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Extreme Life, Extreme Science
Recent discoveries are reshaping our understanding of deep-sea life

Projects and Results
Eighteen new PhD projects and eight completed theses

A BIF Fellow's Guide to Amsterdam
Discover a city full of charming canals and cultural heritage

The cover illustration shows astrocytes, a type of glial cell. Glial cells, the support cells of the nervous system, are found in both the central and the peripheral nervous systems. Rather than being passive bystanders, glial cells are now recognised as key regulators of tissue homeostasis and inflammation. In her PhD project, BIF fellow Julia Karjalainen examines how nerve-associated glial cells in the skin regulate immune responses in atopic dermatitis (see page 23).

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Funding Where Safe Bets End

‘To create something truly great, you have to accept that the risk of failure is as high as the dimension of the possible breakthrough.’

The quote on the left is from BIF alumnus Daniel Dunkelmann from the Max Planck Institute of Molecular Plant Physiology in Potsdam, Germany. We cite it here because we believe it captures the very essence of BIF’s funding philosophy. The quote is part of the answer he gave when asked why his project to develop a synthetic chloroplast genome was funded by the British Advanced Research and Invention Agency (ARIA), and not its German counterpart, SPRIND. The project’s funding – £9.1 million or €11 million – is as substantial as its potential gains: if successful, it could transform agriculture and the bioeconomy by enabling us to optimise crops that produce drugs, biofuels, and tailored materials, while at the same time absorbing CO_2.

We think it is telling that not just one, but two, BIF alumni – the other is Daniel’s group leader Ralph Bock – are closely involved in leading such a risky but potentially game-changing project. BIF, together with its board members, has always striven not just to fund bread-and-butter research, but to support outstanding, innovative science. And such research, by its very nature, cannot play it safe and comfortable. That is why we support people who take risks – scientists who stretch the boundaries of what is known, and who step into the unknown with curiosity and courage.

That kind of science isn’t easy. It comes with uncertainty, failed experiments, and long nights in the lab spent questioning not just hypotheses, but sometimes oneself. It can feel isolating. And in a system that often hides negative results and publishes only positive outcomes, the emotional cost of risk-taking can be high. But at BIF, we see that struggle for what it is – a sign of high ambition. And that means that if you fail, it might be because you tried something new. If you get lost, you get lost because you went into uncharted territory. That is not failure.

True, taking these kinds of risks does not always pay off. But it is the only way to generate the discoveries that have the potential to shape our future.

At BIF, we believe in that future. And, more importantly, we believe in the people striving to reach it. That’s why our approach has always centred on trust – trust in the scientists we fund, and in the journeys they take. We don’t just evaluate projects; we support individuals. We allow for uncertainty – that space between what doesn’t work and what hasn’t yet been discovered – and we stand by our fellows while they search for a path to clarity. We don’t fund fixed plans or guaranteed outcomes, but people who dare to explore uncharted ground.

That’s why we give our fellows the freedom to work within that space – to question, to persist, and to grow.

Stephan Formella

Marc Wittstock

Neural Circuits, not Social Rules, May Govern Animal Swarms

Flocks of birds mesmerise us time and again with their seamless motion. Traditionally, such collective behaviour has been explained by simple rules: align with neighbours, avoid collisions, stay close. But a new theoretical model from researchers at the University of Konstanz and the Max Planck Institute for Behavioural Biology suggests it may instead arise from the brain's intrinsic circuitry. The team proposes that a ring attractor network – a neural circuit for encoding direction – enables animals to track one another relative to environmental landmarks. This is called allocentric coding and leads to synchronised neural activity across individuals, producing spontaneous group alignment. By switching between allocentric and egocentric (body-based) perspectives, individuals can balance global orientation with local responsiveness. Simulations show this improves swarm stability and cohesion. The findings suggest that swarming may emerge from general-purpose neural mechanisms, rather than specialised social rules – offering new insights into the evolution of collective motion.

Salahshour M, Couzin ID. Allocentric flocking. Nat Commun. 2025;16:9051.

Credit: Stocksy / Tim Booth

How **Fermentation** Shapes the Taste of Fine Chocolate

Some folks claim they do not like chocolate – yes, really! For the rest of us, that's a bit like saying you don't like joy. Still, even the most devoted chocoholics know the truth: not all bars are created equal. A new study in *Nature Microbiology* suggests this may have less to do with cocoa bean genetics or roasting, and more to do with microbes.

Cocoa beans must ferment before they become chocolate. Unlike in wine or cheese production, where microbes are deliberately added, cacao fermentation usually occurs spontaneously – driven by local microbial communities that vary by region, climate, and handling. Researchers in the UK and Colombia wanted to understand how much these microbes shape flavour.

They collected beans from three Colombian regions – Santander, Huila, and Antioquia – and tracked temperature, pH, and microbial composition during fermentation. All beans shared similar genetic backgrounds, but the flavour profiles of the resulting cocoa liquors differed significantly. Tasters described Santander and Huila samples as rich and complex, with notes of berries, coffee, and roasted nuts. In contrast, the flavour of the Antioquia samples was simpler and more bitter.

Microbial analysis showed that certain yeasts – particularly *Torulaspora* and *Saccharomyces* – were more prevalent in the better-tasting batches. To confirm causality, the researchers created a controlled fermentation using synthetic microbial communities. Beans fermented under these lab conditions developed the same flavour attributes as the finest farm samples.

The findings show that microbial dynamics, pH, and temperature jointly influence chocolate flavour. With tighter control, chocolate producers may be able to craft designer fermentation profiles – yielding consistently high-quality chocolate.

Gopaulchan D, Moore C, Ali N, Sukha D, Florez González SL, Herrera Rocha FE, et al. A defined microbial community reproduces attributes of fine flavour chocolate fermentation. Nat Microbiol. 2025;10(9):2130-2152.

Wired Without a Brain: **Comb Jelly** Connectome Reveals Unique Circuitry

Comb jellies are among the most enduring animal lineages on Earth. For over 500 million years, they have drifted through the oceans, surviving multiple mass extinctions. Their translucent, shimmering bodies house a nervous system radically unlike any other – decentralised, brainless, and still poorly understood.

Now, researchers have mapped the first complete connectome of such a system. Other mapped nervous systems – such as those of nematodes, marine worms, sea squirt larvae, and fruit flies – all feature a central nerve cord or brain. In contrast, the comb jelly *Mnemiopsis leidyi* coordinates movement via its aboral nerve net (ANN) – a neural network located on the side opposite the mouth.

The ANN lies within the aboral organ, a gravity-sensing structure that helps the animal stay oriented in the water column. At its core are four balancer cells topped with motile cilia. These respond to the shifting weight of a statolith, triggering directional ciliary beating. The connectome shows that just three syncytial neurons – cells containing multiple nuclei within a shared membrane – innervate the balancer cells. One large neuron contacts all four; two smaller neurons each target a specific pair. High-speed imaging confirmed that all cilia begin beating together but stop in pairs, reflecting the ANN's architecture.

Strikingly, none of the ANN neurons receive synaptic input from the balancer cells. This suggests the network functions not as a sensory integrator but as a coordination hub, potentially regulated by intrinsic activity or neuropeptides. The ANN neurons also differ structurally from those in the comb jelly's subepithelial nerve net, revealing two morphologically distinct syncytial systems within a single organism.

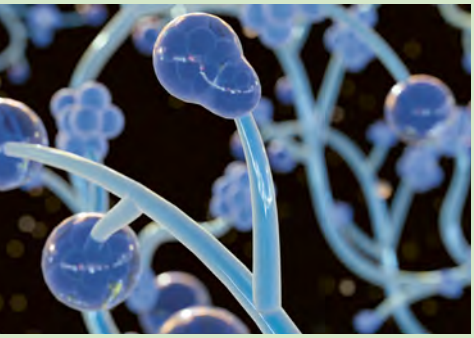
The findings offer rare insight into how decentralised nervous systems organise behaviour – and into the deep evolutionary history of neural circuitry.

Jokura K, Jasek S, Niederhaus L, Burkhardt P, Jékely G. Neural connectome of the ctenophore statocyst. eLife. 2025;14:RP108420.

Candida Albicans' Delicate Balancing Act

Human skin and mucous membranes are home to countless microbes that coexist with us without causing disease. One of these is *Candida albicans*, a fungal commensal that typically colonises the gut, skin, and oral cavity without harm. But in untreated HIV infection or other forms of immune suppression, C. *albicans* can turn pathogenic, causing infections that are both painful and potentially life-threatening.

A new study reveals how C. *albicans* maintains long-term colonisation of the oral mucosa: by producing the peptide toxin candidalysin in precisely controlled amounts. Too little, and the fungus cannot establish itself. Too much, and the immune system detects and clears it. This delicate balance, uncovered by European researchers in Zurich, Jena, and Paris, explains how C. *albicans* survives in healthy hosts while remaining poised to become pathogenic.



Our fungal resident *Candida albicans* produces just enough toxin to stay put without setting off immune alarms.

Candidalysin, previously known for its role in damaging host cells during infection, now appears essential even for benign colonisation – acting as a molecular 'door-opener' for fungal adhesion to mucosal surfaces. In mouse models, virulent strain SC5314 produced large amounts of candidalysin, provoking inflammation and rapid clearance. In contrast, strain 101, naturally adapted to the mouth, produced much less toxin and persisted undetected.

Key to this regulation is the gene EED1, which controls growth and indirectly modulates toxin production. Genetically modifying its activity confirmed its role in calibrating candidalysin levels. Bioinformatic analysis also indicated that this balance is evolutionarily conserved.

The findings reveal candidalysin's dual function: a virulence factor under pathological conditions, and a colonisation factor during commensalism. While not yet translatable into oral therapies, related work suggests that neutralising the toxin may reduce tissue damage in vaginal infections.

Fróis-Martins R, Lagler J, Schille TB, Elshafee O, Martinez de San Vicente K, Mertens S, et al. Dynamic expression of candidalysin facilitates oral colonization of *Candida albicans* in mice. Nat Microbiol. 2025;10:2472–2485.

Concrete Companions: **Lizards Network Tightly**

How social lizards are depends on where they live.

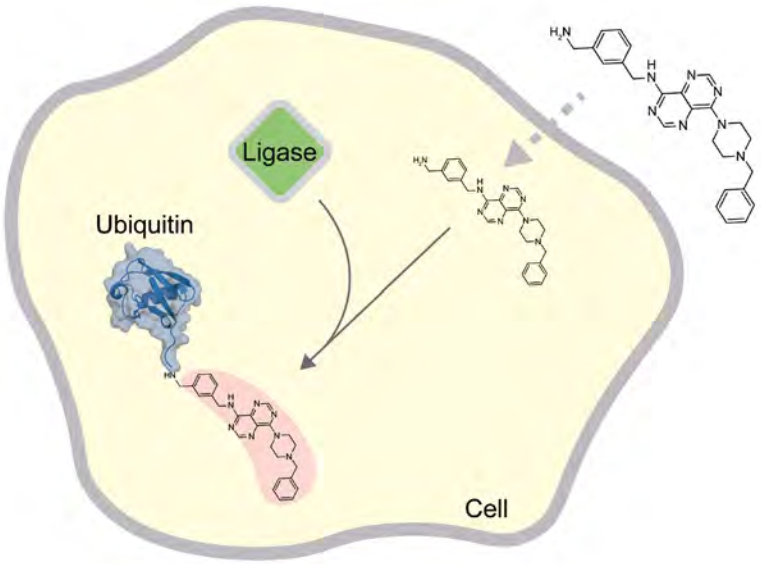
City people call rural types slow and chatty, rural folks see urbanites as rude and rushed. But our surroundings shape how we interact – from how much space we expect to how often we talk. City dwellers often develop larger but weaker social networks, show greater tolerance for crowding, and rely more on indirect communication. Rural populations tend to form smaller, tighter-knit groups with more frequent face-to-face interactions and stronger local ties. A new study shows that similar effects can occur in wildlife. But in wall lizards (*Podarcis muralis*), the pattern is reversed: city-dwelling lizards are significantly more social than their rural counterparts.

Normally highly territorial and solitary, wall lizards in urban areas were found to interact more frequently, maintain more contacts, and form tighter social structures. 'That's remarkable for a species that usually avoids others', says first author Avery Maune, a doctoral researcher at Bielefeld University, Germany.

The team used social network analysis to quantify relationships among individuals in Croatian populations. Lizards in urban settings showed more interactions and stronger social bonds. This behavioural shift appears to be shaped by the physical environment: limited hiding places, sealed surfaces, and uneven resource distribution – such as basking sites and food – force animals into closer proximity.

Rather than increasing aggression, these conditions seem to foster social tolerance. 'Urban life pushes lizards into contact, and they adjust', says Maune. Some humans, trapped in city traffic with an angry neighbour leaning on the horn, might well wish others were a bit more like those lizards.

Maune AL, Wittenbreder T, Lisičić D, Caspers BA, Camerlenghi E, Damas-Moreira I. City lizards are more social. Biol Lett. 2025. doi:10.1098/rsbl.2025.0326.



The ligase HUWE1 can tag synthetic molecules inside cells.

Credit: Blanca Jaime Banos / MPI for Multidisciplinary Sciences (top)

A Surprising Tag

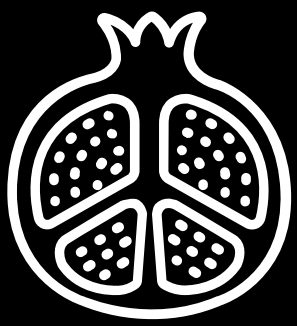
As its name suggests, ubiquitin is found ubiquitously in human cells. It controls the fate of thousands of proteins, determining not only their degradation, but also their localisation, activity, and molecular interactions. Central to this system are ubiquitin ligases: enzymes that recognise specific target proteins and attach ubiquitin to them. When this tagging process is disrupted, for example, proteins may show up in the wrong place, interact with the wrong partners, or fail to act. As a result, people get sick. Therefore, drug developers are trying to find ways to manipulate ubiquitin ligases to treat patients. Though to date, only a small fraction of the more than 600 human ligases are considered druggable.

A new study reveals an unexpected property of the human ubiquitin ligase HUWE1: it can tag not only cellular proteins, but also artificial drug-like small molecules. These findings come from a multidisciplinary team led by Sonja Lorenz at the Max Planck Institute for Multidisciplinary Sciences in Göttingen, Germany. HUWE1 is a ligase with key roles in tumour biology and neurodevelopmental disorders. Although researchers have identified small molecules that seem to inhibit HUWE1, they do not know how they work.

Lorenz's team discovered that the tested compounds are not true inhibitors. Instead, HUWE1 recognises these small molecules as substrates and ubiquitinates them directly. When added in excess, they compete with the natural protein targets of ubiquitin, giving the illusion that HUWE1 is inhibited. This mechanism was validated not only *in vitro* but also in living cells, where synthetic molecules were found to carry ubiquitin tags. Notably, other ubiquitination enzymes besides HUWE1 also contributed to this tagging, marking the first observation of ubiquitination on synthetic, drug-like compounds in cells.

The discovery could open up opportunities for therapeutic advances, as Lorenz notes: 'Our discovery offers tangible strategies for developing new molecular tools to modulate the cellular ubiquitin system and, in turn, influence disease processes'.

Orth B, Pohl P, Aust F, Ji Y, Seenivasan A, Dybkov O, et al. Selective ubiquitination of drug-like small molecules by the ubiquitin ligase HUWE1. Nat Commun. 2025;16:8182.



92 PERCENT

lithium recovery is now possible thanks to punicin, a natural compound extracted from pomegranate leaves. With lithium in high demand for batteries, cheap and effective recycling methods are needed. Researchers at TU Clausthal in Germany have now optimised the natural punicin. When added to molten slag – the hot, leftover material from metal production – they achieved excellent recovery rates.

Source: Fischer MH, Zgheib A, El Hraoui I, et al. Inverse punicines: isomers of punicine and their application in LiAlO2, melilite and CaSiO3 separation. Separations. 2025;12(8):202.

As one of the very few octopuses, the glowing sucker octopus (*Stauroteuthis syrtensis*) shows bioluminescence; in its case, from a line of modified suckers along its arms. This small octopus lives close to the bottom, between 500 and 4,000 metres depth in the North Atlantic Ocean.

Where Extreme Life Meets Extreme Science

By Mitch Leslie

The deep sea makes up the majority of Earth's living space, yet much of it remains poorly understood. Long assumed to be sparsely populated, it is now known to harbour complex ecosystems driven by chemical energy, not sunlight. Recent discoveries – from tubeworms nearly 10 kilometres down to intricate microbial symbioses – are expanding our understanding of where and how life can persist. As technological advances open up the ocean floor, researchers are learning more and more about the diversity, interconnectedness, and beauty of these systems and the risks posed by human intrusion.

During the summer of 2024, the Chinese submersible *Fendouzhe* was cruising near the bottom of the Kuril–Kamchatka Trench in the northwest Pacific Ocean when the crew noticed what appeared to be stalks protruding from the mud. It turned out that the brownish filaments were tubeworms up to 30 cm long, and clambering among the strands were other pale, spiky worms that could be more than 6 cm long. What made the observation noteworthy was that the animals were living at a depth of 9,533 m, about 2,000 m deeper than the previous record for such communities – and almost 1,200 m deeper than the deepest recorded fish, a member of the snailfish genus, spotted in 2022 at 8,336 m.

'The deep sea is 80% of the planet's living space and its largest biome', says ecologist and biogeochemist Peter Girguis of Harvard University. The revelation that such complex communities can thrive nearly 10 km beneath the surface, detailed in *Nature* in 2025, is just one in a series of discoveries that have transformed how scientists think about this biome. For decades, researchers knew that organisms had adapted to live far below the ocean's surface, such as the famous anglerfishes that lure prey with a fishing pole-like protrusion from their forehead. But scientists long thought that because photosynthesis is not possible below about 200 m, life on the barren plains of the sea floor was sparse and dependent on organic material that drifted down from the upper layers of the ocean, including the continuous shower of detritus known as marine snow.

Starting with the landmark discovery in 1977 of ocean-floor oases teeming with life, scientists have come to realise that the deep sea also supports many diverse, rich communities. This profusion of life is largely possible because of microorganisms 'that use chemicals to do what plants do – turn carbon dioxide into sugars – but in total darkness', says Girguis. The identification of these ecologically important microbes not only forced scientists to rethink their ideas about the deep sea but also led to 'a paradigm shift in our view of how life works', says oceanographer Ian MacDonald of Florida State University. 'The discovery that the source of energy doesn't have to be sunlight changed the thinking about how life can exist and how it might have evolved.'

A new view of life

The researchers who triggered the re-evaluation of deep-sea life were geologists and oceanographers, not biologists, and they weren't looking for unusual animals. In 1977, they were using the submersible *Alvin* to hunt for structures called hydrothermal vents in the Pacific Ocean near the Galapagos Islands. The vents are cracks in the ocean floor that release extremely hot, mineral-laden water. The scientists located the

Credit: David Shale (DEEPOL by plainpicture)

vents they were searching for, but they were shocked to also find clams, crabs, fish, and white, metre-long tubeworms living nearby. 'Nobody had seen anything like this and had any idea what it could mean', says MacDonald. And since nobody expected life at the vents, the scientists had not brought formaldehyde to preserve specimens of the animals. They had to use the next best thing they had on board – vodka and whisky.

Scientists now know much more about the vents and the unusual organisms that live there. Vents occur at mid-ocean ridges, strings of underwater mountains where the plates of the Earth's crust are separating and new sea floor is forming. The water jetting from the fissures can be more than 400 °C (it doesn't boil because of the extreme pressure). Some vents release water containing metals and sulphides that precipitate when they hit cold, oxygen-rich seawater, producing a fine black powder resembling smoke. Over time, these so-called black smokers form chimney-like tubes that can grow to more than 50 m tall. Water rich in barium, calcium, and silicon, by contrast, leads to pale structures known as white smokers.

Microbes 'are the world's best biochemical engineers', says Girguis. Hydrothermal vent communities depend on their chemical talents. On land and in shallow waters, plants and algae make food by combining carbon dioxide with water to produce sugars, using sunlight as an energy source. During the process, water is oxidised, losing electrons, and carbon dioxide is reduced, gaining them. In the pitch-black dark at the vents, in contrast, some microbes obtain energy through a different process known as chemosynthesis. During these reactions, hydrogen sulphide is often oxidised and chemicals such as oxygen or carbon dioxide are reduced, releasing energy that the microbes use to synthesise sugars.

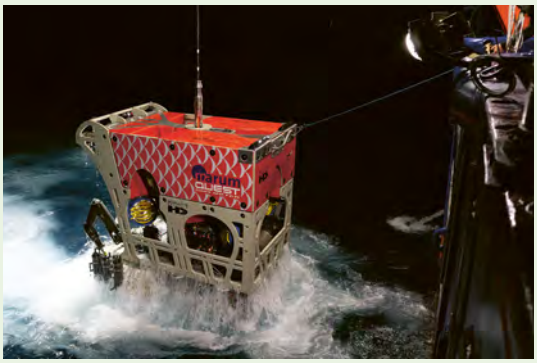
The food produced by chemosynthetic microbes sustains tubeworms, which harbour colonies of the microorganisms in their tissues and are totally reliant on their partners – the worms don't even have a mouth or digestive tract. Chemosynthetic organisms also directly or indirectly support other vent residents, including crustaceans, fish, snails, and, as researchers reported in 2023, a bevy of parasites. The conventional wisdom was that parasites were rare at vents, says marine ecologist and biological oceanographer Lauren Mullineaux of the Woods Hole Oceanographic Institution, Boston, USA. But when she and her graduate student Lauren Dykman dissected 11 types of vent animals, they found that the creatures were riddled with parasites, especially worms known as liver flukes. The parasites 'are pulling the strings behind the curtain', Mullineaux says, because they have a powerful effect on the fitness of their hosts' populations and thus affect the whole vent community.

Not just vents

There are other oases of life in the deep sea. Cold seeps often occur on continental margins where there are thick

Remotely operated vehicles (ROVs)

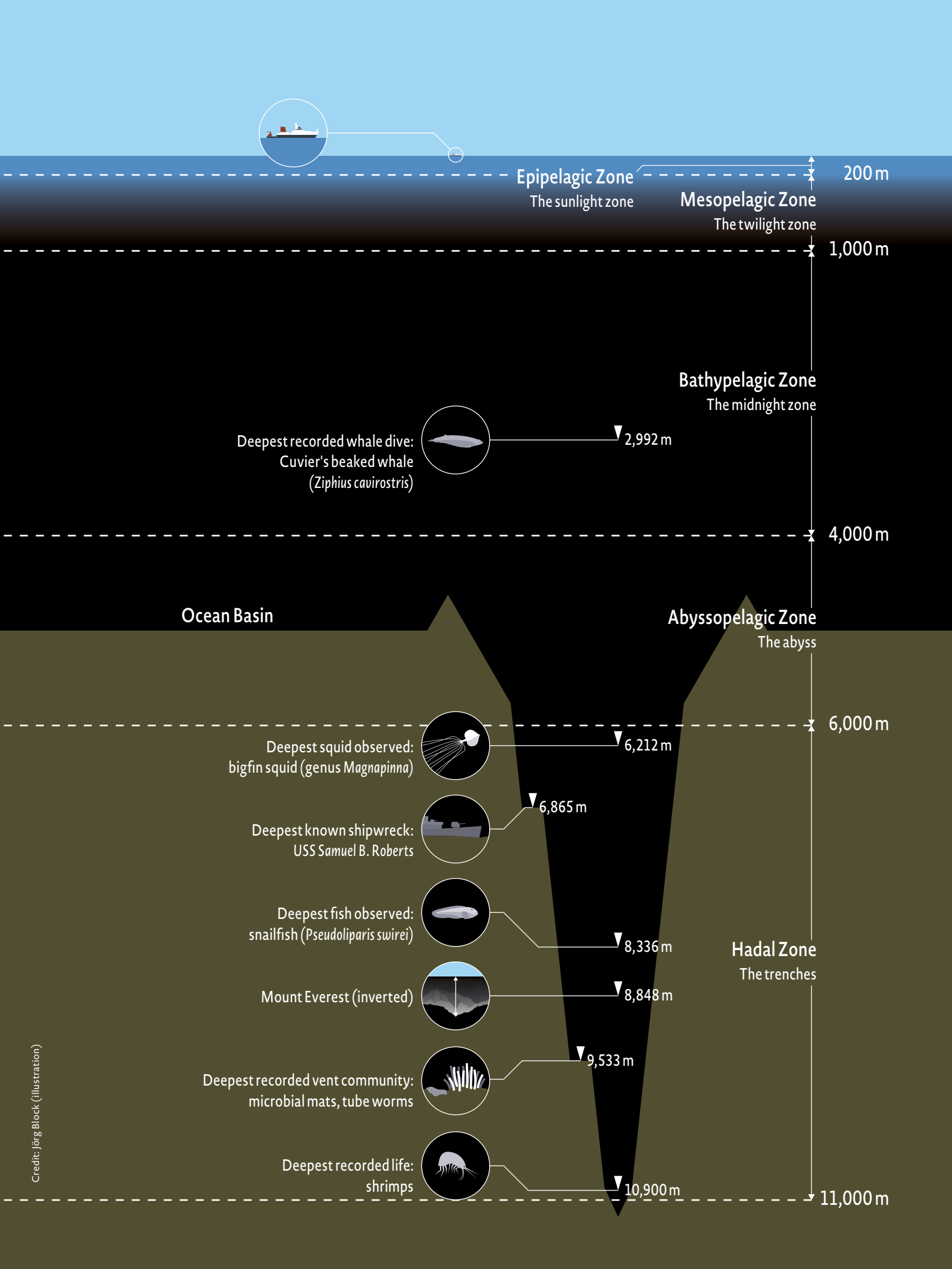
Remotely operated vehicles remain attached by a cable to their support ship as they travel underwater. Using high-definition images delivered in real time, a pilot flies the vehicle while other crew members use the instruments to perform experiments and take samples or measurements. ROVs can remain underwater for days and carry a payload of different instruments, lights, and cameras that are powered through their cable. Their drawbacks include limited manoeuvrability and a large footprint on deck in the form of control containers, a winch and a cable drum, which can weigh tens of tons.



max 5,000 m

Example: MARUM–QUEST 5000

Size (L × W × H)	3 m × 1.9 m × 3 m
Weight	4.3 t vehicle weight + 60 t for control, cable, winch, etc.
Dive length	Theoretically only limited by surface conditions and crew availability, usually a max of 24 h
Equipment	2 arms; 3D thrusters; sonar; 11 4K and HDTV cameras for still and video; high-temperature probe; sampling equipment and containers; up to 300 kg of additional instruments, including gas and water samplers, mass spectrometers, bubble meters, etc.
Deployment	2025; replaced predecessor QUEST 4000, which retired in 2024 after 20 years and 490 dives in all oceans
Maximum depth	5,000 m

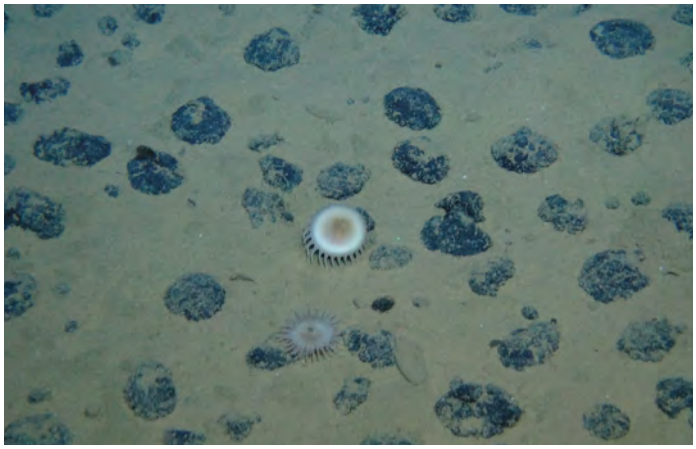

Epipelagic Zone
The sunlight zone
200 m
Mesopelagic Zone
The twilight zone
1,000 m
Bathypelagic Zone
The midnight zone
Deepest recorded whale dive:
Cuvier's beaked whale
(Ziphius cavirostris)
2,992 m
4,000 m
Ocean Basin
Abyssopelagic Zone
The abyss
6,000 m
Deepest squid observed:
bigfin squid (genus Magnapinna)
6,212 m
6,865 m
Deepest known shipwreck:
USS Samuel B. Roberts
Deepest fish observed:
snailfish (Pseudoliparis swirei)
8,336 m
Hadal Zone
The trenches
Mount Everest (inverted)
8,848 m
9,533 m
Deepest recorded vent community:
microbial mats, tube worms
Deepest recorded life:
shrimps
10,900 m
11,000 m
Credit: Jörg Block (illustration)

accumulations of sediment. Here, hydrocarbons formed from organic material in the sediments spill from the ocean floor. As at vents, microbes are the basis for life at these locations. They can live on a wide range of hydrocarbons, including methane, crude oil, and asphalt.

As researchers have discovered, breaking down hydrocarbons for food often involves a division of labour between different types of microorganisms, each of which carries out part of the chemical transformation. One partner belongs to the archaea, a distinctive group of microorganisms that sport unique cell membranes and other characteristic features. The other partner is a bacterium. The archaeal cell oxidises the hydrocarbons to produce carbon dioxide. The bacterium takes the resulting electrons and uses them to reduce sulphate.

The relationship between archaea and their bacterial collaborators is tight. Microbiologist Gunter Wegener of the MARUM Centre for Marine Environmental Sciences in Bremen, Germany, and colleagues revealed in 2015 that the two types of cells can link up with thin filaments that function like wires and permit electrons to pass from the archaeal cell to the bacterium.

The sea floor is just as varied topographically as the land, with mountains, canyons, and plains, says deep-sea biologist Sabine Gollner of the Royal Netherlands Institute for Sea Research. This diversity creates a variety of other ecosystems



Manganese nodules are slow-growing, polymetallic lumps composed mainly of manganese and iron oxides. They support diverse communities of deep-sea organisms including sponges, corals, and specialised invertebrates that rely on the nodules for attachment, shelter, or feeding grounds.

Autonomous underwater vehicles (AUVs)

Autonomous underwater vehicles travel freely, without tether to a support ship. Researchers set their course before they release them. The data is usually only available once the AUV has been picked up by the ship again. No steering or supervision is necessary. Newer models use AI to help them navigate, some can transmit data via satellite. Compared to ROVs and HOVs, most AUVs come cheap and travel light, needing little space on deck. That means, they can be deployed from smaller ships. They travel quickly and cover great distances. This makes them excellent for high-definition mapping of the seafloor and as scouts for identifying research spots. They are the only vehicles that can work under ice cover. However, AUVs have limited battery life and can more easily get lost than ROVs.

max 8,000 m

Example: URASHIMA8000

Size (L × W × H)	10.7 m × 1.3 m × 1.5 m
Weight	7 t
Range	More than 200 km with lithium batteries
Equipment	Side-scan sonar; sub-bottom profiler reaching several tens of metres below ground; cameras; sensors for physical and chemical seawater properties, and depth; optional equipment includes water samplers and magnetometers, AI support to identify worthwhile targets
Deployment	2025; replaced the original URASHIMA, which launched in 2000; with its deep-dive capabilities, it can survey 98% of the ocean floor, including zones important for earthquake research
Maximum depth	8,000 m

besides vents and seeps where organisms can survive. The ocean's plains are the flat, seemingly barren areas that spread out from the bases of the continents between 3,000 m and 6,000 m below the surface and cover about two-thirds of the ocean floor. Strewn about some parts of these so-called abyssal plains are clusters of nodules about the size of tennis balls that contain metals such as cobalt, manganese, and nickel. The nodules provide anchoring points in an otherwise featureless world, one of the reasons why the fields host a surprising diversity of animals, researchers have shown.

Organisms living on the abyssal plains rely on the rain of organic matter from above, and some have evolved unusual strategies to obtain sustenance. In 2022, for instance, researchers identified a crustacean that lives below 5,000 m in the Caribbean Sea and eats only the remains of seaweed that have fallen to the bottom. Sometimes deep-sea dwellers get a windfall, though: whale carcasses provide a bounty of nutrients for deep-sea inhabitants, creating a distinct ecosystem for years.

The trials of life on the ocean floor

Along with the abyssal plains, life has colonised the ocean's deepest canyons. A 2012 expedition detected mats of microbes at a depth of nearly 11,000 m in the Mariana Trench in the western Pacific Ocean. And microbes even dwell from 1 m to more than 2 km beneath the sea floor. These organisms are barely alive – it may take decades for their molecules to turn over. But they play important ecological roles, notes microbial geochemist Karen Lloyd of the University of Southern California. Scientists estimate that up to 15% of Earth's total biomass exists in the deep biosphere below the land and the oceans, with most of it made up of bacteria and archaea. By locking up so much organic material below the sea floor that might otherwise react with oxygen, these microbes help ensure that plenty of oxygen is available for other organisms, including humans, says Lloyd.

Living conditions in the deep sea are generally more stable than on land, but organisms still have to contend with daunting physical challenges. For instance, although much of the deep ocean is around 0–3 °C, temperatures near vents are much higher. Organisms cannot survive the several-hundred-degree-Celsius hot water that emerges from the fissures, but they can endure the somewhat cooler water nearby. Scientists have found that some vent microbes can grow and reproduce at temperatures above 100 °C.

Vents also release toxic hydrogen sulphide. Tubeworms have an adaptation that enables them to cope with the harsh conditions – haemoglobin that binds tightly to hydrogen sulphide. In the worms' bodies, haemoglobin captures hydrogen sulphide and delivers it to the bacterial partners that live in their tissues, which then use the toxin to produce food.

A vampire squid observed by ROV SuBastian, as seen from the control room aboard the R/V *Falkor* during the final dive of the scientific cruise 'Designing the Future 2' of the Schmidt Ocean Institute.

Credit: Jovelle Tamayo / SOI

Deep-sea organisms also have to endure extreme pressures. For every 10 m increase in water depth, the pressure rises by about one atmosphere. The worms that the *Fendouzhe* crew observed in the Kuril–Kamchatka Trench were living at pressures of more than 900 atmospheres. One reason that high pressures are a challenge for organisms is that they can squeeze and distort proteins. However, a molecule known as trimethylamine N-oxide (TMAO) helps proteins retain their shape. In 2014, researchers discovered that the concentration of TMAO in fishes' tissues increases with the depth at which they live, suggesting that the molecule serves as protection against pressure. However, fish tissues can only accumulate a certain amount of TMAO, and this limitation may constrain how deep the animals can live. Scientists estimated that the maximum depth at which fish can survive is around 8,200 m – nicely conforming with the deepest observation of 8,336 m.

Besides warping proteins, high pressures can also compress lipids. As a result, cell membranes that usually behave like fluids can condense into a gel. Scientists are just beginning to investigate how organisms protect their lipids from high pressures, but they recently discovered some clues by studying gelatinous animals known as comb jellies that live at depths of up to 4,000 m. As a research team revealed in 2024, the membranes that surround the animals' cells are rich in a specific type of cone-shaped lipids that retain their shape even when pressure soars. This capability may help the animals' cell membranes remain fluid.

Going deep

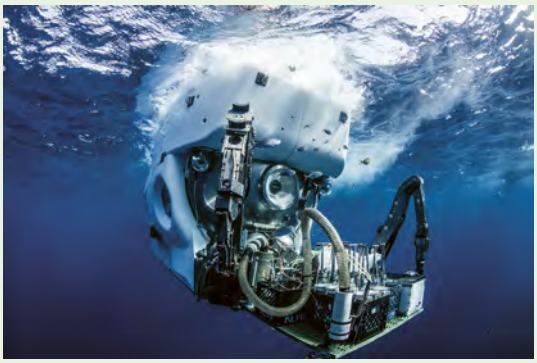
A variety of technologies have opened up the secrets of life in the ocean depths. When the British ship *HMS Challenger* carried out the first global studies of the deep sea in the 1870s, the researchers could only collect organisms from the deep with dredges and trawls. Still, the 4-year voyage yielded about 4,700 new species.

Today, researchers can explore the deepest parts of the ocean themselves – or send in mechanical stand-ins. Crewed submersibles, also known as human-occupied vehicles (HOVs), such as China's *Fendouzhe* and *Alvin*, operated by the Woods Hole Oceanographic Institution, allow scientists to observe deep-sea life up close, perform experiments underwater, and collect specimens.

Researchers can also turn to remotely operated vehicles, or ROVs, machines controlled by personnel at the surface that can perform some of the same tasks. ROVs remain connected to their support ship by a cable, but autonomous underwater vehicles (AUVs) pilot themselves, and researchers are increasingly using them for jobs such as mapping and sample collection. For long-term studies, scientists can combine sensors and instruments on the sea floor with sensor-containing

Human-occupied vehicles (HOVs)

Because these crewed submersibles are not tethered to their ship, the crew has greater freedom to explore during a dive. Researchers can make up-close observations, collect samples, and perform experiments. HOVs feature hydraulic arms that can grasp and manipulate objects. They are very complex and costly to operate, therefore only a few are available. Their dive time and payload are very limited due to the safety and life-support demands of the crew. But HOVs have taken scientists to the deepest parts of the ocean and allowed them to discover, for example, the rich communities at hydrothermal vents and cold seeps, and have greatly advanced the fascination with sea life at depth.



max 6,500 m

Example: *Alvin*

Size (L × W × H)	7 m × 2.6 m × 3.6 m
Weight	20 t
Crew	3
Dive length	6–10 h
Equipment	2 hydraulic arms; 7 thrusters for manoeuvring; 4K UHD and HD cameras for stills and video; sample collection boxes; conductivity, temperature, and depth sensor; heat flow probe; magnetometer; water samplers; sediment corer
Deployment	Latest upgrade in 2022; first launched in 1964
Maximum depth	6,500 m

Credit: Luis Lamar / Woods Hole Oceanographic Institution

buoys floating at different depths, creating arrays that can monitor large areas over long periods.

Each of these technologies has advantages and disadvantages, says Gollner. ROVs are typically cheaper than crewed vehicles and can stay underwater for longer. Moreover, only seven research submersibles that can dive deeper than 2,000 m are in service today, so wait times to use them can be long. In contrast, there are 'uncrewed vehicles galore', says Girguis. ROVs feature high-definition cameras, low-energy lighting, and advanced steering capabilities. With real-time imagery delivered to their pilots on board a support vessel, they can achieve much of what only HOVs could do before. Still, Gollner says, submersibles provide opportunities that ROVs and AUVs can't match. 'There is much more spatial flexibility, as the submersibles are not connected to a cable.'

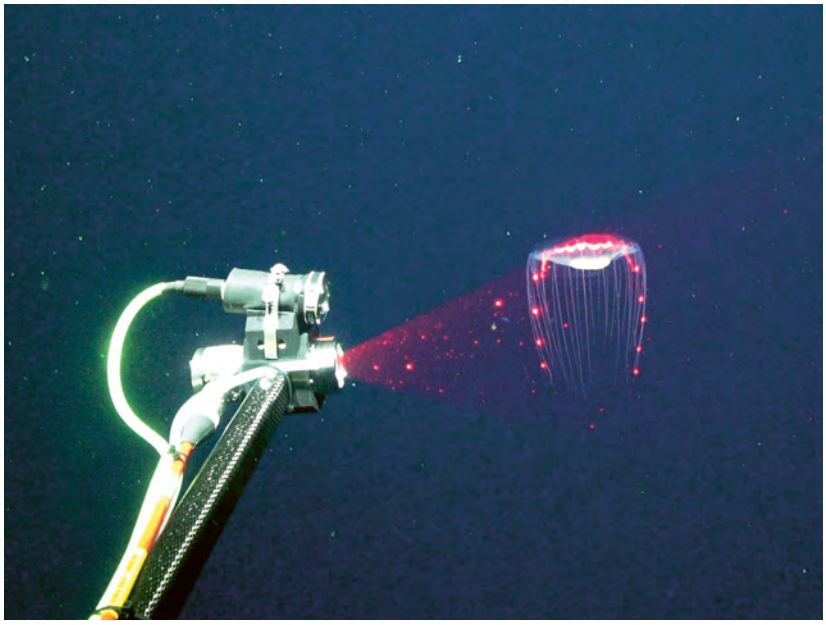
To discover new deep-sea inhabitants and probe how they survive, researchers can also take advantage of advances in the lab. Microorganisms from the ocean depths often will not grow in conventional culture conditions, which can make it hard for researchers to study them or even know that they exist. With DNA and RNA sequencing, researchers can detect microbes in environmental samples, analyse their metabolism, and investigate their evolution. To study deep-sea organisms at the surface, scientists have also developed chambers that can capture and keep species at the high pressures they are accustomed to. When Girguis and his colleagues go to sea, for instance, they bring along their one-of-a-kind laboratory, which fits inside a shipping container and contains an array of 2 L to 5 L pressurised aquaria. This equipment allows them to analyse the metabolism of deep-sea organisms like tubeworms or microbes under natural conditions.

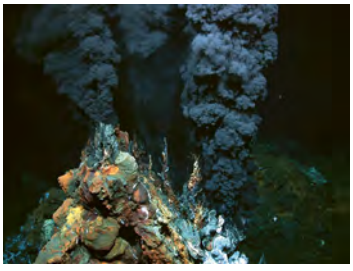
Even with technological advances like these, the tools researchers need to explore the deep sea may not be available, and they often have to do some DIY, says Girguis. He and his colleagues developed a miniature mass spectrometer that can be deployed at depths of up to 6,000 m and will work underwater for up to 16 months. They use it to measure concentrations, in the parts-per-million range, of hydrocarbons that serve as substrates for deep-sea organisms' metabolism, such as methane, alkanes, hydrogen, oxygen, and hydrogen sulphide.

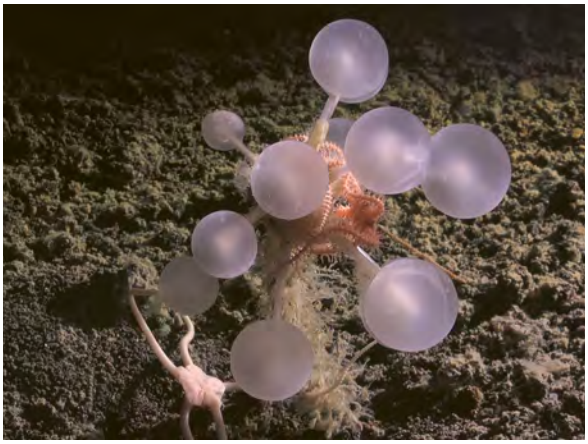
Still in the dark

Despite the progress scientists have made over the last few decades, much about the deep sea remains murky. How many species it harbours is a mystery. 'We are just starting to understand what is there', Gollner says. According to some estimates, deep-sea ecosystems could support 500,000–10 million species, she says.

Another question scientists are trying to answer is how organisms colonise new habitats. For instance, when a new







Hydrothermal vents (bottom right) release hot, mineral-laden fluids that sustain chemosynthetic microbes, forming the foundation of deep-sea ecosystems. White crabs (top right) of the genus *Kiwa* cluster near these vents, where they may rely on symbiotic bacteria growing on their limbs for nutriment. A jellyfish (top left) drifts in the deep ocean, its translucent body and minimal pigmentation reflecting typical adaptations to low-light environments. A newly described species of *Chondrocladia* (the 'death ball sponge') is a predatory sponge discovered in October 2025. Unlike typical filter-feeding sponges, it captures its prey with tiny, hook-like structures.

hydrothermal vent forms, researchers want to determine how tubeworms, clams, and other animals locate this potential home. Mullineaux and her colleagues found that tubeworm larvae, which are microscopic, can travel nearly 100 km by riding undersea currents. The larvae move up and down in the water to optimise their chances of being carried to a promising location, she says. 'They are like balloons that can adjust their height to take advantage of currents.' She and her colleagues are now trying to figure out how the larvae decide to settle down. Their preliminary results suggest that the animals are detecting mats of microbes that could be good landing sites.

Another possible route came to light when Gollner and colleagues used an ROV to flip over slabs of rock on the sea floor. They uncovered cavities that were home to tubeworms and other deep-sea creatures. The animals could be moving through these underground passageways, Gollner and her colleagues suggested in 2024.

The biggest unanswered question about the deep sea, however, is how it will respond to human alteration of the planet. The upper parts of the ocean are already warming and becoming more acidic as they absorb carbon dioxide from the atmosphere, says MacDonald. And human-caused changes are 'beginning to impinge' on the deeper parts of the ocean, he says. For example, plastic waste has turned up even in the Mariana Trench.

Even larger disruptions could be imminent. For instance, some companies hope to mine the sulphide deposits at geothermal vents, which contain copper, zinc, and other metals. Although plans mainly call for exploiting inactive vents, those sites still host unique species, says Mullineaux, and mining them could have severe consequences. The plans for harvesting the nodules of the abyssal plains are more solid, with the first test runs already completed. The structures form very slowly, Gollner notes. 'If you remove nodules, you will change the ecosystem at the mined location for millions of years.'

Damage to undersea ecosystems could rebound on humans, says Girguis, because 'there's a direct link between the deep sea and us'. For example, nutrients rising from deep waters feed some of the most important fisheries in the world, such as off the west coast of South America. 'Even if you have no other concerns than our own well-being, we should make sure [the deep sea] continues to support us', Girguis says.

Not least of all to determine how human impact will affect the deep sea, researchers need to know much more about the largest biome on our planet. But so far, they have explored less than 1% of the ocean floor. Looking at the astounding discoveries of just the last few years, they expect many more surprises from the remaining 99%.

Sea-floor-based observatories

These networks contain, for example, traps, samplers, and sensors deposited on the sea floor, or tethered at specific depths, and/or gliders travelling autonomously, measuring a wide range of parameters. Data transfer can be in real time via cables that supply electrical power or via surface buoys talking to satellites. They need regular service by research ships, but as they can operate for more than a decade, they deliver high-definition, long-running time series even from remote and stormy locations.

max 3,400 m

Example: Global Irminger Sea Array, southeast of the tip of Greenland

Description	Components in triangular formation covering about 173 km²
Location	North Atlantic Ocean southwest of Greenland
Equipment	3 buoys in a 20 km-sided triangle with multiple instruments at differing depths; undersea gliders that travel between buoys or up and down on the mooring cables, collect data, and transmit data from the array to a satellite
Deployment	2014, to study processes driving, for example, the Gulf Stream
Depth	Surface to 3,400 m

Credit: John Lund / Woods Hole Oceanographic Institution

In the interest of our fellows, we publish only final results online, not descriptions of ongoing projects.

Accordingly, this PDF proceeds directly to the PhD Results section.

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

Mother knows best: the role of olfactory cues in postpartum maternal care

cf. BIF FUTURA 37 / 2022

Valentine Andreu
Discipline: Neuroscientist, MA
Institute: Columbia University, New York, NY, USA
Supervisor: Prof. Bianca Jones Marlin

The transition to motherhood in mammals brings dramatic physiological and behavioural changes, but how the maternal brain adapts to process sensory signals from offspring is not fully understood. While olfactory cues are known to guide maternal behaviours in rodents, the specific adaptations of the maternal olfactory system and the role of pup chemical signals are underexplored.

To address these aspects, I investigated whether and how mother mice develop a selective attraction to the scent of pup urine, a potential chemosensory cue. I used behavioural experiments to show that after giving birth, mothers show a strong and specific preference for cotton soaked in their own pup's urine over odourless cotton. This response was absent in virgin females, females in late pregnancy, and mothers who were separated from their pups after birth. The mothers' preference did not extend to other social or neutral odours, indicating a distinct, state-dependent change in olfactory attraction. Other behavioural experiments showed that both the physiological changes of motherhood and direct exposure to pups are required for this preference. Disruption of olfactory input or restriction of contact chemosensation revealed that this preference is not linked to the mothers' ability to retrieve pups that had been separated from them – a core maternal behaviour – suggesting different neural pathways govern these behaviours. By chemically analysing pup urine using gas chromatography-mass spectrometry, I identified several volatile compounds that likely contribute to maternal attraction.

My findings reveal a previously unrecognised, temporary adaptation in the maternal olfactory system that enhances mothers' responsiveness to pup-derived chemical cues during a critical period after birth. By identifying the behavioural specificity, physiological requirements, and likely chemical signals involved, my work provides new insights into the sensory and neural mechanisms supporting maternal care. These results advance our understanding of sensory plasticity in the maternal brain and have implications for research on parental bonding and the regulation of complex social behaviours.

PUBLICATIONS

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Influenza virus weakens lung defences by killing and disabling alveolar macrophages

cf. BIF FUTURA 37 / 2022

Laura Isabel Fisch
Discipline: Immunologist, MSc
Institute: Institute for Molecular Health Sciences, ETH Zurich, Switzerland
Supervisor: Prof. Manfred Kopf

Acute respiratory infections, including influenza A virus (IAV) infection, are a leading cause of morbidity and mortality worldwide. During infection, the lung's resident immune sentinels, alveolar macrophages (AMs), are rapidly depleted. This phenomenon is linked to severe disease, but its underlying mechanisms were not clear. In my PhD project, I combined influenza infection models in mice with *ex vivo* cultures of primary AMs to uncover these mechanisms. I found that influenza virus directly infects AMs, triggering inflammatory cell death with features of both apoptosis and pyroptosis. At the centre of this process is Z-DNA binding protein 1 (ZBP1), an innate immune sensor and executor of multiple cell death pathways. I showed that ZBP1 expression is strongly induced by interferon-gamma (IFN-γ). Blocking IFN-γ or deleting *Zbp1* preserved AMs, improved recovery, and protected mice from lethal secondary infection with *Streptococcus pneumoniae*, without impairing viral clearance. These results establish the IFN-γ–ZBP1 axis as a key determinant of AM death during influenza infection and a promising therapeutic target for preserving lung integrity.

In a second part of my project, I studied the epithelial cell adhesion molecule (EpCAM), which was previously thought to be restricted to epithelial cells but was recently found to be highly expressed on AMs. Deleting EpCAM specifically in AMs revealed that while dispensable for their development and homeostatic functions, it is essential for defence against *S. pneumoniae* and *Legionella pneumophila*. I also showed that EpCAM was downregulated after IAV infection through tumour necrosis factor α (TNF-α) mediated nuclear factor κB (NF-κB) signalling, which reduces the bacterial uptake capacity of AMs and offers another explanation for why viral infections predispose the host to severe secondary bacterial infections.

Together, my findings explain why IAV creates the 'perfect storm' for facilitating bacterial pneumonia: AMs are both depleted during active viral infection and functionally impaired over the longer term. By identifying the IFN-γ–ZBP1 axis and EpCAM as key regulators of AM fate, my research opens new avenues for therapies that preserve lung integrity and improve outcomes in severe respiratory infections.

PUBLICATIONS

The results of this project have not yet been published.

Chromatin regulators safeguard genome stability and fine-tune gene expression

cf. BIF FUTURA 37 / 2022

Philine Guckelberger
Discipline: Molecular Biologist, MSc
Institute: Max Planck Institute for Molecular Genetics, Berlin, Germany
Supervisor: Prof. Alex Meissner

By controlling whether genes are accessible or repressed, chromatin structure contributes to essential processes such as embryonic development and genome stability. Disruption of chromatin regulators is linked to human disease, but their precise functions and contributions are poorly understood. In my PhD project, I studied two chromatin regulators with distinct but complementary functions: helicase, lymphoid-specific (HELLS), which modulates chromatin accessibility and its impact on DNA methylation; and cohesin, which facilitates enhancer-promoter interactions that are critical for transcriptional regulation. Both are implicated in human disease: HELLS mutations cause immunodeficiency–centromeric instability–facial anomalies (ICF) syndrome, while cohesin mutations lead to cohesinopathies.

Using human induced pluripotent stem cells and whole-genome bisulphite sequencing, I found that HELLS is essential for regulating DNA methylation across the genome. I showed that HELLS is required at repetitive heterochromatic regions, where chromatin compaction likely limits access for DNA methyltransferases. Loss of HELLS led to hypomethylation of heterochromatic satellite repeats and immune gene clusters, potentially explaining the immunodeficiency in ICF syndrome. By developing CRUDO (CRISPR interference of regulatory elements upon degron operation), I mapped regulatory interactions for five cohesin-sensitive genes. I found that enhancer-promoter 3D contact frequency quantitatively tunes gene expression. By contrast, analyses of genome-wide prediction maps and published perturbation studies showed that most genes depend on nearby enhancers rather than cohesin-mediated 3D contacts. This helps explain why global transcriptional changes upon cohesin loss are modest despite large changes in chromatin architecture.

My findings refine models of chromatin regulation, illuminate disease mechanisms, and provide a framework for studying how chromatin systems balance robustness with vulnerability in development and disease.

PUBLICATIONS

Guckelberger P, Haut L, Tornisiello R, Kretzmer H, Meissner A. HELLS is required for maintaining proper DNA modification at human satellite repeats. Genome Biol. 2025;26(1):211.

Guckelberger P, Doughty BR, Munson G, Rao SSP, Tan Y, Cai XS, et al. Cohesin-mediated 3D contacts tune enhancer-promoter regulation. BioRxiv [Preprint]. 2024. doi: 10.1101/2024.07.12.603288.

VDAC, a dimeric beta-barrel scramblase, imports lipids into mitochondria

cf. BIF FUTURA 35 / 2020

Helene Jahn
Discipline: Biochemist, MSc
Institute: Weill Cornell Medical College, New York, NY, USA
Supervisor: Prof. Anant K. Menon

The formation of the mitochondrial double membrane depends on lipids crossing, or scrambling, from one leaflet of the outer mitochondrial membrane (OMM) to the other. This process requires proteins called scramblases to help the lipids' hydrophilic headgroups move through the hydrophobic membrane core. In my PhD project, I identified the voltage-dependent anion channel (VDAC), a member of a superfamily of beta-barrel proteins, as the first known OMM scramblase and elucidated its mechanism of action.

I did this by reconstituting purified VDAC into membrane vesicles containing fluorescently labelled lipid analogues. Upon addition of a fluorescent quencher, lipids in the outer leaflet could be manipulated, whereas lipids in the inner leaflet were protected. If a scramblase was present, lipids moved freely between the leaflets and were not protected. With this approach, I showed that human VDAC isoforms facilitate rapid and non-specific lipid scrambling. This activity was highly dependent on the oligomerisation state of the scramblase: lipids were scrambled more rapidly by dimers than by monomers. Using molecular dynamics (MD) simulations performed by collaborators Ladislav Bartoš and Robert Vácha (Masaryk University, Czech Republic), we showed that VDAC dimers support rapid lipid scrambling at dimer interfaces. The most potent was a previously reported interface that has several polar residues pointing towards the membrane core. Our simulations showed that these residues allow water to penetrate the core and induce bilayer thinning, thus facilitating scrambling.

Lastly, I used a lipid flux assay in purified mitochondria to show that phospholipid transport across the OMM is impaired in yeast mitochondria lacking VDAC. I pulsed the mitochondria with fluorescently labelled phosphatidylserine, which converts to phosphatidylethanolamine if it can cross the OMM. Conversion was slower in mitochondria lacking VDAC. Using kinetic modelling of the conversion steps, I found that yeast VDAC was responsible for 90% of the scramblase activity in the OMM. Thus, VDAC represents a novel class of phospholipid scramblase operating via a newly discovered mechanism.

PUBLICATIONS

Jahn H, Bartoš L, Dearden GI, Dittman JS, Holthuis JCM, Vácha R, Menon AK. Phospholipids are imported into mitochondria by VDAC, a dimeric beta barrel scramblase. Nat Commun. 2023;14(1):8115.

Developing genome synthesis methods to reprogram the genetic code

cf. BIF FUTURA 37 / 2022

Askar Alexander Kleefeldt
Discipline: Synthetic Biologist, MSc
Institute: MRC Laboratory of Molecular Biology, Cambridge, UK
Supervisor: Prof. Jason Chin

Genome synthesis provides us with unprecedented control over the engineering of biological systems. A central application is genetic code reprogramming. Usually, 64 codons code for the ribosomal incorporation of 20 canonical amino acids into proteins. Rewriting the genetic code expands the diversity of building blocks that can be incorporated into proteins, thus enabling a wide variety of new protein functions. A principal technical bottleneck in genetic code reprogramming across organisms is the design and synthesis of genomes at megabase to gigabase scale. Standard practice is to build 1–10 kb synthetic DNA fragments into 50–100 kb bacterial artificial chromosomes (BACs) that replace native loci in *Escherichia coli*. Members of the Chin lab and I developed CONEXER (conjugation coupled with programmed excision for enhanced recombination) to accelerate the total synthesis of the *E. coli* genome. CONEXER couples conjugative delivery of 100 kb BACs directly to programmed recombination, removing the need for verification after each replacement step. To extend genome writing to larger (gigabase) genomes, I built on CONEXER to develop BASIS (BAC stepwise insertion synthesis). BASIS is an episome-to-episome recombination method that enables the assembly of megabase-scale constructs *in vivo* in *E. coli*. Using BASIS, my labmates and I assembled the full-length 189 kb gene for the cystic fibrosis transmembrane conductance regulator (CFTR) and a 1.1 Mb segment of human chromosome 21 – the largest bacterially assembled human DNA to date.

My work has advanced biological assembly from hundreds of kilobases to megabases and positioned *E. coli* as a general platform for genome synthesis. This platform enables advances in genetic code reprogramming and paves the way for rewriting the genetic code of diverse organisms with genomes up to gigabases in size.

PUBLICATIONS

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* Shared authorship

Fluorogenic DNA probes illuminate RNA biology at the single-molecule level

cf. BIF FUTURA 36 / 2021

Mirjam Kümmerlin
Discipline: Biochemist, MSc
Institute: Department of Physics and Kavli Institute for Nanoscience Discovery, University of Oxford, UK
Supervisor: Prof. Achillefs Kapanidis

RNA molecules are central to many cellular processes, yet their dynamic behaviour inside cells is difficult to observe directly. Single-molecule fluorescence (SMF) provides a unique window into these processes, offering access to molecular heterogeneity, subcellular localisation, timing, and the sequence of molecular events. However, SMF is limited by photobleaching and background emissions, particularly at high probe concentrations and in live or complex environments.

To overcome these limitations, I developed fluorogenic single-stranded DNA (ssDNA) probes – that is, they emit fluorescence only upon hybridising to a specific target sequence. Use of these probes enabled SMF at high probe concentrations and with high signal specificity. To bypass photobleaching, I developed a labelling strategy called REFRESH (renewable emission via fluorogenic and repeated ssDNA hybridisation), which uses continuous probe exchange to support hour-long observation spans and high temporal sampling. The same probes could also be used for fast super-resolution imaging of viral RNA, achieving <10 nm resolution with imaging times of <3 minutes. These fluorogenic ssDNA probes are thus adaptable to vastly different experimental demands.

The highlight of my work was applying the probes to live-cell RNA tracking. I labelled 16S ribosomal RNA in *Escherichia coli* cells without any genetic modification and used single-molecule tracking to reveal distinct ribosome subpopulations with different diffusion behaviours and spatial localisations. This allowed me to directly visualise and clearly discriminate between individual translating and free ribosomal subunits inside living cells. Overall, my work establishes fluorogenic ssDNA probes as a versatile labelling strategy for real-time, single-molecule studies of RNA biology *in vitro* and *in vivo*, paving the way for applications studying transcription and translation.

PUBLICATIONS

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Dynamics of splenic myeloid cells during blood-stage malaria

cf. BIF FUTURA 36 / 2021

Katharina Mauel
Discipline: Immunologist, MSc
Institute: Life & Medical Sciences Institute (LIMES), Bonn, Germany
Supervisor: Prof. Elvira Mass

The blood stage of malaria infection causes severe, often fatal, symptoms. Infected erythrocytes are predominantly cleared by phagocytes in the spleen, but the precise function and origin of the diverse subsets of splenic macrophages are poorly understood. In my PhD project, I developed a novel fate-mapping model to explore the fate and function of splenic macrophages during development and homeostasis and in response to parasitic and viral infections.

Using single-cell RNA sequencing, high-dimensional flow cytometry, and immunofluorescence imaging, I identified a previously unrecognised dichotomy of splenic red pulp macrophages (RPMs) based on their expression of the haemoglobin receptor CD163. I showed that in murine malaria models of three *Plasmodium* species, $CD163^-$ RPMs are fully replenished by monocyte-derived macrophages, while $CD163^+$ RPMs are depleted by day 7 after infection. The malaria-induced disruption of splenic architecture dissolves the spleen's red and white pulp, and CD163 expression fails to recover even 90 days after infection when the spleen has returned to normal. This loss of $CD163^+$ RPMs also occurs following viral infections. By chemically inducing haemolysis, a common pathology of malaria infections, I transiently depleted $CD163^+$ RPMs, which suggests how CD163 expression is regulated. CD163 is known to be involved in haemoglobin uptake, so my results on the dynamic expression of CD163 on fetal- and monocyte-derived macrophages suggest a role for macrophage-regulated iron metabolism during infections. By infecting $CD163^{-/-}$ mice with malaria, I showed that CD163 deficiency leads to significant loss of splenic iron stores and disrupts regeneration of the structure between the red and white pulp, the marginal zone. I also showed that genetic deficiency of marginal zone macrophages, which leads to a downregulation of CD163 expression on RPMs, was linked to increased parasitaemia during acute malaria infection.

My findings underscore the critical role of splenic macrophage crosstalk and iron availability in the host immune response to infections.

PUBLICATIONS

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More than the sum of its parts: the molecular mechanism of Oskar

cf. BIF FUTURA 35 / 2020

Anastasia Repouliou
Discipline: Molecular Biologist, MA
Institute: Harvard University, Cambridge, MA, USA
Supervisor: Prof. Cassandra Extavour

The *Drosophila melanogaster* protein Oskar organises germline fate determinants in the developing oocyte. While Oskar is well studied, key questions remain about how it interacts with the molecules it recruits into germplasm and how it organises the germplasm into granular ribonucleoprotein assemblies. In my PhD project, I investigated the molecular mechanism of Oskar *in vivo*. Previous *in vitro* experiments have shown that Oskar interacts with the germplasm component Vasa via its LOTUS domain and with germplasm mRNAs via its OSK domain. Biochemical and structural assays have shown that Oskar dimerises *in vitro*. By manipulating this dimerisation potential through domain mutations and substitutions, I showed that Oskar domains act cooperatively and non-redundantly to recruit and assemble germplasm components *in vivo*. These findings align with the role of Oskar in nucleating germ granules, ribonucleoprotein assemblies that are enriched in germline determinants. To study the structure and dynamics of germ granules at high resolution, I established a super-resolution spinning disc confocal microscopy approach for live imaging. This approach enabled me to measure the size and shape distribution of granules, their diffusion coefficients, and the extent to which granular components exchange with the environment. In future, this approach could also be used to study whether specific properties of germ granules influence germline specification.

Finally, as Oskar has a role in forming and transporting neuronal ribonucleoprotein granules, I used anti-Oskar antibodies and mRNA probes to test whether the gene is expressed in the mushroom body, part of the brain with roles in olfactory learning and memory. My work positions Oskar as a powerful model for studying the biophysical and functional logic of granule organisation, showing how local molecular interactions can shape robust cell fate decisions across developmental and cellular contexts.

PUBLICATIONS

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Repouliou A*, Srouji JR*, Rivard EL, Leschziner AE, Extavour CG. The LOTUS domain of Oskar promotes localisation of both protein and mRNA components of Drosophila germ plasm. BioRxiv [Preprint]. 2025. doi: 10.1101/2025.05.02.651258.

* Shared authorship

Foundation The Boehringer Ingelheim Fonds (BIF) is a public foundation – an independent, non-profit organisation 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.

Forty Years of Science and Hiking with the BIF

At first glance, it may not be clear why the BIF summons its current fellows based in Europe to the remote Kleinwalsertal valley in the Austrian Alps. Yet all who have attended understand: by combining intense scientific discussions with demanding mountain hikes, participants push both mind and body, test limits, and challenge themselves within a supportive environment. The talks offer insight into the diverse research fields pursued by BIF fellows. The relaxed atmosphere and shared activities, both on and off the mountain, allow friendships to form and trust to develop. Many collaborations between BIF fellows have begun here.

Already in 1985, just two years after awarding its first fellowships, BIF invited its fellows to a progress seminar in Oberjoch, located in the German Alps. This inaugural seminar also sparked the creation of another of BIF's hallmark events. The then-managing director famously remarked, 'The kids do not understand each other; we need to teach them.' The first communication seminar followed a year later.

In 1996, the progress seminar moved across the border to Hirschegg, Austria. The reason? The house in Oberjoch had become too small – and, as some joked, 'the desserts were too bad.'

Ever since, in sunshine, rain, or snow, to Hirschegg the BIF fellows go. Even in 2005, when heavy rain destabilised the hills, washed away bridges, and the group had to stay indoors for three days, the seminar continued. We cancelled only once – in 2020, due to the coronavirus pandemic.

On this double page, you will find impressions mainly from the 40th Hirschegg seminar, which took place from 30 August to 5 September 2025.

Part of the 2025 group, all smiles at the summit of the Hahnenköpfle (1,735 m). Fortunately, the good weather held until their descent.

Top: participants of the first Progress Seminar in 1985, then still held in Oberjoch. **Bottom:** the first seminar in Hirschegg in 1996 saw lots of snow, but no less enthusiasm or energy.

Credits: Alexander Meyer (panoramic view, top); BIF

As in science, mountain journeys often involve moments of adversity – when conditions deteriorate and the path forward is obscured.

Not all boots are made for walking, as Svenja Küchenhoff discovered on the first day – but she took it in her stride.

Hasso Schröder was BIF's first managing director. Many of his ideas are still alive in BIF's programmes today.

Not everyone can claim to have played beach volleyball in the mountains.

These are the remains of this year's 'thank you' basket full of sweets after just two weeks. The BIF team highly appreciates this tradition.

The lecture hall is packed – just like the schedule, with over 60 talks in five days, plus hikes.

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.

Listening in on cGAS–STING signalling: do it with SIRF

During cancerous changes, viral or bacterial infections, double-stranded DNA (dsDNA) can turn up in the cytosol of a cell from three origins: nuclear, mitochondrial, or external. No matter its origin, its presence usually signals something is wrong. Therefore, dsDNA is strictly monitored by the innate immune system's cGAS–STING pathway: cGAS binds out-of-place DNA and sends a warning signal by producing cGAMP. cGAMP activates STING in all cells it reaches. This triggers an immune response via interferons, such as inflammation, or even planned cell death – something that could be used to treat diseases that lead to aberrant DNA in the cytosol.

So far, listening in on cGAS–STING signalling has been hindered by the lack of fast, specific, direct, and easy-to-use reporters. Now Steve Smarduch from the lab of Sergio Perez Acebron at the University of Heidelberg, Germany, has developed the fluorescent STING–IRF3 reporter (SIRF). SIRF reports on the interaction of STING (activated by cGAMP) with the interferon regulatory factor IRF3 at the Golgi apparatus. It measures the strength, as well as the temporal and spatial distribution, of STING activation by cGAMP, enabling the detection of infection, apoptosis, and aberrant DNA. Steve and his team also developed an algorithm that enables easy-to-use, high-throughput live imaging analysis in single cells and cell populations.

The reporter shows how far and how fast cGAMP travels through tissues in such a sensitive way that it even picks up on differences between cell populations: in highly connected HEK cells, it showed cGAMP to travel 10–12 cells from the cell of origin; in HeLa cells, which are more isolated, the signal travelled at most 3 cells. Further experiments in this vein also support previous findings that cGAMP is transported via gap junctions or vesicles.

With SIRF's reaction time of as little as 45 minutes, Steve could now conclusively show that mitochondrial DNA released into the cytosol during cell death activates STING. This means that mtDNA activation of STING might be used to treat diseases that release mtDNA into the cytosol, such as cancer.

In contrast, Steve found that the cGAS–STING pathway is not activated by nuclear DNA from micronuclei. They form when chromosomes are not properly distributed during cell division – a hallmark of certain cancers. When micronuclei break down, their still histone-bound DNA enters the cytosol. Contrary to expectation, SIRF did not light up when the authors induced the rupture of micronuclei in HeLa cells. Recent work showed that cGAS activity is hindered by histone H2A/B. The authors, therefore, are quite sure that the cGAS–STING pathway is not activated by histone-bound DNA. If confirmed, the idea of using micronuclei to activate STING – now being tested in several clinical trials of cancer drugs – is dead.

These results already hint at SIRF's power for unravelling processes in which cGAS–STING regulation is involved, such as immune system evasion by tumours and pathogens, or autoimmune disease. Stay tuned for more.

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Smarduch S, Moreno-Velasquez SD, Ilic D, Dadsena S, Morant R, Ciprinidis A, et al. A novel biosensor for the spatiotemporal analysis of STING activation during innate immune responses to dsDNA. EMBO J. 2025;44(7): 2157-2182.

Steve Smarduch, fellowship: 07/22–12/25

Blocking histone recycling kills resistant cancer cells

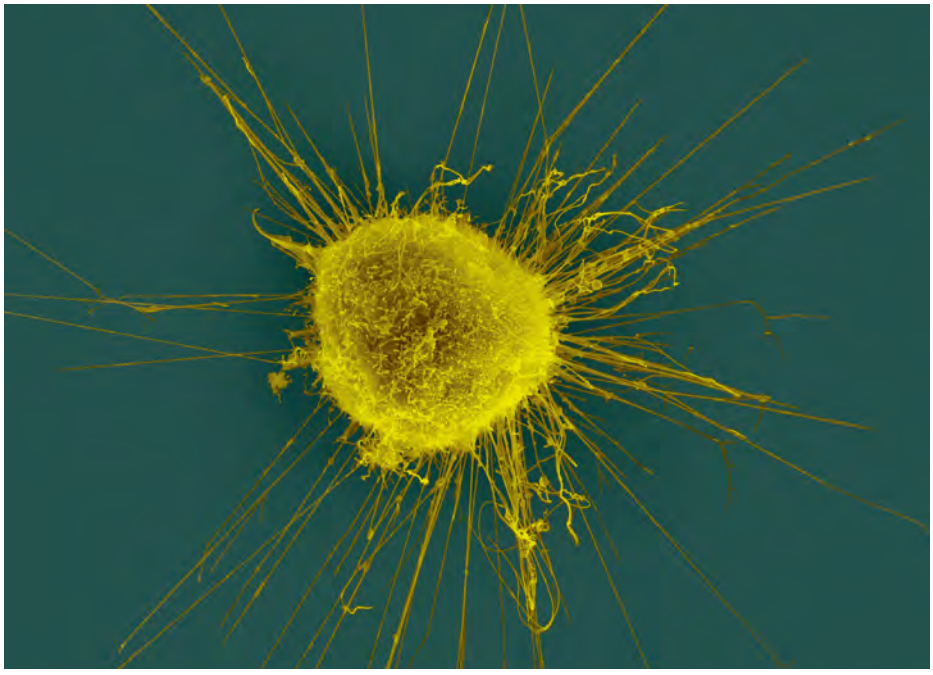
Cancer is an insidious killer, and itself hard to kill for two reasons. First, you have to make sure to target only cancer cells, and not the rest of a patient's cells, and second, many cancer cells become resistant very quickly. For certain breast and ovarian cancers possessing a BRCA1 or BRCA2 mutation, we have a good answer for the first problem.

New research by Sarah Moser from the lab of Jos Jonkers at the Netherlands Cancer Institute in Amsterdam now has answers to the second one. BRCA1 or BRCA2 are DNA repair enzymes. If they are mutated, everyday damage quickly accumulates and often leads to breast and ovarian cancer. Today, these cancers are treated by inhibiting PARP, an important protein in the tumour's fallback repair system. This leads to even more damage the tumour cells can't repair, and eventually they die. 'PARP inhibitors are a comparatively gentle form of chemotherapy', says Sarah. 'Healthy cells have functioning BRCA1 or BRCA2 enzymes and just use them for DNA repair.' But as with all cancers, BRCA1- or BRCA2-mutated cancers also develop resistance – for example by finding other ways to repair their DNA. The cancers stop responding to treatment, and they return. Understanding and preventing this is the greatest challenge in cancer research.

To do so, Sarah wanted to know whether it is possible to interfere early in the process of resistance. She therefore developed a method to find out if and how PARP inhibitors affect the way DNA is packaged and protected from harm in the cell. She observed that before causing DNA damage to accumulate, PARP inhibitors already cause the DNA to unravel and detach from the histone discs it is looped around – a heavy blow to the tumour cells, as histones are involved in critical processes like transcription, replication, and repair, and histone-less DNA is more vulnerable to damage. But cancer cells can recycle the evicted histones to repackage DNA – the better they are at this, the more resistant they are.

Next, Sarah unravelled how the recycling system works: the INO80 complex pulls histones off the DNA, the histone chaperone NASP stores them, and PARP1 and other factors help guide them back into place. She then asked what happens when she takes NASP out of the equation in tumour cells: the recycling system collapsed, and even previously resistant tumour cells died – in the Petri dish, as well as in mice.

Sarah's work shows that delivering the double punch of inhibiting PARP and stopping histone recycling can overcome resistance to PARP inhibitors in BRCA1- and BRCA2-mutated tumours. It also demonstrates the importance of molecular insights in fighting the biggest challenge in cancer research and therapy, giving hope to many people hit by cancer.



Scanning electron micrograph of a breast epithelial cancer cell.

REFERENCE

Moser SC, Khalizieva A, Roehsner J, Pottendorfer E, Kaptein ML, Ricci G, et al. NASP modulates histone turnover to drive PARP inhibitor resistance. Nature. 2025;645(8082):1071-1080.

Sarah Christina Moser, fellowship: 09/19–03/22

Who's Who at the BIF?

Professor Marina Rodnina
Member of the BIF's Board of Trustees

Marina Rodnina studied biology in Kyiv, Ukraine, and in 1989 earned her PhD in molecular biology and genetics at the National Academy of Sciences of Ukraine. In 1990, she moved to the University of Witten/Herdecke, Germany, with an Alexander von Humboldt Fellowship. After her habilitation, she became a professor in 1997 and held the chair of Physical Biochemistry from 2000 to 2009. In 2008, she was appointed director at the Max Planck Institute for Multidisciplinary Sciences in Göttingen, leading the Department of Physical Biochemistry. Besides other notable achievements in the study of large protein complexes, Marina Rodnina has developed a 3D cryo-electron microscope which can show ribosomes in action. With it, she has greatly expanded our knowledge about translation; for example, she discovered how ribosomes can avoid translation errors.

She is a member of EMBO and the German National Academy of Sciences Leopoldina. She has received many honours for her work on the function of the ribosome, including the Gottfried Wilhelm Leibniz Prize, the Hans Neurath Award of the Protein Society, the Otto Warburg Medal, and the Albrecht Kossel Prize. Marina Rodnina joined the BIF's Board of Trustees in 2020.

What is your most remarkable BIF experience?
The most remarkable experience is seeing how amazing the BIF applicants are – their achievements at such a young age, the thoughtfulness of their ideas, and the ingenuity of their projects never cease to impress me.

Why did you choose a science-based career?
I could never imagine doing anything else. Science is the only kind of activity that truly interests me – it combines curiosity, creativity, and persistence in a way that is endlessly rewarding.

What is your favourite activity?
In the lab, I love discussions with my group, generating ideas, looking at data, and fitting the pieces of a research puzzle together. It is incredible fun to see a solution that nobody has reached before and to use that insight to generate new ideas. At home, I enjoy reading good books and watching a good film.

What is your remedy for stressful situations?
I can tolerate a certain level of stress if I do not take myself too seriously. In more dramatic situations, I prefer to spend time alone – often a car ride helps to quiet down – and then I analyse the problem.

What fault in others can you tolerate best?
I do not look too much at 'faults'. If I can tolerate something, I see it more as a character feature than a flaw – after all, we are all different.

Your advice for fellowship holders?
Enjoy science and the opportunities that come with the fellowship – to travel, interact, and learn new things. Do not label yourself as 'stressed'; it is simply part of life and of being deeply engaged.

Which scientific achievement do you admire most?
There are many, but one that has been transformative for my field is the development of cryo-electron microscopy. It revolutionised structural biology in a way that nothing else has.

Name one thing you could not live without.
I could not live without reading literature and taking in culture – art exhibitions, concerts, or opera – from time to time.

Profiles

Professor Simon Elsässer
Institute: University of Freiburg, Germany
Fellowship: 09/08–10/10

In June, **Simon Elsässer,** then at the Karolinska Institutet in Sweden, was awarded an Alexander von Humboldt Professorship, Germany's most highly endowed science award, exclusively given to world-leading researchers. For the funding of five million euros over five years, recipients are expected to move back to Germany on a long-term basis to take up the professorship. In October 2025, Simon joined the University of Freiburg, where he strengthens the 'Signals of Life' research focus, as well as the CIBSS Cluster of Excellence. He receives additional funding of 4.8 million euros from the Carl-Zeiss-Stiftung foundation over ten years to study how epigenetic mechanisms work in humans in relation to the environment and disease, to find possible personalised therapeutic approaches.

Daniel Dunkelmann
Institute: MPI of Molecular Plant Physiology, Potsdam, Germany
Fellowship: 08/18–12/20

Professor Ralph Bock
Institute: MPI of Molecular Plant Physiology, Potsdam, Germany
Fellowship: 09/93–08/96

The SyncSol research consortium, based at the MPI for Molecular Plant Physiology in Potsdam, Germany, receives £9.1 million (approximately €11 million) from the British funding agency Advanced Research and Invention Agency (ARIA). The project leader is **Daniel Dunkelmann,** who is based in the department of **Ralph Bock,** director at the MPI. The project seeks to develop a universal chloroplast genome that can be transferred across different plant species, making plant breeding more efficient and versatile. This could lead to optimised crops that produce drugs, biofuels, and tailored materials while absorbing CO_2 from the atmosphere, contributing to the sustainable bioeconomy of the future.

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

In November 2025, **Volker Haucke** received the Ernst Schering Prize 2025, endowed with €50,000 by the Schering Foundation. Volker Haucke, director at the FMP and chair at the Freie Universität Berlin, is honoured for his pioneering studies on vesicle transport and neuronal signalling, which have fundamentally advanced our understanding of cellular communication in the brain.

Timo Kuschma
Company: Forgent, London, UK
MD-Fellowship: 01/14–11/14

Thomas Pfeiffer
Company: Pangea Bio, London, UK
Fellowship: 06/13–11/15

Robert Macsics
Company: smartbax GmbH, Garching, Germany
Fellowship: 08/17–11/19

Three of our alumni (that we know of) have recently received large sums to develop the start-ups they have co-founded:

Timo Kuschma and his start-up Forgent (not in the biotech sector) have raised €4.3 million in pre-seed funding, the first funding phase of a start-up. Forgent is building AI agents that help companies navigate the complexities of bidding for public contracts, such as roads, power grids, or safety technology, in the EU.

Pangea Bio, of which **Thomas Pfeiffer** is co-founder and Executive Director R&D, has received $1 million from the Michael J. Fox Foundation for Parkinson's Research to advance one of their next-generation TrkB activators for Parkinson's disease.

Robert Macsics has announced that his company smartbax has raised €4.7 million in a pre-Series A round to advance their novel antibiotic compounds through the preclinical stage.

A BIF Fellow's Guide to ...

Amsterdam

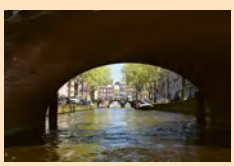
Travelling is fun – especially with insider tips from locals! In each FUTURA, the BIF invites one or more fellows to show you around their city. In this edition, your guide is Klaudia Majszczyk.

Facts and figures

Country: the Netherlands
Population: approx. 750, 000
Area: 219 km²
Students: 110, 000
Famous for: beautiful canals, biking culture, and a vibrant nightlife.
Website: www.amsterdam.nl

Best sights

Rijksmuseum: a must-see for anyone seeking a crash course in Dutch art and history. It houses an extraordinary collection of masterpieces by Rembrandt, Vermeer, and Frans Hals.
Jordaan: a charming neighbourhood of canals, boutiques, and cosy cafés perfect for wandering around.
IJ-Hallen Market: one of Europe's largest flea markets, held once a month in an industrial warehouse.



Canal Cruise: the best way to see Amsterdam and catch its true energy and charm.

Activities

Ice-skating by the Rijksmuseum (winter): from November to January, the museum square turns into an ice-rink and you can buy mulled wine or hot chocolate.

Visit Keukenhof Gardens (spring): a short bus ride takes you to vibrant tulip fields straight out of a postcard.
Open-air festivals (summer): get a drink at a sunny terrace, or lose yourself in the music and dance.
Amsterdam Marathon (autumn): run it yourself, or cheer on thousands of runners as they race through the city's historic streets and scenic parks.

Where to stay

Hotel Hegra by Stanley Collection: a charming boutique hotel in the heart of the city.

The Bedstee Boutique Capsule Hotel: a more budget-friendly hostel with capsule-style rooms.

Restaurants

Moeders: typical Dutch cuisine in a warm, homey setting – book well in advance!

Foodhallen: a vibrant indoor food market in a historic tram depot.
Pllek: a more laid-back spot by a beach and water, with a campfire and live music.
De Kas: a refined restaurant set in a greenhouse.

Nightlife

Radion, Raum, SkateCafe, Shelter: nightclubs that define Amsterdam's underground techno scene.
Waterkant: a canal-side hotspot that transforms into a dance party after midnight on weekends.
De Pijp: this neighbourhood is packed with bars. Try, for example, Glouglou or Bar Buka.
Paradiso and Melkweg: cultural venues hosting concerts, club nights, and other events.

Klaudia Majszczyk is 27 years old and comes from Poland. Her supervisor is Professor Benjamin D. Rowland at the Netherlands Cancer Institute.

2025 Heinrich Wieland Prize Awarded to 'Superhero' of Science

A superhero in regular clothing – that is how Diane Larson describes Adrian Krainer, recipient of the 2025 Heinrich Wieland Prize. The prize is given by BIF's sister foundation, the Boehringer Ingelheim Stiftung (BIS) and endowed with €250,000. Krainer is honoured for his groundbreaking research on how cells edit genetic messages before producing proteins – a process known as pre-mRNA splicing. Based on his discoveries, he developed the first effective therapy for spinal muscular atrophy (SMA), the genetic disorder with which Larson's daughter Emma was diagnosed at just 18 months. Although rare, until recently SMA was the leading genetic cause of death in young children. But not anymore.

In SMA, the gene SMN1 is defective. As a result, the body does not produce enough of a certain protein needed to build the nerve cells that control our muscles, so-called motor neurons. Children like Emma gradually lose control of their muscles; they lose the ability to walk, and, in many cases, even the ability to breathe. However, the body has a second SMN gene: the gene SMN2. Unfortunately, in most people this gene does not produce enough protein to compensate for the lack of SMN1, because of the way its pre-mRNA is spliced. But unlike the genetic defect in SMN1, the splicing defect in SMN2 can be corrected – thanks to the pioneering work of Krainer.

To build a protein, the cell copies the relevant part of the double-stranded DNA into a single-stranded copy. Besides the code for building the protein in question, this pre-mRNA also contains extraneous parts that contain no code for the protein. To act as a template for protein production, the non-coding parts are cut out, and the needed segments are joined together in the correct order. This is called pre-mRNA splicing. By splicing the same pre-mRNA in different ways, a single gene can give rise to multiple protein variants, significantly increasing the diversity of proteins in the human body.

Over several decades of research, Krainer has made seminal contributions to our understanding of this process. Building on this knowledge, he and his collaborators developed a short RNA-like molecule that corrects the splicing defect in SMN2 pre-mRNA. With it, patients' cells produce enough protein to develop and maintain motor neurons. The resulting drug, nusinersen, received regulatory approval in the United States in 2016, and in Europe the following year. It transformed SMA from a fatal condition into a treatable disease, significantly improving the quality of life for thousands of patients globally.

Remarkably, just two months after her first injection, Emma's decline stopped and she even started to improve. It is little surprise that parents like Diane Larson describe the scientist behind the therapy as a superhero.

Adrian Krainer, professor at Cold Spring Harbor Laboratory (CSHL), New York, USA, was recognised for his outstanding achievements during the Heinrich Wieland Award Symposium held on 11 December in Munich.

Len Marks Photography 2022 / CSHL

Upcoming Events

20–22 February
European Alumni Seminar, Glashütten, Germany
Annual meeting of former BIF PhD and MD fellows based in Europe. This year's seminar topic is 'Rare and Spare'.

25 February–1 March
132nd International Titisee Conference (ITC), Titisee, Germany
The 132nd ITC, titled 'Biology 2.0 – the AI revolution in biology and medicine', will be chaired by Alexander Stark and Michael M. Bronstein (both Vienna, Austria). It aims to bring together internationally leading experts in biological and biomedical research, as well as machine learning and artificial intelligence, to explore synergies between the fields and novel approaches on the wet-lab and dry-lab sides.
ITC participation is by invitation only.

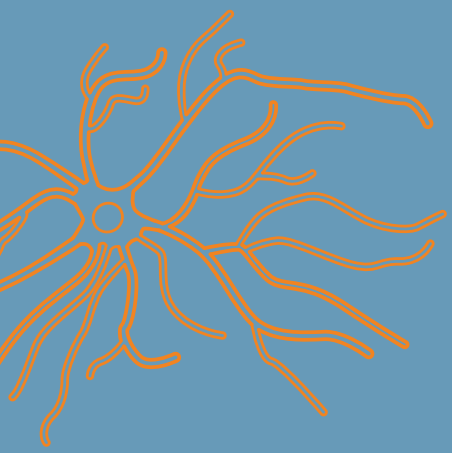
13–14 March
Meeting of BIF's Board of Trustees
The trustees decide on the allocation of fellowships, review the proposals for the International Titisee Conferences, and handle all matters of fundamental importance to the foundation.

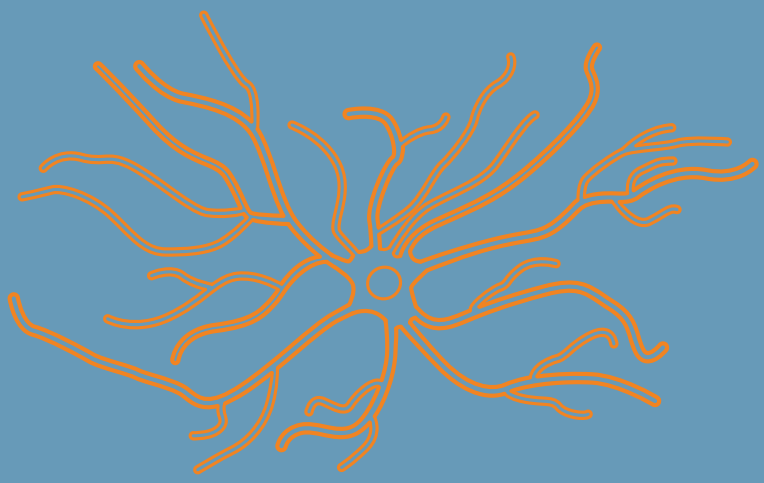
19–24 April
Communication Training, Cold Spring Harbor, NY, USA
Communication seminar for PhD and MD fellowship holders working in North America. The meeting will take place in Cold Spring Harbor, New York, USA. Participants will have the opportunity to work on their writing and presentation skills with various coaches, as well as learn more about designing graphs and figures. Further details will be sent with the invitation.

10–11 July
Meeting of BIF's Board of Trustees
The trustees decide on the allocation of fellowships, review the proposals for the International Titisee Conferences, and handle all matters of fundamental importance to the foundation.

29 August–4 September
Progress Seminar
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 will be sent with the invitation.

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





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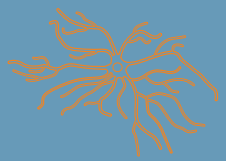

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