostock

THE ROLE OF miRNA-146 IN VASCULAR INFLAMMATION AND ABDOMINAL AORTIC ANEURYSM DISEASE DEVELOPMENT

ISABEL SCHELLINGER

Duration: 6/2013–5/2014

Host institute: Stanford School of Medicine, Stanford University, Stanford, CA, USA

Supervisor: Prof. Philip S. Tsao

Home university: University of Erlangen

ORGAN-SPECIFIC ENDOTHELIAL CELLS IN GRAFT-VERSUS-HOST-DISEASE (GVHD) AND POST-BMT REGENERATION

TOBIAS WERTHEIMER

Duration: 9/2013–8/2014

Host institute: Division of Hematologic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Supervisor: Marcel R.M. van den Brink

Home university: University of Freiburg

THE FOUNDATION The Boehringer Ingelheim Fonds (BIF) is a public foundation – an independent, non-profit institution 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.

FOUNDATIONS WEATHER THE FINANCIAL CRISIS

By Prof. Hans Fleisch, Secretary General, Association of German Foundations

The current low interest rates are a direct result of the financial crisis that began in 2007. For foundations this is a challenge because low rates make it harder to generate high returns on capital. Up to now, however, foundations in Germany and the US seem to handling the situation well.

Despite continuing low interest rates, the number of German foundations has grown steadily. In 2013, the number of new foundations remained at a high level at 638. As a result, there are now 20,150 foundations in Germany. Establishing a foundation remains attractive – and the most sustainable – commitment to public welfare.

In July 2013, we asked 400 German foundations how they were coping with the continuing low interest rates. Their income from capital generally seemed to be stable. However, larger foundations with an endowment of one million euros or more can usually generate significantly higher returns. Most of these returns come from equities such as German stocks that have done well because the domestic economy has performed well. One example is the Gerda Henkel Foundation, which supports national and international academic projects, including those in the fields of archaeology and history. In 2012, it attained record assets and distributed more grants than in any other year since it was established in 1976.

According to the US Foundation Center, the picture for American foundations seems to be similar. In October 2013, it reported that 'even through a period of unpredictability in the national and global economic and political environment, domestic foundation giving grows ahead of inflation'. Even Yale's endowment, which was facing considerable economic troubles during the financial crisis in 2009, announced a 12.5% investment return for the year ending 30 June 2013.

In spite of this good news, the longer the period of low interest rates lasts, the thinner the air for foundations. Fundraising and cooperation are the magic words in this situation. German foundations have huge growth potential for fundraising, for instance, through Germany's enormous inheritance giving. In 2013 alone, approximately 250 billion euros were passed from one generation to the next. Foundations could also increase their efficiency and gain synergies by cooperating with other foundations, non-governmental organizations, corporations and political and governmental institutions.

If the foundation sector reacts carefully and with due consideration, it will remain a stable source of funding and will continue to have an essential impact on public welfare.

More information: www.stiftungen.org

WHO'S WHO AT BIF

DR INGRID OHLERT

Ingrid Ohlert was born in Bonn. After her PhD in biochemistry she joined the Deutsche Forschungsgemeinschaft (DFG) in 1985, where she now heads one of the two life science units within the scientific department. Her special interests include ethical and legal questions related to life sciences. Since 2002, she has represented the DFG on BIF's scientific board as a permanent guest. She is also a member of the board of trustees of the Human Frontiers Science Program. On a more personal level she tries to combine her fascinating and demanding work with raising four children.

What do you like most about your work at BIF?
Board meetings are always great fun, especially when you see the sparkle in the eyes of the scientific board members when they explain a new idea laid out in an application. You can really feel their enthusiasm for great science.

What is your most remarkable experience connected with BIF?
I truly enjoyed being a guest at an alumni meeting at Gracht castle. In my eyes, BIF is absolutely unique in creating a kind of family atmosphere between fellowship holders and alumni.

What is your favourite activity?
Playing tennis and sitting in a café. I also enjoy doing nothing.

Where would you like to live?
My husband is always trying to convince me to move to Singapore – my first choice would be Provence.

What is your remedy for stressful situations?
I am still looking for a good one.

What is your motto?
Stand by your opinion.

What fault in others can you tolerate best?
Being overenthusiastic.

Your advice for fellowship holders?
Follow your dreams, your own ideas and try to enjoy every day of your life.

Which scientific achievement do you admire most?
Frankly, it's difficult for me to name a single scientific achievement. What I admire most are scientists who enthusiastically and successfully follow their own ideas, despite being discouraged by colleagues or superiors.

Name one thing you couldn't live without.
My husband and my children.

NEW TEAM MEMBER

In August 2013, Vera Schlick took over for Ingrid Lee, who has retired. Vera is the first person at BIF that applicants and prospective applicants come in contact with. She takes care of all incoming applications for PhDs and MD fellowships as well as travel grants. From the first email to the final application, she answers all questions on the application process. She makes the first check of the criteria for the applications and transfers the data into the database. She supports the peer review process and informs applicants of BIF's decisions.

Vera also organizes the meetings of the Board of Trustees and interviews for PhD candidates, including travel arrangements for the BIF team. 'What I like most about my work at the foundation are the variety of tasks and the opportunity to communicate with people from all over the world,' says Vera, who worked as a multilingual secretary in the pharmaceutical industry for many years and most recently in the legal department of the Boehringer Ingelheim Corporation.

In her spare time, Vera loves to go on extended hiking tours and one of her favourite places for hikes is the small Canary Island La Gomera, where she can combine her passion for nature and the Spanish language. So, Vera, a welcome to BIF!

Photos: Zhenikeyev/iStockphoto (left), Dr Ingrid Ohlert (top left), Carsten Costard (top right)

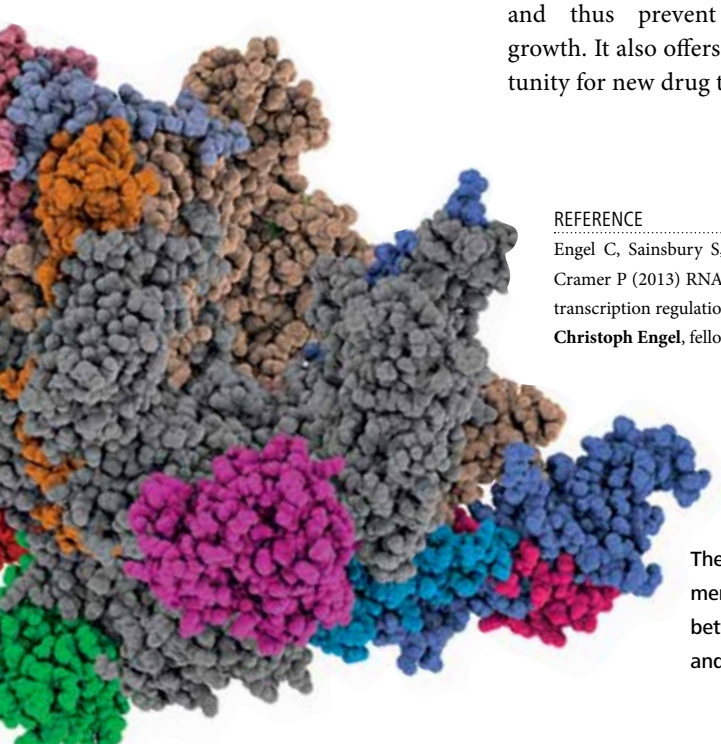
PAPERS IN THE SPOTLIGHT

'Papers in the Spotlight' is a new feature in which we present recent papers from BIF fellows. The selection criteria are not only scientific merit, but also the news value and general interest of the topic. If you would like to see your paper here, send an email to kirsten.achenbach@bifonds.de.

SORRY, BUT WE'RE CLOSED FOR BUSINESS

Some things only work when they are shut. This seems to be the case with RNA polymerase I (Pol I), as Christoph Engel and his colleagues found after ten years of hard work that culminated in resolving Pol I's three-dimensional structure. In an article published in *Nature* in October 2013, first author and BIF alumni Christoph Engel and his supervisor Patrick Cramer from the LMU in Munich, Germany, describe the structure of this large and complex enzyme. They show that, in contrast to Pol II, Pol I has several additional elements that allow it to switch between an open inactive and a closed active state. Pol I is *the* enzyme when it comes to the growth of cells, as it transcribes three of the four ribosomal RNAs, without which protein synthesis could not take place. It synthesizes up to 60% of all RNA in a cell and if it is hyperactive, cancer may result.

In order to gain these insights, Christoph determined the detailed architecture of Pol I at a resolution of 2.8 Å, high enough to localize most residues of its 14 subunits by defining the position of its approximately 35,000 atoms – not counting the hydrogen atoms. From its structure, the researchers could infer information about the enzyme's mode of action: conformational changes close the cleft in which the active site lies, turning the enzyme to 'on'. The researchers postulate that this is a control mechanism that allows Pol I to be continuously inhibited and thus prevent uncontrolled cell growth. It also offers a tantalizing opportunity for new drug targets.



The enzyme RNA Polymerase I (Pol I) can switch between an open inactive and a closed active state.

REFERENCE

Engel C, Sainsbury S, Cheung AC, Kostrewa D, Cramer P (2013) RNA polymerase I structure and transcription regulation *Nature* **502:** 650–655

Christoph Engel, fellow 2011–2013

PERFUMED FOR NO SEX

While humans use perfume in an attempt to heighten their attractiveness to potential partners, juvenile mice do exactly the opposite, as BIF alumnus David Ferrero of Harvard Medical School, Boston, USA, found out in his PhD project. He published the results of his study as first author in *Nature* in October 2013. Together with Professor Stephen Liberles and other colleagues, David found that juvenile mice of both sexes secrete a peptide in their tears, termed ESP22, which deters adult male mice from trying to mate with them.

In their search for new behaviour-controlling pheromones in mice, the researchers determined at what age and in which sex pheromone-encoding genes were expressed. ESP22 was highly expressed only by prepubescent mice, with secretion peaking at the age of two to three weeks, making it the first juvenile pheromone to be reported. The timing of ESP22 expression gave the researchers a preliminary idea of what it does. Behavioural experiments with two strains of mice that do not express ESP22 showed that these mice lost the protection the pheromone offered from sexual advances. However, painting them with ESP22 conferred almost the same protection as that enjoyed by ESP22-expressing pups. It also somewhat dampened the males' ardour towards adult females. ESP22 is detected by the vomeronasal organ (VNO), which is mostly responsible for the detection of pheromones and connects directly to the limbic system. Adult mice in which the

Photos: Christoph Engel and Patrick Cramer (bottom left), Graffizone/iStockphoto (bottom middle), Andrea Danti/shutterstock (bottom right)

VNO did not work properly showed increased sexual behaviour towards juvenile mice. This study helps us to understand how the sensory system and behaviour interact on a molecular level.

REFERENCE

Ferrero DM *et al* (2013) A juvenile mouse pheromone inhibits sexual behaviour through the vomeronasal system. *Nature* **502:** 368–371.

David Ferrero, fellow 2010–2012

Sorry, no sex! A pheromone in the tears of juvenile mice deters adult males from trying to mate.

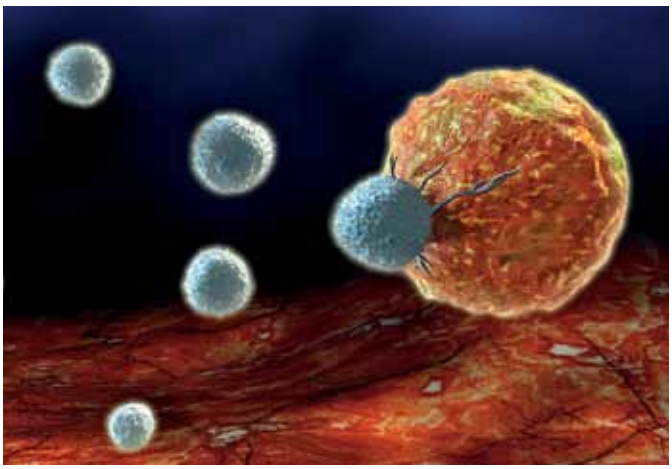
KNOW THY ENEMY AND WIN THE WAR

The immune system's T cells constantly patrol our body in search of enemies such as invaders and abnormal cells. Each T cell has one type of a T cell receptor (TCR) with which it can distinguish between normal and abnormal cells, such as cancerous cells, via the markers present on the cell surface. Each human T cell has encoded in its genes information on which of about 10^{11} possible receptors it will display. The huge variety stems from the almost endless combinations of the more than 100 TCR building blocks in our genome. Carsten Linnemann (BIF fellow from 2009 to 2010) *et al* describe a new method for rapidly identifying TCRs that react specifically against, for example, cancer cells (published in *Nature Medicine*). Carsten and his colleague Ton Schumacher, both at The Netherlands Cancer Institute, used RNA fragments binding to the most common TCR building blocks to fish for TCR-encoding genes. Through deep-sequencing they then identified the genes encoding the whole TCRs. As well as learning more about how the immune system recognizes its targets, they identified 21 new TCRs that could be used to develop immunotherapies to treat a broad range of cancers, including blood, bone marrow, skin and lung cancers.

REFERENCE

Linnemann C *et al* (2013) High-throughput identification of antigen-specific TCRs by TCR gene capture. *Nat. Med.* **19**:1534–1541

Carsten Linnemann, fellow 2009–2010



Digital illustration of several T cells attacking a cancer cell.

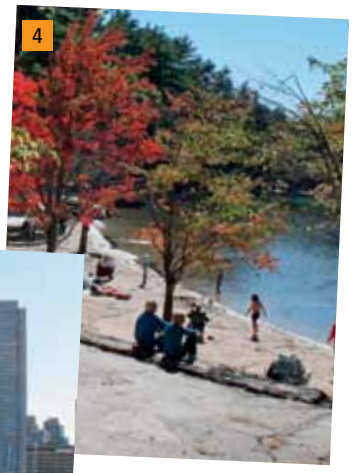
A BIF FELLOW'S GUIDE TO ...

BOSTON


1


2


3


4

You enjoy travelling and are searching for insider tips? In each edition of FUTURA one of our fellows introduces his or her city to you. Here German fellow Benedikt Bauer reports on Boston, capital of Massachusetts and one of the oldest cities in the United States.

FACTS AND FIGURES

Country: USA
Population: About 630,000
Area: 232 km²
Students: About 152,000
Famous for Harvard, J.F. Kennedy, Ben Affleck, baseball
Websites: www.boston.com

WHERE TO STAY

463 Beacon Street: Affordable rooms in a historic brownstone building close to the Charles River.
Newbury Guest House: Charming 19th century guesthouse on Newbury Street, close to the centre of Boston.
Boston's Backpacker Youth Hostel: Affordable rooms near Boston's North Station.

NIGHTLIFE

Middle East Club: Watch the very best air guitarists compete against each other in the Air Guitar Championship.
Paradise Rock Club: Major bands give concerts here on their US tours.
Sommerville Theatre: Watch Boston's interpretation of the *Nutcracker* – the *Slutcracker* – in the weeks before Christmas.

RESTAURANTS

Red Bones: Boston's 'temple of meat', offering southern style BBQ in a rustic atmosphere. Spin the beer wheel if you are unsure what to drink.
Taiwan Café: Chinatown's best dumplings! Try the mini steamed buns with pork.
Squealing Pig: Close to Harvard Medical School, this is where scientists have a drink and enjoy a pulled pork sandwich.

ACTIVITIES

Whale watching: Take the sunset whale watch! The boat leaves at 4 pm and comes back when the sun sets above Boston's scenic harbour. 3
Crane Beach: The most beautiful beach in the area, about one hour north of Boston. 2 If you go during the autumn, also visit the nearby apple farm close to Ipswich.
Boston Red Sox: Have a beef frank at Fenway Stadium while watching baseball.

BEST SIGHTS

Longfellow Bridge: Best view of Boston's scenic Beacon Hill. Go there when the setting sun is reflected in the skyline.
Harvard Square: Take a walk through the old red brick buildings of Harvard University and have a nap under one of the numerous oak trees. 1
Walden Pond: Visit the pond in the fall when the leaves start changing colour. You will also find Henry David Thoreau's hut there. 4

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

Name Benedikt Bauer
Nationality German
Age 29
University Harvard Medical School, Department of Cell Biology
Supervisor Professor Tom A. Rapport

Photos: Benedikt Bauer

PROFILES

Dr Tina Wenz, Institute for Genetics, University of Cologne, Germany, has been awarded the newly established Care for Rare Science Award by the international jury of the Care for Rare Foundation. The €50,000 prize money for her project 'Towards a Targeted Protein Replacement for Mitochondrial Protein Synthesis Defects' will help Tina to introduce innovative targeted treatments for mitochondrial diseases that are, at the moment, incurable. Tina was a BIF fellow from 2002 to 2004.

Prof. Ludger Johannes, BIF fellow from 1993 to 1995 and research director at INSERM at the Institut Curie in France, has been the head of the research unit 'Chemical Biology of Membranes and Therapeutic Delivery' since January 2014. He is also a permanent member of EMBO and has received an ERC Advanced Grant. Ludger's research aims to establish fundamental concepts of endocytosis and intracellular trafficking and to exploit these discoveries to develop new cancer therapy strategies. He has also co-founded two biotech companies, STxB Pharma Technologies Inc. and ImmunoTargets SAS.

Prof. Oliver Daumke, biochemist and protein crystallographer at the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, and the Free University (FU) Berlin, Germany, has been awarded an ERC Consolidator Grant of over two million euros for his project 'Structural Basis of Mitochondrial Inner Membrane Shape and Dynamic'. He intends to investigate proteins that bind to cellular membranes and are involved in the remodelling of their shape. He was a BIF fellow from 2002 to 2004. Germany has the second highest number of ERC Consolidator Awards after the UK.

Dr. Carsten Linnemann, BIF Fellow from 2009 to 2010 – has received the Greiner Award for his dissertation thesis on T cell antigens (see papers in the spotlight). The award is given yearly by the Netherlands Society for Gene & Cell Therapy for the best thesis or publication in gene therapy for work performed at a University or Institute in the Netherlands. The prize comes with 1,000 euros and is traditionally awarded at the society's spring symposium.

UPCOMING EVENTS

8–12 OCTOBER 2014

110th International Titisee Conference

Holger Stark, Max Planck Institute for Biophysical Chemistry, Göttingen, and Matthias Rief, Technical University Munich, both from Germany, are the chairs of the upcoming 110th International Titisee Conference on "Structure, forces and dynamics of macromolecular complexes". At the confernce, experts from all over the world will discuss how the interplay between structure and dynamics determines the activity of biological macromolecules and the novel developments in the techniques to study them.

Participation is by invitation only

13–16 NOVEMBER 2014

Meeting of BIF's Board of Trustees in Barcelona, Spain.

Meeting of BIF's Board of Trustees in Barcelona, Spain. The trustees will decide upon the allocation of fellowships, review the proposals for the International Titisee Conferences and settle all the foundation's matters of fundamental importance.

19 DECEMBER 2014

BIF Christmas Party

Christmas is coming round again – and with it BIF's Christmas party. It takes place on 19 December and starts at 6pm. All fellows and alumni are invited to celebrate with the BIF team. Food and drink will be provided, floor space for people wanting to stay overnight will be available.

FUSION FOR BRAIN SIGNALS

Professor Reinhard Jahn, member of BIF's Board of Trustees, will receive the international Heinrich Wieland Prize, which is worth €100,000 and endowed by BIF's sister foundation, the Boehringer Ingelheim Foundation. He will be honoured for his paradigmatic studies on membrane fusion, synaptic vesicles, and neurotransmitter release – processes that occur when cells grow, transport substances, or signal. The prize turns 50 this year, and this anniversary will be celebrated with a scientific symposium and a festive award ceremony on 21 October, 2014, in the Munich Residenz in Munich, Germany.

More information: www.wielandprize.de

Photo: Tina Wenz (top left); Oliver Daumke (top right); Max-Delbrück Center/D. Ausserhofer; (right); Ludger Johannes (left)

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Boehringer Ingelheim Fonds
Stiftung für medizinische
Grundlagenforschung

Schusterstr. 46-48
55116 Mainz
Germany
Tel. +49 6131 27508-0
Fax +49 6131 27508-11
E-mail: secretariat@bifonds.de
www.bifonds.de