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The heat is on
How different organisms withstand high temperatures

Projects, results, MD fellowships
New PhD projects, completed theses, and 2018 MD fellowships

A BIF fellow's guide to Montreal
A fusion of historical heritage and modern culture

The cover illustration shows a simplified model of *Pyrococcus furiosus,* which is known as one of the most thermostable organisms. Studies on such organisms and the ways they resist high temperatures help us to understand how living things beat the heat. They also draw attention to the difficulties some species will experience with rising temperatures due to climate change.

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NEW PHD RESULTS

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12TH NORTH AMERICA MEETING

PUBLISHING INFORMATION

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BRINGING ABOUT CHANGE

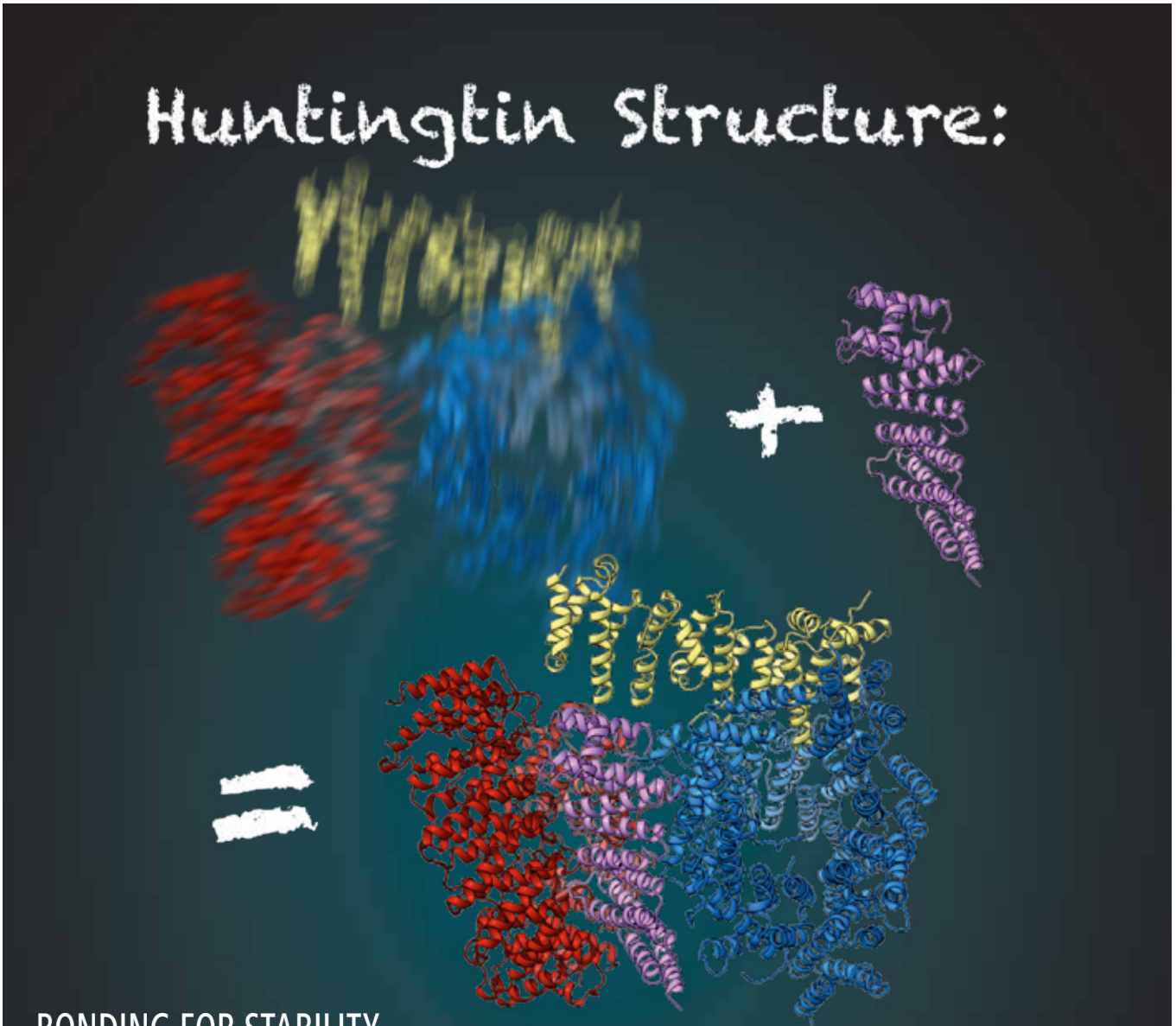
»More possibilities and incentives for scientific research for medical students.«

Last year, we celebrated the 100th fellow in BIF's funding programme for medical students – our most recent and smallest programme. It was introduced in 2006 after the German Council of Science and Humanities (Wissenschaftsrat), the Federal Ministry of Education and Research, and the German Research Foundation (DFG) made yet another appeal for better scientific education and more possibilities and incentives for scientific research for medical students in Germany.

The fellowships are intended for talented MD students with ambitious, high-quality research projects in basic science at a very good laboratory – all evaluated by peer review. Fellows are required to pursue their project in a different city to prevent them from squeezing research into their usual curriculum. In fact, some 80% have used the chance to do research in the USA, where they also learn that clinician scientists combine excellent research in the lab with patient care in the clinic. Importantly, most MD fellows work closely with natural scientists and – thanks to BIF's support, as well as the seminars and meetings – can build networks including MDs and PhDs from a large variety of disciplines. All of this hopefully turns them into bridge builders between the two worlds.

Despite their great talent, impressive CVs, and high ambitions, not all of the MD fellows thrive in the lab. This is due in part to the inherent riskiness of research, but also to their lack of experience in experimental work and scientific matters in general. The next generation of MD students in Germany may be better prepared: strengthening scientific competencies is (again) a declared aim of the new Masterplan Medical Studies 2020. Such competencies are of course a prerequisite for medically trained researchers and internationally competitive medical research. They are, however, also "essential for responsible professional work as a medical doctor", as the German Council of Science and Humanities has put it. In light of the fast-paced scientific and technological advances in medicine, physicians more than ever depend on their capability to think and act in a scientific and evidence-based manner when evaluating new knowledge and applying it for their patients' benefit.

Many of our MD fellows have returned to their home universities with a passion for research. Many would like to combine it with patient care and have encountered a sobering reality. A new initiative gives hope for a more general change: the DFG funds clinician scientist programmes at 13 medical faculties in Germany. Helping to establish structures conducive to research is also required to fight the growing shortage of physicians doing research. The traditional model – going to the lab after a day's work in the clinic and dedicating the weekends to research – tends to find fewer enthusiasts these days with women having a career and children and fathers wanting and expected to be more involved in child care. After all, a day still has only 24 hours.

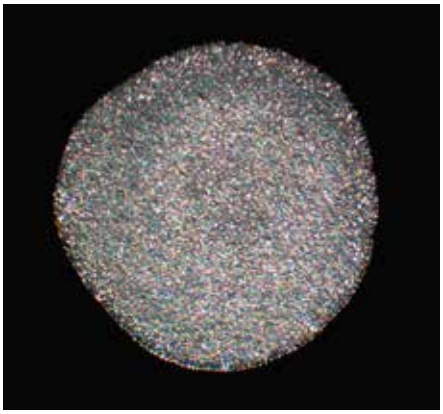


BONDING FOR STABILITY

By Prof. Stefan Kochanek, University of Ulm, Germany
Illustration: Gabriele Stautner, artifox.com.

Previous efforts to determine the structure of Huntingtin (HTT) – the protein altered in Huntington's disease – have not been successful due to HTT's large size and flexible nature, as indicated by its "blurry" appearance (top left). Using cryo-electron microscopy, Stefan Kochanek and colleagues have now managed to determine the structure of HTT while bound to an interaction partner, HAP40 (top right). Binding of HAP40 to HTT's three domains reduced HTT's flexibility to a degree that structure determination became possible. This was a large step towards better understanding and fighting this devastating disease.

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.



Hoilungia hongkongensis: all placozoans look identical.

PLACOZOANS DO THE SPLITS

One species of miniature marine animal known as the placozoan has now become two, thanks to the work of researchers at Ludwig-Maximilians-Universität (LMU) in Munich, Germany. Measuring just a millimetre in length, placozoans are little more than a ball of cells, making them the simplest multicellular animals on earth. This lack of distinguishing features has meant that these simple sea creatures have been classified as a single species, *Trichoplax adhaerens*, for more than a century. Previous studies looking at differences in individual genes from various populations suggested that there might be much more much more genetic diversity in these unusual animals than was previously appreciated. For the new method they termed taxogenomics, the German researchers compared structural differences in chromosomes, the number of genes, or differences in selected sequences of the organisms in question. On this basis, they analysed the DNA from placozoan populations collected from various locations around the world.

Strikingly, they found that the genome of one group (H13) was so different from the rest that it had to be considered an entirely separate species, even though it is indistinguishable from *T. adhaerens* under the microscope. Furthermore, H13 is so distantly related to other placozoans that it has been classed as a whole new genus, based on comparisons with the genetic relatedness of other similar groups of organisms.

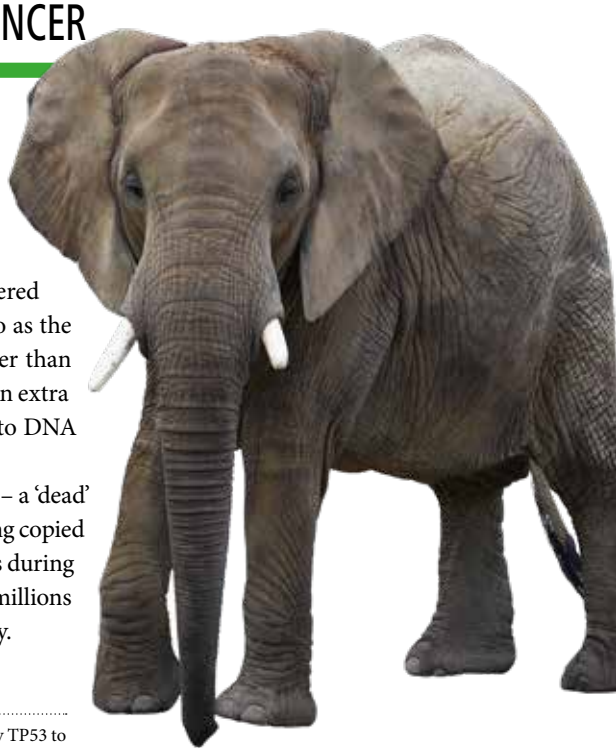
Because these animals were found in the Ho Chung River, Hong Kong, they were named *Hoilungia hongkongensis*, which translates as Hong Kong Sea Dragon. There is an extra layer of symbolism, too: just like the shape-shifting mythological Chinese dragon king, placozoans can easily change their shape.

Significantly, this is the first time a new genus has been described solely using genetic rather than phenotypical characteristics, with major consequences for the identification and definition of species in the future. The researchers plan to apply their method to other seemingly identical small animals such as nematode worms, doubtless leading to the discovery of many new species.

REFERENCE

Eitel M, Francis WR, Varoqueaux F, Daraspe J, Osigus H-J, Krebs S *et al* (2018) Comparative genomics and the nature of placozoan species. *PLoS Biol* DOI: 10.1371/journal.pbio.2005359

"DEAD" GENE PROTECTS ELEPHANTS AGAINST CANCER



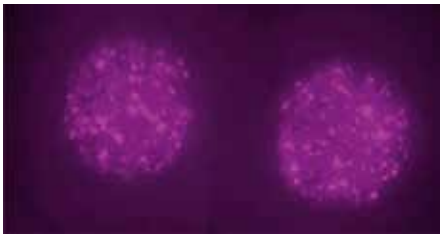
Large animals such as elephants should be more susceptible to cancer than smaller ones like mice, because their bigger bodies contain more cells with the potential to turn into tumours. But this relationship does not hold true, and elephants are actually far less likely to develop cancer than mice – an observation known as Peto's paradox after the statistician Richard Peto.

In 2015, scientists at the Universities of Chicago and Utah, USA, discovered that elephants carry multiple copies of a gene called *p53*, sometimes referred to as the "Guardian of the Genome", which causes cells with damaged DNA to die rather than become cancerous. The Chicago team have now found that elephants also have an extra copy of another protective gene called *LIF6*, which is switched on in response to DNA damage and leads to cell death.

In an unexpected twist, LIF6 turns out to be a pseudogene in most mammals – a 'dead' gene that has lost its function through evolution, either by picking up faults or being copied without all its parts. However, *LIF6* has somehow become reactivated in elephants during evolutionary history. This genetic boost may have helped elephants change over millions of years into the impressively sized and relatively cancer-free animals we see today.

REFERENCE

Vazquez JM, Sulak M, Chigurupati S, and Lynch VJ (2018) A Zombie LIF gene in elephants is upregulated by TP53 to induce apoptosis in response to DNA damage. DOI: 10.1016/j.celrep.2018.07.042



Two-cell mouse embryo stained for LINE1 RNA (magenta), which is expressed in the two cell nuclei.

JUMPING GENES SHAPE DEVELOPMENT

Researchers at the University of California San Francisco (UCSF), USA, have now discovered a role for transposons – also known as jumping genes and long dismissed as "junk DNA" – in the earliest stages of life. Around half of the human genome is made up of transposons, which are virus-like genetic elements that have the potential to duplicate themselves and move around within the DNA. And although most of them are probably little more than inert genetic junk accumulated over many years of evolutionary time, some are still capable of hopping around within the genome and disrupting the normal function of genes.

Led by Miguel Ramalho-Santos, the UCSF team had previously found that the most common transposon, LINE1, which makes up around a fifth of the whole human genome, was highly active in early embryos and embryonic stem cells. Building on this discovery, the researchers have now found that LINE1 is essential for mouse embryos to develop further than the two-cell stage.

Curiously, although LINE1 is active in these embryonic cells – where it is "read" to produce RNA – it does not hop about within the genome. Instead, the RNA combines with proteins to control the activity of essential developmental genes.

REFERENCE

Percharde M, Lin C-J, Yin Y, Guan J *et al* (2018) A LINE1-nucleolin partnership regulates early development and ESC identity. *Cell* DOI: 10.1016/j.cell.2018.05.043

SOUNDS OF THE UNDERGROUND

A new acoustic technique can pick up the sound of roots growing, earth cracking, and worms burrowing, revealing the world hidden in the ground beneath our feet. Sounds are produced when grains of dirt and sand rub together or when tiny cracks appear in dry soil, although they are far too quiet for humans to hear directly.

Using highly sensitive piezoelectric sensors that pick up physical vibrations such as sound waves, scientists from ETH Zurich, Switzerland, and the French National Institute for Agricultural Research in Orléans listened to different types of soils in glass cells in the lab containing either corn plants or earthworms. They were searching for sound patterns that correlate with different biological activities.

Impressively, the sensors were able to distinguish noises caused by roots pushing their way through the soil as they grow, and to detect the sounds made by burrowing earthworms. By revealing the different kinds of activity that take place in the soil at various times of the day and under different conditions, the new technique could form the basis of agricultural sensors that allow farmers to monitor what is going on in their fields and to assess the quality of their soil without having to dig down and get their hands dirty.

REFERENCE

Lacoste M, Ruiz S. and Or D (2018) Listening to earthworms burrowing and roots growing – acoustic signatures of soil biological activity. *Scientific Reports* DOI: 10.1038/s41598-018-28582-9

Photos: Ramalho-Santos lab / UCSF (top left); markara/shutterstock (bottom); Dr. Carolyn Elya (top right)

19 %

A new analysis has revealed that nearly a fifth of all essential medicines sold in African countries are either sub-standard or entirely fake – especially vital anti-malarial drugs and antibiotics. This is far higher than the World Health Organization's estimate of around 10% worldwide. The problem particularly affects low and middle-income countries, costing money and lives through ineffective treatment or poisoning.

Source: Ozawa S, Evans DR, Bessias S, Haynie DG *et al* (2018) Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries. *JAMA Network Open* DOI: 10.1001/jamanetworkopen.2018.1662

Wild *Drosophila* killed by *Entomophthora muscae* Berkeley.

FUNGUS HIJACKS FRUIT FLY BRAINS

It may sound more like the plot of a horror story than a scientific paper, but researchers at University of California Berkeley, USA, are investigating how a fungal infection takes over the brain of a fruit fly, altering its behaviour to help the fungus spread to other victims.

Although the fungus, called *Entomophthora muscae* ("destroyer of insects"), was already shown to affect the behaviour of ants and flies in the wild – causing infected animals to climb up to a high point and adopt a strange pose that provides the right conditions for fungal growth and transmission – the molecular mechanism behind the brain hijacking is still unknown, partly because the tools for studying the affected insects were not available.

To find out more, the Berkeley team tracked infected fruit flies, for which plenty of molecular and neurobiological tools are available, over several days, watching carefully as the insects climbed to their doom, stuck their wings out in the characteristic death pose, and eventually died before being consumed by the fungus.

While it is still not entirely clear how *Entomophthora muscae* causes this behaviour, one explanation may lie in a particular strain of *Entomophthovirus* – an unusual virus that infects the parasitic fungus. Similar viruses can control the behaviour of other species of insects, so it might also be responsible for the mind-controlling effects of the fruit fly fungus, too.

No matter what the reason is, with the *E. muscae–D. melanogaster* system the researchers now have a way to study the mechanics behind parasitic manipulation of host behaviour.

REFERENCE

Elya C, Lok TC, Spencer QE, McCausland H, Martinez CC, and Eisen M (2018) Robust manipulation of the behavior of *Drosophila melanogaster* by a fungal pathogen in the laboratory. *Elife* DOI: 10.7554/eLife.34414.001

PROFILE OF **LABORATORY MICE AND RATS**

By Dr Mitch Leslie

Although the average person might still call experimental subjects "guinea pigs", you will not find these animals in most labs. Today, more than 90% of the animals that scientists study are mice and rats.

These rodents – particularly mice – have become indispensable for many fields, from basic research to developing drugs. Before drugs are tested on humans, they are required by law to be tested on two types of mammals. One is usually a rodent, the other a dog or a mini-pig.

One reason mice and rats have become so popular is that they are good substitutes for humans. Like us, they are mammals, with similar physiology and anatomy. Their genomes, which were the second and third ones from mammals to be sequenced after our own, have versions of nearly all of our genes. They can help researchers better understand human diseases because they are vulnerable to many of the same ones, including cancer.

Mice and rats are also convenient to study. Because they are small, they are cheaper to house and feed than are larger mammals. But compared to nematodes, fruit flies, or cell cultures, they are very expensive. They grow and reproduce rapidly. In some lab mouse strains, a female can give birth to her first pups when she is only around eight weeks old, and she may have four or more litters per year. The rodents typically live for two to three years, allowing researchers to study processes that unfold over a lifetime, such as ageing.

Lab mice and rats have been experimental subjects for hundreds of years, and even Mendel worked with them at first. Later, people also fancied mice as a hobby and bred them extensively. This laid the groundwork for many of today's laboratory strains, which have been bred to be better models. For example, in the early 1900s, mice breeder Abbie Lathrop noticed skin lesions on some of her animals and sent some to Leo Loeb, giving him a strain of well-documented and selectively bred mice prone to cancer, showing that cancer could be transplanted. Also at this time, researchers crossed brother and sister mice repeatedly, resulting in inbred strains of genetically nearly identical mice. Thus results from different labs or different experiments that use the same strain are comparable. Scientists have now generated several hundred inbred mouse and rat strains, including the famous Black 6 mouse strain that accounts for about 60% of all lab mice.

The number of mice in research rose sharply in the 1980s after scientists developed techniques for genetically modifying the animals by removing genes and inserting new or altered ones. Thus, scientists can now investigate not only the functions of particular genes but can also study how the immune system fights pathogens and the brain works. Using these methods, they can also create mouse models that simulate dozens of human illnesses, such as Alzheimer's disease, heart failure, and a large variety of cancers. These models provide insight into how these diseases develop and have helped researchers, for example, to develop the cancer treatments trastuzumab and ipilimumab.

Although rats had a head start as animal models, it took much longer to devise techniques for modifying their DNA. That is one reason why mice are now about three times more common in labs. But some researchers prefer rats because their physiology is more similar to ours, they are less likely to bite, and they are larger. Thanks to these attributes, rats remain favourite models for investigating subjects such as high blood pressure, addiction, and learning. The recently introduced CRISPR/Cas9 technology for editing DNA may also give rats a boost because researchers can use it to change the genes of both kinds of animals more easily and faster than before.

Although the study of rats and mice has provided many insights, their main limitation as models is that, despite sharing so many similarities, their genes, physiology, anatomy, and responses to diseases are not identical to ours. Thus not all results obtained by studying them transfer to humans. Still, without them we would know far less about our biology and have far fewer drugs with which to treat diseases ranging from the common flu to cancer.

WHO ARE WE? A FEW FACTS

About lab mice

- We weigh about 20 to 30 grams.
- We are descendants of several species, and laboratory strains contain mostly genes from *Mus musculus domesticus*, but also from *M. m. musculus* and *M. m. castaneus*.
- We live for two to three years.
- We eat seeds and plants and, in captivity, rodent chow.
- We work in almost all areas of biomedical research.
- We have helped researchers to win 39 Nobel prizes, including those for the discovery of checkpoint inhibitors to treat cancer and for the development of *in vitro* fertilization.

About lab rats

- I am *Rattus norvegicus*.
- I weigh up to 500 grams.
- I live up to 3½ years.
- I eat seeds, plants, meat and, in captivity, rodent chow.
- I work in almost all areas of biomedical research.
- I have helped researchers to win 31 Nobel prizes, including those for the development of magnetic resonance imaging (MRI) and for the discovery that nitric oxide serves as a signal in the circulatory system.

Photos: gettyimages/unoL (bottom)/dra_schwartz (top)

THE HEAT IS ON

By Dr Mitch Leslie

Organisms have adapted to survive high temperatures, but climate change could push some past their limits.

Adaptations to heat can take many different forms and be driven by different forces.

As the sun climbs above the horizon on a summer morning, an Arabian oryx strides across the desert in central Saudi Arabia. An antelope about as big as a medium-sized deer, the oryx is looking for a shady spot where it can take cover for the day. The desert is already starting to heat up, and by afternoon the air temperature in the open could reach 45 degrees Celsius.

The oryx will die if its body temperature rises too high. But the animal manages to keep its cool in one of the hottest land environments on Earth. Some organisms prosper at even higher temperatures. The microbe *Pyrococcus furiosus*, which inhabits hydrothermal vents off the coast of Italy, grows best in water that is nearly 100 degrees Celsius, and other microorganisms can withstand temperatures at least 10 degrees hotter.

Researchers have been probing the effects of high temperatures on organisms for more than 100 years. Thanks to new studies and new technologies, scientists now have a clearer understanding of how living things beat the heat. But these discoveries have also raised questions about whether some organisms will survive as the climate changes.

Heat has been a challenge since the first organisms appeared on Earth, says Robert Kelly of North Carolina State University in the USA: "Life started at high temperatures." Organisms need ways to protect themselves from heat because it can damage cells and molecules. For example, heat causes proteins to denature, meaning they lose their functional structure and therefore do not work properly. Denatured proteins can also form aggregations that harm cells.

Even if only a small percentage of a cell's proteins denature, it can malfunction or die. In a 2017 study, a team led by Paola Picotti of ETH Zurich in Switzerland tested human and microbial cells to determine what fraction of their proteins had denatured at different temperatures. The *Escherichia coli* bacteria that dwell in our intestines reproduce rapidly at our body temperature of 37 degrees Celsius, but their ability to grow declines precipitously when their surroundings hit 47 degrees Celsius. At that temperature, the researchers found, less than 10% of the bacteria's proteins had denatured, but as these were essential proteins mediating crucial cellular interactions it was enough to knock out the cells.

Heat takes a toll on other important types of molecules as well. At high temperatures, the two strands in a DNA molecule can peel apart, and the lipid membrane that encloses a cell becomes more fluid. That change not only makes the membrane leakier, but can also disrupt the functions of proteins embedded in the membrane.

However, cells can take steps to counteract the effects of heat. To prevent the cell membrane from becoming too fluid, some organisms add lipids with a higher melting point to it. For instance, researchers have discovered that one harmful strain of *E. coli* that contaminates food may survive cooking because it can boost the amounts of certain heat-resistant saturated fats and fatty acids in its membrane.

To shield their proteins, cells turn to heat-shock proteins, or HSPs. The molecules' name is a bit misleading, since they also provide protection against a variety of other stresses, including low oxygen levels and ultraviolet light. Humans produce ten types of HSPs, and most other organisms are able to make them as well. Rising temperatures spur cells to increase their synthesis of HSPs. The proteins serve as molecular chaperones, binding to denatured proteins and preventing them from forming dangerous aggregations.

Along with cellular adaptations, organisms have also evolved physiological, anatomical, and behavioural adaptations to heat. If you step outside on a hot day, some of these adaptations kick in quickly. You will start to sweat, releasing water that cools your body through evaporation. Your skin temperature will also climb because more blood diverts to the surface of your body, allowing more heat to escape into the environment. Fifty percent of the blood ejected from your heart may travel to the skin as the body attempts to get rid of excess heat, says Craig Crandall of the University of Texas Southwestern Medical Center in the USA. But sweating "may be even more important than elevated blood flow" for lowering body temperature in humans. Both are more effective with naked skin, which makes us well equipped to cope with heat beyond our body temperature of 37 degrees Celsius as long as it is not too humid. For dogs and many other mammals, however, sweating is less important. Instead, they pant to achieve the same effect.

The body's response to heat starts in the hypothalamus, the part of the brain that manages body temperature and other basic functions. Researchers have long suspected that neurons in the preoptic area of the hypothalamus regulate our temperature, but only recently have they tracked down these cells. In 2016, Zachary Knight of the University of California, San Francisco, →

The body's response to heat starts in the hypothalamus, the part of the brain that manages body temperature and other basic functions.

Photo: Scott/Adobe Stock

USA, and his colleagues identified neurons that responded to input from peripheral sensory neurons in mice and termed them warm-sensitive neurons. The researchers found that if they stimulated these neurons, the animals responded as if they were in a warm room, moving to a cooler part of their environment. Mice do not pant, nor do they sweat enough to reduce their body temperature. One of their main adaptations for dealing with heat involves diverting more blood into their tail, which serves as a radiator. Knight and his colleagues discovered that when they stimulated these temperature-responsive neurons in the animals, blood flow to the tail increased. To find out how the neurons could trigger these effects, the researchers traced the cells' axon projections and determined that they reached other brain areas that control autonomic functions and behaviour. It is still unclear whether these cells react to external temperature changes or whether they are identical with the preoptic neurons in the hypothalamus that are known to be temperature-sensitive and react when they themselves are warmed directly, which might happen e. g. due to fever or exercise.

The warm-sensitive neurons Knight's team discovered probably regulate our body temperature, too, and they do a pretty good job. Our internal temperature typically varies by less than a degree over the day. However, working or exercising in the heat taxes our ability to control our body temperature. Just three minutes of intense exercise increases by many times the amount of heat your muscles produce, notes José González-Alonso of Brunel University London in the United Kingdom. As a result, the body temperature of a person who is running or cycling in the heat can climb above 40 degrees Celsius. Blood flow to the active muscles, heart, brain, and skin also increases rapidly early in exercise. But it reaches a peak and thereafter declines, thereby limiting the body's ability to sustain muscle power and shed heat to the environment. González-Alonso and his colleagues found this by studying cyclists pedaling in hot conditions in the lab. This circulatory and thermal strain is one reason people fatigue more quickly at high temperatures, he says.

To investigate how mammals control their body temperature, scientists used to rely mainly on lab or captive animals. They needed to take regular measurements of body temperature, but that usually was not feasible if the animals were free to roam. Scientists still learned a lot about thermoregulation from those earlier studies, Andrea Fuller of Witwatersrand University in South Africa says, but some of the results have not held up. In the last 20 years or so, small, implantable devices known as data loggers, which can record the internal temperatures of an animal in its natural habitat over months or even years, have revolutionized scientists' understanding of how mammals deal with heat. Data loggers have shown that responses to high temperatures can be very different in free-living animals.

A prime example, Fuller says, involves research on captive camels and antelopes from the 1950s and 1970s. These studies found that the animals' body temperature rose by as much as 7 degrees Celsius during the day, an effect known as heterothermy. Instead of sweating or panting to reduce their body temperature during the day, these animals store the heat they have absorbed. Then at night they gradually cool off. Some researchers have concluded that the animals do this to save water.

Fuller and her colleagues have used data loggers to check for heterothermy in a variety of wild mammals, including cheetahs, gazelles, elephants, and the Arabian oryx. These measurements indicate that the animals usually do not let their body temperature climb by a large amount on hot days. "We do not see that at all as long as large mammals have food and water," Fuller says. The captive animals in previous studies likely got hot because they did not have enough water or could not perform actions that might have helped them cool down, such as escaping into the shade, Fuller says.

Researchers wielding data loggers have also challenged a textbook explanation of how mammals control their body temperature that was based on results from captive animals. Many kinds of mammals, including cats, dogs, and even-toed ungulates such as antelope and sheep, can channel blood heading for the brain into a fine network of blood vessels, known as the rete, at the base of the skull. In the rete, hot blood fresh from the heart passes close to cooler blood that has just come from the animal's nose and mouth – and as a result the temperature of the hot blood falls by half a degree or so. Other mammals, including humans, mice, and odd-toed ungulates such as horses, lack the rete.

For decades, conventional wisdom held that this arrangement of blood vessels prevented the animals' brains from overheating, particularly when they were fleeing from predators or exerting

The body temperature of a person who is running or cycling in the heat can climb above 40 degrees Celsius.

themselves in other ways. Shane Maloney, now at the University of Western Australia, says that when he began studying the rete in the early 1990s, he was "certain that it was cooling the brain" during activity. But when he, Fuller, and their colleagues tracked brain temperatures in free-living oryx with data loggers, they found that the brain was hotter than the blood during exertion. "When the animals are at their most active, they do not cool their brains," says Fuller.

Scientists now suspect that the structure instead helps the animals to maintain their water balance, Maloney explains. If body temperature rises, the hypothalamus will detect the increase and stimulate actions, such as sweating and panting that cause the animals to lose water. But by cooling the blood flowing to the brain, the rete in effect tricks the hypothalamus so that it does not activate these responses. A 2015 study by Fuller, Maloney, and colleagues of sheep living in a hot indoor pen showed how effective this strategy can be. When the sheep had little water, they were more likely to use the rete to cool the brain, and the scientists determined that the average animal saved around 2.6 liters per day. "When the animals are a bit dehydrated, they switch on this mechanism and they do not evaporate as much water," says Maloney.

Data loggers have also helped researchers better understand how the Arabian oryx stays cool in its scorching environment. In one study, Fuller, Maloney, and other researchers implanted the devices into wild oryx and put collars outfitted with thermometers on the animals to monitor the temperature of their surroundings. Although vegetation is sparse in the oryx's habitat, during the day they locate shady refuges where air temperatures can be as much as 12 degrees Celsius cooler than in the open, the researchers revealed. The animals also altered their time of activity across the year. In the summer, oryx searched for food at night and rarely budged during the heat of the day. In the winter, by contrast, they were more active during the day.

The oryx's adaptations allow it to avoid overheating in the desert without using a lot of water. The animals get by on only 355 ml of liquid per day, about the amount in a can of soda, Joseph Williams of Ohio State University in the USA and his colleagues discovered. "I drink a lot more than 355 ml when I am in the desert at 45 degrees," he says.

An oryx can snooze in the shade during the hottest part of the day – but the trees it is resting under do not have that luxury. Plants face different challenges than animals when responding to temperatures, and researchers long thought that plants were mainly passive. Although they have adaptations to protect themselves from heat, such as hairy leaves that reflect sunlight, the general view was that they did not take action to adjust their temperatures. But new studies by Sean Michaletz and colleagues of the University of British Columbia in Canada plotted leaf temperatures against air temperatures for a variety of plant species and found that, at high air temperatures, leaves remain cooler than their surroundings. How do plants modify their temperature? They do not sweat the way mammals do, but they can cool themselves through evaporation, by opening pores called stomata on their leaves, Michaletz says.

In the wild, animals like these Oryx rely heavily on behavioural strategies to deal with heat.

A team of researchers in Australia tested this idea in 2018 by growing eucalyptus trees in clear plastic bubbles that were up to 9 metres tall. The scientists then increased the temperature inside the containers, simulating a heat wave. The trees indeed opened their stomata during the hottest part of the day, when they were photosynthesizing little, suggesting that they are using evaporation through the pores to cool themselves.

The champions of high-temperature survival are thermophiles, the bacteria and other microorganisms that thrive in some of the harshest environments on the planet, such as hot springs in Yellowstone National Park in the USA, sweltering gold mines 6 km below the surface in South Africa, and hydrothermal vents on the ocean floor where the water squirting out of volcanic fissures is over 400 degrees Celsius. These organisms dwell in more familiar habitats as well, such as the water heaters of our homes, notes John Spear of the Colorado School of Mines in the USA.

Thermophiles "cope with heat through a combination of physiology and metabolism", says Spear. However, researchers are still trying to pin down the molecular differences that allow the organisms to survive such high temperatures. The paradox is that the more researchers learn about thermophiles, the more similar they are to their relatives that live in cooler habitats, Kelly says.

One distinction that researchers have identified is that the proteins of thermophiles can withstand higher temperatures →

Photo: Loïc Bourgeois/fotolia

than comparable proteins of temperate microorganisms. On average, the melting points of thermophile proteins are 32 degrees Celsius higher, one study found.

Researchers would love to know why the proteins of thermophiles are so durable, in part so they can engineer better enzymes for industry. Scientists have identified features that seem to promote stability, such as an increased number of bonds between the sulphur atoms carried by some amino acids. In a 2016 study, for instance, Japanese scientists found that a single disulphide bond was crucial for the heat stability of a serine-synthesizing protein from *Hydrogenobacter thermophilus*, a bacterium that lives around hot springs. The bond holds together two subunits of the protein, they discovered. However, says Kelly, researchers have not discovered a simple recipe for heat-resistant proteins. "There are a lot of subtle things that make proteins more stable at high temperatures," says Anna-Louise Reysenbach of Portland State University in the USA.

Recent studies have cast doubt on another potential thermophile adaptation. In the 1960s, researchers hypothesized that the organisms shield their DNA from heat by boosting the amounts of the nucleotide bases cytosine and guanine. In a molecule of DNA, guanine pairs with cytosine and thymine pairs with adenine. Because guanine and cytosine are more strongly attracted to each other than are adenine and thymine, researchers predicted that DNA from heat-loving microbes would contain relatively more guanine and cytosine – a higher G:C content– so that the strands do not separate.

Aerial view of Grand Prismatic Spring in Yellowstone National Park, WY, USA, the third largest hot spring in the world, measuring 75 x 91 meters and coloured by bacteria and archaea.

The idea makes sense, says Spear, because even a 1 or 2% increase in G:C content can increase the DNA's stability. The values for some thermophiles are high. The G:C content of *T. aquaticus*' DNA, for instance, is 68%, versus around 50% for *E. coli*. But the pattern does not hold when researchers analyze many species, says Kelly. Thermophiles that live in the hottest environments do not necessarily have a higher G:C content than their counterparts that live in slightly cooler places, he notes.

Organisms that live in groups have another option for dealing with heat – teamwork. Honeybees, for instance, join forces to keep the temperature in the hive between 32 and 36 degrees Celsius. Researchers have found that when the hive temperature begins to get too high, some bees press their bodies against the warmest sections of the hive's walls, turning themselves into insulation to keep the temperature from rising further. The insects also bring in water that evaporates, cooling the hive.

On hot days, bees line up at the entrance to the hive and beat their wings, a behaviour known as fanning that improves air circulation. The animals are not just flapping away – they fine-tune their wing movements for the task, as a team of researchers led by Jacob Peters, then a graduate student at Harvard University in the USA, found in 2017. The scientists filmed fanning bees with high-speed cameras and discovered that they beat their wings more slowly than hovering bees. Fanning bees also move their wings at a different angle, possibly increasing their ability to circulate air.

Scientists are investigating how bees decide when to start fanning. They seem to take their cue from each other, as Chelsea Cook of Arizona State University in the USA and her colleagues found when they added different numbers of bees to warm jars. "They don't fan alone," says Cook. Rather, two or more bees in a jar will start fanning. Cook is now trying to figure out how the bees communicate to synchronize their behaviour.

Adaptations enable organisms to prosper in some extremely hot environments, but researchers worry about what will happen as the climate changes. Elephants, for example, can live in hot environments such as the Namib Desert in southern Africa as long as they have regular access to water to cool off. But climate change could alter rainfall patterns as well as temperature, notes Fuller. "An elephant alive now will be alive in 2050 and will face a radically different environment." Williams says he worries about how oryx will cope, since climate change could push daytime temperatures in the antelope's environment above 50 degrees Celsius. "If the predictions are true, I'm not sure the animals I worked on could survive."

Photo: Ajith Kumar/iStock

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

Therefore, this pdf continues with the section Results.

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

Shared first authorship is indicated with an *.

STRUCTURAL AND FUNCTIONAL BASIS FOR TRIM25 ENZYMATIC ACTIVITY AND VIRAL SUPPRESSION

cf. BIF FUTURA, VOL. 29 | 2.2014

MARIOS G. KOLIOPOULOS
Discipline: Biochemist, MSci
Institute: The Francis Crick Institute, London, UK
Supervisor: Dr Katrin Rittinger

Ubiquitination, a post-translational modification of proteins, has many roles across the cell. The addition of ubiquitin to target proteins involves the sequential action of three enzymes, the last of which is the E3 ligase. One of the largest subfamilies of E3 ligases consists of the tripartite motif (TRIM) proteins, which are characterized by a conserved motif comprising a RING (really interesting new gene) domain, one or two B-box domains, and a coiled-coil region. Self-association was believed to be crucial for the catalytic activity of TRIM proteins, but the underlying mechanisms were elusive. My work focused on TRIM25, which has a crucial role in anti-viral immunity. Upon viral infection, TRIM25 ubiquitinates retinoic acid-inducible gene-I (RIG-I), a cytosolic pathogen recognition receptor, which leads to its activation. RIG-I then initiates a genetic programme that leads to an immune response. Viruses have evolved mechanisms to counteract the action of TRIM25 and suppress immunity. Using a combination of biochemical, biophysical, and structural approaches, I showed how TRIM25's oligomeric state is linked to its catalytic activity. By solving the crystal structure of the TRIM25 RING domain, the E2 ubiquitin-conjugating enzyme, and ubiquitin, I identified the features that promote the transfer of ubiquitin to RIG-I. I also investigated TRIM25 inhibition upon influenza infection. I solved the crystal structure of TRIM25 in complex with influenza protein NS1 and compared it to the structure of the TRIM25 coiled-coil region and substrate-recognition domain. NS1 binding causes conformational changes to TRIM25 that inhibit RIG-I ubiquitination, allowing the virus to survive. My results extend our understanding of TRIM E3 ligases, which may increase our chances of targeting specific steps of the ubiquitination pathway that are involved in various diseases.

PUBLICATIONS

Koliopoulos MG, Lethier M, van der Veen AG, Haubrich K, Hennig J, Kowalinski E *et al* (2018) Molecular mechanism of Influenza A NS1-mediated TRIM25 recognition and inhibition. *Nat Commun* **9:** 1820

Esposito D, Koliopoulos MG, Rittinger K (2017) Structural determinants of TRIM protein function. *Biochem Soc Trans* **45:** 183–191

Koliopoulos MG*, Esposito D*, Christodoulou E, Taylor IA, Rittinger K (2016) Functional role of TRIM E3 ligase oligomerization and regulation of catalytic activity. *EMBO J* **35:** 1204–1218

BIOLOGICAL FUNCTIONS OF MAMMALIAN iRHOM1 AND iRHOM2

cf. BIF FUTURA, VOL. 29 | 1.2014

ULRIKE KÜNZEL
Discipline: Biochemist, MSc
Institute: Sir William Dunn School of Pathology, University of Oxford, Oxford, UK
Supervisor: Prof. Matthew Freeman

ADAM17 (a disintegrin and metalloproteinase 17) cleaves and releases membrane-tethered proforms of several signalling molecules from the plasma membrane, including the inflammatory cytokine tumour necrosis factor alpha (TNFα) and ligands of the epidermal growth factor receptor (EGFR). ADAM17 is accompanied and regulated by multi-pass membrane proteins called iRhoms, which belong to the conserved rhomboid-like superfamily. Because iRhoms use several mechanisms to control ADAM17 activity throughout the secretory pathway, understanding how they function would provide insights into inflammatory and epidermal growth factor signalling. The goal of my PhD project was to understand how iRhoms are regulated. I developed a screen to identify novel binding partners of human iRhom1 and iRhom2 using co-immunoprecipitation and mass spectrometry analysis. The top hit was the poorly characterized FERM (four-point-one, ezrin, radixin, moesin) domain-containing protein 8 (FRMD8). Using FRMD8 gain- and loss-of-function in combination with co-immunoprecipitation, western blotting, and flow cytometry, I found that FRMD8 binds both iRhoms and stabilizes the iRhom-ADAM17 complex at the cell surface. Accordingly, loss of FRMD8 results in the destabilization of iRhom2 and mature ADAM17, which leads to a reduction in the number of ADAM17 substrates that are released from the plasma membrane. Using macrophages derived from human induced pluripotent stem cells, as well as FRMD8 knockout mice, I showed that FRMD8 regulates the iRhom-ADAM17 pathway *in vivo*. In summary, I discovered FRMD8 as a new regulator of ADAM17-dependent growth factor and cytokine signalling *in vitro* and *in vivo*. Blocking the interaction between FRMD8 and iRhoms may have therapeutic potential for diseases in which ADAM17 activity is uncontrolled, such as inflammation and certain types of cancer.

PUBLICATIONS

Künzel U, Grieve AG, Meng Y, Sieber B, Cowley SA, Freeman M (2018) FRMD8 promotes inflammatory and growth factor signalling by stabilising the iRhom2/ADAM17 sheddase complex. *Elife* **7:** e35012

Grieve AG, Xu H, Künzel U, Bambrough P, Sieber B, Freeman M (2017) Phosphorylation of iRhom2 at the plasma membrane controls mammalian TACE-dependent inflammatory and growth factor signalling. *Elife* **6:** e23968

GAINING INSIGHTS INTO THE BIOLOGY OF HAPLOID MAMMALIAN CELLS

cf. BIF FUTURA, VOL. 30 | 2.2015

TERESA OLBRICH
Discipline: Medical Biologist, MD
Institute: Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Supervisor: Prof. Óscar Fernández-Capetillo

With the exception of the sperm or ovules, human cells contain two sets of chromosomes, one from each parent. However, cells with a single set of chromosomes (haploids), such as those found in yeast or recently isolated from mice and humans, are extremely useful for genetic studies and have been crucial in studying key genes and pathways. When there is only one set of chromosomes, we can easily identify interesting mutants because altering a single allele is sufficient to produce a phenotype. However, cultures of mammalian haploid cells present a problem: they become diploid within a few days. The goal of my PhD was to investigate this phenomenon, known as diploidization. First, I discovered that the loss of haploid cells in culture was due to their limited viability rather than their true conversion to diploid cells. My results suggested that existing diploid cells replaced the haploid cells, gradually taking over the cell culture. I also found that compared to diploid cells, haploid cells had higher levels of cell death mediated by the tumour suppressor p53. This is because the machinery involved in cell division has evolved to handle a fixed amount of DNA (46 chromosomes). Whenever a cell contains more (polyploidy) or fewer (haploidy) chromosomes, mitosis is more prone to errors during chromosome segregation, which leads to the activation of p53. I confirmed this by showing that p53 depletion facilitated the generation and maintenance of haploid mammalian cells. Next, I performed a screen to identify chemicals capable of stabilizing the haploid state. Among several promising compounds, I focused on deacetylbaccatin-III (DAB), a precursor of the chemotherapy drug Taxol, and the strongest hit in the screen. DAB activated the spindle assembly checkpoint, an important checkpoint in mitosis, in a ploidy-dependent manner and thereby facilitated the maintenance of haploidy in culture. DAB also selected preferentially for lower-ploidy cells in culture in multiple cell lines, which suggests that it could be used against tumours carrying a high load of polyploidy cells.

PUBLICATIONS

Mayor-Ruiz C, Olbrich T, Drosten M, Lecona E, Vega-Sendino M, Ortega S et al (2018). ERF deletion rescues RAS deficiency in mouse embryonic stem cells. *Genes Dev* **32:** 568-576

Olbrich T, Mayer-Ruiz C, Vega-Sendino M, Gomez C, Ortega S, Ruiz S, Fernandez-Capetillo O (2017) A p53-dependent response limits the viability of mammalian haploid cells. *Proc Natl Acad Sci USA* **114:** 9367–9372

A NEW PARADIGM TO UNDERSTAND AND STUDY MICROCEPHALY

cf. BIF FUTURA, VOL. 30 | 2.2015

ATTYA OMER
Discipline: Neurobiologist, MSc
Institute: Whitehead Institute for Biomedical Research, Cambridge, MA, USA
Supervisor: Prof. Rudolf Jaenisch

Elucidating the mechanisms of cell division is crucial to understanding the cellular events that contribute to the development of the human cerebral cortex, which likely go awry in microcephaly – a condition in which the head and brain are smaller than normal. Most of the genes found to be mutated in individuals with microcephaly encode centrosomal proteins. In my PhD project, I focused on kinetochore scaffold 1 (KNL1), which encodes a protein with a central role in kinetochore assembly and function during mitosis. While the involvement of centrosome functions is well established in the aetiology of microcephaly, little is known about the contribution of the kinetochore. I studied the role of KNL1 in brain development and its involvement in microcephaly. I generated isogenic human embryonic stem cell lines (hESC) bearing a KNL1 patient-specific mutation using CRISPR-Cas9. I showed that the mutation led to reduced KNL1 expression and decreased cell number in cultures of neural progenitors. Moreover, mutant neural progenitors showed aneuploidy, an increase in cell death, and an abrogated spindle assembly checkpoint. The subsequent differentiation of neural progenitors into two-dimensional neuronal cultures led to the premature generation of neurons and astrocytes, depleting the neural progenitor population in mutant cells. When neural progenitors were cultured as three-dimensional neural spheroids, the mutant spheroids were smaller than the control. While most of the mutated genes found in microcephaly patients encode a cell division-related protein, which is presumably important in all tissues, only the brain is impacted. To obtain insight into the brain-specific mutant phenotype, I differentiated mutant and control hESCs into fibroblasts, astrocytes, and neural crest cells. In contrast to neural progenitors, I found no changes in KNL1 expression, cell proliferation or genomic integrity in these cells. My data suggest that KNL1 has a cell-specific function in neural progenitors during development. Moreover, changes in its expression might contribute to the brain phenotypic divergence that appeared during human evolution. My findings offer a new paradigm to understand the pathogenesis of microcephaly.

PUBLICATIONS

Muffat J, Li Y, Omer A, Durbin A, Bosch I, Bakiasi G et al (2018). Human induced pluripotent stem cell-derived glial cells and neural progenitors display divergent responses to Zika and dengue infections. *PNAS* **115:** 7117-7122

ROLE OF THE VENTROMEDIAL HYPOTHALAMUS IN CONTROL OF INNATE DEFENSIVE BEHAVIOURS

cf. BIF FUTURA, VOL. 30 | 2.2015

NATALIA WRÓBLEWSKA
Discipline: Neuroscientist, BA
Institute: MRC Laboratory of Molecular Biology (LMB), University of Cambridge, Cambridge, UK
Supervisor: Dr Tiago Branco

How does the brain integrate the huge variety of sensory inputs to generate appropriate behaviours? Innate defensive behaviours are a good model to address this question, as they are essential for animal survival and the brain circuits that control them are highly conserved across species. The ventromedial hypothalamus (VMH) is a key brain region for controlling responses to predators. Inactivating the VMH can reduce defensive behaviours, while activating VMH output neurons (SF1+ cells) can produce a variety of behaviours, from immobility to escape. During my PhD, I studied the role of the VMH in the control of defensive behaviours. I began by quantifying these behaviours in mice in response to olfactory and auditory predator cues, as well as to the optogenetic activation of SF1+ neurons. To determine whether the SF1+ neuron population was heterogeneous, which could explain its ability to trigger different behaviours, I performed patch-clamp recordings from acute brain slices. Although the recordings showed that SF1+ neurons are largely homogenous, they revealed other properties suggesting that SF1+ neurons are highly efficient at integrating and transmitting inputs to downstream brain areas. I next investigated how SF1+ neurons integrate excitatory inputs from the medial amygdala (MEA), which receives olfactory inputs from the accessory olfactory bulb. Using optogenetics and slice electrophysiology, I found a high connectivity rate and high probability of vesicular release between these two regions, but also synaptic depression. This means that the VMH is highly efficient at detecting an increase in MEA activity, but cannot be activated to a high level by these inputs, thereby restricting the type of behaviour triggered via this connection. Finally, I investigated *in vivo* activity in the VMH in response to different sensory stimuli by performing calcium imaging of VMH neurons in mice. Some SF1+ cells responded to only one stimulus, while others responded to multiple stimuli. I also found that, on average, the first behavioural response to a stimulus occurred before SF1+ activity. My results suggest that the VMH accumulates information about danger in the environment, priming the circuit to respond to subsequent threats.

PUBLICATIONS

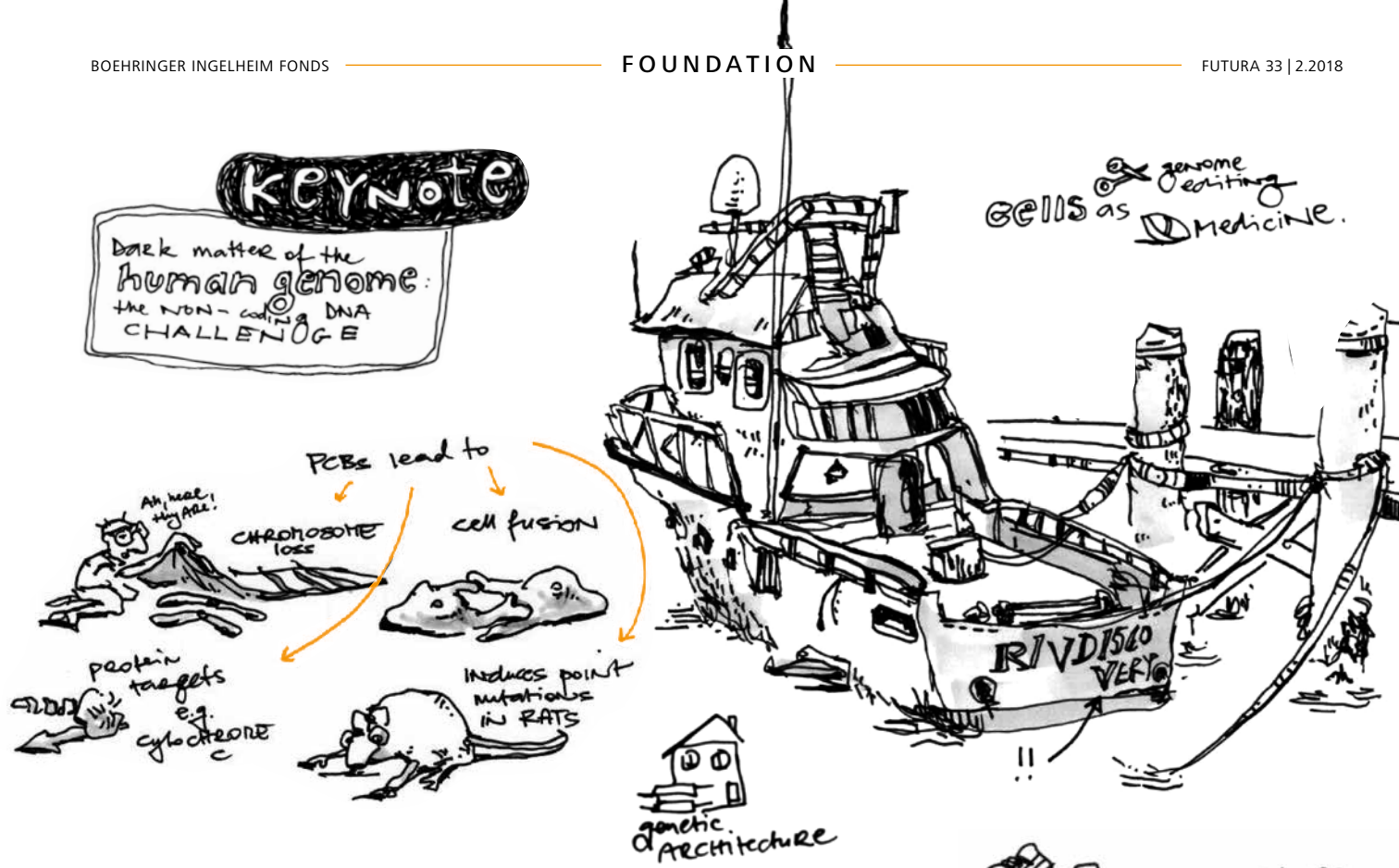
The results of this project have not yet been published.

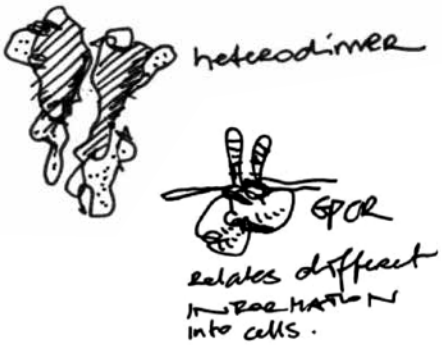
THE FOUNDATION The Boehringer Ingelheim Fonds (BIF) is a public foundation – an independent, non-profit organization for the exclusive and direct promotion of basic research in biomedicine. The foundation pays particular attention to fostering junior scientists. From the start, it has provided its fellowship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

12th North America Meeting

Text by Kirsten Achenbach, drawings by Oliver Höller

Current fellows and alumni of BIF's fellowship programmes gathered for BIF's 12th North America Meeting. Taking place at the Marine Biological Laboratory in scenic Woods Hole, it offered four days packed full of talks by current fellows and alumni, and of course the traditional whale-watching excursion on Sunday.

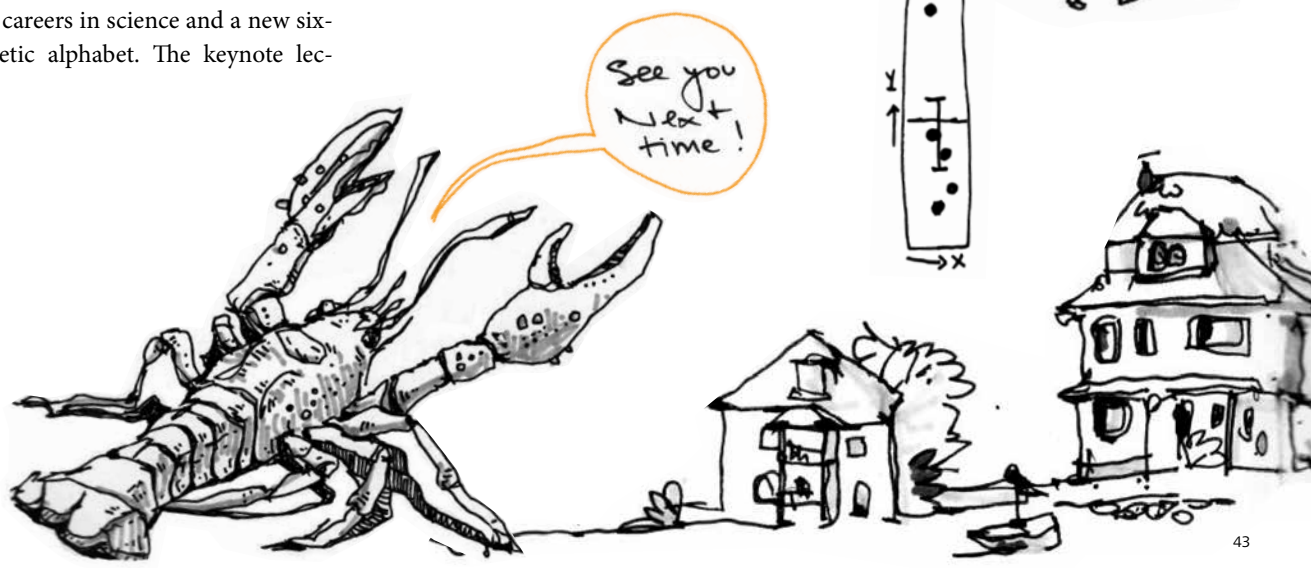




The roughly 80 participants were highly diverse, with more than a third having started their fellowship more than 20 years ago – three even belonged to BIF's "crop" from 1985 – and a third within the last three years. The most recent fellow started only a month before the meeting.

As usual, the current fellows of the PhD and MD programmes all presented their projects and we were able to accommodate the overwhelming majority of interested alumni. The talks covered a broad range of topics, from LSD studies and Alzheimer's disease to careers in science and a new six-letter genetic alphabet. The keynote lectures, given by BIF alumni well established in their fields, provided insights into the unknowns of neuroscience, glial cells that control CNS function, visualized retroviral life cycles, cancerous PCBs, and the "dark matter" of the human genome.

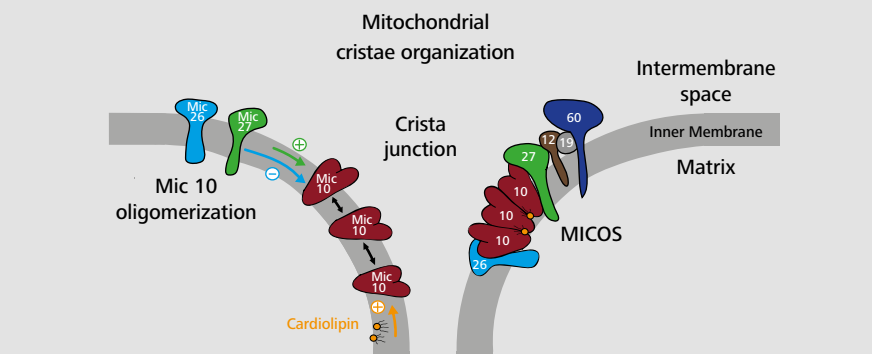
All of this was punctuated by the animated breakfast, lunch, and dinner discussions about science and everything else that is important or pleasant in life. And as you can see, BIF alumnus Oliver Höller drew a very special meeting abstract from which we have taken a few illustrations.



PAPERS IN THE SPOTLIGHT

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

A PUZZLE PIECE OF HOW MITOCHONDRIA FOLD THEIR MEMBRANES



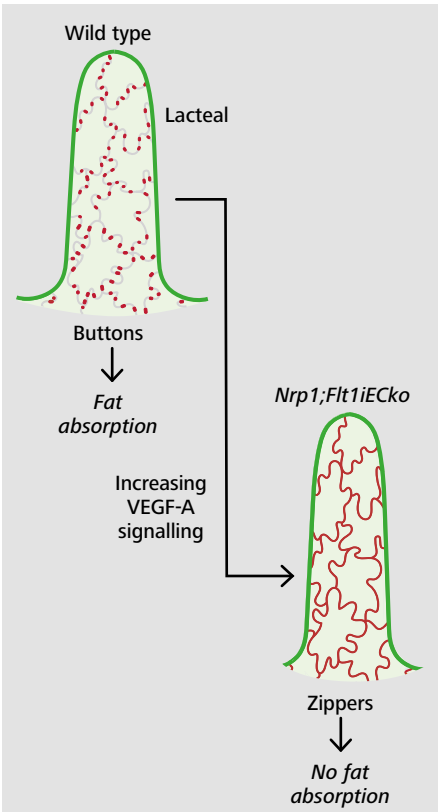
Mitochondria constantly adapt their energy production to the energy demands of the cell. One way of adapting energy output is by regulating the surface area needed to produce energy. Mitochondria have two membranes, and the inner one has many invaginations – so-called cristae – that enlarge the membrane surface for energy production and compartmentalize it into functionally different areas. Florian Wollweber, currently a BIF fellow in the lab of Martin von der Laan at Saarland University, and alumni Heike Rampelt and Maria Bohnert have now further unravelled how these cristae are formed and stabilized. The inner membrane curves inward to form the opening of a crista, an area called the crista junction. The curvature of the junction is stabilized by MICOS – a multi-subunit complex without which cristae would be disorganized or malformed. One of its core units, Mic10, forms curved oligomers which act as scaffold for the membrane curvature. Mic27 was known to stabilize Mic 10 polymers and is thought to bind cardiolipin, a mitochondrial lipid. The authors were able to show in yeast how several components regulate MICOS: Mic26, which is a paralogue of Mic27, counteracts Mic27 by destabilizing Mic10 oligomers, whereas cardiolipin stabilizes Mic10 oligomers. By deleting Mic26, Mic27, and cardiolipin synthase in differing combinations, they showed that the Mic26–Mic27 pathway is independent of the cardiolipin pathway. When both stabilizing elements, Mic27 and cardiolipin, were missing, the MICOS complex was disrupted the most. In conclusion, they propose that regulating Mic26 is a way for the cell to alter the dynamics of MICOS and thereby fine-tune mitochondrial inner membrane architecture to cellular demands.

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

Maria Bohnert, fellow 2008–2010
Heike Rampelt, fellow 2007–2009
Florian Wollweber, fellow 2016–2018

ZIPPING YOUR GUT AGAINST FAT

From the gut to the blood, fat travels via the lymphatic system: intestinal epithelial cells package fat into tiny transport particles, the chylomicrons. These enter the lumen of the so-called lacteals, the finest parts of the lymphatic system extending into the villi of the small intestine. However, it was previously unclear how chylomicrons enter the lacteals, as they are too large to pass through the lacteals' endothelial cells. Anne Eichmann and her group have shed light on this question by testing what role two endothelial cell receptors



Photos: Journal of Molecular Biology (top left); Anne Eichmann (bottom right)

play in fat transport in obesity and diabetes. The cells lining most of the lymphatic – and blood – vessels are tightly joined together through so-called zipper junctions, which prevent leakage. But lacteals possess a different type of cell–cell junction only discovered ten years ago. These so-called button junctions have open regions, allowing entry of chylomicrons and fluid into the lacteals. When Anne and her team deleted the genes for the cell receptors she studied in mice – Vegfr1 and Nrp1 – she found that the button junctions in the lacteals turned into zipper junctions, preventing fat from entering. Put on a high-fat diet, these mice stayed slim. It turns out that the deleted cell receptors normally curb the transformation of button to zipper junctions by binding VEGF-A, which promotes this transformation. This discovery opens the possibility of regulating fat uptake – and therefore diseases like obesity – by changing the type of cell–cell junction in lacteals. However, zipping up too tightly would most likely result in malnutrition or worse – after all, it is the dose that makes the poison.

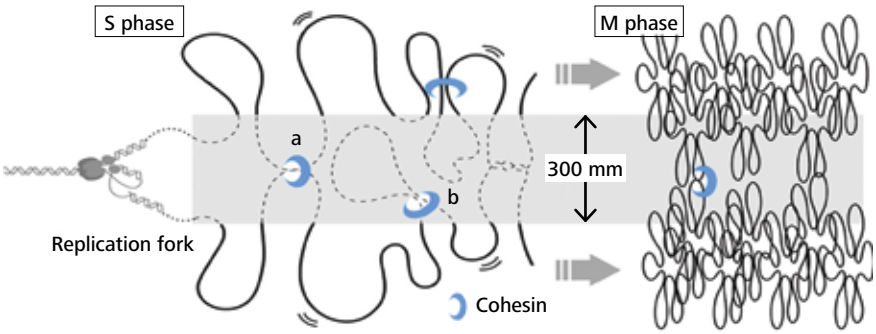
Photo: Journal of Cell Biology (top right)

REFERENCE

Zhang F, Zarkada G, Han J, Li J, Dubrac A, Ola R *et al* (2018) Lacteal junction zippering protects against diet-induced obesity. *Science* **316:** 599–603

Professor Anne Eichmann, fellow 1990–1992

CHROMATID SEPARATION: EARLIER AND FASTER



Chromatids separate quickly after replication, but are still tethered to each other (a) and within each other (b) by cohesin rings. These may also help to prepare a chromatin structure for the compaction necessary for mitosis.

When cells divide, both daughter cells receive one copy of each chromosome. These copies, called sister chromatids, need to separate correctly and on time to ensure that each daughter cell receives a complete set. Rugile Stanyte from Daniel Gerlich's group at the Institute for Molecular Biotechnology in Vienna, Austria, has now devised the first method to visualize sister chromatid separation in living cells during the entire cell cycle. Using CRISPR/Cas9, she targeted small DNA loci containing repetitive DNA elements and fluorescently marked corresponding sequences on both sister chromatids in 16 different human cell lines. Attaching several markers per locus reduced the light energy needed to excite the markers, enabling her to track how fast and how far sister loci separated from each other without damaging the cells. With this elegant method, she found that sister loci split shortly after being replicated, indicating that sister chromatids separate much earlier than previously thought. Additionally, sister loci separated in the order in which the DNA sequences were replicated. After the initial split, the observed sister loci moved rapidly within the cell nucleus, but did not separate beyond a certain distance, suggesting incomplete chromatid separation during interphase. Sister chromatids are known to be linked by cohesin rings. Unexpectedly, cohesin-rich DNA sites were not linked more often or longer than those with a background cohesin level. The authors think that cohesin at these sites does not link chromatids, but instead helps interphase chromosomes to fold into a functional state. Where cohesin does link chromatids thus remains unclear, but the studies' results imply few potentially mobile cohesin rings.

REFERENCE

Stanyte R, Nuebler J, Blaukopf C, Hoefler R, Stocsits R, Peters JM, Gerlich DW (2018) Dynamics of sister chromatid resolution during cell cycle progression. *J Cell Biol* **217:** 1985–2004

Rugile Stanyte, fellow 2012–2014

CELEBRATING OUR 100TH MD FELLOW

This year, BIF's MD fellowship programme welcomed its 100th fellow, Luise Eckhardt – reason enough to have a look at the programme and talk to Luise and two programme alumni, Isabelle Schellinger and Ricardo Grieshaber Bouyer Rodrigues. As Claudia Walther, BIF's managing director, explains in this issue's editorial, the idea behind the programme is "to create an incentive for medical students to learn from leading scientists in internationally recognized laboratories".

The Boehringer Ingelheim Fonds MD fellowship programme offers medical students in Germany the possibility of taking 10 to 18 months off from studying to pursue an experimentally demanding and hypothesis-driven research project in basic biomedical research in a leading laboratory. Applications must shine in three areas: the applicants' achievements, the scientific quality of the proposed research project, and the scientific standard of the laboratory in which the project is to be pursued.

In 2006, the first MD fellowship enabled Michael Breckwoldt to go to Massachussets General Hospital in Harvard, USA. Since then, around ten MD fellowships have been awarded every year, and some 80% of the fellows pursue their project in the UK or the USA. The fellows are required to move to a new institute and location to ensure that they devote themselves fully to their research project and do not pursue it alongside their usual coursework. Although we are aware of at least 65 publications – more than half of them first-author papers – the programme's intention is high-calibre research training for MDs. The BIF's support includes not only the monthly stipend, but also travel allowances for conferences, scientific method courses, or laboratory visits. Further support, such as a childcare allowance, may be applied for. The fellows also receive the typical personal BIF support and are part of the BIF network: they are invited to one progress seminar or, for example, the communication training during their fellowship as well as to the informal meetings and alumni seminars in Europe and the USA.

"WHEN IT COMES TO BENCH WORK, I BASICALLY HAD TO START FROM SCRATCH"

LUISE ECKARDT

MD project: The role of HIF-2/PHD2 in adrenal development and function

Supervisor: Professor Sir Peter J. Ratcliffe

Pursued at: University of Oxford, UK

Home University: University of Heidelberg, Germany

Project start: 8/2018

Why did you apply for an MD fellowship?

I knew I wanted to do my doctoral thesis in the UK and I wanted it to be in basic research. Through my university's exchange programmes, this turned out to be very difficult. But I got lucky and my former professor in physiology had very good connections to the lab I now work in and agreed to supervise my thesis. On the internet, I then learned about the BIF's MD programme – and applied. I am very happy and grateful I got accepted.

What is your project about?

I aim to better understand the physiology and development of the adrenal medulla, the innermost part of the adrenal gland, in relation to the hypoxia signalling pathway, which responds to low oxygen conditions. This is interesting considering that 15 to 20% of all tumours of the adrenal medulla are known to harbour a mutation directly affecting key mediators of the hypoxia signalling pathway. However, the mechanism behind this is so far unknown.

You started in your lab a few months ago. What experiences have you had so far?

So far, it has been an incredible experience – even before I started here, the lab enabled me to go to a Keystone Symposium in my field devoted to the physiology and pathophysiology of hypoxia. It was held in Oxford this year. At the conference, I had the chance to meet many pioneers in the field and learn about the newest developments in hypoxia research. The laboratory itself is quite large and very international – we have postdocs and PhD students from over 10 different nations working together on the same topic. However, each one of them is addressing a different angle of the hypoxia pathway. That way, I profit from their experience and can expand my knowledge tremendously. The atmosphere is very welcoming and I can take part in all the meetings and am encouraged to share my ideas and get valuable feedback.

Also, I really enjoy being able to delve into a topic, to do literature research and then develop new ideas, which I can immediately test at the bench. It gives a greater depth of understanding and in that sense is more intense then my MD studies at home. I would really like research to be part of my working life in the future.

How about bench work?

When it comes to bench work, I basically had to start from scratch and learn all the techniques such as immunhistochemical staining and *in situ* hybridization with the RNAScope assay. My supervisor here in Oxford has been incredibly supportive and it is amazing to see how fast you can progress in a good working atmosphere.

Why do you want to be a clinician scientist?

Both, clinic and research, hold great attraction for me: the clinical side gives you contact with people, it is a bit like detective work to figure out what the diagnosis is. It also gives you the satisfaction of seeing people get better, of making a difference on a day-to-day basis. Through my own research, I hope to be able to increase our collective knowledge about the human body, to find out something that was not known before and that way to make a difference in the long term.

You're studying medicine in Heidelberg and are now working in Oxford, both very traditional university towns. How do they compare?

Both are beautiful cities and have a vibrant student life. In Heidelberg, I was surrounded mostly by other, mainly German, MD students. But here in Oxford I was lucky enough to get into a dorm of Corpus Christi College. The college atmosphere is very special, I live with PhD and master's students from all over the world and from many different disciplines. I can get to know their perspectives, their topics. The exchange and discussions between different fields is very much encouraged by the many events taking place in the historic part of Corpus Christi College.

Photo: Luise Eckardt

What do you hope to achieve during the rest of your research stay?

Of course, I first want to establish my project further and to achieve good and interesting results. But I also hope to learn some more techniques. I've profited enormously from the great knowledge and experience in my group, especially from the older postdocs and seniors, and there is so much more to learn. Also, I'm involved in some long-term experiments here – I'm really looking forward to getting some results for them over the next few months.

"I WAS ALWAYS ABLE TO CALL BIF FOR ADVICE OR FOR PEOPLE TO CONTACT"

ISABEL SCHELLINGER
Now: Clinician scientist and co-founder of Angiolutions, Göttingen, Germany
MD project: The role of miRNA-146 in vascular inflammation and abdominal aortic aneurysm disease development
Supervisor: Professor Philip S. Tsao, PhD
Pursued at: Stanford University, CA, USA
Home University: University of Erlangen, Germany
Fellowship: 6/2013–11/2014

Looking back, what were the main benefits of the MD fellowship for you?
Without the fellowship, it would have been very difficult to afford going to Stanford University for my project – after all, it is quite an expensive area. Besides that, I met many like-minded people, some of whom are now very close friends, as well as independent mentors. Concerning the latter, BIF has always been very supportive. Several times I stood at a crossroads and I was always able to call BIF and ask for advice or for people to contact. In this regard, the BIF network is a safe haven for open discussions. There is a special kind of trust built on the shared experience. It really is about the human connection. For me, BIF is about the people.

Today, you are not only an MD but also a researcher and the co-founder of a company based on the results from your project. You have even been billed as one of "30 under 30" in *Forbes* magazine. Did you ever imagine something like this when you applied for your fellowship?
No, never! This is not something you plan for – and the project didn't look like a success at the beginning: actually, my planned project didn't work out at all. I quickly had to come up with a new plan. Everyone in my lab was very understanding and reassuring, very open, especially my supervisor, Philip Tsao, whom I still see at least once a year and whom I am still very thankful to. He supported me all the way, not once assigning blame, but helping me to develop an alternative route. I can say, facing the challenges and meeting the people I did during my MD project was a formative experience for me.

What made you decide to found your own company?
When we published our results, Stanford approached us and said we should patent our findings. Then I returned to Germany to receive my degree. Everything was very busy for a while. Still, I discussed the topic a lot with my co-founder, Uwe Raaz, who I have worked with during my time in the lab at Stanford, and in 2017, we finally said yes, we will give it a try. One of the things that helped us decide to pursue our idea was probably having been in Stanford for so long. There, start-ups are part of the academic mind-set, wanting to be an entrepreneur, independent, taking risks.

What was your project about?
We worked on abdominal aortic aneurysms that are bulges of the aorta. The greater the diameter, the larger the risk of a deadly rupture. Today, there are only treatment options available to treat large aneurysm disease. We investigated how small aneurysm grow in the first place and identified a new mechanism that laid the foundation for our novel therapeutic approach. The latter will hopefully prevent complicated, major, high-risk interventions that are today the main treatment option.

What are your three tips for someone wanting to go that route?
Do so with people you trust. "Alone against the world" doesn't work. Search for people who have experience. Every time I get stuck, I look for people who can give me an outside perspective – often enough I find those people within the BIF network. You can't know everything when it comes to complex matters like starting a business. And besides hard work, you will also need luck. And we did have that several times, meeting the right people at the right time.

You took part in our communication seminar in Cold Spring Harbor, but you also have taken courses at university – how important is good communication to you?
For me, communicating well is super important. If I don't communicate my science in a way my patients or potential funders understand, I have a problem. If I want to recruit patients for a study, I need to explain it to them without medical jargon. If I can't make a potential investor understand what I want to do, I can't get money. For me, the fallout of bad communication is immediate, just like the benefits. In academia, both can be delayed and therefore many people in my opinion underestimate how important it is to learn to communicate well. I have taken many such seminars, and the trainers at the BIF seminar were very impressive.

Photo: Maria Braun Photography

Would you go that route again?
Yes, most definitely yes. The last year has been exciting – I've met so many people, learned so many things. And being able to see something I developed helping people is such a big motivator for me.

"SINCE I STARTED AT BIF, I'VE DONE RESEARCH AND HAVEN'T STOPPED DOING IT"

RICARDO GRIESHABER BOUYER RODRIGUES
Now: Heidelberg University, Germany
MD project: The Role of CD177 in Neutrophil Biology
Supervisor: Professor Peter A. Nigrovic, MD
Pursued at: Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
Home University: Heidelberg University, Germany
Fellowship: 09/2016–08/2017

Why did you apply for an MD fellowship?

At my university in Heidelberg, I met several BIF fellows – both PhD and MD – who told me about the fellowships, their projects, the BIF support, and how happy they were with it. I got the impression that the scientific level is very high and that being part of this programme would help me to have a successful project. That was exactly what I was looking for.

How did you benefit from the MD fellowship?

I will always be thankful to have been given the chance to delve deeply into my own scientific project for one year without worries. I received valuable support from the lab members, the BIF team, as well as the other fellows. I learned a lot about cell biology and a variety of immunological methods and also picked up many practical skills: how to present and how to write professional manuscripts and grant proposals. Looking back, I can say that my experiences at Harvard were the defining moment for my further scientific career and that the MD fellowship exceeded my already high expectations.

How did you choose your lab?

My criteria were a very good reputation in my field, a mix of basic research and clinical medicine using many different methods, different topics and nationalities, a PI who had a medical background. The scientific community at Harvard has a special quality through its many excellent institutes. In the end, it was not just me choosing the lab, but also the lab choosing me. I am convinced the chemistry between the people is very important. The whole lab, but especially my PI, Peter Nigrovic, supported me in every way and Peter has been a great mentor.

What were your most intense experiences during your stay?

It was exciting to present my own data, hypotheses, and conclusions for the first time in our lab meetings and journal club. My first large conference was also a special experience, and when I went for the second time, I even presented my own project. Another very intensive experience was the submission and revision phase of our first paper. It took a lot of time and energy, but we worked very well as a team.

By now you have already published your third paper – do you plan to stay in science?

Since I started at BIF, I've done research and haven't stopped doing it. I really like the role as a physician-scientist, treating patients and at the same time working on larger basic research questions that will take years or even decades to answer. Also, I have received a lot of great mentoring and I am already looking forward to passing this gift on to other young researchers.

How do you perceive the exchange with the PhD fellows and do you still have contact?

Yes, indeed, I am still in regular contact with many PhD fellows. I have always felt enriched by the interaction, also because it has defined much better what research entails.

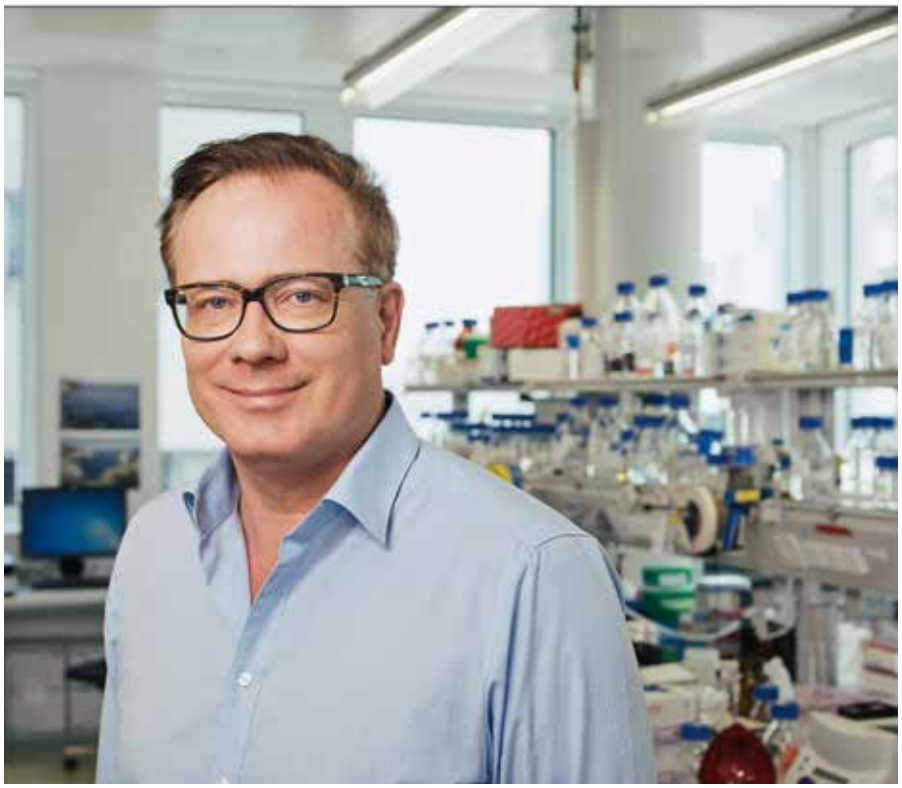
The network feels a bit like being a member of a PhD class and it creates a great sense of community. Medical theses are very heterogeneous in regard to rigor and relevance. At BIF events, you are surrounded by highly motivated, top-level PhD students, many of whom already possess substantial international research experience and have already achieved impressive research results. This is a great incentive to set high scientific standards for your own project and has significantly influenced my own work. I also think it is a good principle for combining research and clinical medicine. Neither patient care nor research quality should suffer because you do both.

What would you recommend to other MD fellows?

Research that pushes the borders of the known is unpredictable, so one of the most critical qualities is persistence. Don't give up when experiments don't work as planned. It can be one of the toughest decisions to revise a favoured hypothesis at a late stage. But that may be the right thing to do to set and maintain high scientific standards. You should be your own greatest critic. If you thrive at working on unpredictable questions, a scientific path can be very fulfilling even after many years, and you can have a lasting impact.

Photo: Ricardo Grieshaber

WHO'S WHO AT BIF?



JAN-MICHAEL PETERS

Jan-Michael Peters was born in 1962 in northern Germany. He studied biology at the Universities of Kiel and Heidelberg. During his PhD at the German Cancer Research Center (DKFZ) he discovered p97 ATPase and was the first to characterize the 26S proteasome. He then did a postdoc at Harvard Medical School in Boston. In 1996, he joined the Institute of Molecular Pathology (IMP) in Vienna and has been scientific director there since 2013. His lab investigates chromosome organization and segregation in mammalian cells. He has been a member of BIF's Board of Trustees since 2008.

Why did you choose a science-based career?
Since I was a small child, I have been fascinated by tiny living things, initially ants, then plankton and protozoa in ponds. From there it was a short step to discover my passion for cells and the molecules they are made of.

What is your most remarkable BIF experience?
There are several. Reading exciting, scholarly proposals is one. This October, I read a proposal that I thought no leader in this field could have written any better. Another is meeting the young scientists behind them.

What is your favourite activity?
They range from spending time with my family to having an uninterrupted morning to think about science after a good night's sleep. Both happen too rarely and are therefore special treats.

What is your remedy for stressful situations?
I remind myself that life will go on, no matter what.

What fault in others can you tolerate best?
Pretty much any, except lack of respect, fairness, or humanity.

Your advice for fellowship holders?
Follow your passion. If you don't have one, identify an important scientific question and ponder what it would take to solve it. Ask yourself whether there is any chance that you could contribute and where the best place would be to do this. Don't give up easily but be as critical with your results and ideas as possible. Keep your eyes open for the unexpected and unimaginable, but don't forget the question.

What scientific achievement do you admire?
When the right combination of logic and intuition creates new and testable ideas. These often advance science more than pure data collection – a big temptation in the age of "omics". One recent example is the crazy, almost heretic idea that protein complexes such as cohesin form loops by active extrusion. It is the only hypothesis so far that can explain how all our DNA is folded according to the principles that we know exist. Of course, this does not necessarily mean it is correct, but its explanatory power is so strong that there has to be something to it.

Name one thing you could not live without.
My glasses. I got my first pair at age three, so they are part of my anatomy.

Photo: IMP, Lukas Beck

PROFILES

PROFESSOR MICHAEL BOUTROS
Institute: German Cancer Research Center, Heidelberg, Germany
Fellowship: 1997–1999

Together with three other researchers from Heidelberg, Michael Boutros has been awarded an ERC Synergy Grant worth 10.6 million euros for six years to decode the interplay of the wiring diagrams of gene activity not just for a single cell, but also for complex tissues in *Arabidopsis* and *Drosophila*. This type of ERC grant was reintroduced 2018, and only 10% of the proposals were successful. As Professor Jean-Pierre Bourguignon, president of the ERC, commented: "The selected projects represent truly daring ideas put forward by some of Europe's top scientists."

PROFESSOR STEFANIE DIMMELER
Institute: University of Frankfurt, Germany
Fellowship: 1991–1992

The newly founded Cardiopulmonary Institute (CPI) of Goethe University Frankfurt and Justus Liebig University Giessen, co-chaired by Stefanie Dimmeler, has been awarded the status of "excellence cluster" in Germany's Excellence Strategy. The CPI will seek to better understand the molecular biology of processes in the healthy and diseased lung and heart at the cellular and tissue level in order to identify new, individualized therapeutic options.

Funding has begun on 1 January 2019 and will run for seven years, with a further seven years subject to review. Of the projected 45 million euros of funding, 75% will be borne by the federal government and 25% by the state government of Hesse.

CORNELIA KILCHERT
Institute: University of Giessen, Germany
Fellowship: 2006–2008

Cornelia Klichert has been selected as an Emmy Noether research group leader by the German Research Foundation (DFG). Her group will study the mechanisms of substrate selectivity of the nuclear RNA exosome complex and address the following questions: What factors are involved in exosome targeting? How is substrate selection regulated in response to external cues? Her overall goal is to better understand how post-transcriptional mechanisms shape gene expression programmes that promote survival and determine cell fate.

PROFESSOR DANIEL KOPINKE
Institute: University of Florida, Gainesville, USA
Fellowship: 2007–2009

PROFESSOR NADJA MAKKI
Institute: University of Florida, Gainesville, USA
Fellowship: 2006–2008

Both Nadja Makki and Daniel Kopinke have taken up assistant professorships at the University of Florida in Gainesville, USA. **Nadja** is with the Department of Anatomy and Cell Biology, where she studies how non-coding variants influence susceptibility to complex human diseases. Additional focuses are gene networks and the molecular pathways underlying connective tissue diseases. **Daniel** is with the Department of Pharmacology and Therapeutics and studies ciliary hedgehog signalling to understand its role in cellular communication between stem cells and their niche during adult tissue regeneration.

PROFESSOR JÖRG RENKAWITZ
Institute: University of Munich (LMU), Germany
Fellowship: 2009–2011

Jörg Renkawitz has just started his own group at the Biomedical Center Munich (BMC) of the University of Munich (LMU) as the endowed Hofschneider Professor for Molecular Medicine. This award is presented for exceptional research by the Experimental Biomedicine Foundation and includes three-year funding for the PI's salary, a PhD student, and additional expenses. Jörg employs immune cells such as dendritic cells, macrophages, and neutrophils to decipher the fundamentals of cell movement. He combines advanced live-cell microscopy, genetic engineering (e.g. CRISPR), custom-made micro-environments (e.g. microfluidics, 3D collagen matrices), and system-wide approaches.

PROFESSOR h.c. MARIO MEZLER
Company: AbbVie Deutschland, Ludwigshafen, Germany
Fellowship: 1997–1998

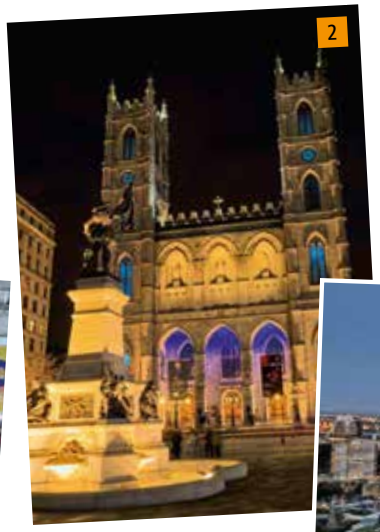
Mario Mezler has been named honorary professor by the University of Applied Sciences Mannheim in recognition of his outstanding professional and scientific expertise and his extensive, diverse services for the University. In addition to teaching courses in its biotechnology master's programme for many years, he has been active on several of its committees. Since 2013, he has also been president of the Society of Friends of Mannheim University and has restructured its funding activities and initiated an alumni network and a career portal. At AbbVie, Mario serves as Senior Group Leader for Drug Development.

Photos: Boutros: DKFZ.de; Dimmeler: University Frankfurt Kilchert: privat; Kopinke: privat; Makki: privat; Renkawitz: IST Austria; Mezler: private

A BIF FELLOW'S GUIDE TO ...

MONTREAL


1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Travelling is fun – especially if you get insider tips from locals! In each edition of FUTURA, one fellow shows you around his or her city. In this edition, your guide is Maximilian Eivaskhani and he will show you around Montreal, a city that brings together history and modern culture.

FACTS & FIGURES

Country: Canada
Population: about 1.7 million
Area: 431 km²
Students: 170,000
Popular for festivals, Old Montreal, architecture, the art and culinary scene, ice hockey
Website: www.mtl.org/en

BEST SIGHTS

Explore the different districts from the busy downtown area to the hip and artsy Plateau and visit the extensive underground city.
Botanical Garden: take a day to see fauna from all around the world.
Ice hockey: in winter, go to a game played by the Habs, the Montréal Canadiens.

NIGHTLIFE

Cloakroom: hidden speakeasy in the downtown area with no menu but custom-made drinks.
Rue St. Laurent: bars, pubs, cafes, and art shops open most of the night. A must!
Old Port: 2 feels like France, busy every night with street performers and light shows.

RESTAURANTS

La Banquise: iconic poutine restaurant, open and frequented 24/7.
Schwartz's: the best smoked meat sandwiches and fries in North America.
St-Viateur: fresh oven-baked bagels. Try the sesame seed bagel with smoked salmon and cream cheese.

WHERE TO STAY

Hotel Nelligan: upscale hotel in the charming and romantic Old Montreal district, great rooftop bar overlooking the river.
Auberge de la Fontaine: rustic hotel with a French touch in the Plateau-Mount Royal quarter close to small art boutiques, street art, and creative restaurants.
Hotel Chez Swann: downtown boutique hotel near great shopping and the Montreal Museum of Fine Arts. 1

ACTIVITIES

Winter: ice skate with a view of the Old Port, eat a doughy beaver tail, or go skiing at a nearby ski resort.
Spring: visit the botanical garden 4 and museums; many offer free admission after the long winter.
Summer: visit the many music, art, and food festivals or watch the Formula 1 race in June.
Fall: enjoy the foliage in the parks or at the panorama platform 3 on Mount Royal.

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

Maximilian Eivaskhani is 27 years old and comes from Germany. He is studying at McGill University and his supervisor is Professor Martin Schmeing.

Photos: Maximilian Eivaskhani

PROFILES

PROFESSOR CHRISTOPH THAISS
Institute: University of Pennsylvania, Philadephia, USA
Fellowship: 2013–2015

Christoph Thaiss has been named the 2018 Grand Prize winner of the Science & SciLifeLab Prize for Young Scientists for his work implicating the microbiome in three phenomena associated with human obesity – the disruption of the biological clock, recurrent weight gain, and enhanced susceptibility to infection. Thaiss and his team discovered that specific molecules produced by intestinal bacteria are altered by these factors and influence disease development. The 30,000-dollar prize recognizes promising early-career scientists who conduct ground-breaking life-science research. It is supported by SciLifeLab (Science for Life Laboratory), a national centre for advanced molecular life sciences in Sweden, by the *Science* journal, and by the Knut and Alice Wallenberg Foundation.

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

Kristin Tessmar-Raible has received an ERC Consolidator Grant worth about two million euros to study the mechanics marine organisms use to establish monthly rhythms based on the moon cycles. She will use the grant to investigate how the highly variable natural environmental conditions compare with those in the laboratory and to identify key molecules responsible for establishing and upholding the circalunar clock of organisms such as the bristle worm *Platynereis dumerilii* and the midge *Clunio marinus*.

HOW BACTERIA INVADE OUR BODIES

BIF's SISTER FOUNDATIONS

Professor Pascale Cossart of the Institut Pasteur in Paris has been awarded the 100,000-euro 2018 Heinrich Wieland Prize by BIF's sister foundation, the Boehringer Ingelheim Foundation, for her fundamental contributions to molecular infection biology. Cossart's innovative research has unravelled how pathogenic bacteria, in particular foodborne *Listeria*, enter human cells, use the host cells' own mechanisms to do so, and trick and evade the immune system. Her discoveries have paved the way for new therapies for bacterial infections, which kill several million people worldwide each year. The award ceremony took place at Nympenburg Palace in Munich, Germany, on 22 November 2018, and was accompanied by a scientific symposium that was attended by about 130 participants.

Listeria monocytogenes, the foodborne pathogen that causes listeriosis, can lead to encephalitis, gastroenteritis, and extreme sepsis. "Pascale Cossart has given us invaluable knowledge on how bacteria infect us and how our bodies respond to them," said Professor Felix Wieland, chair of the board of trustees that selects the Heinrich Wieland laureates.

Photos: Thaiss: Perelman School of Medicine, University of Pennsylvania; A. Griesch (bottom)

UPCOMING EVENTS

15–16 MARCH 2019
Meeting of BIF's Board of Trustees
The trustees decide on the allocation of fellowships, review the proposals for the International Titisee Conferences, and settle all the foundation's matters of fundamental importance.

27–31 MARCH 2019
119th International Titisee Conference
Elly Tanaka from Vienna, Austria, Peter Reddien from Cambridge, MA, USA, and James Sharpe from Barcelona, Spain, will chair the 119th ITC titled "Tissue formation and regeneration: from molecules to models". The conference brings together leading researchers worldwide who work on patterning dynamics and signal interpretation in multiple developmental and regenerative contexts. The chairs aim to discuss the commonalities between embryonic development and regeneration in light of the recent progress in our molecular understanding of embryonic patterning and regenerative mechanisms. Another topic: the exciting developments in organoid biology.
The concerence is by invitation only.

19–24 MAI 2019
Communication training, Köngernheim, Germany
Communication seminar for non-German-speaking PhD and MD fellowship holders working in Europe. The meeting will take place near Mainz, Germany. Participants will have the opportunity to work on their writing and presentation skills with various coaches, as well as to learn more about designing graphs and figures. Further details will be sent with the invitation.

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

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