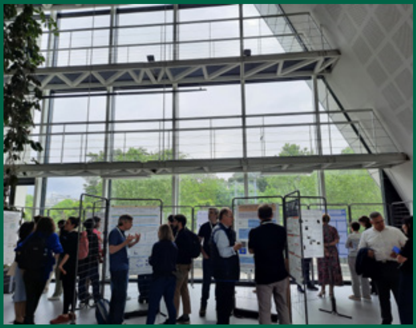
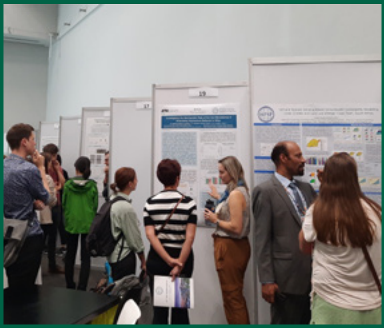
THE HUMAN FRONTIER SCIENCE PROGRAM
ANNOUNCES ITS

2025 Research Grant Awardees





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The Human Frontier Science Program (HFSP) is unique in supporting international collaboration to undertake innovative, risky, basic research at the frontiers of the life sciences. Special emphasis is given to the support and training of independent young investigators, beginning at the postdoctoral level.

The Program is implemented by the International Human Frontier Science Program Organization (HFSPO), supported financially by Australia, Canada, the European Commission, France, Germany, India, Israel, Italy, Japan, New Zealand, Norway, the Republic of Korea, Singapore, South Africa, Switzerland, the United Kingdom of Great Britian and Northern Ireland, and the United States of America.

Since 1990, more than 8,500 researchers from more than 70 countries have been supported. Of these, 31 HFSO awardees have gone on to receive the Nobel Prize.

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Human Frontier Science Program New Awards Booklet – 2025 Grants
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About HFSP's 2025 Grants
Message from the Director of Grants:

Almut Kelber,
Director HFSP Research Grant Program

It is the highlight of the year at HFSP: I am excited to announce the HFSP Research Grant awardees! 30 international teams, with all together 92 members have convinced the Review Committee that they will pursue novel and highly interdisciplinary research projects that will move the frontiers of life science. In addition, 12 scientists will join grant teams awarded in the previous year, adding an additional dimension to their ongoing projects. These Accelerator Grants are new in HFSP's portfolio, and we are excited about the outstanding quality of the proposals and to see how quickly the awardees community has responded to this new opportunity.

This year, we are specifically impressed that the 2025 Research Grants include scientists from across all the HFSPO members - spanning the entire globe.

The 2025 awardees booklet presents the abstracts of all projects that are recommended by the Review Committee because of their creativity, innovative thinking, application of emerging technologies and the prospect to really make a major contribution to advance our scientific understanding.

HFSP awards two types of grants, Research Grants – Program that are open to teams of two to four members at any stage of their independent research careers, and Research Grants – Early Career that are reserved for teams with all members within 10 years after earning their PhD and 5 years after obtaining their first independent position. These teams have not worked together before, bearing the potential to bring together new perspectives and approaches to some of the most challenging research questions in the life sciences. The awarded projects allow the team members to open a new line of research in fields where they have no preliminary data. And finally, we are also proud to see that most teams have members on two, three or even four continents.

Congratulations to all of them! We are looking forward to seeing the new projects unfold and lead to new and exciting discoveries!

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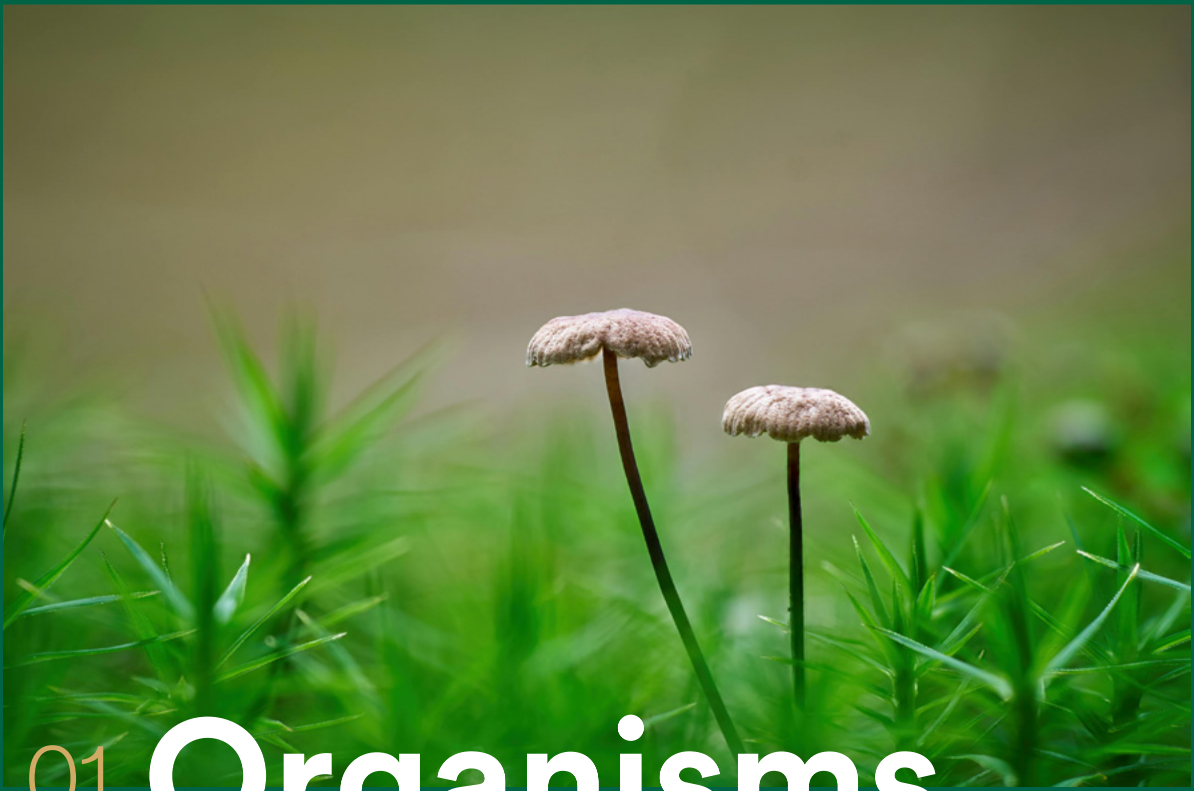


01 Organisms in their environments

Growth rate control in methanotrophs: engineering a biological sink for atmospheric methane

RG Type: Research Grants - Program

- Vasili Hauryliuk, Dept. of Experimental Medical Science, Lund University, Sweden
- Markus Basan, Dept. of Systems Biology, Harvard Medical School, Boston, USA
- Alexander Tøsdal Tveit, Dept. of Arctic and Marine Biology, The Arctic University of Norway, Tromsø, Norway

Global warming is an imminent treat to humanity. One of the drivers behind this process is the accumulation of atmospheric methane, a powerful greenhouse gas. The biological capture of methane is a promising approach that could help redress the situation and counter climate change.

The biggest biological sink of methane is its consumption by atmospheric methane oxidizing bacteria (atmMOB). These microorganisms can live on a unique 'diet' of methane from air as an energy and carbon source. Despite the planetary importance of atmMOBs, we know precious little about these unique bacteria. This is because until very recently it was impossible to growth them in the laboratory. In 2019, this major obstacle was overcome by the team of Alexander Tveit at the University of Tromsø. This breakthrough lays the foundation for the current project, allowing us to understand how atmMOB sense the environment and convert atmospheric methane into biomass.

The key aspect of bacterial macroeconomics of growth is the cellular investment of the metabolic resources into production of the ribosomes, the universal molecular machines the synthesize proteins in all the living cells. Decades of research on model organisms such as *Escherichia coli* have established that the faster bacteria grow, the more ribosomes they need. However, little is known about the laws governing the growth of atmMOB.

In this project we seek answers to the following questions: How do bacteria that live off air coordinate their growth? How do they sense when they are 'hungry' to control their ribosome production? Can we exploit our understanding of atmMOB growth laws to engineer faster growing strains for efficient methane capture? To do so, we have assembled an international consortium bringing together expertise in atmMOB microbiology (Alexander Tveit), protein synthesis and ribosomes (Vasili Hauryliuk) and bacterial growth laws (Markus Basan).

Decoding the evolution of anticipation and decision making in uncertain environments

RG Type: Research Grants - Program

- Martina Dal Bello, Dept. of Ecology and Evolutionary Biology, Yale University, West Haven, USA
- Jacopo Grilli, Dept. of Quantitative Life Sciences, International Centre for Theoretical Physics, Trieste, Italy
- Shawn McGlynn, Earth-Life Science Institute, Institute of Science Tokyo, Japan

Every day, we rely on our ability to remember patterns and associations to help us prepare in advance for later events. For example, when we see dark clouds on the horizon, we might expect rain to come. Research has shown that organisms from the microbial world can also develop pattern associations and predictive models that allow them to prepare in advance for environmental changes. The mechanisms underpinning anticipation involve genome regulation and also individuality between single cells, where individuals uniquely prepare as future "pioneers" to altered conditions. However, only a small number of organisms are typically studied, making it impossible to explain the diversity of strategies observed across the bacterial tree of life. Going further, the mechanisms that microbes might "learn" pattern associations through an evolutionary process are not clear. How much information about environmental dynamics can microbes "remember"? How does this depend on the "complexity" of organisms? Getting a deeper understanding of how the level of predictability of the environment has shaped, and continues to shape, ecological and evolutionary processes is of paramount importance as the Earth and its environments continue to change.

In this project, we seek to develop answers to these questions by bringing international expertise in microbial ecology, single-cell resolved views of populations, and evolutionary-information theory. We will grow a diverse pool of microbial species in different environments ranging from steady, to repetitive (for example day/night cycling as we experience ourselves), to random. We will explore how much cells learn in these environments, as a function of their level of predictability, and the possible variables that affect this, for example genome size, and growth rates. To understand the role of individuality, we will make observations of populations at the single-cell level, quantifying individual cell activity by tracking nutrient uptake rates (how much was eaten, and what was eaten). These experimental observations will be interpreted with a mathematical approach which relates learning to environmental information content. Through evolutionary experiments, we will study the limits and mechanisms of anticipation across diverse organisms, allowing us to develop a general understanding of learning in the microbial world.

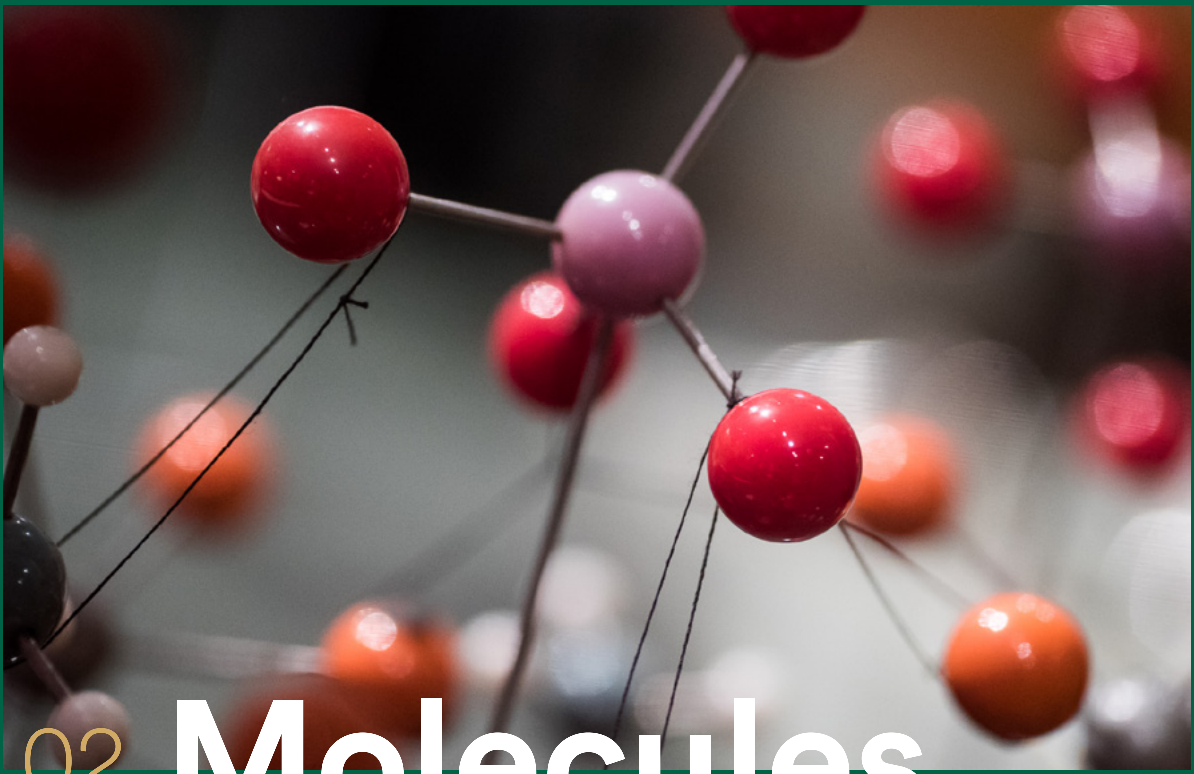
Behavioral adaptation to arsenic-rich environments

RG Type: Research Grants - Program

- Cornelia Bargmann, Lab. of Neural Circuits and Behavior, Rockefeller University, New York, USA
- Christian Braendle, Institute of Biology Valrose (IBV), University of Côte d'Azur, Nice, France
- Elizabeth New, School of Chemistry, University of Sydney, Australia
- Ryoji Shinya, School of Agriculture, Meiji University, Kawasaki, Japan

Climate change is an ongoing threat to humans, plants, and animals that must adapt to newly inhospitable environments. One underappreciated aspect of this threat is the degradation of groundwater and lakes by the accumulation of toxic elements like arsenic that can cause neuronal damage and death. The resulting mineral-extreme environments are increasing worldwide—for example, over 200 million people are currently exposed to toxic levels of arsenic in their drinking water. To inspire better strategies for detoxification and resilience, we will study animals that can naturally thrive in these arsenic-extreme environments.

Our studies will first focus on a nematode worm species that we recently isolated from Mono Lake, an arsenic-extreme natural lake that is incompatible with most animal life. This Mono Lake nematode is highly resistant to arsenic and has behavioral and lifestyle adaptations that promote its survival. For example, almost all nematodes reproduce by laying eggs, but this one incubates its offspring inside its body after hatching, providing nutrients to them and birthing progeny once they reach a stress-resistant stage. Unlike the few other animals that live in Mono Lake, our nematode can easily be grown in the lab, so we can study the properties that allow it to survive. We will ask: what behavioral and physiological specializations in these animals promote their survival in harsh conditions? How are those specializations implemented by their neurons, tissues, and genes? We will then examine these properties in other nematodes from a variety of extreme environments to see if they use similar strategies. We are a team of scientists with expertise in nematode biology, ecology, chemistry, genetics, and neuroscience, so we are ready to address each of these questions in detail.



02 Molecules and structures

Prebiotic route to informational polymers based on H-phosphonate chemistry

RG Type: Research Grants - Program

- Judit Šponer, Dept. of Structure and Dynamics of Nucleic Acids, Institute of Biophysics, Czech Academy of Sciences, Brno, Czech Republic
- Matthew Pasek, Dept. of Earth and Environmental Sciences, Rensselaer Polytechnic Institute, Troy, USA

RNA, a molecule that acquired an intense public attention mainly during the recent COVID pandemic, is believed to be central for the origin of life, as an ancient carrier of genetic information and a catalyst. Its formation in a hostile geological environment, that likely existed on the early Earth about 4 billion years ago, is surrounded with a lot of enigmas. One of them is related to the availability of phosphates, an integral part of all known RNA molecules today. Phosphates represent the highest oxidized form of phosphorus oxosalts, nevertheless, a question arises whether these molecules could have accumulated in a reducing environment that likely existed on our planet at the times when life emerged. Interestingly, phosphate derivatives are less reactive than their reduced form variants, called phosphites.

In this project we set out to explore chemical and geological conditions that enabled accumulation of phosphite salts, the formation of phosphite-containing prebiotic building blocks, their polymerization processes leading to reduced form RNA molecules, as well as the oxidation of the latter to RNA-like polymers. For this research we will use a unique, highly interdisciplinary combination of expertise from two distant research fields: prebiotic nucleic acids chemistry and early Earth geochemistry.

Our main aim is to reconstruct a scenario that accounts for all major steps of the synthetic process leading from accumulation of phosphite ions up to the emergence of short RNA molecules on our planet. Finally, we propose to study whether phosphite linkages incorporated in RNA, as likely remnants of reduced form predecessors of RNA, could give rise to the emergence of the catalytic activity of these molecules.

Mapping and modeling protein evolution on the abundance-activity-toxicity isoclines of fitness

RG Type: Research Grants - Program

- Christian Landry, Dept. of Biology, Laval University Québec, Canada
- Hisao Moriya, Dept. of Agriculture, Okayama University, Japan
- Kimberly Reynolds, Dept. of Bioinformatics, University of Texas Southwestern Medical Center, Dallas, USA

The function of most genes is achieved through the production of a protein that binds other molecules and/or catalyzes biochemical reactions inside the cell. A large fraction of the cellular machinery is dedicated to producing these active proteins in a timely manner and in appropriate amounts. Depending on the gene, protein abundance in cells is set to anywhere from 1 copy to around 1 million copies per cell. Despite this large variance, relatively small changes in the expression of any given gene can cause disease and/or drive evolutionary adaptation. Thus, measuring protein abundance across genes, cells, and different environmental conditions has been the subject of extensive research for the past 50 years. However, we still lack a clear picture of how much or how little of a protein is necessary to support cell growth and function. Consequently, we know which ingredients are vital for making functional cells and but not how much is needed. Evolution can change the ingredients and their quantity, but we do not know which mechanism is favored and why.

In this project, we join our expertise in evolutionary biology (Landry), cell biology (Moriya) and molecular biophysics (Reynolds) to understand how molecular-scale variation in protein activity and abundance contributes to the organism-level fitness (growth) of cells. Our goals are to (1) determine how changes in protein activity and abundance influence growth rate within a biophysical framework, (2) examine how natural systems navigate this space through mutations and selection, and (3) better understand why sometimes evolution is limited in what it can change because cells cannot overcome the toxicity of some proteins and their mutations. We will combine quantitative, high-throughput experiments (in both the bacterium *E. coli* and yeast) with computational modeling.

Together, our work will provide a quantitative framework for considering the “design” of protein systems. It will also offer a quantification of the conditions within which cellular systems evolve and a mechanistic understanding as to why protein abundance can range several orders of magnitudes while a given protein is allowed to exist in a very tiny abundance window by evolution.

MetaCrystal: Metabolic principles of intracellular crystallization

RG Type: Research Grants - Early Career

- Noemi Jimenez-Rojo, Dept. of Biochemistry and Molecular Biology, University of the Basque Country, Leioa, Spain
- Rita Mateus, Biophysical Principles of Vertebrate Growth Lab, MPI of Molecular Cell Biology and Genetics, Dresden, Germany
- Viviana Monje, Dept. of Chemical and Biological Engineering, State University of New York (SUNY), Buffalo, USA

Many living organisms are capable of producing organic crystals inside their cells to fulfill a variety of functions. For example, the compound eyes of certain crustaceans use crystals to amplify their light sensitivity in dim-light habitats. Another well-known example is the chameleon, which takes advantage of the light-reflecting properties of crystals to swiftly alter its skin color. Therefore, failure to regulate crystal formation properly can be detrimental to tissue and organ function, severely affecting the ability of the organism to survive and reproduce. The zebrafish, a vertebrate model species, also produces crystals that play a key role in pigmentation, in specialized skin cells called iridophores. They are formed inside dedicated organelles, known as iridosomes. Control of crystal size, shape, and assembly take place with a precision that currently far exceeds our abilities to grow such structures synthetically.

In the proposed study, we plan to uncover how this process occurs, considering an essential, but so far unexplored, structure: the lipid membrane that encloses each crystal inside a cell. We want to understand which molecules are found at the iridosome membrane, their biochemical nature, and to which extent those can contribute to precise crystal formation. For this purpose, we will apply a highly interdisciplinary approach combining cutting-edge techniques from molecular biology, such as CRISPR-Cas9, with biochemistry, mass spectrometry, and molecular modeling. We will use novel chemical biology methods to measure and manipulate biophysical properties of iridosomal membrane and track protein function in zebrafish *in vivo*, and in iridophore cell cultures. The results will inform us on how to generate and reconstitute synthetically a biomimetic system able to produce crystals at the same scale and morphology as those of zebrafish, using a combination of biological and chemical transformations under physiological conditions.

We expect that our results will facilitate the development of therapeutics to treat diseases where aberrant crystallization occurs, such as kidney stones and gout. In addition, they will contribute to new protocols to synthesize organic crystals for a variety of applications in the areas of optics and material science.

Building mineral pore networks and primitive peptides to assemble biomolecules

RG Type: Research Grants - Early Career

- Martina Preiner, Microcosm Earth Center, MPI for Terrestrial Microbiology, Marburg, Germany
- Liam Longo, Earth-Life Science Institute, Institute of Science Tokyo, Japan
- Cole Mathis, Center for Biocomputation, Arizona State University, Tempe, USA

How did the early environment on earth influence the chemistries that led to life as we know it? If minerals were indeed the predecessors to enzymes, how did they support complex reaction sequences? Did they collaborate with emerging enzymes?

In this proposal, we tackle these questions from three disciplinary angles: catalysis of key metabolic reactions at mineral surfaces, chemistry within porous environments, and resurrection of ancient enzyme structures. The focus of these three approaches centers on organic cofactors, crucial helper molecules that can support catalysis within the enzyme active site and at the mineral surface. These versatile molecules, which are absolutely conserved across the tree of life, are relics of metabolism before enzymes. By binding to early peptides, we hypothesize that cofactors and minerals may have helped spark the emergence of the earliest enzyme structures, allowing them to fold and function. We also posit that patterning of pore networks may have established the earliest reaction “pathways”. To study these processes, we are building a reaction system in which the interacting roles of spatial structure, mineral composition, cofactors, and primitive enzymes can be disentangled. In doing so, we are interrogating the history of reaction control and bias, the properties of the earliest proteins, and the nature of self-sustaining reaction networks. Ultimately, the goal of this work is to construct a pre-cellular, proto-enzymatic, assembly line in which a common cofactor participates in its own synthesis.

03 Genes and gene regulation

Dancing genomes – mapping chromatin's material properties with retinal development & disease

RG Type: Research Grants - Program

- Michael Robson, Max Delbrück Center for Molecular Medicine, Berlin, Germany
- Anders Hansen, Dept. of Biological Engineering, MIT, Cambridge, USA
- Davide Michieletto, School of Physics, University of Edinburgh, UK
- Sandra Tenreiro, Degeneration and Ageing Lab, Universidade Nova de Lisboa, Portugal

Chromatin, the structure that organizes our DNA, is a biological machine made of soft, flexible parts. For this machine to function, it must shift, bend, and rearrange to perform essential tasks, from repairing DNA to activating or silencing genes. However, how chromatin's physical properties—whether it behaves like a liquid, solid, or gel—affect its ability to perform these functions remains largely unknown. This is because observing chromatin's movements in living cells, and across the various size scales it operates on, has been extremely difficult. Traditional models offer limited insight, as chromatin moves too little to capture meaningful data across the range of scales needed to fully understand its behavior. Our project aims to solve this by studying the unique, extreme dynamics of chromatin in the retina, the part of the eye responsible for vision.

In most cells, inactive chromatin stays at the edges of the nucleus, while active chromatin occupies the center. However, in the rod cells of nocturnal mammals like mice, this arrangement is reversed after birth to help the eyes capture more light. This rare "inversion" of chromatin offers a unique opportunity to observe dramatic chromatin movements and uncover its physical properties during global reorganization.

Our approach combines genetic tools, high-resolution imaging, and computational modeling to capture chromatin behaviors across multiple scales. By controlling chromatin inversion in mouse retinal cells, we will observe chromatin's movements in real time. We will measure movements at the level of individual genes and larger chromatin regions, providing a comprehensive picture of chromatin dynamics. Simulations will test different models and parameters to understand whether chromatin acts more like a liquid, solid, or gel and why. We will extend our work to human retinal organoids—lab-grown models of the human retina—to investigate whether inappropriate chromatin inversion occurs in eye diseases like macular degeneration and how this might contribute to vision loss.

This project unites experts in genetics, imaging, computational biology and neurodegeneration to study chromatin in ways not previously possible. By treating chromatin as a dynamic machine that must move and reorganize, we aim to uncover new insights into how our genomes work and how chromatin malfunctions promote disease.

Universal biochemistry of RNA in the cold

RG Type: Research Grants - Program

- Felix Ritort, Dept. of Condensed Matter Physics, University of Barcelona, Spain
- Philipp Holliger, Dept. of Protein & Nucleic Acid Chemistry, MRC Lab of Molecular Biology Cambridge, UK
- Sarah A. Woodson, Dept. of Biophysics, Johns Hopkins University, Baltimore, USA

Life exists even in the coldest environments on earth, yet we know little about how RNA molecules needed for all living things continue to function at subzero temperatures. Using a specialized microscope capable of studying single molecules of RNA at temperatures down to the freezing point of salt water, we recently discovered that RNA molecules acquire new and unexpected properties at subzero temperatures. At low temperatures, sequence-independent 2'-hydroxyl-water interactions become more important than sequence-dependent base pairing. These changes are predicted to profoundly alter the ability of RNA molecules to fold into 3D shapes and catalyze biochemical reactions.

We hypothesize that RNA catalysts may have first evolved at subzero temperatures, potentially within semi-frozen environments such as interstitial brines. Our findings predict a much richer ensemble of RNA structures and more error-prone RNA replication in the cold. This would have accelerated primordial RNA evolution and could profoundly impact the function of present-day RNAs in the cold, with applications to biotechnology, pharmaceuticals, and food science.

To unveil the secrets of RNA in the cold, our multidisciplinary team of three research groups with complementary expertise will determine how low temperatures influence RNA structure and function. We will explore basic rules and principles of RNA in the cold, from simple base-pairing structures such as hairpins, to regulatory RNAs such as riboswitches, and ribozymes such as self-splicing introns and replicases. Our main goal is to find out the consequences of the recently discovered altered RNA biochemistry for understanding cold adaptation in present-day psychrophilic biota and conditions for the emergence of life since primordia.

Filamentous self-assembly – a common mechanism driving transcription factor function?

RG Type: Research Grants - Early Career

- Marcin Jozef Suskiewicz, Dept. of Molecular, Structural and Chemical Biology, Center for Molecular Biophysics, CNRS Orléans, France
- Max Staller, Dept. of Molecular and Cell Biology, University of California, Berkeley, USA
- Antoni Wrobel, Dept. of Biochemistry, University of Oxford, UK

The regulation of gene expression is essential for development, stress responses, and homeostasis. During this process, the information encoded in the genome is turned into functional proteins. The transcription of a deoxyribonucleic acid (DNA) segment creates a ribonucleic acid (RNA) molecule, which acts as a blueprint to make a protein, a functional component of the cell. The transcription of genes into RNA is regulated by proteins called transcription factors. Transcription factors have two main functions: they bind to specific DNA sequences and either activate or repress transcription. Traditionally, it was believed that transcription factors worked alone or in pairs. However, recent research has unveiled a surprising twist: many transcription factors often join forces, forming larger assemblies of molecules that together navigate DNA to identify specific regions. The nature of these assemblies is poorly understood.

Our project focuses on one particular category of these assemblies, called filaments. Filaments are open-ended, rod-like structures composed of multiple copies of the same protein. Based on our preliminary analysis, we propose that many human transcription factors might have unreported abilities to form filaments, which would allow them to simultaneously bind to long DNA sequences. To study how filament formation affects the function of transcription factors and how general this mechanism is, we will rely on various approaches. First, we will use experiments, computational analysis, and machine learning to study known examples of filamentation. We will also use cryo-electron microscopy, an imaging technique suited for tiny objects, to study structures of filaments formed by transcription factors in the presence or absence of DNA. Finally, we will employ a transformative software called AlphaFold to predict new human transcription factors with a propensity to form filaments. Overall, the project will establish the prevalence and importance of filamentation as a mechanism by which transcription factors regulate expression of human genes.

Rediscovering Vienna's lost "epigenetic" treasure

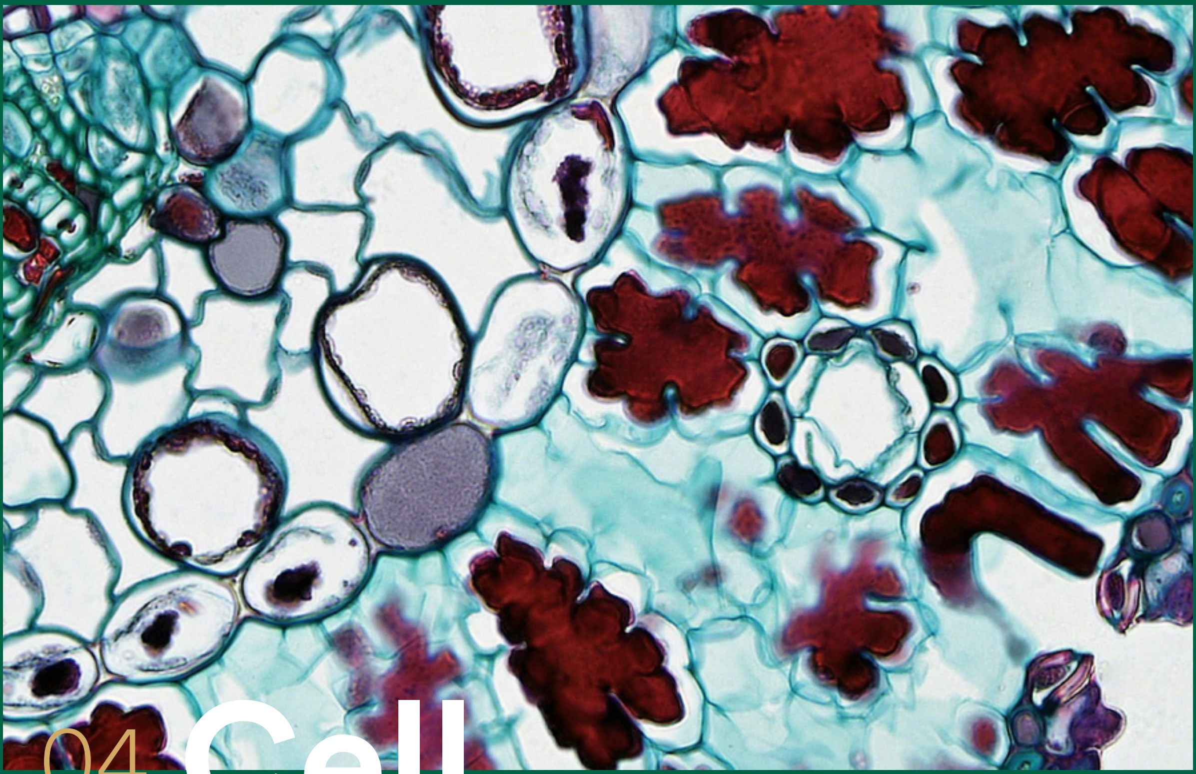
RG Type: Research Grants - Program

- Oded Rechavi, Dept. of Neurobiology, Tel Aviv University, Israel
- Katharina Gapp, Dept. of Health Sciences and Technology, ETH Zürich, Switzerland
- Yasunori Sasakura, Shimoda Marine Research Center, University of Tsukuba, Japan

Our project combines history and biology in a first of its kind interdisciplinary study revisiting the research done over 100 years ago in the Biologische Versuchsanstalt (BVA). The BVA, founded in 1902, stood out with a focus on researching live animals, a new concept in those days, and its founders, led by Hans Leo Przibram, supported long-term experiments in hundreds of species of animals, many of which were never used in research later or even successfully raised in captivity.

Research into acquired traits inheritance was central to the work of the most controversial scientist in the BVA—Paul Kammerer—who won global fame, only later to be called out as a fraud and take his own life. Even if Kammerer's findings are indeed unreliable, many other well respected BVA scientists published hundreds of scientific papers in the decades the institute was active, and inheritance of acquired traits was an important part of the scientific agenda of Przibram, a renowned researcher who also had demonstrated the possibility of this type of inheritance in his own (never disproved) studies. Yet the scandal, the breathtaking success of modern DNA-based genetics, and the tragic end of the institute and its founders and members—most of whom were of Jewish descent who were murdered by the Nazis—meant that the unique science done in the BVA was never continued.

In the past 15 years, the possibility of transgenerational epigenetic inheritance has gained a new life owing largely to research conducted using *C. elegans* nematodes. Oded Rechavi, who is leading the project, is a pioneer in describing an RNA based molecular mechanism enabling such inheritance in the tiny worm. Now, the challenge is to demonstrate the existence of similar mechanisms in other organisms. The research done in the BVA could be discovered as a scientific treasure trove for accomplishing such a goal. Therefore, we propose to (1) translate and study the BVA papers to select the works that are worth revisiting, (2) replicate the rediscovered studies, and (3) use molecular research to discover new inheritance mechanisms in the BVA models. To do this we assembled a unique team of historians and biologists specializing in the different animals we plan to focus our replication efforts on, and in the study and discovery of the molecular mechanisms involved in epigenetic inheritance research.



04 Cell biology

Microbial and chemical mechanisms of rapid fear signaling

RG Type: Research Grants - Program

- S. Craig Roberts, Faculty of Natural Sciences, University of Stirling, UK
- Lindsay Kalan, Dept. of Biochemistry & Biomedical Sciences, McMaster University, Hamilton, Canada
- Jonathan Williams, Dept. of Atmospheric Chemistry, MPI for Chemistry, Mainz, Germany

Many species, including humans, use odors to communicate. These odors are typically complex and describing them is challenging. Furthermore, we do not know much about how they are produced. However, in some species, such as hyenas and some primates, individuals may share similar skin bacteria that produce distinctive chemical compounds as part of their metabolism; these compounds have become co-opted for communication and are how the animals infer species, sex, and social group membership.

We aim to understand the mechanisms by which human odors are produced. We focus on emotional odors, especially fear, for two main reasons. First, we know that humans do produce a distinct 'fear odor,' even though we do not know the precise chemical compounds involved nor whether the skin bacteria are responsible for them. Second, a signal of fear requires a very rapid response change - in a matter of seconds or minutes - that is much faster than any microbially mediated signal studied to date, in any species. Indeed, we do not know whether bacterially produced odors are even possible on this time scale; addressing this possibility is bold and innovative but could lead to a discovery of enormous significance.

Our interdisciplinary team has expertise in the psychology of odor communication, dynamic changes in skin bacteria, and analysis of airborne (volatile) chemical compounds. We will study the odor of fear by showing people scenes that arouse emotional responses (including fear) at the same time as measuring changes in bacterial metabolic activity and the release of chemical compounds from the skin. We aim to provide the first description and identification of rapid changes in bacterial activity and odor chemistry as people experience fear. Next, we will attempt to confirm the odor production pathway by analyzing the chemicals produced by our candidate bacteria in the lab, as they are cultured on an artificial blend of human skin secretions. Finally, we will test how people respond to the identified chemical compounds. We will compare people's emotional responses when they are exposed to the isolated compounds with how they respond to the complete (natural) odor of scared people; if the responses are comparable, it will suggest that we have correctly identified the compounds responsible for the smell of fear.

Coordination of cell consortia via soluble factors

RG Type: Research Grants - Early Career

- Franziska Blaeschke, Dept. of Pediatric Immuno-Oncology, DKFZ Heidelberg, Germany
- John Hickey, Dept. of Biomedical Engineering, Duke University, Durham, USA
- Xavier Rovira Clave, Spatial Biotechnology Group, Institute for Bioengineering of Catalonia, Barcelona Spain

Individual cells self-organize within our bodies to build the tissues and organs that enable life. We know that soluble molecules, like cytokines, chemokines, and growth factors, contribute to guiding cells into specific arrangements. While we know that sometimes one of these factors can direct a cell to perform a specific task, most bodily functions and diseases depend on a complex combination of these factors interacting with each other—often in ways that are not yet predictable. We still do not fully understand how these networks of interacting factors are created and what their function on tissue restructuring is because of limitations with experimental, measurement, and computational approaches.

In this project, we will develop new approaches that enable us to explore for the first time how networks of soluble factors coordinate the behavior of different cell types. We will develop massive sample and experimental barcoding mixed with advanced imaging and computational approaches to: 1) study how immune cells get organized in tumor organoids exposed to specific soluble factors, 2) use soluble factor-releasing particles to analyze how soluble factors influence cell organization, and 3) uncover how networks of factors released by tumor-specific T cells coordinate cellular processes in the tumor microenvironment.

We will combine our unique expertise in advanced tissue imaging, spatial mapping, live tumor models, genetic testing, biomaterials, and computational modeling to decode how these networks function in solid tumors. A better understanding of the interplay between soluble factors and cellular arrangements will not only advance basic scientific knowledge on tissue organization but also pave the way for innovative therapeutic strategies that harness the contributions of soluble factors and the tissue microenvironment.

Trapping targets of dynamic translation to identify novel cellular “band aids”

RG Type: Research Grants - Program

- Olena Zhulyn, Developmental & Stem Cell Biology Program, The Hospital for Sick Children Toronto, Canada
- Neil Kelleher, Dept. of Chemistry and Molecular Biosciences, Northwestern University – Evanston, USA
- Mounia Lagha, The Institute of Molecular Genetics, University of Montpellier, France
- Alexander van Oudenaarden, Developmental Biology and Stem Cell Research, Hubrecht Institute, Utrecht, Netherlands

In humans, a paper cut takes days to seal, and a limb amputation takes more than weeks to heal and months to rehabilitate. In contrast, the axolotl salamander can seamlessly close wounds within hours of injury and regenerate a functional arms or legs within a month after amputation. Their regenerative ability captivated scientist for more than 150 years. In a recent breakthrough discovery, we demonstrated this regenerative ability depends at least partly on the axolotl’s ability to quickly make new proteins at the site of injury. This rapid accumulation of proteins seems to allow skin cells at the edges of the wound to migrate and seal the injury. This in turn allows the animal to regrow a functional limb in the weeks that follow. While we know that protein production is important, we don’t know which proteins are made and where or why they are important. We hypothesize that axolotls produce special proteins that act as “band aids” to help seal wounds more quickly.

In this project we combine the unique and complementary skills of four team members to visualize how skin cells in live axolotls tune protein production to respond to injury. We will use high-resolution imaging and novel protein probes to visualize when and where axolotls make their “band aids”. We will compare the dynamics of this process to that of ‘dorsal closure’ in the fly - a well-studied example of cells closing a naturally occurring ‘hole’ at the back of the embryo. This classic example has been used to understand cell migration; however, the role of dynamic protein accumulation has not been studied. Next, we will apply a newly developed “single cell Ribo-Seq” approach to understand which building blocks are being produced in skin cells that are actively engaged in protein production. Finally, using a cutting-edge protein identification approach, we will determine the location and identity of axolotl band aid proteins and study their function in wound healing and regeneration using genetically engineered axolotls.

Our multidisciplinary approach will (1) elucidate mechanisms of wound healing, (2) provide insight into how different species use proteins production to drive cell rearrangements, and (3) create a pipeline for studying how changes in protein production contribute to cell movement in diverse biological contexts like cancer metastasis.

Molecular memories in single cells: An integrated approach to how cells learn

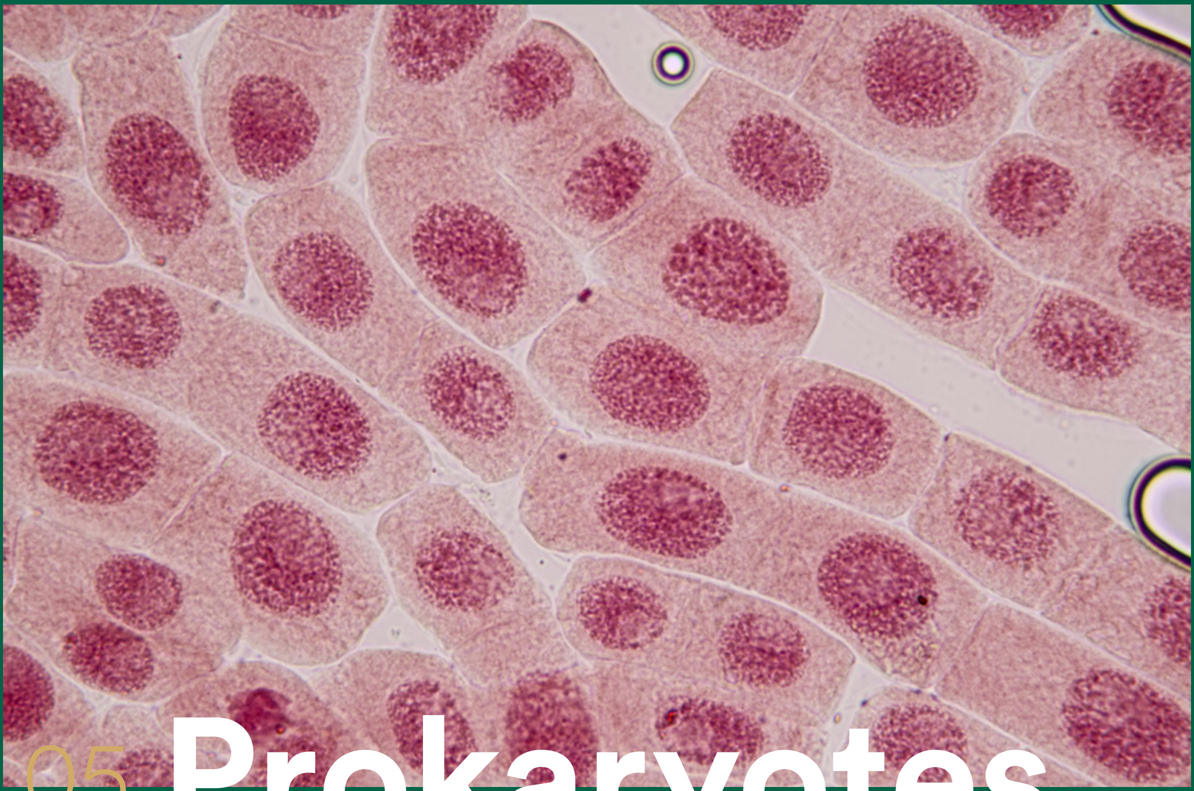
RG Type: Research Grants - Early Career

- Saad Bhamla, School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, USA
- Wanze Chen, Institute of Synthetic Biology, Shenzhen Institute of Advanced Technology, China
- Audrey Dussutour, Research Center on Animal Cognition, University Paul Sabatier, Toulouse, France

It has long been thought that memories are stored in the brain by strengthening the connections between neurons. However, recent discoveries suggest that molecules inside cells, especially RNA, might also be involved in storing and transferring memories. Our project explores this idea by studying a free-swimming organism called *Spirostomum ambiguum* and immune cells known as macrophages.

These single cells are capable of learning from their experiences, much like more complex organisms. For example, they can “train” themselves to respond more effectively to challenges they’ve faced before. A key tool in our research is Live-seq, a cutting-edge technology that allows us to study the activity of individual cells over time without killing them. Traditional methods for studying cells typically destroy the cell during analysis, limiting what we can learn. Live-seq, however, enables us to track gene activity in living cells, making it possible to see how a cell’s behavior and gene expression change as it “learns.”

We are particularly interested in how cells can exhibit associative memory, a form of learning similar to how Pavlov’s dogs learned to associate a bell with food. In cells, this could mean “remembering” a previous stimulus and preparing a stronger response the next time. Additionally, we will explore the possibility of implanting synthetic or “false” memories into cells by transferring RNA from one cell to another, potentially demonstrating that RNA can carry memory-specific information. This research could change how we understand memory in all living organisms and might even lead to new medical applications, such as improved treatments for immune-related diseases.



05 Prokaryotes, good and bad

What drives plant-like growth in filamentous cyanobacteria?

RG Type: Research Grants - Program

- David Lea-Smith, School of Biological Sciences, University of East Anglia, Norwich, UK
- Albena Lederer, Dept. of Chemistry and Polymer Science, Stellenbosch University, South Africa
- Michael Murrell, Dept. of Biomedical Engineering, Yale University, New Haven, USA

All large organisms on Earth belong to a single domain of life, the eukaryotes. Many eukaryotes form large multicellular structures that allow resources to be harvested from different locations and combined. For example, the structure of trees allows the combination of water and minerals from below the soil surface with light and gases from above. The ability to form such structures to exploit resources from multiple environments is generally assumed to be lacking in the other domains of life, the bacteria and archaea. However, we have identified multiple, nitrogen fixing photosynthetic cyanobacteria which form centimeter scale plant-like structures. These species, all sheathed bacteria, incorporate filamentous, interconnected cells within a rigid polysaccharide sheath, which allows them to attach to surfaces via a biofilm and form aerial shoot and subsurface root-like structures. Sheathed bacteria are widely found in nature, predominantly in freshwater and coastal ecosystems, but also in saltmarshes, rocks and lava deposits, where they play an important role in preventing erosion, act as food source and adapt the environment to render it suitable for plant growth. Utilizing a novel model system we have shown that cells can migrate within sheaths at a speed equivalent to a 25-meter carriage train travelling 7 km/hour, and that sheaths can bind together to form the shoot-like structures. What drives this plant-like growth and rapid cell migration is unknown but as in plants, it is probably linked to the exploitation of resources from different environments.

Our multidisciplinary team will apply its expertise in microbiology, analytical polymer science and mechanical engineering to understanding the role of the aerial, biofilm and subsurface cells, for how nutrients, energy and cells travel up and down sheaths and how the properties of sheaths allow the formation of large structures and transport of cells and nutrients. Specifically, we will analyze gene and protein expression in environmental samples and our model system to understand the role of aerial, biofilm and subsurface cells and whether a novel form of nitrogen fixation is occurring in biofilm cells, microscopy to analyze the architectural properties necessary for plant-like growth and movement of filaments and nutrients, and structural and chemical analysis of sheaths to elucidate their role in these processes.

1+1=1: Bioengineering synthetic symbiosis to illuminate how a microalga becomes an endosymbiont

RG Type: Research Grants - Program

- Johan Decelle, Cell and Plant Physiology Lab., CEA Grenoble, France
- Daniel Ducat, Dept. of Biochemistry and Molecular Biology, Michigan State University, East Lansing, USA
- Dietrich Kohlheyer, Institute of Bio- and Geosciences Biotechnology (IBG-1), Research Center Jülich, Germany

Life evolved by multiple symbiotic interactions between merging single-celled organisms that led to acquisition of genes, organelles, and new functionalities. For instance, a symbiosis between a host and intracellular photosynthetic cells (microalgae), called photosymbiosis, occurred several times in the evolution and led to the origin of all the photosynthetic organisms on earth, such as plants, trees and algae. In this process, engulfed photosynthetic cells were gradually transformed into an organelle, called the chloroplast, which produces oxygen and energy with light and feeds earth food webs. Photosymbiosis is still a widespread life strategy in aquatic and terrestrial ecosystems, such as lichens, corals and in the ocean plankton, and plays fundamental ecological roles with economic values. Despite the importance of photosymbiosis in the evolution of life and in ecosystems, we know very little about how the two organisms (host and photosynthetic partners) interact with each other, mainly because they are difficult to maintain and study in the laboratory and there is a lack of high-resolution imaging and genetic tools.

How two cells become one cell (1+1=1) is one of the most intriguing mysteries in life we want to tackle in this project. We propose to create a new photosymbiosis with bioengineered cyanobacteria and a host cell with an interdisciplinary team covering expertise in biology, microfabrication of culture systems, microscopy, and physiology. This will allow us to investigate the fundamental steps of the integration of photosynthetic cells inside a host, and their metabolic responses to the engulfment. At relevant temporal and spatial scales, we will co-culture and scrutinize the two partners in different conditions using genetically modified cyanobacteria that can perform different functions (excretion of sugars). This ambitious project will address fundamental questions in biology and will provide new knowledge on one of the most important events in the evolution of life.

Exploring interdisciplinary frontiers to understand tick-virus dynamics at a global scale

RG Type: Research Grants - Program

- Michail Kotsyfakis, Lab. of Arthropod Disease Vector Biology, FORTH Institute of Molecular Biology and Biotechnology, Heraklion, Greece
- Abdoulaye Diabate, Dept. of Biomedical Sciences, Centre Muraz, Bobo-Dioulasso, Burkina Faso
- Sirri Kar, Dept. of Biology, Tekirdag Namik Kemal University, Turkey
- Ben Mans, Onderstepoort Veterinary Research, Agricultural Research Council, Pretoria, South Africa

The spread of diseases transmitted by ticks is becoming an increasing concern globally, especially with the rapid changes to our environment driven by climate change and human activities. The project focuses on the Crimean-Congo Haemorrhagic Fever Virus (CCHFV), a dangerous virus spread by ticks in many regions across Africa, Europe, and Asia. Ticks, particularly those of the *Hyalomma* species, are the main carriers of this virus. While some regions such as South Africa and parts of Europe are considered hotspots for CCHFV outbreaks, the factors driving the spread of the virus remain poorly understood. The project's main goal is to better understand how the virus, the ticks that carry it, and the environment interact, so that we can predict and hopefully reduce the viral spread in the future.

One area of focus is how *Hyalomma marginatum* and *Hyalomma rufipes*—two closely related species of ticks—spread across different habitats. These ticks can be transported long distances by migratory birds, which may help the ticks to cross geographical barriers, bringing them into new areas. The project also aims to investigate whether these tick species are interbreeding, creating hybrids that could alter how the virus is transmitted. By studying the genetics of these ticks across different regions, we will better understand how different tick populations are related and how their movement might be affecting pathogen spread.

The team will also study the viruses found in the ticks. We know that ticks can carry several different viruses, and this project will identify which viruses are present in different regions. This will help to determine whether specific tick populations carry more dangerous strains of viruses. The research will look at how environmental factors, such as temperature, humidity, and land use, influence where ticks live and how they spread. This information will help us predict how climate change might affect tick populations and viral transmission in the future.

The project is an intercontinental collaboration involving researchers from four countries, who will share their expertise and data to tackle this problem. The findings will help prepare for future disease outbreaks linked to changing environmental conditions. This knowledge will be crucial for public health authorities in planning disease prevention and control strategies in regions at risk.

06 Evolution and development

Evolutionary biophysics of spiralian asymmetric divisions

RG Type: Research Grants - Program

- Hervé Turlier, Center for Interdisciplinary Research in Biology (CIRB), College de France, Paris, France
- Vanessa Barone, Dept. of Biology, Stanford University, Pacific Grove, USA
- Jose Martín-Durán, Dept. of Biology, Queen Mary University of London, UK

Asymmetric cell divisions, which produce two distinct daughter cells, are crucial for multicellularity as they drive the formation of specialized cell types. Traditionally, these divisions have been associated with changes in the position of the plane that separates the mother cell into two daughters. However, many marine invertebrates employ a different strategy to create cellular asymmetries right after fertilization: they form a cellular protrusion known as the "polar lobe," which is inherited by only one daughter cell, leading to a distinct developmental fate. Interestingly, this evolutionary innovation has independently arisen in multiple species, making it an ideal system for studying the origins of asymmetric divisions in evolution.

Key questions arise: How did polar lobes evolve? Do all embryos with polar lobes rely on similar mechanisms? How predictable is evolution when similar solutions emerge independently in different species? To address these fundamental questions, we are bringing together three cross-disciplinary teams with expertise in evolutionary, developmental, and cell biology, as well as cell mechanics, bioinformatics, biophysics, and computational modeling.

Focusing on up to 12 non-model marine invertebrates, we will leverage the work of evolution to explore these mechanisms by: 1) using evolutionary developmental biology (evo-devo) and comparative omics to identify the molecules responsible for polar lobe formation and segregation; 2) employing live imaging and biophysics to dissect the cytoskeletal dynamics that generate polar lobes; and 3) applying theoretical and computational modeling to replicate and interrogate the physical mechanisms underlying asymmetric divisions.

Our collaboration will reveal how cellular mechanics, and developmental genetics interact to generate asymmetries and novel structures during animal embryogenesis. This research will open new avenues at the intersection of biophysics and evolutionary biology, transforming the rich diversity of marine invertebrates into a powerful system for investigating fundamental biological questions with potential insights extending to other animals, including humans.

Visualizing and dissecting spatial translation dynamics across developmental time

RG Type: Research Grants - Program

- Yad Ghavi-Helm, Institut de Génomique Fonctionnelle de Lyon (IGFL), ENS Lyon, France
- Hilary Ashe, Faculty of Biology, Medicine and Health, University of Manchester, UK
- Ahilya Sawh, Dept. of Biochemistry, University of Toronto, Canada

Understanding how genes are precisely regulated at the cellular level is crucial for the proper development and function of organisms. Recent technological advances have allowed scientists to study the abundance and spatial distribution of mRNAs (the molecules that carry genetic instructions from DNA to make proteins) within individual cells. However, just measuring mRNA levels does not always give an accurate picture of how much protein is being produced, as this process is tightly regulated at the translation stage (when mRNA is converted into protein). Unfortunately, the extent of this regulation is still not well understood due to technical challenges.

To address this gap, our goal is to develop a new method called "spatial translatomics" that will allow us to study how translation is regulated during development. We plan to combine expertise in molecular biology, advanced imaging, computational analysis, and developmental biology to achieve this. We will use the fruit fly embryo, *Drosophila melanogaster*, as our model system because of its advantages for studying gene regulation during development.

First, we will visualize and measure the translation of thousands of mRNAs in single cells at key stages of *Drosophila embryogenesis*. This will give us a detailed view of how translation is regulated at the cellular level. Next, we will identify groups of mRNAs that are co-regulated during translation and focus on RNA-binding proteins that control this process. We will use innovative genetic and genomic techniques, and spatial translatomics to uncover the mechanisms behind this regulation. Finally, we will study how mRNAs are directed to specific regions in the cell known as "translation factories," where clusters of mRNAs are efficiently translated into proteins. We will combine chromosome tracing with spatial translatomics to test the idea that genes that are transcribed together may be efficiently directed to these translation factories.

This research will provide a comprehensive view of how translation is controlled at a high spatial resolution during development in *Drosophila*. Moreover, our method will offer new insights into translational regulation that could be applied to other model systems, potentially transforming the way scientists study gene expression in diverse organisms.

Mechanical and morphological evolution of the insect heart

RG Type: Research Grants - Program

- Timothy Saunders, Dept. of Biomedical Sciences, University of Warwick, Coventry, UK
- Kristen Panfilio, Dept. of Molecular Genetics, University of Hohenheim, Stuttgart, Germany
- Andres Sarrazin, Instituto de Química, Pontificia Universidad Catolica de Valparaiso, Chile
- Jennifer Young, Dept. of Biomedical Engineering, National University of Singapore, Singapore

The heart is one of the first organs to form. Genes specifying heart cells (cardioblasts) are highly conserved from insects to humans. The earliest processes of heart shaping are also qualitatively similar between species: two regions of cardioblasts migrate to the embryo midline to form a simple tube, neighbored by extraembryonic tissues. Yet, it remains a major challenge to dissect the biophysical processes (the magnitude and direction of forces) that first build the heart, including the role of extraembryonic tissues.

Here, we bring together two largely separate fields, evolutionary and developmental biology and bioengineering, to tackle this challenge. By combining the strength of comparative approaches in evolutionary biology with quantitative biomechanical measures of cell and tissue properties, we will be able to make advances not possible with more traditional, single approaches.

We will use evolutionary biology methods across four insect species of diverse sizes and geometries and spanning over 400 million years of evolution (hemimetabolous: milkweed bug and earwig, holometabolous: fruit fly and flour beetle). Through imaging and functional perturbations, we will identify heart closure mechanisms, distinguishing species-specific from conserved elements. We will build a novel atlas of earwig development during organ formation, providing a new powerful tool for the community, alongside new methods that extend the toolkits in the fly and beetle.

Indirect evidence suggests early cardioblasts mechanically adjust to changes in their local environment. By leveraging bioengineering tools to measure and perturb material properties both inside intact embryos and in bioengineered microenvironments for extracted cells and tissues (*in vivo*, *ex ovo*, and for isolated cells), we will provide the first quantification of the biophysics of early heart formation across species. Subsequently, we will model how cells interact to build the heart, focusing on mechanical inputs from neighboring tissues, to elucidate general principles of early heart morphogenesis.

Overall, this project offers unique perspectives to tackle a longstanding problem: how does the heart robustly form? It represents a truly interdisciplinary and international team, bringing a diverse range of skills and approaches.

A molecular roadmap for the emergence of air breathing

RG Type: Research Grants - Program

- Máté Varga, Dept. of Genetics, Eotvos Lorand University, Budapest, Hungary
- Peter Fabian, Dept. of Experimental Biology, Masaryk University, Brno, Czech Republic
- Takayuki Onai, Dept. of Anatomy, University of Fukui, Japan

Oxygen demand is a key force driving evolution in animals, and limited availability in certain environments can prompt the development of more efficient uptake strategies. While we understand the basics of such adaptations, detailed molecular insights into environment-induced adaptive changes in the genome remain limited. Our research focuses on the paradise fish as an unconventional model organism to bridge these knowledge gaps.

Paradise fish undergo a fascinating transition from gill respiration to air-breathing during their life cycle, developing a specialized labyrinth organ for atmospheric oxygen uptake. This shift provides a unique opportunity to study the molecular mechanisms governing the evolution of new organs and breathing strategies in vertebrates. Furthermore, as the development of the labyrinth organ is partially dependent on atmospheric air-breathing and without surface access the development of the organ will be stymied, this system can also inform us about the interactions between genes and environmental factors during development.

Our interdisciplinary team aims to create a comprehensive three-dimensional cellular atlas of the adult paradise fish labyrinth organ, alongside a genomic-level description of its development. We will also examine the environmentally triggered labyrinth organ differentiation in fish previously not allowed to access the surface. Finally, we will test if specific genes and regulatory sequences are necessary for this developmental event by manipulating them directly in fish.

Our holistic approach will enable us to explain how vertebrates adapt to new environments and how evolutionary innovations arise. Our research may also shed light on the molecular events that result in transitions in breathing strategies across vertebrate lineages, also revealing how the interplay between genes and the environment influence the traits of an organism. Finally, this work will expand our knowledge about the evolutionary potential of pharyngeal arches, the special embryonic structures that give rise to essential vertebrate features like jaws and teeth.

Musculoskeletal system of head-first burrowers: an interdisciplinary approach

RG Type: Research Grants - Program

- Mehran Moazen, Dept. of Mechanical Engineering, University College London, UK
- Dominique Adriaens, Dept. of Biology, Ghent University, Belgium
- Henrik Birkedal, Dept. of Chemistry, Aarhus University, Denmark
- Tiana Kohlsdorf, Dept. of Biology, University of Sao Paulo (USP), Brazil

Head-first burrowing is a specialized locomotory behavior in vertebrates and is poorly understood compared to e.g. flying and swimming. We do not understand how small, mainly limbless, animals with head sizes less than 10 mm can build tunnels through different soils, or navigate their way forward. They apply forces much greater than their body weight, and their heads have evolved to do so without damage. Understanding how they manage this rather extraordinary task is the main focus of this project.

The interdisciplinary and international team assembled here will decode the musculoskeletal system of a specific group of head-first burrowers called amphisbaenians to an unprecedented level. Amphisbaenians look a bit like snakes but are specialized lizards with four distinctly different head shapes (shovel, spade, keel, round). These different snout shapes are thought to reflect their burrowing methods, but there may be other driving factors that we still do not know about.

The four team members will use a range of advanced techniques to study amphisbaenian: (1) the Moazen lab will characterize the mechanics of their skull bones and joints and how it interacts with different soils using computed tomography, image processing & computer simulations; (2) the Kohlsdorf lab will measure the forces acting on their skulls using real life measurement and unravel their genomes to understand the degree of genetic similarity across the species; (3) the Birkedal lab will examine the chemical composition and nanostructure of their skull tissues and explore potential links with their genetics and overall shape and size; (4) the Adriaens lab will investigate the role of muscles and sensory organs within their skin, and their movement in different soils.

This project will unravel how an understudied group of reptiles function and produce unexpected levels of force. The fundamental findings of this project will have the potential to advance our understanding in several ways. It can inform tissue engineers on the interplay between forces, function, and gene expression that can lead to novel tissue engineering/regeneration approaches. It can enable engineers to develop miniaturized robots for various applications such biomedical engineering or excavation. Most importantly, it will train the next generation of scientists to learn from nature and translate this knowledge into applications for mankind.

07 Senses, brain and behavior

Eyes inside out: Visual coding without a multilayered retina in squid and worms

RG Type: Research Grants - Program

- Tom Baden, School of Life Sciences, University of Sussex, Brighton, UK
- Michael Bok, Dept. of Biology, Lund University, Sweden

"Camera-type" eyes of humans represent perhaps the most fascinating and recognizable of all sensory systems. They are found across the animal kingdom, from spiders to eagles, or even some clams. Looking at these eyes' external similarities immediately suggests that they must share a common origin. However, nothing could be further from the truth! Instead, these eyes evolved independently, possibly more than 100 times in different living and extinct lineages. In nearly all cases, these eyes have remained tiny, but at least three times in the evolutionary history, they have gotten large: In vertebrates such as humans, in cephalopods such as octopus or squid, and in one obscure group of worms: the alciopids, a group of segmented worms akin to earthworms that live in the open ocean.

Inside each of these eyes is a retina—a thin sheet of light sensitive tissue that represents the first neuronal step of vision. In vertebrates, the retina is made up of many dozens of anatomically and functionally distinct neuronal cell types, each with a specific and fascinating job in shaping the way that we see. This diversity is thought to be fundamental to allowing our eyes to perform efficiently. Like a "mini-computer" right in the eyeball, the vertebrate retina preprocesses and compresses the image as it comes in, such that the central brain can predominately worry about 'what to do' with the information. This process is incredibly efficient and probably enables much of what we call 'vision' in the first place.

By contrast, a vertebrate-like neuronally diverse retina is absent in cephalopods and alciopids. Instead, each photoreceptor—essentially a 'pixel'—immediately sends its signal to the brain. This suggests that vertebrate-like preprocessing of the incoming information does not take place. How, then, do these animals see? Do they 'simply dump' the corresponding information straight into the brain (implying very different central processing strategies compared to our own), or do they have unique 'tricks' to deal with the problem? Furthermore, did cephalopods and alciopids independently arrive at the same set of tricks?

Our project brings together a computational neuroscientist and behavioral marine biologist to jointly establish how the retinas of these alien eyes work, how they evolved, and how their strategies for vision relate to our own.

Vibrational sensing and production in fishes: investigations of the underwater vibroscape

RG Type: Research Grants - Program

- Louise Roberts, Dept. of Earth, Ocean and Ecological Sciences, University of Liverpool, UK
- Clara Amorim, Dept. of Animal Biology / MARE, University of Lisbon, Portugal
- James Miller, Dept. of Ocean Engineering, University of Rhode Island, USA
- Joseph Sisneros, Dept. of Psychology, University of Washington, Seattle, USA

While human ears are designed to detect sound, our fingertips introduce us to a sensory world where mechanical waves are “felt” as they travel through surfaces. Substrate-borne communication and sensing through vibration are, in fact, widespread across the animal kingdom. Well known examples are elephants and insects such as lacewings, but little is known about the use of vibration information in aquatic habitats.

Fish behavior frequently involves the production of sounds or visual signals (such as “trembling”) when they are in, on, or near substrates. Over 900 fish species are known to produce sound in courtship of agonistic interactions. However, despite the likelihood of energy transfer between media (water-substrate), the extent to which vibrations travel through surfaces has remained largely unexplored. Many fish produce calls with low frequency and high intensity while they are in direct contact to the surface, but their role in fish ecology has not been studied. The vibrational landscape, or vibroscape, may be a crucial component of a fish’s perceptual world, overlapping with the soundscape.

Our investigation will focus on whether fishes produce and respond to vibrational signals and cues, and how far these vibrations propagate through substrates. To achieve this, we will measure substrate vibrations (using acoustic oceanography and engineering methods), conduct playback experiments (integrating behavior, bioacoustics, neurophysiology), and interpret our data through the lens of biotremology (vibrational communication). Our interdisciplinary team is prepared to uncover a new mode of communication in fish, and to reveal a previously uncharted sensory landscape in marine ecology, the underwater vibroscape.

Plant-like solar tracking in a photosymbiotic animal

RG Type: Research Grants - Program

- Vengamanaidu Modepalli, Marine Biological Association, Plymouth, UK
- Katherina Petrou, School of Life Sciences, University of Technology Sydney, Australia

Among marine invertebrates, many animals have formed a mutual symbiosis with photosynthetic partners, like algae. In this relationship, the animal provides protection and nutrients, and in exchange the algae provide energy through photosynthesis. This partnership is highly prevalent in corals and sea anemones, underpinning the productivity and biodiversity of coral reef ecosystems, which are home to nearly 25% of all marine life. Like plants, photosynthesis represents an important energy source in photosymbiotic animals. Since the mid-19th century, researchers have observed that marine animals living in symbiosis with photosynthetic algae, such as sea anemones, flatworms, and sea slugs, move in response to light, a phenomenon known as phototaxis. Such adaptations may have allowed these organisms to orient themselves toward a specific light environment conducive to optimal photosynthetic activity, allowing them to thrive in shallow marine habitats. While the survival of both organisms relies on a mutually beneficial partnership, nothing is known about how these organisms communicate nor what underlying signal is used to induce these fascinating light-driven behaviors in the animal.

Our proposed research will explore the mechanisms that connect algal photosynthesis with animal behavior. We will do this by investigating the host nervous system and the physiology of the photosynthetic algae. We will conduct experiments to explain how photosynthetic partners influence the behavior of their hosts in order to gain a new understanding of this fascinating process, providing new insights into the fundamentals of the photosymbiotic relationship in animals. Photosymbiosis has been fundamental to the success of coral reef ecosystems, sustaining their growth into one of the most diverse biomes on Earth. However, with climate change threatening their extinction by the end of this century, there is an urgent need to develop innovative techniques and approaches to ensure the survival of corals in the future. The importance of this work therefore extends beyond understanding how one partner manipulates the other; it addresses fundamental aspects of the evolution of photosymbiosis and how this important partnership thrives.

Hippocampal coding of space during sleep-swimming

RG Type: Research Grants - Program

- Niels Rattenborg, School of Life Sciences, MPI for Biological Intelligence, Seewiesen, Germany
- Nachum Ulanovsky, Dept. of Brain Sciences, Weizmann Institute of Science, Rehovot, Israel

Sleep is a mysterious state of reduced environmental awareness that usually occurs when animals are still. However, some animals have evolved ways to sleep while moving. Notably, birds can sleep with one or both brain hemispheres while actively flying or swimming, as recently discovered in Canada geese. However, it is unknown whether and how birds sense and track their position in space when sleeping on the move.

Our team aims to answer this question by recording from place cells—neurons in the hippocampus that track an animal's position in space—during sleep-swimming in geese. Specifically, we will determine if the hippocampus: 1) continues to track the bird's position, 2) retains the last known position when awake and updates it upon awakening, or 3) replays previous position sequences, as described in sleeping stationary rodents. Our team consists of an expert on avian sleep (Rattenborg) who discovered that birds can sleep while flying and swimming and a hippocampal expert (Ulanovsky) who has developed methods for recording and analyzing place cells in freely flying bats and birds. We will combine our expertise to study the behavior and activity of hippocampal place cells in Canada geese that will be sleep-swimming in a large, floating aviary. We will use a training protocol established recently by Rattenborg, in which geese readily display sleep-swimming. This entails imprinting young geese on the experimenters and having them swim back and forth inside a long (70 m) water channel; after completing several laps, the geese become sleepy, close their eyes, and exhibit brain waves typical of sleep. We will use custom neural-loggers developed by Ulanovsky to record place cells in awake and asleep geese on land and as they swim through the water channel.

Our study will produce the first recordings of hippocampal place cells in any animal moving while asleep and will provide novel perspectives on how the brain monitors the outside world during sleep. This research promises to provide insight into sleep walking in humans, a poorly understood and potentially dangerous disorder for which no animal model exists.

Sub-second dopamine dynamics in human basal ganglia during beat perception and rhythmic action

RG Type: Research Grants - Early Career

- Jonathan Cannon, Dept. of Psychology Neuroscience & Behavior, McMaster University, Hamilton, Canada
- Dan Bang, Dept. of Clinical Medicine, Aarhus University, Denmark

When we listen to danceable music, we quickly feel the underlying beat. The beat makes us want to move along, and when we do, we find that we can step or bob our head in precise anticipation of the rhythmic sounds. Evolutionarily, our sense of rhythm has been linked to adaptations that have made the human lineage uniquely successful, including language and upright walking. How does the human brain make these moment-by-moment sound predictions, and why is auditory rhythm so closely connected with body movement?

We assume that the key part of this puzzle is the chemical messenger dopamine. Dopamine levels in a deep brain area called the "basal ganglia" are understood to play an important role in our capacity to make, evaluate, and learn from predictions; they are also believed to be important in motivating and selecting bodily actions. Until now, we have not had the methods to directly investigate the relationship between dopamine and the human sense of rhythm.

Our team has developed mathematical models describing how dopamine supports our perception of rhythm and rhythmic movements. We will now test the model predictions using a cutting-edge method for measuring how dopamine levels change moment-by-moment in the basal ganglia of patients who are undergoing awake brain surgery as part of their treatment. During the recordings, the patients who volunteer to participate in the research will listen to and tap along with different rhythms. We will analyze the relationships between rhythms, movements, and dopamine, and compare what we see to what our models predict. The results will help us to develop models that more accurately describe the role of dopamine in human rhythm and in the brain at large.

Our project will deepen our understanding of the biological basis of rhythm, central to music, dance, speech and many other human activities. It will also provide general insights about dopamine, which may help us better understand dopamine-related disorders like Parkinson's disease and how best to treat them.

Harmony in dynamics: Exploring emergent cooperation through participatory art and neuroscience

RG Type: Research Grants - Program

- Uri Hershberg, Dept. of Human Biology, University of Haifa, Israel
- Hasan Ayaz, School of Biomedical Engineering Science & Health System, Drexel University, Philadelphia, USA
- Luciano Perondi, Culture del progetto, Iuav University of Venice, Italy

People behave in unique and individual ways, yet when they come together in shared environments, emerging groups exhibit consistent and predictable behaviors. Whether it's navigating a busy market, generating an immune response, or participating in rush-hour traffic, the individual actions of people or cells lead to stable patterns of group behavior. These group behaviors emerge naturally, without requiring centralized control, and adapt as situations change. But how do such predictable patterns arise from diverse and independent behaviors?

Our project aims to explore this question by using Ta, a participatory art piece, as a controlled experiment to study how stable groups form from individual actions. In Ta, participants sit around a table in front of several piles of pebbles and follow simple rules to manipulate the pebbles. Without speaking or directly communicating, participants begin by moving pebbles in their own ways, but over time, their actions synchronize, and a collective pattern of pebble movement emerges. This dynamic but stable group behavior provides a model for understanding how group dynamics arise in the real world.

What makes this experiment unique is the use of an evolving art piece as our model. While Ta is an artificial environment, it mimics the complexity of natural settings in ways that engage participants. The collaboration with Ta's creator, Goni Shifron, is essential to ensure that the art piece continues to evolve and reflect the complexity needed for meaningful study.

To study Ta, we will use cutting-edge tools to capture and analyze real-time motion, brain activity, physiology, and eye movements of the participants. By combining expertise in complex systems, interactive design, and neuroscience, we aim to identify patterns of change and synchronization in both the participants' actions and the movement of the pebbles. Through this innovative approach, we hope to uncover the underlying principles that explain how individual behaviors lead to the formation of cohesive and stable group dynamics.

Neurometabolic mechanisms for social foraging

RG Type: Research Grants - Program

- Ahmed El Hady, Dept. of Collective behavior, University of Konstanz, Germany
- Jee Hyun Choi, Korea Institute of Science and Technology, Seoul, Republic of Korea
- Robert Froemke, Depts. of Otolaryngology, Neuroscience and Physiology, New York University Grossman School of Medicine, USA

Animals of all species need to find food in order to survive. Often this is a dangerous and uncertain process, required in order to fulfill their own energetic needs as well as provide for infants or other members of a group or colony. In this project, the team of scientists from Germany, Republic of Korea, and the USA will study how mouse colonies solve this problem in different environmental conditions. Animals must decide when and where to go to get the most resources and decide when to leave resource rich areas to find new ones. Many mammals (including mice and humans) are social foragers and depend on their social group to help find food or know when resources are being depleted.

In this project, we ask how animal groups coordinate their behaviors to achieve a collective goal important for the survival of the individuals and the group as a whole. Mice are an ideal species for this project due to the interesting behaviors they perform for cooperating and competing for resources, and the availability of tools for studying brain activity that have been optimized for lab mice. There have also been remarkable advances in machine learning and documentary approaches that enable long-term 24/7 continuous monitoring of mouse life in naturalistic environments. This will allow us for the first time to document strategies and plans by which animals might cooperate or help each other obtain the necessary resources for survival in a dynamic and potentially dangerous world.

08 Accelerator Grants

The International Human Frontier Science Program strives to strengthen open scientific inquiry by supporting collaborative, interdisciplinary and cutting-edge research in the life sciences by international teams of investigators. The HFSP Research Grants support novel collaborations that may lead to a breakthrough discovery by bringing together scientists with distinct expertise from the life sciences and other disciplines such as mathematics, physics, engineering or psychology to focus on problems at the frontiers of the life sciences.

The new Accelerator Grant was created to increase diversity among awardees and equity among HFSPO members. Starting in with the grants awarded in 2024 there will be annual calls inviting all newly funded Research Grant teams (RG - Program and RG - Early Career) to apply for an HFSP Accelerator Grant to integrate one additional scientist—the accelerator team member—from one of 7 countries: India, Japan, New Zealand, Norway, Republic of Korea, Singapore, or South Africa. The accelerator team member will join the ongoing collaboration for the second and third year of the funded HFSP grant project.

The HFSP Accelerator Grant offers mutual benefit for both the awarded research team and the accelerator member. First, the new team member integrates into a high-quality research team that was successful in one of the most competitive peer-review selections in the life sciences. This will result in full immersion in frontier research and inclusion in international research collaboration. Second, the grant team has the chance to complement their research project by adding an additional member with corresponding expertise, skills, and knowledge.

The objective of this new HFSP program is that accelerator members can become important multipliers and contact points for other investigators, and this can result in more high-quality applications involving scientists from their country in future competitions.

The following pages list all members of the Research Grant teams awarded in 2024 together with the accelerator member (highlighted in yellow) whose integration into the team was awarded in 2025.

Expanding the chemical space of bioactive modified nucleotides to endogenous metal ions

Accelerator Grant

- Pedro Beltrao, Dept. of Biology, ETH Zürich, Switzerland
- Clara Correia-Melo, Dept. of Microbiome in Ageing, Fritz Lipmann Institute, Jena, Germany
- Kasper Fugger, Dept. of Cancer Biology, UCL Cancer Institute, UK
- **Christian Hartinger, School of Chemical Sciences, University of Auckland, New Zealand (Aotearoa)**

Nucleotides are the key building blocks of the nucleic acids which contain the genetic code that is fundamental to life. In biology, chemical or enzymatic reactions can structurally modify nucleotides (modNs'). This can result in a large number of modNs that are critical in cellular processes while others can damage biological material. Metal ions play key roles in many biological processes and are central to the function of many enzymes. Metal ions can also react with nucleotides or cause indirect modifications of nucleotides. This project will uncover the formation of modNs after reaction with endogenous metal ions (Me-modNs) in biological systems, a so far unexplored source of nucleotide modification.

This HFSP Accelerator Project will build on research into the diversity of modNs, their modifying-detoxifying enzymes and their evolutionary history, and bioactivity, and will expand the chemical space of modNs to incorporate endogenous metal ions. We will investigate biological samples for the formation of Me-modNs using advanced analytical methodology, will synthesize metal complexes from modNs and investigate them for their biological activity. Beyond endogenous metal ions levels, we will also evaluate the impact of elevated metal ion concentration in the formation of modNs in biological systems.

Overall, this interdisciplinary project will deliver a fundamental understanding of the effects that metal ions have on modNs and the resulting conjugates in biology. For this purpose, we have established an international research team with complementary expertise ranging from cell biology, computation, and analytical chemistry to synthetic inorganic chemistry.

Strengthening the data analysis pipeline for avian Diffuse Optical Tomography through AI

Accelerator Grant

- Carlos Botero, Dept. of Integrative Biology, University of Texas at Austin, USA
- Joseph Culver, Dept. of Radiology, Washington University in St. Louis, USA
- Onur Güntürkün, Dept. of Psychology and Institute for Cognitive Neuroscience, Ruhr University Bochum, Germany
- **Young-Gyu Yoon, School of Electrical Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea**

Our HSFP project on “Probing the evolutionary ecology of cognition through High-Density Diffuse Optical Tomography, DOT” aims to revolutionize the way in which we study avian cognition by developing new optical imaging technology that can enable the cost-effective characterization of brain functional connectivity (i.e., the ‘blueprint’ of cognition) across hundreds of avian species in a realistic timeframe.

With this HFSP Accelerator project, Young-Gyu Yoon will introduce new expertise to our team by incorporating cutting-edge artificial intelligence (AI) tools into our workflows at two critical stages: signal processing and interspecific comparisons. Specifically, he will support and extend our original goals in three critical ways: (1) by adapting existing AI tools to the denoising of optical imaging data, (2) by contributing to the development of unsupervised AI models that can identify the regions of a brain that operate as single functional units, and (3) by developing algorithms to identify sub-patterns of functional connectivity that are repeated within networks of different species or individuals.

Improved signal-to-noise ratio will allow us to characterize functional variation in neuron activity with greater precision, whereas motif mining will complement the suite of graph theory metrics we originally proposed as targets of comparisons across species/individuals. Data-driven parcellation will represent a major advancement in comparative neurobiology because it will allow for the unbiased characterization of functional connectivity networks in species for which little or no anatomical knowledge is currently available. This accelerator proposal not only extends the scope of our original HFSP project but also the research of the Yoon Lab, through an exciting interdisciplinary exchange of ideas and approaches from computer science, neuroimaging, engineering and eco-evolutionary biology.

Monitoring ATP synthase re-organization linked to LTP by Cryo-Tomography

Accelerator Grant

- Karin Busch, Dept. of Biology, University of Münster, Germany
- Elizabeth Jonas, Dept. of Internal Medicine, Yale University, New Haven, USA
- Nicholas Tomkinson, Dept. of Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK
- **Yoshikazu Tanaka, Graduate School of Life Sciences, Tohoku University, Japan**

The goal of our research is to establish how mitochondria, the energy powerhouses of the cell, rapidly support learning processes at the molecular level, even before genes are activated. We are particularly interested in understanding how mitochondria efficiently provide energy in the form of ATP, during a process called long-term potentiation (LTP), which is crucial for learning and memory formation. The production of ATP utilizes mini-batteries generated by charge separation across the inner mitochondrial membrane. However, it appears that ions are constantly flowing across the membrane, discharging the battery. We believe that mitochondria can increase ATP production by making their internal membranes less permeable to ions, thereby increasing the energy available for ATP synthesis. We also think that the key enzyme in ATP production, ATP synthase, allows ions to pass through without synthesizing ATP. We hypothesize that ATP synthase reorganizes during LTP to work more efficiently, however, we currently lack the tools to directly observe this reorganization.

The Accelerator grant allows the integration of the structural biologist Yoshikazu Tanaka, who specializes in the study of proteins at the molecular level, into the team. Through his expertise, we will observe changes in ATP synthase and its interactions with other proteins in their natural environment before and after LTP. This will allow us to determine whether a different configuration of ATP synthase leads to improved energy production during learning and memory formation. If our research is successful, it could provide new insights into the fundamental processes that drive learning and memory formation in the brain.

Assessing the morphological space of self-assembling abiotic chemistries as potential confounding biosignatures

Accelerator Grant

- Henderson Cleaves, Dept. of Chemistry, The Howard University, Washington, USA
- Sean McMahon, School of Physics and Astronomy, University of Edinburgh, UK
- Mark Van Zuilen, Marine Biodiversity Lab, Stichting Naturalis Biodiversity Center, Leiden, Netherlands
- **Sudha Rajamani, Dept. Of Biology, Indian Institute of Science Education and Research (IISER) Pune, India**

The integration of Sudha Rajamani into the team will greatly expand the scope of this work by providing a large reference dataset of nonbiological self-assembled systems with bio-similar morphologies. The diversity of molecules in the “prebiotic soup” likely provided molecules resembling extant biomolecules. Some of these straight chain fatty acids (8–20 carbon atoms), are endowed with properties that allow them to self-assemble into cell-like structures under prebiotic environmental conditions. Such molecules may have been selected for incorporation into protocells. The diversity of amphiphiles in the prebiotic soup likely resulted in heterogeneous membranes that could have been central to the emergence of cellular life. Of particular interest are mixed amphiphilic systems that robustly formed membranes under plausible prebiotic planetary conditions. This highlights the importance of characterizing such molecules for their role in life’s emergence, and also for searching for life in our solar system, as structures formed from inherent properties of nonbiologically produced molecules may provide evidence of true cells. Some of these self-assembled structures may be stages on the way to life, which is interesting in itself, while others may simply represent propensities of matter to self-organize in non-life producing ways. It is crucial to be able to distinguish between life, emerging life, and simple abiotic systems with no propensity to give rise to life.

We will systematically characterize hybrid amphiphile systems, with a focus on molecules that merge the amphiphilic properties of lipids with biological building blocks. This includes nucleolipids, formed by combining nucleobases/nucleos(t)ides with fatty acids, allowing for the integration of informational and structural roles in early cellular life, as well as aminolipids, composed of amino acids and lipids, which could have contributed to membrane stability and functionality under prebiotic conditions. We have demonstrated synthesis of N-acyl amino acids (NAAs) under early earth conditions and their assembly into vesicles. When mixed with fatty acid derivatives, NAAs produce vesicles over a wide pH range and assemble into compartments under plausible early earth conditions. This work will explore prebiotic hybrid amphiphiles and characterize assemblies that they produce under diverse environmental conditions and compare them with modern and fossil cell morphologies. We will generate a comprehensive catalog of structures that can be used to discern primordial life on extraterrestrial bodies.

Resurrecting the multiple origins of tyrosine kinase activity and phosphotyrosine recognition

Accelerator Grant

- Pau Creixell, CRUK Cambridge Institute, University of Cambridge, UK
- Brian Metzger, Dept. of Biological Sciences, Purdue University, West Lafayette, USA
- **Arun Shukla, Dept. of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, India**

A major goal of evolutionary biology is to determine the mechanisms responsible for generating new biological functions. Molecular systems are particularly attractive for this work due to their experimental tractability and integration into organismal traits. All cells are exposed to a diverse array of stimuli to which they must detect and respond for their growth and survival. Organisms often accomplish this using signal-transduction cascades through protein post-translational modification. While all organisms can use phosphorylation of serine and threonine residues for this purpose, tyrosine phosphorylation is found primarily in eukaryotes and evolved later in history. In addition, the evolution of tyrosine phosphorylation occurred several times independently, offering the rare opportunity to compare the molecular mechanisms responsible for the evolution of a new function and address key questions about the repeatability of evolution across scales. However, the structural basis by which tyrosine phosphorylation evolved in any case is unknown.

Here we propose to use ancestral state reconstruction coupled with X-ray crystallography and cryogenic electron microscopy to identify the structural basis by which tyrosine kinase activity evolved across multiple independent origins. We will use recent advancements in structural biology to visualize the overall architecture, fine details, and molecular dynamics of kinases just prior to and just after the emergence of tyrosine phosphorylation activity. In addition, we will structurally characterize plausible intermediates for one instance—thus identifying not only the structural basis for this new function, but also the specific amino acid substitutions and their individual structural impacts.

This HFSP Accelerator project extends the explanatory power of the original project, which focused on the genetic, molecular, and evolutionary mechanisms underlying the repeated emergence of pY signaling, by adding detailed knowledge of the structural impacts of these historical changes. There is thus synergy gained by creating both structure-function and genotype-phenotype connections within a single system. Furthermore, by identifying the structural impacts of individual historical mutations, this work would provide unprecedented insights into the structural basis by which any new molecular function has evolved.

Decoding invisibility: from genome evolution to tissue optical properties in transparent fish

Accelerator Grant

- Filippo Del Bene, Dept. of Developmental Biology, Institut de la Vision, Paris, France
- Sönke Johnsen, Dept. of Biology, Duke University, Durham, USA
- Mirana Ramialison, Stem Cell Medicine, Murdoch Children's Research Institute, Parkville, Australia
- **Vincent Laudet, Marine Eco-Evo-Devo Unit, Okinawa Institute of Science and Technology Graduate University, Japan**

The transparency observed in *Danionella* species, including *D. cerebrum*, is closely linked to their small size and paedomorphic traits, where adults retain juvenile characteristics. Transparency, an energy-costly and active phenomenon, is often found in small species and is prevalent among fish larvae, suggesting a connection between larval stage, reduced size, and transparency. In teleosts, metamorphosis plays a crucial role in transitioning larvae into juveniles. This process is particularly pronounced in marine species but also occurs in freshwater fish such as zebrafish, where adult pigmentation patterns emerge during metamorphosis. In all teleosts, thyroid hormones regulate metamorphosis, orchestrating the transformation of multiple organs and ensuring proper ecological functionality in the juvenile stage. In paedomorphic species like *Danionella*, metamorphosis is likely attenuated, as adults retain juvenile-like characteristics, including simplified pigmentation patterns—a condition necessary but not sufficient for transparency.

Our project aims to compare the metamorphic processes of *Danionella* and zebrafish to explore how transparency and pigmentation develop, with an emphasis on the molecular, cellular, and endocrinological mechanisms at play. Through bulk RNASeq analysis and comparative studies of thyroid hormone response, we hypothesize that *Danionella* undergoes a highly reduced metamorphosis with minimal gene regulation changes, particularly affecting pigmentation and growth-related genes.

The Accelerator team member Vincent Laudet, renowned for his research on metamorphosis, pigmentation, and thyroid hormone regulation in fish, will lead this comparative analysis. In collaboration with existing team members, the team will also contribute to work packages focused on tissue ultrastructure, genomic loci associated with transparency, and experimental validation of genetic and ultrastructural determinants of body transparency. We also plan to test the trade-off between energetic cost of transparency and predation benefits by conducting predation experiments to rigorously evaluate the evolutionary advantages of transparency in *Danionella*. By integrating genomic, molecular, and ecological perspectives, this project will clarify the complex interplay between metamorphosis, paedomorphosis, and transparency in this unique model.

Cross-talk between the skin microbiome, immunity and sensory innervation in neurophysiology

Accelerator Grant

- Simone Di Giovanni, Dept. of Brain Sciences, Imperial College of Science, Technology and Medicine, London, UK
- Eran Elinav, Dept. of Systems Immunology, Weizmann Institute of Science, Rehovot, Israel
- Rong Fan, Dept. of Biomedical Engineering, Yale University, New Haven, USA
- **Woojung Shin, Dept. of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea**

Skin microbiota plays a crucial role in regulating the physiology of the skin. Given that the skin is body's largest organ that neuronal cells are populated, it has been hypothesized that reciprocal interactions exist between skin microbiome, immune system, and sensory neurons. In our original HFSP research proposal, we assembled a team of experts in neurophysiology, spatial transcriptomics, and bacterial metagenomics to investigate these cross-talk mechanisms. Utilizing mouse models and human tissue explants, we proposed to perturb either the microbiome or neurons and examine the resulting effects on the physiology of other components.

The new HFSP Accelerator project will leverage a human skin cell culture model, called Skin-on-a-chip, to provide the original research project with a scalable human model to investigate causal relationships. This innovative platform recreates the microenvironment of the human skin, including microbiome-immune-neuron interactions, within a microchip. Unlike traditional cell culture models, Skin-on-a-chip enables co-culturing microbiome with human cells with direct contact and microfluidics properties, allowing us to test our hypotheses under conditions highly relevant to humans. By adopting Skin-on-a-chip technology, we can address questions that are challenging to answer using animal models and tissue explants.

The Skin-on-a-chip model will be established based on techniques developed by the research group of Woojung Shin. We will create a synthetic skin microbiome community and co-culture bacteria in Skin-on-a-chip alongside immune cells and sensory neurons. Our investigations will focus on how the changes in the skin microbiome affect the functions of immune cells and neurons. Additionally, we will also specifically activate or inhibit neurons to examine their impact on the skin microbial population. We anticipate that this new sub-project will significantly strengthen our original narrative and enable us to clearly answer the questions in skin physiology by adopting a broader research perspective and complementary methodologies.

Capturing evolution in action using ancestral genotypes resurrected from sand dune seed banks

Accelerator Grant

- Luke Dunning, School of Biosciences, University of Sheffield, UK
- Valerie Reijers, Dept. of Physical Geography, Utrecht University, Netherlands
- Meagan Wengrove, School of Civil and Construction Engineering, Oregon State University, Corvallis, USA
- **Teresa Konlechner, Dept. of Geography, University of Otago, Dunedin, New Zealand (Aotearoa)**

Measuring rates of evolution is crucial for understanding how species adapt to environmental change. However, a challenge in studying evolution is that we often only see the end result—today's species—without direct evidence of how they got there. This can lead to underestimating the speed of evolution and misjudging future adaptation potential. Resurrection ecology, which involves reviving dormant seeds or propagules from the past, allows us to track these evolutionary changes directly. It is like accessing nature's archive, revealing the true pace of evolution and resilience against environmental change.

In this Accelerator project, we use seed banks and a resurrection approach, alongside expertise in geoscience, genetics and ecology, to measure how fast dune grasses have evolved and what this means for coastal dunes in the future. Ultimately, our goal is to understand how small genetic variations in these grasses lead to physical traits that can drive significant changes in our sandy coasts—specifically, how these traits affect dune shape and stability. Accurate measurements of evolution rates are essential for assessing the grasses' adaptive potential and the ability of sand dunes to respond to ongoing environmental changes.

To do this we will use geoscience methods to map sand layers in dunes where seeds have been buried. These buried seeds are time capsules of genetic material. By growing ancient seeds alongside modern plants, we can directly observe trait changes and calculate the speed of evolution. We will also analyze historical environmental data to track how dunes have shifted over past decades and reconstruct past climates, helping us understand how factors like drought and erosion have shaped dune grass evolution.

This data will be integrated with findings from complementary studies, including DNA sequencing and experiments measuring how plant variation impacts sand trapping ability. We will then develop computer models of virtual dunes to simulate how these genetic and ecological changes affect dune formation over time and their capacity to adapt to future climate challenges.

Understanding how dunes are established and maintained is important, as they protect our coasts from floods and storms. By learning how they work, we can better prepare for a future where climate change and stronger storms may pose significant challenges to our dunes.

Mechanisms and origins of glycosylation in giant viruses

Accelerator Grant

- Matthias Fischer, Dept. of Biomolecular Mechanisms, MPI for Medical Research, Germany
- Cristina De Castro, Dept. of Chemical Sciences, University of Naples Federico II, Italy
- Hiroyuki Ogata, Institute for Chemical Research, Kyoto University, Japan
- **Suvarn Kulkarni, Dept. of Chemistry, Indian Institute of Technology Bombay, India**

This HFSP Accelerator project will strengthen and expand the original research into the glycobiology of three marine giant viruses, CroV, ChlorV, and BigV, through the inclusion of an expert in synthetic carbohydrate chemistry.

The first task of the proposal focuses on the structural elucidation of viral glycans. In order to independently assess the structures of viral glycans, it will be highly advantageous to produce relevant amounts of these natural compounds in high purity. In addition, chemical synthesis of viral glycans will allow us to identify interacting proteins from the virus or host via binding assays. The second task aims to decipher the assembly pathway of viral glycans and requires azido-labeled derivatives, which can be difficult to obtain in case these viruses use unusual monosaccharides. Hence, the added expertise will help us to overcome labeling problems by developing new synthesis protocols. Importantly, the third task can now be expanded to studying the biochemistry of viral glycosyltransferases, because the substrates needed for enzymatic assays will become available through the additional team member.

Indirectly, the fourth task will also benefit from the added expertise, as phylogenetic analyses require reliable experimental data from chemical, biochemical, and cell biology approaches, resulting in an improved overall accuracy of computational predictions.

Suvarn Kulkarni is an expert in the chemical synthesis of bacterial glycans, which are composed of highly diverse and complex monosaccharide units, working on state-of-the-art procedures to maximize the yield of target molecules while reducing the number of synthetic steps and the use of toxic organic solvents. Kulkarni has developed several one-pot synthetic strategies and has access to a solid-phase synthesizer 'Glyconeer 3.1', that can assemble oligosaccharides of virtually any size. The integration of Suvarn Kulkarni is therefore ideally suited to facilitate and expand our research on the mechanisms and origins of glycosylation in giant viruses.

Deciphering the evolution, cellular biology and biogeochemistry of symbioses in anaerobic eukaryotes

Accelerator Grant

- Filip Husnik, Okinawa Institute of Science and Technology Graduate University, Japan
- Roxanne Beinart, Graduate School of Oceanography, University of Rhode Island, USA
- Courtney Stairs, Dept. of Biology, Lund University, Sweden
- **Hidetaka Nomaki, X-star, Japan Agency for Marine-Earth Science and Technology (JAMSTEC), Yokosuka, Japan**

This HFSP Accelerator project aims to expand our original project on protist-prokaryote symbioses in low-oxygen environments by incorporating several advanced biogeochemistry methods and foraminifera as a new model system. Foraminifera are large single-celled eukaryotes prominent in low-oxygen environments. However, they differ from other eukaryotes that thrive in such environments by retaining classical mitochondria, suggesting distinct adaptations to oxygen-depleted habitats.

Hidetaka Nomaki's expertise with foraminifera, *in situ* experiments in challenging environments, and stable-isotope labeling coupled with Nanoscale Secondary Ion Mass Spectrometry (NanoSIMS) will significantly advance our research capabilities. The project will integrate NanoSIMS with genomic and transcriptomic analyses to quantify carbon, nitrogen, and sulfur exchanges between foraminifera, ciliates, jakobids, breviates, and their symbionts. NanoSIMS will allow us to test the predicted metabolic interactions and provide quantitative estimates of nutrient transfer between partners. The addition of Nomaki to the original project will enable us to address previously inaccessible questions, pushing the boundaries of the original project's scope.

Scaling the impact of viruses from single cells to the global methane cycle

Accelerator Grant

- Ashish Malik, School of GeoSciences, University of Edinburgh, UK
- Karthik Anantharaman, Dept. of Bacteriology, University of Wisconsin, Madison, USA
- Joanne Emerson, Dept. of Plant Pathology, University of California, Davis, USA
- Graeme Nicol, Laboratoire Ampère, Ecole Centrale de Lyon, Ecully, France
- **Thulani Makhalanyane, Dept. of Microbiology, Stellenbosch University, South Africa**

Wetlands cover roughly 5% of the global land surface and provide important ecosystem services such as wildlife habitat. These ecosystems host diverse microbial and viral communities which have been shown to mediate important cycles. In addition, wetlands store 29–45% of the terrestrial soil organic carbon and are regarded as natural carbon sinks which play profound roles in biogeochemical cycling and carbon sequestration via microbial activity. However, these ecosystems are considered major sources of methane (CH_4), which contribute 30–40% of global emission. Despite their importance, surprisingly little is known regarding wetlands in African ecosystems. Previous studies suggest that the proportional increase in CH_4 emission from the wetlands may be associated with warming conditions. Similarly, increasing temperature may accelerate microbial-viral interaction in the soil. Such a result may not only accelerate the decomposition of soil organic carbon but may speed up microbial lysis (methanogens and methanotrophs) due to viral infection. A direct result is the modulation of methane emission in the wetland ecosystem. Despite this, there is an existing paucity of knowledge on the CH_4 fluxes from the wetland soils due to microbial lysis by the viruses.

The purpose of this HFSP Accelerator project is to elucidate the microbe-viral interaction and methane fluxes from the wetland soils. The study is going to employ high throughput sequencing (16S rRNA and shotgun metagenomics) sequencing as well as qPCR techniques to determine microbial and viral diversity as well as accessing methane emission from in wetlands. The project is envisaged to give an insight into the diversity of microbes and viruses and their distribution pattern based on seasonal temperature changes. It will further reveal the methane emission due to microbial-viral interaction.

Mechanoradicals as a novel form of mechanosensing: from protein stretching to animal aging

Accelerator Grant

- Ronen Zaidel-Bar, Dept. of Cell and Developmental Biology, Tel Aviv University, Israel
- Alexander Dunn, Dept. of Chemical Engineering, Stanford University, USA
- Frauke Gräter, Dept. of Biomolecular Mechanics, MPI for Polymer Research, Mainz, Germany
- **Jie Yan, Mechanobiology Institute and Dept. of Physics, National University of Singapore, Singapore**

In this project, we are exploring how mechanical stress affects tendons at a microscopic level. By applying various forces to slices on a glass surface, we aim to measure the stiffness of the surrounding extracellular matrix (ECM) and observe how these forces trigger the production of reactive oxygen species (ROS), like hydrogen peroxide (H_2O_2). Since the ECM has different properties depending on the direction of force, we need to measure its stiffness in both horizontal and vertical directions.

Through the integration of Jie Yan as an Accelerator Member, we will be able to develop a new tool using a highly flexible micropipette with a tiny bead that can apply both horizontal and vertical forces to the tendons. We will observe how the tendons locally deform under these forces using high-resolution imaging. To detect the ROS produced, we will use special chemical reactions that light up in the presence of H_2O_2. Additionally, we will apply torsional stress with rotating magnetic beads to study the ROS generation more efficiently.

We are also investigating how ROS, particularly H_2O_2, might damage several important proteins in the ECM and within cells that respond to mechanical stress. These proteins often change shape under stress, making them vulnerable to ROS. Our research will focus on how these proteins can be affected by H_2O_2, looking at issues like protein misfolding and aggregation.

Index

Listed by country of research laboratory, scientist, and institution

Accelerator Members indicated with *

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Burkina Faso

Canada

Chile

China

Czech Republic

Denmark

France

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