FUTURA

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The Inside Story of Mitochondria
The fascinating organelle is biology's playground

Projects and Results
Seventeen new PhD projects and twelve completed theses

A BIF Fellow's Guide to Barcelona
Spain's capital is a bustling city full of famous architecture

The cover illustration shows a simplified model of mitochondria, the organelles found in all eukaryotic organisms. Often called "powerhouses of the cell", they provide cellular energy by generating ATP. Mutations in mitochondrial DNA can have severe effects in humans, including seizures, muscle weakness, and developmental delays. Read more about mitochondiria on page 8.

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TOO GOOD TO (ALWAYS) BE TRUE

»The top seems to have become a very crowded place these days.«

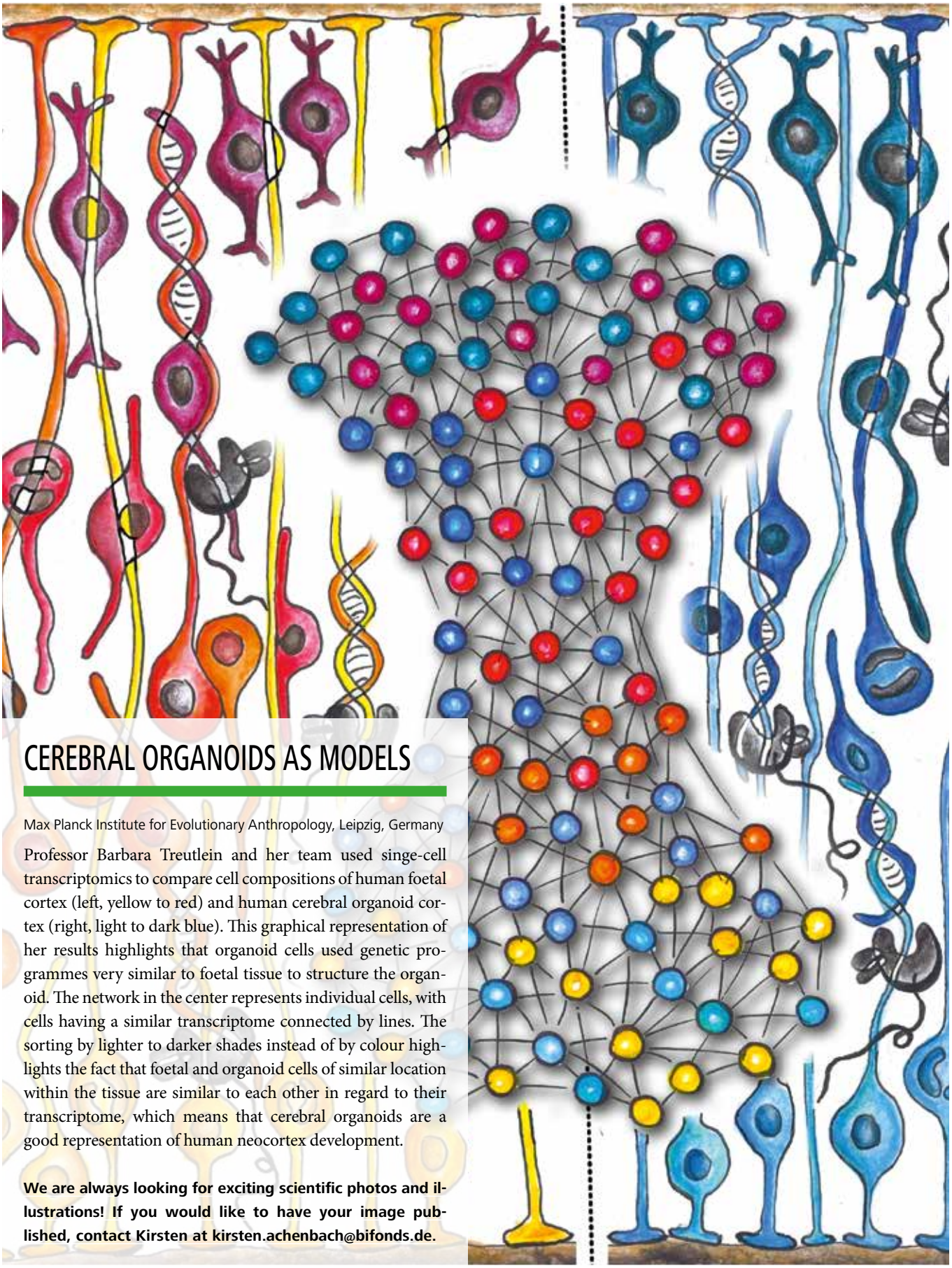
Like Christmas songs in December, the word "excellence" appears to be omnipresent these days. Too many universities and research departments in the world claim to be "excellent" or "outstanding". And there is hardly a major new funding initiative that is not trying to fund just such research. By definition, the top implies a very small number, but it seems to have become a very crowded place these days – at least to judge by these overused adjectives. Such inflation or hyping in too many areas of life (including shows searching for the "superdog") devalues the meaning and significance of "excellence" and similar words.

This hurts the very best in any context and is an injustice to researchers deserving of that label – and hence to science as a whole. Some institutions have already changed the words they use and are now simply looking for "the best". But it is not a semantic problem, solved by exchanging words if usage has altered their meaning (e.g. "silly", which once meant happy or blessed). The system and incentives driving this devaluation remain the same.

Exaggerated labels are misleading signposts, hampering judgement and not providing orientation e.g. for non-experts such as students in search of a great scientist as a mentor. In addition, the inflationary use of words such as "outstanding" devalues science that is "merely" very good or good but forms the bedrock on which excellence builds. It changes how very good and good science are perceived and valued: the science done by researchers who over the course of years or even decades painstakingly collect specimens, generate solid results, and pursue all the important follow-up work of a breakthrough or a major advance. It is often these researchers who build the stepping stones for other groundbreaking discoveries or simply for gradually expanding our knowledge.

The pressure to use superlatives also obscures the fact that promising and talented young scientists need time to flourish and become outstanding in their field; that they may first have to learn what "very good science" is before being able to reach the very top.

The overuse of superlatives in the form of top marks has also long infected school and university education. In biology, for example, the large percentage of master degrees awarded with the highest distinction suggests a pandemic and a lost cause. As a result, top marks are no longer perceived as "outstanding" (or whatever adjective one prefers to describe truly exceptional achievement) and anyone with a grade below the very best may be thought to be mediocre. A few brave individuals and institutions are attempting to counteract such devaluation. But it will take many more and – most importantly – a more general change of attitudes and incentives if we want effective and reliable signposts for true excellence.



CEREBRAL ORGANOIDS AS MODELS

Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

Professor Barbara Treutlein and her team used singe-cell transcriptomics to compare cell compositions of human foetal cortex (left, yellow to red) and human cerebral organoid cortex (right, light to dark blue). This graphical representation of her results highlights that organoid cells used genetic programmes very similar to foetal tissue to structure the organoid. The network in the center represents individual cells, with cells having a similar transcriptome connected by lines. The sorting by lighter to darker shades instead of by colour highlights the fact that foetal and organoid cells of similar location within the tissue are similar to each other in regard to their transcriptome, which means that cerebral organoids are a good representation of human neocortex development.

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.

Easier tracking of eye movements helps to design e.g. better user interfaces.

NEW SOFTWARE TRACKS EYE CONTACT

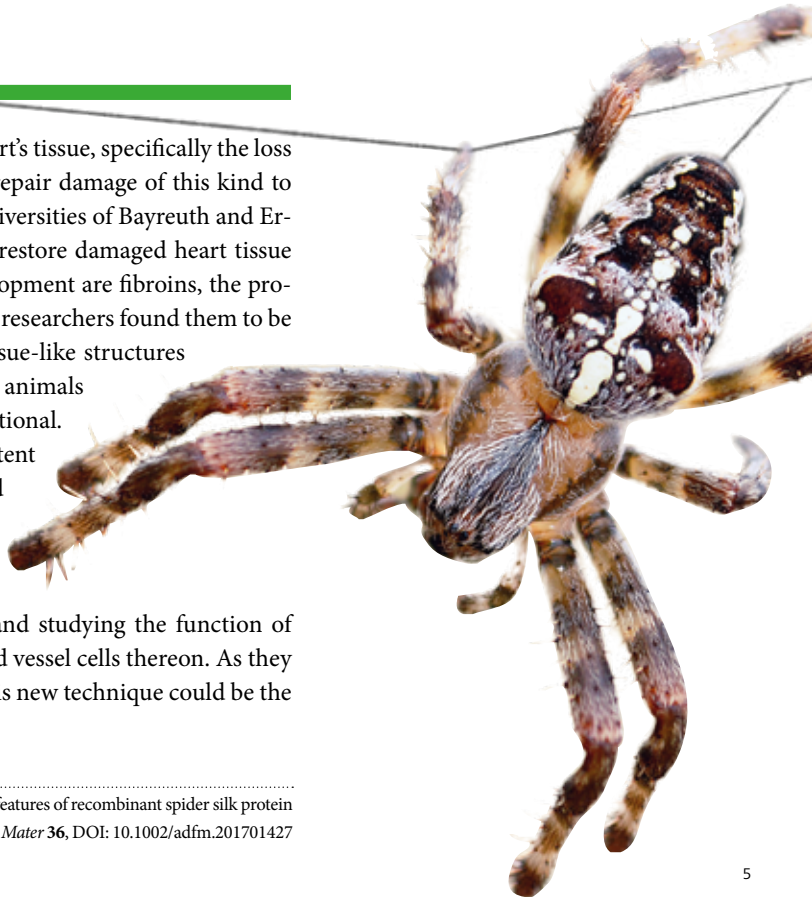
Noticing if someone looks at us is an easy task. Not so for computers: their ability to recognize eye contact in everyday situations is very limited. Different users, gaze targets, camera positions, and illumination conditions make it a challenging task for them. Sure, it can be done, but it is a cumbersome process, involving special eye tracking equipment and subjects that wear a tracker. Gaze estimation methods could be used as an alternative, but they have some technical limitations, too. Now, researchers at Osaka University in Japan, Saarland University, and the Max Planck Institute for Informatics in Germany have developed a novel method that combines state-of-the-art gaze estimation and machine learning that can turn ordinary cameras into eye contact detectors. The estimated gaze direction, which is calculated by algorithms, is not accurate enough on its own. However, it indicates the relative gaze direction from the camera position. In the next step, the estimated gaze directions are grouped into clusters that are assumed to correspond to different objects. From all clusters, the one closest to the camera position is selected as a target and then used for the training of a target object-specific eye contact detector. One big advantage is that the method requires no involvement from the user and, through deep learning, will become even better the longer the camera remains active.

REFERENCE

Zhang X, Sugano Y, Bulling A (2017) Everyday eye contact detection using unsupervised gaze target discovery. *Proc. of the ACM Symposium on User Interface Software and Technology (UIST)*: 193–203

A HEART OF SILK

The main cause for cardiac insufficency is damage to the heart's tissue, specifically the loss of cardiac muscle cells. So far, it has not been possible to repair damage of this kind to normalize heart function. But now researchers from the Universities of Bayreuth and Erlangen-Nuremburg in Germany may have found a way to restore damaged heart tissue using spider silk and 3D-printing. At the heart of the development are fibroins, the proteins that give silk its structure and mechanical stability. The researchers found them to be an excellent material to produce hydrogels from which tissue-like structures can be produced via 3D-printing. Living cells of humans or animals embedded in such hydrogels were stabilized and stayed functional. The problem: large quantities of silk protein of a consistent quality are needed for the scaffolds. The researchers solved this by producing the protein from garden spiders with the help of *E. coli* bacteria. They investigated the suitability of the spider silk protein eADF4(κ16) for growing heart tissue by applying a spider silk film on a glass substrate and studying the function of cardiomyocytes, but also of connective tissue cells and blood vessel cells thereon. As they found no difference to cells in their natural environment, this new technique could be the first step to engineering functional cardiac tissue.



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Petzold J, Aigner TB, Touska F, Zimmermann K, Scheibel T, Engel FB (2017) Surface features of recombinant spider silk protein eADF4(κ16)-made materials are well-suited for cardiac tissue engineering. *Adv Funct Mater* **36**, DOI: 10.1002/adfm.201701427

Photo: shutterstock (top); iStock (bottom)

GUARDIANS OF FERTILITY

From the very start of life, an individual's immune system learns to distinguish its cells from other potentially pathogenic cells. In males, however, sperm only appears at puberty – and therefore may be mistaken for foreign cells by the immune system. To prevent this, special immune cells, testicular macrophages, rush to their defence. By releasing specific molecules, these guardians of fertility prevent other agents of the immune system from entering the testes and attacking sperm cells. In adult testis, two different macrophage populations have been identified. Peritubular macrophages are located on the surface of the tubules that house sperm cell precursors. Interstitial macrophages are found in the space surrounding those tubes. The latter are of embryonic origin: they are present from the beginning of the individual's life. The former, however, only appear with the onset of puberty, as new research from a CNRS team at the Centre d'Immunologie de Marseille-Luminy in France now describes. Using a new cell-tracing method to follow the movement of peritubular macrophages in mice from the bone marrow to the testes, the team found that they first appear two weeks after birth – corresponding to the pubescent stage in men. Once established, both the peritubular and interstitial macrophage populations exhibit a long life span. The next stage of the research will focus on the relationships between macrophages, sperm, and testosterone production, which may yield new treatments for certain kinds of male infertility.

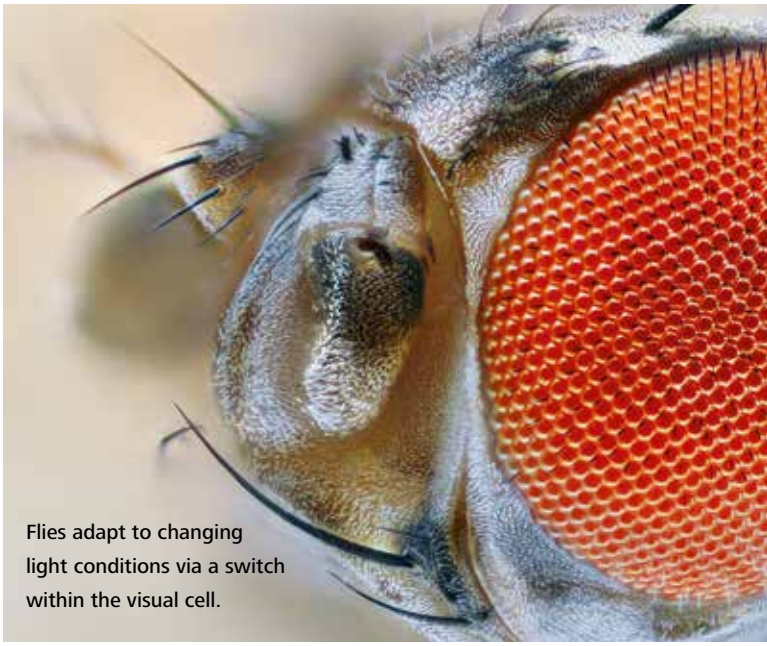
REFERENCE

Mossadegh-Keller N, Gentek R, Gimenez G, Bigot S, Mailfert S, Sieweke MH (2017) Developmental origin and maintenance of distinct testicular macrophage populations. *J Exp Med* **214**: 2829-2841

70%

That's how much light emissions have increased over the past 20 years, particularly in residential areas. And research conducted in the still relatively dark Pre-Alps has shown just how much this is impacting light sensitive insects, with a 62% lower rate of nocturnal pollination visits in artificially lit areas versus unlit ruderal meadows.

Source: Knop E, Zoller L, Ryser R, Gerpe C, Hörler M, Fontaine C (2017) Artificial light at night as a new threat to pollination. *Nature*, Doi:10.1038/nature23288



Flies adapt to changing light conditions via a switch within the visual cell.

SWITCH FROM LIGHT TO DARK

Flies can process light stimuli up to three times faster than humans. But like humans they also take time to adapt to changing light conditions – for example, when going from a light to a dark environment. Researchers from the University of Hohenheim and the Hebrew University of Jerusalem have now discovered the switch within the visual cell which makes this adaptation possible. To test the theory that adaptation to changing light conditions takes place at cell level, the researchers studied the visual cells of the fruit fly *Drosophila melanogaster*, whose multifaceted eye consists of some 800 individual eyes. They located the switch at the so-called TRP channels, passageways through the cell membrane. By opening and closing, these channels regulate the penetration of ions into the cell, changing the electric voltage at the cell membrane and generating a signal which is passed to the nerve cells. To demonstrate the importance of this switch, the scientists genetically altered two groups of flies: in one group they changed the TRP channel so that the switch remained "off", and in the other group they set the switch to "on", regardless of the light conditions. Using an electrode to test how quickly the eye followed the rapidly changing light stimuli, they found that flies where the switch was "on" responded quickly to the light stimuli even when performed at high frequency, while the other flies took at least eight seconds to adapt to the light. The researchers now want to study the enzyme that sets the switch to "on" or "off", especially since in humans TRP channels are involved in perception of heat or pain and the sleep cycle.

REFERENCE

Voolstra O, Rhodes-Mordov E, Katz B, Bartels JP, Oberegelsbacher C, Schotthöfer SK, Yasin B, Tzadok H, Huber A, Minke B (2017) The phosphorylation state of the *Drosophila* TRP channel modulates the frequency response to oscillating light *in vivo*. *J Neurosci* **37**: 4213-4224

Photo: fotolia

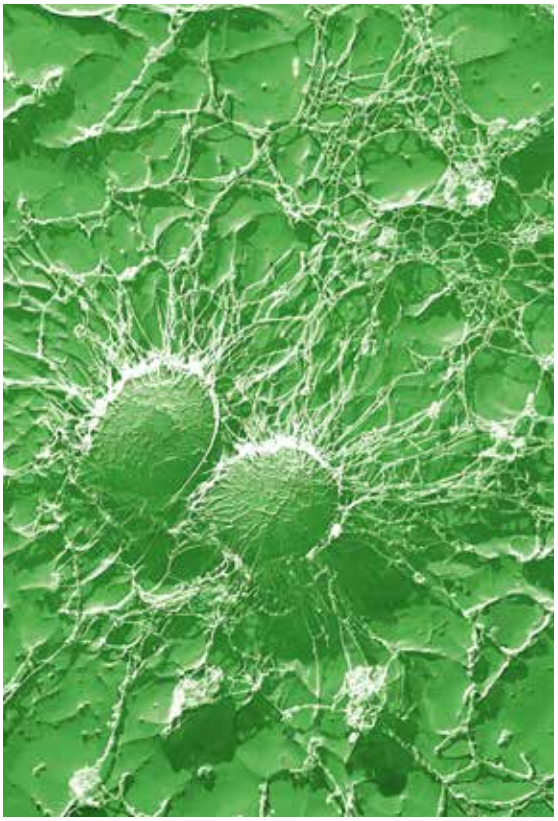
CHEWING GUM RAPID TEST FOR INFLAMMATION

It's the bane of cleaners the world over, but researchers from the University of Würzburg have stuck at it and developed a new, useful purpose for chewing gum – as a rapid test for oral inflammation. Dental implants occasionally entail complications: between 6 to 15 per cent of patients develop an inflammatory response due to bacterial inflammation in the years following treatment. This can destroy the soft tissue and the bone around the implant. But in future, patients could use the new chewing gum-based diagnostic test. If there's an inflammation in the oral cavity, specific protein-degrading enzymes are activated in the mouth when chewing the gum. These enzymes release a bittering agent from the gum, suggesting a visit to the dentist to confirm the diagnosis and receive treatment. In this way, serious complications such as bone loss may be prevented. It is a simple method that can be used anywhere without any technical equipment, and chewing gum tests for other medical applications are currently under development. To launch the gum onto the market the team plans to set up a company.

No time for the dentist? Then the new chewing gum for testing oral inflammation might be for you!

REFERENCE

Ritzer J, Lühmann T, Rode C, Pein-Hackelbusch M, Immohr I, Schedler U *et al* (2017) Diagnosing peri-implant disease targeting the tongue as 24/7 detector. *Nat Comm*, DOI 10.1038/s41467-017-00340-x



Cells of the bacterium *Staphylococcus aureus.*

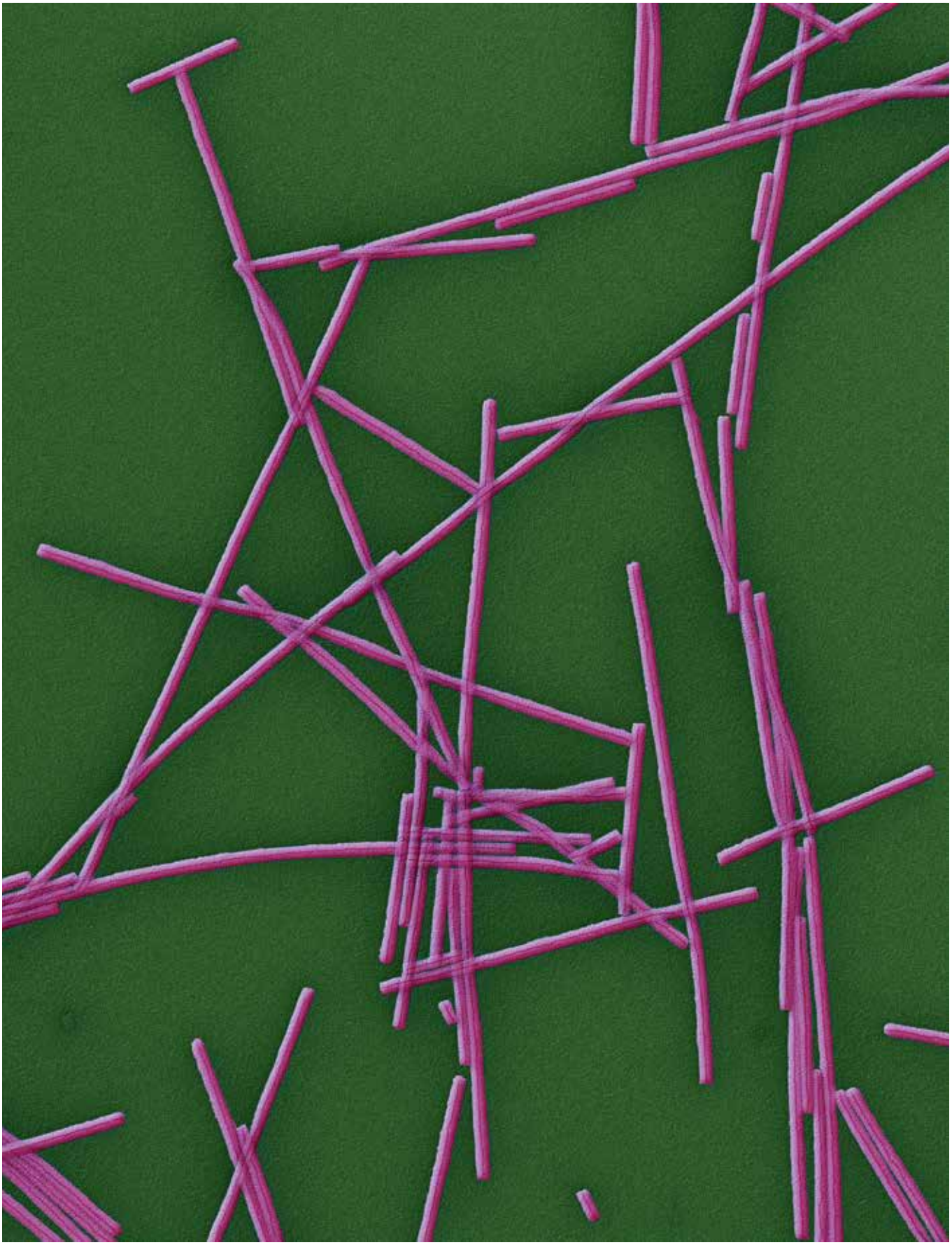
Photo: iStock (top right); Scott Camazine/Science Source (bottom)

KILLING BACTERIA WITH SILVER AND ELECTRICITY

Hospital wards are typically full of plastic surfaces that can harbour dangerous microbes and cause infection. While large electrical currents and high silver concentrations are known to kill bacteria, they also pose a risk to humans. Coatings based on silver nanoparticles (AgNPs) are often applied, with varying clinical success. Researchers at the Swedish Medical Nanoscience Center at Karolinska Institutet have now developed a way to prevent the growth of bacteria using a combination of silver nanoparticles and a small electrical current, reimagining traditional AgNP-based antibacterial technology and forming the basis for an electroenhanced antimicrobial coating. The research focused on the notorious hospital pathogen *Staphylococcus aureus*. Using custom-designed culturing devices, the researchers found that applying tiny electrical currents to a conducting plastic surface had no impact on bacterial growth. Coating the surfaces with a layer of silver nanoparticles reduced growth. By applying a tiny electrical current to the latter, the bacteria were completely destroyed. This method relies on the fact that electrical fields weaken bacterial cells against external attacks. This so-called bioelectric effect makes the bacteria more susceptible to the silver.

REFERENCE

Gomez-Carretero S, Nybom R, Richter-Dahlfors A (2017) Electroenhanced antimicrobial coating based on conjugated polymers with covalently coupled silver nanoparticles prevents *Staphylococcus aureus* biofilm formation. *Adv Healthc Mater*, DOI: 10.1002/adhm.201700435



Tobacco virus particles are on average about 300 nanometres long and 18 nanometres wide, they can attach end-to-end.

PROFILE OF **TOBACCO MOSAIC VIRUS**

By Mitch Leslie

We continue our series of portraits of iconic model organisms in research with the tobacco mosaic virus, which was first studied in 1886 as little more than a plant pest that decreased yield and left tobacco leaves curled, brittle, and unsuitable for cigar making.

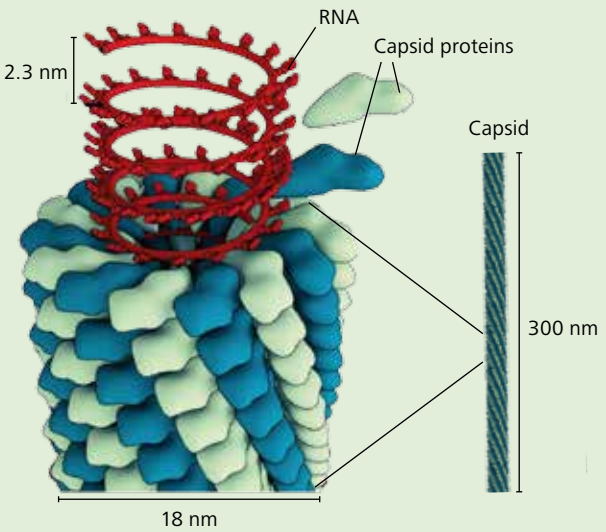
For farmers, the tobacco mosaic virus (TMV) is a scourge that causes millions of dollars in crop losses every year. But for researchers, TMV is one of the most important model organisms. It was instrumental in the discovery of viruses and helped researchers unravel their architecture and understand how complex molecular structures form.

TMV's effects on tobacco plants, which include mottling of leaves and stunting, came to scientists' attention in the late 1800s. At the time, researchers knew about bacteria's role in disease, but when they tried to isolate the microbe that was damaging tobacco plants, they found that it slipped through filters that trapped bacteria, suggesting it was a different kind of pathogen.

The first virus discovered and viewed with the electron microscope, TMV provided researchers with key insights into viral structure. In 1935, Wendell Stanley, at what was then the Rockefeller Institute for Medical Research in New Jersey, demonstrated that TMV consisted largely of protein, a discovery that earned him a share of the 1946 Nobel Prize in Chemistry. Researchers also capitalized on TMV's apparent simplicity – it contains one RNA strand surrounded by 2,130 copies of one kind of protein – to investigate how individual molecules fit together to form larger, more complex structures. Aaron Klug of Cambridge University in the United Kingdom won the 1982 Nobel Prize in Chemistry for working out how TMV particles assemble from these two ingredients.

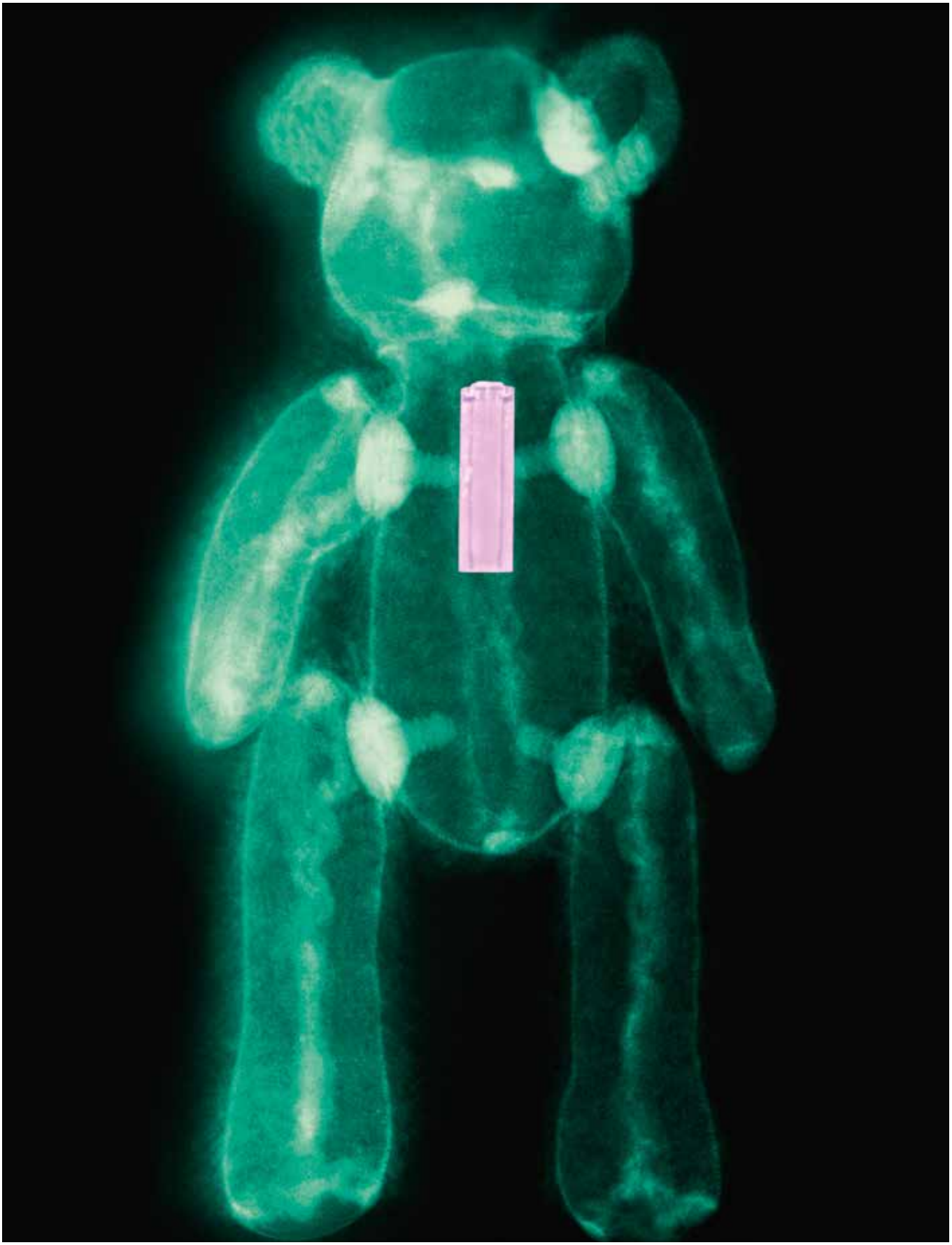
TMV has also been indispensable for plant scientists. For example, they used the virus to help track how plant cells share RNA molecules, a process that is crucial for a plant's development. And researchers have relied on TMV as a gene carrier when genetically engineering plants. Today, TMV remains a lab favourite. Scientists are investigating whether they can harness TMV for vaccines against a range of diseases, from flu to Ebola fever, and for the delivery of chemotherapy drugs to tumours.

WHO AM I? A FEW FACTS



- I weigh about 41 million daltons, or less than 1/100,000,000,000,000th of a gram, and my genome has 6,400 bases.
- I can infect tobacco plants and more than 200 other plant species, but not animals.
- I am easy to grow. From a few infected plants, you can easily extract several grams of virus.
- I have been investigated as an ingredient to build better batteries and nanotechnology.
- I work mostly in virology, structural biology, and plant biology.
- I helped scientists to win two Nobel Prizes.

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



The main task of mitochondria is to generate energy for cells, but the organelles are also involved in processes like cell death or autophagy.

THE **INSIDE** STORY OF **MITOCHONDRIA**

By Sarah Williams

Studying the diversity of mitochondria in living organisms allows researchers to weave a tale of the organelles' past. Their evolution is an intriguing story by itself, but knowledge about how they function also has many implications for our health.

Around a billion years ago, a cell captured a nearby bacterium, enveloping it completely. Once inside, the bacterium became a survival advantage, helping the cell to generate energy from oxygen. The cell divided, and within it the bacterium divided as well, and that happened again and again, and a whole host of cells were born, all containing these little helpers. Over the eons, though, the new organelle – today known as the mitochondrion – lost some of its genes entirely. In some organisms, mitochondria grew so large that they almost took over the cells' interiors. In others, mitochondria shrunk and nearly disappeared – or, in at least one case, disappeared entirely. And in all cases, mitochondria – with their own distinct DNA from the rest of the cell – evolved different ways of doing things than the rest of the cell.

"The mitochondrion is molecular biology's playground," says Michael Gray of Dalhousie University in Canada. "Even though the function of mitochondria is pretty well conserved throughout evolution, the way in which the genes are arranged and expressed is very diverse. As long as you can get those key proteins churned out, you can do it in all sorts of ways."

In March 2017, Gray was one of about 60 researchers who gathered in southern Germany for Boehringer Ingelheim Fonds' 115th International Titisee Conference to discuss the evolution and diversity of mitochondria. For four days, biochemists, geneticists, and physiologists shared perspectives on what has driven some mitochondria to be such outliers, and how the organelles are linked to human health.

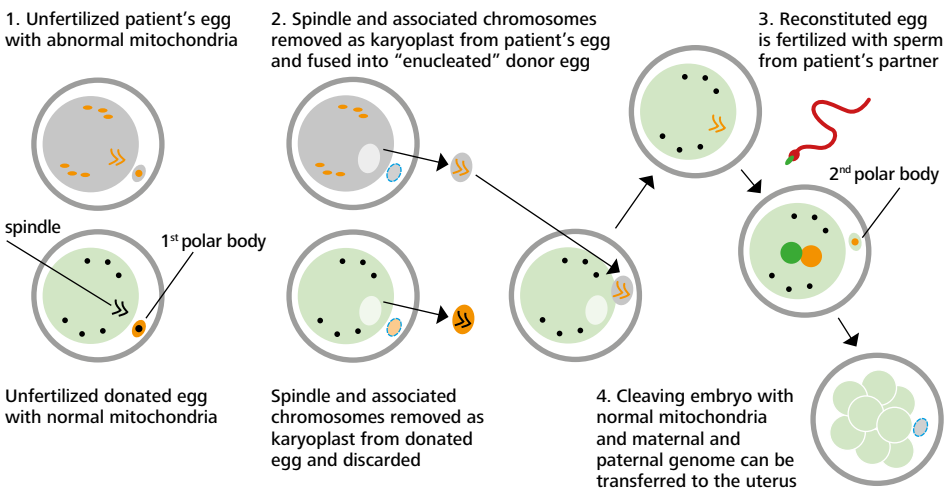
"We are witnessing a renaissance in mitochondrial research," says Vamsi Mootha of Harvard Medical School in Boston, USA, chair of the conference. "Human studies are underscoring the importance of mitochondrial dysfunction in a number of different conditions, and advances in genome sequencing are pointing to the remarkable diversity of mitochondria across the tree of life. For these reasons, it was a terrific opportunity to convene this meeting."

Over the past few decades, researchers have been trying to piece together the evolutionary history of mitochondria and have also uncovered more than 275 disease-causing mutations in the mitochondrial DNA of humans. The severity of the diseases and breadth of symptoms underscore the importance of the organelle – people with mitochondrial diseases can have seizures, muscle weakness, exercise intolerance, developmental delays, and breathing problems, just to name a few symptoms.

Most biology textbooks describe mitochondria with the same catchphrase: they are the "powerhouses of the cell." It is an appropriate analogy, since in nearly all eukaryotic cells, oxidative →

Photo: Stockbyte/Thinkstock; shutterstock

SOMETIMES IT TAKES THREE – HOW WOMEN WITH MITOCHONDRIAL DISEASE CAN HAVE HEALTHY CHILDREN



Source: Maternal spindle transfer Bredenoord, A and P. Braude (2010) "Ethics of mitochondrial gene replacement: from bench to bedside" BMJ 341.

Mitochondrial replacement therapy uses healthy donor mitochondria to replace the mother's abnormal ones.

In 2015, the United Kingdom became the first country in the world to pass laws allowing the creation of human embryos from three people: a mother, father, and mitochondrial donor. The technique – called mitochondrial replacement therapy (MRT) or mitochondrial transfer – allows women with mitochondrial diseases to have children without passing on their defective mitochondrial genes. In MRT, as with all forms of *in vitro* fertilization, eggs are harvested from a woman, sperm collected from a man, and fertilization occurs in a lab dish before an embryo is implanted back into the mother's uterus. But with MRT, eggs are also collected from a female donor with healthy mitochondria. Mitochondria from the donor eggs replace the mitochondria in the mother's eggs or in the fertilized embryo, depending on the exact technique used. To date, a small handful of babies have been born using MRT and dubbed "three-person babies" in the popular press. From a purely genetic standpoint this is correct, as they carry genes from three different people. However, the proportions differ widely, with only a tiny fraction of one per cent – the genes encoded in the mitochondria – coming from the mitochondrial donor.

phosphorylation – the process by which cells convert oxygen and nutrients to the cellular energy currency ATP – occurs inside mitochondria. But it also glosses over the many other functions of the organelles. They house metabolic pathways, export iron-sulphur clusters to modify proteins, and are involved in cell death, autophagy, and other processes such as stress adaptation, immune response, and cell proliferation.

In animals, mitochondria are usually passed to offspring from their mothers; paternal mitochondria are currently thought to be degraded inside sperm or shortly after fertilization. There are rare exceptions. Mollusks, for instance, inherit mitochondria from both parents, and in some insects paternal inheritance of mitochondrial DNA has been reported. The usual inheritance pattern, though, means that maternal lineages can be traced using mitochondrial DNA. By studying the small genetic differences in people's mitochondria, for instance, scientists have calculated that all women today descended from a single woman – dubbed the Mitochondrial Eve – who lived around 200,000 years ago in East Africa.

Many scientists, though, are focused on events even further in the past than the Mitochondrial Eve and are interested in the origin of the mitochondrion itself. Half a century ago this year, in 1967, evolutionary biologist Lynn Margulis, then at Boston University, proposed that mitochondria arose from a bacterium engulfed by an ancient cell. The general idea had been around since at least since 1883, but her paper is now considered a landmark in the modern theory of endosymbiosis. Since then, genetic sequencing has revealed that mitochondria share a number of DNA sequences with α-proteobacteria, a class of bacteria that the organelles most likely originated from. But the details of the endosymbiosis that led to mitochondria are hard to uncover.

"There are lots of α-proteobacteria out there and we don't really know what the α-proteobacteria that became the mitochondria was like," says Gray. "We're inferring from current organisms what might have happened a billion or so years ago."

To make these inferences, Gray has focused on the mitochondria of protists – the most diverse group of eukaryotes. His group was the first to describe the mitochondrial genome of *Reclinomonas americana,* a freshwater protozoan that contains a larger mitochondrial genome (96 genes) than most organisms; human mitochondria, for instance, contain 37 genes, just 13 of which encode proteins. This large collection of genes, Gray's group has

shown, represents a more ancestral state of the organelle. In fact, the protist's mitochondria still possess RNA polymerases resembling those found in bacteria, not animals. The finding was considered one of the final and most convincing pieces of evidence to support the endosymbiosis theory of mitochondrial evolution.

Since characterizing the *R. americana* mitochondrial genome, Gray and his colleagues have sequenced the mitochondrial genomes of other related protists – called jakobids – and found an even larger set of mitochondrial genes in *Andalucia godoyi*. But even these jakobids share only a small handful of their mitochondrial proteins – 10 or 20 at the most – with α-proteobacteria. So what happened to the rest of the bacterial genes? When did the mitochondria lose them, and where else did they acquire genes?

"We have some general answers about how that might have happened," says Gray. "But also a whole series of questions." For instance, there is still debate as to whether mitochondria arose at the same time as the eukaryotic cell. One hypothesis, for example, states that mitochondria and the larger amount of energy they provided were a prerequisite for true eukaryotic cells to arise. An argument in favour of this theory is that eukaryotes arose only once. However, other scientists have suggested that cells gained eukaryotic traits by other means before later acquiring mitochondria, which made them more efficient.

To explain how mitochondria acquired genes that do not resemble α-proteobacteria, Gray proposed what has been dubbed the pre-endosymbiotic hypothesis. It says that another bacteria may have joined with an *Archaea* cell before mitochondria arose to provide some extra energy to help the eukaryotic transition. Later, genes from that other bacteria may have ended up in mitochondria as well. But he admits that it is hard to come by convincing evidence. If the entire story of mitochondria cannot be worked out by comparing them to bacteria, perhaps homing in on the diversity of individual pathways within the mitochondria of organisms can help.

Anastasios Tsaousis of the University of Kent, UK, studies the synthesis of iron-sulphur clusters by the mitochondria of microbial parasites. The ensembles of iron and sulphur are necessary, for example, for the functioning of proteins involved in metabolism and oxidation – both inside and outside mitochondria. The production of these clusters is considered one of the most critical functions of mitochondria; it cannot be done by other organelles.

Most mitochondria generate iron–sulphur clusters using one pathway – called the ISC machinery. But *Blastocystis*, a type of single-celled parasite, also has a sulphur mobilization (SUF) system usually found only in plants and *Archaea*. When *Blastocystis* cells are depleted of oxygen, they switch on the SUF system to synthesize the clusters. Studying how the ISC machinery and SUF system compare, and how and when they each evolved in mitochondrial history, Tsousis says, may teach us more about some of the broader questions relating to mitochondria's past.

Even the energy-generating components of the mitochondria responsible for their powerhouse moniker vary in some organisms. Since the mitochondrial respiratory chain depends on oxygen as an electron acceptor, organisms that live in low oxygen environments often have evolved alternative methods of generating ATP, such as special oxidases. Kiyoshi Kita of the University of Tokyo and Nagasaki University in Japan studies parasites – including those that cause malaria and African sleeping sickness in humans – that can use the chemical fumarate as an electron acceptor. Thus, they can generate energy in places where oxygen is scarce – including the human gut. "This ability to adapt to low oxygen by using fumarate is not only seen in parasites, but also in cancer cells," says Kita. "So it's a good target for chemotherapy." Kita has already begun to screen chemical compounds to identify potential drugs to block the fumarate pathway in the mitochondria. Other researchers are testing in human cell lines whether and how different mitochondrial respiratory chain enzymes from other organisms can help to treat genetic deficiencies in human mitochondria.

While the SUF and fumarate pathways set some mitochondria apart, the details of how some mitochondria package and process their DNA and RNA get researchers to exclaim "strange" and "bizarre". After all, in the nuclei of organisms from amoebas to humans, there is little variation in the mechanisms used to replicate or translate genes, so any deviance is surprising. →

Half a century ago this year, in 1967, evolutionary biologist Lynn Margulis, then at Boston University, proposed that mitochondria arose from a bacterium engulfed by an ancient cell.

All known polymerases lengthen a strand of nucleotides, such as DNA or RNA, by adding to their 3' end. Jackman and her collaborators, however, have found a polymerase in the mitochondria of slime mold that moves in the opposite direction: it adds a histidine to the 5' end of a mitochondrial tRNA molecule. Since discovering this so-called Thg1 enzyme, Jackman has identified members of the Thg1 superfamily in eukaryotes, bacteria, and archaea.

Studying how these mitochondrial enzymes work is not only interesting from an evolutionary and enzymatic perspective, says Jackman, but from a clinical one as well – mutations in the *THG1L* gene in humans have been linked to delays in development.

Julius Lukes of the University of South Bohemia in the Czech Republic finds the massive, oddly packaged mitochondrial genomes of protists very intriguing.

"The story always goes that humans must have more complexity in every way than protists that are a millimetre long," says Lukes. "Curiously, though, protists have more complex and bizarre mitochondria than humans."

Lukes' research revolves around euglenozoan protists, a large and diverse group of organisms that all have a single large mitochondrion – unlike most eukaryotic cells containing many small mitochondria. And while the mitochondrial DNA of most organisms is organized in a relatively simple circle or line of genes, the DNA of euglenozoans is, in general, much more complex. In some cases, it is simply large; in other cases, it is packaged in a way that is unheard of anywhere else – in thousands of tiny, interlocked kinetochore discs.

The best-studied euglenozoans are trypanosomes, which include parasites such as those causing sleeping sickness and Chagas disease in humans. Since their mitochondria are so different from humans, they allow drugs targeting their respiratory enzymes to be highly selective. Trypanosomes and related euglenozoans have exceptionally massive mitochondria – both in terms of the amount of DNA and the size of the organelle, with the mitochondria taking up 80 or 90 per cent of the entire interior in some cells. "It's like the mitochondria aren't just part of the cell, they are actually taking over the cell," says Lukes. And the massive mitochondrial genomes, Lukes has discovered are not big because they encode lots of proteins; rather, their RNA is edited down radically post-transcriptionally, resulting in a similar number of mRNAs or proteins. In some parasites that Lukes has studied, genes – whether contained in the nuclear or mitochondrial DNA – involved in processes in the nucleus, cytoplasm, Golgi apparatus, and endoplasmic reticulum are reduced in number and complexity, while genes involved in mitochondrial processes remain complex. It is as if the cell is shifting more complexity – and perhaps more function and importance – to the mitochondria, Lukes says.

"Molecular biologists tend to see an advantage in everything in biology, and think that everything in a cell must be there with a purpose," he says. In this regard, mitochondria seem to provide us with a particular intriguing snapshot of evolution in progress, he adds. This appears to be confirmed by researchers led by Vladimir Hampl of Charles University in Prague, who recently reported the existence of a protozoan with no mitochondria at all. However, how they evolved is not known.

Of course, most of the mitochondria's functions are not unnecessary; on the contrary, small mutations to mitochondrial genes can cause severe disease phenotypes in humans. The diseases can be difficult to diagnose and the same mutations may cause different symptoms in different people, even affecting different tissues in their bodies. In most cases, treatments are currently limited to lifestyle and dietary changes – such as ketogenic diets, supplemental calories, or anaerobic exercise – to ease symptoms and boost the number of healthy mitochondria in cells.

However, as basic research on mitochondria progresses – whether it aims to uncover their evolutionary history, the enzymology of surprising mitochondrial proteins, or how mitochondria vary between species – we may better understand these diseases and obtain clues toward targeted treatments.

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.

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REGULATION OF AGEING AND METABOLISM BY DFOXO IN *DROSOPHILA*

cf. BIF FUTURA, VOL. 28 | 1.2013

VICTOR BUSTOS
Discipline: Molecular Biologist, MSc
Institute: Max Planck Institute for Biology of Ageing, Cologne, Germany
Supervisor: Prof. Linda Partridge

The Forkhead Box-O (FOXO) transcription factors are important modulators of many biological processes, such as stress resistance, metabolism, and ageing. However, it is not clear how FOXO proteins elicit distinct outcomes in response to different stimuli. The main goal of my PhD was to better understand how *Drosophila* FOXO (dFOXO) is regulated, and how this regulation modulates its *in vivo* functions. I used genomic engineering to develop a tool that allowed me to modify *dfoxo*. First, I generated novel *dfoxo-null* mutants in which tagged *dfoxo* alleles could be reinserted within the endogenous locus. These tagged alleles restored normal gene expression and rescued all the phenotypes caused by *dfoxo-null* mutations, such as reduced fecundity and lifespan. Next, I used this validated genetic tool to generate *dfoxo* alleles containing mutations within the DNA binding domain (DBD). Mutations within the DBD produced similar phenotypes to those seen in *dfoxo-null* flies – such as reduced fecundity, oxidative stress resistance, and lifespan – which suggests that these functions rely on DNA binding. In contrast, DBD mutants were similar in body size and starvation resistance to wild-type flies, indicating that these functions are independent of DNA binding. Furthermore, I showed that *dfoxo-null* flies have trouble mobilizing fat under starvation, but that this ability is rescued in the DBD mutants. My colleagues and I are now trying to elucidate the mechanisms underlying dFOXO-dependent lipid mobilization under starvation. In addition, we are using my newly developed genetic tool to generate novel alleles and study dFOXO regulation by post-translational modifications. My work differentiated *in vivo* dFOXO functions and established a tool that will permit further understanding of dFOXO regulation. Together, they will ultimately allow us to understand the role that FOXO transcription factors play in the modulation of ageing and metabolism.

PUBLICATIONS

Kakanj P, Moussian B, Grönke S, Bustos V, Eming SA, Partridge L *et al* (2016) Insulin and TOR signal in parallel through FOXO and S6K to promote epithelial wound healing. *Nat Commun* **7**: 12972

HOW DOES THE LIGHT SENSOR OF A PHOTORECEPTOR CELL FORM?

cf. BIF FUTURA, VOL. 27 | 2.2012

JANINE DAUM
Discipline: Neuroscientist, MSc
Institute: Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland
Supervisor: Prof. Botond Roska

The nervous system extracts information from the environment via specialized sensory cells, which convert changes in physical quantities into neuronal signals. This conversion takes place in dedicated cellular compartments. Light is detected in outer segments of photoreceptors, mechanical pressure is detected in protrusions of mechanoreceptors and in hair bundles of hair cells, and the concentration of chemicals is detected in cilia of olfactory receptor neurons. Biological sensors are especially sensitive to genetic perturbation and are the most frequent sites of sensory loss. Around half of all cases of blindness are due to the loss of the outer segment. To prevent or repair outer segment loss, we need to understand how this sensor forms under normal conditions. The aim of my PhD was to uncover how outer segments form in the developing animal. I correlated changes in ultrastructure and gene expression in post-mitotic mouse cone photoreceptors every day between birth and eye opening (postnatal day 12). I used serial block-face electron microscopy, confocal microscopy, and RNA sequencing. Unexpectedly, I found that the changes involved in outer segment formation were highly synchronized and occurred on a single day: postnatal day 6. On that day, outer segments formed and there was a sharp, large-scale switch in gene expression affecting more than 14% of all genes expressed in cones. Hundreds of genes switched off, while hundreds of genes switched on. Switched-off genes included many transcription factors and neurogenic genes, while switched-on genes included genes relevant to cone function. Using ATACseq (assay for transposase-accessible chromatin with high-throughput sequencing), I found that extensive chromatin rearrangements accompanied the switch in an asymmetric fashion. First, they occurred before the switch was completed, but not after. Second, the chromatin conformation closed, but did not open. And third, changes were targeted to distal enhancers, but not to proximal regions. My results show that the growth of a key compartment of a post-mitotic sensory cell involves a rapid and extensive gene expression switch, which is accompanied by a loss in chromatin accessibility. This information can serve as a model system for understanding how gene regulatory networks switch a cell to a new state.

PUBLICATIONS

The results of this project have not yet been published.

LONG NON-CODING RNAS FUNCTION DURING HAEMATOPOIETIC DIFFERENTIATION AND LEUKAEMIA

cf. BIF FUTURA, VOL. 28 | 2.2013

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Institute: Watson School of Biological Sciences, Cold Spring Harbor Laboratory, NY, USA; Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK
Supervisor: Prof. Gregory J. Hannon

Mammalian genomes consist of more than three billion base pairs. Of these, fewer than 2% represent genic exons. Cell type-specific expression of genes confers cells with their identity, while gene mutations and mis-expression are implicated in disease. However, many other regions of the genome are transcribed but not translated, thereby producing long non-coding RNAs (lncRNAs). The cell type-specific expression of lncRNAs raised the possibility that they could regulate cell-fate decisions. My PhD project aimed to identify functional lncRNAs in normal differentiation and cancer in mouse haematopoiesis. To this end, my colleagues and I built all the necessary tools, including meticulous transcriptome analysis of annotated and *de novo* assembled lncRNAs, as well as RNA interference (RNAi). We first assessed lncRNA function using an *in vivo* RNAi screen in an acute myeloid leukaemia model. We identified several lncRNAs essential for leukaemia maintenance, and found that a number of them act by promoting leukaemia stem cell signatures. Leukaemia blast cells show a myeloid differentiation phenotype when any of these lncRNAs are depleted, and this effect is mediated via the *MYC* oncogene. I also used our lncRNA assembly and RNAi tools to identify functional lncRNAs that are differentially regulated during the first cell-fate decisions of haematopoietic stem cells. I specifically focused on mouse lncRNAs that had an annotated human lncRNA in the corresponding syntenic region that was similarly expressed in human cord blood progenitors. Our loss-of-function studies using mouse bone marrow transplants identified several of these syntenically conserved lncRNAs as potential regulators of lineage choice and haematopoietic stem cell self-renewal. Overall, my work highlights the importance of lncRNAs as regulators of cell fate and provides key tools for further identifying and characterizing lncRNA functions.

PUBLICATIONS

Delás MJ*, Sabin LR*, Dolzhenko E*, Knott SRV, Munera Maravilla E, Jackson BT *et al* (2017) lncRNA requirements for mouse acute myeloid leukemia and normal differentiation. *eLife* **6**: e25607

Delás MJ, Hannon GJ (2017) lncRNAs in development and disease: from functions to mechanisms. *Open Biol* **7**: 170121

INFLUENCE OF DNA METHYLATION ON TRANSCRIPTION FACTOR BINDING

cf. BIF FUTURA, VOL. 29 | 2.2014

SILVIA DOMCKE
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Supervisor: Prof. Dirk Schübeler

Dynamic gene regulation enables diverse cell types to arise from the same DNA blueprint. Transcription factors (TFs) control gene activity by binding specific sequence motifs in regulatory DNA. However, TFs occupy only a fraction of possible binding sites in each cell type. Chromatin can restrict the accessibility of these sites, but it is not clear to what extent this regulates TF binding. The goal of my PhD was to explore the role of DNA methylation in constraining TF binding. For the TF CCCTC-binding factor (CTCF), DNA methylation prevents binding at some motifs but not others. By comparing CTCF binding in mouse embryonic stem cells (mESCs) with and without DNA methylation, I found that certain motifs and surrounding sequences are crucial for CTCF methylation sensitivity. To identify other methylation-sensitive TFs, I mapped genome-wide chromatin accessibility in mESCs with and without DNA methylation. I showed that sites accessible only in the absence of DNA methylation are enriched for certain TF motifs, especially those of nuclear respiratory factor 1 (NRF1). NRF1 binds thousands more sites in the unmethylated genome, and restoring methylation levels outcompetes NRF1 binding. Deleting neighbouring motifs in *cis* or a TF in *trans* causes local hypermethylation and loss of NRF1 binding. This competition between DNA methylation and TFs reveals co-operativity between TFs that acts indirectly via DNA methylation. Most TF binding events are not affected by DNA methylation in mESCs. To investigate differentiated cells, for which DNA methylation is essential, I generated methylation-deficient mouse neurons. Gene transcription and chromatin accessibility in these neurons were not strongly affected, but a subset of TF motifs was enriched in the fraction of sites bound only in the absence of DNA methylation. By showing that a few TFs are methylation-sensitive and rely on other TFs to keep their motifs unmethylated, my results increase our understanding of gene regulation in development and disease.

PUBLICATIONS

Yin Y, Morgunova E, Jolma A, Kaasinen E, Sahu B, Khund-Sayeed S *et al* (2017) Impact of cytosine methylation on DNA binding specificities of human transcription factors. *Science* **356**: eaaj2239

Domcke S*, Bardet AF*, Ginno PA, Hartl D, Burger L, Schübeler D (2015) Competition between DNA methylation and transcription factors determines binding of NRF1. *Nature* **528**: 575–579

SYSTEMIC CANCER–HOST INTERACTIONS INFLUENCING DISEASE PROGRESSION

cf. BIF FUTURA, VOL. 29 | 1.2014

CAMILLA ENGBLOM
Discipline: Biologist, BA
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Supervisor: Dr Mikael Pittet

Non-malignant cells, including immune cells, can actively shape the progression of cancer by infiltrating solid tumours. In the past decade, targeting the immune system has been validated as an effective strategy to treat cancer, as therapeutically manipulating certain immune cells, such as T lymphocytes, can durably control cancer progression in some patients. Despite these advances, our mechanistic understanding of tumour-immune interactions remains incomplete. For example, cancer-exerted effects on host responses beyond the local tumour microenvironment are less studied, but could be highly relevant because tumour-infiltrating immune cells are dynamically replenished by bone marrow-derived cells. In my PhD project, I interrogated various aspects of systemic cancer-host interactions using pre-clinical tumour models. I focused on lung cancer – which remains the leading cause of cancer-related deaths worldwide, yet lacks effective treatments for many patients – and the bone marrow, which is the main haematopoietic cell production site for all circulating blood lineages in adults. I investigated the bone marrow microenvironment in tumour-bearing mice using *in vivo* imaging of injectable fluorescently labelled probes, bone histomorphometry, and micro-computed tomography analysis. Based on these studies, I found that lung adenocarcinomas alter the bone marrow microenvironment in mice. In subsequent pre-clinical studies, which included transgenic reporter mice and RNA sequencing analysis, I showed that the cancer-induced phenotype involved bone marrow-resident stromal cells. Using genetically engineered tumour-bearing mice that enable the specific manipulation of bone marrow cells, I found that resident bone marrow stromal compartments remotely promote tumour growth in the lung and control distinct elements of the tumour immune cell infiltrate. To further characterize the tumour immune microenvironment, I used flow cytometry and RNA sequencing-based readouts to identify a novel subset of tumour-promoting immune cells, which was in turn regulated by the bone marrow stroma. My findings define new basic mechanisms of long-range tumour-host interactions that could provide novel therapeutic avenues.

PUBLICATIONS

Engblom C*, Pfirshcke C*, Pittet MJ (2016) The role of myeloid cells in cancer therapies. *Nat Rev Cancer* **16**: 447–462

GLOBAL AND SINGLE-CELL ANALYSES TO CONNECT p53 DYNAMICS WITH GENE EXPRESSION

cf. BIF FUTURA, VOL. 28 | 2.2013

ANTONINA HAFNER
Discipline: Systems Biologist, MSc
Institute: Harvard University, Cambridge, MA, USA
Supervisor: Prof. Galit Lahav

The dynamics of transcription factors play important roles in a variety of biological systems. However, how these dynamics control gene expression is not well understood. In my PhD project, I focused on the dynamics of tumour suppressor protein p53, which control cell fate decisions in response to DNA damage. The protein regulates several hundred target genes, but how it selects the genes to activate in response to a specific type of stress or cell type remains unknown. The goal of my work was to connect p53 dynamics with gene expression at the genome-wide level and in single cells. To gain a global understanding, my colleagues and I focused on pulses in p53 protein levels that are induced in response to γ-irradiation. Using genome-wide RNA sequencing and p53 chromatin-immunoprecipitation sequencing, we found multiple distinct patterns of gene expression in response to p53 pulses. The p53 binding dynamics were uniform genome-wide, even for genes with distinct dynamics of gene expression. Using a mathematical model combined with experiments perturbing p53 pulses, we concluded that p53 uniformly binds to and activates transcription of its target genes, while post-transcriptional mechanisms determine the differences in gene expression dynamics. Next, we quantified the dynamics of p53 together with the dynamics of the protein of one of its target genes, p21, and the dynamics of p21 transcription in live single cells. As with our population-level data, p21 transcription depended strongly on p53 in response to γ-irradiation. Moreover, this relationship was conserved across all conditions tested and over long timescales. By contrast, p21 protein showed more complex dynamics. Future work to reveal how p53 levels and p21 transcription affect p21 levels will provide key insights into the cellular outcomes in response to different stresses. The combination of population-level and single-cell approaches led me to identify a general mechanism that enables differential expression between genes in response to p53 pulses as well as to obtain a detailed picture of p21 regulation at the single-cell level.

PUBLICATIONS

Hafner A, Stewart-Ornstein J, Purvis JE, Forrester WC, Bulyk ML, Lahav G (2017) p53 pulses lead to distinct patterns of gene expression albeit similar DNA-binding dynamics. *Nat Struct Mol Biol* **24:** 840–847

SENSITIVITY AND ENGINEERED RESISTANCE OF MYELOID LEUKAEMIA CELLS TO BRD9 INHIBITION

cf. BIF FUTURA, VOL. 28 | 2.2013

ANJA HOHMANN
Discipline: Biochemistry, MSci
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Supervisor: Prof. Christopher Vakoc

The mammalian SWI/SNF complex supports the growth of acute myeloid leukaemia (AML) cells and other cancers, making this chromatin remodeller a candidate drug target in the treatment of human malignancy. Chemical modulation of SWI/SNF activity, however, has not been achieved. Given the pharmacological accessibility of bromodomains (BDs) – protein modules that bind acetyl-lysine motifs – my colleagues and I evaluated the relevance of BD-carrying SWI/SNF subunits for leukaemia maintenance. Using proteomic and genetic approaches, we identified BD-containing protein 9 (BRD9) as a SWI/SNF subunit that is critical for the proliferation of mouse and human AML cells. In these cells, BRD9 binds the enhancer of the proto-oncogene *MYC*, sustains *MYC* transcription, and supports an undifferentiated and rapidly proliferating cellular state. Using complementary DNA (cDNA) rescue experiments, we established that the BD is essential for BRD9 function in AML. Based on these observations, our collaborators at Boehringer Ingelheim derived a small-molecule inhibitor of the BRD9 BD. This compound partially displaces BRD9 from *MYC* enhancer elements and selectively suppresses the proliferation of mouse and human AML cell lines. Given the role of other BDs, specifically those of BRD4, in leukaemia growth, it was critical to rule out potential off-target activity of our BRD9 inhibitor. To this end, we engineered a BD-swap allele of *BRD9* by replacing its BD with that of BRD4. Despite the altered BD pocket, this allele retained functionality similar to that of wild-type *BRD9* in cDNA complementation assays. Expression of this allele in AML cells conferred resistance to the anti-proliferative effects of the BRD9 inhibitor, thus establishing BRD9 as the cellular target. Our results demonstrate a vital role for BRD9 in the proliferation of AML cells, which can be targeted with a small-molecule inhibitor directed against its BD. In addition, we developed a simple genetic strategy for constructing resistance alleles to demonstrate on-target activity of chemical probes in cells.

PUBLICATIONS

Hohmann AF, Martin LJ, Minder JL, Roe JS, Shi J, Steurer S *et al* (2016) Sensitivity and engineered resistance of myeloid leukemia cells to BRD9 inhibition. *Nat Chem Biol* **12**: 672–679

Hohmann AF, Vakoc CR (2014) A rationale to target the SWI/SNF complex for cancer therapy. *Trends Genet* **30**: 356–363

SINGLE-MOLECULE DYNAMICS OF MULTIVALENT CBX5 RECRUITMENT AND CHROMATIN CONFORMATIONS

cf. BIF FUTURA, VOL. 28 | 2.2013

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Supervisor: Prof. Beat Fierz

Chromatin is the nucleoprotein complex of DNA and histones that governs eukaryotic DNA-templated processes. Histone post-translational modifications (PTMs), chromatin-associated effector proteins, and the organization of nucleosomes into chromatin's secondary structure all have key roles in these processes, but the underlying spatiotemporal dynamics are not well understood. Multivalent effectors with specialized binding domains recognize multiple histone PTMs in close proximity and read out their epigenetic states. Heterochromatin protein 1α (also called chromobox homologue protein 5; CBX5) can dimerize to form a multivalent effector capable of binding two histone H3 trimethylated at lysine 9 (H3K9me3). CBX5 contributes to heterochromatin compaction by bridging nucleosomes. However, rather than binding stably to chromatin, CBX5 remains in dynamic exchange with a pool of unbound protein. To reconcile these apparently contradictory findings and elucidate the importance of multivalency for CBX5 binding, I developed chemical biology methods to reconstitute chromatin with defined PTMs. Using the reconstituted chromatin and single-molecule biophysical methods, I investigated the kinetics of CBX5-chromatin interactions. I found that only dimeric CBX5 efficiently competes for H3K9me3, as it binds more efficiently than monomeric CBX5. To probe chromatin dynamics upon CBX5 binding, I introduced fluorescence resonance energy transfer pairs into adjacent nucleosomes for single-molecule measurements at nanometer resolution. Although CBX5 pulled nucleosomes in chromatin with H3K9me3 closer together, the heterochromatin remained dynamic. My novel tools can be used to study the spatiotemporal dynamics of DNA-templated interactions and their impact on chromatin structure. By defining the kinetics underlying multivalent CBX5 recruitment and how chromatin structure changes upon CBX5 binding, my work reveals some of the microscopic dynamics underlying the organization of chromatin into macroscopically stable compartments such as heterochromatin.

PUBLICATIONS

Kilic S, Bachmann AL, Bryan LC, Fierz B (2015) Multivalency governs HP1α association dynamics with the silent chromatin state. *Nat Commun* **6**: 7313

Pick H, Kilic S, Fierz B (2014) Engineering chromatin states: chemical and synthetic approaches to investigate histone modification function. *Biochim Biophys Acta* **1839**: 644–656

ELECTROPHYSIOLOGICAL ANALYSIS OF THE SYNAPTIC VESICLE PRIMING PROCESS

cf. BIF FUTURA, VOL. 29 | 2.2014

DENNIS NESTVOGEL
Discipline: Neuroscientist, MSc
Institute: Max Planck Institute for Experimental Medicine,Göttingen, Germany
Supervisors: Prof. Jeong Seop Rhee, Prof. Nils Brose

Signalling between nerve cells requires transmitter-loaded synaptic vesicles (SVs) to fuse with the presynaptic plasma membrane in response to action potentials. Before fusion, SVs are recruited to the plasma membrane, where they undergo a priming process to reach fusion competence. This process is controlled by members of the Munc13 (mammalian uncoordinated 13 homologue) and CAPS (calcium-dependent activator protein for secretion) families and is thought to involve the partial assembly of fusogenic SNARE (soluble N-ethylmalimide sensitive factor attachment protein receptor) complexes. Despite substantial progress in identifying key SV priming proteins, it is largely unknown how Munc13s and CAPSs co-operate to prime SVs. In my PhD project, I first dissected the functional interplay of Munc13s and CAPSs and showed that they differentially prime SVs in a lipid-dependent manner. CAPSs engage in a lipid-sensitive priming step at low presynaptic Ca^{2+} concentrations, while Munc13-lipid interactions predominate at high Ca^{2+} concentrations. These interactions reflect a discrete step in the priming reaction and likely precede the partial assembly of SNARE complexes, which is mediated by the MUN domain of Munc13s. Subsequently, I studied the relevance of CAPSs in the aetiology of bipolar disorder (BPD). I performed a structure-function analysis of BPD-associated CAPS1 mutations in neurons and generated a knock-in mouse line carrying one such mutation. Some BPD mutations led to altered forms of short-term synaptic plasticity, and preliminary results indicated behavioural abnormalities in the knock-in mice, suggesting that CAPS1 dysfunction may contribute to the aetiology of BPD. Finally, I studied the significance of CAPS1 for short-term synaptic plasticity in the context of visual information processing *in vivo*. I showed that synaptic depression in thalamocortical axons is enhanced in the absence of CAPS1, leading to more pronounced sensory adaptation in cortical neurons. In summary, my PhD project has led to a more detailed understanding of the cell biology of the SV priming process, its relevance for disease, and its involvement in fine-tuning sensory information processing.

PUBLICATIONS

Nguyen Truong CQ*, Nestvogel D*, Ratai O, Schirra C, Stevens DR, Brose N *et al* (2014) Secretory vesicle priming by CAPS is independent of its SNARE-binding MUN domain. *Cell Rep* **9**: 902–909

DISCOVERY AND TARGET IDENTIFICATION OF SMALL MOLECULE AUTOPHAGY INHIBITORS

cf. BIF FUTURA, VOL. 30 | 2.2015

LUCAS ROBKE
Discipline: Chemical Biologist, BSc
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Supervisor: Prof. Herbert Waldmann

Autophagy mediates the degradation of cellular components within specialized subcellular compartments. This degradation not only compensates for a temporary lack of nutrients but also has crucial roles in eliminating the protein aggregates that cause neurodegenerative diseases and the toxic metabolites that can cause cancer. In my PhD, I used phenotypic screening of breast cancer cells to identify three novel chemotypes, or chemically distinct entities, that were responsible for inhibiting autophagy. I synthesized additional structurally related analogues of these chemotypes, which represented even more potent inhibitors, and then evaluated them as autophagy inhibitors to validate them as probes for future research. Using a combination of methods, I identified the target of the first chemotype as the class III phosphoinositide 3-kinase VPS34. The inhibitor bound VPS34 in cellular models, and thus is a useful tool compound for studying autophagy and VPS34 activity. This is particularly important, as other tool compounds of this kinase are unselective. I showed that the second chemotype inhibited mitochondrial respiration by blocking the enzymatic function of complex I (NADH dehydrogenase) within the electron transport chain. Rotenone, a natural-product inhibitor of complex I, has been used for many years to study metabolic pathways and in toxin models of Parkinson's disease. However, rotenone also appears to have activity that is independent of mitochondrial complex I inhibition. Thus, the second chemotype may provide novel opportunities to unravel the role of mitochondrial complex I in pathophysiological processes. The identification of the target protein or the mode of action of the third chemotype is not yet complete. These three novel autophagy inhibitors can be used to interrogate this crucial physiological process, which is often misregulated in disease, and might also present promising starting points for future drug discovery programs.

PUBLICATIONS

Robke L, Laraia L, Carnero Corrales MA, Konstantinidis G, Muroi M, Richters A *et al* (2017) Phenotypic identification of a novel autophagy inhibitor chemotype targeting lipid kinase VPS34. *Angew Chem Int Ed* **56**: 8153–8157

Laraia L, Ohsawa K, Konstantinidis G, Robke L, Wu YW, Kumar K *et al* (2017) Discovery of novel cinchona-alkaloid-inspired oxazatwistane autophagy inhibitors. *Angew Chem Int Ed* **56**: 2145–2150

SKI COMPLEX PHYSICALLY LINKS THE mRNA TRANSLATION AND DEGRADATION MACHINERIES

cf. BIF FUTURA, VOL. 29 | 2.2014

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Institute: Gene Center Munich, Ludwig-Maximilians University (LMU), Munich, Germany
Supervisor: Prof. Roland Beckmann

The translation and degradation of mRNAs are interdependent processes. The degradation of mRNAs is performed in either the 5'-to-3' or the 3'-to-5' direction. In the latter pathway, the cytosolic exosome works with the Ski complex – which consists of the RNA helicase Ski2 and other proteins – and Ski7 to degrade the mRNA. However, the exact function of these factors and how they are linked to the ribosome is poorly understood. During my PhD project, I determined a cryo-electron microscopy structure of a natively purified ribosome-Ski complex from *Saccharomyces cerevisiae* at 3.8 Å resolution, allowing me to build the entire atomic model of the macromolecular assembly. The structure revealed that the Ski complex interacts with the ribosome in such a way that Ski2 is perfectly aligned with the mRNA channel of the ribosome. I could visualize an mRNA molecule in the ribosome that extended into the Ski2 helicase core. Thus, the 3' end of the mRNA is threaded into the active site of the helicase as a substrate for extraction. In collaboration with the Conti lab at the Max Planck Institute of Biochemistry in Martinsried and the Jacquier lab at the Pasteur Institute in Paris, I analysed these ribosome-Ski complexes biochemically. I found that short 3' mRNA overhangs extending from the ribosome, which often occur during mRNA degradation, act as a recruitment signal for the Ski complex. Furthermore, we performed ribosome profiling and mass spectrometry analysis to investigate the nature and composition of ribosome-Ski complex-associated mRNAs. Our findings suggest that the novel interaction that I identified is not limited to specific mRNA degradation events, but is more likely a general feature of the 3'-to-5' degradation pathway and is probably conserved in many higher eukaryotes. Collectively, these results are the first structural proof of how mRNA translation and degradation are linked in the cell.

PUBLICATIONS

Schmidt C, Kowalinski E, Shanmuganathan V, Defenouillère Q, Braunger K, Heuer A *et al* (2016) The cryo-EM structure of a ribosome–Ski2-Ski3-Ski8 helicase complex. *Science* **354**: 1431–1433

Schmidt C*, Becker T*, Heuer A, Braunger K, Shanmuganathan V, Pech M *et al* (2015) Structure of the hypusinylated eukaryotic translation factor eIF-5A bound to the ribosome. *Nucleic Acids Res.* **44**: 1944–1951

MICROBIOME DYNAMICS IN METABOLIC DISEASE

cf. BIF FUTURA, VOL. 28 | 2.2013

CHRISTOPH THAISS
Discipline: Molecular Biologist, MSc
Institute: Weizmann Institute of Science, Rehovot, Israel
Supervisor: Prof. Eran Elinav

The intestinal microbiota contains trillions of microorganisms that strongly influence multiple aspects of host physiology and disease. In my PhD project, I aimed to investigate the temporal dynamics of the intestinal microbiome and how they affect host metabolism. My colleagues and I discovered that the microbiome oscillates with a 24-hour rhythm in both mice and humans. These daily oscillations shape the circadian biology of the host by determining the temporal pattern of serum metabolites, which in turn orchestrate circadian epigenetics and transcription in metabolic tissues. We showed that disrupting the circadian clock – either genetically, environmentally, or by jetlag – provoked the development of an altered microbial community that predisposed the host to obesity. The host-microbiome interface can thus be viewed as a dynamic entity that fluctuates on a timescale of minutes to hours. We also investigated microbiome dynamics at larger timescales. We found that a period of obesity induces long-lasting alterations in the structure of the microbiome, which persist even after successful dieting and a return to normal weight. This memory-like behaviour of the microbiome mediated the susceptibility of the formerly obese host to exacerbated weight regain. The microbiome contributed to diminished post-dieting flavonoid levels and reduced energy expenditure, and flavonoid supplementation ameliorated secondary weight gain in mice. These results uncovered the microbiome's contribution to accelerated weight regain after dieting, a phenomenon commonly known as the "yo-yo effect" of recurrent obesity. My PhD work has highlighted temporal microbiome dynamics as an important principle of host-microbiome interactions and suggests that microbiome features may be used to diagnose and treat common metabolic diseases.

PUBLICATIONS

Thaiss CA, Levy M, Korem T, Dohnalova L, Shapiro H, Jaitin DA *et al* (2016) Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell* **167:** 1495–1510

See also: Nature **514**: 181–6; *Nature* **526**: S59–60; *Nature* **535**: 65–74; *Nature* **540**: 544–551; *Nat Med* **21**: 213–5; *Nat Rev Cancer* **13**: 759–71; *Nat Rev Immunol* **17**: 219–232; *Science* **349**: 1101–1106; *Cell* **159**: 514–29; *Cell* **163**: 1428–43; *Cell* **166**: 1231–1246; *Immunity* **42**: 595–7; *Cell Metab* **23**: 393–4; *Cell Metab* **26**: 99–700; *Cell Host Microbe* **22**: 185–192; *Curr Opin Immunol* **30**: 54–62; *Future Microbiol* **12**: 555–559; *Genes Dev* **30**: 1589–97; *Genome Med* **7**: 120; *J Mol Med* **95**: 1021–1027; *PLoS Pathog* **11**: e1005113; *Semin Immunopathol* **37**: 39–46; *Trends Immunol* **37**: 84–101; *Trends Immunol* **38**: 248–260

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.

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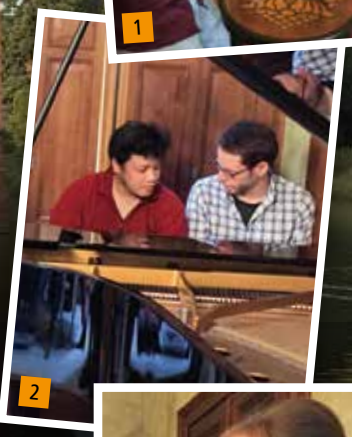
THE SOUNDS OF SILENCE

This year, BIF's annual meeting for alumni based in Europe was all about the topic of sound. It is only fitting, then, that it ended with a stunning performance of a Simon and Garfunkel classic.

By Kirsten Achenbach

This year's Gracht seminar, titled "World of Sounds" and held from July 14 to 16 July, included talks on the biology of hearing and what modern hearing aids can do, the influence of music on the brain, catching criminals by voice analysis, and the not so silent ocean. The first speed-dating event in the history of BIF was well received by the alumni, allowing them to talk to and network with more of the other fellows than would otherwise have been possible. Sunday morning, actor and drummer Christian von Richthofen practised and performed Simon and Garfunkel's classic "The Sounds of Silence" with an orchestra spontaneously formed from the approximately 100 participants. The staff from Gracht Castle had raided kitchen, cupboards, and storage rooms for instruments: bottles, computer keyboards, paper bins, construction pipes, breadbaskets, spoons, chairs, flipcharts, garbage bags, even one of the elephant sculptures from the garden. One participant had brought his clarinet, two played the piano, and several formed an ad hoc choir. After practising for a few hours, the seminar ended with a stunning performance and calls for an encore.


1


2

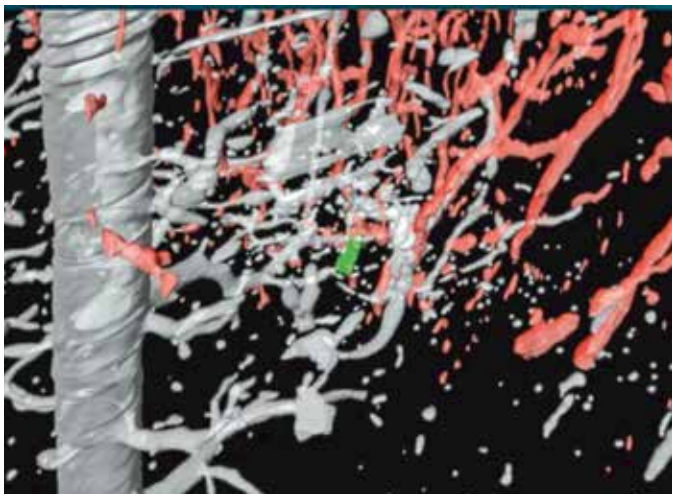

3

1 **Tilman Flock** demonstrates that bar stools make excellent bongos.
2 **Christopher Thaiss and Ha Thi Hoang** playing the piano.
3 **Katharina Nussbaum and Cornelius Ringe** trying out the "sacksophones". At the seminar, Cornelius Ringe delivered a talk on sound design.

Photos: BIF, Kirsten Achenbach

BIF's SISTER FOUNDATIONS

COMING SOON: ACCESS TO ADVANCED IMAGING TECHNOLOGY



This is a screenshot of a 3D animation from the video "Seeing is Understanding". It provides a first impression of the planned Imaging Technology Centre. The video can be found on Youtube.

Advanced light and electron microscopy techniques promise to enable unprecedented insights and findings in life sciences research, especially if they are used in combination. However, even the access to each of the very expensive and complex technologies by itself is currently limited to only a few sites, as BIF fellows using them for their research know. At least one researcher had to do all of her experiments at night. There is hope, though: in 2020, the Imaging Technology Centre at the European Molecular Biology Laboratory (EMBL) in Heidelberg is slated to open its doors. It will be the first centre worldwide to give researchers from all over the world access to the combination of the latest optical and electron microscopy technologies. BIF's sister foundation, the Boehringer Ingelheim Foundation, will donate 5 million euros for the new centre, in particular for training scientists in the use of the highly complex microscopes, and for supporting their research with them. Construction of the new centre will start in 2018 and will be financed by the German federal government and the state of Baden-Wuerttemberg. Most of the equipment will be donated by leading microscopy companies.

Correlative light and electron microscopy (CLEM) – co-developed at EMBL – combines different microscopy techniques and allows scientists to examine a sample under the light microscope before it is put under the electron microscope. Whereas the light microscope enables us to observe functional processes in living cells in the micrometre range, the electron microscope captures protein structures in the nanometre and angstrom range. When combining these two very different microscopy techniques, scientists can bring together functional and structural information to gain new insights. For example, EMBL researchers have used them to reconstruct for the first time how HIV drug resistance is formed and to identify processes in the cell that can lead to infertility in mammals.

UNRAVELLING UBIQUITIN: THE 2017 INTERNATIONAL HEINRICH WIELAND PRIZE

Around 120 scientists were present when the Boehringer Ingelheim Foundation, BIF's sister foundation, awarded Professor Alexander Varshavsky from the California Institute of Technology, USA, the 2017 Heinrich Wieland Prize for discovering the biology of the ubiquitin system. "With his ground-breaking work Varshavsky has demonstrated that cells use the ubiquitin system to finely orchestrate which proteins will be destroyed and when, and that this is as important for balancing protein levels as their production," states Professor Felix Wieland, chair of the Board of Trustees selecting the laureates. "Varshavsky has thereby established ubiquitin as a master regulator in a wide range of processes from the cell's cycle of growth and division, to repairing DNA, to how cells respond to stress." In addition, Varshavsky has developed new biochemical and genetic methods, several of which have become major tools for biomedical research. They include the widely used chromatin immunoprecipitation (ChIP) assay and the first protein fragment complementation assays (PCAs), which led, for example, to the split green fluorescent proteins. The 100,000-euro prize was presented in a festive ceremony which was preceeded by a scientific symposium at Munich's Nymphenburg Palace on 19 October 2017.

Professor Felix Wieland, chair of the Board of Trustees (left), the laureate Prof. Alexander Varshavsky (middle), and Christoph Boehringer, chair of the Executive Committee of the Boehringer Ingelheim Foundation.

Photos: A. Griesch (bottom); J Cell Sci (2016) 129: 444–456 (top)

PAPERS IN THE SPOTLIGHT

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

PLURIPOTENT STEM CELLS: NATURE VERSUS CULTURE

Pluripotent stem cells (PSCs), garnered from the inner cell mass of the embryo, are something of a holy grail – their ability to turn into virtually any kind of cell type makes them extremely valuable for understanding development and perhaps even for healing disease or replacing failing organs. For laboratory study, they are kept under a regime called 2i, in which two kinase inhibitors, one blocking MEK1 and MEK2, and the other GSK3, stop them from developing. Konrad Hochedlinger and Alexander Meissner from Harvard University, USA, have now found that the 2i regime causes male mouse PSCs to lose part of their typical DNA methylation pattern, which in turn allows certain genes to be expressed (a parallel study using female mouse PSCs had similar results). Some cells even lost or gained whole chromosomes. If such cells were injected into mouse embryos, this led to developmental abnormalities and, unlike healthy PSCs, the cells were not able to develop properly alongside the resident cells. The longer PSCs were kept in a naive state by 2i, the more pronounced these problems were. Hochedlinger and Meissner could show that all of these effects were caused by blocking the MEKs. Replacing them only met with limited success. This raises the question as to what the MEK pathway does in early embryonic development, especially as it is one of the most frequently mutated signalling cascades in cancer. It also reminds us once again just how artificial *in vitro* conditions are.

An overgrown mouse pup derived from female ES cells next to a normal pup.

REFERENCE

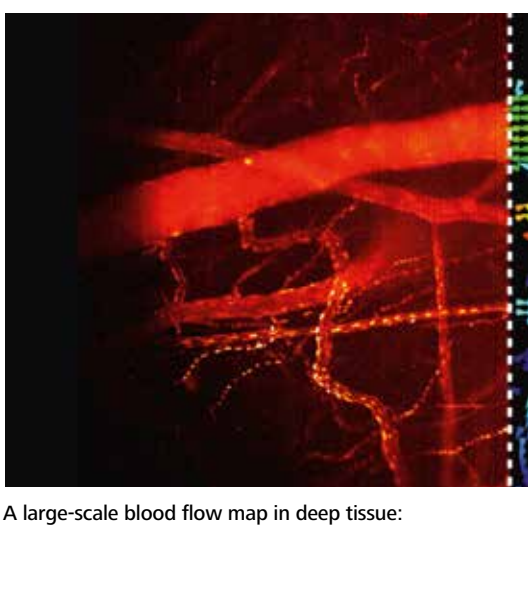
Choi J, Huebner AJ, Clement K, Walsh RM, Savol A, Lin K, Meissner A, Hochedlinger K (2017) Prolonged Mek1/2 suppression impairs the developmental potential of embryonic stem cells. *Nature* **548:** 219–223.

Konrad Hochedlinger, fellow 2000–2003
Alexander Meissner, fellow 2003–2005

LOOKING DEEP WITHIN WITH

Even if something looks opaque to our eyes – which cover a spectrum between 390 and 700 nanometres (nm) – it might be transparent at other wavelengths. Soft tissues, for example, are nearly as transparent as glass to light with wavelengths between 1,000 and 2,000 nm, the so-called short-wave infrared (SWIR) spectrum. But to take full advantage of this effect when observing processes in living tissues, we lacked suitable contrast agents that emit SWIR light. However, Daniel Franke from Moungi Bawendi's group at the Massachusetts Institute of Technology in Cambridge, MA, USA, and his colleagues have now developed a method to construct extremely bright quantum dots – semiconducting crystals at nanometre scale – that emit fluorescent light at SWIR frequencies when excited by a laser. "Our quantum dots are so bright that we can capture high-resolution images of fine structures through skin and bones of mice," says Daniel. "And we can do

Photos: Konrad Hochedlinger (bottom left), Daniel Franke (bottom right)



A large-scale blood flow map in deep tissue:

QUANTUM DOTS

it so fast that we can track even single quantum dot composite particles, enabling us, for example, to measure blood flow in capillaries. We can also use it in freely moving animals to remotely monitor vital signs and internal organs." The injectable quantum dots are based on indium arsenide, a material not likely to be approved for use in humans, but Daniel and his colleagues are already working on safer versions to perform tasks such as imaging how tumours grow or respond to therapy.

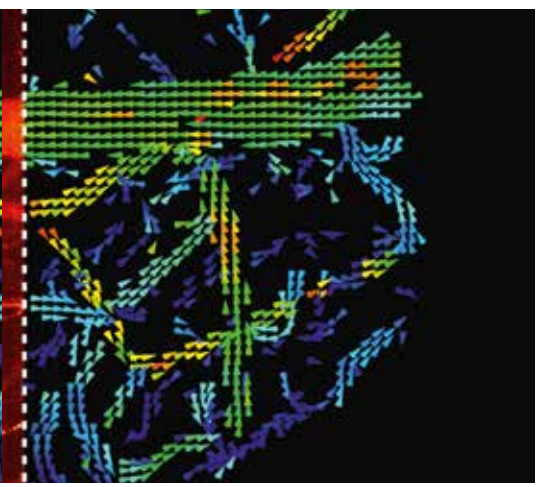
REFERENCE

Franke D, Harris DK, Chen O, Bruns OT, Carr JA, Wilson MWB *et al* (2016) Continuous injection synthesis of indium arsenide quantum dots emissive in the short-wavelength infrared. *Nat Comm* **2016:** 12749.

Bruns O, Bischof TS, Harris DK, Franke D, Shi Y, Riedemann L *et al* (2017) Next generation *in vivo* optical imaging with short-wave infrared quantum dots. *Nat Biomed Eng* **2017:** 0056

Daniel Franke, fellow 2015–2017

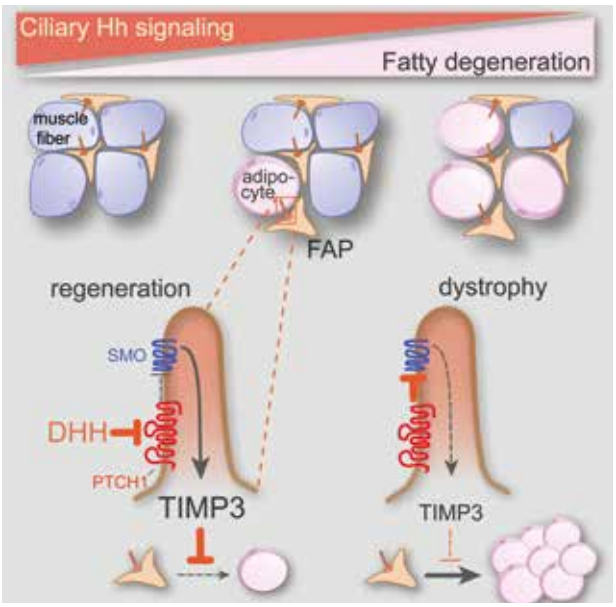
Photos: Daniel Franke, printed with permission from Elsevier from reference given below article



left as seen as in the tissue, right as modelled.

CILIAR HEDGEHOG SIGNALLING KEEPS MUSCLES LEAN

Injured muscles can heal. However, with chronic injuries or age, instead of healing, muscle fibres are replaced by fat cells. Daniel Kopinke from the group of Jeremy Reiter at the University of California in San Francisco, USA, has unravelled how to keep sick and old muscles lean. Muscle fat arises from mesenchymal stem cells called fibro/adipogenic progenitor cells (FAPs). The scientists discovered that in muscles, FAPs are the cells most often possessing a primary cilium, an antennae interpreting extracellular cues. Mice FAP cells, whose cilia were genetically removed, less often converted into fat cells after chronic injury and the muscles healed better. The same held true in a mouse model of Duchenne muscular dystrophy, a chronic disease characterized by fatty muscles. "Just by blocking cilia, we could turn the muscles of a sick mouse into something you would find in a much healthier animal," said Daniel. Probing this process, they uncovered that cilia transduced Hedgehog (Hh) signalling which usually prevents FAPs from turning into fat. In normal injuries, the level of one of the three Hh ligands, Desert Hedgehog (Dhh), goes up. In chronic injuries, however, Dhh goes down, explaining why fat only forms in chronic injuries. The group further showed that when they activated Hh signalling, it induced TIMP3, a secreted metalloproteinase inhibitor. By mimicking the action of TIMP3 in mice, they reduced the number of fat cells formed after chronic injury by 70%, pointing to a strategy to keep sick muscles strong.



Inverse correlation between fatty degeneration of skeletal muscle and Hedgehog signalling, sensed by primary cilia.

REFERENCE

Kopinke D, Roberson EC, Reiter JF (2017) Ciliary Hedgehog signaling restricts injury-induced adipogenesis. *Cell* **170:** 340–351.

Daniel Kopinke, fellow 2009–2010

PROFILES

FRANZISKA BLEICHERT
Institute: Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland
Fellowship: 2005–2007

INES DRINNENBERG
Institute: Institut Curie, Paris, France
Fellowship: 2007–2010

PROFESSOR KAI PAPENFORT
Institute: University of Munich (LMU), Germany
Fellowship: 2007–2008

PROFESSOR BARBARA TREUTLEIN
Institute: Max Planck Institute for Evolutionary Anthropology, Dresden, Germany
Fellowship: 2009–2010

This year, four BIF alumni have been awarded ERC Starting Grants for talented young research leaders. This means that they receive up to 1.5 million euros over five years to set up their own labs.

Franziska Bleichert aims to elucidate how the start sites (origins) of DNA replication are specified in higher eukaryotes and how the chromatin context and DNA structure surrounding these origins influence and regulate the onset of DNA replication.

Ines Drinnenberg is studying how insects could evolve a centromere that is radically different from most other eukaryonts, one that is attached not to a single, but to multiple points of the chromatid.

Kai Papenfort plans to study the workings of a particular signalling pathway that permits members of bacterial populations to coordinate their behaviour. Already in February of this year, he won the junior research prize of the Peter and Traudl Engelhorn Foundation for his advances in the search for new drugs against infectious diseases caused by viruses or other microbes. The prize is worth 10,000 euros.

Barbara Treutlein wants to reconstruct development and malformation of the human cortex using single-cell transcriptomics. She was also awarded the 2017 Paper of the Year award by the German Stem Cell Network for a paper on how single cells work together and use their genomes to develop into human liver tissue. One of the co-authors is BIF fellow Sabina Kanton from her group.

PROFESSOR NICOLAS CHEVRIER
Institute: University of Chicago, MI, USA
Fellowship: 2008–2011

Nicolas Chevrier joined the Institute for Molecular Engineering at the University of Chicago as an assistant professor in September 2017. He will study how the immune system functions across biological scales ranging from molecules to mammalian organisms and search for ways to prime the immune system against diseases.

PROFESSOR MARTIN DENZEL
Institute: Max Planck Institute for the Biology of Ageing, Cologne, Germany
Fellowship: 2005–2008

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

The ERC has granted another two BIF fellows Proof-of-Concept (PoC) Awards.

Christine Selhuber-Unkel has developed a novel microporous material and will use her grant to validate this material for biomedical applications, e.g. for culturing stem cells. A key part of the project will be to investigate the impact of narrow three-dimensional environments on such cells.

Martin Denzel has received an ERC PoC Grant to support a new start-up company that will apply new approaches to identify desired and undesired interactions between small bioactive molecules and proteins. This will allow a detailed understanding of the molecular mechanism of new drug candidates.

PROFESSOR MARC ERHARDT
Institute: University of Berlin, Germany
Fellowship: 2007–2010

Marc Erhardt will join the Humboldt-Universität zu Berlin as professor of bacterial physiology. He aims to unravel how the motile abilities of bacteria help them to colonize their host's gut, how they regulate their gene expression to adapt to fast-changing environments, and how their motility organelle – the flagellum – self-assembles in a coordinated manner.

Photos: Bleichert: private; Drinnenberg: Aida de la Cruz; Nagy: University of Debrecen; Treutlein: Ronny Barr-MPI-EVA; Papenfort: private; Chevrier: private; Denzel: Hajo Drees; Selhuber-Unkel: private; Erhardt: Rainer Jonas, HZI

PROFESSOR TIM GOLLISCH
Institute: University Medical Center Göttingen, Germany
Fellowship: 2001–2003

Tim Gollisch has received an ERC Consolidator Grant of two million euros for five years to study connectivity and functionality of retinal nerve cells. In the long run, he hopes to find ways to re-establish at least partial sight by artificially stimulating retinal nerve cells.

UFUK GÜNESDOGAN
Institute: University of Göttingen, Germany
Fellowship: 2005–2008

Ufuk Günesdogan has received a Sofja Kovalevskaja Award – one of the most valuable academic prizes in Germany – to study how the cells develop from which sperm cells and egg cells are formed, in particular the role of histones in this process. The grant of up to 1.65 million euros will enable him to set up his own research group at a German university of his choice over the next five years "independently and largely untroubled by administrative constraints". The awards are meant to integrate internationally sought-after researchers talents into collaborations with academics in Germany at the beginning of their career.

PROFESSOR CHRISTIAN MENDL
Institute: Technische Universität Dresden, Germany
Fellowship: 2009–2011

Christian Mendl has been accepted as a junior professor at the Technische Universität Dresden, Germany, in the department of applied mathematics. He will design, develop, and implement computational algorithms for simulating many-body quantum systems in an effort to deepen our understanding of high-temperature superconductors and topological materials and to aid the design of future electronic devices.

PROFESSOR DIERK NIESSING
Institute: Ulm University, Germany
Fellowship: 1996–1999

Dierk Niessing has been appointed head of the newly founded Institute of Biochemistry and Pharmaceutical Biotechnology at the University of Ulm in Germany. By combining biochemistry and high-resolution structural biology, he aims to understand molecular principles of RNA-based gene regulation. His lab also performs structure-guided optimization of inhibitory molecules.

PROFESSOR MARY O'CONNELL
Institute: Central European Institute of Technology (CEITEC), Brno, Czech Republik
Fellowship: 1990–1992

Mary O'Connell is among the 56 new members and nine associate members that EMBO formally welcomed in October at the EMBO Members' Meeting in Heidelberg. "Election to EMBO membership is recognition of research excellence, and I am pleased to welcome so many great scientists to our organization," says EMBO director Maria Leptin. With her election, Mary joins a group of more than 1,700 of the best life science researchers in Europe and around the world.

ANNELI PETERS
Institute: Max Planck Institute of Neurobiology, Martinsried, Germany
Fellowship: 2007–2010

Anneli Peters has been named an Emmy Noether Group Leader by the DFG. She will study the underlying mechanisms of how Th17 cells shape a pathogenic B cell response, and – vice versa – how B cells can support a pathogenic Th17 response. Her research aims to provide insight into the cellular mechanisms and kinetics of disease and may enable development of more tailored therapeutic strategies in the future.

PROFESSOR FRANK VOLLMER
Institute: Living Systems Institute, University of Exeter, UK
Fellowship: 2001–2003

Frank Vollmer has received a Royal Society Wolfson Research Merit Award worth 125,000 British pounds. It is jointly funded by the Wolfson Foundation and Royal Society and provides UK universities with additional support to attract or keep "key researchers, with great potential or outstanding achievement". Frank wants to develop the first optical method capable of directly monitoring the movements within individual proteins without needing to label them.

Photos: Gollisch: University Medical Center Göttingen; Günesdogan: private; Mendl: private; Niessing: private; O'Connell: Ceitec; Peters: private

A BIF FELLOW'S GUIDE TO ...

BARCELONA

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 Victoria Rodríguez-Vaello. She reports from Barcelona, Spain, the city best known for the work of architect Antoni Gaudí.

FACTS & FIGURES

Country: Spain
Population: About 1.6 million
Area: 101,35 km²
Students: About 191,000
Famous for: Barcelona FC, Sagrada Familia, Antoni Gaudí, beaches, cava, and good food
Websites: www.conocerbarcelona.com

WHERE TO STAY

Meliá Barcelona Sky: Great modern hotel overlooking the whole city in a lovely neighbourhood close to the best beaches.
Barceló Raval: Cool hotel in the most diverse neighbourhood of Barcelona.
Hotel La Casa del Sol: Nice cute hotel in one of the liveliest plazas of the city.

NIGHTLIFE

Plataforma: This is just the right place for you if you want to dance until sunrise.
Magic: Club with rock music that will keep you awake until dawn every night. A special place for me – you don't know who you'll meet!
Plaza Real: A beautiful square in the Gothic Quarter of the city, full of restaurants and nightclubs of all types.

RESTAURANTS

Escribà: Best paella in Barcelona and right in front of a nice beach.
Bestial: Super tasty dishes cooked with local products served on a beautiful terrace.
Kibuka: Very delicious fusion between Japanese and Brazilian cuisine.
Gocce di latte: The place for ice cream.

ACTIVITIES

Walk around Gracia: Bohemian neighbourhood full of small artistic boutiques mixed with traditional shops, great bars, cafés, and small plazas with a very mixed population from young hipsters and artists to old people and families.
Bogatell/Mar Bella beaches: Cleaner water, nicer sand, fewer people!
A concert in Palau de la Música 1: A beautiful modernist concert hall with great acoustics and a beautifully decorated interior. A must!

BEST SIGHTS

El Borne and the Gothic Quarter 2: Get lost in the narrow medieval streets full of artisan shops. Don't miss the Santa Maria del Mar Church, Mercat del Borne, the Cathedral, and Plaza del Rei.
Sagrada Familia 4: Reserve your spot online and get the audio guide so you can learn about the details in Gaudí's work!
Montjuic 3: Lovely gardens, especially in the afternoon sun. At night, the lighted fountains are impressive.

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

Name: Victoria Rodríguez-Vaello
Nationality: Spanish
Age 30
Research Institute: Centro de Regulació Genomica (CRG)
Supervisor: Dr Manuel Irimia

Photos: Josep Renalias (1); Xavier Caballe (2); Ivan Melenchon Serrano (3); Cezary (4)

WHO'S WHO AT BIF?

CARSTEN LAMBERT, PHD PROGRAMME/TRAVEL GRANT PROGRAMME

Carsten Lambert studied biology at the University of Mainz, Germany, and the University of Manchester, UK. For his PhD he analysed the cell biology of hepatitis B virus infections. His postdoc dealt with entry mechanisms of non-enveloped viruses, mainly papillomaviruses. Before starting at BIF, he worked at the Life Science Incubator in Bonn, developing viral particles as drug delivery systems. Since 2012 he has been in charge of the selection process in the PhD programme and heads the travel grant programme. He loves hiking and photography.

What do you like most about your work at BIF?
Dealing with so many different areas in basic science is challenging, but it also broadens the mind. I enjoy learning about the solutions life has evolved.

What is your most remarkable experience connected with BIF?
The enormous enthusiasm of the applicants. I am privileged to interact with such remarkable young researchers and believe some will have a profound influence on science.

What is your favourite activity?
Hiking in the Alps and taking photos at the "edge of light" early in the morning or late in the evening.

Where would you like to live?
Wherever my children are – if that were New Zeeland, I would not mind.

What is your remedy for stressful situations?
I try to focus on the important things, to work step by step. I look at the broader context and remember what is really important in life.

What is your motto?
Not to judge prematurely; whether it's people or work in the laboratory, many things are too complex to assess at first glance.

What fault in others can you tolerate best?
Impatience, because I often discover that impatient people are driven and engaged and achieve things that are actually good.

Your advice for fellowship holders?
Stay curious. After diving deep into the details, step back and try to see the broader picture. Try to integrate existing knowledge from other disciplines.

Which scientific achievement do you admire most?
Revolutionary insights bridging knowledge from unrelated scientific areas.

Name one thing you couldn't live without.
A world without my family is unthinkable, so is one without chocolate.

Photo: Angelika Stehle

UPCOMING EVENTS

17–18 MARCH 2018
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.

11–15 APRIL 2018
117th International Titisee Conference
The meeting, titled "From Oocyte to Embryo – Illuminating the Origins of Life", will be chaired by Melina Schuh, MPI for Biophysical Chemistry, Göttingen, Germany, and Takashi Hiiragi, EMBL, Heidelberg, Germany. It will bring together investigators from fields such as cell biology, embryology, biophysics, single-cell biology, as well as stem cell biology. They will discuss newly available technologies to study mammalian oocytes and embryos and the results achieved with them to identify synergies, establish collaborative efforts, and generate new ideas for research.
The concerence is by invitation only.

3–8 JUNE 2018
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.

6–8 JULY 2018
European alumni seminar
Annual meeting of former BIF PhD and MD fellows based in Europe. The seminar will take place at Gracht castle in Erftstadt/Liblar near Cologne, Germany. Further details will be sent with the programme.

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

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