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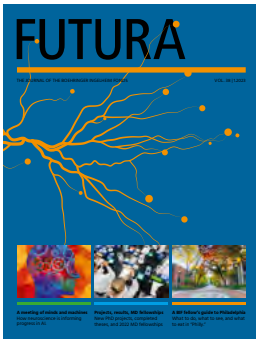
A meeting of minds and machines
How neuroscience is informing progress in AI.

Projects, results, MD fellowships
New PhD projects, completed theses, and 2022 MD fellowships

A BIF fellow's guide to Philadelphia
What to do, what to see, and what to eat in "Philly."



The cover illustration shows an abstract model of a neural network in the brain. In neuroscience, a neural network is defined as any number of interconnected neurons that, as part of a nervous system, form an interconnection oriented towards specific functions.

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A SPACE TO BUILD BRIDGES

What should scientific conferences offer? At best, not just a deluge of data, but an exchange of bright minds that sparks new ideas and concepts at the cutting edge of science. They should be invigorating and exciting, connect the dots between the latest research results, and offer an atmosphere of trust in which new collaborations can flourish.

Marc Wittstock (l) and Dr Stephan Formella (r)

This is what we aim to generate at our International Titisee Conferences (ITCs). Since 1962 – long before the birth of BIF – they have been held at Lake Titisee in the Black Forest region of Germany and are an important but lesser-known part of BIF's funding portfolio. Their concept is simple but has proven very effective over 125 conferences: bring together at most 60 top scientists from two or three disciplines including a number of up-and-coming junior scientists,* give participants ample time by requiring them to stay for the duration of the conference, and choose a great location and create an atmosphere of trust in which unpublished data can be discussed. Such a concept ensures that if participants do not catch someone they want to talk to at breakfast or lunch, they will have a chance at dinner – or the next day. We also invite a number of editors from major journals to foster ties between scientists and publishers.

»An exchange of bright minds that sparks new ideas and concepts at the cutting edge of science.«

The ITC topics cover the entire spectrum of basic research in biomedicine. Suggestions for chairs and topics come from the scientific community, BIF staff, and members of the Board of Trustees. During its annual fall meeting, the board makes the final decision on the general topic and who to approach as chair for the ITC in two years' time. Selection is based on the merits of the proposed chair, the relevance and timing of the topic, and the ways the field will benefit from bringing the proposed subdisciplines together.

The value of such conferences, which spark ideas and build bridges between subdisciplines, is undisputed, but the thought of organizing one may seem daunting in the busy life of a scientist. We therefore endeavour to offer our ITC chairs the full package of support: we fund the entire conference and free scientists from the hassle of organization. We take care of the location, catering, and accommodation. We invite the participants and patiently answer all their questions, prepare the programme, run the conference itself, and deal with all travel reimbursements. Once chosen, the chairs basically only need to flesh out the proposed topic, select a co-chair, and let us know whom they want to have as participants.

If you want to know more about the concept of the ITCs, including how to propose one, please visit our website at www.bifonds.de/titisee-conferences. From page 11, you will also find a brief account of the 126th ITC in March, titled "NeuroAI – Connecting Advances in Machine Learning and Neuroscience". Because of their extreme dominance in the field, an unusually high number of industry researchers attended, which was a rare exception in the series.

We are already busy planning the conferences through October 2024. They deal with somatic mosaicism, organelle communication, and biomolecular condensates and their metabolism.

*If you are a current or recent BIF fellow and your BIF project falls within the scope of the conference's topic, you may also apply for a spot.

Photo: BIF, C. Costard

SYNCYTIALIZATION: CELL FUSION IN THE PLACENTA

Image: Lorenzo Costa, Institut Cochin (Paris , France)

This image shows a trophoblast cell model used to study the process of cell fusion in the placenta. Membranes are shown in green, nuclei in blue. In the placenta, certain cells fuse into a multinucleated giant cell called the syncytiotrophoblast. Here it looks almost like a dragon. It forms the outer layer of the placenta, which is necessary for the exchange between mother and foetus and hormone production. Improper fusion may cause severe pregnancy complications such as preeclampsia. In his project, Lorenzo is studying the fusion capabilities of different cell lines carrying three variants of a gene called *STOX1*, which were observed in women with preeclampsia. He and his team hope to find new biomolecular pathways involved in preeclampsia to better understand this complex disease.

We are always looking for exciting scientific photos and illustrations! If you would like to have your image published, contact Kirsten at kirsten.achenbach@bifonds.de.

Cataglyphis fortis desert ants build their own landmarks to find home.

WHEN NEEDED, DESERT ANTS BUILD LANDMARKS

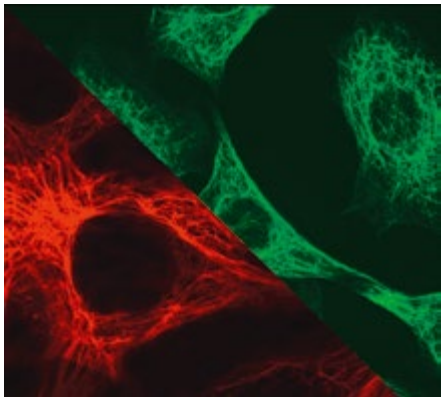
Imagine you are an ant in the hot Tunisian desert in the middle of a featureless salt pan. You have found a morsel of food and want to bring it to your hungry nestmates. But how do you find your way back? Researchers from Jena, Germany, have now found that the desert ant species *Cataglyphis fortis* builds its own landmarks – but only if needed. Over time, these ants had to develop exceptional navigational skills, integrating information from the sun, the number of steps taken, as well as chemical and visual cues. Even so, when the researcher tracked foraging ants on journeys that could be up to two kilometres long, only about 80% made it back to the nest. The researchers noted that nests that lie in the middle of salt pans have much higher nest mounds than nests along the edges, where there are landmarks such as bushes. The team found that ants living in the middle of the salt pan used their own mounds as a visual clue. To find out whether the ants purposefully constructed the mounds as landmarks, the team removed some mounds. As a consequence, the number of ants that got lost rose sharply. At the same time, the ants in the nest waiting for food quickly started to rebuild the mounds. However, they did not rebuild if the researchers put artificial landmarks next to the nests. How the ants know that they can save their energy still remains unclear. The team speculates that mound building is triggered if the number of returning ants drops below a certain threshold. The researchers were fascinated by the ants' navigational feats and their flexibility in using and even constructing their own navigational clues.

REFERENCE

Freire M, Bollig A, Knaden M (2023) Absence of visual cues motivates desert ants to build their own landmarks. *Cur Biol:* https://doi.org/10.1016/j.cub.2023.05.019

CELL SKELETON PROTEINS AS BLUEPRINTS FOR SHOCK ABSORBERS

The makeup of a cell's skeleton differs between stationary cells, such as muscle cells, and mobile cells, such as embryonic or invasive tumour cells. Stationary cells use keratin for their so-called intermediate fibres, while mobile cells use the protein vimentin. To understand the significance of this difference, a Swiss-German research team has now analysed the properties of keratin and vimentin by repeatedly stretching the filaments and measuring changes in length and stiffness. In the case of keratin filaments, it always takes the same amount of force to pull them apart, but with repeated pulling, they get longer. In contrast, the force needed to stretch vimentin filaments lessens with each repetition, but they pull back after being stretched and do not elongate. Based on modelling, the researchers propose that in keratin the filaments have different elements that slide past each other and bind at regular intervals. They always take the same amount of force to break, similar to how metal behaves. Vimentin, on the other hand, behaves more like a gel that is made up of two different components, one of which gives way under tension, uncoiling and not returning to its erstwhile conformation but retracting upon release. Although based on different physical phenomena, both mechanisms explain how cells can withstand the forces generated when the body moves or these cells have to squeeze through tissue. As both protein structures are very good at absorbing energy, these principles may inspire the design of new high-tech materials such as bulletproof vests or shock absorbers.



An epithelial cell with keratin in red and a fibroblast with vimentin as intermediate fibres.

REFERENCE

Lorenz C, Forsting J, Style RW, Klumpp S, Köster S. (2023) Keratin filament mechanics and energy dissipation are determined by metal-like plasticity. *Matter:* https://doi.org/10.1016/j.matt.2023.04.014

Photos: picture alliance/dpa/Harald Wolf (top), Ulrike Rölleke (upper right), Ruth Meyer/University of Göttingen (lower right)

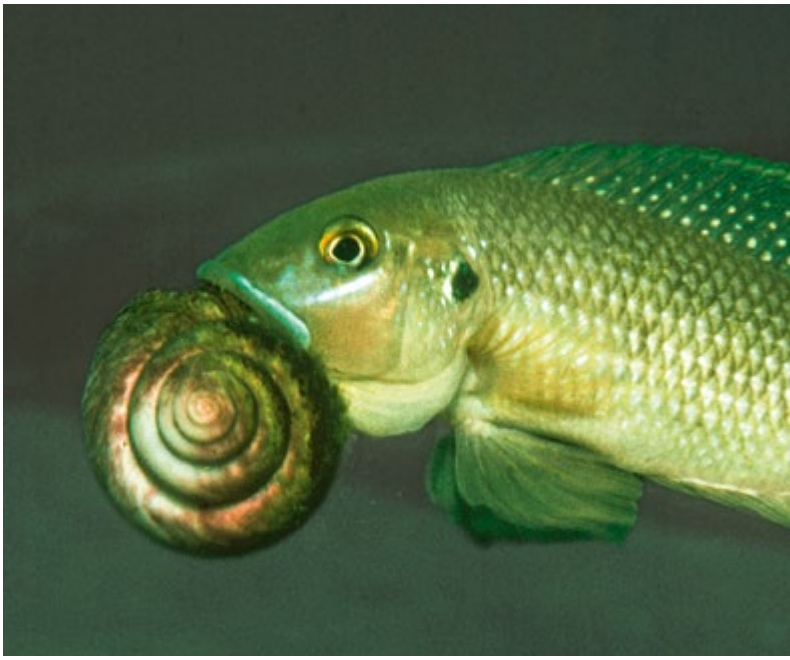
OZONE DESTROYS INSECT PHEROMONES

While the ozone hole is slowly closing, ozone levels in many cities are rising due to ground-level pollution, mainly from traffic. Researchers from the Max Planck Institute for Chemical Ecology have now found that this could seriously impact the mating behaviour of insects and contribute to the current massive decline in insect numbers and diversity. High ozone levels have already been known to degrade the scent of flowers, reducing the number of moths visiting and pollinating them. The researchers have now found that ozone could also heavily affect the pheromones used by many insects to find their mates. Most insect pheromones contain double bonds between carbon atoms, which are easily destroyed by ozone. Males of several different fruit fly species that were exposed to moderately increased ozone levels for a certain time emitted much less pheromone, making them less attractive to females. Male pheromones also serve to repel other males. After ozone exposure, males formed courtship chains in an attempt to mate with one another. The authors concluded, therefore, that ozone has a devastating effect on insect mating behaviour. This conclusion is further supported by exceptions observed by the researchers: one species was not affected by ozone at all. It relies solely on visual cues for mating. Another species was only affected at high levels of ozone. The pheromones known in this species lack the carbon double bonds that ozone targets.

REFERENCE

Jiang, NJ, Chang H, Weißflog J, Eberl F, Veit D, Weniger K *et al* (2023) Ozone exposure disrupts insect sexual communication. *Nat Comm* **14**: 1186

Ground-level ozone pollution severely disrupts mating behavior of some insect species.



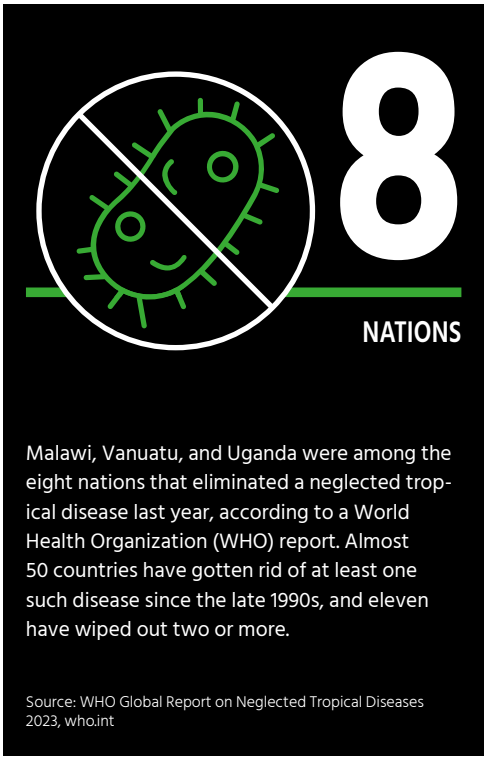
THE GENETICS OF TURNING GIANTS INTO DWARFS

In an African fish species belonging to the cichlid family, females are all about the same size, while males come in two sizes: giants and dwarfs, which differ in weight by a factor of 40. Researchers have now unravelled what drove the evolution of this phenomenon and the genetics of how males pass on their body size to their sons but not their daughters. The giant males of *Lamprologus callipterus* are large enough to collect empty snail shells, which the much smaller females enter to lay eggs. Dwarf males are so tiny they can slip past the females and release their sperm right next to the eggs in the shell. Males of intermediate size have no real chance in this set-up. Through breeding and genetic sequencing, the researchers found that the difference between giant and dwarf is due solely to the allele for the growth factor GHRHR, mutations of which also lead to dwarfism in humans. This factor is encoded in the same region as the genes for male sex. This small Y chromosome-like region is prevented from recombining with its female counterpart so that females cannot inherit the allele for dwarf or giant. If recombination of a chromosome is suppressed, through inversions or similar structural changes, sex chromosomes can evolve over time. While these fish do not – yet? – possess sex chromosomes, they show how an antagonistic trait – either giant or dwarf – can become linked to sex-determining factors and thus lead to the evolution of sex chromosomes. Therefore, these results may provide evidence for the hard-to-prove but widely accepted theory that the evolution of sex chromosomes is driven by traits, where only the extremes are successful.

REFERENCE

Singh P, Taborsky M, Peichel CL, Sturmbauer C (2023) Genomic basis of Y-linked dwarfism in cichlids pursuing alternative reproductive tactics. *Mol Ecol* **32**: 1592–1607

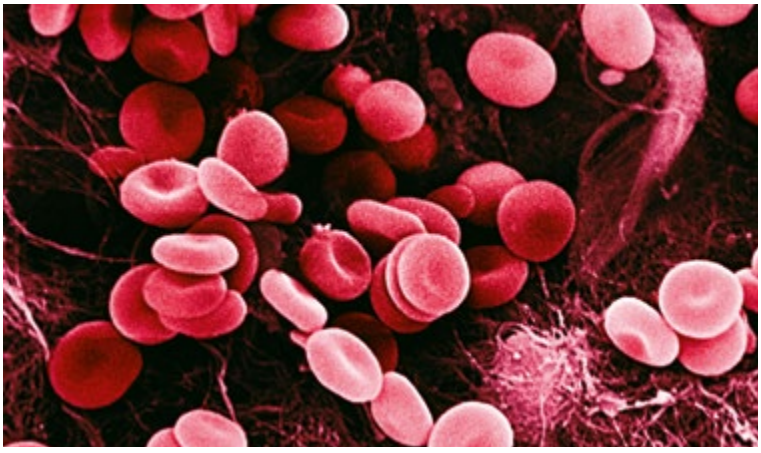
Giant and dwarf males of *Lamprologus callipterus* fish pass their size onto male offspring only, suggesting the evolution of sex chomosomes is driven by antagonistic traits.



Malawi, Vanuatu, and Uganda were among the eight nations that eliminated a neglected tropical disease last year, according to a World Health Organization (WHO) report. Almost 50 countries have gotten rid of at least one such disease since the late 1990s, and eleven have wiped out two or more.

Source: WHO Global Report on Neglected Tropical Diseases 2023, who.int

NEW BLOOD CELLS: FIRST GENERATION STEPS UP PRODUCTION IN AN EMERGENCY



To replace lost blood cells, multipotent progenitor cells mulitply, not blood stem cells.

To keep our immune system in fighting form, our bodies produce several million blood cells every single day. However, when we bleed or fight an infection, we need even more. Blood cells of all types are produced by a differentiation cascade that starts with the blood stem cells in the bone marrow. By genetically marking cells in this cascade, researchers at the German Cancer Research Center (DKRZ) have now learned which cells react in an emergency to supply more blood cells. They studied mice with an infection, blood loss, or a reduced count of certain blood cells, and found that, contrary to long-held beliefs, it is not the blood stem cells that step up production. While the stem cells divided more often, this did not lead to more mature blood cells. These cells merely seemed to ensure that they are healthy themselves, for example, by increasing the transcription of genes involved in self-renewal. It was their first-generation offspring – the multipotent progenitor cells – that started to multiply much faster to replace lost cells. Progenitor cells are more abundant and thus provide a greater pool from which to produce new cells. They can also do so more quickly because they are further along in the differentiation cascade: it takes them only 11 days to supply new, fully mature white blood cells. Progenitor cells are also less valuable to the long-term fitness of the body as they cannot renew indefinitely, unlike stem cells.

REFERENCE

Fanti AK, Busch K, Greco A, Wang X, Cirovic B, Shang F *et al* (2023) Flt3- and Tie2-Cre tracing identifies regeneration in sepsis from multipotent progenitors but not hematopoietic stem cells. *Cell Stem Cell* **30**: 207–218

PROFILE OF APLYSIA CALIFORNICA

By Mitch Leslie

With their plump body and sedentary lifestyle, sea hares are far from anybody's idea of the most charismatic animal, but for one researcher, they represented the perfect solution for his research.

The sea slug *Aplysia*, one 19th-century scholar wrote, has a "disagreeable smell" and a "repulsive figure". But when budding neuroscientist Eric Kandel chanced on the marine mollusk in the late 1950s, he was thrilled. He had finally found the ideal subject for his studies of memory. *Aplysia* "was from a technical point of view quite wonderful," he said. Kandel's successes transformed the animals into the leading model for understanding how the nervous system orchestrates behavior.

The 37 *Aplysia* species are ocean-dwelling relatives of the snails and slugs that torment gardeners. The most commonly used species for research is *A. californica*, which is native to the west coast of North America. When Kandel first decided to begin studying the animals, he was a postdoctoral researcher at the US National Institutes of Health. He and a colleague had just achieved a scientific first by recording the electrical activity of individual neurons from the hippocampus, the mammalian brain structure crucial for creating memories. However, they soon realized that their results did not provide insight into how memories form and persist, the questions they were really interested in. The hippocampus was too complex, and they needed a simpler model. After considering candidates as diverse as crayfish, fruit flies, and nematodes, Kandel chose *Aplysia*.

Three qualities of the sea slugs made them valuable for probing memory. For one thing, their nervous system contains only about 20,000 cells, compared with the roughly one billion in the human brain. *Aplysia* neurons are also enormous, up to 1 mm in diameter. Their size makes it easier to record their electrical activity and allows researchers to readily isolate the cells – or portions of them – for molecular analysis. Another advantage is that scientists can easily manipulate the cells to investigate their functions.

For 30 years, Kandel and his colleagues delved into the neural circuits of *Aplysia* to uncover mechanisms of memory. They determined, for instance, that short-term memory involves changes in how strongly synapses respond to stimuli, whereas long-term memory entails the formation of new synapses. The scientists also teased out many of the molecules that drive these synaptic changes. Kandel received the Nobel Prize in Physiology or Medicine in 2000 for his discoveries.

When Kandel began his research, only a couple of labs in the world were working on *Aplysia*. Although he eventually returned to studying the hippocampus in mammals, other researchers are using the mollusks to tackle a variety of topics, including the mechanisms of Alzheimer's disease and new strategies for reducing chronic pain.

CV OF *APLYSIA CALIFORNICA*

- I can be up to 40 cm long.
- I live for about a year.
- I can produce as many as 80 million eggs.
- I feed on algae.
- I work mainly in neuroscience.
- I have helped researchers win two Nobel Prizes.

Photo: Bruce Sudweeks

A **MEETING** OF MINDS – AND MACHINES

By Liam Drew, PhD

At the recent 126th International Titisee Conference, titled "NeuroAI – Connecting Advances in Machine Learning and Neuroscience", neuroscientists and commercial software developers discussed topics ranging from the details of lab-based experiments to the nature of algorithms and their creation. They also addressed broader philosophical questions such as whether one day we will be able to explain the brain in simple terms.

In 1942, Warren McCulloch – a 43-year-old physician and neurophysiologist – opened his Chicago home to a prodigious teenager named Walter Pitts, a self-taught logician and mathematician. McCulloch was intimately familiar with the gooey mass of cells that is a brain but had long wanted to formalize how neurons might perform the computations underlying mental life. In Pitts he saw a collaborator with the analytical skills this project required.

The following year, Pitts and McCulloch introduced the concept of an artificial neural network (ANN). They had reduced neurons to simple on/off nodes in a connected network of such units. And with each artificial neuron switched on or off by either sensory or synaptic input, their mathematical analysis showed that ANNs could perform logical calculus.

Fusing biological understanding with mathematical insight had birthed a powerful new concept, one that inspired the researchers who would soon advance the nascent fields of digital computing, artificial intelligence (AI), and machine learning (ML).

Today, pretty much weekly, there are reports of new advances in AI, especially from the large language models (LLMs) underlying systems such as OpenAI's GPT-4 and Google's Bard. But numerous other ML systems are transforming computing, society, and the way scientists work – and the tools of AI are now frequently deployed to study the organ that inspired it.

To explore the ever-evolving relationship between AI and neuroscience, the Boehringer Ingelheim Fonds recently gathered experts in both fields for its 126th International Titisee Conference (ITC), titled "NeuroAI – Connecting Advances in Machine Learning and Neuroscience".

"Neuroscience was hugely important for getting AI off the ground," says co-chair Matthew Botvinick, a researcher at DeepMind, an AI research laboratory owned by Google's parent company Alphabet. But, Botvinick explains, once AI was up and running, it became evident that the performance of ANNs and ML algorithms could sometimes be improved by modifying them in ways not derived from known aspects of neurobiology.

"NeuroAI is in principle a bidirectional exchange of information between neuroscience and machine learning," says Caswell Barry, a neuroscientist at University College London and the meeting's second co-chair, about the conference topic. "But there have been periods where the information goes more in one direction than the other." And at present Barry and Botvinick both think neuroscience is gaining more from ML technologies than vice versa.

Barry, for example, works on the brain circuits that allow animals to navigate their surroundings. Since the 1970s, researchers had placed electrodes in rodents' brains and recorded the firing of neurons as those animals moved. They then analysed →

Photo: Getty Images/SEAN GLADWELL

how these neurons fired in relation to the rodent's location and built models of how a sense of space and place might work. Around a decade ago, ML approaches such as deep learning, reinforcement learning, and convolutional networks matured and gave neuroscientists the analytical tools for identifying patterns in their swathes of neuronal data and for building new (and better) models. "This new technology just swept in . . . that could do many of the things that you were labouring over," Barry says. "The dream is that the opposite still happens as well," Barry adds. This means that learning how the brain achieves computational feats that still elude AI will allow researchers to build better AI systems.

The ITC's participants ranged from cognitive and systems neuroscientists to computational neuroscientists and theoreticians. They also included ML developers at companies such as DeepMind, Google, and Meta. It was, Barry says, "a really nice mix of some fields that wouldn't always be talking to each other." This mix is at the core of the ITC's concept of fostering exchange. (See the editorial on page 3.)

WHAT'S THE GOAL?

Everyone at the ITC shared an interest in the generation and use of algorithms that recreate aspects of human or animal intelligence, but the objectives of neuroscientists and software developers often differ. "The goal of engineering is to get things to work," says Botvinick. "The coin of the realm in engineering is performance, and that means that oftentimes there's not as much time available – or, honestly, reward available – for drilling down and trying to understand how a system is working."

"The culture of neuroscience and psychology and cognitive science is very different," he adds. "There, the whole objective is to understand, to shed light on a mechanism." Botvinick himself straddles both worlds and describes his early experiences of using ML: "It was all about building a deep learning system, then going under the hood and trying to figure out: What's going on inside? How is this thing working? Why does it make the mistakes that it makes? How is it accomplishing the things that it gets right?"

Because these are questions that neuroscientists and psychologists have always asked of the brain, Botvinick thinks they have skillsets well suited to this challenge. "It is hard, though," he says. "Deep learning does not bend over backwards to make its results human-interpretable." But perhaps this is relative. The animal navigation field in which Barry works grew out of observations that certain neurons called place cells and grid cells fire only when an animal is at certain points in space. And for 50 years, the field's progression has relied on investigators painstakingly recording neuronal activity as animals explore their worlds.

"If you're a neuroscientist, and you've spent your life poking around with a little wire trying to get one neuron after another," Barry says, "believe me, a deep network looks like a wide-open window! You can literally see what every neuron is doing every time; all the weights between them; how they're changing at any point in learning. It's like a total dream." He does, however, highlight another issue: "There are a lot of ways that deep networks can do the same things as animals and humans that have got nothing to do with the way the brain does it."

Therefore, neuroscientists must determine whether an algorithm is working like the brain does. "Sometimes", Barry says, "you find these little magic spots where it looks like the network has come up with similar solutions." When this happens, it opens many opportunities for him and likeminded researchers. For example, in 2018 Barry and colleagues trained an ANN to do virtual navigational tasks and saw the emergence of artificial neurons that fired just as grid cells do. They could then do experiments on how this system works that would have been impossible with a living brain.

Testing the longstanding hypotheses about how exactly place and grid cells contribute to animals' mental maps has been difficult because neuroscientists cannot silence these neurons without silencing many neighbouring neurons. But in models, they can. After Barry and his colleagues had trained their grid cell-containing ANN to navigate around a virtual environment, they could simply eliminate or otherwise disrupt those grid cells to ask how this changed the ANN's output. In a key experiment, they opened a virtual door and asked whether the system used this new shortcut. "The networks with grid cells could take the shortcut," Barry says (just as an animal naturally would), "whereas if you deleted their grid cells or made them noisy, they reverted back to taking the longer circuitous route."

ASKING WHY

Botvinick says that his DeepMind team often looks for areas of neuroscience where ideas emerge about computations or rules that may apply to the brain – and where using AI tools to mathematically formalize these ideas and to model them might illuminate why the brain operates as it does.

One current project explores why many brains possess separate systems for generating habitual behaviour and deliberative behaviour. Botvinick gives driving and cooking as examples. In each, experienced practitioners mix the stereotyped, seemingly automatic actions required to control a car or to chop and cook with an executive system that allows, say, thoughtful navigation of a new route or the creation of a new dish. Habit systems, Botvinick says, "look across all of the things that you've done in your life – all of the ac-

»Sometimes you find these magic spots where the network has come up with similar solutions to the brain.«

Caswell Barry

ITC – A VERY SPECIAL MEETING

Among the 47 participants in the 126th ITC were six current BIF fellows and alumni, including Florian Hollunder, who uses computer vision and ML to study fruit fly behaviour at The Rockefeller University in New York. He praised the ITC for bringing together leading academic neuroscientists and researchers from the cutting edge of AI research – many of whom work in industry in this specific field – and for the way everyone so seamlessly mixed to explore the meeting's themes.
The computer vision and ML analysis tools that Hollunder uses to study flies have had a huge impact on behavioural neuroscience in recent years. The tracking of rapid changes in movement and the use of algorithms to find patterns in these changes have revealed unprecedented organizational principles of behaviour. At the ITC, Hollunder met the researchers who had created these tools and gained greater insights into how they were developed. He also learned that he was not using the tools to their full potential and that they offered further ways to uncover the structure of behaviour and why it evolved into its current form. "I was really inspired by that," he says. Florian also highlighted the focus on sharing unpublished data and how the meeting was designed to stimulate free-flowing discussion both formally and informally. "I've had memorable exchanges not only with other students, but also with people who are far more advanced and have already contributed widely to the field," he says. Senior scientists echoed these sentiments. "You rarely bring together a group like this," says co-chair Matthew Botvinick. "This is a very special meeting. I think we're all riding high on this experience."

tivities that you've engaged in – and find what's common across them." According to him, the "general common knowledge" is distilled into the habit system so that whenever you encounter a new situation that you recognize as meaningfully overlapping previous experiences, this system can produce an appropriate set of generically useful skills.

"Then", Botvinick says, "you need another computational system – that takes care of the rest." After his group developed mathematical models of such dual processors, they were tested in simulated environments. As Botvinick explains, the advantage of having the shared features, or shared structure, of all the model's training experiences represented separately was that these learned rules could be rapidly generalized and transferred, increasing the speed at which the dual process models operated in new scenarios relative to systems without two separate systems. Exploring further how the model operates also suggested ways in which a habit system might optimally work, offering statistical insights into how memories of multiple experiences are compressed to represent their shared elements while discarding the particularities of individual experiences.

Katharina Dobs is also using ML to ask "why" questions in biology. Dobs trained in both psychology and computer science, and her work as a cognitive neuroscientist at the Justus Liebig University of Giessen enables her to fuse both. Dobs studies visual perception and has a strong interest in facial recognition.

Curiously, there is a specific part of the human visual cortex dedicated to processing faces. Likewise, other regions specialize in bodies and scenes, for example, but evolution has not generated specific regions for other classes of visual input. "There was always this question", Dobs says, "of why for some and not for others? But basically there is no tool in human neuroscience to address this question." When the ability of computer vision to recognize objects began to rival that of humans, Dobs thought it might offer ways to ask questions about why the visual cortex is organized the way it is. Last year she published a paper describing how, when she optimized an ANN for recognizing faces over images of other objects, the model spontaneously formed a separate face-processing subnetwork – recapitulating this distinctive feature of the human brain.

It turned out that optimizing a system for face recognition, over all the different categories of stimuli in our visual diet, was sufficient to explain functional segregation in visual cortex, Dobs says. She had found one of the magic spots Barry spoke of, where ANNs and the brain come up with the same kind of solution. Dobs now thinks this may be a more widely useful heuristic: if an ANN is optimized for a certain task and it produces idiosyncrasies of brains – be it functional separation or susceptibility to certain illusions – this suggests that the task under scrutiny was the one the brain evolved to solve, especially if optimizing the ANN for another task does not produce the chosen feature of brains. "The idea is that we can use these different networks now to understand what the problem is or the task our brain is facing or optimized for," she says.

Then, armed with this insight into why brains have evolved to be the way they are, researchers are also in possession of models with which they can ask how the brain executes these tasks.

BRAINS TO COMPUTERS

One can only imagine the glee with which the ANN pioneers McCulloch and Pitts would view these advances in understanding neurobiology through the application of simulated neural networks. But what about neuroscience's current influence on developing new types of AI? Where AI diverges most fundamentally from the type of work Pitts and McCulloch envisaged is that today many AI systems are being designed to execute specific tasks – for example, to recognize and classify objects or to process language – and their developers are not committed to execut- →

Neuroscience informs AI development by providing concepts on how brains work.

ing these tasks as brains do. Consequently, the ways in which neuroscience feeds into AI development can be quite nuanced. On the one hand, it can involve insights from basic neural circuit analysis; on the other, it can involve AI researchers borrowing higher level concepts of how brains work as guiding principles.

Indeed, Botvinick recalls an experimental neuroscientist colleague once suggesting that the importance of biological research does not lie in what is discovered and verified experimentally, but in the hypotheses and ideas that emerge. "Because", Botvinick says, "as soon as we have a hypothesis, an AI researcher can go try that out and see whether it helps for the kind of work that they're doing. It doesn't really matter in the end whether it's true of brains or not."

One example is attention. How exactly the brain selectively attends to one thing over all others remains somewhat enigmatic, but incorporating an artificial mode of attention into LLMs was essential for boosting their performance.

Andre Lampinen works on LLMs at DeepMind. To incorporate attention into LLMs, a type of neural network architecture called a transformer was added. "I don't think transformers were originally inspired by any detailed mechanistic understanding of the neural basis of attention," says Lampinen. "If anything, they were inspired by loose conceptual or lay theories of attention." Such conceptual inspiration led programmers to design decoding systems that when trained on a great deal of data were able to decide which parts of a sentence are most important. This enabled them to develop an intrinsic representation of the structure of language and to understand the context in which words appear. Lampinen thinks LLMs will continue to improve incrementally by tweaking this core design –and that such improvements, coupled with ever greater training datasets, will have dramatic consequences in terms of performance and potential uses. He adds: "I am excited by work on models that go beyond just language."

Also at the ITC was Aldo Faisal, a computer scientist from Imperial College London and a BIF alumnus. One of his main passions is increasing the practical value of AI. "A lot of neuroscience uses highly simplified tasks," he says, "but we can use these models to analyse data in a very different way, one that allows us to work on real world problems . . . and look at them from a cognitive neuroscience perspective." In particular, Faisal wants AI to improve healthcare – all the way from diagnostics and prognostics to clinical decision-making.

In two recent studies, he attached movement sensors to people with progressive neurodegenerative conditions. "We demonstrated that purely by looking at the movement behaviour of people in their everyday life – not in any specific task – we can predict their disease progression up to a year into the future," he explains, adding that he and his colleagues could even predict gene expression changes in people's brains according to how their movement changed.

Here, the ML is doing something akin to the sort of pattern recognition an experienced neurologist does in observing patients with movement disorders – only in a much more quantified way and not just during a short consultation, but over a longer period via the sensors the patients wear. Such fine-grained monitoring of disease progression could be valuable in assessing the impact of interventions, Faisal says.

He also thinks that AI can help doctors make better decisions. He is currently running a trial across four London intensive care units in which an ML system receives all of a patient's physiological data – which Faisal likens to a doctor's perceptual inputs – as well as time-stamped records of every decision and intervention the medical staff make. From this, he says, the algorithms can map the relationship between these variables and learn what the best course of action is for any set of patient data.

Already these experiments suggest that algorithms can distinguish between many more health states than a human doctor can. Faisal's vision is bold – he talks of medical holograms one day helping doctors to make decisions and treat patients. To bolster the chances of this happening, Faisal is also researching how AI systems might explain themselves to humans – and how humans might come to trust them. "I need to understand", he says, "how I must design something that explains to the human so that the human follows the recommendation." Lest doctors fear their obsolescence, Faisal emphasizes that such technologies will help doctors, not replace them. "It's about AI–human symbiosis – we will have AI colleagues." Then, echoing the ITC's central theme, he says: "It's about how we work together."

If you want to suggest a topic for an ITC,
please see our website for details: www.bifonds.de

Photo: picture alliance/dpa /Monika Skolimowska

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

Therefore, this pdf continues with the section Results.

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

Shared first authorship is indicated with an *.

A *VEGFC-EMILIN2A–CXCL8A* SIGNALLING AXIS REQUIRED FOR ZEBRAFISH CARDIAC REGENERATION

cf. BIF FUTURA, VOL. 33 | 1.2018

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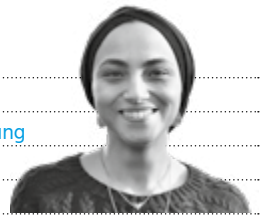
Discipline: Molecular Biologist, MSc
Institute: Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany
Supervisor: Prof. Didier Stainier



Ischaemic heart diseases are a leading cause of death worldwide. Unlike adult mammals, the adult zebrafish regenerates its heart following injury, which enables the study of the underlying cellular and molecular mechanisms. Little is known about how coronary revascularization, one of the earliest responses to cardiac injury in zebrafish, is regulated. The gene for vascular endothelial growth factor C, *vegfc*, is upregulated after injury, and its expression peaks during this process. In my PhD project, I tested the hypothesis that *vegfc* is involved in coronary revascularization. I found that *vegfc* is expressed by coronary endothelial cells after cardiac injury and that Vegfc signalling is required for coronary revascularization during cardiac regeneration. Using transcriptomic analysis, I identified the extracellular matrix component gene *emilin2a* and the chemokine gene *cxcl8a* as effectors of Vegfc signalling. Using loss- and gain-of-function tools, I showed that *emilin2a* increases coronary revascularization and induces *cxcl8a* expression after cardiac injury. During cardiac regeneration, *cxcl8a* is expressed in epicardium-derived cells, while its receptor *cxcr1* is expressed in coronary endothelial cells. I found that both *cxcl8a* and *cxcr1* are required for coronary revascularization. My work suggests that Vegfc promotes *emilin2a* expression, which enhances Cxcl8a–Cxcr1 signalling, thereby promoting coronary revascularization and thus cardiac regeneration. These insights could pave the way for promising new therapies for human heart regeneration.

PUBLICATIONS

El-Sammak H, Yang B, Guenther S, Chen W, Marín-Juez R, Stainier DYR (2022) A Vegfc-Emilin2a-Cxcl8a signaling axis required for zebrafish cardiac regeneration. *Circ Res* **130**: 1014–1029

Hu B*, Lelek S*, Spanjaard B*, El-Sammak H, Guedes Simões M, Mintcheva J *et al* (2022) Origin and function of activated fibroblast states during zebrafish heart regeneration. *Nat Genet* **54**: 1227–1237

Fukuda R, Marín-Juez R*, El-Sammak H*, Beisaw A, Ramadass R, Kuenne C *et al* (2020) Stimulation of glycolysis promotes cardiomyocyte proliferation after injury in adult zebrafish. *EMBO Rep* **21**: e49752

Marín-Juez R, El-Sammak H, Helker CSM, Kamezaki A, Mullapuli ST, Bibli S-I *et al* (2019) Coronary revascularization during heart regeneration is regulated by epicardial and endocardial cues and forms a scaffold for cardiomyocyte repopulation. *Dev Cell* **51**(4): 503–515.e4

ILLUMINATING THE GENOMIC REGULATION OF CELL-FATE DECISIONS IN BRAIN ORGANOIDS

cf. BIF FUTURA, VOL. 35 | 1.2020

JONAS SIMON FLECK
Discipline: Molecular Biotechnologist, MSc
Institute: Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland
Supervisor: Prof. Barbara Treutlein

In human brain development, cells undergo remarkable fate transitions to produce diverse cell types. Dissecting the underlying regulatory mechanisms is a central challenge in developmental biology. The goal of my PhD project was to understand the gene regulatory landscape of human brain development using brain organoids and single-cell genomics. First, I developed VoxHunt, a computational tool to assess organoid cell-type composition by mapping single-cell genomic profiles to reference atlases. Next, I investigated how cell-type diversity arises in organoids. Using single-cell RNA sequencing and single-cell assay for transposase accessible chromatin, another PhD student and I generated a transcriptome and chromatin accessibility atlas of early organoid development. By inferring developmental trajectories from this atlas, I identified critical stages of fate decision. I also developed an algorithm, Pando, to infer gene regulatory networks from such multi-omic measurements. Using a pooled knockout screen to assess the transcription factor requirement for fate diversification, my colleague and I showed that GLI family zinc finger 3 (GLI3) is required for establishing cortical cell types in humans. Using Pando, I resolved the gene regulatory network surrounding regulation by GLI3. Finally, in collaboration with a postdoc in the lab, I probed the epigenetic mechanisms of cell-type diversification and profiled three histone modifications in single cells during organoid development using single-cell Cut&Tag. I identified epigenetic switches controlling fate bifurcations and showed that repression by histone mark H3K27me3 is needed to stabilize neuroectoderm induction. My work provides a framework for using organoids and single-cell technologies to reconstruct human developmental biology.

PUBLICATIONS

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Lust K˚, Maynard A˚, Gomes T*, Fleck JS, Camp JG, Tanaka EM *et al* (2022) Single-cell analyses of axolotl telencephalon organization, neurogenesis, and regeneration. *Science* **377**: eabp9262

Fleck JS˚, Sanchís-Calleja F˚, He Z, Santel M, Boyle MJ, Camp JG *et al* (2021) Resolving organoid brain region identities by mapping single-cell genomic data to reference atlases. *Cell Stem Cell* **28**: 1177–1180

STRUCTURAL ANALYSIS OF HUMAN AND YEAST RNA POLYMERASE III

cf. BIF FUTURA, VOL. 33 | 1.2018

MATHIAS GIRBIG
Discipline: Biochemist, MSc
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Supervisor: Dr Christoph W. Müller

The eukaryotic genome is transcribed by large molecular machines called DNA-dependent RNA polymerases. RNA polymerase III (Pol III) is vital for protein synthesis and other central processes, and its misregulation in humans is linked to cancer and various rare genetic diseases. Pol III synthesizes short and abundant RNA molecules such as transfer RNAs, and it pauses and then terminates transcription on poly-thymidine sites on the non-template DNA strand. The goal of my PhD project was to uncover molecular information about Pol III termination and the three-dimensional structure of human Pol III, which was largely missing. I first determined the high-resolution structure of native human Pol III using cryogenic electron microscopy (cryo-EM). The structure revealed multiple functional elements that are different from those in the yeast Pol III structure and allowed my colleague to map 110 disease-associated mutants. To obtain molecular insights into Pol III transcription termination, I determined the cryo-EM structure of the *Saccharomyces cerevisiae* Pol III pre-termination complex. I found that the complex forms a tight hydrogen-bond network with the non-template strand. This explains how pausing upon recognition of the poly-thymidine termination signal is achieved, which I confirmed using *in vitro* and *in vivo* structure–function studies. My structural analyses advance our mechanistic understanding of the Pol III transcription machinery from both a biomedical and a more general perspective.

PUBLICATIONS

Girbig M, Misiaszek AD, Müller CW (2022) Structural insights into nuclear transcription by eukaryotic DNA-dependent RNA polymerases. *Nat Rev Mol Cell Biol* **23**: 603–622

Girbig M, Xie J, Grötsch H, Libri D, Porrua O, Müller CW (2022) Architecture of the yeast Pol III pre-termination complex and pausing mechanism on poly-dT termination signals. *Cell Rep* **40**: 111316

Xie J, Aiello U, Clement Y, Haidara N, Girbig M, Schmitzova J *et al* (2022) An integrated model for termination of RNA polymerase III transcription. *Sci Adv* **8**: eabm9875

Misiaszek AD, Girbig M, Grötsch H, Baudin F, Murciano B, Müller CW (2021) Cryo-EM structures of human RNA polymerase I. *Nat Struct Mol Biol* **28**: 997–1008

Girbig M*, Misiaszek AD*, Vorländer MK, Lafita A, Grötsch H, Baudin F *et al* (2021) Cryo-EM structures of human RNA polymerase III in its unbound and transcribing states. *Nat Struct Mol Biol* **28**: 210–219

DOPAMINE SIGNALLING IN THE VENTRAL HIPPOCAMPUS CONTROLS DECISION-MAKING IN ANXIETY

cf. BIF FUTURA, VOL. 34 | 1.2019

ARTHUR GODINO
Discipline: Neuroscientist, MSc
Institute: Icahn School of Medicine at Mount Sinai, New York, NY, USA
Supervisor: Prof. Eric Nestler

Resolving approach and avoidance conflicts in anxiety-eliciting situations can promote adaptive behaviours that help animals to survive. However, when these behavioural responses are inappropriate to the level of threat, they can contribute to several psychiatric disorders. Despite evidence implicating both the ventral hippocampus (vHipp) and mesocorticolimbic dopamine circuits in this process, little is known about how dopamine signalling selectively affects vHipp representations of emotionally salient stimuli to inform approach/avoidance arbitration. In my PhD project, I studied dopaminoceptive neurons in vHipp – which express either the dopamine D1 or D2 receptor – to delineate a model for dopamine neuromodulation within vHipp in coordinating decision-making. I capitalized on transgenic mice to characterize (using anatomy and single-nuclei RNA sequencing), record (via *in vivo* calcium imaging and *ex vivo* electrophysiology) and manipulate (using opto- and chemogenetics) vHipp D1 and D2 cells. I also used genetically encoded sensors to detect dopamine release in vHipp – a first in the field. At the histological level, I showed that D1- and D2-expressing cells exhibit a precise topographical organization across vHipp subfields, matching specific transcriptionally defined cell types. At the functional level, I found that anxiogenic environments trigger largely similar patterns of calcium activity in vHipp D1 and D2 cells in concert with dopamine release in this region, which in turn can modulate their electrophysiological properties. However, bidirectional manipulation of vHipp D1 or D2 cells demonstrated their opposing roles in mediating approach/avoidance behaviours in both innate and learned anxiety-inducing situations. My findings suggest that dopamine dynamics in vHipp operate as a feedback loop that tracks anxiety levels to act as a threshold for triggering exploratory behaviours through the differential recruitment of vHipp D1 and D2 neurons. My work paves the way for further studies of dopamine signal processing in limbic regions and underscores the complexity of the circuit and neuromodulatory mechanisms that govern affective states.

PUBLICATION

The results of this project have not yet been published.

GENETIC INTERACTORS OF THE SWI/SNF CHROMATIN REMODELLING COMPLEX IN *C. ELEGANS*

cf. BIF FUTURA, VOL. 34 | 2.2019

LISA LAMPERSBERGER
Discipline: Molecular Biologist, MSc
Institute: The Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK
Supervisor: Prof. Eric Miska

Chromatin remodellers directly alter the structure of chromatin by reshuffling nucleosomes, thereby controlling access to DNA elements. Mutations in the eukaryotically conserved SWItch/sucrose non-fermenting (SWI/SNF) chromatin remodellers cause a multitude of developmental disorders in humans, most of which have no treatment options. The goal of my PhD project was to investigate SWI/SNF chromatin remodellers by identifying compensating mutations that can restore the developmental defects caused by SWI/SNF loss-of-function in *Caenorhabditis elegans*. I used a conditional *swsn-1* mutant model that resembles a complete loss of SWI/SNF function only when the animal is exposed to a restrictive temperature. Using chemical mutagenesis screens, I identified compensating mutations that can restore viability and prevent developmental defects in these mutants. In particular, I found that a specific mutation in the SWI/SNF core subunit *snfc-5* (*SMARCB1* in human) can prevent embryonic lethality in animals harbouring the *swsn-1* mutation. Furthermore, these screens showed that the combination of this *snfc-5* mutation and a loss-of-function mutation in the E3 ubiquitin ligase *ubr-5* can restore development to adulthood in *swsn-1* mutants that would otherwise die as embryos. Finally, I used quantitative Western blotting and, with the help of a collaborator, mass spectrometry using label-free quantification – to show that SWI/SNF protein levels are reduced in *swsn-1–snfc-5* double mutants and partly restored to wild-type levels in *swsn-1–snfc-5–ubr-5* triple mutants. This discovery is consistent with a model in which UBR-5 regulates SWI/SNF levels by tagging the complex for proteasomal degradation. My findings establish a novel link between an E3 ubiquitin ligase and SWI/SNF function and suggest that UBR-5 might be a viable therapeutic target in developmental disorders caused by mutations in SWI/SNF complexes.

PUBLICATIONS

Lampersberger L, Conte F, Ghosh S, Xiao Y, Price J, Jordan D *et al* (2023) Loss of the E3 ubiquitin ligases UBR-5 or HECD-1 restores *Caenorhabditis elegans* development in the absence of SWI/SNF function. *Proc Natl Acad Sci USA* **120**: e2217992120

Berkyurek AC*, Furlan G*, Lampersberger L*, Beltran T, Weick E-M, Nischwitz E *et al* (2021) The RNA polymerase II subunit RPB-9 recruits the integrator complex to terminate *Caenorhabditis elegans* piRNA transcription. *EMBO J* **40**: e105565

FUNCTIONAL CONNECTOMICS OF NEURONAL REPRESENTATIONS IN THE MOUSE VISUAL CORTEX

cf. BIF FUTURA, VOL. 32 | 2.2017

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Discipline: Neuroscientist, MSc
Institute: Max Planck Institute for Biological Intelligence, Planegg, Germany, and Max Planck Institute for Brain Research, Frankfurt, Germany
Supervisors: Prof. Tobias Bonhoeffer, Prof. Moritz Helmstaedter

Neuroscience has made huge progress in deciphering *what* information is encoded in the brain, but much less is known about *how* the brain achieves this. To understand single computations, we need to understand the flow of information. To do that, we need to combine the functional properties of the neurons' inputs and outputs with their precise interconnectivity at the synaptic level. This functional connectomics approach, which combines *in vivo* two-photon microscopy with 3D electron microscopy, has thus far been applied only to local neuronal circuits. In my PhD project, I overcame this limitation by developing a novel long-range functional connectomics pipeline, enabling the study of neuronal circuits spanning different brain areas. Using my technique on the mouse visual cortex, I acquired a multimodal, petabyte-scale dataset that allows, for the first time, in-depth synaptic-level analyses of the functional logic of geniculo–cortical convergence – part of the brain circuit responsible for the flow of information from the retina to the primary visual cortex. Understanding this functional connectivity has been a key challenge in visual neuroscience since 1962, when David Hubel and Torsten Wiesel proposed their feedforward model describing how circular receptive fields in the visual thalamus are transformed into the elongated and oriented receptive fields of simple cells in layer 4 of the primary visual cortex. Although my analysis is ongoing, my colleagues and I are confident that my dataset has the quality and richness required to provide comprehensive evidence of the functional logic of thalamo-cortical connectivity in the mouse visual cortex. Such a functional connectome could allow us to conclusively determine how orientation selectivity is generated in cortical simple cells. I hope my pipeline will provide the neuroscience community with a powerful tool to investigate the causality between neuronal connectivity and computation – in other words, *how* the brain computes information.

PUBLICATIONS

Holtkamp SJ, Ince LM, Barnoud C, Schmitt MT, Sinturel F, Pilorz V *et al* (2021) Circadian clocks guide dendritic cells into skin lymphatics. *Nat Immunol* **22**: 1375–1381

Bauer J, Weiler S, Fernholz MHP, Laubender D, Scheuss V, Hübener M *et al* (2021) Limited functional convergence of eye-specific inputs in the retinogeniculate pathway of the mouse. *Neuron* **109**: 2457–2468.e12

IDENTIFICATION AND CHARACTERIZATION OF PROTEINS THAT PROTECT TELOMERES FROM FRAGILITY

cf. BIF FUTURA, VOL. 33 | 2.2018

ANNA NÄGER
Discipline: Molecular Biotechnologist, MSc
Institute: Swiss Institute for Experimental Cancer Research (ISREC), Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland
Supervisor: Prof. Joachim Lingner

The repetitive DNA sequence and distinct structures at the telomeres can challenge the DNA replication machinery, causing telomere shortening and genome instability. To identify proteins involved in DNA replication at the telomeres, the Lingner lab developed QTIP-iPOND (quantitative telomeric chromatin isolation protocol followed by isolation of proteins on nascent DNA), a proteomic analysis of chromatin near telomere replication forks. In a small interfering RNA screen, my collaborators and I individually depleted 53 proteins identified by QTIP-iPOND as being crucial for DNA replication at the telomeres. Fluorescence *in situ* hybridization showed that 26 of the proteins could prevent telomere fragility, which is indicative of replication defects. One of the proteins, chromobox 8 (CBX8), prevents telomere fragility caused by R-loops, which can stall replication forks and induce homologous recombination. R-loops are formed when telomeric repeating-containing RNA (TERRA) pairs with its complementary telomeric DNA strand and displaces the other DNA strand. CBX8 may be involved in repair activities at stalled replication forks that arise when the replisome encounters TERRA R-loops. This is consistent with my discovery that CBX8 localizes to telomeres lacking a major telomeric protein, telomeric repeat binding factor 2 (TERF2). Previous studies have shown that TERF2-deficient telomeres are deprotected, elicit a DNA damage response, and are fused by non-homologous end joining (NHEJ). I found that localization of CBX8 to TERF2-deficient telomeres depends on TERRA R-loops and DNA damage signalling. I also found that CBX8 promotes NHEJ-mediated fusion of dysfunctional telomeres. I hypothesize that CBX8 is involved in repair activities that influence the choice between NHEJ and homologous recombination at TERF2-deficient telomeres, possibly by counteracting DNA end resection or promoting the removal of the 3' overhang at telomeres. My work increases our knowledge of the proteins involved in DNA replication at telomeres and could lead to insights into the genome instability caused by telomere replication defects in telomere diseases and cancer.

PUBLICATION

Lin C-YG*, Näger AC*, Lunardi T, Vančevska A, Lossaint G, Lingner J (2021) The human telomeric proteome during telomere replication. *Nucleic Acids Res* **49**: 12119–12135

PYK2 AND FYN KINASE DO NOT ACCELERATE TAU SPREAD IN ALZHEIMER'S DISEASE

cf. BIF FUTURA, VOL. 33 | 2.2018

SARAH HELENA NIES
Discipline: Neuroscientist, MSc
Institute: Yale School of Medicine, New Haven, CT, USA, and Graduate Training Center of Neuroscience, University of Tubingen, Germany
Supervisor: Prof. Stephen Strittmatter

In Alzheimer's disease, deposition of the pathological tau protein and amyloid-β (Aβ) peptide drives synaptic loss and cognitive decline. In my PhD project, I hypothesized that the accumulation and spread of tau could be modulated by a signalling cascade in which protein tyrosine kinase 2 (Pyk2), the tyrosine-protein kinase Fyn, and glycogen synthase kinase 3β (GSK3β) interact with one another downstream of the cellular prion protein receptor that binds Aβ oligomers. I observed kinase and tau interactions in an HEK293-T overexpression model but not in neurons derived from induced pluripotent stem cells (iPSCs). In HEK293-T cells, Pyk2 co-immunoprecipitated with GSK3β, and both Pyk2 and Fyn increased phosphorylation of GSK3β and tau. Inhibiting Fyn decreased the Fyn–tau interaction in a proximity ligation assay and decreased tau seeding in primary mouse neurons. However, inhibiting Pyk2 and Fyn in iPSC-derived neurons did not reduce phosphorylation of GSK3β or tau. I also injected mouse models with tau extracts from people with Alzheimer's disease and assessed how tau spreading was affected by Aβ co-pathology, ablation of risk genes for Alzheimer's disease, or inhibition of Fyn. The density and spread of tau inclusions triggered by the human tau seed did not change in these mouse models. When both tau and Aβ were injected, they spread independently, which suggests the presence of distinct propagation mechanisms. By contrast, mouse ageing or replacing the mouse tau sequence with the human sequence enhanced the tau burden in neurites only. My results show that *in vitro* tau interactions do not faithfully translate across different model systems, aiding our understanding of how tau spreads *in vivo*.

PUBLICATIONS

Brody AH, Nies SH, Guan F, Smith L, Mukherjee B, Salazar S *et al* (2022) Alzheimer risk gene product Pyk2 suppresses Tau phosphorylation and phenotypic effects of tauopathy. *Mol Neurodegener* **17**(1): 32

Nies SH, Takahashi H, Herber CS, Huttner A, Chase A, Strittmatter SM (2021) Spreading of Alzheimer tau seeds is enhanced by aging and template matching with limited impact of amyloid-β. *J Biol Chem* **297**(4): 101159

Tang SJ*, Fesharaki-Zadeh A*, Takahashi H*, Nies SH, Smith LM, Luo A *et al* (2020) Fyn kinase inhibition reduces protein aggregation, increases synapse density and improves memory in transgenic and traumatic tauopathy. *Acta Neuropathol Commun* **8**(1): 96

TWO RAPIDLY EVOLVING GENES CONTROL MOSQUITO REPRODUCTIVE RESILIENCE DURING DROUGHT

cf. BIF FUTURA, VOL. 33 | 2.2018

KRITHIKA VENKATARAMAN
Discipline: Neurogeneticist, BA
Institute: The Rockefeller University, New York, NY, USA
Supervisor: Prof. Leslie B. Vosshall

Female *Aedes aegypti* mosquitoes, the primary vector for deadly viral pathogens, require fresh water – which is under threat from climate change – for egg-laying. In my PhD project, I showed that if fresh water is available, mated *A. aegypti* females lay mature eggs ~3 days after blood-feeding. During drought, however, they retain viable eggs in their ovaries for extended periods until fresh water becomes available. To understand this process, I used comprehensive transcriptomics and quantitative proteomics of mosquito ovaries across reproductive time points. I identified two linked genes, which I named *tweedledee* (*LOC5563800*) and *tweedledum* (*LOC5566109*), as strong candidates for enabling female reproductive flexibility. I showed that these previously uncharacterized genes each encode a small secreted protein with predicted signal peptides, no other known domains, and no homology with any non-mosquito proteins. These taxon-restricted genes are both enriched in ovaries compared to other tissues, expressed specifically in somatic ovary cells that encapsulate eggs, and highly upregulated only when a female is holding mature eggs. Both rapidly evolving genes also show signs of positive selection, suggesting they serve an adaptive function. I used CRISPR-Cas9 knockouts to show that females lacking functional *tweedledee* and *tweedledum* feed normally and lay viable eggs moderately well when fresh water is available, but lose this capacity as egg retention time increases. This suggests that these genes allow females to adjust their reproductive schedule based on environmental conditions and likely allow the species to invade otherwise inhospitable ecological niches.

PUBLICATIONS

Venkataraman K, Shai N, Lakhiani P, Zylka S, Zhao J, Herre M *et al* (2023) Two novel, tightly linked, and rapidly evolving genes underlie *Aedes aegypti* mosquito reproductive resilience during drought. *Elife* **12**: e80489

Venkataraman, K*, Jové V*, Duvall LB (2022) Methods to assess blood and nectar meals in *Aedes aegypti* mosquitoes. *Cold Spring Harb Protoc* **2022**(6): pdb.top107657

Venkataraman K*, Jové V*, Duvall LB (2022) Size quantification of blood and sugar meals in *Aedes aegypti* mosquitoes. *Cold Spring Harb Protoc* **2022**(6): pdb.prot107862

Jové V*, Venkataraman K*, Gabel TM, Duvall LB (2020) Feeding and quantifying animal-derived blood and artificial meals in *Aedes aegypti* mosquitoes. *J Vis Exp* **164**: e61835

MOLECULAR MECHANISMS OF CHROMOSOME SEGREGATION

cf. BIF FUTURA, VOL. 34 | 2.2019

STANISLAU YATSKEVICH
Discipline: Biochemist, MBiochem
Institute: MRC Laboratory of Molecular Biology, Cambridge, UK
Supervisor: Dr David Barford

Eukaryotic organisms use large macromolecular machines to accurately pass chromosomes to two daughter cells during cell division. Errors during chromosome segregation are frequently deleterious to the cell and often result in aneuploidy, leading to the formation of cancer cells. Kinetochores are large protein complexes that assemble specifically at the centromeric chromatin and act as structural scaffolds to support chromosome segregation as well as signalling platforms. The inner kinetochore, also known as constitutive centromere associated network (CCAN), recognizes the centromere protein A (CENP-A) nucleosome (CENP-A^{Nuc}) and harnesses the energy of microtubule depolymerization to move chromosomes to the spindle poles. In human cells, the details of CCAN–CENP-A^{Nuc} assembly were unknown. In my PhD project, I reconstituted the 20-subunit human CCAN–CENP-A^{Nuc} complex recombinantly and investigated its assembly principles and structure using cryo-electron microscopy and protein crystallography. I showed that human CCAN forms a pseudo-nucleosome-like particle that specifically recognizes and fully entraps the linker DNA of the CENP-A^{Nuc}, forming very few contacts with the CENP-A^{Nuc} itself. Specifically, CCAN sub-complexes form a central DNA binding element, which is augmented by a histone-fold module comprising four subunits. Together, they form a vault-like structure that encircles the DNA. My results suggest that this topological entrapment enables kinetochores to withstand both pushing and pulling forces exerted by the mitotic spindle during chromosome segregation. In addition, I determined structures of the reconstituted yeast centromere, which showed a similar mechanism of topological DNA entrapment by the yeast CCAN. My work highlights conserved mechanisms of kinetochore assembly and centromere recognition in evolutionarily different organisms.

PUBLICATIONS

Yatskevich S, Muir KW, Bellini D, Zhang Z, Yang J, Tischer T *et al* (2022) Structure of the human inner kinetochore bound to a centromeric CENP-A nucleosome. *Science* **376**: 844–852

Yatskevich S, Kroonen JS, Alfieri C, Tischer T, Howes AC, Clijsters L *et al* (2021) Molecular mechanisms of APC/C release from spindle assembly checkpoint inhibition by APC/C SUMOylation. *Cell Rep* **34**(13): 108929

Further results of this project can be discussed on *BioRxiv*: doi: 10.1101/2022.12.12.520091

MD FELLOWSHIPS 2022

With its MD fellowships, the Boehringer Ingelheim Fonds helps outstanding medical students to pursue an ambitious experimental project in basic biomedical research. Candidates study in Germany and change their workplace (institution and city) for at least ten months to join an internationally renowned laboratory. Here, we present the 16 fellows who were granted an MD fellowship in 2022.

FELIX BAUMANN

Mechanisms of human APOE-mediated myeloid cell modulation in cancer

JOSHUA BOECKERS

Rescuing a synaptic mismatch: an approach to avoid cortical synaptic dysfunction in a mouse model of PCDH19 disorder

LORENZO COSTA

Biomolecular analysis of STOX1 mutations associated to hypertensive disorders of pregnancy

DOMINIQUE DRMIC

ZIP as potential mediator of encephalitogenic T cell function

SOPHIE ECKL

Manipulating microglia for improving axon regeneration after spinal cord injury (SCI)

INA FREDRICH

Serial analysis of tumor microenvironment during IL-12 GBM therapy

NICOLAJ HACKERT

Alternative splicing dynamics during adaptive immune response

LOUISA HEßLING

Investigating how ion channels and transporters regulate T cells

MIN GYU IM

The role of interleukin-6 in NMOSD and MOGAD relapses

SUSANNA KIRCHER

Amyloid proteins in gastrointestinal pathologies

ALEXANDER LI

Preventing arrhythmia evolution in phospholamban cardiomyopathy by SGLT2 inhibition therapy

TABEA MITTMANN

The role of post-transcriptional regulation by rbms3 in the suppression of breast cancer metastasis

HAI-ANH NGUYEN

Imaging neuronal activity using calcium-sensitive MRI

LARS PEGLAU

Analysis of ApoE uptake and its implications on gene expression changes in melanoma cells

JONATHAN SCHMALZRIDT

Proteomic analysis of adaptive myocardial and valvular changes in a murine mitral regurgitation model

NIKOLAS STEVENS

The influence of pro-inflammatory extracellular ATP on multiple sclerosis

MECHANISMS OF HUMAN APOE-MEDIATED MYELOID CELL MODULATION IN CANCER

FELIX BAUMANN

Duration: 03/22–02/23

Project at: The Rockefeller University, New York, NY, USA

Supervisor: Prof. Sohail Tavazoie, MD, PhD, and Mira Patel, MD

Home University: Münster University Hospital

RESCUING A SYNAPTIC MISMATCH: AN APPROACH TO AVOID CORTICAL SYNAPTIC DYSFUNCTION IN A MOUSE MODEL OF PCDH19 DISORDER

JOSHUA BOECKERS

Duration: 6/22–5/23

Project at: Boston Children's Hospital, Boston, MA, USA

Supervisor: Prof. Hisashi Umemori, MD, PhD

Home University: Münster University Hospital

BIOMOLECULAR ANALYSIS OF STOX1 MUTATIONS ASSOCIATED TO HYPERTENSIVE DISORDERS OF PREGNANCY

LORENZO COSTA

Duration: 11/22–10/23

Project at: Institut Cochin, Paris, France

Supervisor: Dr. Daniel Vaiman

Home University: Heidelberg University Hospital

ZIP AS POTENTIAL MEDIATOR OF ENCEPHALITOGENIC T CELL FUNCTION

DOMINIQUE DRMIC

Duration: 07/22–06/23

Project at: NYU School of Medicine, New York, NY, USA

Supervisor: Prof. Stefan Feske, MD

Home University: Heidelberg University

MANIPULATING MICROGLIA FOR IMPROVING AXON REGENERATION AFTER SPINAL CORD INJURY (SCI)

SOPHIE ECKL

Duration: 3/22–9/23

Project at: F.M. Kirby Neurobiology, Boston, MA, USA

Supervisor: Prof. Zhigang He, PhD

Home University: Heidelberg University

SERIAL ANALYSIS OF TUMOR MICROENVIRONMENT DURING IL-12 GBM THERAPY

INA FREDRICH

Duration: 10/22–9/23

Project at: Center for Systems Biology, Boston, MA, USA

Supervisor: Professor Ralph Weissleder, MD, PhD

Home University: Münster University Hospital

ALTERNATIVE SPLICING DYNAMICS DURING ADAPTIVE IMMUNE RESPONSE

NICOLAJ HACKERT

Duration: 4/22–3/23

Project at: Boston Children's Hospital, Boston, MA, USA

Supervisor: Prof. Maria Gutierrez-Arcelus, PhD

Home University: Heidelberg University Hospital

INVESTIGATING HOW ION CHANNELS AND TRANSPORTERS REGULATE T CELLS

LOUISA HEßLING

Duration: 10/22–9/23

Project at: NYU School of Medicine, New York, NY, USA

Supervisor: Prof. Stefan Feske, MD

Home University: University Medical Center Hamburg-Eppendorf

THE ROLE OF INTERLEUKIN-6 IN NMOSD AND MOGAD RELAPSES

MIN GYU IM

Duration: 3/22–8/23

Project at: John Radcliffe Hospital, Oxford, UK

Supervisor: Professor Dr. Sarosh Irani

Home University: Ruhruniversität Bochum

AMYLOID PROTEINS IN GASTROINTESTINAL PATHOLOGIES

SUSANNA KIRCHER

Duration: 05/22–04/23

Project at: Perelman School of Medicine, Philadelphia, PA, USA

Supervisor: Prof. Dr. med. Roland M. Schmid

Home University: University Hospital rechts der Isar

PREVENTING ARRHYTHMIA EVOLUTION IN PHOSPHOLAMBAN CARDIOMYOPATHY BY SGLT2 INHIBITION THERAPY

ALEXANDER LI

Duration: 4/22–3/23

Project at: Stanford Cardiovascular Institute, Stanford, CA, USA

Supervisor: Prof. Mark Mercola, PhD

Home University: University Hospital of Munich (LMU)

THE ROLE OF POST-TRANSCRIPTIONAL REGULATION BY RBMS3 IN THE SUPPRESSION OF BREAST CANCER METASTASIS

TABEA MITTMANN

Duration: 05/22–04/23

Project at: University of California San Francisco (UCSF), San Francisco, CA, USA

Supervisor: Prof. Hani Goodarzi, PhD

Home University: Münster University Hospital

IMAGING NEURONAL ACTIVITY USING CALCIUM-SENSITIVE MRI

HAI-ANH NGUYEN

Duration: 09/22–07/23

Project at: McGovern Institute for Brain Research, Cambridge, MA, USA

Supervisor: Prof. Alan Jasanoff, PhD

Home University: University of Jena

ANALYSIS OF ApoE UPTAKE AND ITS IMPLICATIONS ON GENE EXPRESSION CHANGES IN MELANOMA CELLS

LARS PEGLAU

Duration: 11/22–10/23

Project at: The Rockefeller University, New York, NY, USA

Supervisor: Prof. Sohail Tavazoie, MD, PhD, and King Faisal Yambire, PhD

Home University: Greifswald Medical School

PROTEOMIC ANALYSIS OF ADAPTIVE MYOCARDIAL AND VALVULAR CHANGES IN A MURINE MITRAL REGURGITATION MODEL

JONATHAN SCHMALZRIDT

Duration: 03/22–02/23

Project at: Harvard Medical School, Boston, MA, USA

Supervisor: Prof. Elena Aikawa, MD, PhD

Home University: Heidelberg University Hospital

THE INFLUENCE OF PRO-INFLAMMATORY EXTRACELLULAR ATP ON MULTIPLE SCLEROSIS

NIKOLAS STEVENS

Duration: 6/22–5/23

Project at: Brigam and Women's Hospital, Boston, MA, USA

Supervisor: Professor Francisco J. Quintana, PhD

Home University: Universitätsmedizin Mannheim

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

WHO DOES WHAT AT BIF?

It has been ten years since we last provided an overview of who does what at BIF and its sister foundations – a long period of time that has brought many new faces.


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The past few years have brought many changes to the three Boehringer Ingelheim foundations: the Boehringer Ingelheim Fonds (BIF), the Boehringer Ingelheim Foundation (BIS), and the Siblings Boehringer Ingelheim Foundation for the Humanities (SBIFfH).

We would like to take BIF's 40th anniversary and the fact that together the foundations have now passed a combined age of 150 years as an opportunity to introduce the team at all three foundations with their main responsibilities.

Our two managing directors 1 **Dr Stephan Formella** and 2 **Marc Wittstock** jointly manage the three foundations and address all organizational activities of the team on a day-to-day basis.

They communicate with the founding family and the foundations' committees and boards and represent the foundations to the network and all external stakeholders.

Concerning the SBIFfH, they jointly oversee the activities of the advisory board and decide on the board's suggestions as to which applications to fund.

With regard to their respective focuses at BIF and BIS, Stephan is Managing Director of Science & Research while Marc is Managing Director of Finance & Administration. Stephan manages the existing programmes and projects and develops new ideas for funding initiatives – currently mainly for BIS. Marc is the quiet force behind the scenes. He is in charge of the budget and all other financial and administrative matters such as cash management, controlling, and administrative and regulatory requirements. Most importantly, he manages the financial assets of the foundations to ensure our financial well-being.

3 **Dr Jan Kullmann** heads the selection process for the PhD fellowships. This involves scrutinizing all applications, organizing peer review, and performing personal interviews with most of the candidates. This requires a great deal of travel and report writing. Jan also runs the travel grant programme and approves the applications. In addition, he is responsible for the selection process in the MD fellowship programme and supports our MD fellows during the application and funding phases.

4 **Vera Schlick** takes care of all incoming applications for our PhD fellowships, which involves answering a plethora of questions from applicants from all over the world. She makes sure that each applicant's documentation is complete and that their data are transferred to the database. She organizes the board meetings and the interviews for PhD candidates, including travel arrangements for the BIF team.

5 **Dr Anja Petersen**, 6 **Sandra Schedler,** and – since January 2023 – 7 **Jana Freier**

Photos: Carsten Costard, BIF


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are the support team for our PhD fellows and alumni and provide the personal support that is one of the hallmarks of BIF. Anja is responsible for strategic and conceptual matters and all science-related topics. Sandra and Jana take care of the day-to-day support of our current fellows and alumni, ranging from travel allowances to fellowship extensions and BIF seminars. In addition, Jana is in charge of the applications for BIF's MD and travel grant programmes.

8 **Kirsten Achenbach** is in charge of all press and public relations activities at BIF as well as the programme for the communication and European alumni seminars. She is the executive editor of BIF's international journal FUTURA and writes many of the articles. Kirsten is also responsible for communications for the other two foundations, for example, for their awards and funding programmes.

9 **Iris Bodenbender** organizes the International Titisee Conferences twice a year offering a "full-service package" to the scientific chairs of the conferences. She is also in charge of travel expenses and manages the secretariat, including office administration and infrastructure.

10 **Andrea Epperlein** is responsible for accounting and many administrative tasks at BIF. For example, she ensures that fellows and travel grant holders all over the world receive their stipends and grants securely and on time. She also works for the SBIFfH, handling applications for publication cost grants.

The following colleagues are part of the BIS team, which shares an office with BIF:

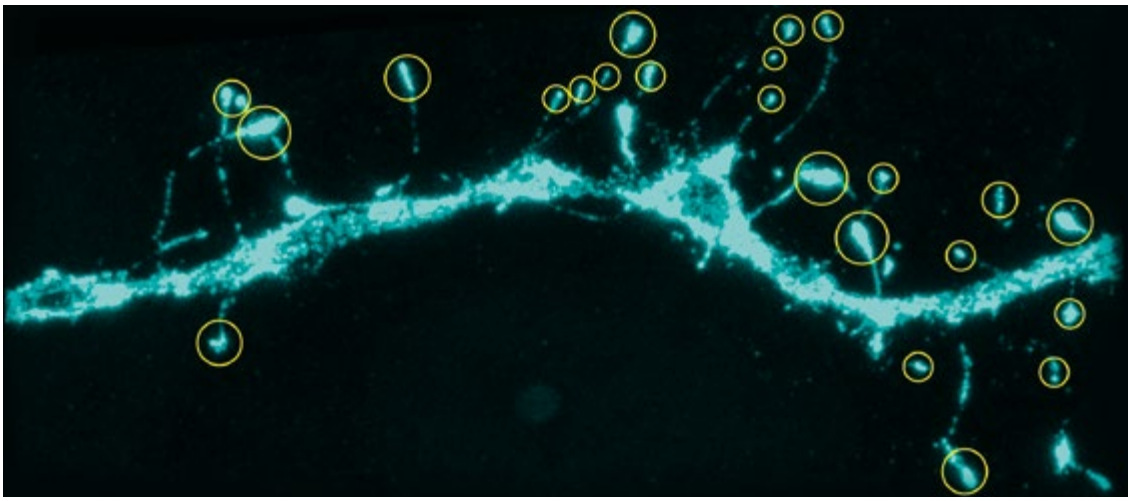
11 **Dr Sabine Löwer** runs the BIS programmes Plus 3, Exploration Grants, and Rise Up! She also oversees institutional funding, the scientific conference programmes, and the Heinrich Wieland Prize. Finally, she develops new funding concepts, evaluates the existing ones, supports the committees and boards in scientific matters, and fulfils representative functions for BIS.

12 **Simone Freimund** (no photo) is the administrative heart of BIS. She supports all applications for the PLUS 3 and Exploration Grants programmes from initial questions to final accounting. She administers the other BIS funding projects, the Boehringer Ingelheim Prize, and the Heinrich Wieland Prize. For this latter award, she organizes the award ceremony and the symposium. She also organizes all the committee and board meetings for BIS and supports Marc Wittstock with BIS's finances.

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.

SILENT SYNAPSES MAKE ADULT BRAINS FLEXIBLE



These tiny filopodia (yellow rings) in the adult brains of mice are silent synapses.

While reading this article, your brain might form new synaptic connections. How do adult brains learn so quickly without forgetting older content? Dimitra Vardalaki and the group of her supervisor Mark Harnett at MIT in Boston, USA, think silent synapses might be the answer. Contrary to established theory, they found that these synapses account for a quarter of all excitatory synapses in the brains of adult mice. Until now, they were thought to be present only during the rapid learning process in early development – until around day 12 in mice or a few months of age in humans.

Dimitra imaged neurotransmitter receptors in dendrites using eMAP, a type of expansion microscopy where all molecules in a cell are physically anchored to a gel substrate. The gel can then be stretched, preserving the spatial relationships of the studied molecules, but allowing super-resolution imaging. The team was astounded to see dendrites in different brain regions of mice covered with filopodia, thin membrane protrusions. These filopodia possessed receptors for the neurotransmitter NMDA, but not for AMPA. As active synapses need both receptors to function, they tested whether the filopodia are silent synapses by trying to activate them. Indeed, they could do so with an electrical signal from the body of the neuron and a glutamate pulse, mimicking the signal of a connected nerve cell. This led to AMPA receptors accumulating at the filopodia within minutes. The now active synapse established a strong connection to the connected nerve cell. As it turned out, activating a silent synapse was much easier than altering a mature one (which did not respond to this treatment). This way, the brain manages to quickly generate new memories while at the same time retaining old ones. These results challenge the assumption that the connections between neurons are established early on and later experiences mostly only modify or delete them. Dimitra and her colleagues are now looking for evidence of silent synapses in human brains and hope to be able to study if and how age and disease impact their number and function.

REFERENCE

Vardalaki D, Chung K, Harnett MT (2022) Filopodia are a structural substrate for silent synapses in adult neocortex. *Nat* **612**: 323–327

Dimitra Vardalaki, fellowship 2020–2022

Photos: Portraits private, D. Vardalaki (top left); Getty Images/slowmotiongli (top right)

SOCIAL ANIMALS: HOW SAME RECOGNIZES SAME

Safety in numbers – many animals group together. But how do their know their brethren?

What does it take to recognize a conspecific and form a herd, a swarm, or flock? Johannes Kappel from Herwig Baier's laboratory at the MPI for Biological Intelligence in Martinsried, Germany, has found a neural circuit for such recognition. Previously, Johannes Larsch from the same group had discovered how little it took to convince a zebrafish larva that it saw one of its own kind: a black dot of the right size moving with the jerky movements typical of zebrafish larvae. In a virtual reality set-up, the fish followed such dots, just as they would real fish. Smoothly moving dots, however, were ignored. The authors used this setting to observe approach behaviour while measuring brain activity. They identified a set of nerve cells in the thalamus that are active during social behaviour. They found that on its way from the eye to the thalamus, the visual signal is already filtered for social cues by nerve cells in the optic tectum. Social signals – those that look like another zebrafish, like the jerkily moving dots, or like real fish – are treated differently by the newly identified thalamic nerve cells. They are passed on with greater urgency to other brain regions involved in social behaviour. When the function of the newly identified nerve cells in the thalamus or the optic tectum was blocked, the fish became uninterested in social interactions – they did not approach virtual fish anymore. The authors thus identified a neuronal pathway controlling how visual signals evoke social behaviour. Humans also possess brain regions that react to facial and body movements. How these regions are involved in our admittedly much more complex social behaviour and whether our thalamus plays a role has not been explored in detail. But perhaps the recognition of "conspecifics" was involved in this research as well, as it is the first paper we know of that features five BIF fellows: Johannes Kappel as first author, co-authors Katja Slangewal and Fabian Svara, and Herwig Baier and Johannes Larsch as senior authors.

Johannes Kappel:
Fellowship: 2019–2022

Katja Slangewal:
Fellowship: 2022–2024

Fabian Svara:
Fellowship: 2011–2013

Herwig Baier:
Fellowship: 1991–1994

Johannes Larsch:
Fellowship: 2010–2012

REFERENCE

Kappel JM, Slangewal K, Förster D, Shainer I, Svara F, Januszewski M, Baier H, Larsch J (2022) Visual recognition of social signals by a tectothalamic neural circuit. *Nat* **608**: 146–152

PAPERS IN THE SPOTLIGHT

OUR IMMUNE SYSTEM USES OLD INFORMATION, BUT CAN LEARN

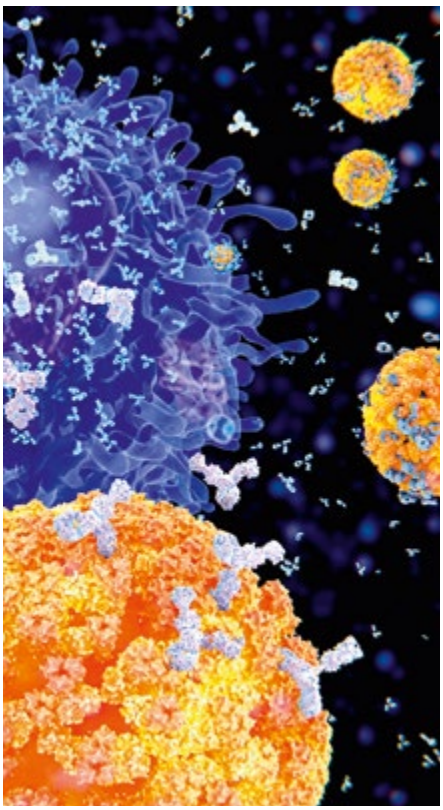


Photo: Getty Images/JUAN GAERTNER/SCIENCE PHOTO LIBRARY

The immune response to a viral infection differs depending on previous exposure.

When you re-encounter a pathogen, your immune system fights the infection by producing antibodies from memories formed during the initial infection or vaccination. Even if the strain has changed and your immune system has since encountered another strain, often your body still produces antibodies based on the very first exposure. It has long been appreciated that this process may result in a suboptimal antibody response to repeat infections with variant strains of a pathogen.

This phenomenon, known as "original antigenic sin" (OAS), has direct implications for vaccine development. To study its effects in detail, researchers need to be able to track which B cells produced the antibodies floating in the blood serum. Ariën Schiepers and the group led by his supervisor Gabriel Victora at The Rockefeller University, NY, USA, have now devised the first method do just that. They tagged antibodies with a molecular flag telling them from which cohort of B cells – primary or a later exposure – the antibodies stem, as well as when the B cells produced them – before or after a particular exposure event. When they repeatedly exposed mice to the same virus strain, they found that the antibodies stemmed almost exclusively from the primary cohort of B cells. They computed that the development of new antibodies was reduced 55-fold, showing an active OAS-type suppression. However, if the repeat exposure(s) involved a strain differing in just a few amino acids in the viral surface antigen, the effect of OAS decreased to only about three times fewer antibodies from new B cells. They also found that antibodies from new B cells were tailored to target mutated antigens inherent to the new strains. Thus, the study demonstrates that while the immune system is wired to respond in an OAS-type manner, antibody responses are updated if the re-exposure strain is sufficiently different. These results are important to better understand how our immune system reacts to recurring exposure to identical and differing strains and will thus help us to design better vaccines against viruses such as flu and SARS-CoV-2.

REFERENCE

Schiëpers A, van 't Wout MFL, Greaney AJ, Zang T, Muramatsu H, Lin PJC, Tam YK *et al* (2023) Molecular fate-mapping of serum antibody responses to repeat immunization. *Nat* **615**: 482–489

Arien Schiëpers, fellowship 2018–2020

PROFILES

LEIF LUDWIG
Institute: Berlin Institute of Health and Max Delbrück Center, Berlin, Germany
MD fellowship: 2011–2012

MD fellow **Leif S. Ludwig** has received the 2023 Paul Ehrlich and Ludwig Darmstaedter Young Investigator Award for developing a new method to analyse the lifelong regeneration of cells in human blood, which is up to 1,000 times quicker, more reliable, and less expensive. With it, researchers can now determine the activity of single blood stem cells in humans with little effort. The award comes with 60,000 euros for research. He has also been awarded the Heinz Maier Leibnitz Prize of the Deutsche Forschungsgemeinschaft (DFG). It is Germany's most important junior research award and now comes with 200,000 euros for further research.

PROFESSOR JULIA KAMENZ
Institute: University of Groningen, the Netherlands
Fellowship: 2009–2011

In the last round of the 2022 funding programme, **Julia Kamenz** was awarded an ERC Starting Grant for her project "CellCycleInVitro". She intends to dissect the molecular mechanism of one of the most fundamental biological timepieces: the cell cycle clock, which underlies and drives cell divisions. In a novel approach, she will isolate the individual parts of the cell cycle machinery and systematically assemble them into a "ticking" cell cycle clock.

Photos: Schiëpers: private, Kamenz: University of Groningen, Ludwig: private, Teichmann: private, Meissner: MPI-MG

PROFESSOR ALEXANDER MEISSNER
Institute: MPI for Molecular Genetics, Berlin, Germany
Fellowship: 2003–2005

PROFESSOR SARAH TEICHMANN
Institute: Welcome Trust Sanger Institute, Hinxton, UK
Fellowship: 1997–1999

Two of this year's 218 ERC Advanced Grants – highly prestigious, competitive grants worth about 2.5 million euros – went to the BIF fellows **Alexander Meissner** and **Sarah Teichmann**, who are thus among the 13.2% of applicants to secure funding. In his project "CancerEpigenome: Dissecting the Cancer Epigenome – Fundamental Lessons from Developmental Biology", **Alexander** will study biochemical, genetic, and physiological aspects of the placenta and cancer epigenomes, which are strikingly similar. Using self-developed techniques and methods, he will investigate the specific molecular switches in the epigenome of the placenta, which are likely to also exist in the cancer epigenome. In her project "ThyDesign: Learning from the Thymic Human Cell Atlas for T Cell Engineering", **Sarah** will create a 3D cell atlas of the thymus to understand the external and internal influences in the microenvironment of the thymus that govern the process of T cell differentiation. She hopes the findings will advance T cell engineering, which has huge potential not only as a research tool, but also in medical applications such as immunotherapy. Sarah has also been awarded the 2023 FEBS-EMBO Women in Science Award by the Federation of the European Biochemical Societies (FEBS) and EMBO in honour of her outstanding contributions to the life sciences, particularly in protein assembly, regulation of gene expression, and single-cell phenotyping. The award also recognizes Sarah as an inspiring role model for women in science.

WHO'S WHO AT BIF?

Professor Christian Klämbt, member of BIF'S Board of Trustees

Christian Klämbt was born in Bonn, Germany, in 1960. He studied biology and graduated with a PhD from the University of Freiburg in 1987. After postdoctoral stays with José Campos-Ortega at the University of Cologne and Corey Goodman at the University of California, Berkeley, he became junior group leader at the Institute of Developmental Biology at the University of Cologne in 1991. Christian Klambt received a Heisenberg fellowship in 1993 and was appointed full professor at the University of Münster in 1997. There, he has served as speaker of two Collaborative Research Centres (SFB 629, 2003–2015, and SFB 1348, 2018–present). From 2008 to 2015, he was also on the DFG review board "Fundamentals of Biology and Medicine". He joined BIF's Board of Trustees in 2013. He is married and has two children.

What is your most remarkable BIF experience?
Before I joined BIF's Board of Trustees, I was impressed by the extremely positive responses from my graduate students who were supported by BIF. Since becoming a board member, I've enjoyed discussing the many superb projects in a great team that has no other agenda than to support excellence and originality in science.

Why did you choose a science-based career?
I've always enjoyed asking questions.

What's your favourite activity?
What I do at the moment.

What's your remedy for stressful situations?
Don't panic, think carefully, and I'm sure you'll find a solution.

What fault in others can you tolerate best?
I can tolerate a lot, except for ignorance and aggression.

Your advice for fellowship holders?
Stay curious and enjoy what you're doing.

Which scientific achievement do you admire most?
I was most influenced by Jose Campos-Ortega and Corey Goodman, who opened my eyes to how genetics and cell biology can be combined, and by the creative ideas of Seymour Benzer, who pioneered the field of neurogenetics.

Name one thing you could not live without.
My Family.

Photo: WWU Münster

A BIF FELLOW'S GUIDE TO ...

PHILADELPHIA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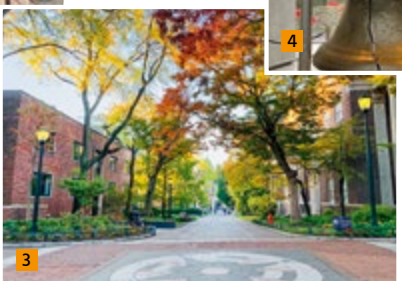
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Travelling is fun – especially if you get insider tips from locals! In each edition of FUTURA, one fellow shows you around their city. In this edition your guide is Susanna Kirchner, who reports from Philadelphia, USA, best known as Philly and for it's cheesesteaks.

FACTS & FIGURES

Country: USA
Population: about 1.6 million
Area: about 367 km²
Famous for rich American history, the Liberty Bell, Independence Hall, Love Park, Philly cheesesteak, the film *Rocky*, the Eagles, the Reading Terminal Market
Websites: discoverphl.com, visitphilly.com

WHERE TO STAY

Apple Hostels: located in the heart of the Old City, close to the Independence National Historic Park.
Club Quarters Hotel, Rittenhouse Square: situated in Center City in walking distance of stores, restaurants, bars, and Rittenhouse Square.

NIGHTLIFE

McGillin's Olde Ale House: oldest continually operating tavern in Philly.
Howl at the Moon: live music bar with dance floor.
PHS Pop Up Garden at South Street: spacious beer garden with blooming flowers, plants, and trees.

RESTAURANTS

Café La Maude: French–Lebanese inspired brunch dishes in a quaint Parisian atmosphere, BYOB.
Brauhaus Schmitz: German beer bar serving house-made sausages, pretzels, and schnitzel.
Marrakesh: authentic Moroccan food, belly dancers on weekends.
Sampan: offers modern Pan-Asian small plates and a tasting menu ideal for sharing.

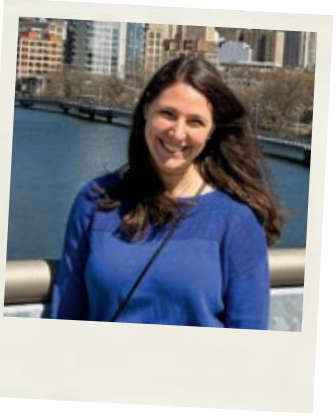
ACTIVITIES

Winter: visit the Museum of Art 1 and snack your way through the Reading Terminal Market, a famous indoor farmer's market.
Spring: enjoy a great view of Philly's skyline from South Bridge and walk along the Schuylkill River Trail.
Summer: check out the floating beer garden at the Spruce Street Harbor Park at Penn's Landing and relax in a hammock.
Fall: visit the UPenn campus to see dazzling fall colors 3 and attend the annual Oktoberfest in South Street.

BEST SIGHTS

Elfreth's Alley 2: America's oldest residential street.
Liberty Bell 4: one of history's most famous symbols of freedom and justice, free admission, best to visit during the week or in the morning to avoid long lines.
Cira Green: one of my favorite spots in Philly, an urban park on the 11th floor of a parking garage with a striking view of the Philly skyline, a green space for relaxing and a massive screen to watch movies.

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



Susanna Kircher is 26 years old and comes from Austria. She is studying at the University of Pennsylvania and her supervisor is Professor Christoph Thaiss.

Photos: private

PROFILES

ASSOCIATE PROFESSOR
SIMON ELSÄSSER
Institute: Karolinska Institutet, Stockholm, Sweden
Fellowship: 2008–2010

PROFESSOR KAI PAPENFORT
Institute: University of Jena, Germany
Fellowship: 2006–2008

ASSISTANT PROFESSOR
MILKA SARRIS
Institute: University of Cambrigde, UK
Fellowship: 2003–2006

Three BIF fellows have received **ERC Consolidator Grants**. These mid-career grants come with up to two million euros in funding over a period of five years. The 2022 call attracted 2,222 proposals, 321 of which received a total of 657 million euros, making for a success rate of about 14%. In his project "ChromaDYN: Quantitative Multimodal Pulse-and-Label Time-Resolved Chromatin Maps", **Simon Elsässer** will study questions of embryonal development such as how cells determine – and later remember – which line of development to follow, how different cell identities are encoded, and how the right genes are turned on and off at the right time. In his project "ArtRNA – Artificial RNA Regulators to Probe, Control, and Design Gene Regulatory Networks in Bacteria", **Kai Papenfort** will develop artificial sRNA molecules to intervene in the genetics of bacteria and study the molecular mechanisms of microbial gene expression. He aims to understand gene functions and regulation circles in organisms in general and systematically investigate the response to antibiotics in pathogenic bacteria. **Milka Sarris** has received funding for her project "LongWayFromFlam: The Uncharted Journeys of Inflammatory Cells and their Functional Implications". She will use zebrafish to study which cellular signals tell leukocytes to travel to the site of an infection, how these cells distinguish between healthy and inflamed tissue, and how their number is regulated at their destination to avoid an overshooting inflammatory response.

PROFESSOR IVAN DIKIC
Institute: University of Frankfurt, Germany
Postdoctoral award: 1997

Ivan Dikic has received the 2023 Louis-Jeantet Prize for Medicine for his contributions to our understanding of the functions of ubiquitin and the mechanisms of ubiquitination. He shares the award with Brenda Schulman. Established in 1986, the prize recognizes completed work and aims to encourage innovative research projects in biomedical research. Of the prize money of 500,000 Swiss francs, 90% goes to fund ongoing research, while 10% goes to the researcher personally.

PROFESSOR SELHUBER-UNKEL
Heidelberg University, Germany
Fellowship: 2004–2006

Christine Selhuber-Unkel has received the Lautenschläger Research Prize 2023. Every two years, the prize honours special accomplishments in leading-edge research by scientists connected to Heidelberg University. Christine was recognized for her outstanding research on biohybrid, life-inspired microsystems, which researchers hope will lead to "living materials".

Photos: Elsässer: private; Papenfort: University of Jena; Sarris: private; Dikic: University of Frankfurt/Uwe Dettmar; Selhuber-Unkel: Heidelberg University

UPCOMING EVENTS

19–25 AUG 2023
Progress seminar for current PhD fellows working in Europe 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 with the invitation.

15–17 SEP 2023
European alumni seminar, Glashütten, Germany
In a nod to BIF's anniversary, the topic chosen for this year's annual meeting of former BIF PhD and MD fellows based in Europe is "The Power of Networks – 40 Years of BIF".

12–16 OCT 2023
North America meeting, Woods Hole, USA
Seminar for alumni and PhD and MD fellows working in North America. Participants will present their scientific results. The programme is complemented by keynote presentations and talks on topics such as career opportunities and includes tours of the scenic surroundings on Cape Cod.

25–29 OCT 2023
127th International Titisee Conference, Titisee, Germany
The 127th ITC, titled "Somatic Mosaicism", will be chaired by Benjamin L. Ebert (Boston, MA, USA) and Peter Campbell (Hinxton, Cambridgeshire, UK) and focus on somatic mutations in health and disease across organ systems, from foetus to old age. It will also address research and therapies.

ITC participation is by invitation only.

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

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