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Metabolism's Hidden Pathways
How metabolites exert control over other essential life processes

Projects, Results, MD Fellowships
New PhD projects, completed theses, and MD fellowships

A BIF Fellow's Guide to Basel
Discover the Swiss city of art, innovation, and the Rhine

The cover illustration shows zebrafish, a common model organism. Their optical transparency and genetic tractability make them ideally suited for live imaging and precise perturbation during early embryogenesis. In this context, BIF fellow Tara Elizabeth McAteer explores how the morphogen Nodal, a signalling molecule, is temporally regulated during gastrulation (see page 24).

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The secret sauce of BIF

"We take an interest in the people we fund as people, not as numbers on a spreadsheet."

At the end of June, about 140 people gathered at Collegium Glashütten for the BIF's yearly European alumni seminar. By now, we should be used to it, but again and again, the atmosphere simply amazes us: the liveliness, the connectedness, and the buzz. One could almost feel flashes of energy pulsing through the room. If we ever ask ourselves whether our efforts are worth it, one moment at a BIF event, especially the alumni seminars at Glashütten, answers this question with a resounding "Yes, it is!"

The feedback we receive shows it's not just us who feel inspired – our fellows and alumni sense it too. They describe it as something unique to the BIF: a sense of belonging that's hard to find elsewhere. In a world that's growing more divided, how does an international community like ours – more than 1,900 fellows from around 70 countries – work so well together? Maybe the answer lies in what we look for in a fellow: a love of science, yes, but also curiosity, openness, and a willingness to listen. These shared values create a strong bond – one that connects people across disciplines, backgrounds, and generations.

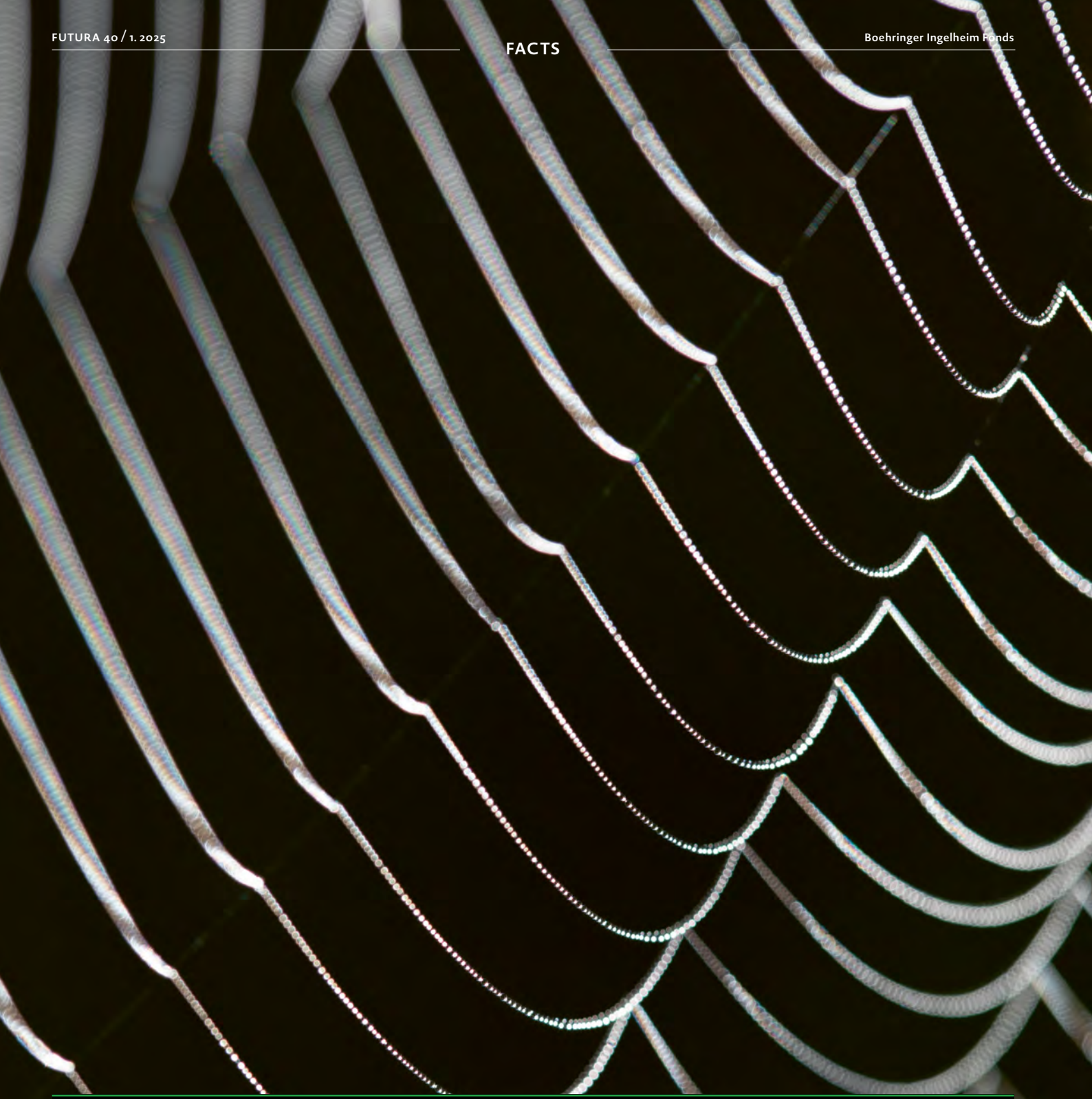
Another reason the BIF community feels different is its spirit of support over competition. While science often involves rivalry and pressure, here, there is no need to compete. From the very beginning, we strive to make everyone feel welcome and part of the BIF family. This starts with clear communication, genuine care, and an interest in the people we fund – not as numbers on a spreadsheet, but as individuals. We listen, we advise, we help.

But most importantly, we aim to set the tone for every interaction: respectful, kind, and thoughtfully engaged. We provide ample time and opportunity to get to know the other fellows, to discuss science and other interesting topics. We believe the friendships and connections that grow during seminars and other BIF events are what truly set our network apart. From shared time and shared values arises something that may outlast even excellent science: a sense of belonging built on trust. This also works by proxy: If you trust BIF, you're more likely to trust a BIF fellow; if you trust one fellow, you're more inclined to trust others. A further sign of this connectedness is that many of our more senior alumni actively seek ways to give back to the network. Two recent examples stand out: the alumni-organized workshop on start-ups held on the Friday of the alumni seminar, and the generous offer of support on intellectual property matters by BIF alumnus Peter Steinecke (see page 62).

BIF has always been – and will always be – about excellent science. But because science is done by people, we've always placed the people behind the science at the heart of our thinking – no matter where they come from, no matter who they are. That is the secret sauce of BIF. But pssst – do not tell anyone else!

Stephan Formella

Marc Wittstock



From Web to Lab: Gene-Edited Spiders Spin Silk With New Properties

You do not have to be Spider-Man to know that spider silk is a remarkable material. It is lightweight and elastic, yet also tear-resistant – ideal for use in medicine, for example in sutures, wound healing, and tissue engineering. But it might do even more if we genetically alter spiders so that they spin a different silk with new properties. In a pioneering study, researchers applied CRISPR–Cas9 gene editing to spiders. Their method involved injecting unfertilised spider eggs with Cas9 components and a red fluorescent protein gene, then fertilising them. In some of the offspring, the silk showed a red fluorescent glow, marking the first successful knock-in of a functional sequence into a spider silk protein. This milestone demonstrates that we can genetically alter spider silk and imbue it with new traits. This opens up many possibilities to make spider silk even stronger, or tailor it to specific needs in medicine and beyond.

Santiago-Rivera E, Scheibel T (2025) Spider eye development editing and silk fibre engineering using CRISPR–Cas. *Angew Chem Int Ed* e202502068, https://doi.org/10.1002/anie.202502068

Credit: Stocksy / Tim Booth

Food as Medicine: How Friendly Gut Bacteria Could Oust Multi-resistant E. *coli*

Multi-resistant *Escherichia coli* lurking in our intestines represent a silent but serious health threat. Normally harmless in the gut, these antibiotic-resistant strains can become lethal if they enter the bloodstream – particularly in immunocompromised patients. Now, scientists at the Helmholtz Centre for Infection Research, in collaboration with Hannover Medical School, both Germany, believe they may have uncovered a microbiome-based defence strategy: competitive exclusion through targeted food competition.

Over 430 non-resistant E. *coli* strains were isolated from healthy human donors and pitted against a multidrug-resistant strain in laboratory assays using sterile mouse intestinal contents. Some of these benign strains proved adept at inhibiting the drug-resistant E. *coli*, effectively starving them of nutrients. The most effective strain not only suppressed one resistant type *in vitro*, but also eliminated it fromthe intestines of mice *in vivo*. Encouraged by these results, the researchers next paired their top-performing E. *coli* strain with *Klebsiella oxytoca*, another benign gut bacterium with complementary nutrient preferences. This two-pronged bacterial cocktail managed to eradicate even those multidrug-resistant E. *coli* types the lone strain could not displace on its own.

These findings might ultimately lead to a new treatment: a safe, food-competitive probiotic duo could serve as a preemptive tool – removing resistant E. *coli* before it causes infection, thereby reducing reliance on last-resort antibiotics. But before this can come true, more research is needed, especially on the safety profile of the candidate strains and their ability to work efficiently in the complex landscape of a human microbiome.

Wende M, Osbelt L, Eisenhard L, Thoma R, Bunk B, Overmann J, *et al.* (2025) Suppression of gut colonization by multidrug resistant *Escherichia coli* clinical isolates through cooperative niche exclusion. *Nat Commun* 16: 5426

When Hearing **Too Well** Hurts

It sounds paradoxical: hearing loss caused by hearing too well. But new research from the University Medical Center Göttingen, Germany, reveals that excessive auditory sensitivity can gradually erode hearing function over time. The study demonstrates that a hyperactive variant of the CaV1.3 calcium channel enhances sound signal transmission between sensory hair cells and auditory nerve fibres. This may help to perceive soft sounds more distinctly – but at a cost.

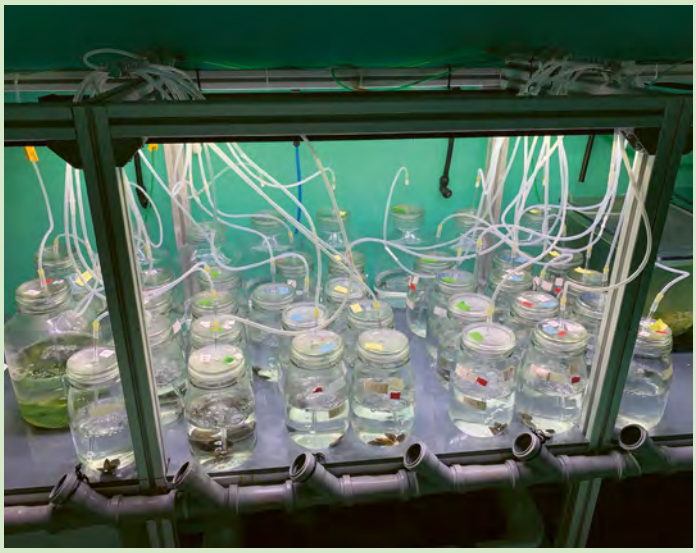
In the inner ear, hair cells detect sound by translating mechanical vibrations into electrical signals. When their hair-like bundles move in response to incoming sound waves, they activate CaV1.3 channels at the synapse, triggering calcium influx and subsequent neurotransmitter release. This initiates the electrical message that ultimately travels to the brain. Calcium channels of the CaV1.3 type are highly sensitive to voltage changes in the cell, which are triggered by the incoming sound signal.

Dysfunction in CaV1.3 channels can lead to impairments ranging from hearing problems to complete deafness. In their study, the researchers investigated a naturally occurring CaV1.3 variant, dubbed CaVAG, which opens more readily in response to voltage changes. In an animal model, this heightened sensitivity made even faint stimuli – like ambient cage noise – sufficient to chronically overstimulate auditory circuits.

The downstream effects were profound. Auditory nerve cells receiving input from CaVAG-expressing hair cells displayed increased spontaneous firing, even in silence. Over time, many of the critical synapses between hair cells and nerve fibres degenerated – despite no exposure to loud noise. This suggests a form of hidden hearing loss that eludes standard audiological tests.

Karagulyan N, Thirumalai A, Michanski S, Qi Y, Fang Q, Wang H, *et al.* (2025) Gating of hair cell Ca^{2+} channels governs the activity of cochlear neurons. *Sci Adv* 11: eadu7898

Mussels at Risk from Offshore Wind Rotor Erosion



In their laboratory, researchers exposed blue mussels to elevated concentrations of microparticles.

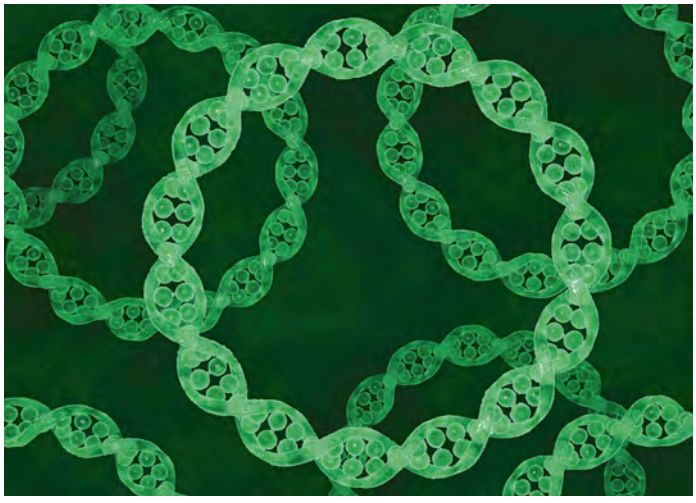
Gale-force winds, salt spray, and relentless waves – offshore turbines in the North Sea endure exceptionally harsh weather. The fierce winds make offshore turbines effective at generating electricity, but they also take a hidden toll: they wear down the rotor blades. A new pilot study led by researchers at the Alfred Wegener Institute (AWI), Germany, has raised concerns about the environmental consequences of rotor blade abrasion, particularly for blue mussels (*Mytilus edulis*), a species under consideration for aquaculture within wind farm zones.

Blue mussels are vital ecosystem engineers – providing habitats for marine fauna, enhancing biodiversity, and improving water quality through filtration. That same filtering capacity also renders them vulnerable to environmental contaminants, as they can accumulate pollutants and microplastics in their gills. In their laboratory, AWI scientists exposed blue mussels to high particle concentrations over a period of 14 days – ground to a size mimicking natural food – and observed their physiological responses. The mussels accumulated notable amounts of metal microparticles, especially barium and chromium, from the blade materials.

The findings indicate that offshore wind farms – while essential to the transition to renewable energy – also introduce new anthropogenic stressors to the marine environment. As mussels from these zones are being considered for human consumption, further research is needed to evaluate potential health risks.

Bedulina D, Korez Lupše Š, Hildebrandt L, Duan Y, Klein O, Primpke S *et al.* (2024) Effect of particles from wind turbine blades erosion on blue mussels *Mytilus edulis*. *Sci Total Environ* 957: 177509.

Blueprint for Speed: How Bacteria Optimise Their Genomes



Computer artwork of rings of double-stranded bacterial DNA.

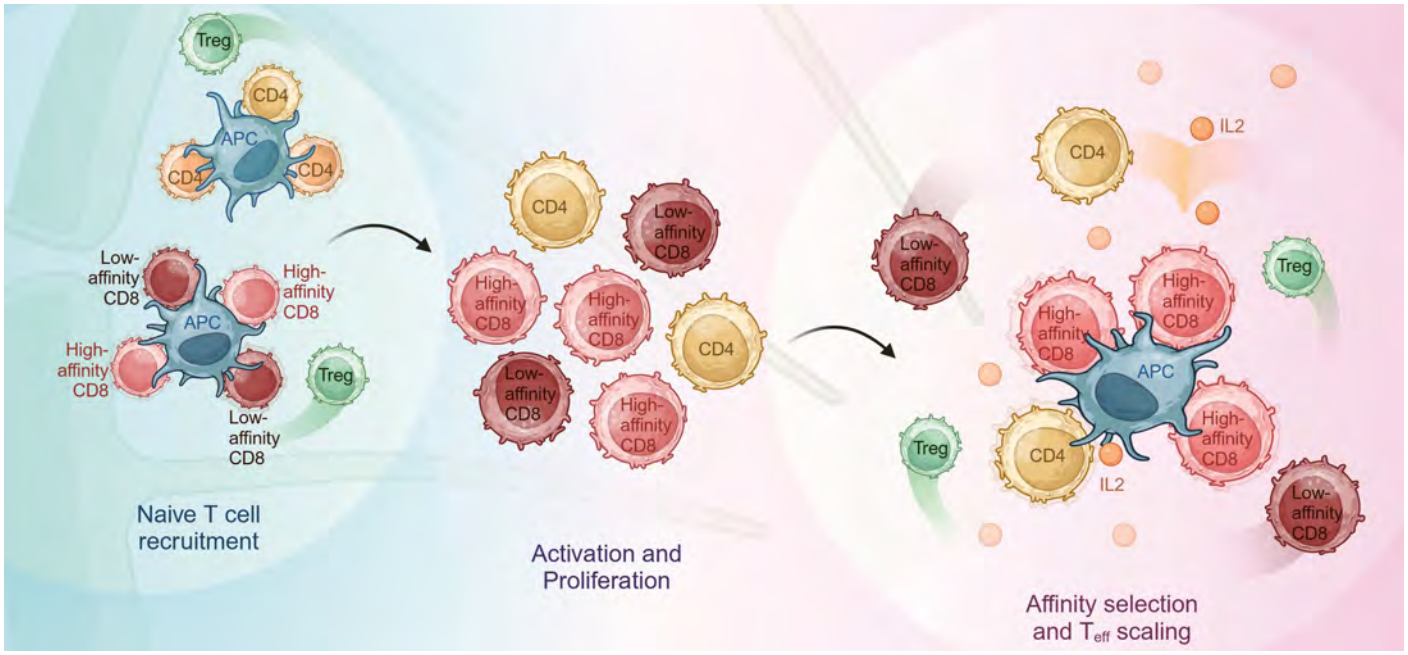
Contrary to long-held assumptions, bacterial genomes are not arranged haphazardly. A team of bioinformaticians from the University of Düsseldorf in Germany and Linköping University in Sweden has revealed that gene positioning along the bacterial chromosome directly supports cellular growth, particularly under fast-replicating conditions.

When bacteria prepare for cell division, they duplicate their circular DNA from a single start point, proceeding in both directions. Genes located closer to this origin are copied earlier and can temporarily exist in higher numbers – up to eight copies during rapid multiplication of cells. This in turn leads to higher expression levels, because they can be read more frequently. Depending on how the demand for the expression of a specific gene changes with growth rate, natural selection drives it to an appropriate position along the chromosome to exploit this gene dosage effect.

By analysing over 4,400 gene families across more than 900 bacterial species, the researchers found a striking pattern: genes with functions that become more critical during fast growth – for example those whose products assemble the bacterial proteins – are consistently positioned near the DNA replication start point.

In contrast, genes that have only limited roles during replication are typically located near the terminus, where they are duplicated later and remain in fewer copies. This genome architecture thus appears to be a product of natural selection and suggests that genome layout is a key factor in microbial fitness.

Hu XP, Brahmantio B, Bartoszek K, Lercher MJ (2025) Most bacterial gene families are biased toward specific chromosomal positions. *Science* 388(6743): 186-191



T-cell activation occurs in two distinct phases.

3.5 TONNES

of the flavouring agent sodium glutamate are produced annually by *Corynebacterium glutamicum* – the equivalent of a freight train with 50,000 wagons and a length of over 850 kilometres. This bacterial workhorse, named Microbe of the Year 2025, was isolated in 1956 during the search for the savoury umami taste and is now vital to the global food industry.

Source: Vereinigung für Allgemeine und Angewandte Mikrobiologie e.V., www.vaam.de

Credits: Max-Planck-Forschungsgruppe / made with Biorender (immune system); The Noun Project (Icons)

Scientists Discover **Second Phase** of T-Cell Activation

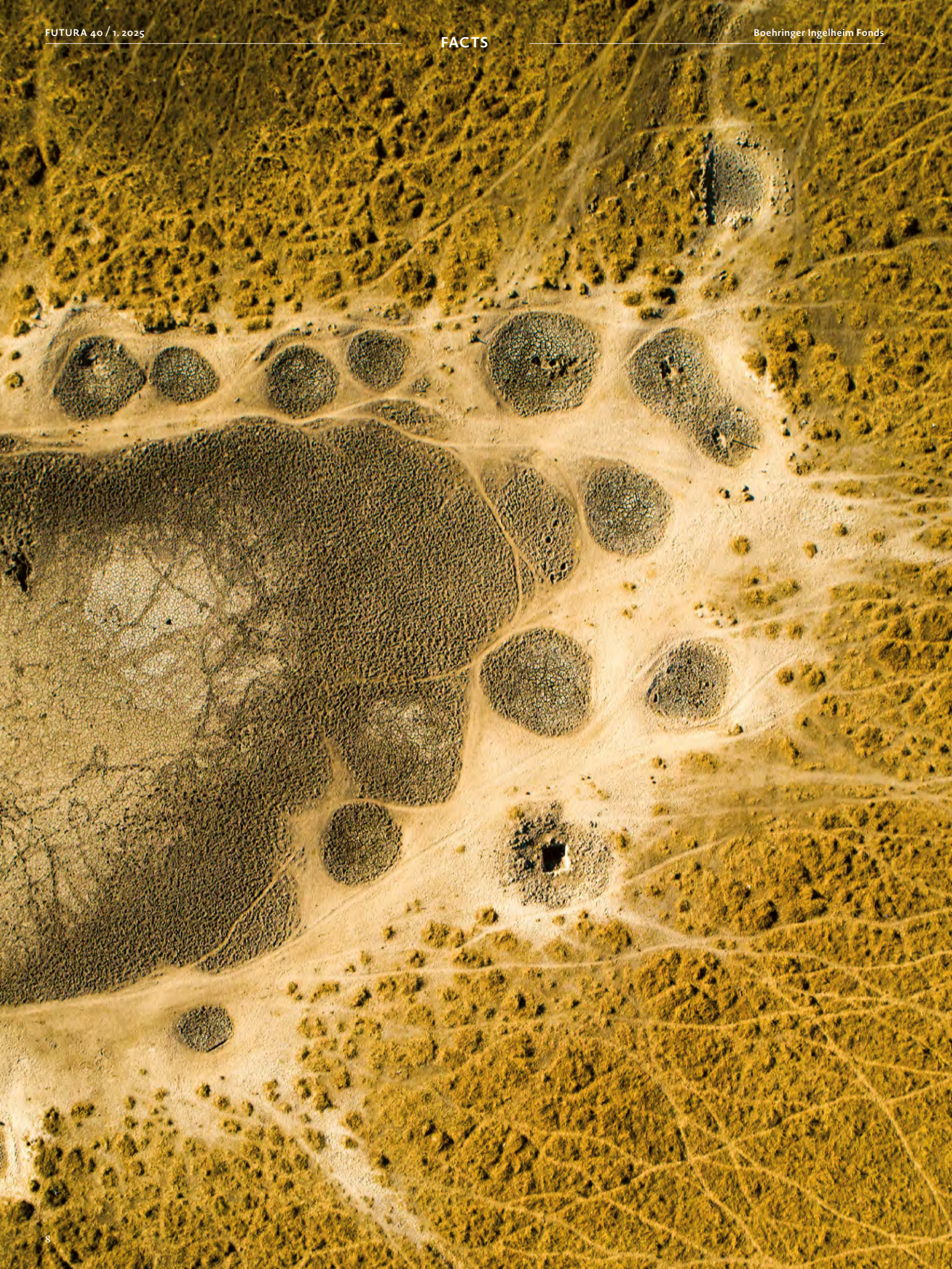
T cells are crucial defence cells in the immune system. But to effectively find and destroy infected cells in the body, T cells with the appropriate specificity must first proliferate, expand, and specialize. This process, known as T-cell priming, begins when T cells encounter dendritic cells in the lymph nodes. These cells present antigens to the T cells and activate them through various signals.

It was long believed that priming occurred in a single, continuous step. Now, the Max Planck Research Group for Systems Immunology in Germany, using advanced microscopy in a viral infection model, has shown that T-cell activation is not a single phase, but a biphasic process with a crucial second round of selection.

While the initial phase of priming activates a broad range of specific T cells, the newly identified second phase selectively expands those T cells that recognise the pathogen most effectively. This ensures an immune response that is optimised for maximum efficiency. In this second phase, occurring days after initial activation, only the most effective T cells – those with strong antigen recognition – are recalled into contact with dendritic cells. There, they receive a critical secondary signal, including interleukin-2 from helper T cells, necessary for robust proliferation and function.

The findings also suggest that T cells enter a transient refractory state after initial activation, regaining responsiveness only two to three days later. This cycling between activation and desensitisation is particularly relevant for chronic infections and cancer, where T-cell exhaustion limits therapeutic success.

Jobin K, Seetharama D, Rüttger L, Fenton C, Kharybina E, Wirsching *et al.* (2025) A distinct priming phase regulates CD8 T cell immunity by orchestrating paracrine IL-2 signals. *Science* 388 (6743): eadq1405



Unveiling Metabolism's Hidden Pathways

By Wynne Parry

Once seen as mere cogs in the biochemical machines that fuel our cells, we now know that metabolites also exert control over other essential life processes. They have emerged as potent signalling molecules that influence cell fate, guide tissue formation, and even shape immune responses. This shift in understanding is transforming the scientific view of metabolism – seeing it not just as a support system, but as a central regulator of life itself. In cancer, stem cell biology, immunology, and other fields, researchers are now working to map the intricate signals these molecules send.

To grow, to maintain themselves, to do much of anything at all, cells need fuel, which they often extract from glucose, a simple sugar. It is an essential process, but cells do not always go about it the same way. After turning glucose into a compound called pyruvate, cells have a choice. Typically, if the cell has access to oxygen, this energy extraction continues in organelles called mitochondria. But some cells – most notably malignant ones – choose to keep more of that pyruvate in the cytoplasm. Jared Rutter, a biochemist at the University of Utah, USA, wondered why.

"The cell has many ways to produce usable forms of energy. And so you could argue it may not matter all that much, whether it does it this way or that way", he says. But it does matter. Experiments in his lab showed that where pyruvate goes – whether it stays in the cytoplasm or travels into the mitochondria – can cause major shifts in the cancer cells' degree of malignancy. In later research, he showed that, in stem cells, pyruvate's path determines their ability to form new tissue.

His results suggested that metabolism somehow controls cell identity and added to mounting evidence that metabolism and its actors accomplish much more than the tasks for which they have long been credited in biology textbooks: extracting energy, building and recycling cellular materials, and removing waste. It turns out that metabolism also controls other, essential life processes, including development, tissue regeneration, and immune function.

And, scientists are finding, metabolism often exerts this influence through metabolites – the starting points, intermediate forms, and end products of cells' biochemical pathways. In addition to their well-known roles in feeding, building, and cleaning cells, metabolites serve a second function as signals that influence non-metabolic processes.

In one context, for example, the metabolite glucose is energy-rich food for cells. In another context, however, glucose conveys a message by interacting directly with proteins in stem cells, altering gene expression and encouraging the growth of mature, or differentiated, tissue.

Discerning metabolites' signalling effects from their better-established metabolic roles can be challenging. But as research increasingly shows, the biological influence of metabolites has been severely underestimated. This realization has led to a "renaissance" of interest, according to Rutter, who discussed this shift at the BIF's International Titisee Conference in March 2025. "Now we have a whole new set of problems and a whole new set of opportunities that many of us are trying to address", he says.

Credit: Adobe Stock / BerndRolauffs

Metabolic Signalling: The Basics

A cell's metabolism is made up of overlapping series of biochemical reactions that cells use to get energy and building materials, create their own structures, and manage waste. Enzymes carry out these reactions; metabolites serve as their starting points, intermediates, and end products.

Researchers are increasingly finding that metabolites can influence life processes distinct from metabolism, from guiding the differentiation of stem cells to facilitating immune responses. To accomplish this, signalling metabolites travel both within and outside of cells. For example, the metabolite alpha-ketoglutarate is produced in the mitochondria, then makes its way to the nucleus where it alters gene expression.

Meanwhile, immune cells called macrophages release another mitochondrial metabolite, succinate, that amplifies an inflammatory response by binding to other cells. Metabolite signalling occurs at the level of organs too: Lipids produced in the liver can affect brain function, as can compounds produced by microbes residing in the gut.

Studies of metabolic signalling generally assess the metabolites present in a sample by using so-called metabolomic tools, such as mass spectrometry. Because metabolites send signals by binding to protein partners, scientists must also search for these interactions and confirm their significance by disrupting the metabolite or the pathway that produces it.

More Than Metabolites: Other Metabolic Signals

Metabolites are not the only features of metabolism that act as signals. A cell's redox state – the equilibrium in electron transfer reactions, which is closely tied to metabolism – can drive its decisions to divide, die, or differentiate. Likewise, reactive oxygen species (ROS), a byproduct of metabolism in mitochondria, appear to be enormously influential.

Research in Navdeep Chandel's lab at Northwestern University, USA, suggests ROS, most notably hydrogen peroxide, are essential for skin development and the creation of memory T cells, which provide long-term immune protection.

Changes in mitochondrial function – specifically declines in energy production and an increase in ROS – have been blamed for ageing. But Chandel argues that changes in the messages mitochondria send may better explain our bodies' decline over the years. "The big challenge is, we don't know whether there's a failure of signalling, or if there's chronic [excessive] signalling", he says.

Discoveries so far have cracked a window onto a new view of how many fundamental biological processes unfold – and how they can go awry. This perspective could one day lead to new ways to intervene in diseases such as cancer.

A second look

The new paradigm took root when a series of studies uncovered an unexpected role for metabolism in the inherited risk for certain cancers. In 2000, researchers studying families whose members suffered from rare head and neck tumours identified the mutation responsible, in a gene that encodes part of the metabolic enzyme succinate dehydrogenase. Two years later, another team traced the mutation responsible for uterine, skin, and kidney growths to a second metabolic enzyme: fumarate hydratase. While not metabolites themselves, these enzymes convert one metabolite to another at different steps within an energy-extracting pathway known as the TCA cycle.

"These were very early, surprising clues from human genetics that the TCA cycle does more than just talk to other metabolic pathways", says Ralph DeBerardinis, a physician-scientistin the Eugene McDermott Center for Human Growth and Development and in Children's Medical Center Research Institute at UT Southwestern, USA, who studies the changes to metabolism that occur in cancer and as a result of genetic errors.

A few years later, genetic studies revealed that mutations in another TCA cycle enzyme, isocitrate dehydrogenase, can drive brain cancer. While these discoveries were pivotal in reshaping how scientists viewed metabolism, they are exceptions, according to Rutter. The vast majority of metabolic signals do not arise from mutations and produce disease. Instead, they help metabolism and, as scientists are learning, many other processes run smoothly. "Metabolic signalling is happening all the time in all of our cells", Rutter says. "It's something that we as scientists need to pay attention to."

Controlling the fate of stem cells

His lab, first using colon cancer cells and later intestinal stem cells, uncovered a metabolically driven switch crucial to cells' identity. That switch hinges on the mitochondrial pyruvate carrier (MPC), a two-protein complex embedded in mitochondria that his lab and others identified. The MPC ferries pyruvate into the interior of mitochondria for further processing. Many cancers, colon cancer among them, reduce the MPC's presence.

To understand why that matters, Rutter's team forced the MPC back into the malignant cells. The result: The cells lost much of their tumour-forming ability along with traits that made them resemble stem cells. The latter change matters because stem-like characteristics tend to make cancer cells more aggressive. In further experiments, they added the MPC to intestinal stem cells, which normally have very little of it. The cells lost some of their stem-like identity and the ability to regenerate the intestinal lining. Inhibiting the MPC dramatically reversed these effects, increasing stem cells' ability to create new tissue.

Taken together, the results suggest the MPC's presence acts as a switch that controls cell identity by shunting metabolism down one path versus another. In its absence, pyruvate stays in the cytoplasm where it is converted to another substance, lactate. This route pushes cells toward a stem-like identity, which can nurture malignancy. Meanwhile, if the MPC is in place, it imports pyruvate into the mitochondria, which processes it differently with the opposite effect on cell identity: inhibiting cancer, promoting differentiation.

As metabolism draws renewed interest, scientists are also rethinking the role of mitochondria.

Researchers have long pointed to hormones, gene expression, and the structure of DNA's packaging as the forces guiding stem cells' decisions about forming new tissue. "Now it's becoming clear that if you manipulate metabolism, it can override all of that", Rutter says. "That's an emerging concept, a paradigm shift in thinking about the role of metabolism in determining cell fate."

His team's discovery of this metabolic switch raised a question: How does altering pyruvate's destination change cells so profoundly? The answer, he believes, likely lies in what happens after the MPC moves pyruvate into the mitochondria. There, pyruvate is converted into acetyl-CoA, which then enters the TCA cycle. Through its eight steps, the TCA cycle generates energy, building materials, and – research increasingly indicates – a suite of influential metabolite signals.

"Perhaps, one of those molecules plays an important role in changing cell behaviour", Rutter has noted. This could push the cell toward a less malignant, more differentiated identity. His lab is now looking to explain the signals by which the MPC's metabolic switch works.

A signalling powerhouse

As metabolism draws renewed interest, scientists are also rethinking mitochondria – the organelles that serve as hubs for these biochemical pathways. Long defined by their role in extracting energy from nutrients, mitochondria are now gaining recognition for a second, equally important job: signalling. Navdeep Chandel, a mitochondrial biologist at Northwestern University, USA, has long championed this broader view. "Instead of you calling mitochondria powerhouses, I call mitochondria signalling organelles", Chandel says.

While mitochondria send out all kinds of signals, a substantial portion of these messages are metabolites, generated through the TCA cycle, which takes place within them. Among the more prominent of the mitochondrial metabolite signals is alpha-ketoglutarate (AKG), which appears to shape stem cell behaviour through indirect means. In research published earlier this year, a team based at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, USA, looked at how stem cells in the lining of the gut decide what kind of tissue to generate. High levels of AKG, they found, favoured the formation of new secretory cells, which secrete hormones and other substances, over new absorptive cells that take in water and nutrients. "You can make one lineage over the other", says Chandel, who wrote a commentary about this research for *Nature*. "They aren't sure how it works, but it's pretty cool."

Scientists do have suspicions, however. AKG appears to regulate enzymes that remove methyl tags from DNA and histones – the proteins around which DNA winds to form chromatin. The loss of these chemical groups alters chromatin structure and, in turn, gene expression. This form of regulation, called epigenetic control, can determine cells' identity and how they behave.

Mutations in the TCA cycle enzymes (succinate dehydrogenase, fumarate hydratase, and isocitrate dehydrogenase), whose discovery cracked open the field of metabolite signalling, tap into this very system. By altering the presence of the signalling metabolites, these changes alter chromatin structure, and consequently, the expression of genes leading to cancer.

Taming cancer through metabolism

Lydia Finley, a cell biologist at MSKCC and contributor to the intestinal stem cell study, became interested in AKG through research she did as a postdoc on the metabolism of embryonic stem cells. Her own interest in metabolism began with a college physiology course. During her graduate school interviews in late 2005 and early 2006, she found others did not share her fascination.

"I would tell people I wanted to study cell metabolism, and professors would say to me, 'Why, that was worked out in the '60s. There's nothing left to do'", she says. Her research has proven otherwise. In the case of AKG, a recent study from her lab suggests that it may play a broad role in cancer, one that extends beyond rare mutations that interfere with its epigenetic activity.

Her team found evidence AKG is important to a tumour-suppressing pathway involving p53, one of the most frequently inactivated genes in cancer. When she and her colleagues restored p53 in pancreatic tumour cells, the cells' metabolism shifted, AKG levels rose, and the cells reverted to a less malignant state. Forcing AKG levels up independently had a similar effect, suggesting that p53 may exert part of its anti-cancer effects through this metabolite. "This is such a source of optimism – the idea that you can take these really horribly aggressive cancer cells and perturb their metabolism to make them less aggressive", Finley says.

New Avenues for Therapies

Researchers have already developed isocitrate dehydrogenase-targeting therapies to treat brain tumours called gliomas and the blood cancer acute myeloid leukaemia (AML). Not all

Cells handle metabolism in different ways, and researchers missed a lot by looking at the average.

links being discovered lately provide such clean targets. Finley and others are attempting to exploit the link between AKG and tumour suppression by increasing AKG. However, in doing so, they risk interfering with the other processes to which AKG contributes. Moreover, they must deliver the metabolite to exactly the right location within cells.

"Absent those mutations [like in IDH-driven cancers], can we leverage metabolism to change who a cancer cell is? That, to me, would be the most exciting frontier", Finley says. But as her own work with AKG demonstrates, doing so will be challenging.

Rutter attempted to use his discovery of the MPC's influence over cell identity to accomplish just that. He and colleagues at a company he co-founded initially sought to reintroduce the MPC into cancer cells, and so force them to shift away from their stem-like, malignant identity. However, their effort failed; the cancer quickly reorganized its metabolism to evade the MPC.

They have since settled on a new condition: pulmonary fibrosis, in which scar tissue accumulates in the lungs, and a new metabolic target, a protein that removes the metabolite lactate from the cell. This lactate exporter appears to be required for the same metabolic switch that happens when the MPC is lost. By inhibiting the lactate exporter, his team hopes to alter the fate and behaviour of certain lung cells and prevent them from forming scar tissue.

Looking Forward

For now, the therapeutic promise of metabolic signalling remains mostly theoretical. Scientists do not yet know enough about the links between metabolite signals and disease, according to DeBerardinis. "We are still laying the groundwork", he says. "But our view of disease is evolving to incorporate the effects of altered metabolic signaling and gene expression. And that could change how we approach treatment."

For Finley, a crucial part of that foundation is better understanding how metabolism varies among cells – especially in rare ones. In earlier decades, researchers studied metabolism by grinding up tissue and combining all the cells it contained. But cells go about metabolism differently, she says.

"We've missed a lot in the past by looking at the average." She sees particular promise in fluorescent, protein-based sensors, already used in neuroscience. With them, she says, scientists could observe metabolism in different types of living cells in real time, contributing to a more precise view of metabolism that makes more precise manipulations possible.

Chandel, meanwhile, calls for better methods to profile metabolites in a sample without needing to target specific ones, and the ability to do studies like this at the single-cell resolution. While such technology is now used to examine gene expression and proteins in single cells, it is not yet capable of doing the same for metabolism. Better understanding how metabolic signals work – that is how they are released and what they target – could make it possible to get at another, bigger question, according to Chandel. "If we have that knowledge, we can design ways to perturb those pathways in living organisms and test whether they're essential for normal physiology", he says, noting that only a select few metabolites are likely to have significant effects.

For his part, Rutter has the broad-scale ambition of determining the interactions between every human protein and its metabolite partners. It is an effort reminiscent of the 20th-century work that charted metabolism's core biochemical pathways. "The foundational discoveries have been made that convince us that this is real", he says. "We now need to build that equivalent map for metabolic signalling."

In the interest of our fellows, we publish only final results online, not descriptions of ongoing projects. Accordingly, this PDF proceeds directly to the PhD Results section.

PhD 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.

Advancing transcriptomic methods to uncover protein-mediated RNA interactions

cf. BIF FUTURA 36 / 2021

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Institute: UK Dementia Research Institute, King's College London, UK
Supervisor: Prof. Jernej Ule

RNA–RNA interactions (RRIs) orchestrate crucial cellular processes, such as RNA interference, transfer RNA to mRNA codon pairing, and small nuclear RNA-mediated splicing events. However, studies of RRIs have focused on double-stranded RNA duplexes resulting from direct base-pairing rather than indirect RRIs mediated by proteins involved in condensate formation *in vivo*, such as enhancer–promoter RNA interactions (EPRIs) in transcriptional condensate initiation. In my PhD project, I investigated the global RRI landscape in the nucleus by using and refining RNA *in situ* conformation sequencing (RIC-seq), a powerful method to map RRIs *in situ* regardless of protein mediators.

To this end, I built a robust, scalable pipeline in the workflow management language Nextflow, which consolidated and fine-tuned more than ten bioinformatics software packages. Compared to existing tools such as RICpipe and Hyb, my pipeline significantly improved the rate and accuracy of chimera discovery while greatly reducing the computational resources required and the entry barrier for users with limited coding experience. I applied this pipeline and RIC-seq to neuronal precursor cells and identified hub RNAs, such as nuclear paraspeckle assembly transcript 1 (*Neat1*) and metastasis-associated lung adenocarcinoma transcript 1 (*Malat1*), which are central to nuclear architecture, and EPRIs critical for transcriptional regulation. In addition, I devised an inducible degradation system on matrin-3 (MATR3), a protein integral to the nuclear matrix that has been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis and frontotemporal dementia. Upon MATR3 depletion, I observed a global increase in EPRI contacts among neuronal development and activity genes, which offers insights into the potential role of MATR3 in priming neurodevelopmental functions.

These findings illuminate how RRIs contribute to gene regulation and chromatin organization, broadening our understanding of the role of RNA in neuronal development. My work also establishes a foundation for further investigations into the involvement of MATR3 in neurodegenerative diseases and RNA-based therapeutic strategies.

PUBLICATIONS

The results of this project have not yet been published.

Azobenzene photoswitches for modulation of bioactivity and super-resolution microscopy

cf. BIF FUTURA 35 / 2020

Benedikt Baumgartner (né Winkler)
Discipline: Chemist, MSc
Institute: Department of Pharmacy, University of Munich (LMU), Germany
Supervisor: Prof. Oliver Thorn-Seshold

Visualization and control of cellular pathways in freely moving animals at subcellular and millisecond resolutions hold great promise for research in health and disease. In the field of photopharmacology, molecular switches are used to manipulate biological targets with high spatiotemporal precision. However, current photopharmaceuticals lack bidirectional on/off switching and light response in the tissue-penetrating near-infrared (NIR) region, hindering their biological application.

In my PhD project, I developed two methods for NIR-induced modulation of bioactivity in live cells and acute brain slices of mice. These methods rely on photoelectron transfer or triplet energy transfer from an NIR-absorbing auxiliary chromophore to an azobenzene, a synthetic molecule that can reversibly change its structure using light. This transfer allows for the near-quantitative *cis–trans* isomerization of the azobenzene, which has not previously been possible. To identify the mechanism responsible, I used femtosecond transient absorption spectroscopy and fluorescence spectroscopy in collaboration with groups at the Leibniz Institute of Photonic Technology and LMU Munich, respectively. Working with a group at Weill Cornell Medicine, I then applied my two methods to an azobenzene photopharmaceutical in murine cell culture and intact tissue to stimulate NIR-induced modulation of metabotropic glutamate receptor (mGluR) activity. During the mechanistic evaluation, we found that azobenzenes can stabilize the organic fluorophores used in super-resolution microscopy and single-molecule fluorescence spectroscopy, outperforming current stabilizing agents. They do this by depopulating the reactive triplet state and rescuing the fluorophores from degradation.

My work shows how azobenzene photoswitches and small-molecule organic fluorophores can benefit each other, whether as bioactivity actuators enabling precise deep-tissue modulation of biological processes or as superior imaging tools in basic biomedical research.

PUBLICATIONS

Thorn-Seshold O, Glembockyte V, Baumgartner B, Wiegand A (2024) Stabilised fluorophores, compositions, methods of preparation, conjugates thereof, and methods of use. US Patent Application 18/737,536

Further results of this project can be discussed on *ChemRxiv*: doi: 10.26434/chemrxiv-2024-vm4n3 and doi: 10.26434/chemrxiv-2023-37sv4

Genome folding principles revealed by advanced light microscopy

cf. BIF FUTURA 35 / 2020

Andreas Brunner
Discipline: Molecular Cell Biologist, MSc
Institute: European Molecular Biology Laboratory, Heidelberg (EMBL), Germany
Supervisor: Prof. Jan Ellenberg

DNA loop extrusion regulates the spatial organization of human chromosomes during interphase and mitosis. Two types of loop extruders are used: cohesins organize chromatin during interphase, while condensins wrap chromosomes into rod-shaped structures during mitosis to allow for their segregation into daughter cells. How the molecule-scale actions of condensins generate the characteristic chromosomal rod shape was not known.

Using LoopTrace, a chromatin tracing method developed in the Ellenberg lab, I observed the folding of individual mitotic chromosomes. I found that condensin-driven extrusion of very large and strongly overlapping loops – and the self-repulsion of these loops – is the fundamental structuring principle of mitotic chromosomes. This self-organization mechanism explains the gradual formation of chromosome rods during mitotic entry and their key mechanical properties. After successful segregation into daughter cells, chromosomes undergo decompaction and adopt the interphase organization, which includes genomically positioned DNA loops that aid gene regulation. This dynamic restructuring is achieved by two cohesin isoforms, but it is not clear how.

To address this question, I systematically quantified the amount of chromatin-bound condensin and cohesin during mitotic exit and correlated this information with high-resolution tracing of DNA. While two condensin isoforms detach from chromatin simultaneously during mitotic exit, the two cohesin isoforms displayed differential DNA binding and loop extrusion. The less abundant cohesin-STAG1 isoform bound DNA first and generated large DNA loops, which the more abundant cohesin-STAG2 isoform sub-structured into smaller loops. The two mitotic condensin isoforms behave similarly during mitotic entry, suggesting that the sequential and hierarchical formation of chromatin loops is a common principle of genome organization during both interphase and mitosis.

PUBLICATIONS

Beckwith KS*, Brunner A*, Morero NR, Jungmann R, Ellenberg J (2025) Nanoscale DNA tracing reveals the self-organization mechanism of mitotic chromosomes. *Cell* 188(10): P2656–2669.E17

Brunner A, Morero NR, Zhang W, Hossain MJ, Lampe M, Pflaumer H *et al* (2025) Quantitative imaging of loop extruders rebuilding interphase genome architecture after mitosis. *J Cell Biol* 224: e202405169

* Shared authorship

HuR is required for innate B-cell homeostasis and function during neuroinflammation

cf. BIF FUTURA 35 / 2020

Dunja Capitan Sobrino
Discipline: Immunologist, MSc
Institute: Toulouse Institute for Infectious and Inflammatory Diseases (INFINITy), France
Supervisor: Dr Manuel-Daniel Diaz Muñoz

In the autoimmune disease multiple sclerosis (MS), the immune system attacks self-antigens in the central nervous system, causing neurodegeneration. B1 cells, a type of B cell involved in innate immunity, can produce high amounts of the anti-inflammatory cytokine interleukin-10 (IL10), which protects against experimental autoimmune encephalomyelitis, a mouse model of MS. Depletion of the RNA-binding protein human antigen R (HuR) in B cells leads to fewer B1 cells and impairs B2 cell activation and germinal centre responses.

While the role of HuR in adaptive B-cell responses is well established, its function in innate B-cell homeostasis and activation remains unclear. I hypothesized that HuR is crucial for the maintenance and activation of innate B cells, particularly in regulating neuroinflammation in experimental autoimmune encephalomyelitis. Using HuR conditional knockout and tamoxifen-inducible Cre mice, I showed that HuR binds and enhances the translation of specific mRNAs involved in tonic B-cell receptor signalling and survival in B1 cells. I demonstrated this using individual nucleotide resolution cross-linking and immunoprecipitation to map RNA-binding sites, RNA sequencing to profile gene expression, luciferase assays and site-directed mutagenesis of HuR-binding sites to determine translation efficiency, and other *in vivo* and *in vitro* experiments. Flow cytometry showed that HuR conditional knockout mice experiencing neuroinflammation had less B-cell infiltration in the brain and produced less IL-10 than control mice. These changes were linked to increased motor paralysis, which I measured through visual assessment. Using flow cytometry and *in vitro* experiments inducing the nuclear factor-κB pathway, I observed that impaired activation of this pathway was the leading cause of the altered production of IL-10.

My work demonstrates that post-transcriptional gene regulation by HuR is essential for innate B-cell homeostasis and regulatory functions during neuroinflammation. My findings underscore HuR's crucial role in regulating innate B-cell functions and offer insights into immune responses in neuroinflammatory diseases like MS.

PUBLICATIONS

Osma-Garcia IC, Capitan-Sobrano D, Mouysset M, Bell SE, Lebeurrier M, Turner M, Diaz-Muñoz MD (2021) The RNA-binding protein HuR is required for maintenance of the germinal centre response. *Nat Commun* 12: 6556

Identifying silencers in the animal genome and their mechanisms of gene repression

cf. BIF FUTURA 35 / 2020

Lorena Hofbauer
Discipline: Molecular Biologist, MSc
Institute: Research Institute of Molecular Pathology (IMP), Vienna, Austria
Supervisor: Dr Alexander Stark

All living cells actively control gene expression to maintain their metabolism and adapt to internal or external changes. Animals use silencers and enhancers, *cis*-regulatory DNA elements (CREs) that repress and activate gene transcription, respectively. Despite the significance of silencers in animal development, our understanding of these elements has been limited due to the challenge of identifying them at large scale.

In my PhD project, I developed a high-throughput reporter assay based on next-generation sequencing, called silencer-seq, to systematically uncover silencers. By screening the entire *Drosophila melanogaster* genome with silencer-seq, I identified more than 800 previously unknown silencers that function through one of three conserved DNA motifs and their corresponding transcription factor (TFs): Suppressor of Hairy wing (Su(Hw)), Phaser, or the uncharacterized silencer-associated factor (Saft) protein. This screening also showed that even though TFs typically cluster together on the DNA to cooperatively regulate their target genes, the silencer-TFs act alone.

By mining public chromatin datasets, I found that nucleosomes closely surround a single silencer-TF motif and lack known epigenetic modifications, unlike the open chromatin at enhancers. This renders silencers invisible to conventional methods for predicting CREs, which are predominantly based on chromatin accessibility and modifications, and challenges the widely held assumption that all CREs share the same chromatin properties. Using proximity labelling mass spectrometry and protein domain truncation, I revealed that Saft mediates repression by recruiting the conserved corepressor protein G9a but that it does not require G9a's histone-modifying activity. Through transcriptomics in Saft-knockout flies, I established that Saft-type silencers repress cell type-specific gene expression programs to protect cell fate during fly development and are crucial for female fertility.

Overall, my discovery of hundreds of novel silencers and their unexpected properties expands our understanding of CREs and will aid future efforts to functionally annotate animal genomes.

PUBLICATIONS

Hofbauer L, Pleyer L-M, Reiter F, Schleiffer A, Vlasova A, Serebreni L *et al* (2024) A genome-wide screen identifies silencers with distinct chromatin properties and mechanisms of repression. *Mol Cell* 84: 4503–4521.e14

Wnt signalling hinders developmental progression at the time of uterine implantation

cf. BIF FUTURA 36 / 2021

Viktoria Holzmann
Discipline: Molecular Embryologist, MSc
Institute: Institute of Molecular Biotechnology (IMBA), Vienna, Austria
Supervisor: Dr Nicolas Rivron

The development of a multicellular organism is coordinated through interactions between the cells of emerging tissues. During uterine implantation in mammals, this process involves interactions among the epiblast, primitive endoderm (PrE), and trophectoderm. Studying the signals exchanged between these tissues is difficult, as mammalian embryos are concealed in the uterus. Alternatively, stem cells that mimic the epiblast, PrE, or trophectoderm can be used to form three-dimensional models that replicate aspects of embryonic development.

To better understand the interactions between the epiblast, PrE, and trophectoderm during implantation, I used publicly available single-cell sequencing data from mouse embryos to predict *in silico* which signals are exchanged among these tissues. This analysis identified the trophectoderm as the main source of canonical Wnt ligands, which are predicted to interact with the corresponding receptors expressed by the epiblast and PrE. In murine embryonic stem cells, the *in vitro* equivalent of the epiblast, Wnt activity is known to prevent differentiation. By culturing PrE stem cells with different Wnt pathway activators and inhibitors, I showed that Wnt activity similarly prevents differentiation of PrE-like cells in the mouse. Moreover, I developed a stem-cell model combining epiblast-like and PrE-like cells that self-organize to mimic the co-development of these tissues during implantation. Experimentally maintaining high cellular Wnt activity during this process blocked some morphological changes typically associated with developmental progression in the model.

Although embryogenesis is arguably a continuous process, some mammalian species, including mice, can undergo diapause, where development is halted right before implantation. My findings could suggest that using Wnt activators to keep stem cells undifferentiated *in vitro* exploits a molecular mechanism used by the embryo during diapause. Similarly, my results could indicate the presence of a developmental checkpoint in which Wnt signals from the trophectoderm act to prevent the epiblast and PrE from differentiating until the embryo is ready to implant. In this way, Wnt-mediated interactions between the emerging tissues of the embryo would regulate synchronized developmental progression at the time of implantation.

PUBLICATIONS

The results of this project have not yet been published.

Role of GADD45 proteins during mouse embryonic heart development

cf. BIF FUTURA 35 / 2020

Gaurav Joshi
Discipline: Molecular Biologist, MSc
Institute: Institute of Molecular Biology (IMB), Mainz, Germany
Supervisor: Prof. Christof Niehrs

Active DNA demethylation orchestrates spatiotemporal gene expression patterns during mouse embryogenesis. The Niehrs lab has shown that growth arrest and DNA damage-inducible 45 (GADD45) proteins actively demethylate DNA by site-specific recruitment of ten-eleven translocation 1 (TET1). However, the genome-wide implications and specific regulatory roles of GADD45 proteins in various physiological contexts are largely unknown.

In my PhD project, I investigated how GADD45 proteins and TET1 influence transcription regulation during embryonic development, using mouse embryonic stem cells (mESCs) as a model system. Using RNA sequencing (RNA-seq) of wild-type (WT) and *Gadd45* triple-knockout (TKO) mESCs, I revealed a significant decrease in the expression of heart development-associated genes in the *Gadd45* TKO mESCs compared with WT mESCs. To assess the impact of this impaired gene transcription, I conducted *in vitro* cardiomyocyte differentiation experiments with WT and *Gadd45* TKO mESCs. I found that cardiac-specific gene expression was lower in the cardiac-differentiated *Gadd45* TKO cells than in the cardiac-differentiated WT cells, which I confirmed using bulk and single-cell RNA-seq. The differentiation of *Gadd45* TKO mESCs also led to a significant decrease in the formation of beating cardiomyocytes. In collaboration with lab colleagues, I used cleavage under targets and tagmentation (CUT&Tag) to identify differences in the TET1 binding patterns and DNA methylation profiles between WT and *Gadd45* TKO mESCs. Notably, TET1 binding increased at downregulated heart development genes in *Gadd45* TKO mESCs. However, this increased binding was not associated with DNA demethylation; instead, these sites were enriched for Polycomb repressive complex (PRC) binding.

I hypothesized that members of the GADD45 protein family modulate the catalytic and non-catalytic functions of TET1 to regulate gene expression during embryonic heart development. In support of this hypothesis, I showed that there were higher levels of H3K27me3 and greater PRC occupancy at repressed heart development-associated genes in *Gadd45* TKO mESCs than in WT mESCs. These novel findings underscore the critical role of GADD45 proteins in inhibiting the non-catalytic effects of TET1 to ensure proper embryonic heart development.

PUBLICATIONS

The results of this project have not yet been published.

Finding a molecular weak spot of SARS-CoV-2

cf. BIF FUTURA 36 / 2021

Florian Kabinger
Discipline: Biochemist, MSc
Institute: Max Planck Institute for Multidisciplinary Sciences (MPI-NAT), Göttingen, Germany
Supervisor: Prof. Patrick Cramer

To replicate its unusually large genome, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the replication-transcription complex (RTC). Some of the RNA processing enzymes in the RTC act as a proofreading mechanism that renders most existing antivirals inactive.

The goals of my PhD project were to decipher the interplay of RTC components and to find ways to inhibit RTC activity. Although I made progress in elucidating the roles of RTC components, I could not reconstitute a complete RTC *in vitro*. Thus, I focused my efforts on finding and characterizing small-molecule tool compounds that can circumvent the proofreading mechanism. I reconstituted the core RTC, which harbours the catalytic subunits for RNA replication, and developed biochemical assays that track RTC behaviour in the presence of small molecules. This enabled me to characterize two promising small molecules that inhibit SARS-CoV-2 replication: molnupiravir, a mutagenic nucleoside analogue; and HeE1-2Tyr, a non-nucleoside inhibitor. Using cryogenic electron microscopy to visualize the core RTC when bound to these small molecules, I deciphered the molecular mechanisms of inhibition.

I found that the RTC cannot chemically distinguish molnupiravir, which resembles endogenous RNA building blocks, from its naturally occurring counterpart, thus explaining how this molecule circumvents the proofreading mechanism. I also showed that HeE1-2Tyr sterically blocks the RTC from binding to RNA, thus preventing RNA replication without being affected by the proofreading mechanism. Interestingly, it is usually difficult to displace large RNA molecules with small molecules because of the size difference, but HeE1-2Tyr overcomes this issue by forming assemblies consisting of three stacked ligand molecules. By uncovering the mode of action of two small molecules that circumvent the RTC proofreading mechanism and thus prevent SARS-CoV-2 replication, my work may facilitate the development of pan-coronavirus inhibitors.

PUBLICATIONS

Kabinger F, Doze V, Schmitzová J, Lidschreiber M, Dienemann C, Cramer P (2025) Structural basis of SARS-CoV-2 polymerase inhibition by non-nucleoside inhibitor HeE1-2Tyr. *Proc Natl Acad Sci USA* 122: e2419854122

Kabinger F*, Stiller C*, Schmitzová J*, Dienemann C, Kokic G, Hillen HS *et al* (2021) Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol* 28: 740–746

* Shared authorship

Investigating the role of C15orf48 as a modulator of innate immune responses

cf. BIF FUTURA 36 / 2021

Julia Kamper
Discipline: Biochemist, MSc
Institute: Gene Center, Ludwig Maximilian University of Munich (LMU), Germany
Supervisor: Prof. Veit Hornung

Lipopolysaccharide (LPS), a component of Gram-negative bacteria, is a potent activator of the innate immune response. C15*orf*48 is among the most strongly induced genes in LPS-stimulated macrophages, but its function is unknown. Based on its homology with NDUFA4, a component of complex IV (CIV) of the electron transport chain (ETC), and NDUFA4L2, a negative regulator of the ETC, I hypothesized that C15*orf*48 is a nuclear factor kappa-B (NF-κB)-inducible negative regulator of the ETC.

The aim of my PhD project was to elucidate its role in innate immunity. Using blue-native polyacrylamide gel electrophoresis, I confirmed that C15orf48 is a component of CIV. I showed that induction of C15*orf*48 expression by LPS stimulation led to a decrease in NDUFA4 levels, which suggests that NDUFA4 is displaced from CIV by C15orf48 and then degraded. Co-immunoprecipitation experiments showed that the proteins are mutually exclusive components of CIV. I detected CIV-associated NDUFA4 long after LPS stimulation, which suggests an equilibrium of C15*orf*48- and NDUFA4-containing CIV. Metabolic flux assays showed that C15*orf*48 overexpression had no effect on CIV activity in THP-1 wild-type cells. I used CRISPR-Cas9 to knock out NDUFA4 and confirmed that loss of its protein results in decreased CIV activity. Surprisingly, overexpression of C15orf48 or NDUFA4 was sufficient to rescue CIV activity. I then investigated the effect of C15orf48 on pro-inflammatory cytokine release using enzyme-linked immunosorbent assay (ELISA). C15*orf*48 overexpression almost doubled the release of tumour necrosis factor (TNF) upon stimulation with Toll-like receptor ligands, but interleukin-6 release was not affected. To uncover the mechanism responsible for the increase in TNF release, I performed a proteomics analysis of the interactomes of C15orf48 and NDUFA4.

My results suggest that C15orf48 function might be explained by an absence of interactions, but further study is required to test this hypothesis. RNA sequencing analysis showed no major effect of C15orf48 on the transcriptome. Thus, the mechanism through which C15orf48 boosts TNF release remains elusive. Although I found that C15orf48 has a moderate pro-inflammatory effect in macrophages, the relevance of this effect *in vivo* remains to be determined.

PUBLICATIONS

The results of this project have not yet been published.

A mechanism for membrane damage-induced T6SS activation in *Pseudomonas aeruginosa*

cf. BIF FUTURA 35 / 2020

Maxim Kolesnikov
Discipline: Biochemist, MSc
Institute: Biozentrum, University of Basel, Switzerland
Supervisor: Prof. Marek Basler

Bacteria compete with each other for access to resources and niches. Gram-negative bacteria frequently challenge other species using the type VI secretion system (T6SS), which delivers toxins across membranes into other cells. The assembly and expression of T6SS components are highly regulated. The main antibacterial T6SS of the human pathogen *Pseudomonas aeruginosa*, H1-T6SS, is assembled in response to outer membrane damage. It produces a characteristic 'tit-for-tat' phenotype in which adjacent cells use their T6SS against each other. This phenotype depends on a pathway that spans the space between the outer and inner membranes and consists of several proteins: a serine/threonine protein kinase (PpkA), a PP2C-family protein phosphatase (PppA), an outer membrane-associated protein (TagQ), a periplasmic protein of unknown function (TagR), and an ABC transporter-like complex in the inner membrane (TagST). These proteins have been proposed to act as a sensor module in which a signal at the outer membrane is transferred to PpkA, but their interactions and the mechanism of signal transfer were unknown.

In my PhD project, I used a combination of biochemical, structural, and microscopy approaches to study the sensor module. After native purification of the sensor module proteins from *P. aeruginosa*, I used western blotting and mass spectrometry to show that TagQ and TagR form a complex. Mass photometry confirmed that the complex has a 1:2 stoichiometry. I found that TagR can form dimers at supraphysiological concentrations, which suggests that binding to TagQ promotes or stabilizes its dimerization. By inducing membrane damage with specific molecules, I showed that the TagQR complex formed immediately. I was also able to detect the formation of a complex between TagQR and PpkA using co-immunoprecipitation. My results support a new working model for H1-T6SS activation where TagQR complexes, formed upon membrane damage, engage two copies of PpkA, resulting in its activation and leading to assembly of the T6SS.

PUBLICATIONS

Brüderlin M, Kolesnikov M, Röthlin F, Lim RYH, Basler M (2025) *Pseudomonas aeruginosa* assembles H1-T6SS in response to physical and chemical damage of the outer membrane. *Sci Adv* 11(10): eadr1713

A stem cell zoo uncovers intracellular scaling of developmental tempo across mammals

cf. BIF FUTURA 36 / 2021

Jorge Lázaro Farré
Discipline: Developmental Biology, MSc
Institute: European Molecular Biology Laboratory, Barcelona, Spain
Supervisors: Prof. Miki Ebisuya, Dr Vikas Trivedi

The speed of embryonic development varies considerably across mammalian species. Differences in the tempo or duration of developmental processes influence organism size and shape, thereby serving as an important mechanism of evolutionary change. The aim of my PhD project was to understand how mammals exhibit species-specific developmental rates despite using seemingly indistinguishable molecular toolkits. To this end, I investigated the timing of axis segmentation in the vertebrate body. The rate at which body segments form is controlled by the segmentation clock, the oscillatory gene expression found in the pre-somitic mesoderm cells. The period of the oscillations differs greatly across vertebrates, but these temporal differences are challenging to study due to the difficulties in obtaining and comparing embryos from different animal species.

To overcome these challenges, I created a 'stem cell zoo' of pluripotent stem cells from various mammals to develop *in vitro* models of the segmentation clock. By differentiating pluripotent stem cells into pre-somitic mesoderm cells, I studied the developmental tempo of six species: humans, mice, rabbits, cattle, rhinoceros, and marmosets. Using bioluminescent measurements of an exogenous reporter under the control of the core clock gene *HES7*, I quantified the oscillations across species and revealed that their period scaled with the duration of embryogenesis rather than with body weight. The biochemical kinetics of *HES7* showed clear scaling with the species-specific period of the segmentation clock. However, experiments measuring oxygen consumption rate and glycolic acidification showed that cellular metabolic rates were not similarly correlated. Instead, the expression of genes involved in biochemical reactions scaled with the period of the segmentation clock, providing evidence of the transcriptional regulation of developmental tempo.

My findings provide further insights into the mechanisms used by evolution to generate morphological diversity across species.

PUBLICATIONS

Lázaro J, Sochacki J, Ebisuya M (2024) The stem cell zoo for comparative studies of developmental tempo. *Curr Opin Genet Dev* 84:102149

Lázaro J, Costanzo M, Sanaki-Matsumiya M, Girardot C, Hayashi M, Hayashi K *et al* (2023) A stem cell zoo uncovers intracellular scaling of developmental tempo across mammals. *Cell Stem Cell* 30:938–949.e7

Studying the effects of host microbial mutualism on early immune development

cf. BIF FUTURA 35 / 2020

Steven Misztal
Discipline: Biologist, MSc
Institute: Department for BioMedical Research, University of Bern, Switzerland
Supervisor: Prof. Andrew Macpherson

At birth, the newborn intestine is rapidly colonized by bacteria, which shapes early immune development during a critical phase known as the window of opportunity. During this window, the immature adaptive immune system relies on specialized immune cells, called γδ T cells, that are especially abundant in barrier tissues such as the gut, lungs, and skin. After a mouse has weaned, γδ T cells expressing the Vγ7 chain dominate its intestine and have a key role in maintaining gut health.

I wanted to better understand the development of Vγ7 γδ T cells and explore the populations and functions of γδ T cells pre-weaning, both of which were poorly characterized. I found that their composition undergoes a lasting shift during weaning. To explore this shift, I studied germ-free and γδ T cell-deficient mice, focusing on the influence of genetics and gut bacteria – particularly *Lactobacillus reuteri*, an early colonizer in both mice and humans. I showed that introducing *L. reuteri* alone or even a highly diverse bacterial community to mice before weaning had little effect on the development of their gut immune system. Instead, gut maturation was driven largely by genetically 'hard-wired' processes within the host that occur around the onset of weaning. I showed that before weaning, γδ T cells were highly diverse, with some populations carrying markers associated with bacterial defense. After weaning, Vγ7 γδ T cells became dominant and promoted intestinal homeostasis. Gene expression analysis suggested a role for these cells in strengthening the intestinal barrier and regulating immune responses. I then used single-cell RNA sequencing to characterize the development and functional maturation of Vγ7 γδ T cells early in life. Notably, I found that both processes occurred independently of microbiota composition.

Based on my findings, I propose that intestinal maturation during weaning contributes to the transition of γδ T cells from a defense-oriented state to a maintenance role, a switch that helps the intestine adapt to new dietary and environmental challenges as solid food is introduced. My results help us to better determine which immune features in the intestine might be shaped by bacteria early in life, which could potentially have implications for health.

PUBLICATIONS

The results of this project have not yet been published.

Function, proteostatic control, and cellular assembly of the mammalian RNA exosome

cf. BIF FUTURA 34 / 2019

Tsimafei Navalayeu
Discipline: Molecular Biologist, MSc
Institute: Max Perutz Labs, University of Vienna, Austria
Supervisor: Prof. Stefan Ameres

The RNA exosome is an evolutionarily conserved protein complex involved in the maturation and degradation of most types of coding and non-coding RNA in eukaryotes. Despite its essential role, its assembly and proteostatic control are poorly understood.

In my PhD project, I examined the contribution of each component of the RNA exosome to its assembly, function, and proteostatic control. I established a dual-guide RNA targeting strategy combined with the inducible CRISPR-Cas9 system (iCas9) in mouse embryonic stem cells (mESCs). Western blot analysis revealed that Cas9 induction led to a progressive and consistent depletion of targeted proteins. To investigate whether the loss of individual subunits affects exosome integrity, I targeted each component in parallel using iCas9 and then monitored the reciprocal depletion of other components using western blot analysis.

I found a specific pattern of protein co-destabilization that suggested a stepwise cellular assembly of the RNA exosome. I validated the existence of assembly intermediates using immunoprecipitation. To determine whether unassembled RNA exosome subunits are eliminated by the ubiquitin proteasome system, I combined inducible depletions with proteasome inhibitors. Subsequent western blot analysis confirmed that proteasome inhibition led to the stabilization of unassembled subunits. Finally, I assessed whether the assembly intermediates retain any functional activity by measuring RNA abundance of an RNA exosome target, promoter upstream transcripts (PROMPTs). Reverse-transcription quantitative PCR analysis following inducible depletions revealed that loss of the catalytically inert exosome core and the nuclear catalytic subunits led to the accumulation of PROMPTs, with the depletion of exosome component 1 (Exosc1) showing the weakest effect among the core components. This indicates that the assembly intermediates do not retain the RNA exosome's function in PROMPT turnover.

By providing detailed insights into the cellular assembly, proteostatic control, and function of the RNA exosome in mESCs, my work establishes a framework for future studies on the molecular basis, biological implications, and biomedical relevance of specific proteostatic mechanisms that control RNA exosome homeostasis.

PUBLICATIONS

Further results of this project can be discussed on *BioRxiv*: doi: 10.1101/2025.03.14.643291

Calling for dendritic cell backup in the fight against infection

cf. BIF FUTURA 36 / 2021

Mariana Pereira da Costa
Discipline: Immunologist, MRes
Institute: The Francis Crick Institute, London, UK
Supervisor: Prof. Caetano Reis e Sousa

When influenza A virus infects the lungs, the immune system rapidly ramps up its defences by mobilizing immune cells. Conventional dendritic cells (cDCs) act as sentinels that capture viral material and present it to cytotoxic T cells, thereby triggering an antiviral response. These rare, short-lived cells arise from precursor cDCs (pre-cDCs), which exit the bone marrow (BM) and seed tissues. But how do pre-cDCs get where they are needed? And how does the body know when to send more?

During my PhD project, I studied how this trafficking is regulated both at steady state and during infection. I showed that at steady state, C-X-C chemokine receptor type 4 (CXCR4) acts as a retention signal, anchoring pre-cDCs in the BM. As pre-cDCs differentiate, CXCR4 is downregulated, allowing mature cells to exit into the blood and migrate to tissues. Reis e Sousa lab members and I found that infection with influenza A virus triggers a rapid accumulation of pre-cDCs in the lungs that is essential for sustaining antiviral T-cell immunity. This surge is due not to local proliferation but to systemic redistribution: the BM increases the output of pre-cDCs, which migrate to the infected lung. My key discovery was that type I interferons (IFN-Is), produced early in infection, drive this process by inducing C-C chemokine receptor type 2 (CCR2) on pre-cDCs. I showed that CCR2 expression enables efficient egress of pre-cDCs from the BM in response to CCR2 ligands produced in the inflamed lung. Mice lacking the IFN-I receptor failed to upregulate CCR2 and had impaired pre-cDC mobilization.

By revealing a tightly coordinated, systemic response to infection, my work provides insights into how the dendritic cell network is rapidly tuned during infection. My findings also create possibilities for enhancing immune responses through targeted manipulation of precursor trafficking, which could inform future vaccine and immunotherapy design.

PUBLICATIONS

Pereira da Costa M, Minutti CM, Piot C, Giampazolias E, Cardoso A, Cabeza-Cabrerizo M *et al* (2023) Interplay between CXCR4 and CCR2 regulates bone marrow exit of dendritic cell progenitors. *Cell Rep* 42: 112881

Cabeza-Cabrerizo M*, Minutti CM*, Pereira da Costa M*, Cardoso A, Jenkins RP, Kulikauskaite J *et al* (2021) Recruitment of dendritic cell progenitors to foci of influenza A virus infection sustains immunity. *Sci Immunol* 6: eabi9331

* Shared authorship

Regulation of the ubiquitin ligase Ubr1 during protein quality control

cf. BIF FUTURA 35 / 2020

Niklas Peters
Discipline: Biochemist, MSc
Institute: Heidelberg University Biochemistry Center (BZH), Germany
Supervisor: Prof. Sebastian Schuck

Eukaryotic cells control the degradation of aberrant or damaged proteins using ubiquitin ligases. When protein misfolding occurs in yeast, regulator of quality control (Roq1) binds ubiquitin protein ligase E3 component N-recognin 1 (Ubr1) as a substrate mimic. This profoundly changes Ubr1's enzyme activity and switches its substrate specificity from substrates with N-terminal degrons to misfolded proteins. However, how the intrinsically disordered protein Roq1 reprograms Ubr1 was not known.

In my PhD project, I biochemically dissected the molecular mechanism underlying Roq1 control of Ubr1 using a defined *in vitro* system. By combining *in vitro* binding experiments using biolayer interferometry and enzymatic assays that monitored Ubr1 substrate ubiquitination, I demonstrated that Roq1 governs the ubiquitination of Ubr1 substrates through two cooperating motifs. Via its N-terminus, Roq1 binds Ubr1 as a pseudo-substrate that mimics substrates with N-terminal degrons, thereby controlling their ubiquitination. Via its hydrophobic motif, Roq1 enhances the ubiquitination of endogenous Ubr1 substrates with internal degrons and of misfolded proteins. This motif, which I identified through an unbiased genetic screen in yeast, consists of at least four hydrophobic amino acid residues that form a second binding interface with Ubr1, which triggers the recognition and ubiquitination of Ubr1 substrates. I used biolayer interferometry and co-immunoprecipitation experiments to show that these two motifs allow Roq1 to bind Ubr1 heterobivalently, thereby increasing its binding affinity.

Whether Roq1 promotes substrate ubiquitination by catalysing ubiquitin chain initiation, chain elongation, or both is not clear. To focus only on chain initiation, I replaced wild-type ubiquitin with an elongation-deficient variant in *in vitro* ubiquitination assays. I demonstrated that Roq1 enhances the ubiquitin transfer by increasing the efficiency of ubiquitin chain initiation. Given the essential role of ubiquitin ligases in disease, the Roq1 bipartite mode of action could inspire the design of new therapeutic modulators for other ubiquitin ligases.

PUBLICATIONS

Peters N*, Kanngießer S*, Pajonk O, Salazar Claros R, Hubbe P, Mogk A, Schuck S (2025) Reprograming of the ubiquitin ligase Ubr1 by intrinsically disordered Roq1 through cooperating multifunctional motifs. EMBO J 44: 1774–1803

* Shared authorship

Control of B-cell development and function by the SAGA complex

cf. BIF FUTURA 34 / 2019

Theresa Pinter
Discipline: Immunologist, MSc
Institute: Research Institute of Molecular Pathology (IMP), Vienna, Austria
Supervisor: Prof. Meinrad Busslinger

The development of B cells from stem cells to plasma cells (PCs) is tightly regulated by cell stage-specific gene expression and repression. The Spt-Ada-Gcn5 acetyltransferase (SAGA) complex drives gene expression via its histone acetyltransferase (HAT) module, but its direct target genes in mammalian cells are largely unknown. Using a CRISPR-Cas9-based screen, I identified several components of SAGA–HAT that are important for PC formation. I investigated the role of the module in B-cell development using conditional mutagenesis in mice. Deleting transcriptional adaptor 3 (*Tada3*), which is required for SAGA–HAT integrity, in mature B cells revealed that no PCs could be generated upon immunization. However, this also led to the loss of germinal centre (GC) B cells, highly active cells that precede the PC stage, indicating an earlier role for the module in the immune response. *In vitro* activation studies confirmed that *Tada3*-deficient cells were initially activated but failed to proliferate, narrowing down when SAGA–HAT is necessary for B-cell development.

To identify genes that are directly controlled by the module, rather than those indirectly affected by the altered expression of direct target genes, I used acute protein degradation. This allows for rapid depletion of the protein of interest and no delay in the resulting change to gene expression. I generated an auxin-inducible degron-tagged *Tada3* mouse that carries a modified *Tir1* gene under the control of a ubiquitously expressed promoter. This system allows the TIR1-containing E3 ubiquitin ligase complex and the tagged TADA3 protein to interact only in the presence of auxin, thereby promoting rapid ubiquitination and proteasomal degradation of TADA3. I depleted TADA3 in the mouse and detected the resulting changes in nascent transcripts in GC B cells using total RNA sequencing.

My results show that SAGA–HAT controls key GC B-cell transcription factors and activation genes. Due to the ubiquitous expression of *Tada3*, the identification of target genes of SAGA–HAT is not limited to B cells but can be extended to any other cell type – thus representing a valuable tool for other disciplines.

PUBLICATIONS

Pinter T, Fischer M, Schäfer M, Fellner M, Jude J, Zuber J *et al* (2022) Comprehensive CRISPR-Cas9 screen identifies factors which are important for plasmablast development. *Front Immunol* 13: 979606

Mechanical disengagement of the cohesin ring

cf. BIF FUTURA 35 / 2020

Martina Richeldi
Discipline: Biophysicist, MRes
Institute: The Francis Crick Institute and University College London, UK
Supervisors: Dr Frank Uhlmann, Dr Maxim Molodtsov

The cohesin complex is essential to life. Its dysfunction leads to an imbalance of genetic material, which is a hallmark of cancer. Cohesin forms a proteinaceous ring that is thought to link sister chromatids by entrapping DNA and counteracting the forces generated by the mitotic spindle. Although the biochemical mechanisms of action of the cohesin complex have been investigated, its biophysical role remains unexplored. Indeed, cohesin's function is, at its core, a physical one: like an elastic band, it holds sister chromatids together, allowing the chromosomes to position themselves symmetrically before segregation. Achieving this balance of forces is critical to the generation of two daughter cells with equal amounts of genetic material.

The objective of my PhD project was to understand the biophysical principles governing sister chromatid cohesion and segregation by studying the cohesin complex. Using real-time single-molecule fluorescence visualization, I showed that individual cohesin molecules can entrap double-stranded and single-stranded DNA as well as establishing interactions between two double-stranded DNA molecules. This finding supports a topological mechanism in which one cohesin holds two DNA molecules by entrapping them inside its ring. I probed the maximum tension that cohesin can withstand by performing force measurements with optical tweezers on individual cohesin complexes bound to either one or two DNA molecules. By covalently closing the three main interfaces in the ring, I found that cohesin's mechanical stability is determined by the weakest domain, the hinge. Forces of ~20 piconewtons disengaged cohesin at the hinge and released DNA, indicating that ~40 cohesin molecules are sufficient to counteract spindle forces.

By focusing on both the biochemical and biophysical aspects of this process, my work paints a mechanistic picture of how cohesin maintains the spindle-generated tension during mitosis while dynamically loading, unloading, and translocating along DNA. These findings will aid our understanding of how cohesin mutations observed in disease affect the mechanical stability of sister chromatid cohesion.

PUBLICATIONS

Richeldi M, Pobegalov G, Higashi TL, Gmurczyck K, Uhlmann F, Molodtsov MI (2024) Mechanical disengagement of the cohesin ring. *Nat Struct Mol Biol* 31: 23–31

Investigating the mechanism of host cap snatching by influenza RNA polymerase

cf. BIF FUTURA 36 / 2021

Alexander Helmut Rotsch
Discipline: Biochemist, MSc
Institute: Max Planck Institute for Multidisciplinary Sciences (MPI NAT), Göttingen, Germany
Supervisor: Prof. Patrick Cramer

Influenza is a viral epidemic disease that causes between 290,000 and 650,000 deaths worldwide every year. During infection, the virus protects its mRNA from the host cell's innate immune response by stealing the host mRNA 5' cap structure. In this process, called cap-snatching, the influenza virus RNA polymerase (FluPol) cleaves capped 10–15 nucleotide-long 5' fragments of host transcripts. These RNA fragments are used to prime viral transcription and to produce viral mRNA products. Cap-snatching is thought to occur co-transcriptionally on host RNA polymerase II (Pol II), because FluPol binds an elongation-specific phosphorylation state of the intrinsically disordered Pol II C-terminal domain (CTD). Despite the importance of co-transcriptional cap-snatching for viral transcription, its molecular mechanism remains elusive.

In my PhD project, I aimed to biochemically and structurally characterize FluPol during the cap-snatching process. Using size exclusion chromatography of the assembled complexes *in vitro*, I showed that CTD phosphorylation is sufficient to recruit FluPol to the elongating Pol II. With fluorescently labelled RNA in a gel-based assay, I showed that the elongation factor 5,6-dichloro-1-β-d-ribofuranosylbenzimidazole sensitivity inducing factor (DSIF) stimulates the endonuclease activity of FluPol *in vitro*. Then, I stalled FluPol while it was cap-snatching the 5' cap from the elongating Pol II. Using cryo-electron microscopy to study the complex before and after RNA cleavage, I showed that FluPol interacts directly with the elongating Pol II on the surface of the Pol II core and with DSIF. Within the complex, DSIF positions the endonuclease of FluPol near the RNA exit channel of Pol II, consistent with the endonuclease stimulation observed in my biochemical assays. My cryo-EM structures also showed that upon RNA cleavage, the capped RNA primer rearranges, directing the capped RNA 3'-end toward the FluPol polymerase active site for viral transcription initiation.

My results suggest that FluPol recognizes both the capped RNA and the protein features of an elongating Pol II. Furthermore, the newly discovered interaction surfaces between FluPol and the elongating Pol II complex might aid the identification of new targets for antiviral strategies.

PUBLICATIONS

Further results of this project can be discussed on *BioRxiv*: doi: 10.1101/2024.08.11.607481

The fitness effect of *glpT* during *Salmonella* infection is context-dependent

cf. BIF FUTURA 36 / 2021

Noemi Santamaria de Souza
Discipline: Microbiologist, MSc
Institute: Institute of Microbiology, Department of Biology, ETH Zurich, Switzerland
Supervisor: Prof. Wolf-Dietrich Hardt

Animals have evolved to recognize microbe-associated molecular patterns to reduce the damage caused by pathogens. As the features recognized by the immune system are often crucial to microbe survival, the genes encoding them face opposing selective pressures that can result in conflicting genetic variants or antagonistic pleiotropy. Since the metabolic requirements of bacterial pathogens depend on the host's diet and vary drastically between infection sites and stages, I hypothesized that examples of antagonistic pleiotropy exist in metabolic genes. A study from the Hardt group on the within-host evolution of the enteric pathogen *Salmonella* Typhimurium showed that glycerol-3-phosphate transporter (*glpT*) was mutated in over 70% of isolated clones. In addition, *glpT* mutations are more prevalent in clinical and wild isolates and laboratory strains of *Salmonella*.

In my PhD project, I set out to determine why such mutations are selected despite the high level of *glpT* conservation in *Enterobacteriaceae*. My bioinformatics analyses confirmed that *glpT* is highly conserved in *Escherichia*, *Salmonella*, *Klebsiella*, and *Shigella*, which infect millions of people and animals worldwide. To compare the fitness of *Salmonella* strains to that of the wild type, I used fitness-neutral genetic tags with quantitative PCR to measure their abundance during infection in mice. This allowed me to test in parallel several strains that were deficient in different genes in the *glpT* and related pathways. I showed that the fitness advantage of *gltP* disappeared when mice were fed a low-phosphate diet. However, I observed this effect only in *Salmonella* growing in the intestinal lumen; cells replicating inside macrophages required *glpT*, meaning that the phenotype was also dependent on whether the microbe replicated intracellularly or extracellularly.

My results suggest that enteric bacterial pathogens' adaptation to their host's diet and distinct niches results in antagonistic pleiotropy in metabolic genes. My results could be useful to the discovery of dietary interventions and other targeted treatments for microbial infections.

PUBLICATIONS

Santamaria de Souza N, Cherrak Y, Andersen TB, Vetsch M, Barthel M, Kroon S *et al* (2025) Context-dependent change in the fitness effect of (in)organic phosphate antiporter *glpT* during *Salmonella* Typhimurium infection. *Nat Commun* 16: 1912

Structural and mechanistic insights into human tRNA splicing and disease mutations

cf. BIF FUTURA 34 / 2019

Samoil Sekulovski
Discipline: Biochemist, MSc
Institute: Institute of Biochemistry, Goethe University Frankfurt, Germany
Supervisor: Dr Simon Trowitzsch

Transfer RNAs (tRNAs) are essential for protein synthesis and cellular health, and errors in their biogenesis are linked to severe neurological diseases. The heterotetrameric human tRNA splicing endonuclease (TSEN) catalyses intron removal from precursor tRNAs (pre-tRNAs), a critical step in tRNA maturation. Mutations in TSEN and its partner, cleavage factor polyribonucleotide kinase subunit 1 (CLP1), cause pontocerebellar hypoplasia (PCH), a group of fatal disorders characterized by brain underdevelopment and motor impairments. The molecular basis of TSEN function and how disease mutations disrupt its activity were poorly understood. My PhD research integrated structural, biochemical, and biophysical approaches to uncover the mechanisms of TSEN-mediated pre-tRNA splicing. Using cryo-electron microscopy (cryo-EM), I showed that TSEN subunits engage intron-containing pre-tRNA, precisely positioning substrates for cleavage through protein-RNA interactions. My structural studies confirmed that while the core structure of TSEN is evolutionarily conserved, novel structural elements that are unique to humans enhance subunit interactions and pre-tRNA binding. My cryo-EM structures also showed that a base pair between the pre-tRNA's anticodon stem and the intron stabilizes an intronic helix, thereby facilitating splice site cleavage. Using differential scanning fluorimetry measurements, I showed that TSEN complexes with PCH-associated mutations had reduced thermal stability. In addition, I used pull-down experiments to show that the flexible interaction between TSEN and CLP1 is a hotspot for mutations that disrupt TSEN-CLP1 assembly and stability.

My findings advance our understanding of tRNA splicing and its links to neurodegeneration and help to explain how TSEN dysfunction contributes to PCH pathogenesis.

PUBLICATIONS

Sekulovski S, Sušac L, Stelzl LS, Tampé R, Trowitzsch S (2023) Structural basis of substrate recognition by human tRNA splicing endonuclease TSEN. *Nat Struct Mol Biol* 30: 834–840

Sekulovski S, Trowitzsch S (2022) Transfer RNA processing – from a structural and disease perspective. *Biol Chem* 403: 749–763

Sekulovski S*, Devant P*, Panizza S*, Gogakos T, Pitiriciu A, Heitmeier K *et al* (2021) Assembly defects of human tRNA splicing endonuclease contribute to impaired pre-tRNA processing in pontocerebellar hypoplasia. *Nat Commun* 12: 5610

* Shared authorship

Innate immune effectors against tick-borne orthoflaviviruses

cf. BIF FUTURA 35 / 2020

Felix Streicher
Discipline: Molecular Biotechnologist, MSc
Institute: Virology Department, Institut Pasteur, Paris, France
Supervisor: Dr Nolwenn Jouvenet

Tick-borne orthoflaviviruses (TBOVs) are a global health concern, as several members of this family cause fatal neurological diseases in humans. The innate immune response, especially interferon (IFN)-dependent signalling pathways, is essential for fighting viral infection. Although IFNs in the type I and III families activate the same signalling cascade after binding their respective receptors, they stimulate different genes. Which genes the two IFN families activate and how they modulate TBOV infection are poorly understood.

In my PhD project, I aimed to identify the IFN-inducible effectors essential for a functional response against TBOVs and to investigate their mechanism of action. I monitored the protective potential of type I and III IFNs against tick-borne encephalitis virus (TBEV) in human cell lines of different tissue origin. By analysing viral protein levels, viral genome replication, and production of infectious virions, I showed that type I and III IFNs interfered with TBEV replication to different extents depending on the tissue of origin. With the Douam lab (National Emerging Infectious Diseases Laboratories, Boston, MA, USA), I established a TBOV infection model in mice with a knockout for the IFN type I or type III receptor. Analysing the viral RNA load in different tissues confirmed the importance of both IFN families for controlling TBOV replication *in vivo*. To assess the role of single IFN-induced effectors in restricting TBOV replication in human cell lines, I screened a guide-RNA library targeting around 2,000 IFN-stimulated genes and found around 20 proteins with potential antiviral activity. Using virological and biological methods coupled to loss- and gain-of-function strategies, I identified one of the proteins, interferon alpha-inducible protein 6 (IFI6), as a key player in IFN type I- and type III-driven responses to TBOVs. Further analyses revealed that IFI6 blocks an early viral replication step.

My work presents new perspectives for targeting weak points in the life cycle of TBOVs and other orthoflaviviruses, which could aid the development of new antivirals for pathogens of global concern.

PUBLICATIONS

Further results of this project can be discussed on *BioRxiv*:
doi: 10.1101/2025.04.06.647422

An end-to-end model of active electrosensation

cf. BIF FUTURA 36 / 2021

Denis Turcu
Discipline: Neuroscientist, MPhil
Institute: Columbia University in the City of New York, NY, USA
Supervisor: Prof. Larry Abbott

Humans rely so much on vision that it can be hard to imagine sensing the world differently. But most organisms primarily use other sensory information, even something as far removed from our senses as electricity. The weakly electric fish *Gnathonemus petersii* localizes and identifies objects by sensing distortions in a self-generated electric field. It can determine the resistance and capacitance of an object, despite these distortions being small and highly dependent on the object's distance and size. Investigating this sensory system can provide insights into neural computations for sensory processing more broadly, and it can expand our understanding of the complex stimuli in our environment that we do not perceive.

In my PhD project, I constructed a model of the responses of the electroreceptors found on the fish's skin, using experimental data collected by my collaborators. I also developed a model of the electric fields generated by the fish and the distortions due to objects of different resistances and capacitances. These models provide an accurate and efficient method for generating large artificial datasets simulating fish interacting with a wide variety of objects. Using these datasets, I trained artificial neural network (ANN) models, representing brain areas downstream of electroreception, to extract the 3D location, size, and electrical properties of objects. I found that the model performance qualitatively matches fish behaviour. I also showed that the performance improves significantly if the ANN operates in two stages: first estimating object distance and size, and then using this information to extract electrical properties.

These results suggest a function for sensory feedback pathways from higher to lower stages of the fish's electrosensory processing circuitry and highlight the potential of end-to-end modelling for studies of sensory processing. By analogy with other sensory systems, notably the visual system, my work provides broader insights into their computational principles. In addition, I am using my electric field model to investigate social interactions in groups of weakly electric fish, with the potential to reveal the neural circuits and computations involved in collaborative group behaviour.

PUBLICATIONS

Turcu D, Zadina AN, Abbott LF, Sawtell NB (2025) An end-to-end model of active electrosensation. *Curr Biol* 35(10): P2295–2306.E4

Reconstituting a mitochondrial membrane contact site

cf. BIF FUTURA 35 / 2020

Barbora Turpin Knotkova
Discipline: Biochemist, MSci
Institute: Heidelberg University Biochemistry Center (BZH), Germany
Supervisor: Prof. Michael Meinecke

Mitochondria are enclosed by a double membrane. Although the outer membrane is relatively flat, the inner membrane is intricately folded, forming subcompartments called cristae that are characteristic of this organelle. Crista membranes ensure efficient cellular respiration and confine the apoptotic messenger protein cytochrome c. However, the molecular mechanisms that shape the inner membrane into cristae are not well understood. It has been suggested that contact sites between the mitochondrial outer and inner membranes have an important role in this process, but their involvement has not been directly shown.

The aim of my PhD project was to gain insight into the molecular details of the best-described mitochondrial membrane contact site that is conserved in eukaryotes, the mitochondrial intermembrane space bridging (MIB) complex. I purified the core subunits of this complex from the baker's yeast *Saccharomyces cerevisiae* – mitochondrial contact site and cristae organizing system complex subunit 60 (Mic60) and sorting and assembly machinery 50 (Sam50) – and reconstituted them *in vitro* into model membranes. Using co-migration assays of Mic60 reconstituted in nanodiscs with Sam50 incorporated into liposomes, I demonstrated that these two yeast proteins are sufficient for the formation of membrane contact sites. This was surprising, as studies in human cells have suggested that a third subunit, mitochondrial cristae protein 19 (Mic19), is required for membrane tethering. Indeed, when I probed for direct interaction between the human orthologues of Sam50 and Mic60, I could not demonstrate any binding *in vitro*, which confirms the need for additional proteins in humans. My experiments with orthologues from the thermophilic fungus *Chaetomium thermophilum*, however, proved that direct binding between Sam50 and Mic60 is conserved among fungal species.

By revealing differences in the architecture of the MIB complex between fungal and mammalian mitochondria, my work paves the way for further structural investigation and manipulation of this mitochondrial membrane contact site in cells from different domains of life. This will allow us to better dissect the function of this supercomplex in the sculpting of one of the most intricately shaped membranes of the cell.

PUBLICATIONS

The results of this project have not yet been published.

Transcription bodies regulate gene expression by sequestering CDK9

cf. BIF FUTURA 35 / 2020

Martino Ugolini
Discipline: Molecular Cell Biologist, MSc
Institute: Center for Integrative Genomics, University of Lausanne (UNIL), Switzerland
Supervisor: Prof. Nadine Vastenhouw

Transcription occurs within specialized nuclear bodies, the structure and function of which are not fully understood. For transcription to happen, components of the transcriptional machinery need to find their target gene and assemble in a sequential manner. The prevailing hypothesis is that transcription bodies locally concentrate these components, thereby facilitating more efficient gene expression. However, this model is supported by only limited experimental evidence.

During my PhD project, I investigated two large transcription bodies that form during early zebrafish development. They represent a novel model that is more powerful than transcription bodies in cell culture. After specifically disrupting the formation of these transcription bodies, I used enriched SH-linked alkylation for the metabolic sequencing of RNA (SLAM-Seq) to measure the expression levels of nascent transcripts and thereby assess the impact of this perturbation on gene expression. My findings revealed that disrupting these structures causes widespread misregulation of gene expression, including both downregulated genes – which are expected if transcription bodies were to increase transcription efficiency – and, unexpectedly, upregulated genes. For transcription to occur, the polymerase is first paused in an initiating state and then released into the elongating state through phosphorylation by cyclin dependent kinase 9 (CDK9). I demonstrated that the upregulated genes, which are poised for transcription, are prematurely expressed in the absence of the two transcription bodies. These two bodies sequester CDK9, stalling many genes in a poised state. When the bodies are disrupted, CDK9 is redistributed to smaller, paused transcription bodies, which then become elongating, leading to premature expression of these paused genes.

My research has thus uncovered a novel role for transcription bodies in regulating gene expression. In addition to enhancing transcription efficiency locally, they inhibit transcription elsewhere by sequestering essential transcriptional machinery.

PUBLICATIONS

Ugolini M, Kerlin MA, Kuznetsova K, Oda H, Kimura H, Vastenhouw NL (2024) Transcription bodies regulate gene expression by sequestering CDK9. *Nat Cell Biol* 26: 604–612

Kuznetsova K, Chabot NM, Ugolini M, Wu E, Lalit M, Oda H *et al* (2023) Nanog organizes transcription bodies. *Curr Biol* 33: 164–173

Memory re-evaluation driven by reward re-exposure in *Drosophila melanogaster*

cf. BIF FUTURA 35 / 2020

Carolin Warnecke
Discipline: Neuroscientist, MSc
Institute: Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
Supervisor: Dr Johannes Felsenberg

Memories are constantly shaped by new experiences, with some being strengthened, modified, devalued, or forgotten. In maladaptive memory disorders such as post-traumatic stress disorder or substance use disorders, altering memories could be beneficial. Understanding the mechanisms of memory updating is therefore crucial for potential therapeutic applications. Associative learning occurs when a neutral cue (or conditioned stimulus, CS), such as an odour, is paired with a reward or punishment (or unconditioned stimulus, US), like sugar or an electroshock.

In my PhD project, I investigated how re-exposure to the US leads to memory update in *Drosophila melanogaster*. Unlike CS-based memory updating, using the US allows us to modify all CS-US associations formed with a specific US. After training flies to associate an odour with sugar, I found that re-exposure to sugar or artificial activation of protocerebral anterior medial dopaminergic neurons (PAM-DANs) led to memory devaluation across multiple odour associations. I hypothesized that PAM-DANs, which signal reward information during learning and whose artificial activation leads to memory devaluation, were also responsible for sugar-mediated memory devaluation. However, blocking PAM-DANs during sugar re-exposure did not prevent memory devaluation, suggesting that PAM neurons are not required. Even though memory devaluation through increased DAN activity and sugar re-exposure produces similar behavioural outcomes, my findings indicate that they rely on different mechanisms involving distinct neural circuits. Despite investigating potential candidates, I could not identify the neurons responsible for sugar-mediated memory devaluation. However, I found that re-exposing starved flies to sugar led to memory devaluation, while re-exposing flies in a different context left the memory intact. This context dependency contrasts with artificial DAN activation, which causes memory reduction regardless of context.

Overall, my work reveals two distinct pathways for memory update: one driven by dopaminergic activity and the other by context-dependent re-exposure to the reward. These findings highlight the complexity of memory modification, providing new insights into how reward memories are updated and suggesting additional circuits yet to be explored.

PUBLICATIONS

The results of this project have not yet been published.

MD FELLOWS 2024 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 institution and city for at least ten months to work in an internationally renowned laboratory.

In 2024, 13 fellows were granted an MD fellowship.

The role of NATF-1-mediated N-terminal acetylation in meiosis

Nina da Costa Huber
Duration: 08/24–07/25
Project at: Harvard Medical School, Blavatnik Institute, Department of Genetics, Boston, MA, USA
Supervisor: Prof. Monica Colaiacovo
Home University: University of Munich (LMU)

Understanding the metabolic interaction between the host and pancreatic tumours

Kian Moritz Eghbalian
Duration: 09/24–08/25
Project at: Massachusetts Institute of Technology (MIT), Koch Institute for Integrative Cancer Research, Cambridge, USA
Supervisor: Prof. Matthew Vander Heiden
Home University: German Cancer Research Center (DKFZ)

Decoding the clonal architecture and dynamics of altered haematopoiesis due to bone marrow failure

Jonas Gudera
Duration: 05/24–11/25
Project at: Boston Children's Hospital, Division of Hematology/Oncology, MA, USA
Supervisor: Prof. Vijay G. Sankaran
Home University: University Hospital of Munich (LMU)

Mosaic chromosomal alterations in B-cell clonality and their impact on the biology of mature blood cells

Bendix Richard Hempel
Duration: 11/24–08/25
Project at: Dana-Farber Cancer Institute, Hematological Malignancies, Boston, MA, USA
Supervisor: Prof. Benjamin Ebert
Home University: Heidelberg University Hospital

Differential wiring in the molecular layer as substrate for cerebellar learning

Adrian Alexander Holtrup
Duration: 04/24–03/25
Project at: Harvard Medical School, Department of Neurobiology, Boston, MA, USA
Supervisor: Prof. Wei-Chung Allen Lee
Home University: University of Münster

The transition of membranous to amyloid-type Lewy bodies in patient-derived neurons

Viktoria Klein
Duration: 04/24–03/25
Project at: University College London (UCL), UK Dementia Research Institute, UK
Supervisor: Dr Tim Bartels
Home University: TUM University Hospital

Unraveling WOLFRAMIN: Oligomeric distribution, atomic structure, and protein interactions

Lukas Kruckenhauser
Duration: 04/24–04/25
Project at: Yale University School of Medicine, Department of Pharmacology, New Haven, CT, USA
Supervisor: Prof. Barbara E. Ehrlich and Prof. Moitrayee Bhattacharyya
Home University: University of Munich (LMU)

Characterizing the role of tumoural LRP1 in breast cancer progression

Anthea Lovisa
Duration: 03/24–02/25
Project at: The Rockefeller University, Meyer Laboratory of Systems Cancer Biology, New York, NY, USA
Supervisor: Prof. Sohail Tavazoie
Home University: University of Freiburg

Slit/Robo pathway in tumour innervation and metastasis

Elisabeth Lea Maria Maichel
Duration: 11/24–10/25
Project at: The Rockefeller University, Meyer Laboratory of Systems Cancer Biology, New York, NY, USA
Supervisor: Prof. Sohail Tavazoie
Home University: Heidelberg University Hospital

Dissecting genetic variation in IKZF1 predisposing to pediatric B-ALL

Luana Miria Messa

Duration: 01/25–12/25

Project at: Boston Children's Hospital, Division of Hematology/Oncology, MA, USA

Supervisor: Prof. Vijay Sankaran, Dr Lara Wahlster

Home University: University Hospital of Munich (LMU)

Characterizing the molecular mechanisms of ageing in the enteric nervous system

Clara Sökler Sanchez

Duration: 03/24–09/25

Project at: Stanford University, Arc Institute, Palo Alto, CA, USA

Supervisor: Prof. Christoph Thaiss

Home University: Technical University of Munich (TUM)

Impact of gene mutations in Aplasia Cutis Congenita

Maya Liv Viktoria van Bon

Duration: 10/24–09/25

Project at: Massachusetts General Hospital, Cutaneous Biology Research Center, Laboratory for Inflammation, Wound Healing and Fibrosis, Charlestown, USA

Supervisor: Dr Alexander G. Marneros

Home University: University of Mannheim

Stem cell-derived 3D human neuromuscular junction model of amyotrophic lateral sclerosis

Justus Wieland

Duration: 04/24–03/25

Project at: Boston Children's Hospital, Center for Life Science, MA, USA

Supervisor: Prof. Clifford J. Woolf

Home University: Heidelberg University

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Crowns of Research: The Art and Heart of PhD Hats

Got a fabulous PhD hat? Don't let it go unnoticed! Snap a picture and send it to kirsten.achenbach@bifonds.de.

Philine Guckelberger

My PhD hat feels like the culmination of my journey, a reflection of perhaps the most influential part of my PhD: my colleagues, who became some of my closest friends along the way. These are the people who crafted my hat with love, taking notes over the years and capturing moments, highlighting how much more than just a work environment a lab can be. They were the ones who celebrated with me and commiserated through tough days (often with Fireball, which made it onto the hat). That's why I love all the photos that cover my hat – they keep the memories of this intense time alive.

Credit: Philine Guckelberger; The Noun Project (Icon)

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.

New screen finds several hundred hidden silencers

Just like humans, cells sometimes need silence – for example, silence from genes that are not needed at a given time or place. So far, we know just a few of the gene regulatory elements, called silencers, that help cells to achieve this. Lorena Hofbauer, in the group of Alexander Stark at the IMP in Vienna, Austria, has changed that: She found 837 silencers and uncovered why we did not find them before.

She took the DNA from fruit fly cells and used a technique called STARR-seq, which normally finds enhancers, and adapted it so that it detects silencers. For the new method – silencer-seq – she built a reporter gene containing a powerful enhancer so that it is always on. Then she took small fragments of fly DNA and looked to see which ones silenced the reporter. A total of 837 hits were classified as silencers. To verify her screen, she put 64 representative elements through a control screen: overall, 80% were confirmed. Just like enhancers, though, they worked if inserted far from the reporter, before or after it, and even in reverse order. Next, she successfully verified for several of the hits that they also silence the genes next to their normal position in the cell. Taken together, this shows that silencer-seq is a valid screen for silencers.

Analysis revealed that the new silencers can be divided into three groups, each containing a different motif, only two of which (Su(Hw) and Phaser) were already known to be associated with a transcription factor (TF). Both factors were known to help space nucleosomes on the DNA. About the third motif, the highly conserved DLM3, little was known. Lorena now showed DLM3 to be a powerful silencing element bound by the TF zinc-finger protein CG11247. To reflect its function, the TF was renamed Saft, short for silencer-associated factor in transcriptional repression. From additional experiments in living flies, Lorena and her co-authors think it is likely that Saft safeguards cell type identity during development.

But there is more: while known gene-controlling elements are in loosely packed areas of DNA with few nucleosomes, the team found the silencers hidden in tightly packed areas, lacking the typical chromatin marks of active elements as well as repressive marks. This makes them nearly invisible to current methods for identifying gene regulatory elements.

It is possible that the new silencers actively shape DNA packaging, making it harder to access the genes around them. However, their own transcription factors can act, as they likely bind by slipping into a tiny gap between the nucleosomes right at their motif. It might help that all three silencer TFs act alone and may therefore be smaller, compared to enhancers, where often several TFs act together.

This study delivers a powerful tool to identify silencers. At the same time, it challenges many assumptions about gene regulation. We may have missed a whole layer by assuming that enhancers and silencers look and work the same. Now we know how to look for silence.

REFERENCE

Hofbauer L, Pleyer L-M, Reiter F, et al. (2024) A genome-wide screen identifies silencers with distinct chromatin properties and mechanisms of repression. Mol Cell 84: 4503–4521, doi. org/10.1016/j.molcel.2024.10.041

Lorena Hofbauer, fellow 12/19–08/22

A genetic tug-of war can help to fight pathogens

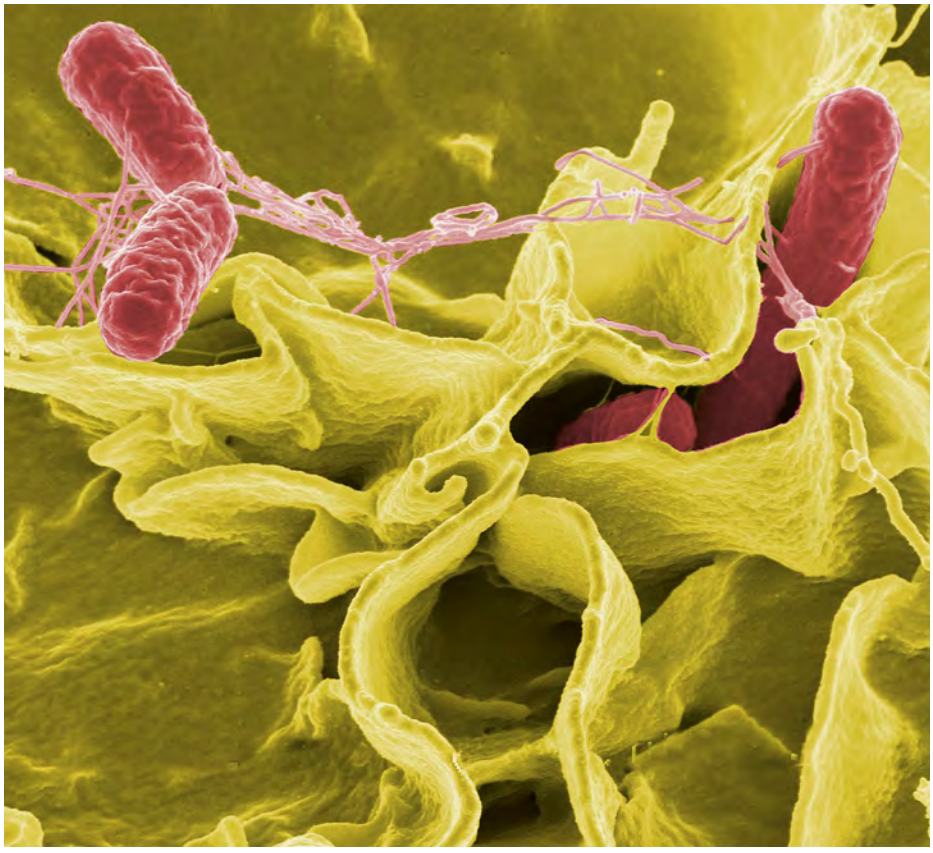
If a genetic trait helps you thrive in one environment but hinders you in others, it results in a tug-of-war of opposing evolutionary pressures called antagonistic pleiotropy (AP). Pathogens often switch environments during their infectious cycle and thus are likely to be subject to AP. Some therapeutics already use the concept of AP by creating pressure inside the body to select for strains with genes that make the pathogen more visible to the immune system.

Now, Noemi Santamaria de Souza from the group of BIF alumnus Wolf-Dietrich Hardt at ETH Zurich, Switzerland, has identified a gene involved in metabolism which shows AP: *glpT*, a highly conserved gene found in many pathogens. Strains found in the lab, the wild, and the clinic often have a non-functional versions. It exchanges inorganic phosphate (P_i) for glycerol-3-phosphate (G3P) or, as Noemi found, vice versa. P_i is mainly used for energy production, but too much of it is toxic. G3P is needed for membranes, as a carbon and phosphate source, and in stress response pathways.

Noemi infected mice with *Salmonella enterica*, a common cause of food-borne illnesses, with either a mutant strain without *glpT* or with the wild type (wt). Over four days, she monitored the ratio of the strains in the faeces. On day one, there were ten times more mutants, indicating that the strain without *glpT* was fitter. In later stages, the ratio decreased to about 1:1, indicating the wild type was more fit. When Noemi fed the mice with low P_i chow or disabled other P_i transporters, the wild type was as fit as the mutant. Adding G3P to the water had the same effect. It seems having *glpT* is only bad during early stages of infection in the gut, where phosphate levels are high. In these conditions, *glpT* imports too much P_i, and the pathogen suffers.

So why has the gene for *glpT* not been lost for good? Usually, by day two of a Salmonella infection, the immune system gets going and kills the bacteria in the gut lumen. Some bacteria escape this by invading macrophages and replicating inside them. From there, they can recolonize the gut. Inside macrophages, that offer very little P_i and actively try to kill them, Salmonella needs *glpT* to survive.

This study explains how the niches in the body push *Salmonella* to lose or retain *glpT* function in a genetic tug-of-war, especially since such mutations can occur during infection. It also shows that pathogens can and should be fought differently depending on where they are, and what they need. Noemi has now given us the blueprint for how to study AP in metabolism – the first step in exploiting the concept to design better therapies.



Salmonella Typhimurium (red) invading cultured human cells.

REFERENCE

Santamaria de Souza N, Cherrak Y, Bill Andersen T, Vetsch M, Barthel M, Kroon S et al. (2025) Context-dependent change in the fitness effect of (in)organic phosphate antiporter *glpT* during *Salmonella Typhimurium* infection. *Nat Comm* 16:1912, doi: 10.1038/s41467-025-56851-5

Noemi Santamaria de Souza, fellow 05/21–04/23

Perspectives

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 reach their current position.

Peter Steinecke
Occupation: Patent attorney
Fellowship: 11/91–10/94

From breeding potatoes to protecting ideas

Peter Steinecke studied biology in Cologne, Germany. In 1994, he completed his PhD, in which he pioneered the use of ribozymes to inhibit gene expression of a virus (Tomato spotted wilt virus) *in vivo*. Here, he first came into contact with intellectual property (IP). After his PhD, he genetically engineered potatoes for a plant breeding company. From 1996 to 2002, he trained as a patent attorney and worked for one year in the patent department of Janssen Pharmaceutica (J&J) in Belgium. In 2004, he founded his first independent patent law firm, specialising in life sciences. He is certified as a German and European patent attorney and registered before the Unified Patent Court (UPC). He is now a partner in his second firm, Witthoff Jaekel Steinecke in Cologne, Germany.

How did you get from working on plant viruses to being a patent attorney?
During my first job, I had time on my hands while I waited for the potatoes to grow, and so I read *all* the job ads. A Munich patent law firm was looking for a scientist with experience in ribozymes – my doctoral field – to assist with patent litigation involving the company of Nobel Laureate Thomas Cech. Curious, I decided to meet the supposedly arrogant patent attorneys. To my surprise, the biotech patent law atmosphere felt much like academic research.

What were the beginnings like?
It was exhausting and exhilarating: My mentor was Hans-Rainer Jaenichen, one of the top biotech patent attorneys in Europe. I got to work at the forefront of biotech inventions: the first patent disputes on recombinant interferons, chimeric antibodies, humanized mice, and ribozymes to name a few. But I needed a high frustration tolerance, and all of us trainees were workaholics – just like back in the lab. My early drafts came back with virtually every section revised. After a year, they needed only minor edits, and I was ready to travel to clients alone. It helped a lot that I had the same kind of argumentative flow as my mentor.

What exactly do you do when someone comes with an idea, a discovery?
I try to understand what exactly they have done and what makes it new or useful. Then we look at what can be protected, what steps should be taken quickly, and what to avoid. Especially for individuals and start-ups, I advise on how to secure their interests – for example, by determining who the true inventors are, who owns the invention, and how ownership can be established. Many stipend holders don't realize they are, in principle, independent inventors, because they are not directly employed by their institution.

What do you enjoy about it, and what should applicants bring?
Watching and supporting a company's growth from early R&D through the final drug product, taking care of IP due diligence in negotiations with pharma companies, is like raising a child until marriage – and more rewarding than only addressing isolated legal questions. I have autonomy, creative freedom, and an informal work culture that echoes academic life. To succeed, you should bring common sense, childlike curiosity, strategic thinking like playing chess, meticulousness, a strong sense of responsibility, and a high frustration tolerance.

Your most challenging case so far?
Last year, we saved an emeritus scientist from having to pay back years of licence fees and instead won him future licence payments exceeding €20 million.
In the 1980s, out of curiosity, the scientist developed an antibody-producing cell line and deposited it in a repository. Later, a company used it to develop a drug against multiple sclerosis and negotiated a licence agreement that lasted from 2006 onward. Recently, the drug was approved in the US and Europe and appears to be becoming a blockbuster. At this point, the company contested the original agreement and asked for repayment. This case shows how basic research can lead to clinical applications – and that precautionary measures should be taken to protect your scientific contributions from exploitation by third parties.

Any further words to our fellows?
I am committed to supporting the BIF community. I would be pleased to offer my expertise as a mentor and advisor to startups and potential BIF inventors, free of charge and separate from my firm. BIF supported me – now I want to give back.

Credit: private

Profiles

Professor Volker Haucke
Institute: Leibniz Institute for Molecular Pharmacology (FMP), Berlin, Germany
Fellowship: 08/94–03/97

Volker Haucke has received the Gottfried Wilhelm Leibniz Prize, Germany's most important research funding award. Every year, the German Research Foundation honours up to ten outstanding scientists and academics with the award, and bestows on them up to €2.5 million to expand their research opportunities and help them employ particularly qualified early-career researchers. Eligible for nomination are researchers from all fields who work in Europe or at a German research institute abroad. Awards go to people "who have demonstrated superior achievements in their research areas both in a national and an international context and who show exceptional promise for future top-level accomplishments". Volker studies endocytosis and has gained new insights into the interaction between neuronal protein complexes, lipid signals, and mechanisms that break down the cell's own components. Based on his findings, he has already developed inhibitors of important enzymes in lipid metabolism, thereby raising hopes of new anti-cancer drugs. This is the sixth time a BIF fellow has received this honour.

Professor Yohanns Bellaiche
Institute: Institut Curie, France
Fellowship: 09/95–08/98

Professor Edward Lemke
Institute: Institute for Molecular Biology, University of Mainz, Germany
Fellowship: 02/03–03/05

Yohanns Bellaiche and **Edward Lemke** have both been elected as members of the Academia Europaea. They were among the 329 people who were invited to join the pan-European science academy in April 2025. Formed in 1988, it has a membership of 5,500 eminent scholars from European countries across all disciplines.

Ida Jentoft
Institute: Research Institute of Molecular Pathology (IMP), Vienna, Austria
Fellowship: 05/19– 02/22

Ida Jentoft has been awarded an HSFP long-term fellowship, which supports three years of training in a new area of research in an outstanding laboratory in another country. Selected projects should be groundbreaking and have the potential to advance knowledge in the applicants' field of study, or to open a new approach to a research problem. Ida is moving from the MPI for Multidisciplinary Sciences in Göttingen, Germany, to the group of Andrea Pauli at the IMP in Vienna, Austria, to study mechanisms of translation reprogramming during embryonic diapause.

Professor Gregor Weiss
Institute: University of Zurich, Switzerland
Fellowship: 12/16 –01/19

Gregor Weiss is now an assistant professor at the University of Zurich, Switzerland, within the Institute of Medical Microbiology, where he continues his study of uropathogenic *E. coli*. He is supported in this over the next five years by a Starting Grant of CHF 1.8 million from the Swiss National Science Foundation. SNSF Starting Grants represent the SNSF's highest level of career funding. Following a two-stage evaluation, the SNSF awarded a total of 61 grants this year. The total funding amounts to CHF 105.4 million.

Professor Wolf-Dieter Hardt
Institute: ETH Zurich, Switzerland
Fellowship: 05/93 –05/95

Wolf-Dieter Hardt has been elected as an EMBO member, one of the 69 outstanding life scientists so honoured in 2025. He studies the infection biology of *Salmonella Typhimurium*, a key cause of foodborne illness. The now more than 2,100 members (among them more than 30 BIF fellows) guide the execution of EMBO programmes and activities, for example by evaluating funding applications, serving on the EMBO Council and committees, and contributing to initiatives such as training, policy, outreach, and mentorship.

Ines Drinnenberg
Institute: Center for Scientific Research (CNRS), Paris, France
Fellowship: 12/07–05/10

Ines Drinnenberg has been awarded an ERC Consolidator Award for her project 'CHROMOGENEVO: The impact of chromatin on genome organisation, function, and evolution', in which she focuses on holocentric chromosomes – a unique organisation where the anchoring of the fibres of the mitotic spindle extends over the entire length of the chromosome, and not over a single region. This peculiarity could transform our understanding of evolutionary mechanisms, as well as genetic abnormalities related to chromosome segregation. The ERC Consolidator Grants offer up to €2 million over a period of five years and encourage groundbreaking research.

A BIF fellow's guide to ...

Basel

Travelling is fun – especially with insider tips from locals! In each FUTURA, the BIF invites one or more fellows to show you around their city. In this edition, your guides are Anja Xu Schwartzlose and Antonio Falasconi.

Facts and Figures

Country: Switzerland
Population: approx. 190,000
Area: 37 km²
Students: more than 13,500
Famous for: the world-renowned Art Basel fair, its vibrant cultural scene, and as one of Europe's leading pharmaceutical hubs
Website: www.basel.com

Best Sights

Altstadt: Basel's charming old town features cobbled streets, colourful medieval architecture, and hidden courtyards.

Foundation Beyeler: A modern art museum with top-tier exhibitions and cultural events.
Kunstmuseum: Switzerland's oldest public art museum, with works from the Renaissance to contemporary masters.
Tinguely Museum: Interactive museum showcasing the kinetic sculptures of Swiss artist Jean Tinguely along the Rhine.

Activities

Swimming in the Rhine River (Summer): Lend a Wickelfisch bag to float by the cathedral spires and keep your things dry for the 30-minute journey.

Basel Autumn Fair – Herbstmesse (Fall): Switzerland's oldest inner-city fair, spreading across seven squares for 550 years, where Ferris wheels compete with hot chestnuts.
Basel Christmas Markets (Winter): Hundreds of wooden chalets serving flame-grilled salmon, cheese fondue, and *Glühwein* beneath the Gothic cathedral.

Where to stay

Hotel Märthof Basel: Elegance on the market square with Art Deco flair and a rooftop terrace.

Hotel Brasserie Au Violon: A former prison turned into a hotel and restaurant, with medieval stone walls and a peaceful courtyard.
Hotel Merian Basel: Combines Swiss hospitality with stunning river views.

Restaurants

Rhyschänzli: A beloved institution in St. Johann, serving traditional fare and regional dishes with an Italian touch.
1777 Basel: A trendy old-town café-bar in the historic Schmiedenhof, offering custom salads, gourmet burgers, and coffee from their own Basel roastery.

Klara: An international food hall where La Manufacture's burgers meet global kitchens – from Tibetan dumplings to Ethiopian injera – all under one roof.
Markthalle: Forty international vendors serve global cuisines beneath one of the world's most spectacular reinforced concrete domes.

Nightlife

Holzpark Klybeck: A rustic, riverside venue with open-air bars, art installations, and spontaneous DJ sets in a relaxed atmosphere.
Nordstern: A converted cargo ship turned electronic music club on the Rhine, known for top DJs and its scenic rooftop terrace.
Rhine riverbank: a popular spot for drinks, barbecues, and socializing under the sun.

Anja Xu Schwartzlose is 25 years old and comes from Denmark. Her supervisor is Professor Flavio Donato. **Antonio Falasconi** is 28 years old and comes from Italy. His supervisor is Prof. Silvia Arber. Both Antonio and Anja study at the University of Basel, Switzerland.

New Team Members at the BIF

Since the start of 2025, the BIF has gained three new team members. **Simone Freimund** is a familiar face: she has been with the sister foundation BIS since 2014. There, she supported grant holders and organized events. In January, she joined the BIF, where she looks after current fellows as part of the PhD support team. "For the past ten years, I shared an office with Sandra and experienced the more personal style of BIF. That, and the fellows I met at BIS events, made it an easy decision when the chance arose." Outside of work, she enjoys family life, cooking, and listening to music.

In April, **Celine Gresch** took over administration of the travel grant programme from Vera Schlick. She also organizes reviews for the PhD selection and helps to organize the International Titisee Conferences. On top of that, she supports the third foundation, the Siblings Boehringer Ingelheim Foundation for the Humanities. Because of her love of languages, she studied German, French, and history. "I greatly enjoy communicating with and helping the different people from all over the world", she says. In her spare time, Celine likes to go running or biking, reading, and learning languages – such as right now: Dutch

In May, **Dr Anna Sichler** joined the selection team, where she supports the preselection of PhD candidates and searches for referees. Together with Jan Kullmann, she runs the travel grant programme. She recently completed her PhD in Munich, exploring the role of the microbiome in colorectal cancer, as well as in liver regeneration. "I'm endlessly curious, and the diversity of projects is incredibly inspiring. I love helping people grow." Outside of work, Anna loves climbing and storytelling – e.g., during improv theatre and pen-and-paper games.

A warm welcome to all three! We are happy to have you!

Upcoming Events

30 August–5 September
Progress Seminar, Hirschegg, Austria
Progress seminar for current PhD fellows working in Europe, held in scenic Hirschegg (Kleinwalsertal), Austria. On the agenda: project presentations by all participants, discussion of career topics, and guided hiking tours in the surrounding Alps. Further details will be provided with the invitation.

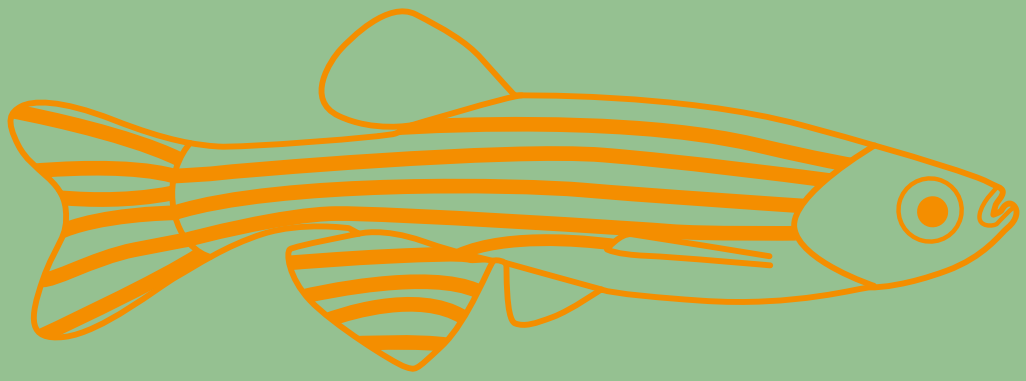
8–12 October
131st International Titisee Conference, Titisee, Germany
The 131st ITC, titled "Warm, cold, and life – the impact of temperature on physiology and behaviour", will be chaired by Jan-Erik Siemens (Heidelberg) and James Poulet (Berlin), Germany, and aims to bring together scientists who study different levels and aspects of temperature to link thermal sensation, thermal adaptation/acclimation, and core physiology, and to foster the idea of systems thermobiology.
ITC participation is by invitation only.

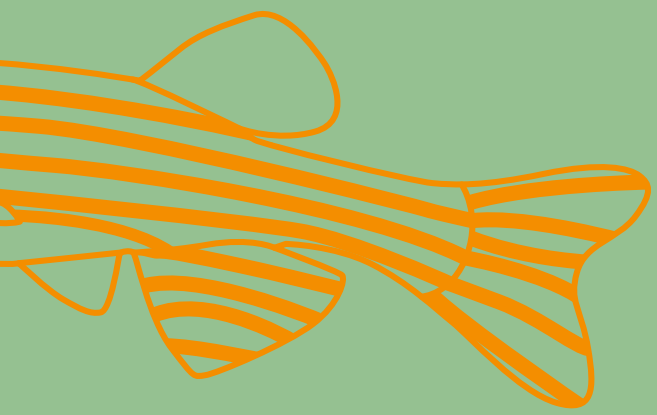
31 October–5 November
Communication Training, Lautrach, Germany
Communication seminar for German-speaking PhD and MD fellowship holders working in Europe. The meeting will take place in Lautrach, Germany. Participants will have the opportunity to work on their writing and presentation skills with various coaches, as well as to learn more about designing figures and graphs. Further details will be provided with the invitation.

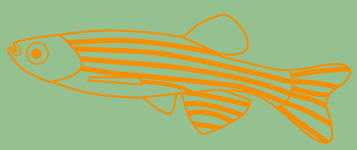
14–15 November
Meeting of BIF's Board of Trustees
The trustees decide on the allocation of fellowships, review proposals for the International Titisee Conferences, and handle all matters of fundamental importance to the foundation.

5 December
BIF Christmas Party
Organized by current BIF fellows, we invite you to our office in Mainz to celebrate the end of the year with us. There will be food, drinks, and music. All BIF fellows and alumni are welcome. We also offer some sleeping places at the office. Registration is needed, info via *Klatschmail*.

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







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