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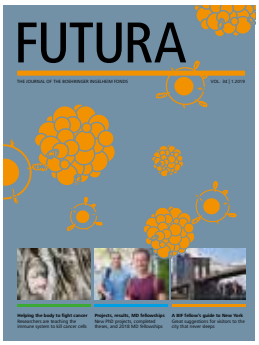
Helping the body to fight cancer
Researchers are teaching the immune system to kill cancer cells

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

A BIF fellow's guide to New York
Great suggestions for visitors to the city that never sleeps



The cover illustration shows a simplified model of how a tumour cell prevents T cells from killing it – so-called T cell inhibition. Some cancer cells exploit an inhibitory receptor called PD-1 on their surface that usually prevents the immune system from attacking normal cells. This discovery led to a new class of drugs that unleash the immune system by switching off these regulatory mechanisms.

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PUBLISHING INFORMATION

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THE OUTSIDE VIEW

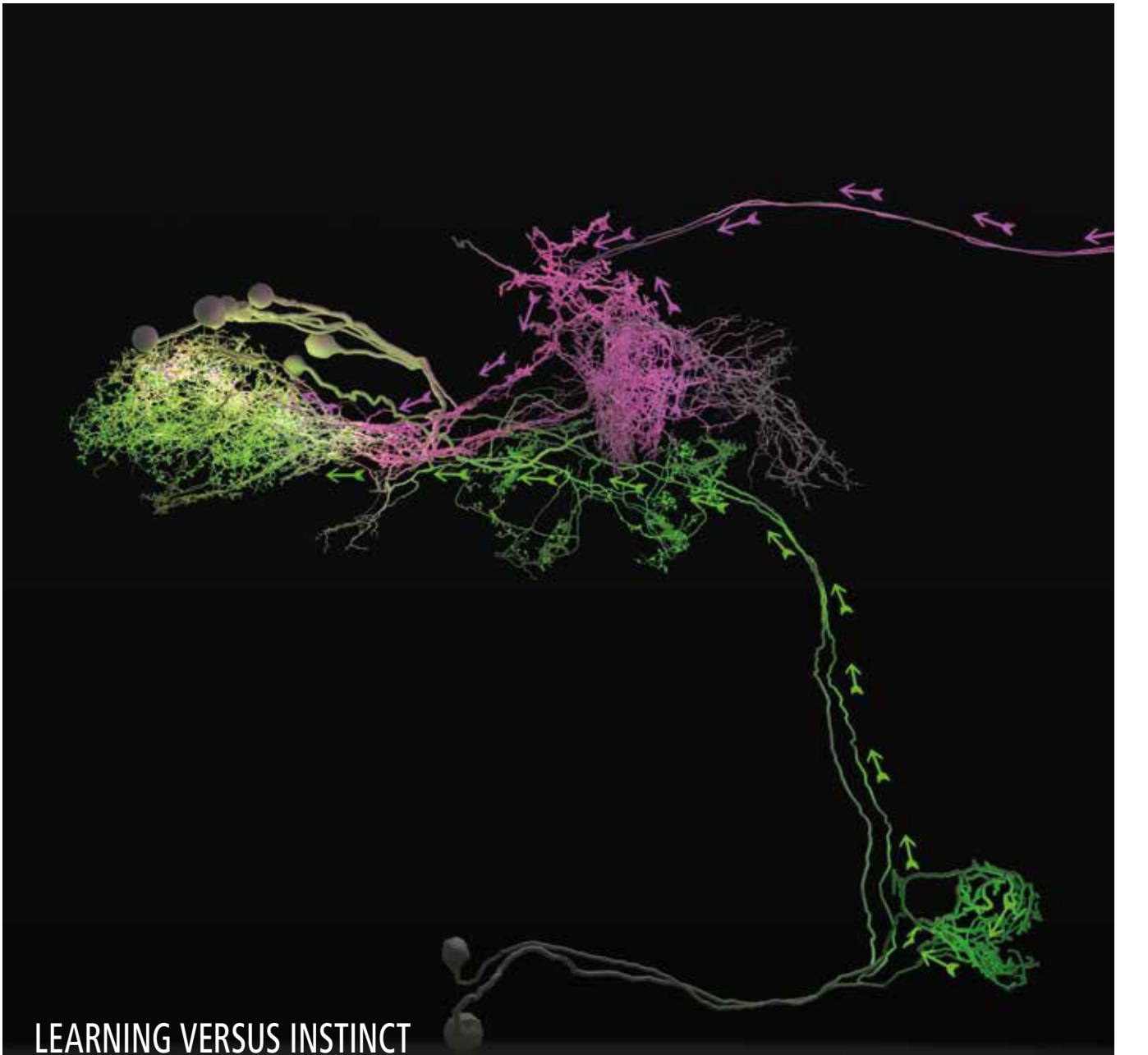
»BIF's purposeful and customized supportive programmes are seen as highly beneficial for academic careers.«

BIF continuously monitors its programmes in the context of international research and funding and systematically collects – and integrates – feedback from applicants and fellows. In addition, the outside perspective and comprehensive evaluations are indispensable. In the past, external experts and scientists assessed our funding strategy – leading e.g. to the stop of our postdoctoral award and to a clear and strong recommendation to continue the PhD fellowships. The evaluation of our selection process compromised a whole PhD project and was the first comprehensive study worldwide on peer review for selecting fellowship holders. Even *Nature* reported on it. One of its conclusions was that our peer-review process indeed selects the best candidates, as seen by the result that publications by BIF fellows were cited far above international reference values.

The latest evaluation of BIF, the results of which are summarized on page 36, was performed by the Centre for Social Investment at Heidelberg University as part of their research project "Learning from Partners" (LfP). This long-term study systematically evaluates the cooperation and relationship between foundations and their partners – applicants, grantees, and others – and was inspired by the Grantee Perception Report developed by the Center for Effective Philanthropy in the United States. The LfP provides systematic feedback not only on the general perception of the individual foundation, its funding, and its contribution to capacity-building, but also on administrative processes and the partners' satisfaction with the relationship. Eight German foundations took part in this third round of the LfP project. In addition to BIF, they included the Volkswagen Foundation, the Fritz Thyssen Foundation, and the Wilhelm Sander Foundation.

The present LfP study found high satisfaction with the work of the eight foundations but also room for improvement, in particular the wish to receive detailed feedback on the applications and more digitization. For BIF in particular, we were happy to learn that our "purposeful and customized supportive programmes" are seen as highly beneficial for academic careers, especially in light of the significant effort BIF invests in the selection and the comprehensive support of its fellowship holders. Furthermore, BIF's transparency was rated as very good and BIF is perceived as a renowned organization that is reliable, has high standards, and "obtains high levels of satisfaction among its partners". The entire study with all details and results can be found on our website.

The project leader sees the challenge for BIF in keeping the already outstanding results. However, we do not intend to rest on our laurels. We intensively discussed the partners' detailed feedback, are already in the process of relaunching our website and online applications, and will continue to optimize our programmes and processes. Last but not least: our sincere thanks goes to all the applicants and grantees who made the effort to complete the detailed anonymous online survey!



LEARNING VERSUS INSTINCT

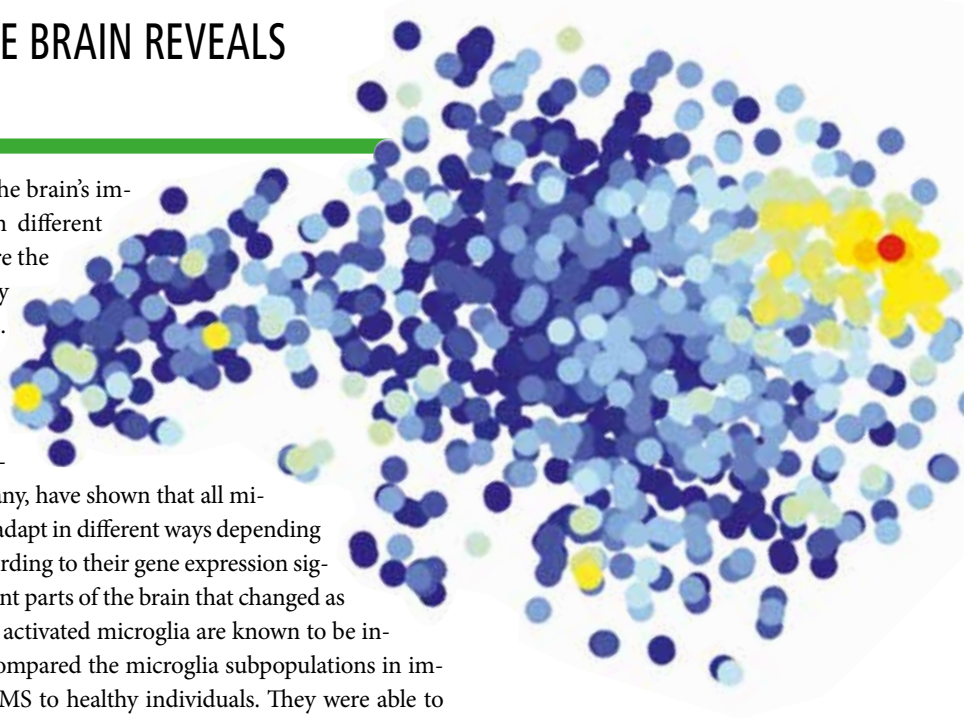
By Michael-John Dolan and Alexander Bates, Laboratory of Molecular Biology (LMB), Cambridge, UK

This illustration shows an electron microscopy reconstruction at synaptic resolution of a neural circuit integrating innate (green) and learned (magenta) signals in the same neurons in *Drosophila melanogaster*. Sensory stimuli can produce learned and innate behaviours. Dolan, Belliart-Guérin *et al* identified neuronal cell types in the brain of the fruit fly that integrate hardwired and experience-dependent olfactory information. They found that the seven neurons shown in the top left corner are necessary for both aversive memory retrieval and innate approach behaviour to some food odours, providing a model for how these two types of sensory representations interact in a single cell type (see also "Spotlight" on page 38).

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.

MAPPING MICROGLIA IN THE BRAIN REVEALS CNS DISEASE SIGNATURES

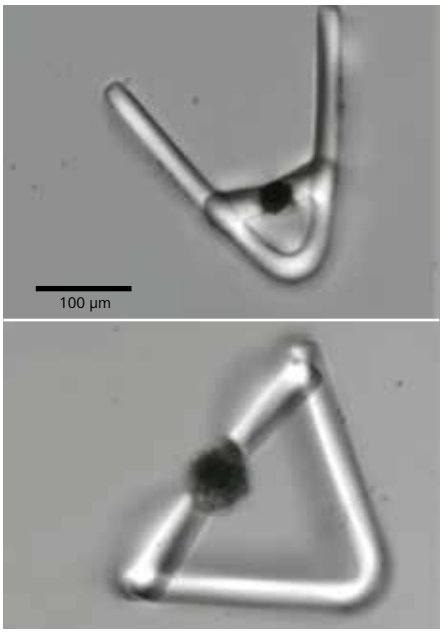
Scientists have developed a detailed map of the brain's immune system by profiling microglia cells in different parts of the brain over time. Microglia cells are the scavenging macrophages of the brain, and they play a key role in neurodegenerative diseases. Previously, it was believed that multiple types of specialist microglia exist in the brain to carry out different roles. Yet, using powerful single-cell RNA sequencing technology, researchers at the University of Freiburg, Germany, have shown that all microglia have the same core RNA signature but adapt in different ways depending on their function. By clustering microglia according to their gene expression signatures, they found distinct subtypes in different parts of the brain that changed as the mice developed from embryo to adult. As activated microglia are known to be involved in multiple sclerosis (MS), they next compared the microglia subpopulations in immune cells from five people with early-stage MS to healthy individuals. They were able to identify distinct disease-related subtypes of microglia in the brains of these patients, and found that these were phenotypically similar to subtypes of microglia in a mouse model of MS. An understanding of how specific microglia responses change during the course of disease may make it possible in the future to target microglia subsets to support healing.



Single-cell RNA sequencing of microglia: immune genes are activated differently in every cell.

REFERENCE

Masuda T, Sankowski R, Staszewski O *et al* Spatial and temporal heterogeneity of mouse and human microglia at single-cell resolution. *Nature* **566**, 388–392



Powered by cell-sized artificial muscles, these tools can carry out complicated manipulation tasks under physiological conditions.

CELL-SIZED "MUSCLE" ROBOTS CAN SIMULATE DISEASE

Mechanical forces are a key component of many diseases. For example, atherosclerotic plaques are most likely to develop at bends in our blood vessels, and the mechanical interactions between cancer cells and the microenvironment are key determinants of metastasis. Now, researchers at the Institute of Mechanical Engineering and Institute of Bioengineering in Lausanne, Switzerland, have built micromachines to mechanically stimulate cells and tiny pieces of tissue, recreating the natural forces and pressures experienced in the human body. The machines are powered by cell-sized artificial muscles: these are constructed using hydrogel "lego" bricks to create a "skeleton" and are connected by polymer "tendons" to the components that control movement – the actuators – to create the micromachine. When activated by near infra-red light, the actuators – which are distributed throughout the micromachine – contract, tugging on the surrounding components and powering the machinery. This allows for the subtle manipulation of the machine in milliseconds, enabling it to grip, bend, twist, pull, or push. In addition to studying mechanical forces in disease, the technology could be used as tiny medical implant devices to mechanically stimulate tissue or switch on the delivery of drugs.

REFERENCE

Özkale B, Parreira R, Bekdemir A *et al* (2019) Modular soft robotic microdevices for dexterous biomanipulation. *Lab on a Chip* **19:** 778–788

Photos: Takahiro Masuda/Universitätsklinikum Freiburg (top); Ecole polytechnique fédérale de Lausanne (bottom)

NEW METHODS FOR IDENTIFYING T-CELL TARGETS

Identifying the antigens that T cells bind to is a crucial step towards designing more powerful vaccines and immunotherapies. Scientists at the California Institute of Technology, Pasadena, USA, recently developed two new methods to identify antigen targets of T cells. In the first approach, researchers attached a signalling domain to the antigen-presenting major histocompatibility complex (MHC) to make the complex glow bright green when bound to a T cell. It then becomes possible to use a library of thousands of such altered MHC complexes, each presenting a different antigen, to see when antigens have bound to T cells and thus identify the unique antigen a particular T cells binds to. The second approach takes advantage of a natural biological process called trogocytosis, in which a T cell and its target cell exchange proteins from their surfaces. The team made a pool of antigen-presenting cells (APCs), each displaying a unique antigen, and then added T cells expressing a particular receptor. Only APCs with antigens that the T cell could bind to acquired the receptor from the T cell. The methods could be used to identify the unique and evolving antigens expressed on an individual person's tumour cells, allowing more personalized and powerful immunotherapy.

REFERENCE

Joglekar AV, Leonard MT, Jeppson JD *et al* (2019) T cell antigen discovery via signaling and antigen-presenting bifunctional receptors. *Nature Methods* **16:** 191–198

Li G, Bethune MT, Wong S *et al* (2019) T cell antigen discovery via trogocytosis. *Nature Methods* **16:** 183–190

Photo of an *Aedes aegypti* mosquito.

PUTTING MOSQUITOES ON A DIET

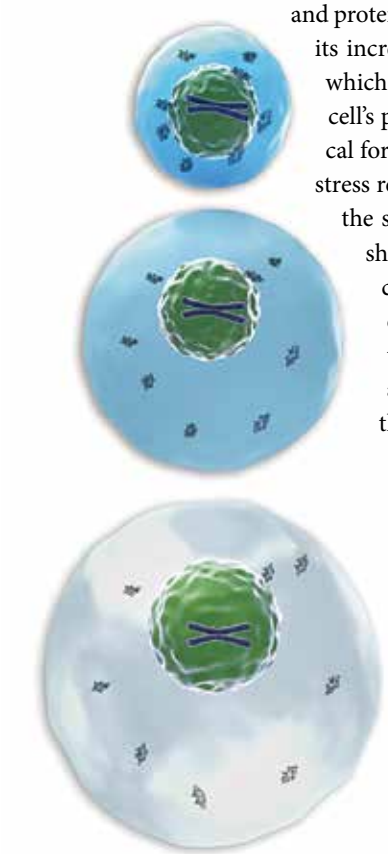
A satiated mosquito is a harmless one. That's the theory behind research suggesting that human diet pills could halt the mosquito's desire to feed. Mosquitoes only transmit disease when they move between humans to gorge on blood. Once they are full, their attraction to humans is suppressed for days, but the mechanism for this was not known until now. Researchers at The Rockefeller University in New York, USA, wanted to test if the same hunger hormones that act in humans might also trigger a mosquito's appetite. They gave female mosquitoes diet pills that activate human neuropeptide Y receptors, and found they were no longer interested in flying towards a piece of nylon stocking containing bodily odours that would ordinarily scream "mealtime". When they fed mosquitoes a drug that inhibits the Y receptors, they behaved as if they had not eaten at all. It seems there is striking similarity between human and mosquito hunger pangs – and exploiting this could be a way to combat malaria. From a screen of all 49 neuropeptide receptors in the mosquito, they pinpointed NPYLR7 as the key target, and identified six highly selective substances as potential mosquito-specific "diet pills". The next step is to determine how best to expose mosquitoes to the drug in their natural environment, and to see if other blood-feeding insects could also be put on a "diet".

REFERENCE

Duvall LB, Ramos-Espiritu L, Barsoum KE (2019) Small-molecule agonists of *Ae. aegypti* neuropeptide Y receptor block mosquito biting. *Cell* **176:** 687–701

HOW DO CELLS STAY THE SAME SIZE?

Although different cell types vary dramatically in size (just think of the difference between tiny blood cells and large neurons), cells of the same type deviate very little in size. How is this controlled? To find out, researchers at Massachusetts Institute of Technology, Cambridge, USA, grew yeast cells to ten times their normal size by preventing them from dividing. They found that this impaired gene expression, cell-cycle progression, and cell signalling – and that the amount of DNA in relation to the volume of the cytoplasm was the limiting factor. Thus, the cells were unable to scale up nucleic acid and protein biosynthesis to keep pace with the demand of producing enough protein for its increasing size. The lack of protein production led to dilution of the cytoplasm, which researchers predict would slow reaction rates and disrupt many more of the cell's processes, including cell division. Beyond a certain size, especially genes critical for transcription and translation were transcribed less due to the environmental stress response (ESR). However, yeast cells with doubled DNA content grew to twice the size of the normal cells without problems. Similar experiments in fibroblasts show that this holds true for primary mammalian cells, too. Even if it is not yet clear what exactly triggers the ESR, the results help to explain observations that older, senescent cells tend to be larger than younger cells and display many of the hallmarks of the large cells in this study. So not only does the study answer a fundamental and intriguing question in biology, but it also implicates larger-than-normal cell growth as an important process in many age-related diseases.



Excessive cell growth causes cytoplasm dilution and contributes to senescence.

REFERENCE

Neurohr GE, Terry RL, Lengefeld J *et al* (2019) Excessive cell growth causes cytoplasm dilution and contributes to senescence. *Cell* **176:** 1083–1097

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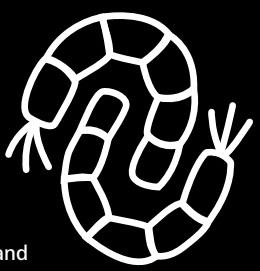
NEW BACTERIA



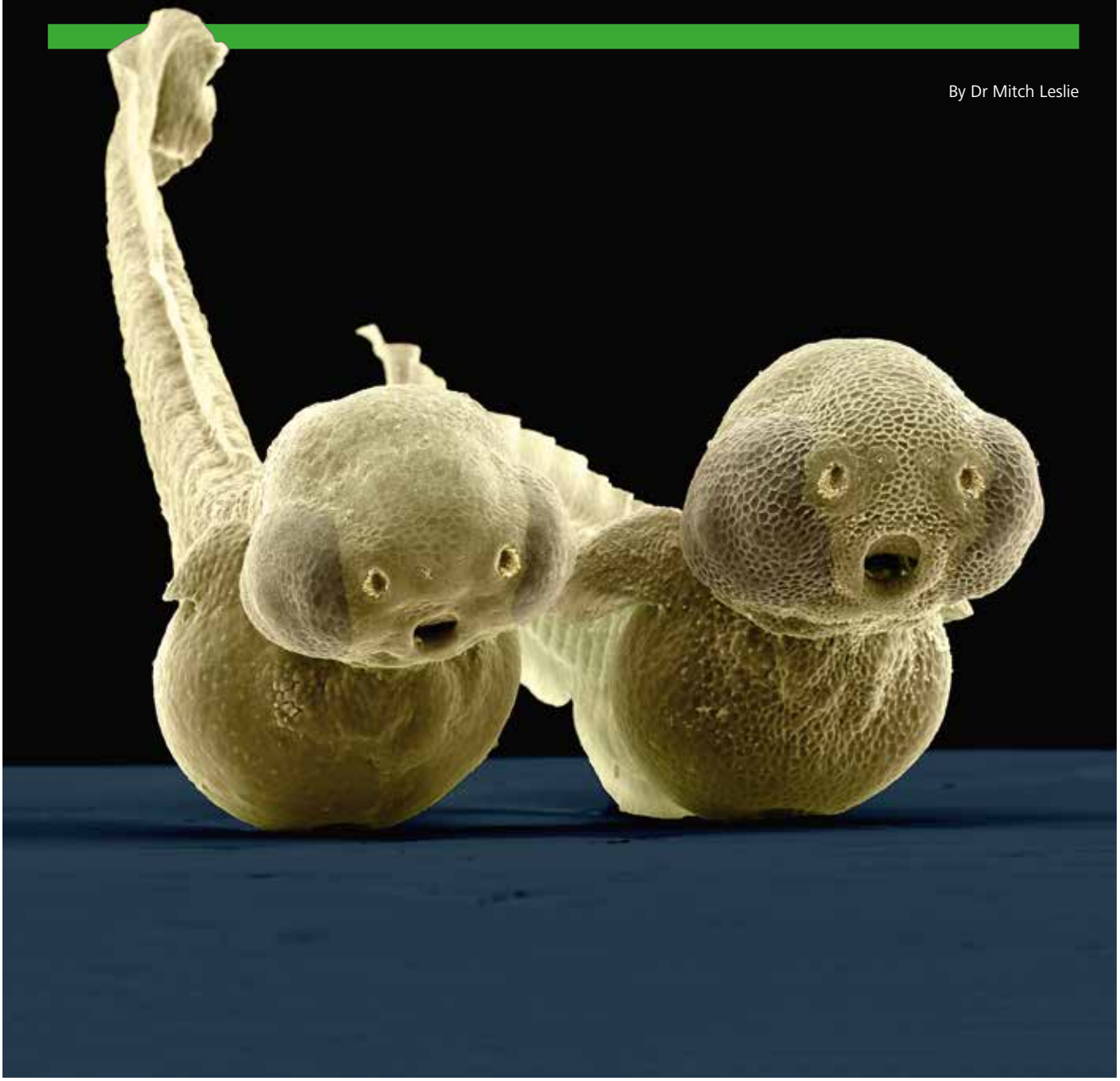
were identified in the human gut with the help of metagenomics. This work substantially expanded the known species repertoire. Although the full picture of gut flora diversity is far from complete, these new species improve classi-fication of understudied African and South American samples by more than 200%.

Source: Almeida A. *et al* (2019) A new genomic blueprint of the human gut microbiota. *Nature*

Photos: Adobe Stock/Boonchai (left); Neurohr /Cell 176 (right)

PROFILE OF THE ZEBRAFISH **DANIO RERIO**

By Dr Mitch Leslie



Scanning electron microscope photo of four-day-old zebrafish larvae.

Scientists who want to find out how to regrow a heart, screen potential drugs, trace the growth of skin cancers, probe the intricacies of development, or study a variety of other questions are lucky that George Streisinger was so fond of tropical fish.

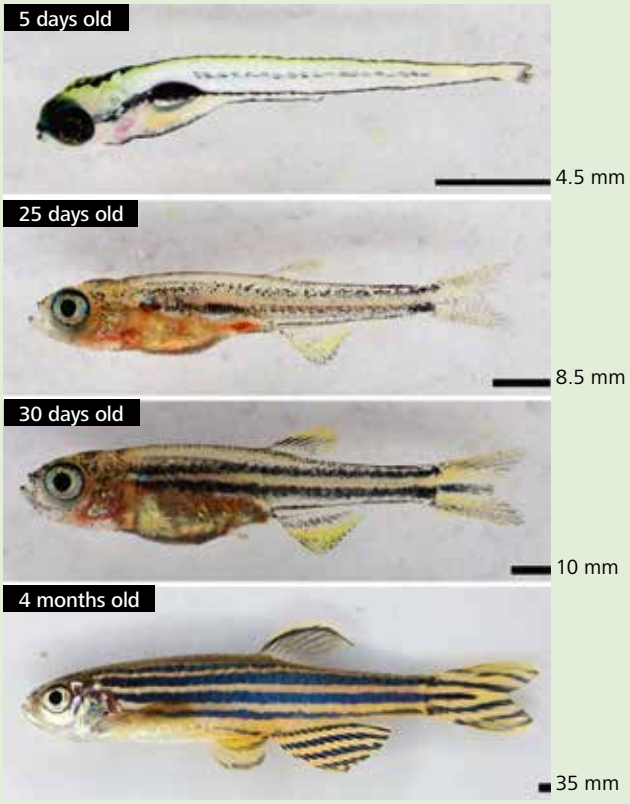
In the 1960s, Streisinger, a molecular biologist at the University of Oregon in the US, was eager to investigate how genes shape the development of the nervous system, but the viruses he had been working on were not suitable models. An aquarium aficionado as well as a scientist, Streisinger knew of a species common in the pet trade that might suit his needs, the zebrafish (*Danio rerio*), a native of Asia.

Although Streisinger was not the first to study the fish in the lab, he and his colleagues were instrumental in making it a scientific star, even though it took almost ten years for the first paper to come out. The researchers honed the procedures for raising and breeding zebrafish, devised techniques for mutating their genes, and were the first to clone them. Streisinger only published a handful of papers on zebrafish before his untimely death in 1984, but more than 1,000 labs worldwide are now working on them.

Zebrafish boast several advantages as model organisms. They breed rapidly, laying up to 200 eggs a week, and mature fast, taking only 10 to 12 weeks to grow from eggs into adults. The embryos and larvae are transparent and develop outside of the mother, making it easy to study embryogenesis, experiment on young fish, and observe the effects of mutations or drugs. The larvae can also regrow parts of their heart and thus serve in regeneration studies. Streisinger described the fish as "a phage with a backbone", and another upside is that they are evolutionarily closer to humans than, say, animal models such as nematodes and fruit flies. A downside is their polyploid genome which makes it more difficult to knock out or change genes.

Researchers now have a wealth of techniques for investigating zebrafish. They have sequenced the fish's genome and can remove, add, or modify genes. With the fish and larvae transparent, a powerful genetic tool is fluorescent proteins that illuminate details of development, uncover gene functions, and monitor environmental toxins. The fish are also proving their worth in medical and drug research, as researchers use them to quickly evaluate large numbers of drug candidates and better understand a range of human illnesses, including muscular dystrophy, Parkinson's disease, kidney disease, and cancer.

CV OF *DANIO RERIO*



- I first entered the lab in the 1930s, but only shot to prominence in the 1990s.
- I usually grow to around 4 cm long and live about 4 years.
- I eat plankton and insects in the wild, fish food in the lab.
- I work mainly in developmental biology, genetics, and neurobiology.
- I am still waiting for my first Nobel Prize.

With their unchecked growth, tumours can overwhelm the body.

HELPING THE **BODY** TO **FIGHT** CANCER

By Dr Mitch Leslie

Our immune system protects us from many diseases and parasites. But when our own cells slip the tight leash of proliferation control and overrun the body, the immune system needs help in order to identify and combat the rogue cells. For almost a century, researchers have tried to figure out how to achieve this. It seems we are getting closer to that goal.

One of the most promising new weapons against cancer is not a new type of chemotherapy, a novel surgical procedure, or a more focused variety of radiation – it is our own immune system. "The immune system is one of the most powerful therapeutic agents that exists," says Marcela Maus, director of Cellular Immunotherapy at the Cancer Center of Harvard Medical School in Boston, USA. A study of patients who received one type of genetically engineered cancer-killing cells demonstrated that "one T cell can kill kilograms of tumour cells," she says. After more than a century of work, researchers have finally figured out how to harness and direct this power. They have developed new treatments called immunotherapies that stimulate the immune system to destroy cancer cells. In the last decade or so, immunotherapies have transformed cancer treatment, saving the lives of thousands of patients. "We have very good evidence that the immune system safeguards us against cancer and that we can use it to eradicate existing cancers," says Haval Shirwan, professor in the Department of Microbiology and Immunology at the University of Louisville, USA.

Today's immunotherapies could be just the beginning. Researchers are scrambling to improve the treatments' performance and to develop new approaches for circumventing the mechanisms that guard cancer cells against the immune system.

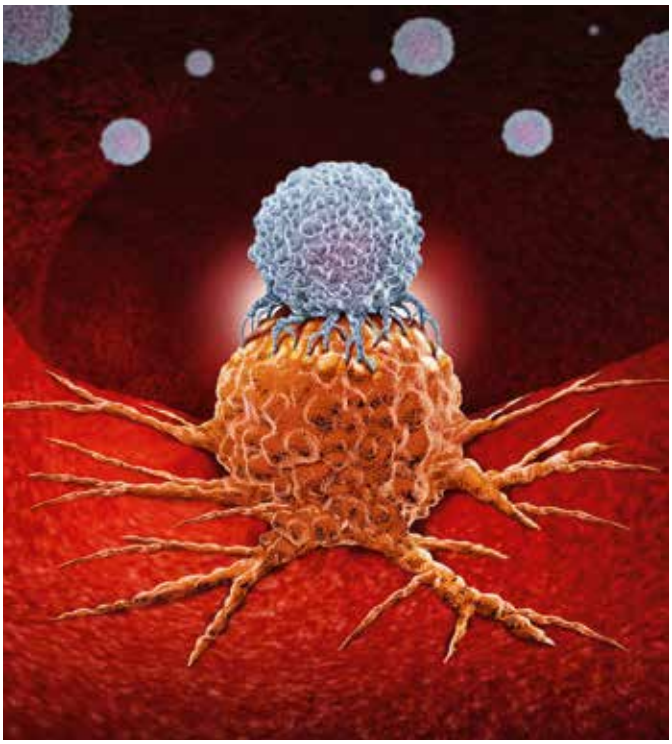
Doctors first began trying to exploit the immune system to fight cancer more than 100 years ago. At the time, scientists knew little about how the body defends itself in general, but they had observed that tumours occasionally shrank in people with infections. To reproduce this effect, some doctors began injecting cancer patients with living or dead bacteria, often giving the injections directly into the tumours. A New York surgeon named William Coley, the most famous advocate of this bacterial therapy, used it on thousands of patients between the 1890s and 1930s.

Coley and his colleagues were on to something. Their injections did sometimes appear to induce a tumour-fighting response from the immune system, especially in patients with bone and soft-tissue sarcomas, which are rare cancer types (less than 1% of cancers diagnosed today in the US, according to the statistics of the American Cancer Society). However, their techniques produced inconsistent results and were crude by today's standards.

Developing more sophisticated and reliable treatments has proven difficult because the relationship between cancer and the immune system is so complicated. The immune system identifies invading bacteria and viruses as non-self by the distinctive molecules they carry on their surface. Although cancer cells are not foreign invaders, researchers have found that their mutations result in altered proteins that can serve as so-called neoantigens, triggering a response from immune cells comparable to the one against pathogens.

Once mutations transform a cell into a cancer cell, the immune system is the most important factor that determines what happens to it next, notes cancer immunologist Mark Smyth, head of the Immunology in Cancer and Infection Laboratory at the QIMR Berghofer Medical Research Institute in Australia and the most highly cited Australian immunologist. As scientists have →

Photo: gettyimages/Westend61



In immunotherapy, T cells (white) are primed to recognize and attack cancerous cells.

discovered, the immune system is constantly on the lookout for altered cells, and it can usually eliminate them before they become a problem. But tumour cells are devious. They deploy a range of countermeasures that enable them to evade or suppress immune attacks, starting with creating a microenvironment favourable to their survival and growth. A tumour can even fool immune cells into changing sides and becoming its helpers. These tricks allow some tumours to persist or to begin growing and spreading. At that point, "the immune system effectively loses the battle," says Smyth, and the cancer can become a threat to the patient's life.

The winners of the 2018 Nobel Prize for Physiology or Medicine helped to identify two of the mechanisms that shield cancer cells from the immune system. One of the researchers, James Allison, now chair of the Department of Immunology at the University of Texas MD Anderson Cancer Center in Houston, USA, and his colleagues showed that a T cell protein known as CTLA-4, which prevents the immune system from attacking our own healthy cells, also curtails immune attacks on cancers. In a dramatic demonstration of CTLA-4's power, they injected mice with colon cancer cells and then treated some of the animals with an antibody that blocks the protein. Within days, tumours were growing rapidly in the untreated animals. But the mice that received the antibody were still tumour-free three months later, the scientists reported in 1996.

The other Nobel laureate, Tasuku Honjo, professor in the Graduate School of Medicine at Kyoto University in Japan, and his colleagues exposed another trick that allows tumours to elude the immune system. The researchers found that T cells carry an inhibitory receptor called PD-1 on their surface that, like CTLA-4, prevents the immune system from attacking normal cells. Some cancer cells exploit this off-switch by producing a protein known as PD-L1 that stimulates the PD-1 receptor. In this way, they shut down T cells trying to destroy them.

The Nobel Prize committee stated that the seminal discoveries of Allison and Honjo "revolutionized cancer treatment and fundamentally changed the way we view how cancer can be managed". Their work led to a new class of drugs known as checkpoint inhibitors, monoclonal antibodies that unleash the immune system by switching off these regulatory mechanisms. The first of these drugs to win approval for use in patients, ipilimumab, blocks CTLA-4. Regulators have now okayed another six checkpoint inhibitors, including nivolumab, pembrolizumab, and atezolizumab, that target either PD-1 or PD-L1.

Since their introduction in 2011, checkpoint inhibitors have become standard therapies for a range of cancers, such as melanoma, non-small cell lung cancer, and certain kinds of colon cancer. By allowing T cells to attack cancer cells, the drugs produce dramatic effects in some patients, causing tumours to disappear. In addition, the benefits of the drugs seem to last, says Smyth. He notes that some of the patients with metastatic melanoma who were treated in the first clinical trials of ipilimumab in the mid-2000s are still alive and free of cancer. Other patients, however, never responded in the first place, or their tumours progressed after shrinking initially.

Therapy with checkpoint inhibitors rouses patients' unmodified T cells. Another immunotherapy approach that has proven successful against some cancers improves these cells, creating what are known as chimeric antigen receptor (CAR) T cells. Producing the cells involves removing T cells from a patient's blood and genetically altering them to carry a re-engineered receptor, or CAR, that recognizes a particular protein. Once they are returned to the patient's bloodstream, the T cells destroy cancer cells that display the target protein. So far, two kinds of CAR T cells have been approved by the US and the EU regulatory bodies FDA and EMA for treating the blood cancers large B-cell lymphoma and acute lymphoblastic leukaemia.

Patients treated with CAR T cells receive their own T cells, eliminating some of the side effects that can occur after the transfer of T cells from another person. In both therapies, the CAR T cells home in on a protein called CD19 that is found on some leukaemia and lymphoma cells. Normal B cells of the immune system also carry CD19, and therapy with the approved CAR T cells can destroy them as well. However, says Maus, "You can live a relatively

Photo: Adobe Stock/freshidea

normal life with no B cells." Still, both kinds of CAR T cells are only used when standard therapies have failed. Several clinical trials are evaluating CAR T cells for a variety of solid tumours, but the cells have not been approved for treating any of these cancers.

Despite their impressive successes, immunotherapies have some drawbacks that currently reduce their usefulness. For one thing, they can trigger serious side effects. CTLA-4 and PD-1 perform an important job in the body – reining in the immune system to prevent autoimmunity. Checkpoint inhibitors that block these molecules can lead to immune attacks on healthy tissues, resulting in side effects such as rashes, colitis, lung complications, heart inflammation, and even organ failure. One 2015 study, for instance, found that 85% of patients with melanoma who were treated with ipilimumab showed signs of such attacks, and 35% of the patients needed steroid treatment to suppress the symptoms. Similarly, CAR T cells can spur a surge in cytokines that can lead to fevers and dangerously low blood pressure. Doctors are getting better at treating these problems, says Maus. But side effects like these can limit which patients benefit from immunotherapies.

Treating cancer with drugs can also be very hard on the body as a whole. To improve the risk-benefit ratio, over the last couple of decades, cancer treatment has been moving towards increased use of personalized therapies. In this approach, patients receive different drugs depending on the molecular characteristics of their cancers. Not only are these tailored therapies often more effective, but they may also reduce side effects. Some immunotherapies allow this kind of personalized treatment. For example, patients who have non-small cell lung cancer receive the anti-PD-1 checkpoint inhibitor pembrolizumab only if an antibody test determines that their tumours carry high levels of PD-L1. However, researchers are still searching for the best ways of identifying patients most likely to respond to immunotherapy, says Professor Leisha Emens, co-leader of the Hillman Cancer Immunology and Immunotherapy Program at the University of Pittsburgh, USA. "We are in need of good biomarkers."

Finding such biomarkers in tumours could help to overcome one of the biggest limitations of current immunotherapies: they do not work for all patients or cancer types. On average, only about 20% of patients improve after treatment with individual checkpoint inhibitors, for instance. The drugs also perform poorly against some kinds of cancer, such as pancreatic and prostate tumours. CAR T cells also have a subpar record when it comes to solid tumours.

One possible way to boost immunotherapies is to convert cancers that do not respond to the treatments into ones that do. Earlier this year, chemistry professor Matthew Disney of the Scripps Research Institute in Jupiter, FL, USA, and colleagues revealed a procedure that worked on breast cancer cells. Some breast tumours make the receptor HER-2 and are vulnerable to the drug trastuzumab, which blocks cell growth, and ado-trastuzumab emtansine, which binds to the receptor and delivers a lethal compound to the cancer cells. But some tumours do not produce HER-2 and are not affected by the drugs. Disney and colleagues managed to turn three different breast cancer cell lines from HER2-negative to HER2-positive by dosing the cells with a micro-RNA molecule that bound to non-coding RNA, which regulates the transcription of the relevant genes. Healthy cells were unaffected by either drug. The downside of the approach is that HER2-positive cancers are more aggressive. However, as Disney explains, "For breast cancer patients with dwindling options, switching on HER2 sensitivity might be life-changing."

To bring the benefits of immunotherapies to a broader range of cancers and a larger fraction of patients, researchers are also combining existing treatments to improve their effectiveness. For example, several combinations of checkpoint inhibitors, such as nivolumab and ipilimumab for kidney cancer, have already been approved in the US and the EU.

Scientists are also developing a new generation of immunotherapies that may overcome other defenses, besides CTLA-4 and PD-1, that protect tumours from the immune system. One of these defenses involves adenosine, an immune-suppressing molecule produced by the breakdown of ATP. Extracellular ATP is a danger signal that ramps up the immune system, but its decay product adenosine dampens that response. The tumour microenvironment →

Since their introduction in 2011, checkpoint inhibitors have become standard therapies for a range of cancers, such as melanoma, non-small cell lung cancer, and certain kinds of colon cancer.

is often rich in adenosine, says Smyth. "A lot of tumours are addicted to adenosine and are using it to keep the immune system at bay." The molecule stymies two types of cells that are crucial for combating cancer – natural killer cells and cytotoxic T cells – by binding to receptors on their surface, including one known as A2A. Cloaked in a protective cloud of adenosine, tumours can prevent these cells from attacking them.

A wealth of evidence from animal research shows that blocking the effects of adenosine makes tumours more vulnerable to the immune system. In a 2016 study, for instance, Smyth and colleagues dosed mice that had lung cancer with a molecule that obstructs the A2A receptor and an antibody that inhibits CD73, an enzyme that helps generate adenosine. This combo more than doubled the length of time the animals survived, the researchers found. Pharmaceutical companies have already developed drugs that disrupt adenosine (they were originally designed to treat neurological diseases). Clinical trials are now testing whether these drugs – alone or in combination with checkpoint inhibitors – are effective against cancer.

Another cancer cell defense causes resistance to CAR T cells. Cancer continually changes, and the cells can essentially make themselves invisible to CAR T cells by curbing production of the protein that the CAR targets. In response, scientists have created CAR T cells that carry two or three types of receptors, each of which recognizes a different molecule on cancer cells. Even if a cancer cell sheds one of the target proteins, these CAR T cells can use their other receptors to identify the abnormal cell. In patients with B-cell acute lymphoblastic leukaemia, clinical trials are now evaluating CAR T cells with two kinds of receptors that can distinguish two proteins found on leukaemia cells, CD19 and CD22.

For more than 30 years, scientists have also been attempting to use vaccines to stimulate the immune system to combat cancer. These vaccines differ from immunizations for infectious diseases such as measles, rubella, and the flu. Instead of preventing cancer, they spark the immune system to attack tumours that have already formed. However, almost every cancer vaccine that reached clinical trials has failed. Only one therapeutic cancer vaccine, sipuleucel-T, for treating prostate tumours, has been approved in the US and Europe.

But now researchers think they can do better. Many cancer vaccines may have failed because they targeted suboptimal antigens, notes Emens. Although cancer cells often carry neoantigens, identifying them was impractical until recently. So most vaccines targeted unaltered proteins on cancer cells. But because these proteins also occur on healthy cells, the immune response against them is usually weak. With powerful genome sequencing technologies, researchers can now quickly determine which neoantigens a cancer harbours and then create a custom vaccine against those antigens.

Professor Michael Platten of the German Cancer Research Center in Heidelberg, who received the 2019 German Cancer Research Award for his clinical work, and his colleagues have developed one such neoantigen vaccine for patients with gliomas. These brain tumours are good targets for vaccines because they spread rapidly and develop resistance very quickly but are difficult to treat. Therefore, the rate of recurrence is high. As their neoantigen, Platten and his team chose an enzyme mutated in about 80% of gliomas, isocitrate-dehydrogenase type 1 (IDH1), which is recognized by the immune system. A clinical trial the researchers reported on in 2014 showed that the vaccine did not cause serious side effects in patients and created an immune response in most of them. Whether this response is sufficient to fight the tumour and prevent it from coming back is still under investigation.

Another vaccine approach allows immune cells called dendritic cells to identify the important neoantigens. Dendritic cells gather antigens from pathogens and neoantigens from cancer cells and use them to spark a counterattack by the immune system. "They are the spies of the immune system," says Lana Kandalaft, assistant professor in the Department of Oncology at the University of Lausanne, Switzerland. She and her colleagues have demonstrated a dendritic cell vaccine in women with ovarian cancer. The researchers obtained some of each patient's dendritic cells and exposed them to samples of their own tumour. The scientists then incorporated the dendritic cells into a vaccine. They were able to make a personalized vaccine for each woman within seven to ten days, says Kandalaft. As the scientists reported in 2018, the vaccines stimulated T cells that attack the tumours and extended the patients' survival.

To boost cancer vaccines' performance, researchers are also pairing them with checkpoint inhibitors, which may counteract the tumours' immune-suppressing environment. A 2018 study provided mice with such a combination treatment, which cleared their cancer. Even when researchers injected the animals with cells from the same type of cancer, tumours did not regrow, suggesting that the T cells stimulated by the vaccine remembered the malignant cells and that the treatment could prevent a recurrence. Several early clinical trials also suggest that checkpoint inhibitors improve the effectiveness of anti-cancer vaccines.

Whether the novel immune checkpoint inhibitors, upgraded CAR T cells, vaccines, adenosine-blockers, or other approaches researchers are developing will pan out remains to be seen. But scientists are confident that they will be able to build on the successes of immunotherapy and continue to improve cancer treatment. "We have all the right elements to give the field a big push," says Shirwan.

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

Therefore, this pdf continues with the section Results.

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

Shared first authorship is indicated with an *.

NUCLEOSOME-INDEPENDENT FUNCTIONS FOR THE HISTONE VARIANT H3.3

cf. BIF FUTURA, VOL. 29 | 2.2014

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Histone variants replace their canonical counterparts within specialized genomic contexts through the action of variant-specific histone chaperone complexes. The complex composed of the α thalassaemia/mental retardation X-linked (ATRX) protein and the death domain associated protein (DAXX) binds the replication-independent histone variant H3.3 and facilitates its targeted deposition into chromatin, particularly at repetitive regions such as telomeres and pericentromeres. The molecular architecture of the ATRX–DAXX complex and the functions of H3.3 in chromatin are not fully understood. The goals of my PhD project were to further characterize the molecular assembly of the ATRX–DAXX complex and to study how it regulates the repression of transposable elements. In collaboration with the lab of Prof. Dinshaw Patel, I investigated the structural basis of the interaction between ATRX and DAXX via X-ray crystallography. In particular, we identified a short amino-acid stretch in ATRX that is both necessary and sufficient for its interaction with DAXX. By interfering with this interaction surface, I then explored ATRX-dependent and independent functions of DAXX. Surprisingly, I found that DAXX – but not ATRX – is required for the repression of a class of transposable elements, referred to as endogenous retroviruses (ERVs), in mouse embryonic stem cells. Using several purification approaches from mammalian cells, I showed that DAXX associates with histone methyltransferase and histone deacetylase enzymes independently of ATRX and thereby helps to repress ERVs. In addition, I observed that H3.3 stabilizes DAXX protein levels in cells. To interrogate how H3.3 levels can influence DAXX-dependent functions, I designed a non-depositable H3.3 mutant that maintained DAXX binding and steady-state protein levels but was not stably incorporated into chromatin. My results show that H3.3 can affect DAXX-regulated repression of ERVs and genes without being incorporated into nucleosomes. The molecular insights gained in this study will aid our understanding of human malignancies harbouring mutations in histone chaperones and the histone proteins themselves.

PUBLICATIONS

Hoelper D, Huang H, Jain AY, Patel DJ, Lewis PW (2017) Structural and mechanistic insights into ATRX-dependent and -independent functions of the histone chaperone DAXX. *Nat Commun* **8**: 1193

ACTIVE SAMPLING ENHANCES NEURAL ODOUR REPRESENTATION IN THE MOUSE OLFACTORY BULB

cf. BIF FUTURA, VOL. 29 | 2.2014

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Discipline: Neuroscience, BA
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Supervisor: Prof. Andreas Schaefer

We experience the sensory world using active movements – we feel with our fingers, search with our eyes, and sniff with our noses. These movements, known as active sampling behaviours, are thought to improve how our nervous system processes sensory input, thereby enhancing our perception. However, how active sampling behaviours affect neural representations of sensory stimuli is not known. During my PhD, I trained animals to complete an olfactory discrimination task in which the goal was to display different behaviours in response to two odours. By recording nasal airflow, I found that mice developed rapid sniffing strategies during odour sampling as they learned this task. At the same time, I recorded the electrical activity of neurons in the olfactory bulb – the site where odour information is first processed. Alongside the changes in sniffing behaviour, the neurons' electrical activity increased in response to these odours, thereby enhancing the neural representation of odours and thus potentially enabling faster behavioural responses to the stimulus. To investigate the mechanisms underlying the connection between faster sniffing and enhanced neural activity, I manually controlled the airflow through the nasal passage of anaesthetized mice so they underwent the same sniffing changes in the absence of an olfactory task. The neural activity recorded during these manipulations revealed that odour responses were stronger during rapid sniffing when it occurred within the context of an olfactory task – in other words, when the animal was paying attention to odour. Thus, the enhanced neural representation during active sniffing is probably caused by more odour information being delivered to the olfactory bulb (via more sniffs) as well as the neuromodulation – or neuron-based regulation – of attention. My work is the first to demonstrate not only improved early sensory representations during active sampling, but also the concurrent influence of attention on early sensory responses. My results open many new avenues of further research, such as identifying which neuromodulators are involved and how they affect information processing within the olfactory bulb.

PUBLICATIONS

Jordan R, Fukunaga I, Kollo M, Schaefer AT (2018) Active sampling state dynamically enhances olfactory bulb odor representation. *Neuron* **98**: 1214–1228.e5

SINGLE-MOLECULE NUCLEOSOME CURTAINS SHOW THAT CONDENSIN KEEPS NUCLEOSOMES IN THE LOOP

cf. BIF FUTURA, VOL. 29 | 2.2014

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Supervisor: Prof. Eric C. Greene

Eukaryotic nuclei look like a dense soup of chromatin – the polymer of nucleosomes, which are themselves formed from DNA and histone proteins. During mitosis, this dense soup organizes into neatly defined and condensed chromosomes in a matter of minutes. Chromosome condensation is carried out principally by the protein condensin. Single-molecule studies of *Saccharomyces cerevisiae* condensin showed that this motor protein can perform loop extrusion, a process that leads to chromosome condensation. These experiments, however, were performed on naked DNA, whereas the canonical substrate of condensin is chromatin. In my PhD project, I sought to determine whether condensin is sufficient for DNA condensation in the presence of nucleosomes. First, I developed a single-molecule technique, called nucleosome curtains, to observe nucleosomes in real time at high throughput. This technique is based on DNA curtains, a method in which DNA molecules are aligned in a microfluidic chamber so that the molecules and bound proteins can be observed using fluorescence microscopy. By purifying histones from *S. cerevisiae*, labelling them with small organic dyes, and using these labelled histones to reconstitute nucleosomes on our DNA substrate for DNA curtains, I was able to observe single nucleosomes and titrate them on DNA. I added condensin on these nucleosome curtains to determine whether it would still condense DNA in the presence of nucleosomes. I found that the presence of nucleosomes does not alter the velocity or processivity of condensation by condensin. I also discovered that condensin is able to condense DNA and bypass nucleosomes without pausing or slowing down, which suggests that nucleosomes are not a barrier to DNA condensation by condensin and that condensin is sufficient for chromosome condensation. Overall, my work has helped to elucidate the mechanisms through which chromosome condensation arises during mitosis. The development of the nucleosome curtains technique will allow scientists to further study the interplay between nucleosomes and DNA-associated enzymes in other processes, such as replication and DNA repair.

PUBLICATIONS

The results of this project have not yet been published.

QUANTITATIVE BIOLOGY OF CELL CYCLE DECISION-MAKING

cf. BIF FUTURA, VOL. 29 | 2.2014

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Discipline: Molecular Biologist, MA
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Supervisor: Sir Paul Nurse

In metazoans and the fission yeast *Schizosaccharomyces pombe*, the G1/S and G2/M transitions are focal points of cell cycle regulation. Cells perform these transitions at defined cell sizes, and they adjust their growth to compensate for being too large or small. The cell cycle is driven by cyclin-dependent kinase complex (cyclin-CDK) activity, and multiple signals are integrated by a single inhibitory phosphorylation site on cyclin-dependent kinase (CDK). This phosphorylation is regulated by the kinase Wee1 and the phosphatase Cdc25. In my PhD project, I sought to quantify if and how cell size directly regulates CDK activity in single cells, and to what extent cyclin levels contribute to cell size at division. By perturbing cyclin levels with a newly designed promoter and using a high-throughput image analysis pipeline that I developed, I found that by altering the activity of Wee1 and Cdc25, the cell establishes a certain threshold of CDK activity that is required for G2/M entry. Cyclin levels scale with cell size, and the probability of a cell having suprathreshold levels of cyclin dictates its probability of entering mitosis. To study the effect of cyclin-CDK concentration on CDK activity, I engineered a fluorescent biosensor that translocates from the cytoplasm to the nucleus in response to phosphorylation by CDK. I showed that CDK activity is ultrasensitive to cyclin-CDK level and that the larger the cell, the more the dose-response relationship resembles a switch, with CDK activity being on or off. This size-dependent ultrasensitivity is dependent on CDK phosphorylation, as it was absent when non-phosphorylatable cyclin-CDK was used. By knocking out the canonical CDK regulatory pathways and repeating the cyclin-CDK dose-response experiment, I showed that small cell size decreases intrinsic cyclin-CDK activity. My work demonstrates for the first time that cell size directly regulates CDK activity, providing unprecedented insights into the cell cycle.

PUBLICATIONS

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THE CONDENSIN COMPLEX: A MULTIFUNCTIONAL GENOME ORGANIZER

cf. BIF FUTURA, VOL. 29 | 2.2014

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The positioning of the genome within the nucleus can constrain processes such as transcription. The condensin complex is often posited as the interface between genomic organization and function. The relationship between the two is difficult to study, because cells lacking condensin falter during cell division in all eukaryotes, obscuring its function during interphase. Targeted studies have implicated condensin in regulating several specific loci, but how it acts across the whole genome was not well understood. The goal of my PhD project was to get a global view of condensin-mediated genome organization in *Saccharomyces cerevisiae* using genome-wide chromosome conformation capture. I found that condensin acts both locally and globally, which raises questions about its mechanism of action. In the currently favoured model, condensin walks along the DNA and pushes out a DNA loop. This fits with my finding that condensin causes short-range interactions between adjacent regions on a chromosome. However, I also found that condensin mediates long-range interactions between genes over long distances and between chromosomes, which suggests that its mechanism of action is multifunctional and more complicated than the loop extrusion model. To study how genome organization affects genomic function, I used mRNA sequencing to check whether gene transcription changes when condensin is inactivated. Surprisingly, the massive amount of work that condensin puts into configuring the three-dimensional organization of the genome has little effect on transcription. Together, my results show that global gene expression in *S. cerevisiae* is resistant to condensin inactivation and the associated changes in genome organization. Errors in genome organization are a major player in a huge variety of pathologies, such as cancer, and understanding how and why these changes contribute to disease is essential. My work demonstrates that assumptions about the link between genome organization and transcription – and the prevailing theories of how architectural proteins work – need to be questioned.

PUBLICATIONS

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MECHANISM AND CONSEQUENCES OF miRNA URIDYLATION IN *DROSOPHILA MELANOGASTER*

cf. BIF FUTURA, VOL. 29 | 2.2014

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MicroRNAs (miRNAs) are involved in most developmental and physiological processes in eukaryotes, and aberrant miRNA levels are linked to various human diseases. miRNA levels are regulated post-transcriptionally by the non-templated addition of ribonucleotides to the 3′ ends of miRNAs. This process, called tailing, is catalysed by terminal nucleotidyltransferases (TNTases). The function and identity of many TNTases remain enigmatic. The aim of my PhD was to systematically characterize miRNA tailing, identify the TNTases involved, and dissect its functional consequences in flies. By coupling high-throughput sequencing and biochemical approaches, I contributed to the identification of the first terminal uridylyltransferase in *Drosophila melanogaster*, Tailor. Tailor is required for most 3′ end miRNA uridylation and predominantly targets precursor miRNA (pre-miRNA) hairpins. Mirtron hairpins, which are intron-derived splicing products that structurally resemble canonical pre-miRNAs, can enter the miRNA biogenesis pathway and generate non-canonical miRNAs that could be detrimental. Tailor preferentially uridylates mirtron hairpins, impeding the maturation of these non-canonical miRNAs. I also showed that Tailor physically interacts with the previously uncharacterized uridine-specific 3′-to-5′ exoribonuclease dmDis3l2. Tailor-mediated uridylation of mirtron hairpins triggers their efficient decay by dmDis3l2. Together, Tailor and dmDis3l2 form the terminal RNA uridylation-mediated processing (TRUMP) complex, which targets misprocessed, non-coding RNAs for decay, thus providing a mechanism for cytoplasmic RNA quality control. My work adds to our understanding of the functional impact of RNA uridylation and how Tailor-mediated uridylation shapes cellular miRNA repertoires in *Drosophila*.

PUBLICATIONS

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Rif1 MAINTAINS TELOMERES AND MEDIATES DNA REPAIR

cf. BIF FUTURA, VOL. 29 | 2.2014

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Double-stranded DNA ends occur at telomeres (the ends of chromosomes) and as a consequence of DNA damage. Lesions such as double-strand breaks (DSBs) are the most dangerous to the cell because they pose an immediate risk to genome integrity. DSBs therefore need to be detected and repaired, by either non-homologous end joining (NHEJ) or homologous recombination (HR). To avoid being mistaken as DSBs, telomeres are packaged into a protein meshwork and thereby protected. The evolutionarily conserved protein Rif1 participates in a multitude of seemingly unrelated genome maintenance processes, ranging from DNA repair to telomere protection. In budding yeast, Rif1 is part of the telomere meshwork, where it inhibits telomerase and maintains telomere length. In mammals, RIF1 is not telomeric but suppresses DNA end resection at DSBs, promoting repair by NHEJ. In my PhD project, I determined the crystal structure of the conserved 125 kDa N-terminal domain of Rif1 from budding yeast (Rif1-NTD). The extended architecture consists of an irregular alpha-helical repeat that is shaped like a shepherd's crook. I showed that Rif1-NTD binds DNA *in vitro* with high affinity. In the presence of DNA, Rif1-NTD forms a figure-8-shaped head-to-tail dimer, encasing double-stranded DNA. *In vivo*, binding of the Rif1-NTD to telomeres is essential to regulate telomere length. My collaborators and I also showed that Rif1 binds DSBs *in vivo*, attenuates DNA end resection, and facilitates the NHEJ pathway in budding yeast. In mammals, RIF1 recruitment to DSBs is strictly dependent on phosphorylated tumour suppressor p53-binding protein 1 (53BP1). However, whether RIF1 and 53BP1 interact directly or require a mediator protein was not known. I found that the 53BP1-Rif1 interaction is direct and showed that complex formation is strictly dependent on a phosphorylated 53BP1 motif. By dissecting these molecular interactions, my work adds to our mechanistic understanding of how telomeres are protected in budding yeast and which DSB repair pathway is chosen.

PUBLICATIONS

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FUNCTIONAL INTEGRATION OF MITOCHONDRIAL PROCESSES

cf. BIF FUTURA, VOL. 31 | 1.2016

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Mitochondria have a vital role in energetics and metabolic processes such as ATP synthesis. More than 99% of the mitochondrial proteome is imported by translocation machineries. This import is mediated mostly by an N-terminal targeting sequence that is positively charged and 15–50 amino acids long. As little is known about the spatial and functional organization of mitochondrial core components, I set out to analyse selected mitochondrial proteins in human cells. I generated cell constructs incorporating a nanoscopy tag that allows a protein of interest to be detected without using bulky antibodies or genetically encoded labels, which can disrupt protein function. Furthermore, I used biochemical methods to study the regulation of the stability of mitochondrial proteins. I identified reactive oxygen species modulator 1 (ROMO1), a known mitochondrial protein, as a constituent of the human translocation machinery with an extremely short half-life. To study its function, I used CRISPR-Cas9 to generate a knockout cell line displaying aberrant inner membrane structure. Biochemical analyses of this cell line showed that the processing of OPA1, a protein involved in mitochondrial morphology, was disturbed and that steady-state levels of the OPA1 processing protease, YME1L, were reduced. Although general protein import was not dependent on ROMO1, *in vitro* import assays showed that YME1L import was reduced by 60% in the absence of ROMO1. The reason for this import defect is that the targeting sequence of YME1L is 150 amino acids long and has very few positive charges. Introducing positively charged amino acids by site-directed mutagenesis and importing these constructs into isolated mitochondria *in vitro* alleviated the observed phenotype. My discovery of the relationship between protein import and inner membrane morphology in mitochondria reinforces the idea that these processes are indeed linked, which is necessary for the organelle to function properly.

PUBLICATIONS

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BIOPHYSICAL ANALYSIS OF NEURONAL COMPUTATIONS IN THE ZEBRAFISH OLFACTORY FOREBRAIN

cf. BIF FUTURA, VOL. 30 | 1.2015

PETER RUPPRECHT
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The types of computation performed by a neuronal network in the brain depend strongly on the biophysical properties of the network itself. In my PhD project, I analysed how these properties constrain and support stable pattern classification in the zebrafish homologue of the mammalian olfactory cortex. Pattern classification is a generic computation that maps sensory inputs to discrete categories like "dog", "red", or "smell of cinnamon". I began by devising a method to image neuronal activity in three dimensions across more than 1,500 neurons with a two-photon laser scanning microscope using an electric motor inspired by the working mechanism of loudspeakers. To analyse neuronal activity, I tailored artificial neuronal networks to extract spiking activity from calcium signals. In addition, I used whole-cell voltage clamp recordings to investigate the co-ordination of excitatory and inhibitory inputs to single neurons. I found that strong excitatory and inhibitory inputs establish a balanced state in the network and are largely due to local recurrent connections – that is, network outputs fed back in as inputs. Contrary to assumptions about classical balanced networks, I found that the balanced state is maintained precisely in time and stimulus space. This means that inhibitory and excitatory inputs are correlated, both on a timescale of a few milliseconds and across different stimuli, which suggests the existence of a synaptic plasticity or connectivity rule that couples excitatory and inhibitory synaptic strength in a stimulus-specific way. The precision of this balance makes the network stable for many different input patterns and thus an ideal biophysical substrate for pattern classification. At the same time, the intrinsic computational properties of a balanced network give it specific advantages, such as the capacity to process both external inputs and internal dynamics at high speed.

PUBLICATIONS

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THE DUAL CODING OF PROTEIN- AND RNA-LEVEL INFORMATION IN SEQUENCE EVOLUTION

cf. BIF FUTURA, VOL. 29 | 2.2014

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Discipline: Evolutionary Biologist, MSc
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Supervisor: Prof. Laurence D. Hurst

The human genome frequently superposes several layers of information. For example, coding regions contain not only the information necessary to determine amino acid sequence but also binding sites for splicing factors and other RNA-binding proteins. The need to preserve both layers of information imposes a double constraint during evolution. In my PhD project, I asked two questions regarding such constraints. First, is the evolution of coding sequence also constrained by the need to avoid inappropriate signals? For instance, individuals without splice-promoting motifs in intronless genes might have an evolutionary advantage over individuals with the motifs in these genes, since the latter might lead to inappropriate processing. However, when I analysed intronless genes, I found that they were under selection to preserve their splice-promoting motifs. This is likely due to these motifs having roles in addition to splicing, such as in nucleocytoplasmic export. Having failed to uncover evidence of avoidance, I next studied target motifs for RNA-binding proteins more generally. I discovered that target motifs for exon-binding proteins tend to be selectively maintained within the coding sequence, whereas target motifs for proteins binding introns and untranslated regions tend to be avoided, perhaps to prevent interference with exon recognition. This suggests that coding regions must both preserve necessary regulatory signals and actively avoid inappropriate ones. Second, I asked whether exonic splice regulation was achieved through few strongly selected or many weakly selected elements. Through population genetics analysis, I discovered that ~15–20% of human coding sites overlap functional splice-promoting motifs. Contrary to the belief that selection on regulatory elements overlapping coding regions is weak, I found that it is strong at most of these sites. This finding suggests that splicing regulation is a major force in the evolution of coding regions.

PUBLICATIONS

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AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL STUDY OF DEVELOPMENTAL PATTERN FORMATION

cf. BIF FUTURA, VOL.. 31 | 2.2016

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The spatial organization of cells during development is thought to be controlled by the formation of repetitive structures known as patterns. Understanding these patterns is crucial for the creation of synthetic tissue. Alan Turing proposed a mechanism that could explain how patterns arise. Turing patterns (TPs) involve at least two proteins – an activator and an inhibitor – that diffuse between cells at different speeds, thus producing patterns of activated and inhibited regions. TPs match biological observations well in theory, but many of their key properties seem to contradict biology. To determine if TPs alone can achieve robust patterning or if other patterning mechanisms are required, it is necessary to engineer a TP in the absence of endogenous patterning. The aim of my PhD project was thus to create a man-made TP within a layer of epithelial cells. I first developed an algorithm to test what kind of protein interaction networks can generate TPs and to identify the required parameter ranges. Contrary to a previous hypothesis that only 10% of the tested networks form TPs, I showed that >60% form TPs. However, <1% of all tested parameter combinations produced TPs, even for the network most likely to form TPs. I chose the hepatocyte growth factor (HGF) as the activator and NK4 as the inhibitor, which, when combined with their receptor and promoter, can generate one of the theoretically more robust TP networks. To test this circuit and its sub-components, I developed a framework to integrate different HGF-dependent networks into an endogenous HGF-inducible locus using CRISPR-Cas9. I showed that stable integration was key to controlling circuit behaviour: it prevented endogenous DNA regulatory elements from interfering with the promoter, and the endogenous locus provided enhancer elements crucial for its function. Unfortunately, safety mechanisms within the HGF signalling pathway prevented HGF-dependent self-activation and thus TP formation. However, the rules and guidelines derived from my work are currently being used to engineer the first fully synthetic TP within a different engineering scaffold.

PUBLICATIONS

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NOVEL *IN VITRO* iCLIP TECHNIQUE FACILITATES UNDERSTANDING OF SPLICEOSOME REMODELLING

cf. BIF FUTURA, VOL. 31 | 1.2016

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Institute: MRC Laboratory of Molecular Biology (LMB), University of Cambridge, Cambridge, UK
Supervisor: Dr Kiyoshi Nagai

In most eukaryotic genes, protein-coding sequences (exons) are interrupted by non-coding sequences (introns). After transcription, the introns are removed and the exons are ligated to produce a continuous protein-coding sequence. This fundamental two-step process, known as splicing, is catalysed by a large RNA-protein assembly called the spliceosome. The spliceosome is assembled stepwise on an RNA transcript, and its catalytic centre is modified after the first step of splicing to allow the components of the second step to enter. Remodelling of the spliceosome is initiated by eight helicases that use the energy from ATP hydrolysis to disrupt RNA-RNA and RNA-protein interactions. Spliceosomal helicases have traditionally been studied in isolation on model RNA substrates; genetic studies using mutant helicases have provided insights into the time of action and their RNA substrates. To obtain a more precise mechanistic understanding of remodelling, I investigated interactions between individual helicases and their substrates within purified yeast spliceosomes at specific catalytic states, generating global helicase binding profiles in defined, natural contexts. First, I modified and tailored the individual nucleotide–resolution ultraviolet cross-linking and immunoprecipitation (iCLIP) technique, which is based on next-generation sequencing, and validated it by determining the binding profile of an integral spliceosomal protein. I then used this method to determine the binding profile of the spliceosomal helicase Prp16p. I found that Prp16p is located at an invariant distance from a recognition sequence in the intron, ready to remodel the spliceosome before the second catalytic step of splicing. This distance seems to be defined by the spliceosome core acting as a molecular ruler. My finding supports the hypothesis that helicases such as Prp16p can remodel the spliceosome – and other RNA-protein complexes – by pulling on its RNA substrate from a peripheral position, which destabilizes RNA-RNA and RNA-protein contacts buried within the complex. By applying this technique to other spliceosomal helicases, this novel biochemical method can be used to deepen our understanding of the remodelling processes undertaken by a multitude of helicases in all aspects of nucleic acid biology.

PUBLICATIONS

The results of this project have not yet been published.

SELECTIVITY AND GATING MECHANISMS OF THE CALCIUM-ACTIVATED CHLORIDE CHANNEL, BEST1

cf. BIF FUTURA, VOL. 30 | 2.2015

GEORGE VAISEY
Discipline: Biochemist, MBiochem
Institute: Gerstner Sloan Kettering Graduate School of Biomedical Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Supervisor: Dr Stephen B. Long

Bestrophins are a family of chloride-selective ion channels that are activated by cytoplasmic calcium. Mutations in BEST1, one of the four human bestrophins, cause retinal degenerative diseases. A detailed understanding of bestrophins has remained elusive, in part because they are unrelated to other ion channels. In contrast to previous work that studied bestrophin channels overexpressed in cells, I took a reductionist approach in my PhD studies. I made electrophysiological recordings of purified chicken BEST1 (of which there is an X-ray structure) in lipid bilayers. Recordings of wild-type and mutant BEST1 showed that distinct regions of the channel control ion selectivity and calcium-dependent activation. A hydrophobic "neck" constriction within the ion pore acts as the calcium-dependent activation gate, while a cytosolic "aperture" controls the relative permeabilities of anions. Currents of BEST1 also showed calcium-dependent inactivation, which I found was a direct property of the channel. BEST1 inactivation occurs through a unique allosteric mechanism wherein binding of a peptide to a surface-exposed receptor controls a structurally distant gate. From this work, it became apparent that the X-ray structure of chicken BEST1 represents an inactivated conformation. Using single-particle cryo-electron microscopy of a C-terminally truncated BEST1, which does not inactivate but maintains characteristic channel properties, I obtained the first high-resolution structure of an open-channel conformation. Whereas localized twisting or domain motions often constitute the activation mechanism of ion channels, a dramatic, concerted rearrangement of hydrophobic amino acids within the BEST1 protein core is responsible for channel opening. This represents a new molecular paradigm for ligand-gated ion channels. My results offer a detailed description of how this unusual channel works, as well as why mutations cause disease.

PUBLICATIONS

Miller AN, Vaisey G, Long SB (2019) Molecular mechanisms of gating in the calcium-activated chloride channel bestrophin. *Elife* **8**: e43231

Vaisey G, Long SB (2018) An allosteric mechanism of inactivation in the calcium-dependent chloride channel BEST1. *J Gen Physiol* **150**:1484–1497

Vaisey G, Miller AN, Long SB (2016) Distinct regions that control ion selectivity and calcium-dependent activation in the bestrophin ion channel. *Proc Natl Acad Sci USA* **113**: E7399–E7408

MD FELLOWS 2018

With its MD fellowships, the Boehringer Ingelheim Fonds helps outstanding medical students to pursue an ambitious experimental project in basic biomedical research. Candidates study in Germany and change their workplace (institution and city) for at least ten months to join an internationally renowned laboratory. Here, we present the nine fellows who were granted an MD fellowship in 2018.

LUISE ECKARDT

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

PHILLIP HARMS

The contribution of extracellular ATP and e-NTPDase1 (CD39) to large vessel vasculitis

DANIEL LEIBLE

Local microcircuitry and long-range control of PFC neurons projecting to the PAG in compulsive alcohol drinking

ANNIE LI

Characterizing the role of a hemidesmosome-like structure in PDAC-stroma crosstalk

MARIUS MÄHLEN

Amoeboid reprogramming – an outside-in perspective: consequences of adhesion shutdown for the cytoskeleton

ANNA MEURER

Immunomodulatory and melanoma-intrinsic PD-1 receptor functions and their significance in immune checkpoint therapy

LEA SCHULZE

R03 – Implementing a CRISPR-Cas screen for druggable host genes required for Powassan virus replication and cell cycle

FELIX SCHUSTER

The role of a newly identified transmembrane protein in flavivirus infection

KAI WESSEL

Investigating the role of tumour endothelial cells in metastasis formation and immune cell recruitment

THE ROLE OF HIF-2/PHD2 IN ADRENAL DEVELOPMENT AND FUNCTION

LUISE ECKARDT

Duration: 08/18–07/19

Project at: University of Oxford, Nuffield Department of Medicine, Target Discovery Institute, Oxford, UK

Supervisor: Professor Sir Peter J. Ratcliffe

Home University: Heidelberg University

THE CONTRIBUTION OF EXTRACELLULAR ATP AND e-NTPDase1 (CD39) TO LARGE VESSEL VASCULITIS

PHILLIP HARMS

Duration: 04/18–03/19

Project at: Stanford University, School of Medicine, Division of Immunology & Rheumatology, Stanford, CA, USA

Supervisor: Dr Cornelia Weyand

Home University: University Medical Center Hamburg-Eppendorf

LOCAL MICROCIRCUITRY AND LONG-RANGE CONTROL OF PFC NEURONS PROJECTING TO THE PAG IN COMPULSIVE ALCOHOL DRINKING

DANIEL LEIBLE

Duration: 06/18–05/19

Project at: Massachusetts Institute of Technology (MIT), Department of Brain and Cognitive Sciences, Cambridge, MA, USA

Supervisor: Professor Kay M. Tye

Home University: Heidelberg University

CHARACTERIZING THE ROLE OF A HEMIDESMOSOME-LIKE STRUCTURE IN PDAC-STROMA CROSSTALK

ANNIE LI

Duration: 09/18–09/19

Project at: Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Supervisor: Andrew S. Liss, PhD

Home University: Heidelberg University Hospital

AMOEBOID REPROGRAMMING – AN OUTSIDE-IN PERSPECTIVE: CONSEQUENCES OF ADHESION SHUTDOWN FOR THE CYTOSKELETON

MARIUS MÄHLEN

Duration: 12/18–09/19

Project at: Radboud University, Microscopical Imaging of the Cell, Nijmegen, the Netherlands

Supervisor: Professor Peter Friedl

Home University: University of Münster

IMMUNOMODULATORY AND MELANOMA-INTRINSIC PD-1 RECEPTOR FUNCTIONS AND THEIR SIGNIFICANCE IN IMMUNE CHECKPOINT THERAPY

ANNA MEURER

Duration: 04/18–03/19

Project at: Harvard Medical School, Brigham and Women's Hospital, Department of Dermatology, Boston, MA, USA

Supervisor: Professor Tobias Schatton, PhD

Home University: RWTH Aachen University Clinic

R03 – IMPLEMENTING A CRISPR-CAS SCREEN FOR DRUGGABLE HOST GENES REQUIRED FOR POWASSAN VIRUS REPLICATION AND CELL CYCLE

LEA SCHULZE

Duration: 09/18–09/19

Project at: The Rockefeller University, Laboratory of Virology and Infectious Disease, New York, NY, USA

Supervisor: Professor Charles M. Rice, PhD

Home University: Münster University Hospital

THE ROLE OF A NEWLY IDENTIFIED TRANSMEMBRANE PROTEIN IN FLAVIVIRUS INFECTION

FELIX SCHUSTER

Duration: 10/18–10/19

Project at: The Rockefeller University, Laboratory of Virology and Infectious Disease, New York, NY, USA

Supervisor: Professor Charles M. Rice, PhD

Home University: Technische Universität Dresden

INVESTIGATING THE ROLE OF TUMOUR ENDOTHELIAL CELLS IN METASTASIS FORMATION AND IMMUNE CELL RECRUITMENT

KAI WESSEL

Duration: 09/18–09/19

Project at: The Rockefeller University, Laboratory of Systems Cancer Biology New York, NY, USA

Supervisor: Professor Sohail Tavazoie, MD, PhD

Home University: University of Münster

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.

STUDY CONCLUDES: APPLICANTS AND FELLOWS HIGHLY SATISFIED WITH BIF

By Kirsten Achenbach and Dr Anja Petersen

BIF took part in a long-term research project by scientists from Heidelberg University who studied the relationship between foundations and their partners – in BIF's case PhD and Travel Grant applicants. Accepted and not accepted applicants were asked to give extensive feedback about how satisfied they were with the partnership with BIF, its staff, and administrative processes. They were also asked about the effects of the funding and how they perceive BIF in general. Overall, the evaluation shows a consistently positive image of BIF from the first steps in the application process to the funding phase and beyond. BIF is seen as a renowned and reliable organization with high standards. It achieves high levels of satisfaction among its partners and its customized supportive programmes are rated as highly beneficial for academic careers.

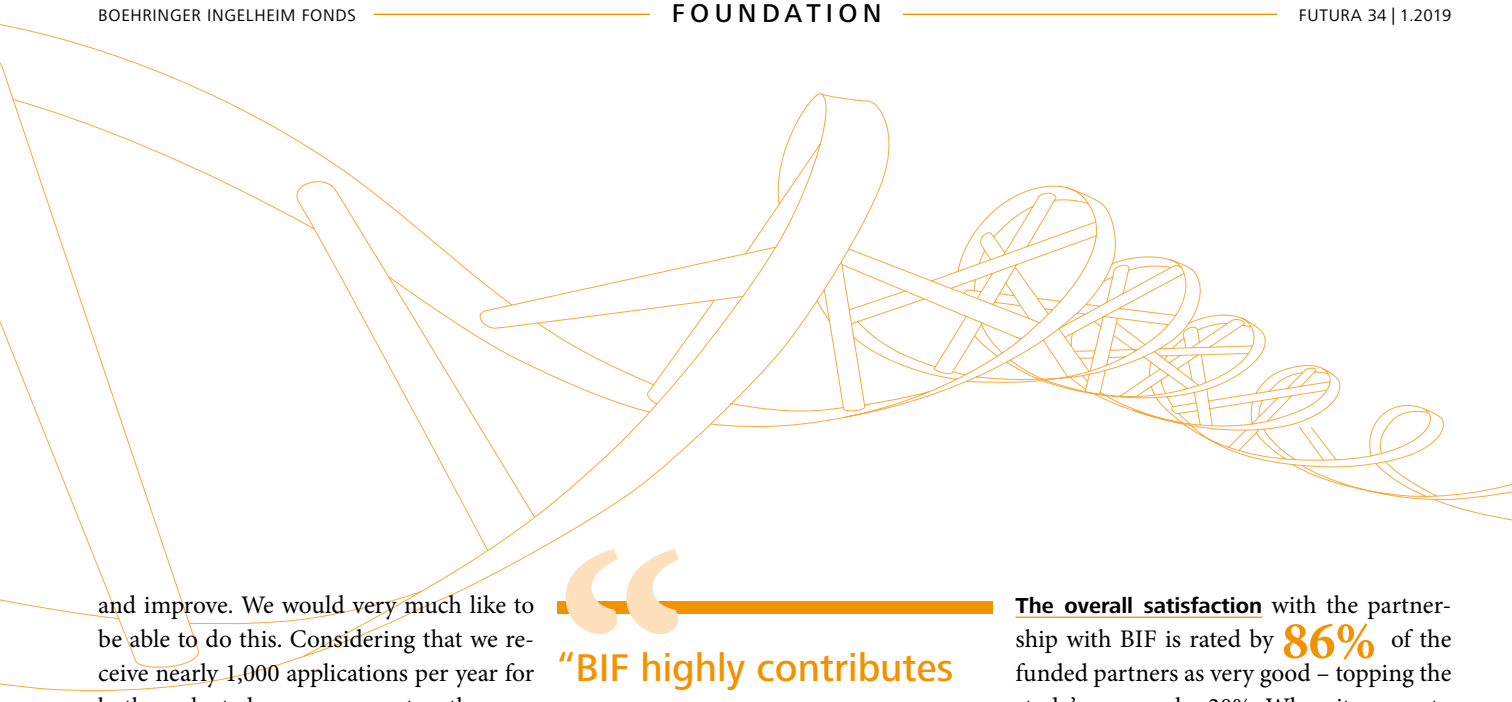
In 2017 and 2018, the Centre for Social Investment (CSI) at Heidelberg University carried out the third round of its "Learning from Partners" study (LfP), which systematically evaluates "the cooperation and relationship between foundations and their partners". Via an anonymous online survey the scientists collected comprehensive feedback from the partners of eight foundations, among them the Volkswagen Foundation, the Wilhelm Sander Foundation, the Fritz Thyssen Foundation – and BIF. The full report and BIF's results as well as an executive summary can be downloaded from our website. Before we present the most important results, we want to very warmly thank all respondents for their time and effort!

"I found the entire process very transparent and professional."

Am I eligible to apply? This is usually one of the first questions applicants have to answer with the help of our website and emails to BIF before preparing an application. The formal criteria and how they are presented are thus critical to reach the right target group and to minimize the number of applications that are not properly prepared or not within our range of funding. We were thus very happy to learn that **95%** rate our formal criteria as being clear and straightforward (aggregated consent with 82 % in the top score). This high score is remarkable as our applicants are comparatively young and inexperienced with grant processes and are very international, coming from more than 50 different countries. It also reflects our continuous efforts to adapt and optimize the information we provide based on the feedback from applicants.

Once an application is sent, the transparency of the processes within the foundation becomes an important issue. Do applicants know what happens to their applications and how a decision is reached? Or is the selection process more like a "black box"? In regard to this transparency, BIF achieves high aggregated scores of **79%** and **69%**, respectively. Nevertheless, the most frequent wish expressed by the study's respondents was to receive detailed feedback on the application in order to learn

"The seminars offered by BIF are outstanding in terms of both the stimulating intellectual environment and the general atmosphere created by the fellows – one of the highlights of my PhD so far."



and improve. We would very much like to be able to do this. Considering that we receive nearly 1,000 applications per year for both evaluated programmes together, we hope it is understandable that we offer feedback only to the PhD applicants who passed the first round of selection and put our limited resources into the comprehensive support of the funded junior scientists.

Especially our PhD fellows report benefits from the support beyond the monthly stipend and **89%** rate the support programme as very good or good (and 8% state that they could not yet judge it at the time of the evaluation). The fellows profit from BIF seminars tailored to their career stage, the many opportunities to meet interesting people through the BIF network, and the very personal support provided by BIF, which **95%** acknowledge. These numbers reflect what makes BIF unique – our dedication to outstanding support for outstanding talent: in any given year, there may be some 400 face-to-face contacts between the fellows and the BIF team at seminars and other events hosted and organized by BIF. As some fellows put it in their comments, this also leads to their evolution from fellow to family member.

We were surprised how positively our Travel Grants (not to be confused with the travel allowances for PhD and MD fellows) were rated in regard to their long-time effects, even though they are given as a one-time payment and for a maximum of three months. Grantees reported, for example, that BIF's funding marked the start of a long-time cooperation between different laboratories and – in some cases – acted as a life-changer.

> "BIF highly contributes to a successful academic development and career."

Taken together, both PhD fellows and Travel Grant recipients rate BIF's support as highly beneficial, leading to positive personal development (80%), a larger professional network (81%), better project management skills (51%), and improved career chances (76%). They also stated that BIF helped them to develop new skills (63%) and find interesting cooperation partners (59%).

In some areas of the study we do receive rather low ratings, for example in "furthering contact with the press" and "direct profit for the awardee's institution." However, these are not goals of our programmes. Apart from the wish for detailed feedback, our partners suggested improving our homepage and online platforms. Our PhD application platform was one of the first of its kind when we established it and thankfully it proved to be very reliable and robust. However, it is now dated, and we are already working on replacing it. We are also in the process of relaunching our website.

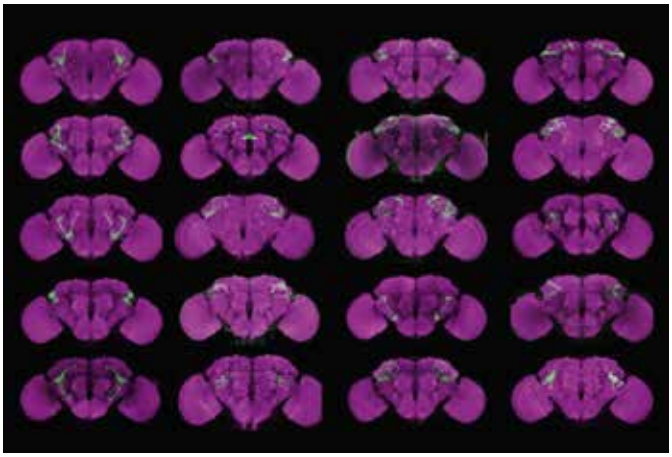
The overall satisfaction with the partnership with BIF is rated by **86%** of the funded partners as very good – topping the study's average by 20%. When it comes to BIF's reputation, the study's results are also very satisfying: **76%** of all respondents (approved and non-approved ones) see support by BIF as a mark of excellence within the community. The LfP study also shows that BIF as a whole is seen as a renowned organization and as a reliable partner with high standards. It concludes that BIF "provides purposeful and customized supportive programmes" for up-and-coming scientists and "highly contributes to a successful academic development and career". Summarizing the feedback from LfP project leader Martin Hölz: "The challenge for BIF may not lie in improving on these outstanding results, but in keeping the bar where it already is."

> "For me, it was very motivating for my career as a scientist to be a part of BIF's funding programme. BIF has the extraordinary talent to create a feeling of belonging."

PAPERS IN THE SPOTLIGHT

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

HOW TO UNLEARN AN INSTINCT



To override an instinctual behaviour, brain areas for innate and learned behaviour need to communicate.

Fruit flies just love the smell of vinegar. It is in their genes – literally. So far we do not know how the brain manages to suppress such innate behaviour when the animal has learned new information. Together with colleagues, Michael-John Dolan and Alexander Bates from the group of Gregory Jefferis at the Laboratory of Molecular Biology (LMB) in Cambridge, UK, were the first to unravel a complete circuit which integrates innate and learned behaviour, in part using a nanometre resolution map of the *Drosophila melanogaster* brain. Learned behaviour is known to be located in the mushroom body, the arthropod analogue of the mammalian associative cortex, while innate behaviour is thought to be situated in a region called the lateral horn, analogous with the mammalian amygdala. The team trained fruit flies with small electric shocks to produce behaviour that superseded their innate responses. By blocking particular neuronal cell types, they found two types of neurons in the innate center that receive input from the learning center during memory recall. These two neuron types also receive input from food odour-encoding neurons, whose activation usually leads to flies approaching an instinctively "good" odour like vinegar. However, the memory of the shocks relayed by the mushroom body neurons lowers the activity of these two neuron types in the innate center – effectively dampening the innate attractivity of the smell. This work demonstrates that a single neuronal cell type is sufficient to integrate both innate and learned olfactory responses to produce the correct behaviour.

REFERENCE

Dolan MJ, Belliart-Guérin G, Bates AS, Frechter S, Lampin-Saint-Amaux A, Aso Y *et al* (2018) Communication from learned to innate olfactory processing centers is required for memory retrieval in *Drosophila*. *Neuron* **100:** 651–668.e8.

Michael-John Dolan, fellowship: 2012–2015
Alexander Bates, fellowship: 2016–2018

TYPE III CRISPR DELIVERS A TWO-HIT PUNCH

The bacterial immune system known as CRISPR has taken the biological sciences by storm, enabling the editing of genes with pinpoint precision. To achieve this precision, CRISPR uses short genetic sequences derived from invading phages or plasmids as a guide, the so-called crRNAs. However, as Jakob T. Rostøl from the group of Luciano Marraffini at The Rockefeller University in New York, USA, has shown, bacteria sometimes use a more brute force approach to get rid of invaders. The type III CRISPR systems Jakob studies are unique in that they cleave DNA and RNA. In type III-A, DNA and RNA matching the crRNA are cleaved by a complex containing Cas10 and Csm3. The role of Csm6, the accessory RNase of the com-

Bacteria have different ways to get rid of DNA inserted by phages or plasmids.

Photos: J. Dolan, Flylight Team, Janelia Research Campus (top left); Markus Schnatmann/Adobe Stock (bottom)

plex, has been less clear so far. Jakob studied how Csm6 helps bacteria to get rid of plasmids. He found that it is only needed for clearing plasmids when plasmid transcription is low and the Cas10–Csm3 complex therefore finds only few targets. In this case, Csm6 is activated by a factor produced by the complex. Csm6 acts independent of crRNAs, degrading transcripts of host and invader alike. It thus arrests the growth of the bacteria but also destroys the transcripts plasmids need for maintenance and replication. Csm6 basically holds the invader captive while the Cas10–Csm complex slowly demolishes it – described as a two-hit punch by the authors. Being independent of crRNA, Csm6 can also protect the bacteria when target and crRNA do not match well. Usually, bacteria resume growth when the complex has destroyed the plasmids and no longer induces Csm6 activity. If not, continuous Csm6 activation could be a last line of defence, killing the host before the invader can spread to nearby bacteria.

REFERENCE

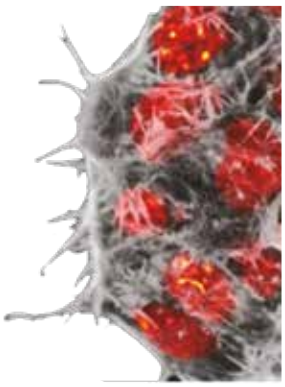
Rostol J, Marrafini LA (2019) Non-specific degradation of transcripts promotes plasmid clearance during type III-A CRISPR-Cas immunity. *Nat Microbiol* **4:** 656–662, doi: 10.1038/s41564-018-0353-x.

Jakob T. Rostøl, fellowship: 2016–2018

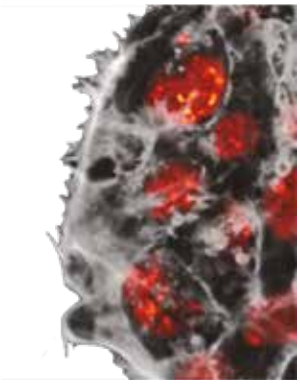
HOW TO COMPENSATE FOR MUTATIONS

A mutated gene can lead to diseases such as cystic fibrosis where one faulty protein can cause a devastating build-up of mucus. However, in many cases, our body can compensate for a mutation, dampening its effect. One of the proposed mechanisms behind such genetic robustness is adaptation of transcription, which involves increased expression of compensating genes. Mohamed El-Brolosy and colleagues from the lab of Didier Stainier at the MPI for Heart and Lung Research in Bad Nauheim, Germany, have now unravelled the process in zebrafish and mice. They found that mutant genes only trigger transcriptional adaptation if they are transcribed and their faulty mRNA is subsequently degraded. Moreover, they discovered that the process is sequence-dependent as a substantial proportion of the genes that exhibit sequence similarity with the mutated gene's mRNA were upregulated. This might be due to modulated histone marks as the team found that the COMPASS complex, which helps to mark chromatin for transcription, plays a role in this process. They also suggested that mRNA degradation products of the faulty gene can repress transcription of antisense RNAs at the compensating gene locus, which in turn upregulates transcription of the respective sense DNA strand.

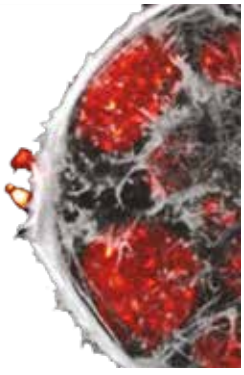
This study thus shows that the mRNA surveillance machinery initiating mRNA decay is not just a quality control mechanism but that it can also modulate gene expression and enhance genetic robustness. The study's results also suggest that to view the full range of a gene's influence on a phenotype without the masking effect of transcriptional adaptation, its transcription must be blocked.



Wild type



Knock-out



Non-transcribing

Mouse embryonic cells with a non-transcribing Actb allele had a more severe phenotype than Actb K.O. cells did, where transcription and therefore genetic compensation took place.

REFERENCE

El-Brolosy MA, Kontarakis Z*, Rossi A*, Kuenne C, Günther S, Fukuda N *et al* (2019) Genetic compensation triggered by mutant mRNA degradation. *Nature* **568:** 193–197

Mohamed El-Brolosy, fellowship: 2017–2019

Photo: Andrea Rossi, Zacharias Kontarakis, MPI-HLR, *Nature* (right)

PERSPECTIVES

A TAKE ON LEADERSHIP AND SELF-ADMINISTRATION IN ACADEMIA

In this section, we introduce BIF alumni from various scientific backgrounds and professional contexts. They describe their career paths, highlighting important steps and decisions that helped them to reach their current position.

INTERVIEW WITH PROFESSOR CHRISTIAN UNGERMANN, UNIVERSITY OF OSNABRÜCK, GERMANY

Christian Ungermann studied biochemistry and biophysics at the University of Tübingen and at Oregon State University, Corvallis, USA. After finishing his PhD at the University of Munich in 1996, he went back to the USA for a postdoc at Dartmouth Medical School in Hanover, NH. He returned as a group leader to Heidelberg University and, in 2006, was named the endowed Hans Mühlenhoff Chair of Biochemistry at the Department of Biology/Chemistry of the University of Osnabrück. Since 2011, he has been the speaker of the Collaborative Research Center (SFB 944) of the DFG. Christian Ungermann is married and has three children (and a dog named Lucy). He and his team study vacuoles – the yeast equivalent to the lysosome of eukaryotes – to understand how cells form and maintain lysosomes and use them to recycle nutrients.

You moved back and forth between the US and Germany twice. What where your main motives?

I wanted to get a broader, more biological perspective than Tübingen offered. The US education system with its graduate school system was everything I had hoped for, confronting me early on with how research is done. In the end, I stayed two years in Oregon and returned with my wife to Germany to join Walter Neupert's lab, which offered exciting tools for my PhD in mitochondrial protein import and export. Later, I realized that only a postdoc would enable me to go abroad to a self-selected lab. I chose Bill Wickner's group for the science, his reputation, and network and because many excellent scientists came from it. But also as a family, we wanted to go to a small town, just like Hanover. During this time I realized that the success of a project is not a given. I always had an alternative approach in mind and somehow knew what to drop and what to continue.

You hold an endowed chair – does that make any difference?

No, it just allowed the university to fill the position five years earlier. There is no interference with my science and I would have strongly objected to that. Initially, I often met with the founder, but by now he is more than 90 years old. I am thankful for his tremendous support and thus keep the name even if it is not required anymore.

You have been or are active in university self-administration, as speaker of a research consortium, etc. What have you taken from that?

In particular, the senates of German universities are a good system of checks and balances, but it takes you out of the research mindset. I see it as a duty as long as it does not impinge on my research and teaching. In my opinion, the dean's office should be run at least in part by professional science administrators as it takes too much time.

In 2010, I was asked to serve as speaker of our local research consortium, the SFB 944. In such a position, you need to build bridges and motivate people to work together, you need ties to the different fields, and a dose of altruism to advance the common goal. Everyone likes you when the consortium gets funded, but you are the one who is blamed if it fails. However, the department and university have profited tremendously from the SFB, and we feel our scientific advances are acknowledged by the cell biology/biochemistry field.

In 2016, I was elected to the DFG panel on biochemistry and biophysics. I consider this an honour and a sign of trust from the community that I am being fair and constructive, but also see it as a chance to learn how other people design experiments and write grants – it definitely widened my horizon.

My advice – if you are asked to serve as a reviewer, do it. It will help you to grow and build your network and reputation.

What is your advice for young group leaders?

You have to learn how to lead and motivate your team and every member in it according to their differences in style and personality and how to deal with conflicts. We as scientists are a special bunch, and learning how to deal with our own leadership limitations takes time and benefits from professional training. However, leading others well can be very rewarding.

Photo: private

PROFILES

MAREIKE ALBERT
Institute: Technical University Dresden, Germany
Fellowship: 2005–2007

Mareike Albert has been selected as a fellow of the Emmy Noether Programme of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). She started her new group "Gene Regulatory Mechanisms of Neocortex Evolution" in January 2019 at the Center for Regenerative Therapies at TU Dresden. The group wants to develop *in vivo* epigenome editing tools to study which role epigenetic mechanisms play in neocortex development. They also want to find gene regulatory regions that have contributed to human brain evolution and investigate the role of non-coding genetic variants in neurodevelopmental diseases.

PROFESSOR HERWIG BAIER
Institute: Max Planck Institute of Neurobiology, Martinsried, Germany
Fellowship: 1991–1994

Herwig Baier has received his second Program Grant from the Human Science Frontier Program. For three years, this grant will fund him and Jeffrey Todd Streelmann from the Georgia Institute of Technology, Atlanta, GA, USA, to jointly work on the project "How Complex Behaviour Is Encoded in the Genome and Wired in the Brain". The HFSP Program Grants are given to international – preferably even intercontinental – teams to broaden the character of their research and to combine different fields of expertise to create novel approaches to problems in fundamental biology.

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

Bernd Bodenmiller has received the Friedrich Miescher Award 2019, the highest distinction for young scientists performing outstanding research in the field of biochemistry in Switzerland. It is worth 20,000 Swiss francs and bestowed by the Friedrich Miescher Institute in Basel. Using mass cytometry methods, he studies how different cells in cancer tissue interact and visualizes their relationships.

MARIA BOHNERT
Institute: University of Münster, Germany
Fellowship: 2008–2010

Maria Bohnert now heads the group "Lipid Droplet Communication" at the Institute of Cell Dynamics and Imaging at the University of Münster, Germany. Her lab uses robotic high-throughput screening approaches combined with in-depth biochemical and microscopic mechanistic analyses to unravel the molecular basis of lipid droplet communication. It focuses on the formation and function of contact sites between lipid droplets and other organelles, which molecules are exchanged there, and how that affects cellular homeostasis.

KATHARINA BRAUNGER
Institute: University of Oxford, UK
Fellowship: 2015–2017

The German Society for Biochemistry and Molecular Biology awarded Katharina Braunger this year's Bayer Pharmaceuticals PhD Prize for her outstanding dissertation "Cryo-EM Analysis of Mammalian Cotranslational Member Protein Insertion and N-Linked Glycosylation". The award was presented during the 70th Mosbacher Colloquium of the GBM and is endowed by Bayer Pharmaceuticals.

PROFESSOR ANNE EICHMANN
Institute: Yale University, MA, USA, and National Institute of Health and Medical Research, Paris, France
Fellowship: 1990–1992

Anne Eichmann has received an ERC Advanced Grant for her project "Targeting Endothelial Barriers to Combat Disease". The 11th call had a success rate of below 11% with 222 grants worth a total of 450 million euros going to scientists across Europe. The grants of up to 3.5 million euros each will enable top researchers to execute their best ideas at the frontiers of science.

Photos: Albert: CMCB Dresden; Baier: MPI-Neurobiologie Kuhl; Bodenmiller: Wim Möllmann; Bohnert: Uni Münster; Braunger: GBM; Eichmann: private

A BIF FELLOW'S GUIDE TO ...

NEW YORK CITY

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 Krithika Venkataraman. She reports from New York, USA, best known as "the city that never sleeps".

FACTS & FIGURES

Country: United States of America
Population: about 8.6 million
Area: about 784 km²
Students: about 595,000
Famous for its skyline and energy, Times Square, pizza, bagels, and delicatessens
Websites: nycgo.com, timeout.com/newyork

WHERE TO STAY

Local NYC: shared and private rooms in Long Island City, Queens.
Pod 39 Hotel: fair price, chic with a roof-top lounge in the heart of Manhattan.
Hotel Marlton: upscale, but charming. Visit the espresso bar and cocktail room with its snug couches and grand fire.

RESTAURANTS

Roberta's: scrumptious New York-style pizza with a sprawling summer patio and cosy oven in the winter.
Mamoun's Falafel: delicious, cheap, open 24/7. Beware of their famous hot sauce.
Smorgasburg 1**:** weekly XXL open-air food market offering NYC's best food in front of the Manhattan skyline.

NIGHTLIFE

Karaoke in Korea Town (K-Town): reserve a private room and throw it back to all your favourite tunes.
Red Room at the KGB: classic speakeasy with live music, literary events, a solid cocktail menu, and an eclectic theatre.
Jazz Standard: the best names in jazz with Southern cuisine or mac 'n cheese.
Brooklyn Steel 2**:** warehouse-style music venue.

BEST SIGHTS

Dumbo 3**:** ice cream at Brooklyn Bridge Park, then cross the bridge to Chinatown and view the Statue of Liberty.
Financial District: the bull and bear on Wall St. and the World Trade Center with its 9/11 memorial.
Broadway: walk down Broadway, catch a ballet at Lincoln Center, admire the lights on Times Square, and snag reduced show tickets.

ACTIVITIES

Winter: explore the many museums with their events or visit the Uncommons, a lively board game café.
Spring: walk the High Line, a converted old railway track, and grab artisanal fusion food at Chelsea Market.
Summer: Central Park offers many free events, including open-air movies, concerts, and theatre plays.
Autumn: stroll through Central Park 4 or see the autumn foliage in Hudson Valley.

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

Krithika Venkataraman is 26 years old and comes from Belgium. She is studying at the Rockefeller University and her supervisor is Dr Leslie B. Vosshall

Photos: Krithika Venkataraman

PROFILES

REBECCA JORDAN
Institute: Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
Fellowship: 2014–2016

Rebecca Jordan has been awarded an HSFP Long-Term Fellowship for her project "Mechanistic Investigation into the Driving Forces of Sensorimotor Learning in the Visual Cortex", for which she has moved to the FMI in Basel, Switzerland. The Human Science Frontier Program gives these grants for innovative, ground-breaking projects. Applicants are expected to take a new research direction. For this, they are funded to obtain training in a new area of research in an outstanding laboratory of their choice in another country.

PROFESSOR FRANK SPRENGER
Institute: University of Regensburg, Germany
Fellowship: 1988–1990

Frank Sprenger has been honoured with the 2018 Ars Legendi Faculty Award in the area of mathematic and natural sciences. He received the award for his outstanding achievements in teaching students in the Department of Biology at the University of Freiburg. In addition to other improvements, he has been instrumental in restructuring the study of biology, has incorporated digital teaching platforms, offers "backstage" talks that enable individual feedback, and has introduced a module in key competencies. The prize comes with 5,000 euros and is jointly awarded by the Stifterverband für die deutsche Wissenschaft (Donors' Association for the Promotion of Sciences and Humanities in Germany) and the associations for biology, chemistry, physics, and mathematics in Germany.

PROFESSOR DIERK NIESSING
Institute: University Ulm, Helmholtz Zentrum München, Germany
Fellowship: 1997–1999

Dierk Niessing has been honoured with the 2018 Care-for-Rare Science Award for his research on the rare disease PURA syndrome. The severe neurodevelopmental disorder was only identified in 2014 and affected children suffer – among other symptoms – from epileptic seizures. So far, treatment is hardly possible. Dierk aims to elucidate the molecular basis of the symptoms using his expertise in structural biology and biochemistry. He is in close contact with the patient organization for the disease and works closely with other researchers in fields such as stem cell research. He will share the 50,000-euro prize from the Care-for-Rare-Foundation with Professor Tobias Hirsch from Münster University Hospital, who works on a different disease.

PETER NESTOROV
Institute: Scailyte AG, Lucerne, Switzerland
Fellowship: 2010–2012

Scailyte, co-funded and headed by Peter Nestorov, has been listed by Forbes as one of the 30 most promising start-ups in the Germany/Austria/Switzerland region for its development of machine learning technology. The company specializes in the analysis of single-cell data to accelerate biomedical research and to enable the discovery of novel biomarkers for precision medicine. The spin-off of the ETH Zurich was founded in June 2017 and has already raised 2.75 million Swiss francs in seed funding.

UPCOMING EVENTS

13–18 SEPTEMBER 2019
Communication training in Cold Spring Harbor, USA
Five-day intensive communication seminar for current PhD fellowship holders working in North America. The meeting will take place in Cold Spring Harbor, New York. Participants will have the opportunity to work on their writing and presentation skills with various experts, as well as to learn more about designing graphs and figures. Further details will be sent with the invitation.

16–20 OCTOBER 2019
119th International Titisee Conference
Thomas Boehm from Freiburg, Germany, and David G. Schatz from New Haven, CT, USA, will chair the 120th ITC "Evolution of Immune Defense Mechanisms". The meeting will address multiple levels: molecular, cellular, tissue, organismal, and "social". It will ask how interactions at these different levels determine the evolution and function of immune systems, highlight different immune recognition strategies, debate the defining features of adaptive immunity, and elaborate on the evolutionary trajectories and interconnection of immune defense functions.
The conference is by invitation only.

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

Photos: Jordan: private; Sprenger: Stifterverband; Nestorov: T. Dürring; Niessing: BrauerPhotos / G.Nitschke für pro.movere