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2023

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Project ID:	Project Acronym:	Evaluation Panel:
947709	**Hydegronomics**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Itay Koren**
Host Institution:	Bar Ilan University - ISR

Cracking the Code for Protein Quality Control Mechanisms Recognizing Exposed Hydrophobicity in Protein Substrates

Proteostasis is a highly regulated process by which cells maintain a healthy proteome. Loss of proteostasis is a common feature of aging and disease. To preserve proteostasis, the cell has developed protein quality control (PQC) pathways that monitor a proteins's fate from synthesis to degradation. Exposed hydrophobic residues in aberrant or mislocalized protein substrates is a key feature recognized by distinct PQC mechanisms. If not handled properly, exposed hydrophobicity can result in protein aggregation and subsequent reduced cell fitness. To prevent accumulation of toxic aggregates, cells are equipped both with chaperones and proteolytic pathways. Within the degradation systems, E3 ligases are the major determinants of specificity, which is achieved through their selective recognition of specific short peptide motifs, or degrons, in substrate proteins. Despite the growing list of PQC players and substrates, it has yet to be determined what are the client range, selectivity and specificity of each of the PQC mechanisms. The objective of this proposal is to systematically investigate the exposed hydrophobicity "code" and to advance the state-of-the-art of the PQC field. Here, we utilize the GPS-peptidome method that we recently developed together with genetics, biochemistry, cell biology and proteomic approaches to: (1) map distinct classes of hydrophobic degrons to elucidate the specificity of substrate selection; (2) identify novel E3 ligases playing a role in PQC pathways, explore redundancies among them and identify endogenous substrates proteome- wide; (3) investigate the physiological significance of PQC mechanisms. This work will provide a comprehensive view of PQC pathways that recognize hydrophobicity. This is critical to further our understanding on how aberrant features in proteins are recognized and can provide valuable information for the development of new therapeutic intervention strategies that target abnormal proteins implicated in disease.

Link to the ERC project webpage: www.thekorenlab.com

Keywords of the ERC project: protein quality control, ubiquitin, E3 ligase, degron

Keywords that characterize the scientific profile of the potential visiting researcher/s: proteomics, proteasome, ubiquitination

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Project ID:	Project Acronym:	Evaluation Panel:
101020697	**RESPICHAIN**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Leonid Sazanov**
Host Institution:	Institute Of Science And Technology Austria - AUT

Structure and mechanism of respiratory chain molecular machines

Eukaryotic life is made possible by energy production in mitochondria, where several large membrane protein complexes of the respiratory chain work in series to produce ATP. The structure and function of these complexes have been intensively studied over decades, but the mechanistic understanding is lacking due to their elaborate architecture. This proposal's goal is to reveal the mechanism of energy transduction by the least understood of them: complex I, respiratory supercomplexes and transhydrogenase. Complex I is the largest respiratory enzyme, containing up to 45 subunits with a total mass of ~1 MDa. We have determined the first atomic structures of complex I from bacteria and mitochondria. Mammalian complex I usually exists as a supercomplex with complexes III2 and IV: we have determined the first architecture of this ~1.7 MDa physiological "unit" of respiration. The nicotinamide nucleotide transhydrogenase couples proton motive force to mitochondrial redox homeostasis, working in tandem with the respiratory chain. We recently determined the first structure of transhydrogenase but its coupling mechanism remains controversial. Huge conformational changes are envisaged but not yet observed. The mechanism of coupling between spatially separated electron transfer and proton translocation in complex I is also a mystery. It is likewise not known why respiratory complexes are organised into supercomplexes. We will tackle all these questions by an integrative approach, solving the atomic structures of different catalytic states of the complexes by applying the latest cryo-EM methods to these extremely challenging targets. The comparison of structures, complemented by functional and computational analyses, will reveal the mechanistic basis for the function of these molecular machines, solving fundamental questions in biology. As these enzymes are involved in many severe human disorders, the acquired knowledge will also be instrumental to tackle mitochondrial diseases.

Link to the ERC project webpage:

Keywords of the ERC project: cryo-EM, membrane protein structure, bioenergetics, mitochondria

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101040138	**cofactau**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Yann Fichou**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Cofactors at the core of tau prion behaviour

Tau is an intrinsically disordered protein that regulates microtubule activity in neurons. Aggregation of tau into amyloid fibrils is diagnostic of several diseases, termed tauopathies, that include Alzheimer's disease. Distinct amyloid aggregate structures, so-called "strains", are involved in different tauopathies. These assemblies can spread and recapitulate pathological phenotypes when injected in cells and animals. This is the hallmark that tau aggregates follow a prion behaviour. To date, the factors guiding the formation or propagation of specific strains are unknown. Showcasing this crucial gap in knowledge is the fact that none of the brain-extracted tau amyloid structures has been reproduced in vitro. This project intends to establish a paradigm shift for the very definition of tau strain. I propose the novel hypothesis that the co-aggregation of tau with other biomolecules such as lipids or polyanions, so-called cofactors, is a defining property of tau prion strains. To demonstrate this hypothesis, I will test that the tau-cofactor interactions (i) dictate the structure of tau aggregates, (ii) enable structure replication through seeding and (iii) dictate the neuropathology developed in cells and mice after inoculation of tau seeds. My approach is to study the pathological properties and the conformational evolution of tau aggregates in the presence of biologically-relevant cofactors possessing different physico-chemical properties. By mapping the interactions between tau and cofactors, my goal is also to establish the canonical rules governing tau structural differentiation. This proposal combines multiple methods including EPR and NMR spectroscopy, AFM-based nanospectroscopy, biochemistry, cell biology and animal histology. The proposed paradigm shift would have a very high impact in the field of tauopathies, for example by enabling accurate structure-based drug discovery, revealing new drug targets and pinpointing key deleterious metabolic pathways.

Link to the ERC project webpage: https://www.fichou-lab.cnrs.fr/home

Keywords of the ERC project: Tau protein, amyloid, EPR, seeding, cryoEM

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101042046	**deuterON**	**LS1** Molecules of Life: Biological Mechanisms

Principal Investigator:	**Dr Johannes Broichhagen**
Host Institution:	Forschungsverbund Berlin Ev - DEU

Introducing deuterium for next generation chemical biology probes and direct imaging

The ideal microscopy experiment would take place in native cells without genetic engineering, with 3-dimensional resolution on the single molecule scale (<10 nm) by observing the endogenous molecule itself. I propose the introduction and use of deuterium ("deuterON") as a general method for a multimodal approach, to i) synthesize a first-in-class deuterated silicon-containing cyanine (SiCy) fluorophore for super-resolution imaging, ii) to design and test deuterated, next-level photoswitches to restore vision, and iii) use these probes and deuterated drugs for direct and bioorthogonal, spectroscopic imaging. In particular, deuterated SiCys will allow stochastic reconstruction microscopy (STORM) by using near infra-red light to break new ground in protein localization in live tissue, opening the gates for thick sample imaging (~100 □m axial) with retained super-resolution (~20 nm). In addition, deuterated azobenzene photoswitches will be designed to finally reach the indispensable, and to-date unobtained. light sensitivity to remote control neural signalling and vision restoration in vivo. Lastly, the use of "label-free" labelling and imaging will be explored with deuterated drugs to observe drug uptake and metabolism by utilizing the unique properties of the carbon-deuterium bond in Raman spectroscopy. Coupled to a confocal microscope, deuterated drugs will be tracked in native and live cells, without any genetic engineering strategies, and on the molecule of interest itself, reducing perturbations and artefacts to a minimum. This ground-breaking approach holds promise to be generalizable to Chemical Biology disciplines, and as an unconventional, yet attractive and powerful method to design and synthesize next generation small molecule probes. Developing a pipeline for these aims will be a game changer, with ramifications for the life sciences, cell biology, drug development and with prospective translational impact.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101045340	**GTPaseNet**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Martin Loose**
Host Institution:	Institute Of Science And Technology Austria - AUT

Synthetic and structural biology of Rab GTPase networks

Eukaryotic cells are characterized by their compartmentalization into hundreds of different membrane-bound organelles with unique biochemical identities. Small GTPases of the Rab family play a central role in this organization, but how they are able to generate spatiotemporal order in the complex cellular environment is currently not known. Most previous studies on Rab GTPases have either relied on describing their behavior in living cells or in highly reductionist biochemical assays. However, neither of these two approaches can explain the dynamic activity patterns of Rab GTPases associated with their cellular functions. It has become clear that Rab GTPases are controlled in sophisticated regulatory networks with emergent, self-organizing properties. To obtain a mechanistic understanding of these Rab GTPase systems, new experimental assays are now required. In this proposal, we will use a “bottom-up” synthetic biology approach to rebuild the biochemical networks of Rab GTPases from purified components and demonstrate their self-organization into spatiotemporal activity patterns in vitro. We will combine these reconstitution experiments with cryo-electron microscopy to elucidate the structures of membrane-recruited Rab GTPase regulators. Finally, we will use microfabrication and laser lithography to prepare a mimic for the compartmentalized cell and find out how Rab GTPase signaling systems sense and process preexisting geometric and biochemical cues as in the living cell. This project will provide novel, quantitative information from different scales, from the emergent ensemble behavior down to the molecular structure of protein complexes. Together, this data will reveal how signaling systems of Rab GTPases control membrane identities in space and time, thereby improving our understanding of the intracellular organization of the eukaryotic cell.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101054429	**BEYOND STRESS**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Kathrin Thedieck**
Host Institution:	Universitaet Innsbruck - AUT

The stress granule machinery controls metabolic signalling through mTOR at steady-state

mTOR kinase is an oncogenic master regulator of metabolism and cell growth and is known to reside in two multiprotein complexes. Upon stress, mTOR is inhibited by stress granules (SGs), which recruit mRNAs and signaling factors to promote survival. Current work largely addresses the functions of SG proteins under stress, focusing on their RNA binding properties and SG assembly. However, non-stress functions are emerg-ing. I propose that SG proteins have prime functions in mTOR signaling at metabolic steady-state, in the absence of SGs. Our preliminary data show that core SG proteins bind mTOR at steady-state and suggest that they are key controllers of the known mTOR complexes, as well as forming novel, hitherto unknown mTOR complexes. In BEYOND STRESS, we will investigate SG proteins as a novel class of mTOR regulators at steady-state. By means of deep proteomics, proteo-metabo-flux, RNASeq, systems modelling, mechanistic and cell biological studies, we will identify and functionally characterize the SG interactome of the known and novel mTOR complexes. We will delineate the steady-state inputs that signal through SG proteins to mTOR, and we will unravel the mechanistic interplay through which SG assembly impinges on metabolic signaling upon stress. As levels of core SG proteins correlate with cancer outcome, we will explore their linkage with metabolic signaling, prognosis and drug response in breast cancer. BEYOND STRESS is ground-breaking as (i) it links SG protein research in stress to steady-state mTOR signaling; (ii) a unifying paradigm of mTOR regulation at steady-state and stress, and novel mTOR complexes will open new horizons for research on metabolic signaling; and (iii) SG proteins are emerging as markers and targets for oncogenic signaling through mTOR. While focusing on mTOR and breast cancer, BEYOND STRESS will likely translate to further networks and tumor entities, opening new avenues to signaling and cancer research.

Link to the ERC project webpage: www.metabolic-signaling.eu

Keywords of the ERC project: mTOR signaling, metabolism, stress granule proteins, nutrients, cancer

Keywords that characterize the scientific profile of the potential visiting researcher/s: biochemistry, cell biology, systems modeling, data science, proteo-metbolomics

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Project ID:	Project Acronym:	Evaluation Panel:
101054950	**CHROMSEG**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Arockia Jeyaprakash Arulanandam**
Host Institution:	Ludwig-Maximilians-Universitaet Muenchen - DEU

Structural Basis for Centromere-Mediated Control of Error-free Chromosome Segregation

Accurate chromosome segregation during cell division requires bipolar attachment of sister-chromatids to microtubules emanating from opposite spindle poles and maintenance of sister-chromatid cohesion until all chromosomes achieve bi-orientation. Two chromosomal sites regulate these processes: centromeres, the microtubule attachment sites defined by the enrichment of CENP-A nucleosomes, and the inner centromere, a region between the sister-chromatids that recruits enzymatic activities (kinases, phosphatases and motor proteins). The inner centromere associated enzymes selectively stabilise chromosome-microtubule attachments suitable for chromosome bi-orientation, control sister chromatid cohesion and achieve timely chromosome segregation. Errors in these processes can lead to aneuploidy, a numerical chromosomal aberration implicated in miscarriages, birth defects and cancers. Using an integrative structure-function approach (X-ray crystallography, cryo electron microscopy, Crosslinking/Mass Spectrometry, biochemical/biophysical methods with human cell-line based functional assays), we will obtain detailed mechanistic understanding of: (1) how the inner centromere is assembled, (2) how the inner centromere associated interaction network recruits regulators to achieve chromosome bi-orientation and accurate segregation, and (3) how centromere identity is maintained through multiple generations. This work builds on our recently obtained exciting structural/molecular knowledge that have led to unexpected insights and new questions and will exploit our recently generated battery of molecular reagents. Outcome of our work will provide unprecedented details of centromere-mediated control of chromosome segregation and allow us to build a comprehensive mechanistic model for error-free chromosome segregation, a process that has been fascinating researchers for more than a century.

Link to the ERC project webpage:

Keywords of the ERC project: Centromere, Kinetochore, Chromosome structure, Chromatin structure, Histone modifications, Epigentics, cryoEM, Cell Biology, Structural Biology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101077859	**META-SURVEILLANCE**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Kumar Somyajit**
Host Institution:	Syddansk Universitet - DNK

The molecular nexus coupling Cell Metabolism to Cell cycle and Genome Surveillance

Metabolic fluctuations and changes in DNA replication and cell cycle dynamics orchestrate early development and tumorigenesis. Of particular interest are reactive oxygen species (ROS), by-products of basal metabolic reactions, and major signaling molecules driving cell proliferation, differentiation, and cancer cell growth. However, despite their utmost importance in cell physiology, how ROS signals communicate to the cell cycle and genome safeguard mechanisms remains poorly explored. My postdoctoral work has illuminated this topic by discovering novel redox-sensitive mechanisms that directly couple metabolic nucleotide fluctuations and oxygen starvation to DNA replication dynamics. These findings revealed that ROS-signaling could operate as a prime and cell cycle checkpoint-independent surveillance for replicating genomes. Since profound alterations in metabolic pathways and redox state naturally entail embryonic growth, cell differentiation, and cancer transformation, in such scenarios, can metabolic cues in the form of ROS align cell cycle states and DNA replication? In this application, I propose to address this question by dissecting the mechanisms that align core cell cycle machinery and replisome dynamics to endogenous ROS fluctuation in tailor-made cellular models of early mammalian development (stem cells) and cancer. By combining innovative analytical tools, including CRISPR-based tagging of endogenous proteins with biochemistry and advanced cell biology (e.g., quantitative single-cell imaging of redox-state, Cyclin-CDKs, and genome caretakers; replication fork sequencing), I will define the molecular nexus coupling metabolism with genome surveillance at the global (genome-wide) and local (replisome) level. These investigations will provide an unmatched picture of regulatory foundations of cellular and genome integrity in normal and pathophysiological contexts, enhancing understanding of genome surveillance in development mechanisms and disease.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101087140	**FuncAmyloid**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Meytal Landau**
Host Institution:	Stiftung Deutsches Elektronen-Synchrotron Desy - DEU

Structure, Function and Regulation of Antimicrobial and Virulent Amyloids at High-resolution

Self-assembly of proteins and peptides into amyloid fibrils produced across kingdoms of life is associated with antimicrobial activity, microbial pathogenicity, and a wide range of diseases. The correlation of fibrillation and morphology to function is poorly understood, and high-resolution structural information and mechanistic models are lacking. Our lab pioneered the atomic-level analysis of bacterial amyloids and eukaryotic functional fibrils involved in cytotoxicity, biofilm structuring, and antibacterial activity. We revealed novel morphologies extending beyond canonical amyloid cross-β structures of tightly mated β-sheets, to include, for example, cross-α fibrils composed on amphipathic α-helices. In addition, we exposed a unique lipid-induced cross-α/β secondary structure switch in fibrils of the same sequence. Here we investigate amyloid fibrils which serve as key virulence determinants in S. aureus and Pseudomonas acting as cytotoxins and in biofilm scaffolding, and as antimicrobials produced across different species. We will leverage the knowledge and expertise, and newly emerging methods in electron, light and force microscopy, to understand how fibrillation propensity, fibril morphology and structural switches are connected to function, membrane interactions and toxicity mechanisms at high resolution. The findings are expected to identify structural features that underlie the formation, regulation, and activity of these fibrils, providing advantages in specific environments. Understanding these structure-function relationships will help to clarify the link between amyloid formation and antimicrobial activity. We will use the insights gained from these studies for the rational design of antimicrobial peptides and small molecules targeting virulent determinants towards potential applications in the management of infectious diseases. Our findings on functional amyloids can overall advance life, material, medical and environmental sciences.

Link to the ERC project webpage:

Keywords of the ERC project: amyloid, structural biology, fibrils, CryoEM, virulence,

Keywords that characterize the scientific profile of the potential visiting researcher/s: AI, data management, machine learning, biofilms, Cryo-CLEM,

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Project ID:	Project Acronym:	Evaluation Panel:
101087830	**PROMISE**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Elodie Laine**
Host Institution:	Sorbonne Universite - FRA

Proteome diversification in evolution

Proteins are essential and incredibly versatile actors for all biological processes in living organisms. Massive amounts of data describing their amino acid sequences and 3D shapes are now openly accessible. Yet, we still know little about how they interact and function with one another in vivo. Nor how they diversified throughout evolution to orchestrate highly specialised behavioural traits. This ERC CoG proposal, PROMISE, meets the urgent need for decrypting protein sequences and structures toward guiding biological intervention. It will assess and harness the protein variations naturally occurring in multi-cellular organisms to unlock critical questions across developmental, evolutionary, and molecular biology: - What are the sites in a protein crucial for selecting its cellular partners and binding to them? How can they be modified toward modulating protein functioning? - How did the proteomes responsible for the ability of humans and zebra finches to learn "language" from their peers expand in evolution? Are there convergent amino acid patterns, beyond the striking analogies in the underlying anatomical structures and in gene expression and regulation? PROMISE will leverage the tension between evolutionary divergence, gene duplication, and alternative splicing by combining massive high-throughput protein-related data integration and cutting-edge artificial intelligence techniques. It will bring a paradigm shift on assessing protein diversity and its impact on rewiring interaction networks in evolution. The expected results will provide efficient and scalable solutions to extract biological meaning from big data and transform it into interpretable and actionable models. This new knowledge will be transferable to a broad range of impactful societal issues, such as the inter-individual variability in disease susceptibility, the design of more specific drugs and more bio-compatible de novo proteins, or strategising human adaptation to climate change.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101087830

Keywords of the ERC project: protein evolution, alternative splicing, proteome diversity, representation learning, deep learning, bioinformatics, computational biology, genomics, transcriptomics, proteomics, molecular modelling, protein design, comparative biology, vocal learning

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101094471	**MetaQ**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Andrea Mattevi**
Host Institution:	Universita Degli Studi Di Pavia - ITA

When enzymes join forces: unmasking a mitochondrial biosynthetic engine

Enzymes have been classically investigated as standalone catalysts operating in a relatively diluted milieu. However, the cell micro-compartments are highly crowded environments and biological catalysis cannot be fully understood on the bases of simple diffusive models. We are tackling this challenge by reconstituting a full-scale biosynthetic pathway where multiple enzymes coordinate within a metabolon - a structurally defined setting that allows the vectorial transfer of substrates and products. Our system for exploration is the fascinating biosynthesis of coenzyme Q, an essential redox mediator for many pathways. The juxtaposition between its highly polar head group and hydrophobic tail renders this compound a challenging feat to handle. To synthesise its highly substituted aromatic head group, nature has amassed a large soluble supra-molecular complex consisting of no less than eight functionally distinct proteins that adheres to the inner-mitochondrial membrane. This infrastructure can extract the substrate whilst providing a shielded, hydrophobic environment for molecular transit. We will systematically characterize the functional, structural and evolutionary aspects of the involved protein machineries in interplay with the membrane. Our approach starts by exploiting ancestral sequence reconstruction to generate proteins of enhanced stability. We will build the metabolon in vitro to assess how the enzymatic activities are coupled in the context of a metabolon. Structural studies will reveal how the active sites are spatially organized with respect to the order of the enzymatic steps and substrate trafficking. Our integrated strategy will unveil the pivotal evolutionary transitions that create a biosynthetic machinery. This research will go beyond classical enzymology by exploring a new paradigm of cellular biochemistry where metabolic pathways are fuelled and governed through interactions between enzymes, and between enzymes and other proteins.

Link to the ERC project webpage: http://www-9.unipv.it/biocry/

Keywords of the ERC project: Metabolism, enzymes, metabolon, molecular evolution, enzyme structure and function

Keywords that characterize the scientific profile of the potential visiting researcher/s: structural biology, enzyme biochemistry, protein evolution, cryoEM, crystallography, protein engineering

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Project ID:	Project Acronym:	Evaluation Panel:
101116848	**REEL-EM**	**LS1** Molecules of Life: Biological Mechanisms, Structures and Functions

Principal Investigator:	**Dr Bonnie Murphy**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

Development of Reconstructed Electron Energy Loss techniques for Elemental Mapping in macromolecular structures

A perfect macromolecular structure would provide an all-atom description of the molecule, including not only the well-ordered polypeptide or polynucleotide framework but all other species: metals and other ions, cofactors, lipids, substrates and inhibitors. However, current structural data include no or very little information on elemental composition, leading to significant errors and omissions in atomic models. To address this issue, I propose to develop a method, Reconstructed Electron Energy Loss - Elemental Mapping (REEL-EM), that will map elemental distribution within macromolecular complexes by bringing together well-established principles in analytical electron microscopy (EM) and biological cryogenic EM. Atomic-resolution elemental mapping in the electron microscope is well established for dose-tolerant samples. Electron Energy Loss (EEL) techniques capture information from inelastic scattering events in the sample, and energy losses are characteristic of the element and chemical state of the scattering atom. These techniques require a high electron dose to achieve useable signal-to-noise ratio, severely limiting their application to biological samples. Our novel approach combines the image processing tools of single-particle cryo-EM with EEL techniques, allowing us to add EEL signal in the 3D particle space, effectively dividing the dose required for sensitive elemental analysis between many images. Preliminary work in my research group confirms that our proposed approach is valid - we are able to generate maps of specific elements in the 3D particle space. I propose to extend this early work to achieve single-atom detection at 1-nm spatial resolution in the course of this five-year project. Our work will characterise and optimise all aspects of data collection and processing for REEL-EM. We will apply our methodology to two important macromolecular complexes: the skeletal muscle ryanodine receptor and the mitochondrial F-type ATP synthase.

Link to the ERC project webpage:

Keywords of the ERC project: cryo-electron microscopy, elemental mapping, low-dose STEM-EELS, structural biology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
948219	**EPYC**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Falk Hildebrand**
Host Institution:	Quadram Institute Bioscience - GBR

Evolution of pro- and eukaryotic commensals within the human gut

The EPYC project will characterize the evolution of long-term human associated eukaryotes and prokaryotes, using colonization patterns in 3 human generations. The gut microbiome is important for human health, supporting nutrition, pathogen defence and immune homeostasis, with more than 200 species inhabiting each human gut. In recent years metagenomics led to notable breakthroughs in describing this microbial diversity, yet 50-90% of species are typically present at too low abundance to be genome or strain resolved. Thus, most gut microbiome studies focused to date on dominant bacteria and very little is known of the highly diverse, yet low abundance, pro- and eukaryotes (elusive microbes). Importantly, elusive microbes are an inherent part of ecosystem successions persisting at different ages of the host. I propose that niche adaptation and persistence are key indicators of a taxa's importance to the gut ecosystem and host health. I will determine which microbes persist for years within a human, or even a family for several generations. This should be reflected in microbial genetic adaption, also indicating which genes are likely important to successfully colonize the human gut. I hypothesize that low abundance pro- and eukaryotes are adapted to persist for multiple generations in the human host, indicating their importance, despite being largely ignored so far. To investigate this knowledge gap in EPYC, I will (O1) Enable high-precision metagenomics of elusive microbes (O2) Estimate pro- and eukaryotic strain persistence across three human generations (O3) Describe the microbial genetics of gastrointestinal persistence EPYC will develop the next-generation of high-resolution metagenomics of an extended taxonomic range, enabling me to research microbial evolution in the human gut.

Link to the ERC project webpage:

Keywords of the ERC project: metagenomics; evolution; microbiology; population genetics

Keywords that characterize the scientific profile of the potential visiting researcher/s: microbiologist; bioinformatician;

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Project ID:	Project Acronym:	Evaluation Panel:
948770	**DECIPHER**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Marnix Medema**
Host Institution:	Wageningen University - NLD

A computational framework to interpret the chemical language of the microbiome

Humans, animals and plants are covered in microbes. Such microbiomes have a major impact on the health of their hosts and have been linked to traits like growth promotion, stress resilience, and diseases. However, the mechanisms underlying microbiome-host interactions remain poorly understood. Recent studies have shown that microbiome-associated phenotypes are often mediated by specific molecules, a 'chemical language' that enables microbes to interact with each other and with the host. The biosynthesis of these molecules is encoded in metabolic gene clusters (MGCs) that are subject to frequent horizontal transfer and are therefore highly strain-specific. Current computational methods for analysing microbiomes largely focus on comparative taxonomic analyses and generic metabolism, and overlook this complex "chemical dialog". Indeed, no adequate methods are available to systematically study the roles of MGCs in microbiomes. At the same time, metabolomics data from microbiomes are full of 'dark matter': unknown molecules that cannot be traced to their producers. Here, I propose to develop the first comprehensive computational framework to study the chemical language of the microbiome. In the past years, I have developed technologies that lay the foundation for this ERC project, including automated identification of MGCs, grouping them into families and annotating them using reference data. With DECIPHER, I will move my research to the next level, by developing new algorithms to link MGCs to their metabolic products and to predict their molecular and ecological functions in microbiomes. I will then apply this new framework in a systematic study of microbiome- associated phenotypes in plants and humans. Together, the innovations proposed here will fill a key gap in the analysis of microbiome function and pave the way toward precision-engineering of microbiomes with specific metabolic capabilities for designer soils and microbiome-based therapies.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: microbiome, natural products, specialized metabolism, bioinformatics, machine learning, computational biology

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Project ID:	Project Acronym:	Evaluation Panel:
949624	**DNA_MICROSCOPY**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Ian Torao Hoffecker**
Host Institution:	Kungliga Tekniska Hoegskolan - SWE

In situ DNA sequencing-based microscopy for subcellular spatial transcriptomics

New tools are needed in spatial transcriptomics, which uses imaging to resolve the positions of RNA in their native biological contexts to reveal molecular mechanisms underlying cell states and interactions. The developing embryo exhibits complex transcriptional regulation during the maternal-to-zygotic transition, when the reservoir of maternal RNA is phased out and the zygotic genes are turned on. Existing spatial sequencing approaches cannot simultaneously achieve subcellular resolution, whole transcriptome coverage, isotropic 3D resolution, and the parallel mapping of proteins and genetic regulatory elements that is desirable to form a mechanistic picture of transcriptional regulation in any system as complex is the embryo. The nascent field of DNA microscopy is perfectly suited for the high-throughput, multiplexed, molecular mapping needs of such problems. DNA microscopy uses carefully engineered in situ PCR, next-generation sequencing, and the mathematics of stochastic geometry instead of optics to convey microscale spatial information. In 2018, I developed a 2D DNA microscopy approach based on topological reconstruction of adjacent patches of barcoded DNA “polonies”. My work is among a few papers appearing just in the last year that together constitute a new field. I will adapt my 2D topological DNA microscopy method to one based on in situ whole-transcriptome sequencing in 3D, aiming to achieve subcellular resolution. I will also develop the mathematical basis of topological reconstruction and new computational tools to deal with the 3D data. Finally, I aim to incorporate the capability to localize other molecules in parallel with the transcriptome such as oligonucleotide-conjugated antibodies targeting specific transcription factors and other genetic regulatory elements. The technique, deployed on developing C. elegans embryos, will be used to study spatially dependent regulatory mechanisms such as the determination of cell polarity and fate during cleavage

Link to the ERC project webpage: https://hoffeckerlab.com

Keywords of the ERC project: spatial biology, network inference, polymerase chain reaction, molecular programming, chemical reaction networks, dna sequencing-based microscopy, dna microscopy, imaging-by-sequencing

Keywords that characterize the scientific profile of the potential visiting researcher/s: molecular programming, network inference, graph theory, machine learning, optimal transport, spatial inference, scRNAseq, spatial transcriptomics, spatially resolved transcriptomics, next gen sequencing

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Project ID:	Project Acronym:	Evaluation Panel:
950655	**Silencer**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Baoxu Pang**
Host Institution:	Academisch Ziekenhuis Leiden - NLD

The dark side of the genome: systematically studying the biology of repressive elements—silencers—in the human genome

Less than 1.5% of the human genome contains protein coding information of the estimated 25,000 genes. The rest of the non-coding genome includes many regulatory elements that control the spatial and temporal transcription of genes. With the help of the non-coding regulatory elements, the diverse cell types and tissues of a complex human body could be derived from the combinational expression of a limited number of genes from the same copy of the genome. Most regulatory elements (REs) have been characterized extensively, e.g. promoters, enhancers and insulators. These REs have been implicated to play very important roles in cell physiology, tissue development and disease onsets. Surprisingly, one class of REs—silencers—which repress the transcription of genes, have not been systematically characterized and studied. I have developed a lentiviral system to systematically identify functional silencer elements. In the small-scale proof-of-principle experiments, by focusing on the transcriptional factor (TF) accessible DNA sequences, I showed that this system is robust to identify novel and bona fide silencers, which could be validated using complementary functional assays such as luciferase and CRISPR knockout assays. In this proposed research plan, I aim to identify silencers in an unbiased way, rather than focusing on TF accessible regions, to have a more general understanding of the biology of silencers. Based on the unbiased identification of silencers, I aim to identify a general pattern of epigenetic modifications of silencers, unique combination of sequence motifs, responsible regulatory TFs, biological pathways that are regulated by silencers, diseases that might be related to mutations in silencers, and finally better manipulation strategies of silencers.

Link to the ERC project webpage: https://ccb.lumc.nl/about-the-pang-lab-177

Keywords of the ERC project: Silencer, non-coding genome, CRISPR screening

Keywords that characterize the scientific profile of the potential visiting researcher/s: Silencer, non-coding genome, CRISPR screening

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Project ID:	Project Acronym:	Evaluation Panel:
101001634	**vRNP-capture**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Alfredo Castello**
Host Institution:	University Of Glasgow - GBR

Towards the discovery of cellular RNA-binding proteins with master regulatory roles in virus infection

RNA is a central molecule for RNA virRNA is a central molecule for RNA virus infection. However, viral genomes encode very few proteins that are able to interact with viral RNA. Hence, viruses co-opt cellular RNA-binding proteins (RBPs) to support infection. The host cell also employs RBPs to combat viruses through the recognition of unusual signatures present viral RNAs. Despite these critical roles, the complement of cellular RBPs involved in infection remains largely unknown. This research programme aims to discover comprehensively and unbiasedly the repertoire of cellular RBPs endowed with master regulatory roles in virus infection. To achieve this, we will exploit a novel method developed in my laboratory, named viral RNA interactome capture (vRIC), that allows the elucidation of viral ribonucleoprotein (RNP) composition with unprecedented depth and specificity. It employs pulse-labelling of viral RNA with a photoactivatable nucleotide analogue, UV crosslinking, viral RNA purification with antisense probes and quantitative proteomics. (Aim 1) I hypothesise that cellular RBPs that interact with a broad-range of viral RNAs are likely endowed with master regulatory roles in infection. To test this, I will apply vRIC to cells infected with different RNA viruses to discover RBPs that are shared across viral RNPs. Moreover, we will employ interferon α to investigate if the engagement of these RBPs with viral RNA is regulated by the antiviral state. (Aim 2) To test if these broad-spectrum RBPs display master regulatory roles in infection, I will apply a novel functional screen using genetically modified cells and a broad library of fluorescent viruses. (Aim 3) We will then decipher the molecular mechanisms underpinning the ability of these RBPs to support or restrict infection. In summary, this innovative research programme will discover cellular RBPs with master regulatory roles in infection with great potential as targets for broad-spectrum antiviral therapies.

Link to the ERC project webpage: https://www.castellolab.com/research

Keywords of the ERC project: Virus, RNA, protein-RNA interactions, host-virus interactions

Keywords that characterize the scientific profile of the potential visiting researcher/s: RNA biology, virology, proteomics, cellular and molecular biology

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101001684	**PHAGENET**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Andrey Shkoporov**
Host Institution:	University College Cork - National University Of Ireland, Cork - IRL

PHAGENET: PHAge GEnetic NETworking in the microbiome

Horizontal gene transfer (HGT) is one of the primary forces driving rapid adaptation and long term evolution of complex microbial communities such as the human microbiome. The same process is involved in the dissemination of virulence and antimicrobial resistance genes and emergence of "superbugs". The precise mechanisms and role of HGT in the structure and function of the microbiome remain largely unexplored. Bacteriophages are ubiquitous and highly abundant members of the human microbiome, accounting for ~5% of total microbial DNA. Many of them, such as crAssphage, are highly prevalent and have evolved complex relationships with their microbial hosts. At the same time their role in microbiome composition and function is unclear. Recently we observed the accumulation of considerable amounts of bacterial genomic DNA in the phage-encapsulated fraction of human faeces (up to 50% in some instances). Analysis of this chromosomal fraction reveals that it does not appear to be due to contamination, but rather represents phage-mediated mobilisation and transfer (transduction) of DNA from specific bacterial taxa and specific genomic regions. PHAGENET argues that phage-mediated transduction plays a significant role in the genetic plasticity of the human microbiome, and that the phageome provides individual microbes with access to a wider pangenome and enables dissemination of genes both within and across individual human microbiomes. I propose to thoroughly test this hypothesis at molecular, cellular and organismal levels. This will involve an array of approaches, including long-read high-throughput sequencing, faecal chemostat models, random transposon insertion libraries in gut bacteria and animal models. By addressing an important gap in our understanding of the microbiome, PHAGENET will impact across the research areas of microbiology, virology, gastroenterology, evolutionary ecology and epidemiology.

Link to the ERC project webpage:

Keywords of the ERC project: gut microbiome; bacteriophage; phage; horizontal gene transfer; phageome; phage transduction

Keywords that characterize the scientific profile of the potential visiting researcher/s: gut microbiome; bacteriophage; phage; horizontal gene transfer; phageome; phage transduction

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Project ID:	Project Acronym:	Evaluation Panel:
101021019	**TWIGA**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Joakim Lundeberg**
Host Institution:	Kungliga Tekniska Hoegskolan - SWE

Tissue-wide identification of genome alterations in cancer

We aim to develop the first generation of spatially resolved DNA methodologies to uncover the underlaying molecular landscape of cancer genomes in tissues. Our efforts will focus on a novel genome-wide technology to study genomic integrity in its spatial context, currently a major challenge in the field. The research program is based on developing new experimental protocols and new computational analysis methods. We aim to demonstrate the utility of the method in cancer applications focusing on prostate and breast cancer that display genomic alterations with hallmarks of multiclonality, amplifications and gene fusions. We have previously demonstrated the Spatial Transcriptomics (ST) technology to successfully resolve the transcriptomic landscapes of tissue sections in situ. This was the first demonstrated method to provide transcriptome-wide analysis in a spatial tissue context (Ståhl et al, 2016, review by Asp et al 2020). With the establishment of the technology we have been able to develop advanced computational strategies to explore spatially barcoded transcriptomes. We have, in a series of papers, demonstrated the value and impact to capture and link gene expression information to morphology. For example, we have employed our know-how in (i) cell atlas projects (Asp et al, 2019; Ortiz et al, 2020) (ii) understanding temporal aspects of neurological disease (Maniatis et al, 2019, Chen et al, 2020) (iii) deconvoluting the heterogeneity in cancer (Berglund et al, 2018, Ji et al, 2020). This ambitious proposal seeks to pioneer the use of the tools to perform tissue-wide identification of genomic alterations in cancer (TWIGA) through spatial barcoding on glass slides. This effort will enable us to, in an unsupervised manner, describe genomes in tissue sections for the first time. We are convinced that an increased knowledge of genomic alterations in situ will improve our understanding of cancer from precancer conditions to malignancy and spread.

Link to the ERC project webpage:

Keywords of the ERC project: Spatial Genome Methodology

Keywords that characterize the scientific profile of the potential visiting researcher/s: Cancer molecular biologist (breast cancer)

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Project ID:	Project Acronym:	Evaluation Panel:
101042634	**i-SignalTrace**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Anna Alemany**
Host Institution:	Academisch Ziekenhuis Leiden - NLD

Deciphering signalling pathway dynamics during cell-fate commitment in stem cells

Understanding the identity and intensity of the specific extracellular signals that a cell experiences at different times during its differentiation is essential to develop advanced cellular therapies. However, uncovering the sequence of these signaling events, their intensities, timing, and relevance in development and disease is proving to be very challenging. Here, I propose to build i-SignalTrace: a CRISPR/Cas9-based molecular recorder with the capacity to store both lineage information and signalling pathway activity for multiple signals over time in single cells. By performing kinetic experiments and mathematical modeling, I will use i-SignalTrace to extract the probability of signalling pathways to be activated in stem cells when subject to different extracellular signals and reconstruct the lineage tree of pathway activities during differentiation with single-cell resolution. In combination with single-cell RNA sequencing, i-SignalTrace will make it possible to characterize transition and intermediate states along differentiation trajectories, and quantify the integration between extracellular signals and autonomous programs of gene expression. These results will allow predicting the differentiation trajectories that stem cells follow when subject to external perturbations, and deciphering the role of heterogeneity in signalling pathway activity during cell-fate commitment. Using i-SignalTrace, I will identify missing or redundant signalling pathways induced during in vitro differentiation protocols. Therefore, I expect that exploitation of i-SignalTrace will allow establishing new criteria to design protocols to differentiate stem cells on demand. As a proof-of-concept, I propose a framework to improve the functionality of monolayer-derived cardiomyocytes. Taken together, i- SignalTrace will find applications in both fundamental developmental biology and translational regenerative medicine, which will benefit a much wider scientific community.

Link to the ERC project webpage:

Keywords of the ERC project: scRNAseq, signalling, lineage tracing, embryo development, next generation sequencing, epigenetics

Keywords that characterize the scientific profile of the potential visiting researcher/s: embryo development, epigenetics, modeling, lineage tracing, sequencing data, machine learning

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Project ID:	Project Acronym:	Evaluation Panel:
101076432	**FishTRIM**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Diego Robledo**
Host Institution:	Universidad De Santiago De Compostela - ESP

The evolution and function of fish TRIM E3 ubiquitin ligases

FishTRIM aims to study the evolution and function of the TRIM family of E3 ubiquitin ligases in fish. This family has undergone several clade-specific expansions across the fish phylogeny, with single-copy mammalian TRIMs frequently present in large numbers in fish genomes. TRIM E3 ligases and their direct interactions with viral proteins are key in host-pathogen relationships, and several fish TRIMs have been associated to antiviral responses. Additionally, positive selection has been observed in fish TRIM protein domains involved in protein-protein interactions and pathogen recognition. This suggests that this family of fish E3 ubiquitin ligases may act as an immune mechanism against specific viral pathogens, and therefore the repeated independent expansions of the TRIM repertoire in fish could be the result of an arms race between fish and viruses. To address these questions, FishTRIM will focus on understanding the function of this family in fish, and their potential co-evolutionary interactions with viruses. Recent advances in the fields of functional genetics and genomics, such as single-cell technologies and genome editing, allow us to interrogate gene function at unprecedented scale and resolution. Nonetheless, a phylogenomic approach will be fundamental to determine potential functional overlap across independent expansions, and selection patterns in the context of TRIM protein domains will contribute to illuminate the function of the expanded TRIM repertoire. FishTRIM aims to deliver frontier knowledge on the biological significance of the different fish TRIM expansions, with potential to revolutionise our understanding of fish immune systems and the evolution of the ubiquitination machinery. FishTRIM will also explore the role of TRIMs in resistance to viral diseases in fish, with potential transformative outcomes leading to improved fish welfare and food security.

Link to the ERC project webpage:

Keywords of the ERC project: TRIM, fish, ubiquitination, immunity

Keywords that characterize the scientific profile of the potential visiting researcher/s: Fish, genetics, genomics, aquaculture, post-translational modifications

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Project ID:	Project Acronym:	Evaluation Panel:
101077037	**ORIGIN**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Mathias Wilhelm**
Host Institution:	Technische Universitaet Muenchen - DEU

Learning Isoform Fingerprints to Discover the Molecular Diversity of Life

Did you know that ~80% of all proteomic data is not utilized? Proteins play a vital role in all biological processes and organisms. We believe that different versions of a single gene product – protein isoforms – shape the molecular diversity of life. However, comprehensive evidence on protein-level is not available. Chromatography-coupled tandem mass spectrometry (LC-MS/MS) is the de-facto standard for measuring proteomes, but it is not good at identifying isoforms because at least 80% of the recorded information is never used. I argue that isoforms leave a deterministic multi-dimensional fingerprint (ORIGINs) representing their physicochemical properties in each proteomic measurement. Therefore, the central aim of this project is to discover and quantify protein isoforms systematically by a novel MS-based proteomics data analysis strategy. By tapping into the wealth of data the proteomics community has already amassed, I will train deep neural networks that allow the prediction of ORIGINs. Second, I will implement an innovative data analysis strategy that utilizes ORIGINs to identify and quantify isoforms. Third, I will demonstrate that ORIGINs can be used to substantially broaden our understanding of the molecular diversity of life by showcasing its application on four emerging and challenging questions in proteome research of varying biological and technical complexity. This will allow me to address a fundamental open question in biology: to which extent and prevalence isoforms are actually translated and what functional roles they might be associated with. ORIGINs will improve the sensitivity, biological resolution and accuracy at which proteins and their isoforms can be identified and quantified. Beyond this, the concept of ORIGINs can be applied to and improve any proteomics experiments, and thus holds the potential to revolutionize MS-based proteomics as a technology and elevate the whole field of protein-based research.

Link to the ERC project webpage:

Keywords of the ERC project: AI-based computational proteomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: machine learning, deep learning, data science, mass spectrometry, proteomics

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101078247	**PROTEGE**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Stephen Jones**
Host Institution:	Vilniaus Universitetas - LTU

Profile nucleases and Repurpose Off-Targets to Expand Gene Editing

Programmable nucleases reside at the nexus of advanced gene editing and microbial defense. These nucleases degrade phage DNA but avoid genomic DNA to provide the microbe with adaptive immunity. The standard-bearer, CRISPR-Cas9, relies on a guide RNA (gRNA) – its program – to precisely cut a complimentary genetic sequence – its target – for precision gene editing. These programmable nucleases deliver cure for genetic diseases like anemia, blindness, and cancer; quick disease model development; and diagnostics for viruses like SARS-CoV-2. Hunts across microbial genomes have exposed thousands of programmable nucleases. Each could be another valuable tool for genome engineers, but we know just too little about them to use them safely. Even Cas9 does not have guide-target parity: It cuts partially matched 'off-target' genome sites, which can lead to dangerous side effects. Though we work hard to avoid off-targets, partial matching may have a bright side. What if we leverage it, using it to make gene editing more predictable? Using high-throughput biochemistry, we will Profile nucleases and Repurpose Off-Targets to Expand Gene Editing. The PROTÉGÉ research program will profile guide-target parity – specificity – across promising, newly discovered programmable nucleases. It will deliver a toolset for assessing this critical safety feature rapidly and broadly. Finally, we will test the hypothesis that purposefully misprogramming nucleases can direct specific repair outcomes. We intended to benefit Europe and the world community with safer and more diverse gene editing tools for achieving its Horizon Europe health, technology and environmental goals.

Link to the ERC project webpage:

Keywords of the ERC project: gene editing, crispr, biochemistry, high throughput, bioinformatics

Keywords that characterize the scientific profile of the potential visiting researcher/s: translational, gene therapy, biophysics, bioinformatics, biotech engineering

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Project ID:	Project Acronym:	Evaluation Panel:
101078353	**GutTransForm**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Michael Zimmermann**
Host Institution:	European Molecular Biology Laboratory - DEU

Gut microbiota drug biotransformation as a tool to unravel the mechanisms of metabolic microbiota-host interactions

The variability of the human gut microbiome (entirety of microorganisms inhabiting the intestine) far exceeds human genome variability, and has been connected to various aspects of human health. Although microbiome differences are often linked to altered metabolism, the current view on metabolic interactions between the microbiota and the host remain mostly descriptive due to several limiting factors. First, most sequencing-based human microbiome studies rely on correlative analyses between microbiome composition and human phenotypes, depend on largely incomplete microbial genome annotations, and are not targeted to identify community-mediated functional traits. Second, many metabolites can be both of microbial and human origin, which makes it conceptually and methodologically challenging to disentangle metabolic microbiota-host interactions. To overcome these limitations, I propose a systematic bottom-up strategy to mechanistically study metabolic microbiota-host interactions by harnessing gut microbiota's capacity to biotransform (chemically modify) drug molecules. The large chemical diversity and exogenous origin makes medical drugs ideally suited for experimental in vitro and in vivo approaches to probe microbiota-host interactions in a controlled way. We will combine high-throughput culturing protocols, genetics, metabolomics measurements, genomics analyses, gnotobiotic mouse work, and computational modeling to connect interpersonal differences in microbiome composition to differences in metabolic functions of individuals' gut microbiota, and ultimately link them to molecular host phenotypes. Generating these mechanistic insights and transformational resources is essential to understand the fundamental principles of the microbiota-host relationship. In addition, this project has direct medical relevance, as it provides actionable microbiome-based links to interpersonal differences in medical drug response, which remain a widespread problem in clinical practice.

Link to the ERC project webpage:

Keywords of the ERC project: Gut microbiome, drug metabolism, biotransformation, gnotobiology, metabolomics, bacteriology

Keywords that characterize the scientific profile of the potential visiting researcher/s: drug response, microbial ecology, metabolomics, functional genomics

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101087575	**SAMEY**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Annaliese Mason**
Host Institution:	Rheinische Friedrich-Wilhelms-Universitat Bonn - DEU

Stabilising autopolyploid meiosis for enhanced yield

Hybrid breeding has been one of the biggest contributors to yield increase of the last century. Hybrids are individuals which have genetically different parents, which results in a “hybrid vigour” effect. This hybrid vigour effect can confer advantages over inbred parent lines in growth, yield, and resilience and tolerance to different types of environmental stresses, important for securing agricultural production in a changing climate. An even greater hybrid vigour effect is possible in autopolyploids, which can have up to four different copies of each chromosome, than in diploids, which have can only have up to two different copies of each chromosome. In effect, “double hybrids” can be made in autopolyploids, with up to four different parents contributing to hybrid vigour in a single individual. However, to date the double hybrid effect has almost never been used for breeding. Most of our crops are not autopolyploids. We can induce autopolyploidy through chromosome doubling, but this causes meiotic instability, where multiple crossovers occur between the four chromosome copies during meiosis. This pairing disruption leads to potential loss of chromosomes and chromosome fragments essential for seed fertility and viability. Although induced autopolyploids are meiotically unstable, this is not the case for established autopolyploids. In the majority of established autopolyploids, a maximum of one crossover per two homologous chromosomes during meiosis is strictly enforced, thus achieving 100% pairing and correct segregation of chromosomes into daughter cells. I propose to stabilise meiosis in induced autopolyploid Brassica rapa (turnip, Chinese cabbage) by knock-out of crossover promoting genes, over-expression of crossover suppressing genes and selection of natural genetic variants. Stable autopolyploids will be used to produce double-hybrid lines, which will be evaluated for hybrid vigour for yield-related traits.

Link to the ERC project webpage:

Keywords of the ERC project: polyploidy, meiosis, Brassica

Keywords that characterize the scientific profile of the potential visiting researcher/s: cytogenetics, biotechnology, genomics

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Project ID:	Project Acronym:	Evaluation Panel:
101097317	**ViveRNA**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Andrzej Dziembowski**
Host Institution:	Miedzynarodowy Instytut Biologii Molekularnej I Komorkowej W Warszawie - POL

Principles of endogenous and therapeutic mRNA turnover in vivo

During the COVID-19 pandemic, we witnessed the application of mRNA vaccines for SARS-CoV-2, paving the way for the widespread use During the COVID-19 pandemic, we witnessed the application of mRNA vaccines for SARS-CoV-2, paving the way for the widespread use of therapeutic mRNAs in medicine. However, lack of knowledge regarding mRNA metabolism in vivo limits the optimization and refinement of such therapies. Our preliminary data, acquired via Direct RNA Sequencing (DRS), shows that variability of poly(A) tail length and, therefore, stability of endogenous and therapeutic mRNAs in different tissues and cell types is much larger than previously thought. Here, we propose the ViveRNA project, which will enhance the DRS (eDRS) pipeline and combine it with analyses of mouse models, primary cell cultures, and synthetic biology approaches to examine the nature of mRNA turnover in vivo and characterize the metabolism of endogenous and administered mRNAs. The goal of the ViveRNA project is to elucidate the complexity of mRNA lifetime regulation. Specifically, our aims are: • Part 1: Construction of an enhanced nanopore Direct RNA Sequencing pipeline (eDRS) for comprehensive analyses of mRNA metabolism. eDRS will assess the composition and lengths of poly(A) tails, modifications, isoforms, and dynamics. • Part 2: Comprehensive analysis of the lifecycle of endogenous mRNAs, analyzing: dynamics, ribosome association, and poly(A) tail metabolism in organs and primary cells and providing insights into the role of particular enzymes. The reach data resource will help designing better mRNA therapeutics and enable the formulation of testable mechanistic hypotheses. • Part 3: Description of the metabolism of therapeutic mRNAs in relevant cell types and tissues. Then, together with the knowledge gained in Part 2, the design of more stable mRNAs with therapeutic potential will be initiated. The ViveRNA project will facilitate the rational design of next-generation mRNA therapeutics.

Link to the ERC project webpage:

Keywords of the ERC project: mRNA, polyadenylation, mRNA theraputics, mRNA decay

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101114879	**HoloRECOMB**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr André Marques**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

How to evolve without centromeres: meiotic recombination dynamics in holocentric plants

Centromeres strongly affect genomic architecture and meiotic recombination distribution and also play a key role in constraining karyotype evolution. The recombination landscape is also heavily influenced by chromosome number and structure (i.e., karyotypes), as at least one crossover per chromosome (and rarely more than three) occurs in most species, making chromosome number the primary driver of recombination frequency. In addition, centromeres inhibit recombination, and therefore crossovers tend to occur mostly at chromosome ends. However, several unrelated eukaryotic lineages do not have centromeres, or at least, not conventional ones. Such is the case for plants with holocentric chromosomes, where hundreds of small centromere-like units are evenly distributed across the length of the chromosome. Notably, holocentricity has evolved repeatedly across the tree of life and at least four times during plant evolution. Holocentric plant species offer a unique opportunity to study the plasticity of meiotic recombination control. These species have lost typical centromeres, making them ideal for investigating how the recombination landscape was reshaped after the transition to holocentricity. Moreover, holocentricity unleashes changes in the karyotype, offering the possibility to analyze the effects of chromosome breaks and fusions on recombination frequency and distribution. The HoloRECOMB project aims are as follows: I. Analyze how transitions to holocentricity affect meiotic recombination dynamics in different holocentric plant lineages. II. Explore the effect of chromosome breaks and fusions on crossover number and distribution. III. Examine whether the crossover regulation in holocentric plants acts in a similar manner as in monocentric ones. Understanding how holocentricity affects recombination dynamics will provide insights into important mechanistic aspects of meiosis with potential practical applications for crossover regulation in centromeric regions.

Link to the ERC project webpage:

Keywords of the ERC project: holocentric chromosomes; chromosome biology; meiotic recombination; meiosis; genome evolution

Keywords that characterize the scientific profile of the potential visiting researcher/s: genomics; cytogenetics; bioinformatics; CRISPR-Cas9; meiosis; centromere; plant transformation

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Project ID:	Project Acronym:	Evaluation Panel:
101115930	**MeioPoly**	**LS2** Integrative Biology: from Genes and Genomes to Systems

Principal Investigator:	**Dr Heidi Serra**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Meiotic adaptation to allopolyploidy

Hybridization between related species resulting in allopolyploidy is ubiquitous in the evolutionary history of plants. Such nascent allopolyploids face the challenge of ensuring accurate chromosome segregation during meiosis in the presence of related, but non-identical chromosome sets (called homoeologues), inherited from the allopolyploid's progenitors. Essential for fertility, this relies upon the formation of physical connections (crossovers) between homologous chromosomes, while crossovers between homoeologues - that could lead to aneuploidy - must be prevented. Meiotic stability in the allopolyploid context thus requires a tight control of recombination partner choice. The existence of highly fertile natural allopolyploids shows that solutions exist and have arisen many times during evolution, but the mechanisms involved remain poorly understood. My goal is to elucidate the evolutionary processes of meiotic stabilization of nascent allopolyploids, with a special emphasis on the molecular mechanisms that prevent recombination between homoeologous chromosomes. I propose to recreate in the lab the natural hybridization that happened ~16 Kya between A. thaliana and A. arenosa leading to Arabidopsis suecica in order to characterize the mechanisms underlying the evolution of the young allopolyploids over the first generations as they acquire meiotic stability and full fertility. The proposed project has three main objectives: (1) map and characterize genome-wide recombination between homoeologues; (2) identify the factors that control homoeologous pairing and recombination and (3) elucidate how this control is progressively set up in newly formed allopolyploids. Our studies have the potential to bring new and fundamental insights on the evolutionary processes enabling meiotic stabilization of nascent allopolyploids and to contribute to polyploid crop improvement through knowledge transfer to plant breeding programs.

Link to the ERC project webpage:

Keywords of the ERC project: Meiosis; Recombination; Polyploid; Homoeologues; Arabidopsis

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
835312	**PLASTINET**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Austin Smith**
Host Institution:	The University Of Exeter - GBR

Plasticity of the Pluripotency Network

A few days after fertilisation mammalian embryos form a blastocyst comprised of three tissues; trophoblast and hypoblast are the forebears of extraembryonic structures, while naive epiblast cell are the pluripotent source of the embryo proper. Classical mouse embryological studies indicate that lineage potencies are determined concomitant with segregation of the three founder tissues. Textbook definitions of pluripotency thus exclude extraembryonic potential. Consistent with this paradigm, mouse embryonic stem cells are generally ineffective in producing trophoblast or hypoblast derivatives. However, we have discovered that human naïve pluripotent cells have high intrinsic competence for trophoblast formation. Furthermore, unlike in mouse, extraembryonic transcription factors are present in human epiblast in vivo. These findings challenge the dogma of early lineage restriction but may be compatible with the ancestral origin of pluripotency. We hypothesise that extraembryonic plasticity underlaid by entwined regulatory networks is the evolutionary template of pluripotency. Consequently, signal modulation to suppress extraembryonic specification may be crucial for capture of stem cells representative of naïve epiblast in most mammals. We will examine human and non-human primates, farm animals in which embryos undergo extended development before implantation, and a marsupial in which pluripotent cells are generated from the trophoblast. In a cross-disciplinary approach we will employ transcriptomics, embryo and stem cell experimentation, and formal computational modelling to uncover the core biological program moulded by evolution into different forms. We aim to establish hitherto elusive chimaera-competent embryonic stem cells from species of importance for research, biomedical applications and livestock improvement. We will obtain fresh insight into the molecular logic governing early development, lineage plasticity, pluripotent identity, and stem cell self-renewal.

Link to the ERC project webpage: https://lsi.exeter.ac.uk/groups/smith-group/

Keywords of the ERC project: stem cells, pluripotency, gene regulatory network' single cell 'omics

Keywords that characterize the scientific profile of the potential visiting researcher/s: computational biologist; bioinformatician

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Project ID:	Project Acronym:	Evaluation Panel:
852136	**LIP-ATG**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Amelie Bernard**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

The missing link: how do membrane lipids interplay with ATG proteins to instruct plant autophagy

Autophagy is an intracellular catabolic process critical to eukaryotic life and indispensable for plant survival to drought, nutrient scarcity or pathogen attacks. Autophagy relies on the formation of specialized vesicles called autophagosomes (AP) which engulf and deliver cell components to the lytic vacuole. AP biogenesis is carried out by a group of dedicated proteins (named ATG) and hinges on intense remodelling events and on the remarkable capacity of an initial membrane, the phagophore, to assemble de novo, shape like a cup, expand while maintaining structure and function and re-shape to a complete vesicle. To date the molecular mechanisms underlying these events remain elusive. Research has focused on the role of autophagy proteins but, despite AP biogenesis being a membrane-based process, the fundamental contributions of lipids to AP membrane formation, identity and activities have been largely unexplored; in other words, when it comes to AP formation we are only looking at half of the picture. I propose to address the fundamental question of how APs form and shape from a novel angle: by exploring how lipids' nature, dynamics and lateral heterogeneity instruct the phagophore structure, its protein composition and its functions. The project builds on our recent results and expands on strategies that we have developed, integrating proteomic/bioinformatic approaches, lipidomics and high-resolution 3D imaging. We will tackle 3 complementary objectives: 1) Reveal the dynamic lipid signature of the phagophore, 2) Elucidate the implication of lipids nature and repartition in the phagophore ultrastructure, 3) Decrypt the molecular mechanisms by which lipids interplay with ATG proteins to control autophagy activity and plant physiology. Overall the project will articulate an integrated vision of the molecular processes controlling autophagy and provide fundamental knowledge in our understanding of plant adaptive programs.

Link to the ERC project webpage:

Keywords of the ERC project: autophagy, plant, lipid, membrane

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
863952	**ACE-OF-SPACE**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Patrick Müller**
Host Institution:	Universitat Konstanz - DEU

Analysis, control, and engineering of spatiotemporal pattern formation

A central problem in developmental biology is to understand how tissues are patterned in time and space - how do identical cells differentiate to form the adult body plan? Patterns often arise from prior asymmetries in developing embryos, but there is also increasing evidence for self-organizing mechanisms that can break the symmetry of an initially homogeneous cell population. These patterning processes are mediated by a small number of signaling molecules, including the TGF-β superfamily members BMP and Nodal. While we have begun to analyze how biophysical properties such as signal diffusion and stability contribute to axis formation and tissue allocation during vertebrate embryogenesis, three key questions remain. First, how does signaling cross-talk control robust patterning in developing tissues? Opposing sources of Nodal and BMP are sufficient to produce secondary zebrafish axes, but it is unclear how the signals interact to orchestrate this mysterious process. Second, how do signaling systems self-organize to pattern tissues in the absence of prior asymmetries? Recent evidence indicates that axis formation in mammalian embryos is independent of maternal and extra-embryonic tissues, but the mechanism underlying this self-organized patterning is unknown. Third, what are the minimal requirements to engineer synthetic self-organizing systems? Our theoretical analyses suggest that self-organizing reaction-diffusion systems are more common and robust than previously thought, but this has so far not been experimentally demonstrated. We will address these questions in zebrafish embryos, mouse embryonic stem cells, and bacterial colonies using a combination of quantitative imaging, optogenetics, mathematical modeling, and synthetic biology. In addition to providing insights into signaling and development, this high-risk/high-gain approach opens exciting new strategies for tissue engineering by providing asymmetric or temporally regulated signaling in organ precursors.

Link to the ERC project webpage: https://www.biologie.uni-konstanz.de/mueller

Keywords of the ERC project: self-organization, pattern formation, signaling, zebrafish, biophysics, deep learning, mathematical modeling

Keywords that characterize the scientific profile of the potential visiting researcher/s: self-organization, pattern formation, signaling, zebrafish, biophysics, deep learning, mathematical modeling

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Project ID:	Project Acronym:	Evaluation Panel:
866537	**CollectiveDynamics**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Alexander Aulehla**
Host Institution:	European Molecular Biology Laboratory - DEU

Collective signaling oscillations in embryonic patterning – revealing underlying principles

In this proposal, we study collective signaling oscillations during embryonic patterning. Signaling oscillations during vertebrate embryo segmentation are governed by a molecular oscillatory machinery referred to as segmentation clock (Palmeirim et al., 1997). The segmentation clock is linked to periodic activity of the Notch, Wnt and Fgf pathway in presomitic mesoderm (PSM) cells (period~2 hours in mouse embryos). Importantly, PSM cells display complex, collective synchronization and, as a result, wave-like activity patterns (phase waves) sweep periodically along the embryonic axis. We have previously shown that phase waves are an emergent and collective phenomenon in PSM cells (Tsiairis and Aulehla, 2016). Conceptually, this proposal builds on our previous discovery that the relative timing between Wnt/Notch oscillations is critical for proper mesoderm patterning (Sonnen et al., 2018). What are the principles underlying the emergence of collective synchronization and how do PSM cells decode relative timing of signalling oscillations? As outlined in this proposal, we are now in a unique position to address these fundamental questions in novel ways. Importantly, we have established an entrainment strategy that enables, for the first time, precise experimental control of oscillation dynamics (Sonnen et al., 2018). Our strategy is to further expand the entrainment approach, including the future use of optogenetics, and also combine it with our expertise in quantitative, multi-scale analysis of signalling dynamics and functional, genetic perturbations. A central aim of this ERC proposal is to build on discoveries made in versatile in vitro assays that we developed and to address their significance in vivo. To this end, we propose a novel line of research using the medaka fish model. We will entrain and challenge collective synchronization in vivo to address how signalling oscillations are integrated with growth dynamics to yield robust embryonic patterning.

Link to the ERC project webpage:

Keywords of the ERC project: Developmental Biology, Non-linear dynamics, Oscillations

Keywords that characterize the scientific profile of the potential visiting researcher/s: Physics, Developmental Biology, Non-linear dynamics, Oscillations

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Project ID:	Project Acronym:	Evaluation Panel:
101021349	**TAaGC**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Didier Stainier**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

Transcriptional Adaptation and Genetic Compensation

Organisms utilize several mechanisms to compensate for the damaging consequences of genetic perturbations. One such mechanism is the newly identified process of transcriptional adaptation (TA): in this process, certain deleterious mutations trigger the transcriptional modulation of so-called adapting genes. In some cases, e.g., when one of the upregulated genes is functionally redundant with the mutated gene, TA leads to functional compensation. Notably, unlike other modes of compensation, TA is not triggered by the loss of protein function. This unexpected observation has prompted studies into the machinery of TA and the contexts in which it functions. Following our discovery of TA (Rossi et al., 2015), we have shown that in zebrafish embryos and mouse cell lines, mutant mRNA degradation triggers this process (El-Brolosy et al., 2019). We also observed TA in C. elegans and found that small RNA biogenesis, in addition to mutant mRNA degradation, is required for this process (Serobyan et al., 2020). While these and other studies have documented the importance of TA and its occurrence across phylogenetically distant organisms, several key questions remain in terms of how TA arises and how prevalent it is. In this proposal, we aim to investigate the mechanisms that underlie TA, including 1) what determines which genes are targeted as adapting genes during TA, and 2) how the expression of these genes is modulated during TA. These studies will be carried out in zebrafish, C. elegans, mice, and multiple mouse and human cell lines, capitalizing on the genetic and biochemical approaches available in each model system, while simultaneously allowing us to analyze the conservation of the mechanisms underlying TA. In addition, we will investigate the relevance of TA in human health and disease. Ultimately, this work will further our understanding of the mechanisms that modulate genetic and phenotypic robustness in humans.

Link to the ERC project webpage:

Keywords of the ERC project: transcriptional adaptation, genetic compensation, robustness, small RNAs, mutant mRNA degradation, zebrafish, C. elegans, mouse, human

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101039998	**UnderPressure**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Morgan Delarue**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Elucidating the phenotypic convergence of proliferation reduction under growth-induced pressure

Growth-induced pressure necessarily emerges when a cell population, whichever the organism, proliferates in a 3D spatially-limited environment. Growth-induced pressure imposes physical constraints on cell physiology. A reduction of growth and division is observed in evolutionarily distant organisms such as bacteria, fungi, plants, or mammals. However, some cells are more capable of coping with these physical limitations and proliferate than others. This is in particular the case of cancer cells, for which growth-induced pressure participates in tumorigenesis and chemoresistance. Despite its importance, we are still at a loss to identify the basic sensing mechanisms associated with 3D proliferation under pressure. It is notably unclear if the mechanical control of proliferation stems from specific signaling or is a consequence of associated changes in the physical properties of cells. The goal of UnderPressure is to elucidate the phenotypic convergence of the mechanical-control of cell proliferation. We hypothesize that a large part of proliferation reduction comes from the physical limits imposed by the obligatory increase of macromolecular crowding under 3D confinement. Crowding relates to the high fraction of macromolecules in the cell and has the potential to kinetically alter biochemical reactions. We expect crowding to limit key processes associated with growth and division, and to elicit specific signaling essential to circumvent these limitations. Using unique microfluidic devices, we will investigate in bacteria, fungi, and mammalian cells how compressive forces physically limit growth and division and unravel the signaling pathways associated with the control of cell proliferation. We will mainly focus on crowding, investigate its consequences and its link with other physical properties such as membrane tension. We will use this knowledge to control cell proliferation in 3D compressed tumors, with the hope to notably reduce chemoresistance.

Link to the ERC project webpage:

Keywords of the ERC project: mechanobiology, macromolecular crowding, microfluidics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101041597	**STORMtheWALL**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Kalina Haas**
Host Institution:	Institut National De Recherche Pour L'Agriculture, L'Alimentation Et L'Environnement - FRA

Resolving the mechanism of plant cell expansion at high spatio-temporal resolution.

Plants critically shape ecosystems and our societies by converting sunlight and CO2 into O2 and bio-mass while they grow. Understanding this growth process constitutes a major frontier in plant research. Growth is a multi-scale process. At a subcellular scale, it depends on the expansion of the cell walls, which involves changes in the chemistry and architecture of constituent polymer networks. Very little is known on the nature and the control of the cell wall changes that are critical for growth, in striking contrast to the, often detailed, knowledge of growth-regulating signaling networks. This is in part due to the lack of appropriate tools to study changes in the complex cell wall polymer assemblies that often occur at fast (~s) and small (<micrometer) scales. In this project, I propose firstly, to breach the spatial limits of the tools by using multi-target optical nanoscopy to visualize cell wall architecture and remodeling, and secondly, to overcome their temporal limits by using light-gated actuators and multiplexed intracellular biosensors to simultaneously perturb and monitor the system dynamics in vivo. In particular, I will address pectin remodeling, the role of which in plant growth was shown to be critical, but without clearly understanding the mechanism. My objectives are to (1) reveal the key changes in cell wall architecture and chemistry during growth, (2) understand the fast signaling by which cells perceive and coordinate wall remodeling, and (3) build a dynamic hybrid model to explain how plants coordinate wall expansion. This interdisciplinary project will provide new insights into the nanoscale organization of cell walls and propose a novel pectin-based mechanism for its active reorganization during growth. This will provide an essential framework, not only for understanding plant growth and morphogenesis but also for the study of life beyond the plasma membrane, for instance in relation to immunity, multicellularity, or symbiosis.

Link to the ERC project webpage: https://ijpb.versailles.inrae.fr/annuaire/recherche/kalina-t-haas

Keywords of the ERC project: cell wall, pectin, plant morphogenesis, plant cell expansion

Keywords that characterize the scientific profile of the potential visiting researcher/s: protein biochemistry, polysacharide biochemistry, structural biology, optogenetics, FRET, FLIM

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Project ID:	Project Acronym:	Evaluation Panel:
101042198	**HOT-AND-COLD**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Petra Marhava**
Host Institution:	Sveriges Lantbruksuniversitet - SWE

How plants deal with heat and cold: Molecular mechanisms of auxin transport and signaling in response to temperature stress

Ambient temperature above or below a threshold can adversely affect plant growth and development, and even lead to death. The tightly regulated distribution of the hormone auxin throughout the plant body controls an impressive variety of developmental processes that tailor plant growth and morphology to environmental conditions. Although non-optimal ambient temperature can alter auxin transport, the precise nature of this alteration and the underlying molecular mechanisms remain enigmatic. Hence, the aim of HOT-AND-COLD is to dissect the molecular mechanisms involved in auxin transport and its downstream signaling upon temperature stress, down to the tissue and cell-type-specific level, focusing on the root of the model organism Arabidopsis thaliana. To achieve this aim, I will combine high-resolution imaging techniques integrated with a temperature-controlled stage system, mass-spectrometry-based phosphoproteomics, TRAP-seq and chemical screens in a multifaceted approach that has never been used for such a study in plant root systems. Using this approach, I expect to reveal: (i) the temperature-responsive phosphoproteome of membrane proteins; (ii) the link between changes in membrane fluidity and the dynamics of auxin transport components within the plasma membrane; (iii) cell-type-specific translatomes that orchestrate auxin transport upon temperature shock as well as in the gradual temperature stress response; and (iv) sensors and components of the signaling pathways controlling plant acclimation to temperature stress. Taken together, the fundamental knowledge obtained through this research will contribute to the mechanistic understanding of plant responses to the temperature variability that will accompany climate change. Such understanding is key for anticipating the impacts of climate variability on agricultural and natural ecosystems.

Link to the ERC project webpage:

Keywords of the ERC project: auxin, heat, cold, cell-type specificity, cell biology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101042865	**CARDIOCALC**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Anabela Bensimon-Brito**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

The fundamentals of cardiovascular calcification: from cells to therapy

With this project I propose to identify fundamental mechanisms of cardiovascular calcification (CVC) and new therapeutic targets using zebrafish as a model system. CVC, characterised by progressive calcification of the soft tissue causing impaired blood circulation, is a frequent form of cardiovascular disease. Because the pathophysiology of CVC is highly heterogeneous, the exact cell types and signalling pathways triggering tissue calcification are still unknown, thus limiting therapy options. Most studies on CVC rely on in vitro systems, which fail to reproduce the multicellular environment, or mammalian in vivo models, limited for live-imaging and high-throughput analyses. By combining my expertise in cardiovascular research and bone biology, I propose to use zebrafish as a model to elucidate the multifactorial mechanisms of CVC, focusing on different developmental stages and cardiovascular tissues. In Aim 1, I will use a broad array of zebrafish genetic models to characterise the cellular dynamics, molecular mechanisms and functional impact of CVC in vivo. I will also study the role of specific cell populations present in regenerating valves and human valve implants with CVC. In Aim 2, I propose to identify new local and systemic therapeutic strategies to block/reverse CVC, taking advantage of the zebrafish amenability for genetic manipulation and high-throughput screening. I will recruit bone-degrading cells to the CVC site and determine their potential to reverse tissue calcification. Moreover, I will select a short list of small molecules identified in a large-scale screen in zebrafish and will test their therapeutic potential in cardiovascular cells derived from hiPSCs of CVC patients. Altogether, with this interdisciplinary approach, I expect to bring a new perspective on the mechanisms and therapeutic targets to block/reverse CVC, which could have a considerable impact on the European population, severely affected by these diseases.

Link to the ERC project webpage:

Keywords of the ERC project: Zebrafish, cardiovascular, live imaging, cell dynamics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101044951	**MitoSignal**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Alena Zikova**
Host Institution:	Biologicke Centrum Akademie Vid Ceske Republiky Verejna Vyzkumna Instituce - CZE

Mitochondrial signaling drives parasite differentiation

Mitochondria perform three essential functions: ATP production, metabolite synthesis and cellular signaling. These signals, communicating the bioenergetic and biosynthetic fitness of the organelle to the nucleus, play a powerful role in determining cellular fate. The incorporation of mitochondrial reactive oxygen species (mROS) in cellular signaling is an interesting evolutionary outcome, as excess levels of these potent oxidizers have been implicated in many pathologies. While most research focuses on these outcomes of oxidative stress, much less is known about how mROS drive a range of physiological responses. Furthermore, the available studies are limited to a few traditional model organisms, featuring complex cellular systems with numerous mitochondria at different energetic states. Here, we propose to utilize the unicellular parasites, Trypanosoma brucei and T. congolense, as simplified but elegant models to define mROS-driven cellular differentiation. As these protists undergo programmed development between several distinct life cycle forms, there are striking changes to the structure and physiology of their single mitochondrion that manifest in elevated ROS levels. Importantly, we demonstrated that these ROS molecules are essential for the developmental progression of the parasite. Employing these well-chosen models and combining next-generation biosensors, advanced bioenergetic methods, redox proteomics and a CRISPR/Cas9 genetic screen, we will answer the following fundamental questions: Does mROS drive Trypanosoma cellular differentiation? What molecular processes are responsible for the elevated mROS levels during differentiation? How is the redox signal propagated to the rest of the cell? The proposed research aspires to unravel the fundamental mechanisms underlying the intricate communication between mitochondria and the rest of the cell, featuring cellular hallmarks of cell fate decisions.

Link to the ERC project webpage:

Keywords of the ERC project: mitochondria / signaling / differentiation / parasite

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101077271	**ChroMeta**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Jan Zylicz**
Host Institution:	Kobenhavns Universitet - DNK

Unravelling specificity of epi-metabolic regulation in mouse development

When environment of the embryo changes or when development progresses metabolic reactions are rapidly affected. These alterations to chemical reactions are coupled to epigenetic memory. However, without mechanistic data on how this coupling occurs it is difficult to understand how normal embryogenesis can proceed. This project will elucidate how metabolic changes result in specific epigenetic outcomes and address the function of such regulation. As a model we will use mouse implantation, a process tightly linked to dramatic alterations to chromatin and transcription. We found that this is also associated with extensive metabolic rewiring and that disrupting metabolic flows results in both lineage-specific and mark-specific changes to chromatin. While multiple studies uncovered that metabolism fuels chromatin modifiers with co-factors, the fundamental biological question of how specificity is achieved remains unanswered. Here we will address this challenge by directly testing the three most likely hypotheses: 1) that metabolic reactions shuttle into the nucleus where they specifically fuel chromatin changes; 2) that chromatin-bound metabolic enzymes regulate gene expression and 3) that only specific chromatin modifiers are sensitive to metabolic changes. To address these questions, we will go beyond description as we supplement multi-omic approaches with mechanistic experiments both in vitro and in vivo. Firstly, will use perturbations of nuclear metabolic enzymes and their chromatin binding. Secondly, we will implement protein engineering to render chromatin modifiers resistant to the availability of their co-factors. By uncoupling epi-metabolic regulation, we seek not only to uncover its importance for controlling chromatin states but also the implantation developmental program. This project will form a framework of how future studies can mechanistically unravel intertwined regulatory processes and assess the role of environment and nutrition in early pregnancy.

Link to the ERC project webpage: https://renew.ku.dk/research/reseach-groups/zylicz-group/

Keywords of the ERC project: stem cells, epigenetics, metabolism, development, IVF

Keywords that characterize the scientific profile of the potential visiting researcher/s: metabolism, development, chromatin

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Project ID:	Project Acronym:	Evaluation Panel:
101078070	**gutTEimpact**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Kasia Siudeja**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Illuminating the role of selfish genetic elements in somatic tissue homeostasis and aging

Life-long tissue homeostasis requires sustained function of differentiated cell types as well as progenitor cells, which ensure tissue self-renewal. Little is known about the role that non-genic repetitive DNA sequences play in the maintenance of cellular homeostasis in divers somatic tissues in vivo. Transposable elements (TEs) are omnipresent, highly repetitive DNA sequences that mobilize and propagate within host genomes. Though previously thought to be fully repressed in the soma, TEs can be actively transcribed and, at least to some extent, mobile in certain somatic tissues. Indeed, somatic TE activity was proposed to contribute to normal development, aging, and pathologic conditions, such as cancer or neurodegeneration, underscoring the potential bearing that these selfish genetic elements could have in the soma. Nevertheless, the dynamics of activity and tissue-specific regulation of TE sequences are poorly understood, as is the impact of TE activity on different somatic cell-types and tissues. We have recently uncovered that prevalent, tissue-specific TE mobility occurs in the Drosophila intestine and can lead to gene inactivation and tumor formation. Here, using this powerful and genetically amenable in vivo model system, I aim to combine genomic techniques with developmental and cell biology approaches to address the intriguing interplay between TEs and somatic tissue function in vivo. I will ask: 1- How TE activity differs between diverse cell types and how it changes in a tissue under normal or pathological conditions, as well as during aging? 2- What processes control TE activity in somatic cells in vivo?; and 3- What are the direct consequences of TE transcriptional activity and mobility on somatic cell function, and the long-term impacts at a tissue and organism level? Ultimately the proposed research program will shed new lights on the importance of mobile DNA sequences in the maintenance of lifelong tissue homeostasis in vivo.

Link to the ERC project webpage: https://www.i2bc.paris-saclay.fr/nuclear-dynamics-and-repetitive-dna-in-tissue-homeostasis/

Keywords of the ERC project: genomics, development, adult stem cells, transposable elements, Drosophila, aging

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101078291	**KaryodynEVO**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Gautam Dey**
Host Institution:	European Molecular Biology Laboratory - DEU

Evolutionary principles of nuclear dynamics and remodelling

Every eukaryote has a nucleus, a double lipid membrane-bound compartment that encapsulates the genome, but almost every nucleus is different - in shape, size, molecular composition, spatial organisation, and dynamics through the cell cycle. Given its fundamental and universal functional roles in protecting the DNA and regulating the exchange of information and control machinery between genome and cytoplasm, one might ask the question: why are there so many ways to build and remodel a nucleus? Bringing together comparative genomics, phylogenetics, quantitative cell biology and experimental evolution in multiple microbial model systems drawn from across the eukaryotic tree, we set out to elucidate the genomic, biophysical and evolutionary factors that determine nuclear dynamics and remodelling - karyodynamics - within the context of cellular architecture and function. A comparative perspective driven by phylogenetics will enable us to separate universal principles of karyodynamics from species- and niche-specific adaptations, and dissect the reasons for the evolutionary and developmental plasticity that we observe experimentally. In turn, we can use these principles to infer, predict and validate phenotypes in novel and emerging model systems. Finally, a more comprehensive understanding of the mechanisms responsible for karyodynamic phenotypic diversity would allow us to reconstruct evolutionary trajectories all the way back to the origins of the nuclear compartment, a landmark event in the evolution of eukaryotes from an archaeal-bacterial symbiosis over 2 billion years ago.

Link to the ERC project webpage: https://erc.easme-web.eu/?p=101078291

Keywords of the ERC project: evolutionary cell biology; nuclear remodelling; mitosis; biodiversity

Keywords that characterize the scientific profile of the potential visiting researcher/s: phylogenetics; protistology; marine microbiology

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Project ID:	Project Acronym:	Evaluation Panel:
101087656	**EpiPhys**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Jean-Léon Maître**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Physics of the first mammalian epithelium

Epithelia operate major biological functions throughout the human body. Forming de novo during preimplantation development, the trophectoderm (TE) is our first epithelium. The TE mediates the formation of the first mammalian lumen, which involves considerable physical challenges. Indeed, pressurized fluid, pumped through the TE, fractures intercellular contacts before cells squeeze this fluid into a single lumen. We recently found that cell adhesion and cell contractility determine the position of this lumen, which then controls further differentiation of the TE. This suggests that physical cues can determine the first mammalian axis of symmetry and TE patterning. However, most physical properties of epithelia controlling this process remain unknown, as their study in vivo has been so far very limited. In this project, we will investigate how the physics of the TE shapes and patterns the mouse preimplantation embryo, by using novel approaches, such as microfluidics and optical tweezers, that allow direct measurement of physical properties in vivo. First, we will determine epithelial transport properties of the TE and their regulation during lumen opening. We will next map plasma membrane reservoirs and membrane mechanics during preimplantation development. We will then characterize how the nuclear envelope and chromatin regulate nuclear mechanics during epithelial thinning. With this broad and unprecedented in vivo physical characterization, we will determine how epithelial transport, plasma membrane and nuclear mechanics influence epithelial stretching and patterning during lumen growth and positioning. Finally, we will determine the relative contributions of these physical properties in this process, and investigate their relationship. Together, we will build an integrated view of how uncharted physical properties of epithelia control stretching and patterning, in the context of a process that is key to the fertility of the ageing European population.

Link to the ERC project webpage: https://institut-curie.org/team/maitre

Keywords of the ERC project: morphogenesis, mammalian development, biophysical measurements

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101097801	**PASSAGE**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Maria Mota**
Host Institution:	Instituto De Medicina Molecular Joao Lobo Antunes - PRT

Plasmodium liver stage schizogony: high replication and genetic diversity

A world free of malaria is certainly a desirable goal. However, in spite of the significant incidence reduction achieved globally between 2000-2015, malaria still kills a child every minute. The limited understanding of Plasmodium's biology hampers the development of novel intervention strategies. Upon transmission by Anopheles mosquitos, Plasmodium parasites must reach the liver and infect hepatocytes. Inside a hepatocyte, each parasite replicates into thousands of new erythrocyte-infectious forms, which lead to disease. The parasite biomass generated during the liver stage (LS) of infection is directly associated with malaria severity, but how the parasite achieves such a high replication rate, and the consequences of that, remain utterly unexplored. Notably, Plasmodium replication is unusual. The parasite divides by schizogony, with divisions occurring without cytokinesis and it cannot salvage pyrimidines from the environment, relying solely on nucleotides synthesized de novo. Using a Plasmodium transgenic line specifically designed to study DNA replication throughout parasite development, I unveiled for the first time the temporal dynamics of DNA replication throughout parasite LS and show that Plasmodium's LS high replication rate is accompanied by DNA damage. Thus, I hypothesize that DNA damage accumulation during LS schizogony is a generator of genetic variability prior to intra-erythrocytic infection. By using a combination of molecular, cell biology and genetic approaches, I now propose to characterize the mechanisms, define the molecular players, and reveal the causes and consequences of such a high replication rate in the outcome of infection and progression of disease, by exposing the consequences for parasite genetic diversity and virulence. Connecting LS schizogony with parasite genetic diversity and virulence for the first time will be conceptually transformative, and will certainly provide valuable targets and tools for the combat against malaria.

Link to the ERC project webpage:

Keywords of the ERC project: Cell cycle, cell division and growth; Biology of pathogens; Plasmodium Replication; Schizogony; Parasite Genetic Diversity

Keywords that characterize the scientific profile of the potential visiting researcher/s: Motivated and highly enthusiastic about science

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Project ID:	Project Acronym:	Evaluation Panel:
101117931	**Chloro-Import**	**LS3** Cellular, Developmental and Regenerative Biology

Principal Investigator:	**Dr Michal Breker**
Host Institution:	The Hebrew University Of Jerusalem - ISR

Systematic mapping of the chloroplast protein import system

Protein import into a membrane-bound organelle in eukaryotes has been intensively studied, leading to the discovery of the central intracellular import machineries. Yet, this field has undergone a fundamental paradigm shift following recent discoveries of non-canonical import pathways in the mitochondria and ER. While the chloroplast is still thought to have but one import machinery (TIC/TOC), accumulating evidence indicate it, too, has non-canonical pathways. Technological constraints have so far barred the systematic search for alternative import pathways, as well as the exploration of central aspects relating to this import system: Are there additional import pathways other than the canonical chloroplast translocon apparatus? What ensures correct targeting of proteins in the highly crowded cytosol to the chloroplast? What mediates between quality control processes and protein import? In Chloro-Import, we will go beyond the state-of-the-art by implementing multipronged, genome-wide, unbiased approaches we developed or adopted to elucidate all the targeting pathways en route to the chloroplast in Chlamydomonas. Specifically, we will use advanced genome-wide screening to comprehensively elucidate chloroplast import pathways (Aim1); uncover the functional organization of import pathways using genetic-interaction profiling and protein-protein-interaction mapping (Aim2); and conduct an in-depth biochemical investigation of the function of unstudied/novel import factors (Aim3). To the best of our knowledge, this is the first-ever study of this scale in a photosynthetic eukaryote cell. The outcome will be a complete map of the chloroplast protein-import system (pathways, components, regulators) and a genetic platform for this system's in-depth characterization. It will further offer insight into basic questions in chloroplast functioning, and may also pave the way to the synthetic engineering of crops that are more efficient for projected climate changes.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
759880	**DAMOCLES**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Yacine Boulaftali**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Modelling brain aneurysm to elucidate the role of platelets

In the European Union, 15 million people have an unruptured intracranial aneurysm (IA) that may rupture one day and lead to subarachnoid haemorrhage (SAH). The IA rupture event is ominous and lingers as a clinical quandary. No safe and effective non-invasive therapies have, as of yet, been identified and implemented in clinical practice mainly because of a lack of knowledge of the underlying mechanisms. Increasing evidence points to inflammation as one of the leading factors in the pathogenesis of IA. Intrasaccular clot formation is a common feature of IA occurring unruptured and ruptured IA. In addition to forming clots, activated platelets support leukocyte recruitment. Interestingly, platelets also prevent local hemorrhage in inflammatory situations independently of their ability to form a platelet plug. We hypothesize that the role of platelet may evolve throughout the development of IA: initially playing a protective role of in the maintenance of vascular integrity in response to inflammation and contributing later to intrasaccular thrombus formation. What are the platelet signaling pathways and responses involved and to what extent do they contribute to the disease and the rupture event? To answer these questions, we designed an interdisciplinary proposal, which gathers biophysical, pharmacological, and in-vivo approaches, with the following objectives: I) To investigate platelet functions from patients diagnosed with intracranial aneurysm at the sites of aneurysm sac. II) To delineate platelet mechanisms and responses in a cutting-edge technology of a 3D reconstruction of IA that will take into account the hemodynamic shear stress. III) To test in a preclinical mouse model of IA efficient anti-platelet therapies and define a therapeutic window to intervene on platelet activation. The proposed project will yield new insights in IA disease and in life science, from cell biology to the discovery of potential new targets in cardiovascular medicine.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
819543	**metaboSENS**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Ganna Panasyuk**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Metabolic integration by nutrient SENSing

Nutrient sensing enables metabolic homeostasis by matching energy use with fuel availability. The vast body of knowledge on pro-anabolic nutrient sensors, such as insulin and class 1 phosphoinositol-3 kinase (PI3K) signalling exposed the missing links in molecular coordination of catabolism. The cellular catabolism relies on mitochondrial activities and on lysosomal pathway of autophagy, both paced by the biological clock. However, how pro-catabolic nutrient sensors synchronize these catabolic activities is not well understood. We discovered that class 3 PI3K, the only PI3K present in all eukaryotes, is essential for catabolic homeostasis in vivo, but the mechanisms of its metabolic functions are still lacking. We found novel roles for class 3 PI3K in metabolic adaptation to fasting and mitochondrial activity, beyond its established functions in autophagy and endosomal trafficking. These findings form the basis of our innovative interdisciplinary research program that will investigate the molecular bases of Metabolic integration in vivo by a nutrient SENSing pathway of class 3 PI3K (MetaboSENS). In the MetaboSENS research program, we seek to identify transcription factor networks and regulatory complexes of class 3 PI3K that serve its catabolic integrator function. We aim to reveal the physiological oscillation of class 3 PI3K signalling and its reciprocal impact on metabolic timekeeping. Finally, the MetaboSENS project will combine patient analyses and the medical expertise of my team to reveal, for the first time, genetic alterations in class 3 PI3K signalling in inborn metabolic disease. The new mechanisms that we discover may provide therapeutic targets that we will test in the pre-clinical models. Altogether, the MetaboSENS project will redefine our view of systemic catabolism.

Link to the ERC project webpage: www.panasyuklab.fr

Keywords of the ERC project: Nutrient sensing, metabolic homeostasis, transcriptional control of metabolism, circadian clock, PI3K class 3 signalling, lysosomal signaling and metabolism

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
850622	**MOLEC ANTI-ARRHYT**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Sara Liin**
Host Institution:	Linkopings Universitet - SWE

Resilience and Trigger Factors in Cardiac Arrhythmia: Risk Stratification and Drug Design

Up to 30% of individuals with inherited cardiac arrhythmias such as Long QT syndrome are not protected from sudden cardiac death despite state-of-the-art treatment. A major hurdle for effective risk stratification and treatment of inherited cardiac arrhythmias is the poor correlation between genetic variant and clinical manifestations. Affected individuals, who harbour the same arrhythmia-causative mutation, paradoxically display a spectrum of clinical phenotypes ranging from a lifelong asymptomatic state to sudden death in infancy. Up to 40% of genotype-positive individuals, depending on type of arrhythmia, do not display clinical manifestation. Based on our unpublished observations, I propose that an important, yet unexplored, underlying cause of the diverse clinical manifestations are endogenous resilience and trigger factors, which interact with mutated cardiac ion channels to alter arrhythmia severity. MOLEC ANTI-ARRHYT utilizes front-line experimental and computational approaches and the cardiac IKs potassium channel, which is strongly linked to lethal arrhythmias and sudden cardiac death, as a prototype. We aim to: (i) identify major classes of endogenous ligands with therapeutic (resilience factors) or pathological (trigger factors) effects on the IKs channel, (ii) provide proof of mechanism for how the effect of resilience and trigger factors is determined by arrhythmia-causative mutations in the IKs channel, (iii) utilize resilience mechanisms to develop a fundamentally novel concept of anti-arrhythmic drug development: Resilience-Mimetic Drug Development. The successful completion of this project will open up new avenues for personalized risk stratification and clinical management, which ultimately will improve the clinical outcome for individuals with inherited arrhythmias.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
852761	**ONco-Energetics_OFF**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Mohamed Elgendy**
Host Institution:	Technische Universitaet Dresden - DEU

Dissection of Bioenergetic Plasticity of Tumors

Tumors reprogram their metabolism to fuel rapid growth. Glycolysis and oxidative phosphorylation "OXPHOS" are the main energy-producing pathways. For decades, metabolic reprogramming of tumors was perceived as only increased glycolysis (Warburg effect). This dogma has recently been revised as we started to realize the importance of OXPHOS in tumor metabolism. We are now entering a new era as metabolomics studies show that tumor metabolism is more heterogeneous than initially assumed. In the preparatory phase of this proposal, using an integrated transcriptional and metabolic profiling, a panel of cancer cell lines was first classified according to the bioenergetic pathway they predominantly utilize (glycolysis or OXPHOS). Second, the response of glycolytic and OXPHOS-dependent cells to the inhibition of their wired bioenergetic program was assessed. My findings show that regardless of their dependency at baseline, cancer cells can be collectively categorized according to their adaptability into "bioenergetically-committed" to one of the two pathways or "bioenergetically-plastic" cells which are able to switch from one to the other upon metabolic challenges. This proposal uses an integrated system approach to dissect the molecular signature, regulation and implications of bioenergetic plasticity. We will answer three key questions: 1-Why some cancer cells are bioenergetically-plastic while others are committed? What are the differences in metabolic machineries and oncogenic switches between both? 2-How heterogeneous tumor cell subpopulations are in terms of bioenergetic plasticity? Does metabolic crosstalk contribute to bioenergetic plasticity of tumors? 3-What are the implications of bioenergetic plasticity in drug resistance and metastasis and finally how to design approaches to target this plasticity? Only handful drugs targeting tumor energetics have made it to clinical use. ONco-Energetics_OFF has a realistic and immediate translational potential.

Link to the ERC project webpage:

Keywords of the ERC project: cancer metabolism, metabolic plasticity, flexibility, drug resistance, metastasis

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
866240	**EXPLOSIA**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Jacob Bentzon**
Host Institution:	Aarhus Universitet - DNK

EXpansion and Phenotype Loss Of SMCs In Atherosclerosis: Causal effects and therapeutic possibilities

Atherosclerosis is considered an inflammatory disease caused by the accumulation, modification and immune cell recognition of low-density lipoproteins in the arterial wall. Plaque macrophages are held to be the main drivers of disease activity, whereas smooth muscle cells (SMCs) have traditionally been considered protective by forming fibrous tissue that stabilises plaques from undergoing rupture and causing thrombosis. In the present project, we challenge this dichotomous view of cellular villains and heroes in atherosclerosis. Using lineage tracking techniques in mice, we and others have uncovered a large population of SMCs in plaques, which has escaped detection because the cells completely lose conventional SMC phenotype. Strikingly, we have found that the entire plaque SMC population derives from only few founder SMCs that undergo massive clonal expansion and phenotypic modulation during lesion formation. We hypothesise that the balance between the different modulated SMC subtypes and the functions they carry are central to lesion progression. In EXPLOSIA we will address this hypothesis in 3 steps. First, we will conduct a comparative analysis of clonal structure in mice, minipigs, and humans. Second, we will determine links between SMC subtypes, their gene expression programs, and atherosclerotic disease activity by combining single-cell transcriptomics with novel techniques to alter atherosclerotic disease activity in gene-modified mice and minipigs. Third, we will develop techniques for manipulating genes in modulated plaque SMCs and test the causal role of perturbing SMC subtypes and function for lesion progression. The aim of the project is to answer the following key questions for a deeper understanding of atherosclerosis: - What is the clonal architecture of SMCs in human atherosclerosis? - What is the SMC gene expression signature of atherosclerotic disease activity? - Can interventions targeting SMCs prevent dangerous lesion development?

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101000948	**PROSPECTS**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Guillaume Canaud**
Host Institution:	Universite Paris Cite - FRA

PIK3CA-Related Overgrowth Syndrome, Pluripotency, Expression in speCific Tissue and Secretion

Overgrowth syndromes (OS) are rare genetic disorders that can be either localized or generalized. In most cases, the mutations are not inherited but occur during embryogenesis leading to somatic mosaicism. The genes involved in OS are not well characterized but most appear to be part of the PIK3CA/AKT/mTOR pathway, a major actor in cell growth and proliferation. Among the different genes, gain-of-function mutations of PIK3CA have a prominent role. Patients with PIK3CA gain of function mutation (PROS) usually have complex tissue malformations, including abnormal vessels, anarchic adipose tissue, muscle hypertrophy and/or bone deformation. Currently, there are no specific treatments for PROS patients. Patients mainly receive supportive care including debulking surgery, sclerotherapy and nutritional support. PROS often result in severe disabilities with deleterious social consequences and premature death. We recently generated a mouse model of PROS that, for the 1st time, recapitulates the patient phenotype, identified BYL719, a PIK3CA inhibitor undergoing development in oncology, as a potential therapeutic for PROS and demonstrated the efficacy of this drug in our mouse model (Venot et al, Nature 2018). Based on these very promising results, we were authorized to treat adults and children suffering from very severe forms of PROS. The clinical outcome is very promising. Now, in this project, we will decipher the physiopathology of PROS, identify biomarkers and new treatments. To this aim, we will combine in vitro and in vivo approaches using very innovative technologies and new mouse models of OS. Consistently with my previous works, we will extend our findings to Human through our unique PROS Biobank. The accomplishment of this project may lead to the discovery of novel therapeutic targets and strategies to slow down the progression of PROS. But, more importantly, based on the pleiotropic role by PI3KCA in cancer, our findings will open new perspectives in oncology.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101001355	**Behaviome**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Omry Koren**
Host Institution:	Bar Ilan University - ISR

Aggression and the Gut Microbiome

Aggression is one of the most important social behaviors in nature for procreation and survival. However, understanding the underlying pathways and networks leading to aggression remains a major challenge. Although there has been some progress deciphering genetic factors and neural mechanisms influencing aggression, the precise networks and environmental factors controlling aggression remain a mystery. In this proposal, we suggest the novel concept that host aggression may be regulated in part by the microbiota. We and others have recently linked the gut microbiota, the overall constellation of microorganisms residing within our gut, to behaviors such as risk taking, mating and sexual behavior, as well as hormone production, regulation, and secretion. Here, we aim to characterize the effects of antibiotics, germ-free animal models, and specific microbes on aggression in flies and mice. We further hypothesize that these processes are mediated by pheromones, bacterial and host gene products, and host brain hormones, and will therefore test the involvement of these factors. Considering the microbiota as a novel element regulating aggression is an audacious concept. However, we have demonstrated in a preliminary study that elimination of the gut microbiota significantly raises aggression levels in both D. melanogaster and in mice, thereby providing strong initial support for our hypothesis that the microbiota is involved in regulation of aggression. Outcomes of this research will lead to a better understanding of the effects of microbiota on behavior in model systems, and open new horizons in recognition of pathways linking microbiota, hormones and aggression

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101001814	**AngioUnrestUHD**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Rui Benedito**
Host Institution:	Fundacion Centro Nacional De Investigaciones Cardiovasculares Carlos Iii - ESP

Understanding and modulating vascular arrest with ultra-high definition

Therapeutic modulation of vascular cell proliferation and migration is essential for the effective inhibition of angiogenesis in cancer or its induction in cardiovascular disease. The current view is that an increase in growth factor levels or mitogenic stimulation is beneficial for angiogenesis, since it leads to an increase in both endothelial proliferation and sprouting. Through the use of innovative genetic and imaging approaches, we have recently elucidated a previously unappreciated, context-dependent mechanism whereby highly mitogenic environments can be detrimental for angiogenesis and lead to the cell-cycle arrest of endothelial cells (ECs), which ultimately impairs vascular growth. The identified mechanism may explain the failed or inefficient promotion of functional angiogenesis by vascular growth factor delivery therapies, such as those used to treat ischemic cardiovascular disease. We propose that a better understanding and modulation of the identified hypermitogenic arrest process may allow angiogenesis to be induced more effectively. Taking advantage of recent advances in DNA synthesis, CRISPR gene editing, microscopy and single-cell profiling technologies, we have developed new genetic tools, animal models and methods of broad relevance that enable the study of gene function with higher reliability, throughput and definition. We propose to use these novel research tools and methods to significantly increase understanding of the biology of blood vessels in distinct physiological and pathological contexts. We will then use this new knowledge to identify better strategies to promote vascular development in ischemic cardiovascular disease, heal vascular malformations, or inhibit angiogenesis in tumours.

Link to the ERC project webpage:

Keywords of the ERC project: Angiogenesis, Vascular Biology, cardiovascular regeneration

Keywords that characterize the scientific profile of the potential visiting researcher/s: Angiogenesis, Vascular Biology, cardiovascular regeneration

European Research Council
Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
101002927	**ProtMechanics-Live**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Jorge Alegre-Cebollada**
Host Institution:	Fundacion Centro Nacional De Investigaciones Cardiovasculares Carlos Iii - ESP

Uncovering Protein Mechanics in Physiology and Disease

Protein mechanics is a key contributor to the form and function of biological systems by mechanisms that are just starting to be unraveled. An ensuing hypothesis is that alteration of protein mechanics can trigger disease, particularly in mechanical conditions such as cardiomyopathies in which primordial underlying molecular mechanisms remain elusive. Although tempting, this possibility has not been tested due to the absence of methods that can modulate the mechanics of proteins in vivo. My proposal aims to overcome technical barriers to scientific progress by establishing manipulation of protein mechanics in living cells and animals as a new research field. In aim 1, we will address current technological limitations through the generation of genetic, protein-engineering-based mechanical loss- and gain-of-function models to interfere acutely and reversibly with protein mechanics in living systems (mLOF and mGOF, respectively). We will apply these first-of-their-kind tools to the giant protein titin, a major contributor to the force-generating and sensing properties of cardiomyocytes with strong links with heart disease, and a workhorse protein that has been instrumental in the past to understand the biophysics of polypeptides under force. In aim 2, we will exploit cellular mLOF and mGOF to define how perturbations of titin mechanics result in altered cardiomyocyte force generation, mechanosensing, mechanotransduction, differentiation and proliferation. Leveraging on our cell studies, in aim 3 we will use murine mLOF and mGOF to shed light into the contribution of titin mechanics to the onset and progression of genetic and acquired cardiomyopathy. ProtMechanics-Live builds on our unique expertise in protein mechanics and engineering, biophysics, biochemistry and cardiovascular biology to enable investigation of mechanical proteins in their functionally relevant, physiological context

Link to the ERC project webpage: https://www.cnic.es/en/investigacion/molecular-mechanics-cardiovascular-system

Keywords of the ERC project: titin, mechanobiology, heart, protein mechanics, cardiomyocyte

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101041737	**StemMemo**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Krzysztof Szade**
Host Institution:	Uniwersytet Jagiellonski - POL

What does your blood remember? The memory of hematopoietic stem cells.

Human organism produces over a million new blood cells each second. The hematopoietic system dynamically reacts to environmental stress and forms adaptive immunity to memorize and effectively fight the encounter pathogens. However, based on our recent studies and preliminary results, we propose that the adaptive capabilities and memory of the hematopoietic system reach far beyond the classical adaptive antigen-specific immunity. We hypothesize that hematopoietic stress induces clonal expansion of lineage-biased hematopoietic stem cells (HSCs) with epigenetic memory that faster and more effectively respond to secondary stimulation with a given stress factor. We propose that lineage-biased HSCs accumulating during aging provide a broad adaptive memory of the hematopoietic system, that is not restricted to immune cells, but includes all blood cell lineages. The aim of our proposal is to understand how the HSC-stored memory is created, maintained and recalled, and to clarify the underlying mechanisms. First, we will selectively stimulate granulopoiesis, erythropoiesis and thrombopoiesis to define the specificity and physiological role of hematopoietic memory provided by HSCs, both in vitro and in vivo. Second, we will use single-cell level fate mapping and sequencing to investigate clonal and epigenetic mechanisms driving the HSCs-based memory in mice. Third, we will test if aging pool of human HSCs consists of lineage-biased HSCs that store memory of the previously encountered stimuli. The humanized mice models will determine the clonal expansion of human HSCs upon primary and secondary stimulation with stress factors. Altogether, the expected outcome of the project is to understand how and why hematopoietic system adjusts to the environmental challenges upon aging. The proposed novel concept of the hematopoietic system adaptivity may help to design strategies to train patients' hematopoiesis and improve the transplantations of HSCs.

Link to the ERC project webpage: https://www.nicheworks.eu/hscs-and-leukemia

Keywords of the ERC project: hematopoiesis, stem cells, hematopoietic stem cells, clonal tracing, single cell genomics,

Keywords that characterize the scientific profile of the potential visiting researcher/s: stem cell biology, bioinformatics, next generation sequencing, single cell data analysis, genomics

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Project ID:	Project Acronym:	Evaluation Panel:
101042738	**OralNiche**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator: **Dr Kai Kretzschmar**

Host Institution: Universitaetsklinikum Wuerzburg - Klinikum Der Bayerischen Julius-Maximilians-Universitat - DEU

Dissecting the impact of epithelial stem cell niches on oral cancer heterogeneity

The oral epithelium is a unique tissue with a high degree of structural heterogeneity and distinct microenvironments (niches). However, the molecular mechanisms underlying the site-specific proliferation and differentiation of oral epithelial stem cells (OESCs) remain poorly understood. Oral squamous cell carcinoma (OSCC), one of the most common oral cancers, is a heterogeneous cancer type. Occurrences of metastatic lesions and treatment response differ from oral site to site, indicating a causal link to the heterogeneous nature of distinct OESC pools. In the OralNiche project, we will for the first time systematically and comprehensively characterise the OESC pools, dissect key mechanisms underlying oral epithelial site-specificity and define their contribution to OSCC heterogeneity. To achieve this, we will combine novel mouse models and patient material with cutting-edge methodology, including whole mount imaging, single-cell sequencing and organoids. Initially, we will profile the proliferative activities of OESCs and explore how stemness is regulated within defined niches in homeostasis, OSCC and chemotherapy-induced mucositis. Subsequently, we will functionally assess cellular cues that modulate stemness in the oral epithelia to generate a comprehensive single-cell atlas of OESCs and their cellular niches. Lastly, using OSCC patient material, we will validate key observations to define potential new biomarkers and therapeutic targets. In summary, this multidisciplinary approach will reveal how the distinct OESC pools maintain homeostasis, and how they respond to challenges, such as mucositis and OSCC. OralNiche will deliver new knowledge on the impact of tissue site-specificity on tumour heterogeneity and therapy response, which will have significant implications for OSCC patients. Moreover, the knowledge gained and the technological advances proposed will be applicable to other tissues and tumour types and thus provide a model approach in cancer research.

Link to the ERC project webpage: https://www.med.uni-wuerzburg.de/msnz/research-projects/junior-research-groups/kretzschmar-group/

Keywords of the ERC project: oral mucosa, oral cancer, tissue stem cells, lineage tracing, organoids, single-cell sequencing

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics, image analysis, biophysics, oral microbiome

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Project ID:	Project Acronym:	Evaluation Panel:
101045257	**CancAHR**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Christiane Opitz**
Host Institution:	Deutsches Krebsforschungszentrum Heidelberg - DEU

Understanding the complex biology of AHR activation in cancer

The aryl hydrocarbon receptor (AHR) is a critical regulator of tumor progression by modulating both tumor cell intrinsic malignant properties as well as anti-tumor immunity. However, depending on the context, the AHR can exert either tumor-promoting or tumor-suppressive effects, thus limiting its potential as a drug target. To exploit the AHR for cancer therapy a comprehensive understanding of its activation and biological outcomes is necessary. The opposing effects of the AHR in cancer likely stem from the complexity of its activation and biological functions, which are cell type-, ligand-, and context-specific. Moreover, recent results from our laboratory suggest that nutritional stress conditions also affect AHR activity. The detection of AHR activation in tissues mainly relies on the quantitation of AHR target gene expression. However, until recently, the context specificity of AHR target gene expression had impeded systematic investigation of AHR activity across human cancers. Our team has developed a pan-tissue AHR signature that detects AHR activity irrespective of cell type or ligand, and enables the analysis of the biological functions mediated through AHR activation. The combination of the AHR signature with iterative cycles of computational biology analyses and laboratory experimentation puts us in a unique position to investigate AHR activation and its downstream effects. CancAHR will hence systematically delineate how the AHR is activated in cancer, why AHR activation is cell type-specific, and which AHR downstream mediators drive clinical outcomes. The identification of the molecular mechanisms underlying the diverse outcomes of AHR activation in cancer will enable (i) the identification of patients, in which AHR activation contributes to clinical outcome; (ii) the development of clinical interventions tailored to the specific mechanisms of AHR activation; and (iii) stratification of patients to precision therapies modulating AHR activity.

Link to the ERC project webpage:

Keywords of the ERC project: bioinformatics, immune oncology, metabolism, aryl hydrocarbon receptor, cancer

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics, data science or metabolomics expertise

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101076407	**ENDOMET-STEER**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Jeffrey Kroon**
Host Institution:	Academisch Medisch Centrum Bij De Universiteit Van Amsterdam - NLD

Endothelial metabolism dictates the bone marrow niche and the plaque microenvironment

Inflammation is an important driver of atherosclerosis, the primary cause of global morbidity and mortality in emerging and developed countries. New strategies to reduce atherosclerotic cardiovascular disease (CVD) risk are therefore eagerly needed. I recently found that atherogenic inflammatory stimuli rewire cellular metabolism in endothelial cells (ECs) and thereby contribute to atherosclerosis progression. Defining the intricate link between EC inflammation, metabolic rewiring and functional consequences for the vasculature will open new avenues for therapeutic strategies in CVD. My recent work shows that CVD-associated metabolic changes in ECs can affect their secretome. In turn, the endothelial secretome disrupts both stem cell function in the bone marrow niche and macrophage activation in the plaque microenvironment, two highly vascularized tissue compartments that drive atherosclerosis progression. Based on these findings, I hypothesize that CVD-associated EC metabolic changes impact the micromilieu in both tissue compartments, propagating the proinflammatory state in CVD patients. With this ERC project I aim to define (1) how EC metabolism is affected in atherosclerosis, (2, 3) what the impact of altered EC metabolism is for stem cell function in the bone marrow niche and for macrophage activation in the plaque, and ultimately (4) to define how interventions in EC metabolism improve tissue function and halt CVD development. I will apply innovative 3D organ-on-chip models that accurately reflects the human bone marrow and plaque microenvironment. By combining this with a unique collection of human ex-vivo atherosclerotic plaques, human bone marrow cells and novel transgenic in-vivo models, I will generate essential new insights that help to understand the development of atherosclerotic CVD. Hereby, this ERC will yield important insights that the field urgently awaits to develop novel therapeutic strategies for the reduction of the burden of CVD.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101076407

Keywords of the ERC project: atherosclerosis, endothelium, inflammation, metabolism, bone marrow, macrophages

Keywords that characterize the scientific profile of the potential visiting researcher/s: interest in cellular crosstalk, bio-informatics, wet-lab

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101076506	**ONCO-COMP**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Alexandra Avgustinova**
Host Institution:	Fundacio Privada Per A La Recerca I La Docencia Sant Joan De Deu - ESP

Oncogenic competence during development – When, Where and Why?

Childhood cancers are believed to be rooted in aberrant development, a notion supported by their (i) generally low mutational burden, (ii) high prevalence of single (often epigenetic) driver events and (iii) occurrence during confined developmental periods. Yet, the exact origins of developmental tumours remain one of the principal enigmas of pediatric oncology. A prime example are malignant rhabdoid tumours (MRTs): they are astoundingly genomically simple but extremely deadly childhood cancers that arise almost exclusively in the first two years of life, and are driven by biallelic inactivation of the SWI/SNF chromatin remodelling complex subunit SMARCB1 (>95% of cases). We still do not know what determines oncogenic competence upon SMARCB1 loss. In particular we wonder: (1) What are the cell(s)-of-origin of rhabdoid tumours and what is their normal differentiation potential? (2) What is the molecular framework that facilitates oncogenic transformation upon SMARCB1 loss? (3) What is the contribution of the niche (local and systemic) to the acquisition of oncogenic competence? And, considering the epigenetic nature of the oncogenic event, (4) is the oncogenic MRT state reversible, and how? To answer these questions, we will combine state-of-the-art lineage-barcoded single-cell genomics, spatial transcriptomics, single-cell resolution wholemount imaging, CRISPR/Cas9 and epigenomic approaches, as well as integrative computational analyses, using transgenic mouse, induced pluripotent stem cell and patient-derived xenograft rhabdoid tumour models. This project will provide fundamental insights into the cell autonomous and non-autonomous determinants of oncogenic competence upon SMARCB1 loss. Based on our findings we hope to unlock targeted treatments for MRT patients. Importantly, the conceptual and experimental framework we establish will open up new investigative opportunities for a multitude of developmental cancers.

Link to the ERC project webpage:

Keywords of the ERC project: Chidlhood cancer; Epigenomics; Lineage tracing; Single-cell genomics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101077374	**SynaptoMitophagy**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Konstantinos Palikaras**
Host Institution:	Ethniko Kai Kapodistriako Panepistimio Athinon - GRC

Decoding mitochondrial selective autophagy in synaptic homeostasis during ageing

Age-dependent accumulation of damaged mitochondria and synaptic loss represent early pathological hallmarks of brain ageing leading to neuronal death. Mitochondria-selective autophagy (mitophagy) is triggered to eliminate defective organelles promoting cellular and organismal survival. Mitophagy declines with age, while its induction extends lifespan and confers neuroprotection across diverse species. Although the pivotal role of mitophagy in neuronal physiology is steadily emerging, its contribution to synaptic homeostasis remains elusive. Building on our previous pioneering studies, SynaptoMitophagy aims to reveal the molecular underpinnings of age-dependent synaptic impairment, focusing on mitochondrial maintenance and turnover. We will combine the nematode Caenorhabditis elegans, which offers a well-defined nervous system, with cutting-edge technologies, such as super resolution imaging, microfluidics and optogenetics, to manipulate spatiotemporally mitochondrial damage and monitor synaptic mitophagy at nanoscale resolution, in vivo. Mammalian neurons will be used to address the functional conservation of synaptic mitophagy components. The objectives are four-fold: 1) Establish mitophagy reporters for in vivo monitoring of mitochondrial fate at synapses during ageing and under neuroprotective conditions 2) Use optogenetic tools to stimulate synapse-restricted mitochondrial damage and, thereby, to detect mitophagy induction and its contribution to neurotransmission. 3) Characterize the synaptic defects and assess behavioral deficits arising from mitophagy impairment. 4) Conduct forward genetic screen for synaptic mitophagy modulators, towards augmenting mitochondrial quality control and resistance to age-related synaptic failure. The cumulative results of this proposal will decode the molecular mechanisms of neuronal mitophagy compartmentalization at synapses during ageing, providing critical insights with broad relevance to human health and quality of life.

Link to the ERC project webpage:

Keywords of the ERC project: ageing, autophagy, mitochondria, mitophagy, neurons, neurodegeneration, synapses

Keywords that characterize the scientific profile of the potential visiting researcher/s: ageing, autophagy, mitophagy, organelle biology, neuroscience, muscle biology, calcium homeostasis, physiology

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101078188	**AquaAgeRate**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Itamar Harel**
Host Institution:	The Hebrew University Of Jerusalem - ISR

Genetic Design of Biological Time in Fish

Every species experiences a unique pace-of-life, which determines the duration of its embryonic development, onset of puberty, and rate of aging. However, how these traits are scaled so differently between species is largely unknown. Here, I propose to develop the tools to systematically study how the pace of life is regulated in vertebrates. To date, progress in our understanding has been experimentally hindered by the relatively long lifespans of classical vertebrate models. To address this challenge, I recently pioneered a genetic platform for rapid exploration of aging in the naturally short-lived turquoise killifish. Killifish species display up to 10-fold differences in their lifespan, thus providing a "microcosm" of extreme life-history adaptations. Here, we will significantly advance the state of the art by transforming selected species into genetic models. Specifically, we will use unbiased chemical screens to explore the molecular switch that allows killifish development to be suspended for years, in a process called diapause. We will then use our findings to establish genetic control of diapause and the aging processes that co-evolved in this clade. Interrogation of the transcriptional networks in play will be made possible by developing a CRISPR screen platform for fish cells. Finally, we will explore the co-regulation of rapid puberty and compressed lifespan in killifish, by developing multiplexed and reversible genetic approaches. Aging is the primary risk factor for many human pathologies. Thus, developing a quantitative and mechanistic understanding of the pace of life could revolutionize the way we manipulate aging, treat related diseases, and even control complex traits. Identifying such new principles will also have a broader impact, such as affecting developmental rates in in-vitro fertilization. Furthermore, providing precision genome editing tools for fish, and accelerating the generation time will greatly impact commercial aquaculture.

Link to the ERC project webpage:

Keywords of the ERC project: Vertebrate aging, age-related diseases, reproduction, genetics

Keywords that characterize the scientific profile of the potential visiting researcher/s: computational, fish, genome editing

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101078307	**KetoCardio**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Gabriele Schiattarella**
Host Institution:	Charite - Universitaetsmedizin Berlin - DEU

Linking Ketone Metabolism and Signaling in Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF) is a burgeoning public health problem for which there are little to no evidence-based therapies. This syndrome has proven particularly challenging because of the limited insight into its underlying molecular mechanisms. Metabolic adaptations are critical for cardiomyocyte response to stress. Ketones are metabolites actively produced in heart failure and their role as metabolic rheostat capable of modulating cardiac metabolism and cardiomyocyte signaling pathways has been postulated. However, there is fundamental, open gap in understanding how ketones are utilized as source of energy in HFpEF and how β-hydroxybutyrate (β-OHB) – the most abundant ketone – plays a role as non-energy carrier governing cardiomyocyte function. In this project proposal, I hypothesize that ketones are major regulators of cardiomyocyte biology representing an alternative source of fuel in HFpEF ("energy" role) and act as protein modifiers trough β-hydroxybutyrylation – a lysine-based post-translational modification (PTM) – thereby regulating chromatin architecture, gene transcription and metabolic signaling in cardiomyocytes ("non-energy" role). The overall aim of KetoCardio is to define mechanisms integrating ketone metabolic adaptation with signaling pathways and epigenetic changes in HFpEF-stressed cardiomyocyte. Coupling proteomics, transcriptomics and genomics approaches together with cardiac and systemic metabolic evaluation and rigorous preclinical experimental modeling of HFpEF, I will be able to define the previously unrecognized role(s) of ketones as energy substrates in HFpEF and as substrate for proteins PTM impacting on cardiomyocyte function. In summary, focusing on metabolic pathways that govern cardiomyocyte abnormalities in preclinical HFpEF, this project will provide a transformative molecular understanding of ketones biology in cardiomyocyte fostering innovation in the field and beyond.

Link to the ERC project webpage:

Keywords of the ERC project: heart, metabolism

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101086997	**GRACE**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Henriette Uhlenhaut**
Host Institution:	Technische Universitaet Muenchen - DEU

The Glucocorticoid Receptor in Aging and Circadian Endocrinology

The pandemic is stressful for many. In response to stress, glucocorticoids are released. They play essential roles as endogenous hormones and clinically as drugs. High levels are associated with cardiometabolic disorders and with aging. In contrast, diets like caloric restriction ameliorate metabolic dysfunction and prolong lifespan. These diets, however, also increase glucocorticoids. Now the open question is: What are the molecular and physiological effects of increased hormone levels, and are these diets beneficial because or in spite of elevated glucocorticoids? We recently found that nutrition reprograms glucocorticoid responses independently of the hormone level and that diurnal glucocorticoid action controls rhythmic gene expression to regulate circulating glucose and triglycerides during day and night. I hypothesize that the benefits of caloric restriction are due to higher glucocorticoid amplitudes, and that their study will uncover transcriptional features prolonging healthspan. I propose to functionally distinguish between diet-induced positive and stress-induced negative glucocorticoid responses. GRACE will identify diet-specific, 'rejuvenating' transcriptional complexes and target genes, versus detrimental pathways triggered by excess glucocorticoids such as stress. Glucocorticoid receptor targets unique to caloric restriction will be determined via ChIP- and RNA-seq in Aim 1. The functional impact of diurnal glucocorticoid release will be dissected with a constitutively active receptor allele in Aim 2. I propose to map active transcriptional regulomes in caloric restriction, in youth and old age, by ChIP-MS in Aim 3. I postulate that enhanced glucocorticoid activity at the right time of day may boost circadian rhythms and promote longevity. Ultimately, applying omics to study the molecular mechanisms of stress hormones will identify pathways and genes amenable to pharmacological or nutritional intervention for longer, healthier lives.

Link to the ERC project webpage: https://www.mls.ls.tum.de/metabolism/home/

Keywords of the ERC project: caloric restriction, circadian clock, liver metabolism, glucocorticoids

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101088636	**HEAT-UP**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Zachary Gerhart-Hines**
Host Institution:	Kobenhavns Universitet - DNK

Harnessing an energy-expending, appetite-suppressing fat-brain axis to unlock novel pharmacotherapies

Obesity and cardiometabolic diseases are global crises that threaten to cripple healthcare infrastructures. These disorders originate from an excess calorie burden caused by consuming too much food and expending too little energy. Yet despite recent advances in obesity drugs, weight-lowering pharmacotherapies only reach about half the efficacy of surgical interventions. This difference could be due to existing drugs only acting to reduce food intake and not boost calorie-burning. Therefore, I believe our discovery of a leptin-independent signaling axis between adipose tissue (AT) and the central nervous system (CNS) that both decreases food intake and increases energy expenditure poses a breakthrough in obesity research. We uncovered this axis through receptor profiling and human genetic association studies and engineered a highly selective agonist that significantly decreases bodyweight and improves glucose and lipid homeostasis in obese mice. Our preliminary data have already led to a spinout company. However, the physiological signaling mechanisms of this receptor in AT and the CNS that shape systemic energy balance through peripheral calorie-burning and central control of food intake remain unknown. Thus, in HEAT-UP, we will delineate AT and CNS receptor circuits with single cell resolution and functionally test this signaling in 3D cultures of mouse and human AT. Tissue-specific contributions to whole-body metabolism will be assessed by combining our proprietary, selective agonist with state-of-the-art viral, genetic, and surgical manipulation of the receptor and neuronal wiring in AT and the CNS. Viral and genetic cell-labeling strategies will be used to characterize novel secretory cells that we found in mouse and human AT to contain the ligand for this receptor. Collectively, these studies will provide a comprehensive, physiological overview of a previously unknown fat-brain signaling axis and insight into its potential for counteracting metabolic diseases.

Link to the ERC project webpage:

Keywords of the ERC project: energy expenditure, appetite control, weight loss, obesity, diabetes, adipose tissue, CNS

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101096948	**SENATR**	**LS4** Physiology in Health, Disease and Ageing

Principal Investigator:	**Dr Martin Eilers**
Host Institution:	Julius-Maximilians-Universitat Wurzburg - DEU

Sensing Aberrant Transcription by MYC Multimers

Deregulated expression of MYC or one of its paralogues, MYCN and MYCL, maintains the growth of most human tumors. All current models explain the oncogenic potential of MYC proteins by their ability to form complexes with MAX that universally bind to active promoters and the ability of these complexes to induce a tumor-specific gene expression pattern. While MYC conforms to this model during unperturbed cell growth, we have discovered two paradigmatic situations in which MYC proteins undergo fundamental changes in their biochemical state, association with MAX and localization on chromatin: In response to pharmacological or physical disruption of transcription elongation, MYC moves away from active promoters to form large, spherical multimers that surround stalled replication forks. These multimers contain transcription termination factors and form a zone that shields stalled forks from RNA polymerase. Second, MYCN forms high molecular weight complexes during the S phase of the cell cycle that do not contain MAX and, like MYC multimers, contain termination factors. Their assembly depends on RNA that is normally degraded by the nuclear exosome, arguing that they too form in response to aberrant transcription. The switch between heterodimeric and multimeric states depends on non-proteolytic ubiquitylation of MYC, which alters protein-protein interactions that retain MYC at promoters. Our data show that MYC proteins exist in a hitherto unknown dynamic equilibrium between globally promoter-bound heterodimers and multimers that form locally in response to perturbed transcription. We aim to show that these dynamics enable tumor cells to cope with stress arising from deregulated transcription and are crucial for MYC´s oncogenic function. We expect that inhibiting MYC multimerization will maintain normal growth but block the ability of tumour cells to cope with deregulated transcription and is therefore a valid therapeutic strategy for targeting oncogenic functions of MYC

Link to the ERC project webpage:

Keywords of the ERC project: Tumor Biology; MYC; Immune Evasion; RNA; Phase Transition

Keywords that characterize the scientific profile of the potential visiting researcher/s: Protein Chemistry and Structural Biology;

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Project ID:	Project Acronym:	Evaluation Panel:
865592	**GliomaSignals**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Gilles Huberfeld**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Oncometabolitic control of tumor growth and epileptogenesis in IDH mutated gliomas: D2HG signaling mechanism.

Dysregulated growth processes of gliomas interact with pro-epileptic plasticity of brain circuits in such a way that the excitatory transmitter glutamate promotes autocrine tumor invasion as well as epileptic synchrony in surrounding cortical regions. Most low-grade gliomas are associated with mutations of Isocitrate DesHydrogenase (IDH) genes which lead to an excess of the oncometabolite D-2-Hydroxyglutarate (D2HG). With a structure mimicking glutamate, D2HG is thought to participate in both epileptogenic and oncologic processes. Importantly, while epileptic activity is accentuated, tumor prognosis is improved in affected people. My preliminary data now suggest a dual function for D2HG, acting as a glutamatergic agonist at high levels, but as an antagonist in the presence of glutamate. Solving this paradox will be a step forward in glioma science. The GliomasSignals project will examine the role of D2HG in the neurobiology of gliomas bringing electrophysiology concepts and tools to neuro-oncology, seeking to transform our understanding. It seeks to better understand how D2HG modulates glutamatergic signaling, affects neuronal excitability and tumor growth, and to detect the extent to which tumor infiltration colocalizes with epileptic remodeling. In vivo and in vitro work mostly on human tissue will aim at: 1- Map biomarkers of epileptic activity / tumor infiltration by cortical recordings during surgery using unique next generation Neurogrid electrodes. 2- Correlate D2HG levels, glutamate concentrations and tumor infiltration with recordings in peritumoral cortex at an unprecedented resolution. 3- Identify D2HG effects on glutamate signaling in human tissue slices producing epileptic activities and in a rodent model. 4- Explore D2HG long-term effects on epileptic activity and tumor growth / infiltration in co-cultures of tumors with surrounding peritumoral cortex by exploiting our unique capabilities for long-term human cortex organotypic cultures.

Link to the ERC project webpage:

Keywords of the ERC project: Glioma, ECOG, epilepsy

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
865634	**PreSynPlast**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Stefan Hallermann**
Host Institution:	Universitaet Leipzig - DEU

Molecular mechanisms of presynaptic plasticity

The ambitious goal of this project is to reveal the molecular mechanisms of presynaptic plasticity in the vertebrate brain. Synaptic plasticity occurs in the form of alterations in both presynaptic neurotransmitter release and postsynaptic receptor function. However, due to technical reasons and in contrast to intensely studied postsynaptic plasticity, the presynaptic half of the brain's synaptic plasticity remains enigmatic. This is a crucial knowledge gap for our understanding of learning and memory. My ambitious aim is therefore to uncover the molecular and biophysical mechanisms of presynaptic plasticity. Building on my strong track record in presynaptic research, my group made a technical breakthrough by establishing patch-clamp recordings from small nerve terminals of cultured neocortical neurons with unprecedented high resolution. In addition, we use an innovative super-resolution-microscopy approach resolving the rearrangement of proteins within the presynaptic neurotransmitter release site, which allows high-throughput screening of all major classes of synaptic genes for their involvement in presynaptic plasticity. To reveal the neuron- and plasticity-type specificity, the identified molecular pathways will be analysed in different types of neurons in culture and acute brain slices. Building on these unique abilities, I will also investigate physiological and pathophysiological modulations of presynaptic plasticity. Specifically, I will test the hypothesis that metabolic constraints regulate presynaptic plasticity and that the amyloid pathology of Alzheimer's disease impacts presynaptic plasticity.

Thus, for the first time in the history of neuroscience, neocortical nerve terminals can be investigated with direct electrophysiological recordings and super-resolution microscopy providing unprecedented spatial and temporal resolution for the analysis of presynaptic plasticity. The results could pave the way for new approaches treating neurological diseases.

Link to the ERC project webpage: https://physiologie.medizin.uni-leipzig.de/?en,id73

Keywords of the ERC project: LTP, metabolism, presynaptic

Keywords that characterize the scientific profile of the potential visiting researcher/s: Electrophysiology, metabolism, imaging, field potentials

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Project ID:	Project Acronym:	Evaluation Panel:
884281	**SynapseBuild**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Volker Haucke**
Host Institution:	Forschungsverbund Berlin Ev - DEU

Mechanisms of Presynaptic Biogenesis and Dynamic Remodeling

Our ability to move, to process sensory information or to form, store and retrieve memories crucially depends on the function of neuronal synapses. Synapses comprise a presynaptic compartment harboring the machinery for neurotransmitter release and an associated postsynaptic compartment that processes the neurotransmitter signal. During decades of research we have acquired a wealth of knowledge regarding the mechanisms of neurotransmitter release and information processing in the postsynaptic compartment. In great contrast, we know surprisingly little about the pathways that direct the formation, transport, and assembly of the complex molecular machines that make up a functional presynapse. In particular, it is unclear where and how synaptic vesicle (SV) precursors are formed in the neuronal cell body, in which form they are transported along the axon, and which maturation steps occur to allow their assembly into functional units for neurotransmitter release. How cytoplasmically synthesized presynaptic active zone (AZ) proteins that organize SV release sites are transported and assembled is equally unclear. Here, we combine genome engineering in stem cell-derived neurons and genetically altered mice with proteomic, high-resolution imaging and systems biology approaches to identify the origin and composition of SV and AZ precursors, dissect the mechanisms of their axonal transport and integration into developing synapses and unravel the pathway that controls axonal transport and presynaptic assembly of newly made SV and AZ proteins to set synaptic weight. Our high risk/ high gain studies will yield groundbreaking insights into the mechanisms that mediate the formation, maintenance, and dynamic remodeling of the presynaptic compartment during development and thereby fill a crucial knowledge gap in neuroscience. Furthermore, they may pave the way for the future development of therapeutics to cure nerve injury or neurological disorders linked to synapse dysfunction.

Link to the ERC project webpage: www.leibniz-fmp.de/haucke

Keywords of the ERC project: Synapse formation/ biogenesis; stem cell derived human neurons; proteomics; local translation; synaptic weight; active zone; synaptic vesicles; axonal transport; neurological disease

Keywords that characterize the scientific profile of the potential visiting researcher/s: live imaging; electron microscopy; stem cells; organdies; electron microscopy; proteomics; synapse function; neuronal development

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Project ID:	Project Acronym:	Evaluation Panel:
949838	**reptiCode**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Mark Shein-Idelson**
Host Institution:	Tel Aviv University - ISR

The Evolution and Function of Ancestral Brain States

One of the oldest enigmas in neuroscience is the function of brain states. During these states, dramatic transitions occur in the firing patterns of neurons in the cerebral cortex. These transitions are correlated with behaviour during wakefulness but, strikingly, are even more prominent during sleep, when interaction with the environment is limited. The similarities between sleep and awake patterns remains unexplained, thus complicating our understanding of the global function of brain states. Additionally, state transitions are prominent in both the cortex and hippocampus, but the interplay between these areas during different states remains ambiguous. Why is the function of brain states so elusive? A likely explanation is that state transitions are inextricably intertwined with many other processes, rendering their dissection difficult. This project is motivated by the notion that to understand brain states we need to: a) examine them in a simpler model system, b) understand how they evolved, c) identify which state properties are fundamental and which are species specific. I suggest that studying brain states in the cerebral cortex of reptiles offers a unique opportunity for achieving all three goals. We will utilize the simpler and highly structured state organization in Pogona Vitticeps, to expose the full repertoire of brain states in a naturally behaving animal. We will take advantage of the limited diversity of motor movements in Pogona, to expose the link between population patterns and defined behaviors. We will furthermore exploit the unique evolutionary positions of reptiles as closest to stem amniotes, in which the layered cortex and hippocampus first emerged, to reveal the forces that pushed the emergence of brain states in evolution. Finally, through a comparative analysis of brain state properties between different lizards and mammals we will extract the fundamental properties and functions of brain states and the network that supports them.

Link to the ERC project webpage: https://www.evolutionaryneuralcodinglab.sites.tau.ac.il/

Keywords of the ERC project: reptiles, amphibians, evolution, neurophysiology, visual processing, sleep, behavior, neural coding

Keywords that characterize the scientific profile of the potential visiting researcher/s: reptiles, amphibians, computation, signal processing, coding, neural networks

European Research Council
Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
950328	**FLEXPEPNET**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Isabel Beets**
Host Institution:	Katholieke Universiteit Leuven - BEL

Nervous system reprogramming by flexible neuropeptidergic networks

Animal brains are wired according to a series of remarkable genetic programs that have evolved over millions of years. Much of our behavior, however, is the product of experiences that happen to us on much shorter time scales. The ability of the nervous system to properly respond to aversive stimuli is crucial for animal well-being and survival. In many vertebrate sensory systems, persistent stimuli are coded by tonically active neural circuits. As opposed to phasic sensors that adapt rapidly, tonic neurons reliably convey stimulus intensity over long time periods and are essential for cues that need to hold attention, e.g. harmful stimuli. How persistent aversive stimuli are molecularly encoded and reprogram behavior remains elusive. My working hypothesis is that aversive challenge recruits a network of neuropeptide signaling pathways that is sculpted by experience and mediates diverse acute and long-lasting behavioral responses. I will test this hypothesis on the small and well-described oxygen-sensing circuit of C. elegans. Because neuropeptidergic networks are notoriously complex, such a highly controlled context for pioneering research on their involvement in tonic aversive signaling is preferable. First, my team will develop a tool for the in vivo reporting of neuropeptide GPCR activation, establishing SPARK for the first time in a living animal, which will allow conceptual advancements with unprecedented detail. Pertinent questions I will then address include: 'How do cellular networks respond to changes in neuropeptidergic network activities in a tonically signaling context?'; 'What are behavioral implications of neuropeptidergic network activity upon aversive challenge?'; and 'Do neuropeptidergic networks contribute to cross-modality?' I expect that on the long term, this project will impact our understanding of how tonic circuits influence and organize habituation, learning, forgetting and modus operandi of nervous systems in general.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101002704	**Emactive**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Luca Bonini**
Host Institution:	Universita Degli Studi Di Parma - ITA

The interactive side of emotion: A neuroethological approach in freely-moving monkeys

A general principle of brain functioning is the exploitation of neural substrates for self-related processes, such as action planning, decision-making and space coding, to map those of others. Indirect evidence indicates that similar agent-based coding may characterize emotion as well. How does the primate brain represent emotional displays (EDs) of self and others from the single-neuron to the network level? EMACTIVE will leverage state-of-the-art wireless recording technologies developed during my previous ERC StG to crack the code of agent-based representation of EDs. I will first record single-neuron activity from the anterior cingulate cortex (ACC) (WP1) and amygdala (WP2) alongside physiological data of freely moving pairs of macaques, aiming to identify self- (ST) and other-type (OT) neurons encoding EDs: I hypothesize that an animal's ST neurons drive its Eds, which in turn trigger OT neurons of the partner, facilitating behavioural coordination. By means of neural decoding approaches, chemogenetic inactivation and wireless intracortical microstimulation, I will assess the causal role of each region in the control of specific EDs during interactive situations. Next (WP3), neuronal tracers will be injected in the amygdalar and ACC territories hosting ST and OT neurons, providing the connectional fingerprint of agent-based representation of EDs. Finally, in WP4 we will record neuronal activity simultaneously from multiple regions anatomically connected with the ACC and amygdala (capitalizing on findings from WP3) in two additional pairs of freely interacting monkeys (multiareal hyperscanning), thereby revealing the neural and contextual factors affecting interbrain synchrony and its role in behavioural coordination. EMACTIVE will reveal the single-cell and network mechanisms underlying EDs of self and others during social interactions, thought to be altered in several poorly understood neuropsychiatric diseases, such as anxiety disorders and autism.

Link to the ERC project webpage: https://www.boninilab.unipr.it/en/projects/ongoing-projects/emactive/254/

Keywords of the ERC project: Freely-behaving monkeys; social interaction; multielectrode recordings; emotional displays; neuroethology

Keywords that characterize the scientific profile of the potential visiting researcher/s: Computational skills; motivation; creativity; behavioural analysis

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Project ID:	Project Acronym:	Evaluation Panel:
101003187	**VALENCE**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Ana João Rodrigues**
Host Institution:	Universidade Do Minho - PRT

Challenging current models of valence encoding in the mammalian brain

In an ever-changing environment, organisms evolved to filter information and focus on stimuli that are associated with relevant outcomes. Even the simplest animals assign valence to otherwise neutral stimuli in order to survive. A positive (rewarding) valence stimulus elicits approach, whereas a negative (aversive) valence stimulus supports avoidance behaviors. Decades of research revealed that some regions of the limbic system encode valence, including the nucleus accumbens (NAc), which is considered a prime candidate to interface valence and behavior. The NAc is mostly composed of GABAergic medium spiny neurons (MSNs), divided into those expressing dopamine receptor D1 and dynorphin, and those expressing D2 and enkephalin. D1 and D2 neurons were assumed to encode opposing valence, but recent data by us and others revealed this model to be overly simplistic. That is - to date, it is still not known how valence is encoded in this region. The main goal of this project is to determine how NAc neurons encode valence. Based on preliminary data, we hypothesize that valence is encoded by distinct patterns of MSN activity. These patterns differentially signal via GABA and opioids (dynorphin, enkephalin), triggering rewarding/aversive behaviors. To test this hypothesis, we will record neuronal activity of rodents performing tasks with opposing valences, in combination with time- and spatially-resolved analysis of opioidergic transmission, using newly-developed opioid fluorescent sensors. This information will then be used to mimic/block patterns of MSN activity and opioid events in order to show causality. This cutting-edge approach will unravel with unparalleled accuracy how NAc encodes valence, the role of endogenous opioids, and how these signals are decoded in the circuit to drive behavior. VALENCE is a frontier opening project that will answer long-standing questions in the field, deepening the knowledge on how the mammalian brain encodes rewarding and aversive events.

Link to the ERC project webpage:

Keywords of the ERC project: neuronal circuits, reward, aversion, optogenetics, calcium imaging, electrophysiology, machine learning

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101021560	**IMAGINE**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Benedikt Berninger**
Host Institution:	King'S College London - GBR

In vivo Imaging Genesis and Circuit Integration of Interneurons Engineered from Glia

Direct lineage reprogramming of cell identity in the nervous system offers the prospect of remodelling diseased brain circuits. Recent years have provided evidence for the possibility of converting brain glia into neurons in vivo. Yet, the process by which glial cells give up their original identity and adopt a neuronal fate remains by large enigmatic. Moreover, it is unclear how neurons induced from glia may integrate into the pre-existing circuits of non-neurogenic brain regions such as the cerebral cortex. Finally, can they participate in cortical information processing and even restore dysfunctional cortical circuits? We have discovered a specific cocktail of reprogramming factors that gives rise to induced neurons with hallmark features of fast-spiking, parvalbumin-expressing interneurons, a neuronal subtype that is highly vulnerable in neuropsychiatric and neurological disorders. Here, we aim at visualising the conversion of glia into these induced interneurons in real time by in vivo imaging. This will not only unambiguously demonstrate the genuineness of the identity switch, but also unveil cellular intermediates along the reprogramming process. By measuring single cell gene expression during conversion, we will be able to relate intermediate states to their molecular underpinnings. Moreover, in vivo imaging will allow us to follow structural remodelling of dendrites as induced interneurons integrate into pre-existing cortical circuitry. By using in vivo calcium imaging in primary visual cortex, we will examine whether induced interneurons become recruited into sensory information processing circuits. Finally, we will scrutinise induced interneurons for their ability to rescue excitation-to-inhibition balance in a mouse model of endogenous interneuron dysfunction. IMAGINE will thus break new ground towards unveiling the full potential of engineered neurogenesis for brain repair.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101039145	**InsulaBodyLoop**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Yoav Livneh**
Host Institution:	Weizmann Institute Of Science - ISR

The Insula-Body Loop for Neural Control of Gut Physiology

The brain and body are in a continuous dialog. Our brains constantly receive sensory information from within our body, as well as from the external environment, and then use it to regulate bodily function. Brain-body communication is essential for our physical and mental health, yet little is known about how it is achieved at the neurobiological level. A large corpus of work implicates the insular cortex as a central node in the brain's interoceptive network. Current models suggest that insular cortex integrates internal and external sensory information to regulate bodily physiology. Yet direct experimental evidence has been scarce. I propose a research program that focuses on the insular cortex as part of a dynamic loop with the gastrointestinal system, which regulates peripheral metabolic function and feeding behaviour. Two fundamental questions form the core of this proposal: (1) How do the sight, smell, and taste of a savoury dish, or a sweet dessert, enable our brains to predict the post-ingestive nutrients they will supply? (2) How are these predictions relayed to our body to pre-emptively prepare it for consumption, e.g., by inducing salivation and insulin release? To answer these questions we need to understand both cortical predictive computations, as well as peripheral physiology. I therefore propose to build on my expertise and use an inter-disciplinary approach, combining cutting-edge neuroscience and computational methods with recordings and optogenetic control of peripheral physiology. This will reveal: (1) how insular cortex represents internal sensations, (2) how insular cortex forms associations between internal and external sensory information, and (3) how these associations are relayed to the body to maintain homeostasis. This study will provide a conceptual and methodological foundation for future elucidation of how different internal sensory modalities act together within the brain-body loop to maintain our physical and emotional health.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101040951	**RADIOGUT**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Maria Rodriguez Aburto**
Host Institution:	University College Cork - National University Of Ireland, Cork - IRL

Radial Glia as Neurodevelopmental Mediators Of Gut Microbiota Signals

Increasing evidence points to the importance of gut microbiota in the aetiology of neurodevelopmental and neuropsychiatric conditions. However, the mechanisms and conduits through which microbiota influences brain development in the critical perinatal period, potentially leading to cognitive deficits in later life, remain largely unknown. My hypothesis is that the dynamic early-life gut microbiota modulates the primary brain neural stem cells, the radial glia (RG), thereby sculpting the concurrently maturing neurodevelopmental trajectory. RG are in direct contact with cerebrospinal fluid (CSF), whose composition relies on a functional blood-CSF barrier (BCSFB) at the choroid plexus. BCSFB-RG interface is thus ideally positioned to receive peripheral circulating signals, such as those from gut microbiota. My preliminary data indicating alterations in RG dynamics and BCSFB integrity in neonatal mice with disrupted gut microbiota provides credence to my hypothesis. Building on this, RADIOGUT aims to mechanistically understand the interactions between gut microbiota, RG-led neurodevelopment and BCSFB function at molecular and cellular levels. To accomplish this, I will employ distinct models of early-life microbiota disruption in mice and assess the impact on RG and BCSFB using in vivo tracer imaging, ex vivo models combining explant cultures with microbial metabolites from a faecal fermenter, and an integrated multi-omics analysis. We will identify key microbial metabolites that operate at the BCSFB-RG interface, discern their signalling mechanisms and their potential to rescue RG-derived neurodevelopmental deficits as well as later life aberrant behaviours. RADIOGUT will explore for the first time how RG can act as cellular sensors of microbial signals that modulate neurodevelopment. It will fill a large gap in the understanding of microbiota-gut-brain axis development and its communication code, as well as deliver tangible future translational value.

Link to the ERC project webpage: aburto-lab.org

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101041799	**NEUROGROUP**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Raymundo Báez Mendoza**
Host Institution:	Deutsches Primatenzentrum Gmbh - DEU

Neuronal basis of group cooperation and social ties in monkeys and humans

The negative impact on society's mental health by social distancing during the current COVID-19 pandemic highlights the importance of social interactions in maintaining a healthy life. Reputation, cooperation, and an individual's social ties play a crucial role in social interactions. My proposal will examine the interdependence and neural correlates of these psychological processes. I hypothesize that a social tie's strength influences cooperative behavior; similarly, cooperative behavior fosters social ties. Further, I hypothesize that the interplay of neuronal activity in the dorsomedial prefrontal cortex (dmPFC) and insular cortex underpins these processes. My recent studies of human and non-human primate dmPFC showed its involvement in encoding social processes. Yet, its role in cooperation and social tie formation is unclear. To test these hypotheses, we will first characterize the neuronal representations underlying group cooperation. Second, we will identify the neuronal mechanisms underlying fundamental behavioral processes in forming and maintaining social ties during naturalistic interactions in monkeys. Third, we will compare in a new world monkey and humans the association between group cooperation and social ties? formation and maintenance. This new line of investigation will shed light on how elementary social computations during group interactions such as social dilemmas are computed at the single-neuronal and population levels within the primate brain. Overall, this proposal will allow us to study social interactions in a way that has never been done before and will lay the foundation of future work in my independent laboratory. By using an innovative approach, this project aims to identify the brain's mechanisms underlying the formation of non-kin and non-reproductive alliances. The information gleaned from this work will lay the groundwork for a comprehensive behavioral and neuronal mechanistic understanding of social ties.

Link to the ERC project webpage: baezlab.co

Keywords of the ERC project: social behavior; neurophysiology; cooperation; social ties

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101042309	**Ethofearless**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Bianca Ambrogina Silva**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Attenuation of ethological traumatic memories

Traumatic experiences generate among the strongest memories that can result in trauma-related disorders. Despite the high prevalence of these disorders, effective treatment options are scarce, calling for a deterministic understanding of the neuronal mechanisms underlying traumatic memory attenuation. For this, rodent studies classically use fear extinction paradigms where aversive experiences are modeled with the exposure to an electrical foot shock. However, the simple nature of this stimulus does not mirror the complexity of traumatic events in humans which is likely to be processed by equally complex networks. Here, I propose to investigate for the first time the neural circuits underlying the extinction of traumatic memories induced by exposure to naturalistic threats, namely, predators and aggressive conspecifics. First, we will compile a comprehensive atlas of brain activity underlying extinction of these ethological traumas and generate network organization models, which will be causally probed by pathway-specific chemogenetic manipulations. Second, we will characterize the functional input-output connectome of ethological extinction centers using a combination of viral tracing, neuronal activity and optogenetically assisted circuit mapping. This set of data will, third, provide the substrate for the study of the neurophysiological and molecular mechanisms underlying efficient extinction of ethological traumas, which will be analyzed by pathway-specific in-vivo Ca2+ imaging, closed-loop optogenetics, ex-vivo electrophysiology and RNA sequencing. Lastly, we will investigate whether impairments at the level of these newly identified networks underlie extinction deficits at the basis of trauma-related disorders. Together, these results will pave the way for the identification of novel therapeutical targets for trauma-related disorders and shed light on how the brain can flexibly update complex memories.

Link to the ERC project webpage:

Keywords of the ERC project: fear, circuits, extinction, thalamus

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101043584	**HUMANE**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Tarja Malm**
Host Institution:	Ita-Suomen Yliopisto - FIN

Window to the brain: a game changer in the discovery of human neuronal circuitry, cellular heterogenicity and biomarker profile indicative of early Alzheimer's disease -related pathology

The molecular mechanisms leading to Alzheimer's disease (AD) are poorly understood. This is due to lack of human tissue samples for research representing early changes of AD pathology. The accumulating pathology, including beta-amyloid and tau proteins, are manifested by concomitant neuroinflammatory reactions geared by malfunctional microglia. Microglia in the human and mouse AD brain exist in various subpopulations from which a specific, disease-associated microglia population is thought to be involved in AD pathogenesis. However, there is no evidence on whether and how these specific microglial subpopulations actually impair neuronal functions in human AD brain. I will now assess neuron-glia network activities and functions indicative of early AD pathology in humans. I hypothesize that early AD pathology selectively impairs neuronal circuits and that glial cells, especially specific microglia subpopulations, contribute to neuronal dysfunction and cognitive decline. These events contribute to a detectable vesicle-based biomarker profile in cerebrospinal fluid and blood prior the clinical disease. Due to early AD pathology present in a subpopulation of idiopathic normal pressure hydrocephalus (iNPH) patients, the brains of the iNPH patients offer a unique window to evaluate cellular and molecular events occurring during early AD. I combine a series of state-of-the art techniques to answer how and what glial cell subpopulations are associated with altered neuronal network activities at subcellular and spatial resolution in human brain impacted by early AD-related pathology. Novel methodologies established in my lab, knowhow and access to unique brain samples make me uniquely positioned to form a holistic view on how early AD-pathology impacts cellular functions at multiple levels. This will pinpoint novel molecular targets for further validation and new fluid biomarkers.

Link to the ERC project webpage:

Keywords of the ERC project: alzheimer, neuroinflammation, microglia, electrophysiology, multi electrode arrays, biomarker, prediction, bioinformatics

Keywords that characterize the scientific profile of the potential visiting researcher/s: electrophysiology, computer science, bioinformatics, electron microscopy, high-resolution microscopy

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101045054	**PlasticSite**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Alexander Walter**
Host Institution:	Kobenhavns Universitet - DNK

Plasticity of neurotransmitter release sites in temporal coding, homeostasis, learning and disease

Virtually all neural computation relies on synaptic plasticity, the dynamic change of chemical synaptic communication achieved by transmitter exocytosis from vesicles at presynaptic release sites to activate postsynaptic receptors. Plasticity mechanisms must be powerful, scalable and sustainable over all timescales of neural processing. Which part of the synaptic machinery is the best suited plasticity target? The number of synaptic vesicles greatly outnumbers that of release sites, essentially making the sites gatekeepers of all neural communication. Release site plasticity could thus be pivotal to all neural processing. We recently discovered the molecular identity of release sites (conserved Unc13 proteins) and found evidence of potent release site plasticity on timescales of milliseconds, minutes and days. We are now in the position to use this molecular handle to unravel the principles of this plasticity which will be key to understand neural function, behaviour and disease. Owing to the conserved process and machinery, we will harness the power of Drosophila genetics to elucidate general mechanisms and broad relevance of three distinct release-site plasticity phenomena: 1. Release site switching for millisecond facilitation of transmission and its contribution to network pattern generation as needed for locomotion. 2. Release site activation for minutes' potentiation of transmitter release and its role in homeostasis and learning. 3. Release site accumulation for long-lasting potentiation with regained dynamic range and its role in homeostasis and memory. Finally, disease mutations accumulate in proteins relating to release site function. We will thus (4.) investigate whether these mutations affect release site plasticity in flies and attempt treatment of their induced defects by artificial enhancement of plasticity. My work will set the stage to establish the investigation of the role of this novel and fundamental plasticity in neural function and disease.

Link to the ERC project webpage:

Keywords of the ERC project: synaptic plasticity, neurotransmitter release sites, Drosophila melanogaster, synaptic disease mutations

Keywords that characterize the scientific profile of the potential visiting researcher/s: behavioural analysis, live- and super-resolution microscopy

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Project ID:	Project Acronym:	Evaluation Panel:
101045253	**DEEPRETINA**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Olivier Marre**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

A perturbative approach to model retinal processing of natural scenes

A major goal of sensory neuroscience is to understand how sensory neurons process natural scenes. Models built from the responses of sensory neurons to simple stimuli do not generalize to predict how complex, natural scene are processed. Even as early as in the retina, this issue is not solved. Deep network models have been proposed to predict the responses of visual neurons to natural stimuli. However, they are still far from being a realistic model of the visual system. First, the sensitivity to perturbations of the stimulus can thus be very different for a deep network model and for our visual system. Second, it is not clear how the model components can be related to actual mechanisms in the brain. Our purpose is to understand how the retina processes natural scenes. We will follow an interdisciplinary approach where we will build realistic deep network models of retinal processing and test them in experiments. We will develop deep network models that can predict ganglion cell responses to natural stimuli, and map the components of these models to specific cell types in the retinal network. Our project is original because it will use two novel methods, that will be key to achieve our goal. The first one is a novel approach to characterize retinal function, where we will probe the selectivity of the retina to perturbations of natural stimuli. The second one is a novel tool based on 2-photon holographic stimulation to decompose the retinal circuit. They are tailored to address the specific issues of deep networks. Each ganglion cell has a receptive field center, the region of visual space whose stimulation evokes the strongest responses. Our project is divided in three parts. We will first understand how natural images are integrated inside the receptive field center. We will then ask how stimulation outside the receptive field center affects ganglion cell processing of natural images. Finally, we will focus on motion processing during natural scene stimulation.

Link to the ERC project webpage: http://oliviermarre.free.fr/

Keywords of the ERC project: Retina ; vision ; computational neuroscience ; optogenetics ; machine learning ; holographic stimulation

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101054467	**DynaHear**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator: **Dr Tobias Moser**

Host Institution: Universitaetsmedizin Goettingen - Georg-August-Universitaet Goettingen - Stiftung Oeffentlichen Rechts - DEU

Solving the dynamic range problem of hearing: deciphering and harnessing cochlear mechanisms of sound intensity coding

Our sense of hearing processes stimuli that differ in sound pressure by more than six orders of magnitude. Yet, while the presynaptic inner hair cells (IHCs) cover this wide dynamic range, each postsynaptic spiral ganglion neuron (SGN) encodes only a fraction and the intensity information is then reconstructed by the brain. This so-called “dynamic range problem” of hearing is known for decades, but how sound intensity information is decomposed into different neural pathways remains elusive. In vivo recordings report major functional SGN diversity and ensembles of such diverse neurons collectively encode intensity for a given sound frequency. Recently, a major heterogeneity of afferent SGN synapses with IHCs as well as different molecular SGN profiles have been discovered. How these relate to the diverse sound coding properties of SGNs remains to be elucidated. DynaHear sets out to close this gap by testing the hypothesis that an interplay of synaptic heterogeneity, molecularly distinct subtypes of SGNs, and efferent modulation serves the neural decomposition of sound intensity information. This is enabled by innovative approaches to cochlear structure and function, some of which we have recently established, while others will be developed in DynaHear. We will combine electrophysiology, optogenetics, molecular labelling and tracing, multiscale and multimodal imaging, with computational modeling. We will elucidate the molecular underpinnings of afferent synaptic heterogeneity, decipher mechanisms establishing such heterogeneity, and relate them to functional SGN diversity. DynaHear promises to fundamentally advance our understanding of sound intensity coding and contribute to solving the dynamic range problem of sound encoding. Moreover, the proposed work will help to better understand synaptic hearing impairment, assist current hearing rehabilitation, and pave the way for innovative therapeutic approaches such as gene therapy and optogenetic restoration of hearing.

Link to the ERC project webpage: http://www.auditory-neuroscience.uni-goettingen.de/

Keywords of the ERC project: Coding hearing synapses neuroscience

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101054886	**NeuRemodelBehavior**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Oren Schuldiner**
Host Institution:	Weizmann Institute Of Science - ISR

Sculpting circuits and behavior by developmental neuronal remodeling

Neuronal remodeling is a conserved strategy to refine neural circuits during development. Defects in remodeling have been associated with neuropsychiatric disorders, but direct mechanistic causality is lacking. Despite its fundamental significance, how remodeling of neuronal processes affects circuit architecture and function, and how this ultimately shapes behavior, is not only unknown, but also extremely challenging to study in complex organisms. Our lab is a world-leader in the molecular mechanisms of neuronal remodeling. We use the stereotypic remodeling of the Drosophila Mushroom Body (MB), a complex circuit within the fly brain, as powerful genetic model to study this question. Recently, we uncovered that MB remodeling is coordinated at the circuit level. Furthermore, we generated a detailed expression atlas of MB neurons during development, which highlighted genes and pathways mediating cell-cell interactions as prime remodeling regulators. Thus, our discoveries suggest that the time is ripe to take on the challenge of integrating the molecular, cellular, circuit and behavioral aspects of remodeling. The MB is a perfect system for this due to its well-characterized structure and function. To accomplish this goal, we will build upon our developmental expression atlas to identify molecules that mediate cell-cell interactions during remodeling (Obj 1). We will then investigate how specific genetic/cellular perturbations of remodeling impact overall circuit architecture and connectivity (Obj 2). Finally, taking a new direction for the lab, we will use behavioral readouts of MB function to understand how specific genetic perturbations of remodeling and connectivity affect circuit function and behavior (Obj 3). While each objective is independent and expected to yield high-impact discoveries by itself, it is their combined implementation that is expected to provide the first holistic picture of neuronal remodeling from molecules to cells, circuits and function.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101075541	**CollectiveDecisions**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Armin Bahl**
Host Institution:	Universitat Konstanz - DEU

Neural basis of zebrafish collective decision-making

It is challenging for isolated animals to reliably extract and integrate behaviorally relevant information from the natural environment. Due to the limited sensory capacity of individuals, many animal species therefore share and evaluate cues collectively, allowing them to solve complex decision-making tasks as a group. The behavioral algorithms and neural mechanisms that give rise to these cognitive abilities remain poorly understood. In many fish species, these behaviors are largely vision-based, providing the opportunity to decipher the underlying general computational principles under well-controlled experimental conditions in the lab. At the same time, it is becoming possible to employ powerful neuroscientific techniques, enabling new detailed analyses of the neural circuitry that orchestrates behavior. I propose to establish the juvenile zebrafish as a model system that is optimally suited for the study of collective decision-making. At this intermediate developmental stage, zebrafish offer an excellent compromise between cognitive ability and experimental accessibility. They can temporally and spatially integrate information, they start to socially interact, and one can characterize and manipulate brain activity in intact behaving animals. Using closed-loop virtual reality experiments, I will initially dissect the algorithmic rules by which juvenile zebrafish make decisions when swimming in heterogeneously biased groups. I will then characterize brain activity related to this behavior, in freely swimming fish, and in restrained preparations. Finally, to causally link neural circuit function and group decision-making performance, I will carry out targeted laser ablation and optogenetic activation experiments. Thus, my proposed research in juvenile zebrafish will, for the first time, provide key insights into the behavioral algorithms and neural mechanisms of how individual animals and animal collectives acquire sensory information and make complex decisions.

Link to the ERC project webpage: https://www.neurobiology-konstanz.com/

Keywords of the ERC project: zebrafish, two-photon imaging, collective behavior, decision-making, modeling

Keywords that characterize the scientific profile of the potential visiting researcher/s: modeling, microscopy, behavior

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Project ID:	Project Acronym:	Evaluation Panel:
101088375	**StarTicking**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Mariana Astiz**
Host Institution:	Achucarro Basque Center For Neuroscience Fundazioa - ESP

The early ticking of the central circadian pacemaker: when and how

The 24-h (circadian) timing system develops during the perinatal period and rules our physiology later in life. It has the essential task of anticipating daily recurring changes in the environment (day/night) to find the best time for each molecular and cellular process. It is organised hierarchically, with a master pacemaker in the hypothalamic suprachiasmatic nucleus (SCN), which is able to perceive environmental light and tell the body what time is it. Our modern 24/7 lifestyle favours a disruptive environment for the circadian system, which is especially negative during pregnancy. We have found, in mice and pre-term infants, that when mothers are exposed to glucocorticoids (GCs) at the wrong time of day, the offspring show behaviour disorders later in life. Our mechanistic findings showed for the first time, a role of the foetal clock before birth, challenging the view on the clock being immature and non-functional. StarTicking proposes to answer a long-standing question in the field: When and how the circadian clock starts ticking. With a multidisciplinary and integrated approach, we will go beyond the state-of-the-art to understand mechanistically the development of the central circadian pacemaker in mice and humans. We will investigate: 1) How the SCN forms by a detailed assessment of the developmental trajectory of the mouse SCN with single cell resolution. 2) When the SCN becomes functional by testing a yet unexplored player: Astrocytes as drivers of the gain of functionality of the mouse SCN. 3) What the influence of the early environment on the human SCN maturation is. The generation of a human SCN organoid will allow us to test maternal signals in vitro with high-throughput. We will link mechanistic findings to the development of SCN-driven rhythms in a cohort of pre-term babies. StarTicking will provide ground-breaking mechanistic evidence and valuable knowledge to alleviate the behavioural consequences of the circadian disruption early in life.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101088375

Keywords of the ERC project: circadian clock, suprachiasmatic nuclei (SCN), mouse, human, development, pregnancy, early environment,
premature babies, glucocorticoids, neurons, astrocytes, organoids, foetal brain, single nuclei RNA seq, organotypic, Per2Venus, in utero electroporat

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101088437	**ReplaceMi**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Kiavash Movahedi**
Host Institution:	Vrije Universiteit Brussel - BEL

Microglia engineering and replacement to treat brain disease

Microglia are highly versatile brain resident cells that offer tremendous therapeutic opportunities. They are instrumental for maintaining healthy brain physiology and act as the primary modulators of neuroinflammation and disease. Microglial dysfunction has been convincingly linked to a myriad of neurological disorders, making these cells a prime target for therapeutic intervention. Remarkably, microglia are embryo-derived cells that self-maintain for life, with negligible replacement by the bone marrow. This astonishing self-renewal capacity offers a unique opportunity for cell therapy. The ability to replace dysfunctional microglia with healthy or genetically enhanced counterparts may transform the way we treat brain disease. But how can we replace a cell that is so adept at self-renewal in a tissue that is shielded from the periphery? Currently there are no translatable approaches for the specific replacement of microglia. Furthermore, bone marrow progenitors are unable to adopt the embryonic microglial phenotype. By building on our unpublished observations and developing innovative technologies, I aim to lay the foundation for microglial replacement therapy. We intend to develop an original and translatable strategy for the specific and near-complete replacement of embryonic microglia with adoptively transferred progenitors. Next, by combining iPSC differentiation with genetic barcoding, single-cell analysis and in vivo screening, we aim to identify progenitors that efficiently traffic to the brain and engraft as bona fide microglia. Moreover, we will investigate how we can transform microglia into local protein production factories, as a potential basis to treat neurodegenerative diseases. Finally, we will set up in vivo pooled CRISPR screens to identify the gene networks that can modulate and positively enhance microglial disease responses. ReplaceMi has the potential to result in a new and eagerly awaited breakthrough in treating brain disease.

Link to the ERC project webpage:

Keywords of the ERC project: Microglia, Brain immunology, Neurodegeneration, Microglia replacement, Cell therapy

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101088881	**CNS Hidden Door**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Ayal Ben-Zvi**
Host Institution:	The Hebrew University Of Jerusalem - ISR

Uncovering molecular and cellular mechanisms of immune cell trafficking across the blood-CSF barrier in autoimmunity

Immune cells continuously traverse our body, crossing vascular and epithelial barriers; from lymphatic organs into the blood, and from the blood into various tissues for surveillance or to fight infection. However, the brain has long been considered an immune-privileged organ. Barriers protecting the brain against infection or harmful toxic agents were also thought to block entry of immune cells, leaving immune functions to brain-resident microglia cells. This dogma was recently overturned when it became clear that immune cells cross, mainly for surveillance, especially at the Blood-CSF barrier. Furthermore, while harmful immune cell trafficking is a hallmark of brain autoimmunity, e.g. Multiple Sclerosis and Neuro-Lupus, enhanced trafficking might help to fight brain tumours, and even to resolve neurodegenerative conditions, e.g. Alzheimer's Disease. Yet the study of immune cell trafficking across the Blood-CSF barrier is severely hampered by a shortage of suitable methodologies. We investigated Blood-CSF barrier dysfunction in Lupus and discovered a brain lymphoid structure with enhanced immune cell trafficking. Dominant transepithelial leukocyte migration (through, rather than in between, cells) will enable us to catch the trafficking events 'red-handed' and to identify molecular and cellular trafficking mechanisms. Harnessing innovative methodologies involving single-cell RNAseq, Super-Resolution microscopy, Imaging cytometry, and genetic/pharmacological interventions, we aim to decipher the fundamental question of how leukocytes enter the brain. We will classify specialized immune and epithelial barrier cell types, identify trafficking molecular pathways, and develop approaches to regulate the process. We will also assess this barrier involvement in the pathobiology of human Neuro-Lupus disease. Understanding immune trafficking mechanisms may be the key to a specialized brain portal, leading to therapeutics that can modulate brain-immune interactions.

Link to the ERC project webpage:

Keywords of the ERC project: BBB, Autoimmune, Lupus, Choroid Plexus, epithelial transmigration

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101089288	**DeepCoMechTome**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Jakob Macke**
Host Institution:	Eberhard Karls Universitaet Tuebingen - DEU

Using deep learning to understand computations in neural circuits with Connectome-constrained Mechanistic Models

Advances in experimental techniques yield detailed wiring diagrams of neural circuits in model-systems such as the Drosophila melanogaster. How can we leverage these complex connectomes, together with targeted recordings and perturbations of neural activity, to understand how neuronal populations perform computations underlying behavior? Achieving a mechanistic understanding will require models that are consistent with connectomes and biophysical mechanisms, while also being capable of performing behaviorally relevant computations. Current models fail to address this need: Mechanistic models satisfy anatomical and biophysical constraints by design, but we lack methods for optimizing them to perform tasks. Conversely, deep learning models can be optimized to perform challenging tasks, but fall short on mechanistic interpretability. To address this challenge, we will provide a machine learning framework that unifies mechanistic modeling and deep learning, and will make it possible to algorithmically identify models that link biophysical mechanisms, neural data, and behavior. We will use our approach to study two key neural computations in D. melanogaster. We will build large-scale mechanistic models of the optic lobe and motor control circuits which are constrained by connectomes and physiological measurements, and optimize them to solve specific computational tasks: Extracting behaviorally relevant information from the visual input, and coordinating leg movements to achieve robust locomotion. Our methodology for building, interpreting and updating these `deep mechanistic models' will be applicable to a wide range of neural circuits and behaviors. It will serve as a powerful hypothesis generator for predicting neural tuning and optimizing experimental perturbations, and will yield unprecedented insights into how connectivity shapes efficient neural computations in biological and artificial networks.

Link to the ERC project webpage:

Keywords of the ERC project: Deep learning, computational neuroscience, connectomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: Machine learning, computational neuroscience, connectomics, numerical simulation

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Project ID:	Project Acronym:	Evaluation Panel:
101097053	**SynProtect**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Stephan Sigrist**
Host Institution:	Freie Universitaet Berlin - DEU

The synaptic active zone as a signaling hub for sleep homeostasis and resilience

Resilience designates the ability of the brain to cope with and adapt to stressful situations. Sleep homeostasis is tightly linked to resilience, and the sleep deficits observed alongside neurodegeneration probably operate as direct “drivers” of neurodegeneration. However, the knowledge gaps still remain huge and causally bridging the molecular/cellular with the behavioral and organismic level remains a challenge, hampering progress equally for biomedical and basic research. Our recent data suggest that a form of presynaptic active zone plasticity (“PreScale”), widely triggered in sleep-deprived Drosophila brains, can enhance the brain resilience to cope with the adverse effects of sleep deprivation. Concretely, genetically fostering PreScale in sleepless mutants rescued them from their reduced lifetime, stress sensitivity, cognitive deficits and hyperexcitability due to too low levels of voltage-gated potassium channels. In SynProtect, we seek to test our hypothesis that PreScale constitutes a globally-operating homeostatic plasticity mechanism remodeling presynaptic terminals comprehensively to tune resilience states. In order to test this idea, we will elucidate the core molecular scenario executing and bidirectionally regulating PreScale and, consequently, decipher how exactly the remodeling of the mere presynaptic active zones and local excitability tuning via potassium channels intersect at the presynaptic terminal. In parallel, we will test whether PreScale is needed to enhance resilience in a brainwide fashion or if its modus operandi is more local. Genetic manipulation of PreScale will allow us to define brain states of high and low resilience, which we will dissect combining super-resolution and in vivo activity imaging and proteomic tools. Thus, we will open the way towards a comprehensive insight into the activity, signaling and metabolic profile of brain resilience.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101116500	**ZoomINs**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Gali Umschweif**
Host Institution:	The Hebrew University Of Jerusalem - ISR

The missing link: inhibitory interneurons as the core of anxiety and depression comorbidity

Rates of depression and anxiety are constantly surging, resulting in a growing global mental health crisis. These two disorders have a remarkably high prevalence of comorbidity, with anxiety generally preceding depression. However, the biological basis of these disorders and their comorbidity is poorly understood, leaving millions of patients with inadequate treatments and thus an urgent need for improved medications. Accumulating evidence suggests that both disorders involve GABAergic deficits, but the nature of these deficits is undefined and may be the holy grail for cracking the mysteries of depression and anxiety comorbidity. Here, I will apply cutting-edge technologies to focus on hippocampal GABAergic interneurons (INs) and propose a data-driven hypothesis for the cellular and molecular basis of anxiety and depression comorbidity. I suggest that INs selectively recruit microglia to reshape inhibition in the depressed brain. This hypothesis may provide the missing link between major hallmarks of depression: GABAergic deficits, synaptic loss, and neuroinflammation. I seek to unravel the molecular adaptations of INs to stress that lead to microglia recruitment and connect them with anxiety preceding depression. Finally, I will elucidate a novel model for innate anxiolysis mediated by local dendritic translation in INs. I will combine, for the first time, the robustness of two analytical methods: translating ribosome sequencing and spatial transcriptomics to identify the involved genes, the INs subtypes expressing them, and their hippocampal location. These data will be complemented by calcium imaging, behavioral tests, imaging, connectomics, and electrophysiology. ZoomINs targets an urgent public health concern by providing a novel hypothesis for a long-standing question: what causes anxiety and depression comorbidity? The results of this ambitious project will set the ground for the development of INs-targeting medications, giving hope to millions worldwide.

Link to the ERC project webpage:

Keywords of the ERC project: depression, anxiety, hippocampus, GABA, interneurons

Keywords that characterize the scientific profile of the potential visiting researcher/s: spatial transcriptomics, slice electrophysiology, molecular biology, in-vivo calcium imaging, bioinformatics

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Project ID:	Project Acronym:	Evaluation Panel:
101116996	**TEMPRODROME**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Lukas Groschner**
Host Institution:	Medizinische Universitat Graz - AUT

Temporal processing in Drosophila melanogaster

All information processing in nervous systems relies on spatial and temporal patterns of neural activity. While spatial patterns are dictated by neuroanatomy, the mechanisms that give rise to temporal activity patterns are diverse. They range from fast voltage dynamics of single neurons at one end of the spectrum to slow transcriptional and structural changes at the other, but the rules that shape signals at timescales in between milliseconds and minutes are poorly understood. The proposed research aims to uncover mechanisms of temporal information processing at these intermediate timescales, at which temporal patterns are thought to emerge from recurrently connected circuits. Detailed insight into the function of these circuits has been limited by the large number of circuit elements, by the lack of knowledge about their connectivity, and by the impracticability of recording from all circuit elements under naturalistic conditions. In Drosophila melanogaster, these limitations no longer apply. The comparatively low number of neurons, their well-mapped connectivity, and our ability to record and control their activities make mechanistic concepts testable. We will focus on three processes in the brain of Drosophila that unfold over three timescales ranging from milliseconds to minutes: 1) temporal filtering in the motion vision system, 2) sequential sampling of motion information in the lead-up to a perceptual judgement, and 3) temporal integration of distance during locomotion. Patch clamp experiments in the smallest of invertebrate neurons in vivo will allow us to record activity at the highest temporal resolution. We will combine this technique with behavioural, genetic, and imaging experiments to test the roles of individual neurons, their biophysical properties, and their synaptic connections in processing signals at intermediate timescales. The proposed experiments will further our understanding of motion vision, perceptual decision-making, and path integration.

Link to the ERC project webpage: www.groschner-lab.org

Keywords of the ERC project: Neuroscience, neural circuits, Drosophila, physiology, behaviour, temporal processing

Keywords that characterize the scientific profile of the potential visiting researcher/s: Neuroscience, neural circuits, Drosophila, physiology, behaviour, temporal processing

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101117791	**DrugsAndMemory**	**LS5** Neuroscience and Disorders of the Nervous System

Principal Investigator:	**Dr Magdalene Schlesiger**
Host Institution:	Universitatsklinikum Heidelberg - DEU

How do drug-associated contexts drive behaviour? The role of entorhinal circuitry in addiction

Addiction to drugs is a ubiquitous neuropathological disease that inflicts immense societal costs. A core aspect of addiction that poses a major challenge for treatment is the propensity to relapse in environmental contexts that are associated with drug use. Identification and mechanistic characterization of novel addiction-relevant circuitry linking the motivation to take drugs to the complex spatial and non-spatial features that constitute a drug-associated context are at the core of this proposal. These insights will be used to identify the best constellation of anatomical targets to prevent and reverse the expression of context-triggered drug-seeking. The medial and lateral entorhinal cortex (MEC and LEC) are two central components of the episodic memory system integrating all features relevant for the formation of contextual memory. Crucially, MEC and LEC receive strong bottom-up dopaminergic input from the midbrain and send top-down projections to the nucleus accumbens (NAc). The dopaminergic system is the primary target of all addictive drugs. We will 1) study how bottom-up dopaminergic projections are implemented into drug-context associations in MEC and LEC and 2) determine how these associations influence NAc-mediated drug-seeking behaviour. We will utilize a multidisciplinary approach by developing electrophysiological in vivo recording paradigms in behaving mice that allow the assessment of complex spatial, contextual and non-spatial codes in conditioned place preference and self-administration paradigms typically used to model addiction in rodents. This will be combined with optogenetically-assisted circuit analysis of molecularly-defined pathways to link identified functions to the underlying circuitry. Pathway-specific optogenetic silencing will be used to prevent and reverse the manifestations of drug use on a neuronal and behavioural level. This will guide the evidence-based development of therapies in the future, such as deep-brain stimulation.

Link to the ERC project webpage:

Keywords of the ERC project: Entorhinal cortex, grid cells, addiction, memory

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
866448	**TrojanDC**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Carlos Filipe Ribeiro Lemos Pereira**
Host Institution:	Lunds Universitet - SWE

Harnessing dendritic cell reprogramming for cancer immunotherapy

An important hallmark of cancer is the ability to evade the immune system. Genetic mutations in tumor cells result in the accumulation of tumor antigens (TAs), however, increased cell heterogeneity, downregulation of antigen presentation or inhibition of immune cell infiltration allows immune surveillance evasion. For the first time, direct cell reprogramming offers exciting opportunities to overcome these challenges. My group has recently identified a combination of transcription factors (TFs) sufficient to reprogram mouse fibroblasts into antigen-presenting dendritic cells (DCs), providing a new strategy to set in motion antigen-specific immune responses. I hypothesize that a similar combination reprograms tumor cells into antigen presenting cells (APCs). This proposal aims to test a cancer immunotherapy concept based on DC reprogramming and endowed APC function in tumor cells. The work will proceed in three steps. First, I will define optimal TF combinations and external cues to efficiently reprogram human fibroblasts into DCs employing an innovative single-cell screen. Then, I will reprogram mouse and human tumor cells into tumor-APCs followed by characterization of transcriptome, chromatin accessibility, surface peptidome and ability to present antigens to T cells. Finally, I will test whether reprogrammed cells mount an attack against tumors in mouse models. I will further test the hypothesis that intratumoral delivery of reprogramming factors elicits in vivo antigen presentation, immune cell recruitment and tumor regression. The approach proposed here will combine DCs' antigen processing and presenting abilities with the endogenous generation of TAs. The induction of DC identity in cancer cells with ability to present a constellation of TAs will open new research and therapeutic avenues. This project represents a pioneering contribution by merging cell reprogramming and cancer immunotherapy, paving the way for an entirely new approach to cancer gene therapy.

Link to the ERC project webpage: Pereiralab.com

Keywords of the ERC project: Cellular reprogramming; Immunotherapy; dendritic cell; tumor immunology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
949613	**WePredict**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Ziad Al Nabhani**
Host Institution:	Universitaet Bern - CHE

Microbiota and immune responses at weaning predict the susceptibility to chronic inflammatory diseases in adulthood

Microbiota dysbiosis is associated with chronic inflammatory diseases such as allergy, inflammatory bowel diseases, cancer and metabolism-related disorders. It has been reported that exposure to microbial and dietary components early in life may program the immune system to develop tolerance or susceptibility to chronic inflammatory diseases with age. We have recently showed that vigorous immune responses induced by gut microbiota at weaning, prevent the development and exacerbation of chronic inflammatory diseases in adult mice. Such immune alterations are termed the “weaning reaction”. Antibiotic exposure or excessive fats intake during this critical window deregulates the weaning reaction and increases the subsequent susceptibility to develop immunopathology. Induction of regulatory T cells (Treg) or B cells by microbiota at this stage of breast-feeding cessation, but not later, prevents the pathological memory that is assessed as increased susceptibility to colitis or obesity in adulthood. However, how perturbing the generation of these cells, at a critical developmental period causes long-lasting susceptibility to pathology remains largely unknown. Here we aim to 1) validate microbial and nutritional signatures at weaning that predict the susceptibility to adult pathology using machine-learning algorithms on large mouse datasets and by gnotobiotic models; 2) define the molecular mechanisms involved in regulation of weaning reaction by Treg and B cells; 3) identify the kind of immune memory carried by Treg and B cells from weaning until adulthood, through exploring the antibody repertoires and epigenetic modifications using high-throughput sequencing; 4) reverse the pathological memory in adult mice using immuno-adoptive transfer or successive colonization by neonatal-like gut bacteria. This project will decipher how nutrition and microbiota at weaning orchestrate the immune system development and impact adult chronic inflammatory pathologies susceptibility.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: Mucosal immunology, Epigenetic

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101039538	**DELV**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Karim Majzoub**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

DELta Virus infection in animal and human hosts

The emergence and rapid transmission of viruses pose increasing risks and challenges to modern societies, threatening public health and economic stability. A thorough understanding of basic virology is therefore critical for an informed development of preventive and control strategies. Although for more than 40 years the only known member of deltaviruses was the human Hepatitis Delta virus (HDV), it was recently discovered that HDV-like agents are present in a variety of animal vectors and reservoirs including bats, rats, snakes, birds and insects. Metagenomic data indicate that these satellite viruses possess an unrecognized host shifting capacity enabling them to cross the species barrier. As no efficient antiviral treatment is available against HDV, the emergence of novel deltaviruses poses a significant potential threat to human health. To date, animal deltaviruses have not been functionally characterized and little is known about their basic biology. The proposed project (DELV) aims to generate essential knowledge about the biology of deltaviruses, their interactions with host cells, their zoonotic potential and evolutionary fitness. Using newly generated deltavirus molecular clones coupled to unbiased proteomic and genetic approaches, DELV will identify host factors interacting with deltaviruses in their natural animal and human hosts (Aim 1). Further, it will determine and characterize host factors that are essential for deltavirus replication in the human host when they cross the species barrier (Aim 2). Finally, DELV will discover viral elements favoring deltavirus host shifting and adaptation capacities (Aim 3). DELV aims to shape novel paradigms in virology, RNA biology and host-pathogen interactions. Knowledge generated through DELV will guide the development of novel antiviral strategies and will have profound implications for understanding the ecology and evolution of these newly discovered, yet mysterious, viral elements.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101044248	**Let T Be**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Maria Mittelbrunn**
Host Institution:	Agencia Estatal Consejo Superior De Investigaciones Cientificas - ESP

Letting up senescence and inflammaging through T cells

With the increase in human life expectancy, there is an urgent need to understand the common molecular pathways by which aging results in a progressively higher susceptibility to chronic morbidity, disability, and frailty. In the last years, immunometabolism has emerged as a new field to boost immune responses for cancer immunotherapies as well as to dampen autoimmune diseases. A recent discovery from my lab has revealed the critical role of T cell metabolism in accelerating the onset of age-associated diseases and multimorbidity. This finding has opened a new path to investigate the diverse T cell intrinsic and external stimuli that instruct T cell differentiation towards a dysfunctional state during aging, with the final goal of designing effective strategies to promote healthy aging. LetTBe will address the hypothesis that the time-dependent deterioration of T lymphocytes contributes not only to immunosenescence but also to the general aging process. The LetTBe project proposes to use multidisciplinary approaches to target age-associated T cells for preventing inflammaging, senescence and age-associated multimorbidity. Our central goals are: 1) To define age-associated T cells heterogeneity with special focus in their cellular origin, clonality, metabolic vulnerabilities and transcriptomic signatures; 2) To decode the environmental signals that are imprinted on age-associated T cells and contribute to their development; 3) To identify new strategies to targeting age-associated T cells for slowing down immunosenescence, and for boosting resilience to inflammaging, systemic senescence and age-related multimorbidity. In sum, LetTBe puts forward an ambitious but feasible program with the wide purpose of understanding the specific molecular mechanisms and metabolic requirements of age-associated T cells, with the final goal to guide new strategies to improve healthy aging.

Link to the ERC project webpage:

Keywords of the ERC project: T cells, Aging, Senescence, Inflammaging

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101044428	**VirulenceControl**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Moritz Treeck**
Host Institution:	Fundacao Calouste Gulbenkian - PRT

The role of an expanded family of exported effector kinases in environmental sensing and regulation of virulence in human malaria.

The most severe form of malaria in humans is caused by Plasmodium falciparum. Cytoadhesion of infected red blood cells (iRBCs) to host endothelium and iRBC rigidification are the major contributors to pathology. Cytoadhesion is mediated by transport of a protein called PfEMP1 onto the surface of the iRBC. It prevents clearance of iRBCs in the spleen and promotes parasite survival, but can cause the obstruction of blood vessels leading to pathology. Thus, the parasite has to strike a fine balance between preventing its own clearance through sufficiently strong cytoadhesion and control of rigidity, and killing the host. The paradigm in the field is that the strength of cytoadhesion is dominated by expression of PfEMP1 variants with different affinities for host cell receptors. We now have strong evidence that the parasite can rapidly regulate its cytoadhesive properties using a family of atypical kinases (the FIKK kinases) it exports into the host cell. This gives the parasite a yet unrecognized ability to respond to conditions encountered in the host, such as fever or hypoxia in areas of high parasite sequestration, and influence disease outcome. This is important: Of the 6 human infecting Plasmodium species only P. falciparum exports FIKK kinases into the host cell. As this species is responsible for ~95% of all fatal human malaria cases, it is paramount to understand FIKK- function in pathogenesis. We will use cutting edge approaches to: (1) identify the function of FIKK kinases in controlling cytoadhesion and rigidity in conditions frequently encountered in the human host and determine RBC remodelling in samples from patients. (2) Identify the molecular underpinnings of FIKK function in controlling cytoadhesion and (3) perform a thorough biochemical characterisation of the atypical FIKK kinase family. In summary we aim to answer the paramount question about the functional role and the evolution of the FIKK kinases and the pathogenesis of P. falciparum malaria.

Link to the ERC project webpage:

Keywords of the ERC project: Host-pathogen interaction, Malaria, Virulence, Pathogenesis

Keywords that characterize the scientific profile of the potential visiting researcher/s: cell biology, biochemistry, structural biology, medicinal chemistry, protein expression

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101053576	**virluminous**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Frank Van Kuppeveld**
Host Institution:	Universiteit Utrecht - NLD

Illuminating the enteroviral life cycle

Enteroviruses are highly prevalent pathogens that have enormous clinical and socio-economic impact. Well-known examples are poliovirus, coxsackievirus, enterovirus-A71, enterovirus-D68, and rhinovirus. Although important insights have been obtained in the enteroviral life cycle, many important questions remain unanswered due to shortcomings of current imaging and biochemical methodologies. There is a high need for novel technologies that allow sensitive and real-time observation of the dynamics and localisation of viral RNA, viral proteins, and host factors at the single-cell level. My long-term goal is to understand enterovirus replication and translate knowledge into the development of antiviral drugs. My lab has a long-standing track record and has made many important contributions to understanding the molecular mechanisms of enterovirus replication and the formation of viral replication organelles. Recently, we constructed a reporter virus that in combination with high-resolution microscopy allowed for the first time to visualize translation, and the regulation thereof, of single (entero)viral RNAs in living cells. The goal of this project is to visualize and dissect the spatial and temporal regulation of different phases of the enterovirus life cycle. As a first step, novel recombinant reporter viruses for application in real-time imaging technologies will be developed. These viruses will be used to study viral RNA replication, virus assembly, and pre-lytic virus release in living cells. Moreover, they will be instrumental to study the structure and composition of the viral replication organelles and the associated replication complexes through advanced cryo-electron microscopy and tomography technologies, and proteomics/lipidomics analysis, respectively. This project will lead to important new insights into the molecular interplay between enteroviruses and their hosts, which is essential for developing urgently needed antiviral drugs.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101055093	**BecomingCausal**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr George Kollias**
Host Institution:	Biomedical Sciences Research Center Alexander Fleming - GRC

Contextual specification of fibroblast-driven causalities in chronic intestinal inflammation and fibrosis

Inflammatory bowel disease (IBD) is a severe, chronic pathology presenting with progressive intestinal inflammation and fibrosis, whose exact causes and key pathways remain poorly defined. Stromal–immune cell interactions have recently gained momentum in conceptualizing tissue homeostasis and our lab offered solid evidence establishing fibroblast heterogeneity and dominant roles in intestinal pathophysiology. Our recent preliminary evidence, indicated diverse spatial distribution of subsets of activated fibroblasts and revealed synergistic interplays of important inflammatory pathways driving pathogenicity. Detailed insights into such contextual complexities remain obscure. Here, we propose a novel unifying hypothesis that progressive IBD is orchestrated by specific subsets of fibroblasts, becoming causal to pathogenesis, depending on contextual information dictated by origin, topology, and cross-talks with immune or stromal cell types. We propose to use single-cell spatiotemporal phenotyping to deconvolute fibroblast subset-specific functions in disease-staged, fibrotic and non-fibrotic animal models of IBD. We aim to: (1) Map dynamic chromatin and gene expression programs that define cellular heterogeneity and infer cell interactions to build an 'IBD connectome' atlas (2) Analyse the origin, spatial distribution, plasticity and lineage trajectories of intestinal fibroblasts and reveal potential functions of pathogenic subsets (3) Perform discovery screens and functional validations on known (TNF, IFNγ, TGFb and interleukins) and novel fibroblast-subset-specific pathways focusing on potential synergistic interplays (4) Employ clinical material to validate involvement of the most prominent new pathways in human. The proposed research should help tackle the complexities of chronic inflammatory and fibrotic disorders in the intestine and beyond, advance mechanistic concepts in immune disease pathophysiology and promote fibroblast-targeting therapeutic discovery.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101055093

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101076967	**gutMAP**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Lisa Maier**
Host Institution:	Eberhard Karls Universitaet Tuebingen - DEU

Gut microbiome-mediated activities of psychotropic drugs

Mental illnesses are among the most prevalent health burdens, with major depression ranking fourth among the leading causes of disease worldwide. Although diverse psychotropic drugs are available, the delayed onset of drug action, high non-responder rates and frequent side effects still pose significant challenges. Several observations suggest the gut microbiome as major contributor to high inter-individual differences in drug responses. While there is evidence that these drugs lead to changes in the microbiome composition of patients, it has not yet been explored whether these effects are part of the drug mode of action and/or whether they contribute to side effects. The aim of this project is to investigate to what extent gut microbes are involved in the therapeutic outcome of psychotropic drugs by employing model synthetic and patient derived microbiome communities (from stool of drug responders, non-responders and healthy controls), and in vivo gnotobiotic mouse models. We will systematically characterize the reciprocal interactions between gut microbes and commonly used psychotropic drugs ex vivo – from microbial drug metabolism to drug-induced bacterial secretion of neuroactive compounds. For intriguing interactions, we will elucidate the underlying mechanisms and use the knowledge to design engineered microbiomes. We will then employ gnotobiotic knockout mice deficient for primary drug targets of psychotropic drugs and colonize them with microbiome communities carrying the different mapped traits to separate the contribution of drug effects originating from the microbiome from those of the host. Overall, our results will inform microbiome-guided therapeutic strategies whose improved efficacy we will test in vivo. Due to the transferability of the developed technology and if successful, this new research direction could not only revolutionize psychotropic drug therapy, but also pave new ways for improving personalized drug therapy for many other diseases.

Link to the ERC project webpage:

Keywords of the ERC project: microbiome, psychotropic drugs

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101077734	**MycoViralPath**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Neta Shlezinger**
Host Institution:	The Hebrew University Of Jerusalem - ISR

The role of fungal viruses in shaping fungal pathogenesis and mammalian host responses

Fungal pathogens present a significant threat to global health. As eukaryotes, they share considerable homology with their hosts, necessitating the development of innovative, non-cross-reactive therapies. Mycoviruses, viruses of fungi, can transform fungal virulence. Yet, despite their ubiquity and importance, the underlying mechanisms driving mycoviral infection and their consequences on fungal pathogenesis remain understudied. Using a naturally mycovirus-infected Aspergillus fumigatus strain, a model human fungal pathogen, we found that the mycovirus bestows a survival benefit to the fungus under oxidative stress and in the murine lung. We posit that mycoviral pressure modulates fungal fitness and virulence, thereby shaping the fungal host repertoire and facilitating the emergence of new fungal diseases. The proposed research aims to elucidate the mycoviral, fungal and mammalian determinants governing fungal cell fate during infection. We will:1) determine the molecular details governing mycoviral impact on fungal fitness, virulence, and host adaptation, 2) identify fungal antiviral mechanisms, and 3) determine how mycoviral infection affects the mammalian antifungal response. This complex multipartite pathosystem (mycovirus-fungal host-mammalian host) is highly heterogenous and dynamic, and this diversity can trigger different infection outcomes. To this end, we have developed a suite of fluorescent probes of fungal and mycoviral infection and of fungal physiology that enable tracking of virus-fungus-host interactions at single-cell resolution, and assessment of the physiological state of phagocytosed fungi in the host tissue. We propose the first in vivo interaction map of a virus within a fungus within an animal in the context of in vivo infection. We anticipate that this work will fundamentally shift our paradigms of fungal pathogenesis, and lay the groundwork for the development of novel therapeutics that operate in an entirely unexploited target space.

Link to the ERC project webpage:

Keywords of the ERC project: Mycovirus, Fungal pathogenesis, Fungal virulence

Keywords that characterize the scientific profile of the potential visiting researcher/s: Virologist, immunologist, cell biology, computational biologist, structural biologist

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101078069	**iMOTIONS**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Ahmed Hegazy**
Host Institution:	Charite - Universitaetsmedizin Berlin - DEU

Immune-stromal crosstalk in inflammation and fibrosis: Exploiting the spatiotemporal dynamics of the OSM-OSMR axis in inflammatory bowel disease to develop novel antifibrotic therapies

Intestinal fibrosis is a common and serious complication of inflammatory bowel disease (IBD). While intestinal inflammation can be treated pharmacologically based on our current understanding of the underlying pathogenesis, little is known about the mechanisms driving fibrogenesis. Thus no approved therapies exist for intestinal fibrosis. While stromal cells lie at the heart of fibrogenesis, our knowledge of how immune-derived signals instruct aberrant tissue repair and fibrosis is limited. We recently highlighted that the immune-stromal cell axis is a crucial component of IBD pathogenesis. Our research discovered that the IL-6 family cytokine oncostatin-M (OSM) plays a central role in immune-stromal crosstalk in human IBD, and drives pro-inflammatory responses in patients with refractory disease. Genetic deletion of OSM significantly reduced acute intestinal inflammation. Furthermore, our current findings suggest that OSM is required for intestinal remodeling and the regulation of collagen homeostasis by controlling immune cell recruitment. Thus, the OSM-OSMR axis serves as a rheostat for tissue inflammation and repair. We will investigate how OSM modulates intestinal fibrosis and identify upstream and downstream signaling events controlling intestinal fibrosis. I will use (i) newly generated reporter and conditional knock-out mice, (ii) contemporary mouse models of intestinal inflammation and fibrosis, (iii) primary human tissue samples from carefully clinically annotated IBD patients with intestinal fibrosis, and (iv) cutting-edge technologies including single-cell sequencing and imaging mass cytometry to dissect the crosstalk between the immune system and stromal cells driving intestinal fibrosis. This project will deepen our understanding of the intestinal aberrant tissue repair mechanisms acting in IBD and other fibrotic diseases, define novel biomarkers to identify patients at risk of fibrosis and provide the means to prevent and treat fibrotic disease.

Link to the ERC project webpage: hegatzylab.com

Keywords of the ERC project: Inflammatory bowel diseases, Host-immune interactions, Immune system, Microbiota, T cells responses

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101087480	**ENDo-HERPES**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Benedikt Kaufer**
Host Institution:	Freie Universitaet Berlin - DEU

Endogenous Human Herpesvirus: Germ line integration and effects on host cell and organism

Endogenous viruses present in the human genome control physiological processes, modulate aging, and can cause diseases. Intriguingly, a herpesvirus has entered the human germ line by integrating its genome into telomeres of germ cells and is present in about 80 million people. The virus, human herpesvirus 6 (HHV-6), can reactivate from the integrated state, which is associated with a number of diseases. These include seizures, encephalitis, heart failure and graft rejection. We recently analysed the virus genomes present in hundreds of individuals with this inherited chromosomally-integrated HHV-6 (iciHHV-6). The data show that today's endogenous virus sequences are quite diverse and derived from dozens of independent integration events that were passed on for generations. There are critical gaps in our knowledge on the functionality of iciHHV-6 genomes with respect to virus replication, gene expression and latency, its effects on the host cell, and the role of telomere shortening that occurs during aging on virus reactivation. ENDo-HERPES will make use of novel technology to close these gaps and provide the basis for elucidating whether diseases are associated with or caused by iciHHV-6. Specifically, we will 1) identify which iciHHV-6 genomes are still functional and could contribute to disease development; 2) determine iciHHV-6 integration sites within the highly repetitive telomere region and assess the integration and reactivation process on the DNA level; and 3) investigate the effects of the iciHHV-6 genome on host cells and if telomere shortening can induce reactivation. The proposal utilizes state-of-the-art technology and pioneers new approaches, particularly when investigating the integration sites of endogenous virus genomes and the mechanisms facilitating integration and reactivation. Altogether, we will shed light on the life cycle and effects on the host cells of this endogenous herpesvirus present in the genome of about 1% of the human population.

Link to the ERC project webpage:

Keywords of the ERC project: endogenous viruses; virus integration; host telomeres; next generation sequencing;

Keywords that characterize the scientific profile of the potential visiting researcher/s: highly motivated; good communication skills; team player; strong interest in academic career

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101088596	**artFibro**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Maria Tsoumakidou**
Host Institution:	Biomedical Sciences Research Center Alexander Fleming - GRC

Artifying fibroblasts: Perturbation modelling in the lung tumor phase space to rewire fibroblasts for immunotherapy.

Lung cancer is the leading cause of cancer death. Immunotherapy improved survival rates, but efficacy is limited to selected patients. We recently discovered universal antigen presenting fibroblasts (apFibros) across human and murine lung tumors and showed that they directly stimulate cancer-specific CD4 T cells, creating immunological hot spots that support immune rejection. These studies achieved a breakthrough on the role of in situ cancer antigen presentation and proposed a novel model whereby tumors can sustain T cells independently of lymph nodes. Preliminary data suggest that lung apFibros help overcome resistance to checkpoint inhibitors. For their immunotherapeutic exploitation of apFibros two bottlenecks must be overcome: low numbers and incomplete understanding of their configurations. We will integrate computational and laboratory experiments and work in parallel in human and mouse models to generate perturbation datasets across single-cell/cell systems, transcriptomics/epigenomics, spatial/temporal levels, and dissect the molecular landscape that regulates fibroblast states. Our ultimate goal is to unravel perturbations that can diverge cancer-associated fibroblasts to antigen presenting states. The following questions are at the core of our proposal i) how do diverse fibroblast states emerge and evolve? ii) which gene regulatory networks drive specificity of these states? ii) which are the functional modules that are driven by apFibros and how are they mechanistically explained? iv) how can we transdifferentiate existing fibroblasts to acquire antigen presenting states? v) how can fibroblast reprogramming help overcome immunotherapy resistance? The proposed research should help advance mechanistic concepts in what we term the “adaptive immune mesenchyme”, decode the complexity of peripheral antigen presentation in tumors and beyond and promote targeting of the stroma for immunotherapy.

Link to the ERC project webpage: https://www.fleming.gr/research/ibi/researchers/tsoumakidou-lab

Keywords of the ERC project: fibroblasts, mesenchyme, cancer antigens, transdifferentiation, cell reprogramming, immunotherapy, in vivo gene editing

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101088622	**InVIRium**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Caroline Goujon**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Investigating Virus-Host Interplay in Human Primary Models of Genetically Modified Respiratory Epithelium

Respiratory viruses can rapidly spread worldwide with a devastating impact, as dramatically highlighted by the COVID-19 pandemic. In addition to the pandemic threat posed by influenza A viruses (IAV) or coronaviruses, respiratory viruses, including IAV, influenza B virus (IBV), seasonal coronaviruses and respiratory syncytial virus (RSV), are the cause of yearly epidemics, with a huge impact on human health. The vast majority of in vitro studies has been performed with model cancer cell lines. However, they share limited features with the primary cells found within the human respiratory epithelium. Robust and relevant, ex vivo models of human primary airway epithelia, cultured at the air-liquid interface (ALI) have been developed over the years and nicely recapitulate the structure and composition of the in vivo respiratory epithelium. Nevertheless, in depth studies on the genes and the potent innate immune, interferon (IFN)-induced, defences regulating viral replication in such pertinent models are still lacking. The InVIRium project will address this knowledge gap by combining a newly acquired expertise in the generation and gene editing of human ALI airway epithelia, with a strong expertise in CRISPR screens and virology. The objectives of InVIRium will be to explore in depth the relationships between major human respiratory viruses, SARS-CoV-2, IAV, IBV and RSV, and their relevant, primary target cells. InVIRium will characterize the IFN-stimulated-genes responsible for the potent antiviral state, explore the mechanisms of SARS-CoV-2 escape from the IFN system and define the landscape of host genes regulating respiratory virus infection in this physiologically relevant ALI model. InVIRium will bring a change of paradigm in the way we study respiratory viruses, by implementing cutting-edge approaches in highly pertinent human models and will gather fundamental knowledge that is currently lacking on the interactions between viruses and their primary target cells.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: molecular virologist, innate immunity, restriction factors

European Research Council
Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
101097830	**NeurImmKisses**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator: **Dr Henrique Veiga Fernandes**

Host Institution: Fundacao D. Anna De Sommer Champalimaud E Dr. Carlos Montez Champalimaud - PRT

Architecture of Peripheral Neuroimmune Circuits and Synapses

Maintenance of health requires the coordination of multiple cellular networks. For example, the immune and nervous systems cooperate to regulate tissue homeostasis. In agreement, our recent work demonstrates that innate lymphoid cells (ILC) integrate neuronal signals to control tissue health and immunity. These findings are provoking a paradigm shift in our understanding of the immune response, neuroimmune crosstalk and its potential therapeutic value. Nevertheless, the dynamics of neuroimmune modalities remain elusive, and progress in the field has been hindered by the lack of approaches to explore the identity and plasticity of neuroimmune interactions in vivo. Here, we hypothesise that dynamic circuitry codes orchestrate neuro-ILC2 interactions and disease outcomes. To test this hypothesis, we have developed a set of disruptive intercellular labelling neuroimmune toolboxes that we termed KISS and LIPSTIC, and which can probe the dynamics of neuro-ILC2 axes in vivo, with cellular specificity and single-cell resolution. Using these innovative platforms, we plan to unravel the architecture of pulmonary neuro-ILC2 circuits and to define cellular identities, outcomes, and plasticity at the neuroimmune interface. Sequentially, we propose to unravel unappreciated neuro-ILC2 synaptic communication and to define the ultrastructure of theses intercellular entities using high-resolution imaging. Finally, by conditionally harnessing the activity of synaptic neuronal partners during airway inflammation and infection, we will investigate their impact on ILC2, their environment, and on disease progression. Together, these experiments will tackle multiple facets of pioneer, frontier questions, bringing to bear an array of cutting-edge technologies to address and advance, with unprecedented mechanistic and conceptual detail, how the neuroimmune interactome unfolds, in health and disease.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101098003	**4D-SkINFLAM**	**LS6** Immunity, Infection and Immunotherapy

Principal Investigator:	**Dr Eicke Latz**
Host Institution:	Deutsches Rheuma-Forschungszentrum Berlin - DEU

Spatio-temporal integration of skin inflammation

To 'feel comfortable in one's own skin' is an idiom referring to one's confidence in interacting with others. However, when the skin is inflamed, as in atopic dermatitis or psoriasis, patients carry a sub-stantial burden leading to opposite effects. Current therapies target redundant, late-stage inflammatory events but not the disease drivers, leading to heterogeneous and insufficient efficacy. Understanding the proximal mechanisms of inflammation will stimulate the development of better therapies. Among the innate immune sensors for stress and microbes in keratinocytes, mutations in the NLRP1 and NLRP10 inflammasomes are linked to skin disorders. These molecules and the pro- and anti-inflammatory IL-1 family members they regulate are differentially expressed in the different layers of the epidermis. We hypothesize that inflammasome signaling in keratinocytes needs context-dependent and spatio-temporal control to avoid inflammation, which poses unique analytical and conceptual challenges. Therefore, to understand how inflammasome signaling in specific keratinocytes drives skin inflammation, 4D-SkINFLAM will i. optogenetically activate specific inflammasome components with spatio-temporal precision and perform a spatial analysis of transcriptomes and proteomes in neighboring cells. With loss-of-function approaches and pathway activity reporters, we will ii. define the 'sensome' and the activity of inflammasomes in different areas of the epidermis. Using mouse models, we will iii. evaluate how spatial inflammasome activity drives skin inflammation. Through iv. AI-driven deep visual proteomics combined with an analysis of inflammasome activity, we will discover spatial in-flammasome activation and its effects in inflammatory skin disorders. A precise understanding of spatio-temporal inflammasome signaling in the skin will be critical for se-lecting therapeutic targets acting as upstream drivers of prevalent diseases with high unmet needs.

Link to the ERC project webpage:

Keywords of the ERC project: Innate immunity, Regulation of the immune response, Innovative immunological tools and approaches including therapies

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
758151	**CHIPS**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Marie Pedersen**
Host Institution:	Kobenhavns Universitet - DNK

Effects of Prenatal Exposure to Acrylamide on Health: Prospective Biomarker-Based Studies

Background: Acrylamide is a chemical formed in many commonly consumed foods and beverages. It is neurotoxic, crosses the placenta and has been associated with restriction of fetal growth in humans. In animals, acrylamide causes heritable mutations, tumors, developmental toxicity, reduced fertility and impaired growth. Therefore, the discovery of acrylamide in food in 2002 raised concern about human health effects worldwide. Still, epidemiological studies are limited and effects on health of prenatal exposure have never been evaluated. Research gaps: Epidemiological studies have mostly addressed exposure during adulthood, focused on cancer risk in adults, and relied on questionnaires entailing a high degree of exposure misclassification. Biomarker studies on prenatal exposure to acrylamide from diet are critically needed to improve exposure assessment and to determine whether acrylamide leads to major diseases later in life. Own results: I have first authored a prospective European study showing that prenatal exposure to acrylamide, estimated by measuring hemoglobin adducts in cord blood, was associated with fetal growth restriction, for the first time. Objectives: To determine the effects of prenatal exposure to acrylamide alone and in combination with other potentially toxic adduct-forming exposures on the health of children and young adults. Methods: Both well-established and innovative biomarker methods will be used for characterization of prenatal exposure to acrylamide and related toxicants in blood from pregnant women and their offspring in prospective cohort studies with long-term follow-up. Risk of neurological disorders, impaired cognition, disturbed reproductive function and metabolic outcomes such as obesity and diabetes will be evaluated. Perspectives: CHIPS project will provide a better understanding of the impact of prenatal exposure to acrylamide from diet on human health urgently needed for targeted strategies for the protection of the health.

Link to the ERC project webpage: https://ifsv.ku.dk/ansatte/?pure=da/persons/196264

Keywords of the ERC project: Early life environmental epidemiology, biomarkers, diet, acrylamide, fetal origin of health and wellbeing

Keywords that characterize the scientific profile of the potential visiting researcher/s: Epidemiology, statistician, nutrient, psychology

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Project ID:	Project Acronym:	Evaluation Panel:
803880	**Epilepsy_Core**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Maeike Zijlmans**
Host Institution:	Universitair Medisch Centrum Utrecht - NLD

The core and effects of epilepsy: from chronic disease to curable disorder through innovative guided surgery

Epilepsy burdens 1% of the population. Brain surgery can cure seizures and stop cognitive decline, but it is complex and often unsuccessful. I aim to advance cure from epileptic brain disease radically by 1) pinpointing the core of epilepsy and 2) understanding the effects on normal brain functioning. High-frequency oscillations (HFOs) are novel markers of the core of focal epilepsy, discovered in long-term invasive EEG. I initiated direct HFO-based guidance of epilepsy surgery with intra-operative invasive electrodes. However, HFOs still appear stochastic epiphenomena. Therefore, I will now uncover the direct microlevel high-frequency EEG reflection of the distorted cortex. I will use three macrolevel signal prerequisites for seizure and HFO generation to innovate intra-operative recording and signal analysis: susceptible (evoke with long-distance electrical stimulation; cross-frequency coupling), sudden (low-noise adhesive electrodes; auto-regression) & spreading (high-density recordings; functional connectivity). I will pilot test technical solutions and optimize analyses with supervised machine learning based on pivotal epileptogenic versus healthy tissue and on postsurgical outcomes. Next, I will explore the broad effect of epileptic on physiological high frequency brain activity taking cognitive performance as epitome, especially in people without seizures. Current electrocorticography data come from limited, diverse and complex cases with no gold standards for diseased and normal cortex. I will therefore obtain data from 200 otherwise unguided brain surgeries with different levels of epileptogenicity and cognitive impairment: highly epileptogenic tumors (simple), gliomas (many) and meningiomas which compress healthy brain (uniform; partly without seizures). I will integrate techniques in a neurosurgical real-time recording and projecting device that simplifies finding and removing epileptogenic tissue to stop the distorting effect in focal brain disorders.

Link to the ERC project webpage:

Keywords of the ERC project: epilepsy; EEG

Keywords that characterize the scientific profile of the potential visiting researcher/s: biomedical engineering

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
864832	**ANTIBIOCLICKS**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Ruben Hartkoorn**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

BioInspired Clicked Siderophore-Antibiotics

The frightening increase in antibiotic drug resistance is threatening global healthcare as we know it. To this extent the World Health Organisation that has classes M. tuberculosis and Gram-negative nosocomial infections as the highest priority for novel R&D strategies. A major obstacle to drug discovery programs is to design inhibitors that can efficiently enter into bacteria. One such stealth strategy is exemplified by natural siderophore-antibiotics conjugates (sideromycins) that piggyback the bacterial iron acquisition machinery to enter bacteria. This Trojan-horse strategy has inspired the chemical synthesis of numerous sideromycin conjugates, with cefiderocol a current preclinical candidate. Despite the advances in this field, natural examples of sideromycins are still scarce, and finding new examples may provide further insight into siderophore antibiotic formation and delivery. ANTIBIOCLICKS will investigate a unique bioinspired conjugation chemistry that has been uncovered from a newly discovered natural sideromycin. This natural “click” chemistry is ideal for the coupling of catecholate containing siderophores (such as those of the WHO prioritised M. tuberculosis, A. baumannii, E. coli, P. aeruginosa and K. pneumonia) to antibiotics or other molecules. This project will aim to define the exact chemical mechanism behind this novel and surprisingly simple conjugation reaction, and use this unique and facile chemistry to generate a combinatorial library of siderophores with antibiotics and fluorophores. These products will subsequently be used to probe the exact mechanism of bacterial sideromycin uptake, potential intracellular decoupling and target engagement. Finally, the antibiotic and diagnostic potential of the generated siderophore conjugates will be evaluated. To this extent, ANTIBIOCLICKS will provide illuminating insight into new bioinspired conjugation chemistry, and evaluate its potential for novel bacterial therapeutics and diagnostics.

Link to the ERC project webpage:

Keywords of the ERC project: antibiotic design development and mechanism of action

Keywords that characterize the scientific profile of the potential visiting researcher/s: antibiotic, resistance, trojan horse

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Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
866510	**TRANSLATIONAL**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Anders Rosengren**
Host Institution:	Goeteborgs Universitet - SWE

A new translational strategy for tailored treatment of type 2 diabetes

Type 2 diabetes (T2D) is an escalating health problem of enormous proportions. Current treatment strategies are unable to stop disease progression and prevent the devastating complications. Clinical guidelines emphasise the need for personalized treatment. However, this is currently implemented on trial-and-error fashion. We have recently found that T2D patients can be divided into four clusters, each with different characteristics. This represents a major step forward by pointing out the high variability of the pathophysiology and leads us to propose that anti-diabetic treatment should ideally target the underlying pathophysiology of each patient. The overall goal is to test this proposition by targeting existing and new treatment to patients who are archetypes of the two most severe T2D clusters, characterised by poor insulin secretion and pronounced insulin resistance, respectively. As a starting point, we will study how treatment response to existing drugs is influenced by pathophysiological features and also the gut microbiota. Next, we will expand on our recent demonstration that b-cells dedifferentiate in T2D and define the functional and gene expression changes that cause secretory failure. These mechanistic insights will be used to identify new targets for b-cell preservation, which is essential to stop disease progression, in particular in patients with poor secretion. Finally, we will study new compounds for tailored treatment, including sulforaphane as an early intervention for those with severe insulin resistance. My combined training in cell-physiology, bioinformatics and clinical medicine is unusual but necessary to conduct this multi-disciplinary programme. Whilst the programme builds firmly on my past research, it extends far beyond what I have attempted previously by exploiting novel state-of-the-art methodology to address central metabolic questions of high relevance to understand the causes, management and – ultimately – prevention of diabetes.

Link to the ERC project webpage: https://www.gu.se/en/research/anders-rosengren

Keywords of the ERC project: type 2 diabetes, personalized medicine, precision medicine, clinical studies, metabolism, islet physiology, insulin secretion, insulin resistance, single-cell sequencing, bioinformatics

Keywords that characterize the scientific profile of the potential visiting researcher/s: type 2 diabetes, personalized medicine, precision medicine, clinical studies, metabolism, islet physiology, insulin secretion, insulin resistance, single-cell sequencing, bioinformatics

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Project ID:	Project Acronym:	Evaluation Panel:
949667	**CARsen**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Judith Feucht**
Host Institution:	Eberhard Karls Universitaet Tuebingen - DEU

Senolytic CAR T cells as novel therapeutic concept for solid tumors and senescence-associated diseases.

The adoptive transfer of T cells expressing CD19-directed chimeric antigen receptors (CARs) has yielded remarkable efficacy in patients with hematological B-cell malignancies. CARs are a class of synthetic receptors that reprogram T cell specificity, function and metabolism. Engineered T cells are applicable in principle to other cancers and diseases, but clinical success will critically depend on further progress to overcome current limitations such as antigenic heterogeneity or impaired T cell trafficking and function. We propose to develop CAR T cells targeting senescent cells as a novel therapeutic concept for cancer and senescence-associated diseases. Cellular senescence is a stress-response program characterized by stable cell cycle arrest that serves as a potent tumor-suppressive mechanism. Conversely, accumulation of senescent cells generates a chronic inflammatory milieu, which contributes to a plethora of pathologies, such as liver or lung fibrosis and can even promote tumor progression. Our preliminary data demonstrate that CAR T cells can efficiently clear senescent cells, providing therapeutic benefit in a murine model of liver fibrosis. We thus firmly believe that senolytic CAR T cells have broad therapeutic potential. To this end, we will apply innovative engineering strategies to develop modular CAR designs tailored to senescence-specific requirements. We will determine safety and efficacy of senolytic CAR T cells in murine models of cellular senescence and solid tumors. Importantly, we will evaluate combined treatment approaches of senescence-inducing therapies with CAR T cells targeting senescent and proliferating tumor cells. Finally, we will investigate engineering tools to optimally direct senolytic CAR activity to mediate durable tumor regression. This project combines two emerging concepts of anticancer therapies and goes beyond current applications of CAR therapies. The efforts may lead to promising new therapeutic avenues.

Link to the ERC project webpage:

Keywords of the ERC project: CAR T cells, immunotherapies, senolytics, anticancer treatment

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101001016	**PADRE**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Timo Laaksonen**
Host Institution:	Helsingin Yliopisto - FIN

Photoactivatable Drug Releasing Implants

This proposal introduces a next-generation platform for next generation optimally personalised drug therapy: on-demand drug releasing implants triggered and controlled by blue/UV light. The technology is based on novel light generation pathways and a light-sensitive nanocellulose drug reservoir. A formidable physiological barrier for light-triggered drug release has been the inability to use high-energy blue/UV light as the triggering signal. This is because the penetration depth of light drops to from a few cm to under 100 micrometers when moving from near-infrared to UV light, making deeper targets within tissues accessible only to red light. However, red light, with its intrinsically lower energy, has limited value in photochemical reactions because the photocleavage of covalent bonds typically requires UV-light. This is why many groups are looking at e.g. red-to-blue photon upconversion strategies. The major objective in PADRE is to circumvent the issue of unavailable blue light in implants through local light generation. Having access to light with higher energy will enable a much wider chemical toolbox, including photocleavable linkers. I will use blue/UV light to trigger and precisely control drug release. The approach creates an unconventional way to modulate the release profiles without unwanted drug leakage. The light will be generated through either 1) photon upconversion, or 2) integrated light sources. With the first approach, I will pioneer efficient red-to-blue/UV triplet-triplet annihilation upconversion in a hydrogel environment, while in the second approach I will generate light by a co-implanted light source. Both approaches are feasible according to my preliminary results on efficient triplet-triplet annihilation upconversion and photoresponsive liposomes and will be demonstrated in a working implant prototype. The core breakthrough of PADRE will be a viable solution to employ blue excitation in precisely-tailored drug-releasing implants.

Link to the ERC project webpage:

Keywords of the ERC project: light-activation, drug delivery, hydrogel, liposome

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101001237	**I-PACE**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Matthijs Brouwer**
Host Institution:	Academisch Medisch Centrum Bij De Universiteit Van Amsterdam - NLD

Improving Prognosis by using innovative methods to diAgnose Causes of Encephalitis

Background: Encephalitis is a severe inflammation of the brain that can be caused by viruses, bacteria and other microorganisms, or autoimmune disease. The impact is high: the case fatality rate is 10-20% and half of patients have neurological deficits. Identifying the cause of encephalitis is essential for early initiation of therapy and thereby improves outcome. The clinical challenge: Current diagnostics for encephalitis are insufficient. My prospective pilot study showed that the cause of encephalitis could be identified in only half of patients. Aim: The aim of I-PACE is to improve the cause-specific diagnosis of encephalitis using innovative diagnostic methods. Methods: I will use my encephalitis network of Dutch hospitals to study innovative diagnostic methods in 3000 patients with suspected encephalitis and validate the results in 2000 patients from Denmark, the UK and Zambia. I will collect clinical data, cerebrospinal fluid (CSF) and blood to enable state-of-the-art diagnostic studies and identify novel causes of encephalitis. First, I will perform virus discovery and DNA metagenomics sequencing to identify new infectious causes of encephalitis, combined with phage-display antibody sequencing. Second, I will perform CSF single cell gene expression studies to identify transcription patterns specific for the cause of encephalitis. Third, single cell immune profiling and anti-neuronal antibody detection assays will be used to identify new causes of autoimmune encephalitis. Finally, I will perform extensive metabolite and lipid analysis in the CSF to identify new biomarkers enabling a syndromic diagnosis to quickly differentiate between causes. Impact: With I-PACE I aim to increase the proportion of patients with a cause-specific diagnosis of encephalitis from 50% to 80%, facilitating direct and targeted treatment to improve the prognosis. I will discover novel causes of infectious and autoimmune encephalitis, and provide insights in its pathophysiology.

Link to the ERC project webpage:

Keywords of the ERC project: Encephalitis Diagnostics CSF Meningitis Lipidomics Meta-genomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: Translational researchers

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Project ID:	Project Acronym:	Evaluation Panel:
101020342	**TARGET**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Alberto Bardelli**
Host Institution:	Universita Degli Studi Di Torino - ITA

Targeting DNA repair pathways, sparking anti cancer immunity

This project will test for the first time the hypothesis that therapeutic inactivation of DNA repair pathways in cancer cells can be exploited for patient benefit by reawakening an anti-tumor immune response. Genomic instability and molecular heterogeneity, which occur in cancer cells with DNA repair deficiencies, fuel tumour progression and are associated with poor outcome. An exception is represented by Mismatch repair (MMR) deficient cancers as these tumours are exceedingly genetically heterogeneous but show favourable prognosis and remarkable response to immunotherapy. The molecular basis for the clinical outcome of MMR deficient cancers has long remained a mystery. Only recently it has become apparent that their biological properties are associated with increased levels of mutations, which unleash adaptive immunity and trigger immunosurveillance. We have reported that when MMR is impaired, cancers cells grow in immune-deficient mice but are unable to do so in immune competent animals. MMR inactivation increased the mutational burden and led to dynamic mutational profiles, resulting in persistent renewal of neoantigens and engagements of antigen-specific T cells. These data suggest an unprecedented high risk-high gain approach: the pharmacological blockade of proteins involved in DNA-repair as an anticancer therapy. This unconventional strategy builds on the concept that the immune system can identify and selectively target tumor cells carrying DNA alterations. Using in vitro and in vivo functional assays we will systematically assess whether and how inactivation of DNA repair genes provokes an immune response and restrict cancer growth. Notably, TARGET will discover and develop inhibitors of MMR and other DNA repair proteins that induce tumor immunity. The identification of DNA repair pathways which, when disabled, reawaken the immune system will provide transformative knowledge and could lead to the development of an entirely new class of anticancer drugs.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101021043	**Cor-Edit-P**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Christian Kupatt-Jeremias**
Host Institution:	Klinikum Rechts Der Isar Der Technischen Universitat Munchen - DEU

Cardiac open reading frame edition to study cardiomyopathies in pigs

Heart failure represents a common cause of death in European societies and is frequently based on dilated cardiomyopathy (DCM) which might be caused by mutations in cardiomyocyte genes. While no specific treatment exists, new therapeutic options are a major unmet clinical need. As attractive novel key approach, Cor-Edit-P will use Crispr-Cas9 based gene editing for distinct gene therapy of genetic cardiomyopathy, using pigs as a unique, clinic-related large animal model system. My lab tailored highly cardiotropic adeno-associated viral (AAV) vectors and their use in pigs in vivo, applying precise, reliable and versatile Cas9 technology. Pioneering this approach, we were able to restore significant dystrophin expression in muscles and hearts of pigs suffering from Duchenne muscle dystrophy. Exploiting unique and cutting-edge technology, Cor-edit-P aims at specifically eliminating the underlying cause of genetic DCM to improve cardiac function, reduce the risk of deadly arrhythmias and increase span and quality of life. Cor-edit-P will - generate currently lacking porcine models of genetic cardiomyopathy, using AAV-Cas9 to induce mutations in sarcomere genes, e.g. titin (TTN) and ß-myosin heavy chain (MYH7); - exercise curative Crispr-Cas9 mediated gene editing of DCM in pigs in vivo, using the PLN-R14del mutation in the phospholamban (PLN) gene as prominent example; - use human patient-derived PLN-R14del ventricular progenitor cells for gene correction ex vivo followed by transplantation of corrected cells into PLN-R14del pigs. Our approach implements a new paradigm for treating genetic cardiomyopathy and develops Crispr-Cas9 based gene therapy in pigs to foster clinical translation. Our work will influence the development of gene therapy by industry and academia and will benefit patients suffering genetic cardiomyopathy, but also further genetic diseases which are manifold prevalent in Europe.

Link to the ERC project webpage: https://med1.mri.tum.de/sites/default/files/redaktion/dateien/20221114_text-for-the-url_cor-edit-p_with-logo.pdf

Keywords of the ERC project: Crispr-Cas9 based gene editing; therapy of genetic cardiomyopathy; large animal models

Keywords that characterize the scientific profile of the potential visiting researcher/s: enthusiasm for cardiovascular research; eager for knowledge; experienced in molecular biological methods

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Project ID:	Project Acronym:	Evaluation Panel:
101021417	**FIBCAN**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Thomas Baumert**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale - FRA

Targeted strategies for prevention and treatment of fibrosis-associated liver cancer

Advanced liver diseases such as cirrhosis and hepatocellular carcinoma (HCC) are major challenges for global health. HCC is the second leading and fastest rising cause of cancer death worldwide. Viral and metabolic liver disease are the main risk factors for HCC, which nearly always arises in advanced liver fibrosis. For metabolic liver disease approved therapies are absent. Cure or suppression of viral infection cannot eliminate the HCC risk in patients with advanced fibrosis. Despite significant progress, therapeutic options for established HCC are still limited in efficacy and safety. Importantly, patient survival in HCC is dependent on the underlying fibrotic liver disease which is not targeted by approved HCC therapies. Addressing these unmet medical needs, FIBCAN aims to identify urgently needed targets for prevention and treatment of fibrosis-driven liver cancer. A key focus of FIBCAN will be the investigation of Claudin-1 as a previously undiscovered target for prevention and treatment of fibrosis-driven HCC. Our own data obtained in patient-derived model systems and tissues provide solid evidence that Claudin-1 is implicated in liver fibrosis and hepatocarcinogenesis, and overall and liver-specific patient death. To discover novel targets, we will apply a liver disease discovery platform modeling the clinical cell circuits of cirrhotic patients progressing to HCC combined with single cell RNA-seq and spatial transcriptomics of patient tissues. Proof-of-concept studies of target-specific compounds combined with biomarker discovery in cutting-edge patient-derived model systems will deliver novel strategies for further clinical development. A strong collaboration with pharma will lead to rapid translation of the FIBCAN program into the clinic. By delivering urgently needed therapeutic strategies for advanced liver disease and HCC, this proposal will have a marked impact on the management and outcome of patients with advanced liver disease in Europe and beyond.

Link to the ERC project webpage:

Keywords of the ERC project: liver disease, liver cancer, hepatitis C, hepatocellular carcinoma, cellular pathways, kinases, phosphatases, viral hepatitis, drug target, biomarker, cell circuits

Keywords that characterize the scientific profile of the potential visiting researcher/s: liver cell biology, liver cell signaling, animal models, drug development, computational analysis, data integration

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Project ID:	Project Acronym:	Evaluation Panel:
101021500	**LEGENDARE**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Fernando Rivadeneira**
Host Institution:	Erasmus Universitair Medisch Centrum Rotterdam - NLD

Leveraging genomic discoveries and skeletal phenotyping to improve osteoporosis patient care

Osteoporosis is a silent, systemic skeletal disease leading to fragility fracture. While the deleterious consequences for the individual, their families and society are well established, the causes of the disease remain elusive. Despite exhaustive clinical, epidemiological and genomic research, scarce understanding of the complex underlying disease mechanisms leading to bone fragility has hindered the improvement of clinical care. This LEGENDARE programme aims to implement a holistic integrative approach directed at discerning the underlying mechanistic pathways leading to bone fragility. The approach seeks translating genomic and imaging discoveries into meaningful clinical strategies to stratify risk; re-evaluate treatment indication; and ultimately, redefine (molecular) disease classification of patients with osteoporosis and other skeletal diseases. LEGENDARE will progress beyond the state-of-the-art by integrating genomic information from thousands of loci (genome regions) associated with musculoskeletal traits and other diseases, into "optimized" polygenic risk scores providing novel biological insight about skeletal disease. Skeletal research will be brought to a new level by enriching skeletal imaging with BIG DATA obtained with advanced whole-body EOS 3D X-rays. Approaching the whole skeleton as a unified organ will allow the unprecedented study of hidden relationships across bone compartments. Further, using artificial intelligence approaches, the complexity of the skeletal system will be modelled, integrating genomic, imaging and clinical data across epidemiological cohorts and patient settings. LEGENDARE will deliver knowledge on fundamental processes regulating skeletal fragility, unveiling new strategies for translational exploitation leading to improved clinical outcomes of osteoporosis patients. Discoveries will hold wider significance through potential spinoffs able to mitigate the societal impact of other diseases surging with bone fragility.

Link to the ERC project webpage: www.bonecraft.eu (under construction to be online in January 2024)

Keywords of the ERC project: Skeletal fragility; imaging; polygenic risk score; genetics; machine learning;

Keywords that characterize the scientific profile of the potential visiting researcher/s: data scientist; biostatistics; bioinformatics; geneticist; mechanical bioengineer;

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Project ID:	Project Acronym:	Evaluation Panel:
101039320	**MEGI CD**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Timon Adolph**
Host Institution:	Medizinische Universitat Innsbruck - AUT

Metabolic Gut Inflammation in Crohn's disease

The rising incidence of inflammatory bowel diseases such as Crohn?s disease (CD) has become a global health care issue in the 21st century. The complex genetic underpinning is increasingly appreciated, while environmental cues and specifically a Western diet are suspected to impact development and course of disease. Mechanistic insights that would support this assumption remain scarce and specific nutrients that trigger a flare are unknown. Westernisation of dietary habits is partly characterised by enrichment of long-chain fatty acids, which fuel metabolic inflammation of tissues beyond the gut. Here, we propose to establish the concept of metabolic gut inflammation as a fuel for CD. By analysing transgenic mice, human CD organoids and two independent CD patient cohorts, we seek to establish how dietary polyunsaturated fatty acids (PUFAs) affect gut inflammation and disease course. The proposed work is based on our previous observations that dietary PUFAs trigger a chemokine response and Crohn?s-like enteritis in mice, which is restricted by intestinal epithelial Glutathione peroxidase 4 (GPX4). GPX4 is an evolutionary conserved anti-oxidative enzyme which shows impaired activity in CD epithelium. The proposed work will identify how dietary PUFAs elicit gut inflammation in mice and which epithelial lineage executes the inflammatory response. In a next step, I propose to establish a critical crosstalk between GPX4 and metabolic hubs in gut epithelium to provide a basis for the concept of metabolic gut inflammation. Finally, we seek to translate findings by establishing that PUFAs evoke an inflammatory response from CD epithelium, and that PUFA intake impacts disease course. MEGI CD comprehends basic and translational science to set the basis for novel therapeutic strategies in a complex illness that requires better treatment modalities. The study will prove the concept of metabolic gut inflammation as a major driver of human CD, a basis for nutritional therapy.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101041424	**CIRCLE**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Piotr Kowalski**
Host Institution:	University College Cork - National University Of Ireland, Cork - IRL

Synthetic Circular RNA therapeutics for prevention of sepsis-associated organ failure

Reversing organ failure, a leading cause of death in sepsis, requires specific modulation of biological pathways in endothelial cells, which is currently not possible with the existing drugs available. Employing RNA-based drugs to control protein expression could offer a novel therapeutic strategy in the fight against sepsis. Circular RNAs (circRNAs) are a new class of non-coding RNAs with a unique closed-loop structure that could help address the current limitations of the RNA drugs in the disease context and open new therapeutic avenues. Therapeutic delivery of engineered synthetic circRNAs can allow taking full advantage of their unique features and functions, including increased intracellular stability, the ability to affect multiple biological pathways by sponging microRNA or proteins, and their potential for cellular context-specific control of protein expression via internal ribosome entry site (IRES)-mediated cap-independent translation. I recently co-developed methods for the circularization and purification of large synthetic circRNAs, and pioneered their use for robust and stable protein expression in eukaryotic cells, to address the short half-life of mRNA in biological systems. I also synthesized a new type of degradable polymers that enable tissue and cell-type selective delivery of large RNAs with low toxicity. Building on those findings, CIRCLE aims to expand the toolbox of therapeutic RNAs by engineering novel synthetic circRNAs for modulation of protein expression in sepsis (WP1 and WP2) and investigate the potential of synthetic circRNA delivery for developing RNA-based pharmacological intervention to reverse sepsis-associated lung and kidney failure (WP3 and WP4). By addressing an important gap in the knowledge on the utility of circRNAs for translational research the scientific impact of CIRCLE will extend across the research fields of pharmaceutical sciences, synthetic biology, and medicine.

Link to the ERC project webpage:

Keywords of the ERC project: nanotechnology, circular RNA, RNA delivery, sepsis, biomaterials engineering

Keywords that characterize the scientific profile of the potential visiting researcher/s: drug delivery, polymer chemistry, machine learning, synthetic biology, RNA biology,

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Project ID:	Project Acronym:	Evaluation Panel:
101041677	**TRANSIT-ND**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Ahmad Aziz**
Host Institution:	Deutsches Zentrum Fur Neurodegenerative Erkrankungen Ev - DEU

Tandem Repeats Associated with Neurogenomic Somatic Instability and Neurodegeneration

Dementia and other neurodegenerative diseases are among the leading causes of disability worldwide and have an immense societal impact due to lack of effective treatments. For developing better preventive and therapeutic strategies, it is essential to clarify their still largely elusive genetic basis and pathophysiology. Emerging insights from the study of rare hereditary repeat expansion disorders caused by elongations of repetitive DNA sequences ("tandem repeats" (TRs)) indicate that TRs could induce instability of neuronal DNA ("neurogenomic somatic instability"), and thereby instigate molecular changes that lead to neuronal degeneration. However, the role of highly prevalent TR variations or their somatic instability in the pathogenesis of common age-associated neurodegenerative diseases is unknown. Here, I aim to assess the role of TRs and their somatic instability in the pathogenesis of neuronal degeneration, the defining hallmark of all neurodegenerative diseases. To this end, I will 1) systematically identify TRs whose size or somatic instability are related to neuronal degeneration in the general population and/or disease severity in repeat expansion disorders, using an innovative approach combining "liquid biopsy" of neuronal tissue, high-throughput ultra-deep long-read DNA sequencing and ultrasensitive biomarkers of neuronal degeneration, 2) delineate the neuroanatomical pathways affected by TR somatic instability through comprehensive neuroimaging analyses, and 3) disentangle the underlying molecular and cellular mechanisms, using an extensive integrative multi-omics approach with experimental validation in neuronal cell lines and post-mortem human brain tissue. The wealth of unique insights from TRANSIT-ND could substantially increase our understanding of the pathogenesis of neuronal degeneration and provide shared targets for the prevention and treatment of a range of different neurodegenerative diseases that afflict millions of people globally.

Link to the ERC project webpage:

Keywords of the ERC project: genomics, multiomics, neurodegenerative disease

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics

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Project ID:	Project Acronym:	Evaluation Panel:
101042183	**SUBTREAT**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Yi Lu**
Host Institution:	Karolinska Institutet - SWE

Subtype as a key to reduce heterogeneity of treatment effects in major depressive disorder

Major depressive disorder (MDD) is a leading contributor to disability and suicide. It is the most costly brain disorder in Europe. Although multiple treatments are of proven efficacy, individual responses to treatments vary considerably and MDD recurrence is common. There is considerable motivation to improve treatment regimen for individuals with MDD. However, it has been challenging because of the fundamental lack of understanding about the causes of variable treatment outcomes. MDD is widely accepted as a heterogeneous disorder; yet, most research strategies effectively consider MDD as a single disorder. Progress in understanding the variable treatment response will depend on "patient stratification", i.e., identifying and accounting for patient heterogeneity when evaluating treatment efficacy. SUBTREAT proposes a unique direction which considers subtype as the key to link aetiological and treatment effect heterogeneity. Our approach is to break down the heterogeneous treatment outcomes of MDD into more narrowly defined subtypes with divergent aetiologies. Specially, I propose three work packages: 1) dissect treatment heterogeneity across subtypes; a particularly innovative aspect of SUBTREAT is that we will use advanced data science approaches to identify novel subtypes which correlate with differential treatment outcomes; 2) determine divergent causes underlying MDD subtypes; we will comprehensively investigate causes at three levels including genetic and causal epidemiological risk factors, and brain cell types; 3) develop a novel prediction algorithm for treatment outcomes stratified by patient subgroups. SUBTREAT will illuminate the causes of MDD subtypes and the principal patterns of how subtypes contribute to differential long-term treatment outcomes. SUBTREAT findings will promote targeted drug development and treatment optimization for patient subgroups to achieve precision psychiatry.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101042183

Keywords of the ERC project: depression, heterogeneity, treatment outcome, genetics, prediction, machine learning

Keywords that characterize the scientific profile of the potential visiting researcher/s: machine learning, statistical genetics, neuroscience

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Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101043848	**ARCHIMEDES**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Dario Greco**
Host Institution:	Tampereen Korkeakoulusaatio Sr - FIN

dAta-dRiven integrated approaches to CHemIcal safety assessMEnt and Drug dEvelopment

Traditional in vivo tesTraditional in vivo tests are hampering the development of new, safe and effective chemicals and drugs. If on one hand we need to ensure that dangerous chemicals do not emerge, on the other, we also need to promote rapid and sustainable innovation to successfully overcome the modern challenges of humankind. Toxicogenomics aims at clarifying the mechanism of action (MOA) of chemicals by using omics assays. The Adverse Outcome Pathways (AOP) concept is also emerging to contextualise toxicogenomics-derived MOA. Efforts are ongoing to anchor AOPs to molecular assays, but systematic embedding of AOP-derived in vitro tests and Integrated Approaches to Testing and Assessment (IATA) are still unestablished. At the same time, toxicogenomics-based evidence still struggles to gain regulatory acceptance. I aim to implement an integrated strategy based on state-of-the-art big data science, artificial intelligence (AI), toxicogenomics, molecular assays and cell technology via a novel Knowledge Graph approach. I will do so by developing the Toxicology Knowledge Graph (TKG), an innovative data platform where the currently fragmented knowledge in the field is going to be curated and integrated. The TKG will serve as a learning platform for artificial intelligence (AI) algorithms, which will be used to: 1) find new characteristics of chemicals/drugs; 2) infer associations between exposures and diseases; 3) select the most relevant cell lines to study specific phenotypes/chemical classes; 4) find the best genes to be used as reporters for specific AOPs; 5) define the applicability domain of computational, experimental and IATA models. I will also establish and validate regulatory-relevant high-throughput molecular assays to investigate the point of departure (PoD) of exposures. The ARCHIMEDES project will shift the paradigm of chemical and drug development, facilitating the emergence of new, smarter, greener, and more sustainable chemicals, drugs and materials.

Link to the ERC project webpage: Www.FHAIVE.fi

Keywords of the ERC project: Systems biology. Systems theory. Network modelling. Toxicology. Pharmacology. Knowledge graph. Graph learning. Pulmonary fibrosis

Keywords that characterize the scientific profile of the potential visiting researcher/s: Same as above.

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Project ID:	Project Acronym:	Evaluation Panel:
101044180	**CoM-BraiN**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Tim Dyrby**
Host Institution:	Region Hovedstaden - DNK

Non-invasive Conduction Velocity Mapping in Brain Networks: A novel imaging framework for axonal fingerprinting of brain connections in health and disease

Axonal bundles in cerebral white matter form the structural basis of functional brain networks, enabling effective integration of neural activity. The axonal connections are not homogenous structures. Axons differ in diameter and myelination, enabling signal conduction at different velocities. This axonal diversity is a clinically relevant microstructural feature, as neurodegenerative or neuroinflammatory processes can affect axon diameters differently. Recent advances in Magnetic Resonance Imaging (MRI) have enabled the non-invasive mapping of the microstructural properties of brain network connections in live brains. But attempts to correlate these structural features with brain function have not yet been successful. I have pioneered the mapping of axon diameters that are directly linked to the conductive properties of axonal connections by using diffusion MRI in living human brain. Also, I have established an unique cross-disciplinary validation setup for such methods by combining nanoscopic 3D Synchrotron Radiation Imaging and functional cell-specific targeting techniques. By Conduction Velocity Mapping in Brain Networks (CoM-BraiN) I will be able to unravel the altered functional dynamics of the microstructural connections in the diseased brain. Methodologically, I will push the frontiers of MRI by creating a new translational CoM-BraiN framework for non-invasive and in-vivo studies in animals and humans. Clinically, CoM-BraiN will provide a new window into the characterization of neuropathological changes in the diseased brain and contribute to the identification of structure-function fingerprints of psychiatric and neurodegenerative disorders that are thought to be a major pathogenic factor in many brain diseases.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101044387	**PredictCOPD**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Maria Rosa Faner**
Host Institution:	Universitat De Barcelona - ESP

Understanding the host-environmental interactions across the lifespan determining lung function trajectories and COPD

Chronic Obstructive Pulmonary Disease (COPD) has been traditionally understood as a self-inflicted disease caused by tobacco smoking occurring in old individuals. Over the past few years, however, our group and others have proposed that the pathogenesis of COPD goes beyond smoking, and that there is a range of lung function trajectories through life (trajectome); some of them have roots in early life and can lead to COPD, cardiovascular and metabolic morbidity as well as premature death, while others are associated with healthy ageing. Here I propose that, detrimental gene (G) and environment (E) interactions occurring early in life (T) constitute a 'first injury hit' that alters the normal lung developmental program and modify the pace of normal lung aging by reducing the resilience of the lungs to future GxExT interactions. Accordingly, lifelong GxExT interactions determine the individual trajectome and, eventually, the occurrence of COPD and associated multimorbidity. PredictCOPD aims to identify the interactions and mechanisms that determine which individuals will develop COPD and multimorbidty at some point of their life. The specific aims are: 1) to identify the lifelong environmental and host risk factors associated with the trajectome, COPD and multimorbidity, 2) to use a novel liquid biopsy method to identify biological factors driving the trajectome, COPD and multimorbidity; 3) to identify clinically relevant preventive and/or early therapeutic targets integrating the results from aims 1 and 2 with novel analytical approaches and 4) to validate findings both in vitro and in other available cohorts. The project will leverage from several available population and COPD patient studies with available clinical data and biological samples. The results of PredictCOPD have the potential to: 1) promote healthy ageing by preventing and eventually eradicate COPD and associated multimorbidity; and, 2) change COPD treatment from palliative to causal.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101044665	**PROTECT**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Daniel Aili**
Host Institution:	Linkopings Universitet - SWE

Protease Profiling and Triggered Drug Delivery for Personalized Cancer Therapy

Proteases are involved in all hallmarks of cancer and are key regulators of tumor progression. The difficulties to monitor protease activity in vivo with sufficient sensitivity and selectivity make development of protease targeting cancer drugs and implementation of protease activity as a diagnostic and prognostic biomarker very challenging. The aim of PROTECT is to develop a novel comprehensive protease activity profiling platform for cancer-associated extracellular proteases that can address the main limitations of current strategies for in vivo protease activity monitoring with the ambition to enable a dramatic increase in sensitivity and multiplexing capabilities. We will design Liposomal Activity-Based Sensors (LABS) that can amplify proteolytic cleavage by triggering release of liposome encapsulated synthetic biomarkers. We will further leverage the possibilities to extract tumor specific protease profiles for development of personalized protease-triggered liposomal drug delivery vehicles (PROVES) for precision medicine. Sophisticated protease-responsive membrane active peptides (proMAPs) will be developed to couple protease activity to biomarker and drug release. Methods to correlate biomarker release patterns to protease activity profiles in 3D breast cancer models will be explored. The PROTECT platform can then rapidly be repurposed for precision drug delivery. The PROVES concept will combine the excellent properties of liposomes for drug delivery and the optimal combination of proMAPs, based on the protease activity profile retrieved from the LABS, for optimized protease-triggered liposomal drug release. Combined, the LABS and PROVES concepts represent a unique and comprehensive platform for diagnostics and personalized cancer therapy. The proposed work goes far beyond stat-of-the-art and will address a significant and real bottleneck that hampers drug development and exploitation of proteases as diagnostics and prognostic cancer biomarkers.

Link to the ERC project webpage: https://liu.se/en/research/m2lab

Keywords of the ERC project: Proteases, Liposomes, Peptides, Drug delivery, Breast cancer

Keywords that characterize the scientific profile of the potential visiting researcher/s: lipid biophysics, peptide design, membrane active peptides, breast cancer models

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Project ID:	Project Acronym:	Evaluation Panel:
101044753	**READIHEAR**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Waldo Nogueira Vazquez**
Host Institution:	Medizinische Hochschule Hannover - DEU

Rehabilitation and Diagnosis of Hearing Loss based on Electric Acoustic Interaction

Hearing loss is the most common sensory deficit in the elderly, and it is becoming a severe social as well as a health problem. Across the whole lifespan, from new-borns to the elderly, hearing loss impairs the exchange of information, thus significantly impacting everyday life, causing loneliness, isolation, dependence, frustration and communication disorders. Cochlear implants (CIs) are hearing prosthetics that stimulate the auditory nerve with electrodes placed inside the cochlea. CIs are gradually being implanted in subjects retaining low-frequency residual hearing. In general, these subjects obtain large benefits in speech perception from electric acoustic stimulation, although large variability exists and some subjects do not benefit. Therefore, it is highly desirable to create objective diagnostics to assess acoustic low-frequency hearing to indicate cochlear implantation, to monitor and preserve hearing during the implantation procedure and to understand the mechanisms related to electric acoustic stimulation benefits. The ground-breaking nature of the READIHEAR project is to investigate the fundamental interaction mechanisms between electric and acoustic stimulation across the auditory pathway, from the cochlea up to the auditory cortex. The fundamental understanding will set the basis for a new generation of diagnostic devices of hearing loss that combine for the first time minimally invasive electric acoustic stimulation. Moreover, READIHEAR will assay a novel auditory prosthetic that makes use of the interaction mechanisms between acoustic and electric stimulation delivered through minimally invasive electrodes. These developments will be beneficial for a large population suffering from hearing loss across the whole lifespan, from young children who will benefit from improved hearing diagnostics to the elderly population who will benefit from minimally invasive electric acoustic stimulation technology as the treatment for age-related hearing loss.

Link to the ERC project webpage: https://vianna.de/01_workgroups/nogueira/research/eas.html

Keywords of the ERC project: Auditory, hearing, diagnostic, hearing aid, cochlear implant

Keywords that characterize the scientific profile of the potential visiting researcher/s: Engineer, audiologist, Signal Processing, psychoacoustics, electrophysiology, computational model

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Project ID:	Project Acronym:	Evaluation Panel:
101045236	**DISSECT-HF**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Peter Vandermeer**
Host Institution:	Academisch Ziekenhuis Groningen - NLD

Dynamic engIneered heart tiSsue to Study intEr-individual susCeptibily and improve Treatment of Heart Failure

The objective of DISSECT-HF is to generate engineered heart tissue (EHT) with the use of human induced pluripotent stem cells (hiPSC) from specific forms of heart failure (HF). It focusses on three etiologies of HF with a clear trigger and a large inter-individual susceptibility (pregnancy induced HF, anthracycline cardiotoxicity and PLN cardiomyopathy) to unravel common pathophysiological mechanisms involved in the development of HF. The rationale is: - Better understanding of molecular pathways leading to HF and knowledge about inter-individual susceptibility is needed to improve treatment. - For detection of changes on a molecular level cardiac tissue is needed. - Using innovative experimental approaches, such as dynamic loaded EHT (dyn-EHT), patient specific cells, unbiased target finding and deep phenotyping, I will dissect common disease pathways in the development of HF. SPECIFIC OBJECTIVES: 1. Construction of dyn-EHT from patient specific hiPSC derived cardiomyocytes, endothelial cells and fibroblasts. 2. Generation and deep-phenotyping of dyn-EHT from: A) Females with pregnancy induced HF (susceptible) and siblings with a normal pregnancy (resilience) B) Cancer patients with severe HF after anthracyclines (susceptibility) and patients who could resist high dose anthracyclines (resilience) C) Patients with an early PLN cardiomyopathy phenotype (susceptible) versus elderly asymptomatic PLN mutation carriers (resilience) 3. Identify overlapping and diverse factors. 4. Validate discoveries and apply in unique human cohorts with data on incident HF. WORKPACKAGES: WP1: Optimize construction of dyn-EHT from patient specific hiPSC. WP2: Phenotyping of dyn-EHT from the three HF etiologies focussing on susceptibility and resilience. WP3: Explore the transcriptome and proteome and apply a systems biology approach. WP4: Validate results and explore human relevance in a large cohort with unique phenotyping.

Link to the ERC project webpage: www.vandermeerlab.com

Keywords of the ERC project: tissue engineering - stem cells - heart failure

Keywords that characterize the scientific profile of the potential visiting researcher/s: interest in translational research related to cardiac diseases

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Project ID:	Project Acronym:	Evaluation Panel:
101053225	**CLOCKrisk**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Eva Schernhammer**
Host Institution:	Medizinische Universitaet Wien - AUT

Targeting the circadian clock in personalized disease prevention

Virtually every cell of our body follows the 24-hr 'circadian' rhythm of a hypothalamic master pacemaker that evolved in the natural light-dark cycle. Decoding this circadian clock culminated in the Nobel Prize in Physiology or Medicine 2017 for the discovery of molecular mechanisms controlling the circadian rhythm. It is now recognized that a strong, unperturbed circadian clock is a hallmark of healthy aging. The introduction of electric light, however, presents unique challenges: today, 20% of the global work force engages in alternate working hours associated with light in unnatural times. Increases in the risk of major chronic disease and mortality have been associated with night work. Further, night-activity is widespread also outside of work, implicating potential risk for many. This project targets the urgency of alleviating adverse health consequences of a perturbed clock. It does so by aiming to decipher individual risk and related mechanisms 1) using a cutting-edge multi-polygenic score approach; 2) employing transgenerational, deeply phenotyped cohort approaches; and 3) carrying out interventions using genetic risk stratification. This epidemiological project builds on pioneering work of the applicant who conducted the first prospective study to demonstrate significant health effects of chronic clock dysregulation, leading WHO to classify night work as a probable carcinogen. Using transdisciplinary approaches, she implemented field and genetic studies and developed circadian biomarkers, establishing the field circadian epidemiology. Tying the transformative body of her work together, she proposes to take the next ground-breaking leap: To 1) identify the night-active individual who develops disease, 2) profile mechanisms involved, and 3) optimize effectiveness of interventions to improve sleep and shift work disorder, facilitating immediate implementation of risk-based prevention strategies aimed at promoting healthy aging in spite of clock perturbations.

Link to the ERC project webpage:

Keywords of the ERC project: genetic risk score, shift work tolerance

Keywords that characterize the scientific profile of the potential visiting researcher/s: interest in genetic epidemiology, adding value by extending research to other national biobanks with existing GWAS

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Project ID:	Project Acronym:	Evaluation Panel:
101055029	**circRNA4DMD**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Dan Peer**
Host Institution:	Tel Aviv University - ISR

Circular RNA Therapeutics for Duchenne Muscular Dystrophy

RNA therapeutics is an emerging field explored in various types of diseases such as genetic disorders, cancer, inflammation and viral infections. Currently, most of the research focuses on the delivery of mRNA molecules that will transiently express a desired protein that can replace a defective protein or manipulate gene expression in the cells. My lab was the first to show systemic, cell-specific delivery of mRNA molecules in animals. Our approach and our novel amino lipids were translated to several clinical trials in the field of infectious and monogenic diseases. In protein replacement therapy, the main hurdle of using mRNA is the relative short half life of the mRNA. To address this, I suggest an approach for long-term expression: Circular RNA (circRNA), a covalently closed loop single stranded RNA that has a significant prolonged stability compared to linear mRNA. Thus, presents an immense advantage in protein replacement therapy. Duchenne muscular dystrophy (DMD) is caused by X-linked recessive mutation in dystrophin gene, leading to lack of functional dystrophin protein. This disease affects 1:5,000 males, causes a progressive loss of muscle tissues, ultimately leading to disability and premature death. Because DMD pathology is caused by the lack of functional dystrophin, restoring the function of dystrophin is a potential therapeutic strategy. As Lipid nanoparticles (LNPs) are the most clinically advanced candidate for RNA delivery, able to entrap large RNA payloads, herein I propose an innovative multidisciplinary approach for the specific delivery of circRNA-LNPs to muscle cells that will express the dystrophin protein and replace the defective one in a DMD mouse model. The long-term expression of the circRNA will offer new hope for the treatment of monogenetic diseases such as DMD. This approach may ultimately become a novel therapeutic modality for DMD and open new avenues for implementing circRNAs for other types of genetic disorders and vaccines

Link to the ERC project webpage: https://dan-peer.tau.ac.il/research/circular-rna-therapeutics-for-duchenne-muscular-dystrophy/

Keywords of the ERC project: DMD; LNPs; circRNA; mRNA

Keywords that characterize the scientific profile of the potential visiting researcher/s: expert in circRNA; DMD mouse models;

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Project ID:	Project Acronym:	Evaluation Panel:
101075118	**DailySAM**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Simon Jochems**
Host Institution:	Academisch Ziekenhuis Leiden - NLD

Understanding respiratory tract infections through minimally-invasive, daily nasal sampling in children

Pneumonia is the number one infectious cause of death in children worldwide. Many of the viruses and bacteria that cause pneumonia regularly infect, or colonize, the upper respiratory tract (URT) without causing disease. This drives community transmission but is also an important source of immunity. The processes and key host immune and microbiota factors that determine the infection kinetics, transmission and development of immunity during such infections need elucidation. I have recently optimized minimally-invasive nasal sampling analysis methods using Synthetic Absorptive Matrix (SAM) strips that now allow me to address these knowledge gaps. Through the daily collection of such well-tolerated nasal samples in children, I will study non-pathological, naturally-acquired URT infections, but also controlled infections in an ethical and safe manner using the live attenuated influenza vaccine. In addition, I will perform high frequency nasal sampling in groups of schoolchildren to precisely measure transmission events over time and even infer exposure. Incoming bacteria, viruses and the resident URT microbiome as well as mucosal host innate and adaptive immune responses will be quantified in parallel throughout infections using existing and new high-throughput assays, including an antigen array and microfluidic qPCR for 32 pathogens. Multi-omics integrative time-series analyses and mathematical modelling will be used to identify parameters that are central and predictive for pathogen acquisition, replication and clearance; as well as for transmission and immune boosting. Key novel markers and concepts will be validated using state-of-the-art in vitro mucosal models. The comprehensive and detailed understanding of URT infections obtained in this project can lead to better diagnostics, mucosal targeted therapies and vaccines, and provide a basis for the improved predictions of pathogen spread and public health effects of interventions at the population level.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101075421	**ExMilk**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Trine Moholdt**
Host Institution:	Norges Teknisk-Naturvitenskapelige Universitet Ntnu - NOR

Exercised breastmilk: a kick-start for childhood obesity prevention

Innovative preventive strategies are urgently required to halt the rising prevalence of childhood obesity given the inefficacy of current interventions. Mother-to-child transmission of obesity accounts for a large proportion of childhood obesity, more than what can be explained by genes. Nutrition during the first 3 months of life is crucial, with rapid weight gain in this period associated with subsequent obesity. Breastmilk is considered optimal for infant nutrition, but its composition depends on the mother's metabolic health: the concentrations of some breastmilk compounds linked to infant obesity are associated with maternal body mass index. Maternal lifestyle factors, such as diet, can alter breastmilk composition. Little is, however, known about the effect of exercise during lactation. Exercise is a major regulator of systemic metabolism affecting multiple tissues and organs. In this ambitious, inter-disciplinary project, I will determine how exercise during lactation influences breastmilk composition in women with overweight/obesity and whether exercise-induced changes in breastmilk will influence infant obesity risk. My preliminary data show acute effects of exercise on breastmilk concentrations of adiponectin and lipid metabolites relevant for energy metabolism. In ExMilk, I will determine both acute effects and adaptations after regular exercise on a complex matrix of breastmilk compounds. By linking breastmilk data to comprehensive data for the infants, I will investigate the potential mechanisms underlying the effects of maternal exercise on infant obesity risk, mediated by changes in breastmilk composition. To reach my goals, I will perform gold-standard randomised trials and analyse biological samples from mothers and infants on multi-omics platforms. My experience in metabolomics and exercise intervention trials in reproductive-aged women will enable me to break new ground in understanding how exercise during lactation modifies infant obesity risk.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: https://excar.info/research/ex-milk

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Project ID:	Project Acronym:	Evaluation Panel:
101075494	**MultiPRESS**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr David Marlevi**
Host Institution:	Karolinska Institutet - SWE

Multiscale Imaging of Cardiovascular Pressure Gradients – a Paradigm Shift in Hemodynamic Risk Prediction

Regional quantification of cardiovascular pressure gradients is critical for diagnosis, treatment planning, and risk prediction of many cardiovascular diseases. Still, for a large number of conditions, non-invasive assessment is obstructed by inherent method limitations, and a wide range of cardiovascular instances exist where regional pressure behaviour remains unexplored. The MultiPRESS project main objective is to develop a novel imaging paradigm for non-invasive assessment of cardiovascular pressure gradients, overcoming critical limitations of existing techniques through a unique multiscale approach. Doing so, the MultiPRESS project seeks to – for the first time – extend non-invasive hemodynamic risk prediction into previously inaccessible cardiovascular domains, advance our knowledge of complex hemodynamic behaviour, and tackle remaining urgent clinical challenges across the heart, aorta, and brain. Using deep integration of advanced full-field magnetic resonance imaging (4D Flow MRI), super-resolution networks, and physics-informed image processing, a set of core developments will allow for unique, comprehensive image-based pressure gradient assessment across (1) spatial (big/small vessels), (2) temporal (fast/slow flows), and (3) flow (laminar/turbulent) scales, with developments consistently validated in dedicated in-silico, in-vitro, and in-vivo cohorts. These developments will then be utilized on a set of core applications across (4) cardiovascular scales (heart/aorta/brain), addressing urgent clinical challenges and extending image-based pressure gradient quantification through previously inaccessible domains. Based in a unique multidisciplinary setting at Scandinavia's largest university hospital, successful delivery of MultiPRESS will represent a paradigm shift in clinical hemodynamic risk prediction, and pave way for new scientific knowledge revitalizing risk stratification of complex cardiovascular disease across the heart, aorta, and brain.

Link to the ERC project webpage: https://academic.oup.com/eurheartj/article/44/19/1676/7046109

Keywords of the ERC project: 4D Flow MRI, machine learning, medical imaging, cardiovascular

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101075873	**DYE-LIGHT**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Félix Sauvage**
Host Institution:	Universiteit Gent - BEL

Pulsed Laser Light and Nano-encapsulated Ocular Dyes for Advanced Therapies in the Eye

Ocular diseases affect the quality of life of millions of patients. Despite improvements in pharmacological treatments, the arsenal of medications to treat severe ocular diseases today remains rather restricted to traditional drugs. Use of most modern biotherapeutics like proteins and nucleic acids, could be a major step forward. However, current ways of administration such as eye drops and intravitreal injections, are no longer sufficient to deliver these drugs to most targets in the eye. Therefore, novel concepts allowing biotherapeutics to safely overcome ocular barriers are of high interest. In ocular surgery, pulsed-lasers (P-Ls) are used for 'tissue cutting', though safety concerns remain. DYE-LIGHT hypothesizes that strategies which would allow the use of P-Ls in the eye at much lower energy than today, could considerably improve safety and pave the way for both novel ocular therapies and advanced surgical interventions. DYE-LIGHT will explore vital dyes, as used by ocular surgeons to stain tissues, as photosensitizers. DYE-LIGHT follows the recent observation that P-L irradiation of ocular dyes can result in the formation of water vapor nanobubbles ('dye-based nanobubbles') and thermophoretic transport ('dye-based thermophoresis'). Interestingly, these biophysical phenomena occur at a laser energy that is ~ 1000 times less than a P-L alone. As compared to free dyes, dyes encapsulated in nanocarriers are expected to penetrate less into the retina, which might improve safety. Therefore, focus in DYE-LIGHT will be on nano-encapsulated ocular dyes. DYE-LIGHT will explore the potential of dye-based nanobubbles for delivery of nucleic acids in the corneal endothelium and for spatial selective vitreolysis in the eye. Finally, DYE-LIGHT will explore dye-based thermophoresis for controlled transport of nanomedicines injected in the vitreous towards the retina. If successful, this might open new perspectives to improve the efficacy of retinal drug and gene delivery.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101076351	**SMHEART**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Aurelien Bustin**
Host Institution:	Universite De Bordeaux - FRA

Smart Cardiac Magnetic Resonance Delivering One-Click and Comprehensive Assessment of Cardiovascular Diseases

Cardiovascular disease (CVD) causes at least 1.8 million European deaths annually, exceeding fatalities from cancer, chronic respiratory disease, and diabetes. Consequently, the fight against CVD has become the main priority of the World Health Organization. In the pursuit of understanding and treating CVD, cardiac magnetic resonance imaging (CMR) has remained the only modality capable of providing a comprehensive assessment of the heart's function and structure without harmful radiation. Unfortunately, current CMR systems remain too slow, too complex, require highly trained specialists and, as such, have presented a barrier to a wider adoption of CMR. The aim of my ERC project is to unleash the full potential of CMR to transform patient trajectories by introducing a fast, one-click, fully automated, and comprehensive imaging pipeline applicable to diagnosis, prognosis, and therapy selection in cardiology. This aim will be achieved by (i) creating a novel imaging technology that collects CMR data in a single continuous free-breathing scan, taking into account post-processing requirements at the very origin of CMR sequence design; (ii) exploiting the unique contrasts generated by this technology to automatically extract quantitative markers on cardiac anatomy, function, and tissue characteristics; and (iii) translating this transformative technology from a pre-clinical to a clinical setting. This will be the first-ever integrated cardiac imaging pipeline in which CMR images are acquired in a single click, jointly represented in a single volume, and automatically analysed. This will unlock obstacles for broader acceptance of CMR and unleash the full potential of CMR to maximize its impact on patient trajectories. The results of this project will pave the way towards robust image-based strategies for personalized patient care (diagnosis, risk stratification, therapy selection, monitoring, and image-guided interventions).

Link to the ERC project webpage:

Keywords of the ERC project: Cardiac Magnetic Resonance Imaging Artificial Intelligence

Keywords that characterize the scientific profile of the potential visiting researcher/s: MR physicist, Artificial Intelligence, Medical Imaging

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101078711	**VascularID**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Sebastian Weingärtner**
Host Institution:	Technische Universiteit Delft - NLD

MRI-based ID of the Vasculature across the Heart-Brain Axis

Microvascular impairment is a hallmark of many of today's most burdening diseases, including forms of ischemic heart disease, stroke, and dementia. It is also the most promising candidate to explain the link between cardiovascular and brain disease (so-called heart-brain axis). However, only histology provides comprehensive assessment of the microvasculature, and is rarely available in vivo as it requires invasive biopsy. The lack of early, non-invasive markers limits our pathophysiological understanding and crucially affects treatment success, as preventive intervention is the only successful clinical management strategy available. With a major leap in Magnetic Resonance Imaging (MRI) physics, I will address this need and develop VascularID, a fully non-invasive toolset for the quantitative assessment of cardiac and cerebral microvasculature. This non-invasive biopsy exploits microscopic magnetic fields around the vessels to obtain structural information about the microvasculature. It is contrast-free and resilient against field inhomogeneities and can, for the first time, be used in both the heart and the brain. Combined with a new generation of non-contrast perfusion MRI, VascularID will provide comprehensive functional and structural information. My approach will first be validated in a micro-printed 3D model of the vasculature. In vivo feasibility will be demonstrated in an animal model. Proof-of-principle studies with VascularID in a cohort of patients suffering from heart disease and a cohort of patients with cerebral small vessel disease will demonstrate the clinical feasibility. I will develop, validate, and disseminate VascularID for research and clinical use to enable groundbreaking insights into the smallest blood vessels. These insights are perfectly poised to provide the missing key to the vascular underpinnings of diseases that form the major burden to our health care system in the years to come.

Link to the ERC project webpage: www.mars-lab.eu

Keywords of the ERC project: Magnetic Resonance Imaging, Nuclear Magnetic Resonance, Relaxometry

Keywords that characterize the scientific profile of the potential visiting researcher/s: 3D Micro printing, relaxometry, nmr

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Project ID:	Project Acronym:	Evaluation Panel:
101078824	**FEMALE-PH**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Konda Babu Kurakula**
Host Institution:	Stichting Vumc - NLD

Mending sex differences: Unravelling the female predominance in pulmonary hypertension

Pulmonary hypertension (PH) is a rare but progressive fatal disease characterized by accumulation of persistently activated cell types in the pulmonary vascular wall exhibiting abnormal expression of genes driving proliferation, inflammation, and metabolism. The currently used vasodilatory therapies have little or no impact on this activated phenotype and therefore offer no cure or even substantial survival benefit. PH has a high female predominance (3:1 to 9:1). This proposal aims to understand the mechanism behind the high female predominance to identify novel therapeutic targets to attenuate disease progression in male and female PH patients. Female predominance can be linked to sex hormones and/or incomplete X chromosome inactivation (XCI) leading to biallelic expression of immunoinflammatory and metabolic genes. To understand the impact of oestrogen and androgen signalling on abnormal vascular remodelling in PH, I will develop a unique opposite-sex lung transplantation rat model, identify oestrogen metabolites in a large set of patient serum samples and explore their biological relevance using pulmonary vascular cells from male and female PH patients in cell-based assays. Preliminary experiments suggest there is incomplete XCI in PH. I propose to combine sequencing and molecular studies to extensively characterize the impact of incomplete XCI on the physiology of male and female PAH cells and identify genes and druggable targets regulating incomplete XCI in PH. Finally, I will explore a novel pulmonary endothelium-specific drug delivery method to deliver identified promising genes/compounds to selectively inhibit the activated pulmonary vasculature thereby minimalizing side effects compared to current delivery methods. Together, this high risk-high gain study will dissect the molecular mechanisms underlying the unresolved female predominance in PH and offer novel pulmonary endothelium-specific therapies for both male and female PH patients.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101078824

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

Project ID:	Project Acronym:	Evaluation Panel:
101087883	**SARCOMAkids**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Eleni Tomazou**
Host Institution:	St. Anna Kinderkrebsforschung Gmbh - AUT

Developmentally programmed pediatric sarcomas: a versatile platform for drug discovery and molecular precision medicine

Pediatric sarcomas account for ~20% of childhood cancers. They have disappointing survival rates, with very little therapeutic progress over the last three decades. We clearly have to rethink the science and find new ways to tackle these devastating tumors. I propose that new cellular models are needed that account for the developmental origins of pediatric sarcoma, in order to accelerate drug discovery and molecular precision medicine. Focusing on Ewing sarcoma, which is a developmental cancer caused by a (known) fusion oncogene expressed in (unknown) cells-of-origin, we will pursue a "build it to understand it" approach and construct in vitro and in vivo tumor models starting from human pluripotent stem cells (hPSCs). We will validate these models against our single-cell and spatial maps of Ewing sarcoma tumors, and we will pursue initial applications in academic drug discovery – targeting the regulatory programs of Ewing sarcoma cells, metabolic dependencies of the tumor microenvironment and developmentally programmed tumors in their in vivo context. To build Ewing sarcoma models in a molecular defined manner, we will map oncogene-competent cell states by inducing EWS-FLI1 expression in hPSC-based models of human development (Aim 1). We will create supportive tumor microenvironments by 3D differentiation and CRISPR screening in stromal cells (Aim 2). Finally, we will evaluate the ability of in vitro models to form tumors in mice, and we will pursue full in vivo modeling of Ewing sarcoma using genetically engineered teratomas (Aim 3). Compared to patient-derived xenografts, organoids or cell lines, our approach captures early events of tumorigenesis, providing complementary in vitro and in vivo models of Ewing sarcoma for biomedical and translational research. This approach will generalize to other tumor types, as it takes the concept of developmental cancers seriously and operationalizes it using cellular programming and high-throughput functional biology.

Link to the ERC project webpage: https://ccri.at/research-group/eleni-tomazou-group/

Keywords of the ERC project: pediatric sarcomas, disease modeling, epigenetics, transcription regulation, oncogenic fusion proteins, stem cell biology, CRISPR screening, single-cell sequencing, precision medicine

Keywords that characterize the scientific profile of the potential visiting researcher/s: developmental biology, cell fate engineering, in vivo cancer modelling, functional screens

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Project ID:	Project Acronym:	Evaluation Panel:
101088351	**GLUCO-SCAN**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Wolfgang Bogner**
Host Institution:	Medizinische Universitaet Wien - AUT

Deuterium labeling of GLUCOse improves magnetic resonance imaging Sensitivity to CANcer metabolism

The targeted scientific breakthrough of GLUCO-SCAN is the development and clinical evaluation of a disruptive whole-body molecular imaging concept for cancer assessment. The only currently established whole-body molecular imaging device is positron emission tomography (PET). Glucose (Glc)-sensitive PET is widely used in cancer diagnosis and treatment assessment, but has several major limitations: PET involves harmful ionizing radiation, is expensive, not widely available, and cannot differentiate between cancer-specific and normal cellular glucose uptake. These limitations prohibit an even more widespread use of PET, e.g. for screening. We propose a new Magnetic Resonance Imaging (MRI) concept, whole-body deuterium metabolic imaging (DMI) that will overcome these limitations. Deuteration is a simple chemical procedure with which it is possible to artificially label a broad range of molecules with an equally broad range of potential applications, e.g., targeting Glc metabolism in cancer. After ingestion, this labeled Glc is metabolized in cells and the label is transferred to all metabolic products, which can be tracked by DMI. Building on our recent preliminary results in Nature Biomed, we propose a combination of novel MRI hardware, dynamic spectroscopic data sampling, deep learning algorithms, and a clinical validation to answer the following three research questions in a 5-year project: (i) Is DMI a viable alternative for whole-body cancer assessment? (ii) How is DMI positioned compared to Glc-sensitive PET? (iii) Can DMI be performed on widely available MRI systems and simultaneous with standard MRI? GLUCO-SCAN will fill a gap in current medical imaging by offering an alternative for whole-body PET examinations and potentially even for screening of high risk populations. Ultimately, it will pave the way for a new generation of MR scanners with all-in-one whole-body imaging capability that would capture morphologic and molecular information simultaneously.

Link to the ERC project webpage:

Keywords of the ERC project: magnetic resonance imaging, glucose metabolism, neoplasms

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101088365	**ImmuneSynapsEngagers**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Rony Dahan**
Host Institution:	Weizmann Institute Of Science - ISR

Immune Synapse Engagement as a Novel Approach for Cancer Immunotherapy

Monoclonal antibodies (mAbs) targeting immune checkpoints have revolutionized cancer treatment but exhibit several challenges, most notably, limited intratumor efficacy and relatively low patient response rates. Endowing these mAbs with immune-cell-recruitment capabilities may offer the solution to these drawbacks. This assumption is based on our recent findings that the effectivity of a given checkpoint mAb relies not only on its binding to its target T-cell's receptor but also on the direct interaction of the targeted T-cell with dendritic cells (DCs). Our results suggest that the low-frequency or dysfunctionality of such stimulating immune synapses following checkpoint mAb treatments hinder their anti-tumor efficacy. Therefore, the outcome of not taking this T-cell-DC licensing loop mechanism into account in mAb design is suboptimal checkpoint mAbs. To overcome these limitations, we propose here to develop a series of bi- and muti-specific immune synapse engager antibodies as a new approach to enforce immune interactions for cancer immunotherapy. We will apply in-vivo genetic tools and high-dimensional analysis of the immune response on the spatial, cellular, proteomic and transcriptomic levels to provide critical insights into immune synapses that mediate effective T-cell anti-tumor activity. We will then harness this knowledge to apply antibody-engineering approaches and treatment regimens to maximize anti-tumor activity. We will explore and target T-cell-DC synapses that enable antagonistic (Aim 1) and agonistic (Aim 2) checkpoint mAbs and additional types of immune cell interactions underlying favourable immune surveillance of tumors (Aim 3). This study will introduce a novel approach for cancer immunotherapy using drugs that engage physical crosstalk between key immune cells. Ideally, this study will yield reagents with potent anti-tumor efficacy and well-characterized in-vivo activities that can be readily translated for evaluation in human patients.

Link to the ERC project webpage: https://www.weizmann.ac.il/immunology/dahan/

Keywords of the ERC project: cancer immunotherapy, dendritic cells, bispecific antibody, therapeutic antibody

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101088594	**TAIPO**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Florian Buettner**
Host Institution:	Deutsches Krebsforschungszentrum Heidelberg - DEU

Trustworthy AI tools for personalized oncology

Modern machine learning algorithms have the potential to accelerate personalized medicine in a fast pace. To date, first tasks in medicine are being addressed with machine learning algorithms that surpass humans in terms of accuracy and speed, including diagnosis, outcome prediction and treatment recommendation. However, for a widespread adoption in clinical practice, a good performance in terms of speed and accuracy is not sufficient: practitioners also need to be able to trust a model's prediction in all stages of its life cycle. I will facilitate an efficient interaction of clinicians with AI models by developing trustworthy AI tools for personalized oncology: First, I will develop trustworthy AI tools and algorithms for diagnosis and stratification of cancer patients. Second, I will establish a framework for reliable and transparent modelling of personalized outcomes and therapy decisions in oncology. TAIPO will result in novel algorithms and software tools for quantifying and improving the trustworthiness of AI models that I will apply to three clinical applications: (i) trustworthy AI-based skin lesion classification based on dermoscopic images, (ii) stratification and personalized outcome modelling for patients with acute myeloid leukaemia (AML) based on omics data, and (iv) therapy recommendation for metastatic breast cancer patients based on electronic health records. TAIPO will increase the throughput of trustworthy diagnoses of skin lesions and pave the way for low-cost access to diagnostic care. It will empower clinicians to make personalized and reliable therapy decisions, which we will demonstrate at the example of AML and metastatic breast cancer. Our novel algorithms to evaluate and improve the reliability of AI models are a crucial contribution to close the gap between in-silico AI-bench and bedside and will further push the field of trustworthy machine learning with many applications of AI in medicine.

Link to the ERC project webpage: https://mlo-lab.github.io/

Keywords of the ERC project: artificial intelligence; AI; personalized medicine; trustworthy AI; reliable AI; machine learning

Keywords that characterize the scientific profile of the potential visiting researcher/s: machine learning; computer science; statistics; data science; oncology

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Project ID:	Project Acronym:	Evaluation Panel:
101089218	**MRStain**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Siawoosh Mohammadi**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

Non-invasive staining of tissue microstructure in temporal lobe epilepsy using in- vivo MRI

Ex-vivo histology is the gold standard to investigate human brain microstructure. However, its invasive nature precludes its use in monitoring disease progression and the investigation of the pathophysiological origin of neurological disorders. MRStain will address this shortcoming by exploiting the sensitivity of the Magnetic Resonance Imaging (MRI) signal to estimate aggregated histological metrics in the human brain non-invasively. Like established histology staining methods (e.g., myelin-basic protein), MRStain will be sensitive to changes in cellular populations, axons, myelin, and iron. This will be achieved by augmenting the MRI measurements with computational biophysical models, which can disentangle tissue metrics at the micron-scale using the macroscopic spatial resolution (1–4 mm) of MRI. However, the clinical use of these models has not been employed because their validity and generalizability across disease trajectories has yet to be tested against the ex-vivo histological gold standard. This project will address this shortcoming by generating a globally unique multi-modal dataset that combines novel in-vivo and ex-vivo MRI techniques with biophysical models as well as cutting-edge large-scale 3D histology. The project will benefit from a unique translational university hospital environment where large sections of freshly excised brain tissue from drug-resistant temporal lobe epilepsy patients (TLE, 80 sections of about 3 x 2 x cm^3) can be examined, enabling in-vivo MRI-based biophysical tissue parameters to be validated against their histological gold standard. I will develop an MRStain model to identify TLE relevant changes that will achieve a paradigm shift in how epilepsy is treated by identifying target brain areas for surgery that will help to predict seizure-free outcome after surgery. The final validated MRStain models will also pave the way for similar noninvasive investigations of other neuropsychiatric diseases with unprecedented precision.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101089218

Keywords of the ERC project: MRI, MR Physics, biophysical models of MR signal, 3D ex vivo histology in the human brain, physical-informed models for artifact correction in MRI, machine learning and cell segmentation, machine learning and MRI

Keywords that characterize the scientific profile of the potential visiting researcher/s: MR Physics, Maschine Learning, MRI, Computer Science, Physics, Mathematics

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Project ID:	Project Acronym:	Evaluation Panel:
101089334	**AXES.Histo**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Martin Bech**
Host Institution:	Lunds Universitet - SWE

Advanced X-ray Energy-sensitive Microscopy for Virtual Histology

In the last 20 years, phase-contrast x-ray imaging has evolved from first proof-of-principle experiments with relatively poor contrast, to a mature research field with many branches. Standing on the shoulders of scientific achievements and technological development, the time has come where virtual histology for biomedical applications is within reach. The aim of this research project is to design and construct a prototype x-ray microscope for three-dimensional histology. In the clinics we are used to non-invasive three-dimensional image modalities such as e.g. computed tomography (CT), ultrasound and magnetic resonance imaging (MRI). The ability to visualise and track structures through a volume is extremely valuable for the purpose of diagnosis. But for microscopy of tissue biopsies, our golden standard is histological procedures involving thin slicing of the tissue before imaging in a microscope, rendering volumetric interpretation very difficult of not impossible. With the proposed phase-contrast micro-CT scanner, tissue samples can be imaged in three dimensions such that the computer rendering of the sample can be sliced in any arbitrary plane, and we have the possibility of volumetric data analysis. In this fashion, useful volumetric information can be extracted for various applications in biomedical research. As a direct application, we will use this 3D Histology setup to obtain detailed volumetric understanding of the development of lung lesions, and complement with gold standard microscopy techniques. A lab-based setup for virtual histology will allow full studies of disease pathologies with statistical significance and make optimisation of experimental protocols possible. For achieve the goal of soft tissue micro-CT, we will implement a novel inverse-geometry single-grating interferometer. When combined with state-of-the-art detector and source technology a scanner for high-resolution phase-contrast tomography of soft tissue will be realised.

Link to the ERC project webpage:

Keywords of the ERC project: X-ray phase-contrast imaging, grating interferometry, micro-tomography

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101097332	**ResistSOS**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Yosef Yarden**
Host Institution:	Weizmann Institute Of Science - ISR

Overcoming Resistance to Anti-cancer Drugs by Blocking Mutation-prone DNA Polymerases and the SOS Response

Background: A large fraction of cancer patients die because their tumors initially respond to drugs but later they evolve tolerance. Thus, resistance to diverse drugs, along with the soaring costs of new treatments, are emerging as major societal issues of the 2020s. Herein, we explore one of the most distressful examples, tolerance of lung cancer to EGFR-specific tyrosine kinase inhibitors (TKIs). Working hypothesis: In similarity to bacteria exposed to antibiotics, when cancer cells are exposed to TKIs they enlist SOS responses, which activate endogenous mutators. Hence, we will combine the relatively effective but mutagenic TKIs with drugs that disarm the mutators. This scheme will be applied on models of EGFR+ lung cancer, a disease that repeatedly evolves mutations and resistance, but eventually leaves millions of patients with no treatment choices. Specific aims: Our initial studies identified one triad of the SOS system: a sensor of cell death - GAS6, a mediator - AXL, GAS6' receptor, and a mutator - low-fidelity DNA polymerases. Remarkably, blocking AXL using an antibody irreversibly prevented relapses when combined with EGFR inhibitors. Along with establishing this triad, we will employ transcriptomics, protetomics and metabolomics to resolve parallel mutators and sensors. Likewise, we will explore alternative ways to block resistance, for example by directly targeting DNA polymerases, MYC and purine metabolism. Aiming at strategies that minimize SOS enlisting, we will explore the premise of boosting immune destruction of cancer cells. Significance: According to the current status quo, next-generation inhibitors are being applied when resistance emerges. However, this scheme does not cure, only buys time. ResistSOS offers an alternative that might eradicate resistance and cure disease models following treatments that are based on deep understanding and blocking the mutagenic SOS response.

Link to the ERC project webpage:

Keywords of the ERC project: cancer, resistance to anti-cancer drugs, therapeutic antibodies, targeted therapy, kinase inhibitors, growth factors

Keywords that characterize the scientific profile of the potential visiting researcher/s: cancer mechanisms and therapy

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Project ID:	Project Acronym:	Evaluation Panel:
101098372	**HEART2BEAT**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Robert Passier**
Host Institution:	Universiteit Twente - NLD

Advanced human models of the heart to understand cardiovascular disease

Cardiovascular diseases (CVD) are the cause of the highest mortality and morbidity rates worldwide and are expected to increase in coming years, leading to epidemic proportions. Traditional experimental in vitro and animal models are not predictive enough, which hampers the emergence of novel therapies for treatment of CVD. Consequently, there is an urgent need to establish realistic human models that lead to a better understanding of CVD, providing the opportunity to identify and validate druggable targets. In Heart2Beat I will develop innovative human heart models for mimicking cardiovascular disease. I will use an innovative in-air microfluidic platform for ultra-high throughput encapsulating of human pluripotent stem cells in microgels to generate self-organised multicellular 3D human cardiac organoids that replicate the architectural design of the human heart. Furthermore, I will integrate and develop innovative technologies from the fields of human stem cell biology and engineering to create 3D (micro)-engineered heart tissues, coupled to a versatile and automated microfluidic platform, enabling assessment of multifunctional analysis (e.g., contraction, relaxation, metabolism, morphology). Finally, I will build a functional human mini-heart with the capacity to pump fluid, the main function of the human heart and then assess clinically relevant readouts in healthy and diseased conditions. These first-of-its kind advanced 3D human cardiac models and platforms are complementary to each other and form a highly innovative and comprehensive pipeline for modelling human CVD, enabling (ultra)high throughput screening and in-depth multifunctional pre-clinical analysis of healthy and diseased heart tissues. Successful implementation of Heart2Beat will provide insight into mechanisms of disease and will initiate a paradigm shift for personalised medicine and drug discovery, leading to tailor-made therapy for patients suffering from CVD.

Link to the ERC project webpage:

Keywords of the ERC project: human pluripotent stem cells, tissue engineering, cardiac disease, organ-on-chip, microfluidics, disease modelling, drug discovery, mini-heart,

Keywords that characterize the scientific profile of the potential visiting researcher/s: 3D-(bio)printing, engineering, organ targeting/delivery (viral constructs, exosomes, nanolipid particles), imaging, disease modelling, artificial intelligence, computational modelling, drug screening/discovery, molecular engineering, cardiac biology, adva

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Project ID:	Project Acronym:	Evaluation Panel:
101117435	**SC-Plasticity**	**LS7** Prevention, Diagnosis and Treatment of Human Diseases

Principal Investigator:	**Dr Rachel Thijssen**
Host Institution:	Academisch Medisch Centrum Bij De Universiteit Van Amsterdam - NLD

Applying novel single-cell multiomics to elucidate leukaemia cell plasticity in resistance to targeted therapy

Novel targeted therapies are increasingly applied against a wide range of cancers. Although such agents can induce cures, most patients suffer from relapsed disease. Acute myeloid leukaemia (AML) is a prime example of a deadly disease, but we have a chance to dramatically improve outcomes if we can better understand resistance mechanisms against targeted agents that are transforming AML treatment, such as the BCL2 inhibitor venetoclax. AML is characterised by profound alterations in the epigenome that are correlated with poor survival. I therefore hypothesise that targeted drug pressure induces epigenetic plasticity that allows cancer cells to sample alternate chromatin or transcriptional states, a subset of which confer drug resistance. A major challenge is to define how mutations of epigenetic regulators in AML affect therapy responses due to clonal heterogeneity. To address this challenge, I will use and further develop my recently published single-cell Rapid Capture Hybridization sequencing (scRaCH-seq) method to link the genotype of expressed genes to transcription and methylation profiles of thousands of single cells. In this research proposal, I aim to (1) develop a new method linking epigenetic landscape, genotype and transcriptome at a single-cell level and define the impact of treatment on these interactions. (2) Analyse the genome-wide impact of epigenetic therapies. (3) Define the association between drug sensitivity and epigenetic modifications regulating pro-survival genes. To achieve my goals, I will apply my novel single-cell multiomics to samples from AML patients treated with venetoclax alone or in combination with epigenetic therapies and apply state-of-the-art technologies to established laboratory models. Our new approaches to fully understand the relationship between the genome, epigenome and transcriptome will advance fundamental biology. This has the potential to yield new therapeutic strategies to prevent and overcome resistance.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
883621	**SoilResist**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Richard Bardgett**
Host Institution:	The University Of Manchester - GBR

Diversity, stability and functioning of the soil microbiome

A major challenge for advancing our understanding of the functional role of highly complex soil microbial communities is to systematically link changes in their structure and functioning to biogeochemical cycles under realistic scenarios of global change. This is a formidable challenge: not only does it require a step change in our understanding of the factors that shape soil microbial communities and their functioning, but also it requires new knowledge of the ecological and genetic mechanisms that underpin its stability, or ability to resist and recover from abiotic perturbations associated with global change. By embracing technological and theoretical developments in microbial ecology, SoilResist will make a major step forward in our understanding of the mechanisms that underpin the resistance and resilience of soil microbial communities and their functioning to natural and anthropogenic perturbations. Specifically, I seek to develop a novel mechanistic understanding of the factors that underpin the resistance and resilience of complex soil microbial communities and their functioning to different types of anthropogenic perturbations, and, for the first time, identity critical thresholds for abrupt transitions of microbial communities to alternative states and consequences for soil functioning. My overarching hypothesis is that the stability of microbial functions, in terms of their capacity to resist and recover from a pulse perturbation caused by climate extremes, is determined by microbial functional diversity, based on range and relative abundance of microbial traits. I also hypothesize that shifts in microbial functional diversity resulting from press perturbations erode the capacity of soil microbial communities to buffer climate-related pulse perturbations, rendering them more vulnerable to an abrupt transition to alternative taxonomic and functional state with negative consequences for soil functioning.

Link to the ERC project webpage:

Keywords of the ERC project: soil microbial ecology, stability, biodiversity, biogeochemical cycles

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
945026	**METASCALE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Oleg Simakov**
Host Institution:	Universitat Wien - AUT

Modes of genome evolution during major metazoan transitions

Our understanding of how genomic changes translate into organismal novelties is often confounded by the complexity of the underlying genome architecture. My previous studies revealed a complex interplay between several levels of genomic organization during major metazoan evolutionary transitions, ranging from modifications of regulatory elements to the gene order on the chromosomal scale. A major gap in our understanding is the extent to which those different genomic scales are evolutionarily linked and reflect an inherent functional property or mode of genome evolution. In this proposal, I focus on the emerging model system within the highly advanced clade of cephalopod molluscs, the Hawaiian bobtail squid Euprymna scolopes, to study how changes in the mode of metazoan genome evolution have yielded unique cephalopod innovations (e.g., the largest invertebrate brain). To address this question, I will (1) take a novel global pan-metazoan comparative genomics approach to test and reveal the extent of genomic character co-evolution, identifying, for the first time, modes of genome evolution. I will then (2) test whether co-evolving characters form inherent regulatory units in metazoan genomes by an in-depth characterization using emerging and available regulatory genomic data. Finally, using latest molecular approaches, I will (3) study the regulatory composition of co-evolving character units associated with cephalopod brain development and functionally test their organismal impact. This proposal will develop a novel and holistic approach to study genome evolution, constituting a departure from the previous analyses based on individual genomic characters. It will link genomic evolutionary units to their function, revealing the genomic changes behind major innovations (cephalopod brain). Finally, this project will develop predictive models that use evolutionary data to identify novel regulatory units aiding both biological and biomedical applications.

Link to the ERC project webpage: https://neurodevbio.univie.ac.at/simakov-research/

Keywords of the ERC project: genomics, evolution, cephalopods

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics

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Project ID:	Project Acronym:	Evaluation Panel:
948181	**COGNITIVE CONTROL**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Tomer Czaczkes**
Host Institution:	Universitaet Regensburg - DEU

Revolutionizing invasive alien species control using behavioural economics and animal cognition

The aim of COGNITIVE CONTROL is to gain fundamental insights into collective cognition and apply them to the emerging global challenge of invasive animal control. Invasive ants are ecologically devastating, economically damaging, and almost impossible to control. Ants are protected physically and by social immunity. However, their cognitive abilities are almost universally ignored, and offer novel angles of attack. Applying behavioural economic and psychological concepts, I will open the new field of Cognitive Control of invasive animals. In Work Package 1 I will use microeconomic tools to gain unprecedented insights into insect preference structures. Individual choice will be steered using behavioural economic and cognitive interventions. Psychological effects, such as conditioned taste aversion, which may cripple current alien species management, will be tested and overcome. Finally, I will use neuroactives (e.g. caffeine) to improve learning and manipulate preference. In WP2 I will take the WP1 manipulations on to the colony level to gain deep insights into collective cognition. By tracing trophallactic networks I will broaden our understanding of social immunity, which protects ant colonies from attack, and learn to disrupt it. Finally, in WP3, I will translate our results into field interventions. These will be tested in buildings with an industrial partner, and in natural environments to combat a damaging invasive ant infestation. Ignoring cognition has left a critical knowledge gap in invasive species control. This project brings comparative psychology and behavioural economics to conservation, and will establish Europe as a major player in invasive ant control. The interdisciplinary approach will yield innovative insights into decision making in insects, by offering new conceptual frameworks. Introducing cognition to manipulate preferences will revolutionize invasive species control worldwide.

Link to the ERC project webpage: https://www.animal-economics.com/

Keywords of the ERC project: Invasive species; ants; animal behaviour; comparative psychology; learning; memory

Keywords that characterize the scientific profile of the potential visiting researcher/s: behavioural ecology, ethology, comparative psychology, ecology, conservation, invasive species, ants, bees, pollination

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Project ID:	Project Acronym:	Evaluation Panel:
948465	**ROCKS-PARADOX**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Kjetil Voje**
Host Institution:	Universitetet I Oslo - NOR

Dissecting the paradox of stasis in evolutionary biology

There is something deeply disconcerting about the current state of knowledge on rates of morphological evolution across different timescales: Why do most species in the fossil record exhibit negligible morphological change when contemporary populations often respond rapidly to selection? The ROCKS-PARADOX project will address this fundamental question – known as the paradox of stasis – along mutually reinforcing lines of enquiry, by merging theory and data across paleontology and evolutionary biology. The prevalence of stasis and other patterns of change are hard to evaluate without knowledge of evolution on timescales unattainable by studies of contemporary populations (microevolution) and comparative species-data (macroevolution). The ROCKS-PARADOX project will address this by analyzing the world's largest collection of data on within-lineage evolution – spanning decadal to million-year timescales – using a statistical framework (developed by the project) where new and already established mathematical models of evolution are implemented. The ROCKS-PARADOX project also will conduct an unprecedented assessment of the effects of genetic constraints and evolvability on evolution beyond microevolutionary timescales. To do this, we will break new ground by estimating quantitative genetic parameters from fossil samples using machine-learning algorithms on a collection of 150,000 fossil clonal organisms (bryozoans) from a rich and highly-resolved stratigraphic section spanning 2.3 million years. The ROCKS-PARADOX project will bridge our current understanding of phenotypic evolution across timescales into a single cohesive theoretical framework, and open up new avenues for how fossil data can be collected and analyzed to inform questions within evolutionary biology. The project will develop new methodology with broad applications, including long-awaited tools for high-throughput phenotyping.

Link to the ERC project webpage: https://kjetillysnevoje.wordpress.com/

Keywords of the ERC project: phenotypic evolution, fossil time series, quantitative genetics connecting micro- and macroevolution

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
949880	**KleptoSlug**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Sonia Cruz**
Host Institution:	Universidade De Aveiro - PRT

Kleptoplasty: The sea slug that got away with stolen chloroplasts

Rationale: Photosynthesis is almost exclusively restricted to algae and plants, with the exception of some protozoans, flatworms and marine slugs that acquire chloroplasts from algae. In metazoans, the capacity to incorporate functional chloroplasts (kleptoplasty) for long periods of time has only been described in sacoglossan sea slugs. Some species retain kleptoplasts photosynthetically active for several months that persist without access to algal gene products and despite the release of potentially dangerous metabolites, including reactive oxygen species (ROS). While kleptoplasty is intriguing from an evolutionary perspective, there are many unresolved questions on how the algal organelle is incorporated into the metabolism of an animal cell and what the host-associated benefits are. Aim: This proposal will unravel the cellular mechanisms supporting the sequestration and maintenance of functional chloroplasts inside metazoan cells and determine the host benefits of harboring kleptoplasts. Approach: The expertise in keeping a variety of species will form the backbone of my state-of-the-art experimental strategy, comparing a wide range of different animal-alga associations in their response to chloroplast incorporation and variable ability to functionally maintain them. Lipidomic and transcriptomic analyses will unravel in a comparative approach the species-specific maintenance strategies underlying kleptoplasty. In addition, the impact of cytotoxic compounds produced by active kleptoplasts and in particular ROS production and scavenging will be explore. Finally, I will determine the fate of inorganic carbon and nitrogen to explore the contribution of photosynthesis-derived compounds to the physiology of the host. Impact: This analysis will resolve some of the long-standing questions regarding the maintenance of photosynthetically active chloroplasts in animal cells and produce crucial insights about long-term kleptoplasty in sacoglossan sea slugs.

Link to the ERC project webpage: https://mplab-kleptoslug.com

Keywords of the ERC project: Kleptoplasty, photosymbiosis

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101000504	**EYESPOT**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Miguel Carneiro**
Host Institution:	Associacao Biopolis - PRT

The Genetic, Cellular, and Photonic Mechanisms of Avian Structural Colouration

Structural colouration is widespread in nature and generates some of the most stunning visual effects known (e.g. eyespots in a peacock tail). In bird feathers, structural colours are produced by the combination of pigments and precise arrangements of nanostructures that interact both chemically and physically. Currently, almost all published studies on structural colour have focused on the optical and physical aspects of this phenomenon, while the underlying molecular mechanisms remain almost totally unexplored. This proposal seeks to decipher the genetic and cellular basis of structural colours by: 1) exploiting the extraordinary diversity of peacock colour mutants that have emerged from captive breeding, and 2) investigating wild bird species that exhibit structural colouration. My proposal is divided across four multidisciplinary aims that integrate techniques and expertise in the fields of genetics and genomics, cell and molecular biology, and photonics. Aim 1 will elucidate the nanoarchitectural basis of aberrant feather colouration in multiple Mendelian peacock mutants by combining microscopy, spectrophotometry, and chemical analysis of pigment content. Aim 2 will theoretically and experimentally model how abnormalities in the architecture of the photonic lattice result in aberrant light-scattering in these mutants. Aim 3 will combine genetic mapping together with molecular and functional genomic tools for experimental validation and identification of genes controlling the peacock colour phenotypes. Aim 4 will refine our understanding of the evolution of this trait in nature by combining transcriptomic and epigenomic data generated from wild bird species with comparative genomics across the entire avian phylogeny using publicly available genomes. Overall, these studies will significantly expand our understanding of the mechanics and molecular changes underlying a spectacular trait that constitutes a major component of bird phenotypic diversity.

Link to the ERC project webpage:

Keywords of the ERC project: Coloration, Genomics, Genetics, Evolutionary Biology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101001341	**SelectHaploid**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Simone Immler**
Host Institution:	University Of East Anglia - GBR

Testing the Evolutionary Consequences of Haploid Selection in Animals

Selection occurring during the haploid gametic phase of any sexually reproducing eukaryote may have far-reaching consequences for major biological processes. Selection acting on a haploid genome results in efficient removal of deleterious alleles and rapid fixation of beneficial alleles, which in turn affect adaptation, genetic load and the evolution of recombination rates. Despite their potential importance, we know surprisingly little about the genetic processes occurring during the time window after meiosis until the fusion of male and female pronuclei. This is particularly true for haploid selection in the gametes of predominantly diploid animals. Male gametes (sperm) are produced in vast numbers but only few fertilise eggs and therefore offer a strong opportunity for selection. A prevailing view that such haploid selection is of minimal consequence in animals has been recently overturned by evidence from our lab, which revealed strong links between sperm phenotype and offspring fitness, as well as sperm phenotype and its haploid genotype. The genetic mechanisms underlying these observations are currently poorly understood. In this project, I will tackle three key questions arising from these recent findings: i) How strong are purifying and positive selection during the haploid phase? ii) What are the mechanisms maintaining genetic variation in genes expressed during the haploid phase? iii) How does haploid selection affect the interaction between male and female gametes? By combining carefully designed innovative experimental approaches with cutting-edge single-cell genome and transcriptome sequencing technologies, this project will provide entirely novel insights into the process that is shared by all eukaryotic life. Findings from this project will illuminate not only the fields of evolutionary biology and genetics but far beyond into the areas of animal breeding and human reproduction.

Link to the ERC project webpage: https://simoneimmler.wordpress.com/

Keywords of the ERC project: Genetics, genomics, reproduction, fertility

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101001993	**Behavior-Island**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Yossi Yovel**
Host Institution:	Tel Aviv University - ISR

Navigating, Decision-Making and Sociality, Studying Behavior in the Wild from Birth to Adulthood

In the movie the 'Truman Show', Truman Burbank is astonished when discovering that he spent his entire life in a TV show. Monitoring a human's life is unethical, but many sociologists secretly dream about running such an experiment. Behavior-Island will allow to continuously monitor and manipulate a large population of bats from birth to adulthood. Behavior-Island will be established on Mauritius - the home of P. niger, which is a very interesting bat-model that: (a) lives for decades relying on long-term memory; (b) roosts in large colonies and is highly social; (c) exhibits immense spatio-temporal memory; and (d) is large enough to carry many sensors allowing to track its pups from day one. Even with current state-of-the-art technologies, studying animal behavior in the wild is highly limited because: (1) it is extremely difficult to monitor the same individual over long periods while also monitoring its environment and (2) it is almost impossible to monitor a substantial part of a population and thus we know little about social interactions. We will overcome these limitations by using a new reverse-GPS system (ATLAS) allowing simultaneous tracking of 1000 bats. Notably, because the bats never leave the island, we will monitor individuals from birth to adulthood. ATLAS also provides locations in real-time, allowing to manipulate specific individuals in the wild and to examine their response. We have already tracked bats with a preliminary ATLAS system on Mauritius. Combined with an arsenal of additional technologies, ATLAS will allow studying fundamental aspects of behavior in the wild, for the first time, including: Navigation and its ontogeny; Long-term spatio-temporal memory, Decision making and Sociality. We will examine how experience and personality interact to shape behavior, and we will monitor an entire colony, documenting behavior in the population level. Because, P. niger is endangered and threatened, our work will also contribute to its protection

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101002644	**BEE-MOVE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Mathieu Lihoreau**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Pollination ecology: how do bees move across the landscape and fashion plant reproduction?

How pollinators, such as bees, exploit plaHow pollinators, such as bees, exploit plant resources is a fundamental question in biology, with deep ecological, economical and societal consequences. When foraging on flowers, pollinators transfer pollen and mediate the reproduction of plants on which most animals (including us humans) rely on. Understanding the spatial foraging strategies and interactions of pollinators across the landscape is thus a critical scientific challenge to discover their influence on plant mating patterns and pollination efficiency. BEE-MOVE will use an interdisciplinary approach to mechanistically link pollinator movements to pollination efficiency at field scales, thereby crossing boundaries between research on pollinator behaviour and plant ecology. I will focus on two key pollinators worldwide: the buff-tailed bumblebee and the Western honey bee. 1) I will develop a new radar system to record and analyse the individual 3D movements of hundreds of bees foraging simultaneously. 2) I will use arrays of communicating radars and robotic plants to study how bees search and exploit food resources in field setups of several square kilometres, by manipulating key environmental factors such as the density of bees, the 3D distribution of plants, and the nutritional content of nectars and pollens. 3) From these observations, I will build computational agent-based models to investigate the influence of bee spatial strategies on pollination efficiency. Critical experiments will test model predictions in populations of natural plants. The dialogue between observations and simulations will create a positive feedback towards a robust, multi-level understanding of plant-pollinator interactions at the scale of landscapes. In addition to exploring entirely new grounds in pollination ecology, my results could be used to design practical interventions for conservation, sustainable agriculture and green development in the worrying context of pollinator declines.

Link to the ERC project webpage: http://www.mathieu-lihoreau.com/bee-move/

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
101003296	**MyGardenOfTrees**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Katalin Csilléry**
Host Institution:	Eidgenossische Forschungsanstalt Wsl - CHE

A range-wide transplant experiment using participatory science and genomic prediction to assess local adaptation in forest trees

How organisms adapt to their environments is the most fundamental question in evolutionary biology and is of utmost importance given climate change threats. Identifying key traits involved in adaptations and understanding how they interact with each other, and with the environment, is a particularly urgent task for foundation and resource-production species, such as forest trees. Existing experiments assessing local adaptation lack scalability and predictability in natural environments, especially at the species range margins. Landscape genomics studies could reveal adaptive loci across environmental gradients, but they are hindered by the assumptions of a neutral model and the highly polygenic nature of most traits. To address these shortcomings, I will conduct a species range-wide transplant experiment using participatory science and genomics to (i) reveal major patterns and drivers of adaptation and (ii) to build a predictive model for selecting optimal seed sources for a given location that accounts for gene-environment interactions and demography. I will develop a participatory network of foresters as well as ordinary citizens, who will establish a large number (>2500) of micro gardens (4 to 36 m2). Seeds source populations of Fagus sylvatica and Abies alba, and their sister species, will be selected from across their ranges. To evaluate plant performance in novel climate conditions, garden locations will also cover locations beyond the species' current distribution range. Early survival and growth traits, which are under the highest selection pressure in trees, will be monitored and analyzed herein. An unprecedented nearly full factorial design transplant data set will be obtained using a genomic prediction (GP) model that exploits the genetic similarity between populations and the environmental similarity between garden locations. Finally, I will implement the GP model for forest managers to aid assisted migration decisions with evoluti

Link to the ERC project webpage: https://www.mygardenoftrees.eu/

Keywords of the ERC project: evolutionary genetics, forest trees, common garden experiment, population genomics, plant breeding

Keywords that characterize the scientific profile of the potential visiting researcher/s: population genomics, plant breeding, quantitative genetics, forest trees

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Project ID:	Project Acronym:	Evaluation Panel:
101039066	**ForestFuture**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Michał Bogdziewicz**
Host Institution:	Uniwersytet Im. Adama Mickiewicza W Poznaniu - POL

Climate change impacts on trees reproduction and forecasts of forest recruitment change

The capacity of future forests to support biodiversity and deliver ecosystem services will depend on reproductive capacities that keep pace with 21st century climate change. The European continent is warming and drying out fast, and similar changes are happening word wide. The decade-scale trends in biodiversity will be governed by tree fecundity?the capacity of trees to produce seed and to disperse it to the habitats where populations can survive in the future. From the boreal to the tropical forests, including in majority of European tree species, reproduction happens through synchronized, quasi-periodic, non-stationary variation in fruit production, termed masting or mast seeding. Despite the crucial role of mast seeding in plant regeneration and wider ecological processes, our understanding of this process is rudimentary. Poor understanding of the mechanisms that govern it are challenges for anticipating alternations in forest reproduction and function. Reliable predictive models are consequently not available, and the unpredictable recruitment of trees has become a key obstacle to understanding forest change. Recruitment, including reproduction and dispersal, is the most undeveloped demographic process in Earth system models. This work will transform our understanding of mechanisms governing trees reproduction and deliver tools for predicting forest reproduction trajectories under climate change. The main outcomes will be the first experimental description of how masting emerge at proximal level, and how this is conserved among species. This will be also the first explicit test of how variation in masting patterns matters for forest regeneration trajectories. Together with analysis of global reproductive patterns, our work will deliver a step-change in identifying species and regions of special conservation care.

Link to the ERC project webpage: https://forestbiologycenter.amu.edu.pl/

Keywords of the ERC project: forest ecology, tree reproduction, growth, seed production, climate change

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

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Project ID:	Project Acronym:	Evaluation Panel:
101039501	**FrogWY**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Wen-Juan Ma**
Host Institution:	Vrije Universiteit Brussel - BEL

Evolutionary Genomics of Unconventional Sex Chromosomes in Frogs

In sharp contrast to model organisms with degenerated Y/W chromosomes, many reptiles, fish and amphibians have mostly undifferentiated sex chromosomes and exhibit dynamics of birth and death of sex chromosomes. Why and how early-stage sex chromosomes and frequent turnovers are so prevalent across eukaryotes remain mysterious. This also raises pressing questions on alternative mechanisms leading to sex chromosome recombination arrest, their dynamics and stability. Frogs are ideal systems because they have mostly early-stage sex chromosomes and frequent turnovers. In this project, I will use the robber frogs to study unconventional sex chromosome evolution, challenging the paradigm predicted by the canonical model of ?degenerate Y/W?: 1. Does genome-wide reduced recombination always associate with the heterogametic sex? I will study an alternative mechanism driving sex chromosome recombination arrest, sex-specific telomere-restricted recombination, in 12 robber frogs with XY, ZW systems in a phylogenetic framework. 2. Do sex-determination turnovers repeatedly occur in frogs with heteromorphic sex chromosomes? I will identify sex chromosomes for each species and analyse the rate of turnovers in XY and ZW systems in a phylogenetic framework. I anticipate several independent transitions between sex-determination mechanisms, and more transitions within the XY or ZW system. 3. What are the genomic consequences of giant Ys and Ws, how do they form and differ? I will perform chromosome-level genome assembly to identify gene content on the Ys/Ws. I will detect inversions, evolutionary strata, compare transposable elements dynamics and dosage compensation mechanisms between XY and ZW systems. If successful, this project will uncover alternative mechanisms driving sex chromosome recombination arrest, their dynamics and genomic features. It will reveal the mysterious formation of giant Ys/Ws. Together, this will conceptually extend boundaries of the canonical model.

Link to the ERC project webpage:

Keywords of the ERC project: Sex chromosome evolution, Recombination suppression, Comparative genomics, Sex chromosome turnover, Meiosis

Keywords that characterize the scientific profile of the potential visiting researcher/s: Meiosis and cytogenetics, Genetic basis of sex determination, CRISPR/Cas9 in frogs, Comparative genomics

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Project ID:	Project Acronym:	Evaluation Panel:
101039541	**HoloE2Plant**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator: **Dr Claudia Bartoli**

Host Institution: Institut National De Recherche Pour L'Agriculture, L'Alimentation Et L'Environnement - FRA

Exploring the Holobiont concept through a Plant Evolutionary Experiment study

The evolutionary processes underlying interactions between hosts and their associated microbes is a black box on which biologists have long attempted to shed light. A limiting factor has been knowledge of the precise molecular events, which are now increasingly possible to elucidate with the advent of next-generation sequencing technologies. The Big Data era have revolutionized evolutionary studies through sequencing of thousands of genomes allowing tracing genomic changes. Coupled to these technologies experimental evolution transformed evolution from a predictive to a functional science by opening a window on evolutionary changes in real-time. The challenge that now awaits evolutionary science is in identifying the trajectories simultaneously driving evolution in hosts and microbes. In this context, HoloE2Plant will validate the holobiont concept by looking at the simultaneous evolution of the host and its microbiome. This will be possible thanks to an experimental coevolution approach applied to fast-cycling Brassica rapa plants and Synthetic Microbial Communities (SynComs). SynComs will be selected from bacterial and fungal collections previously established from wild B. rapa populations. This ambitious project is timely and feasible thanks to the combination of high-throughput sequencing, cutting-edge modelling methods for microbial functional network reconstruction and a novel co-evolutionary quantitative genetic approach that will be developed here. Experimental evolution will be carried out in presence/absence of the fungal pathogen Rhizoctonia solani and the genetic bases underlying microbial-plant interactions and associated with disease resistance will be identified. HoloE2Plant will contribute to validating the holobiont concept and will provide unique methods to identify rapid evolutionary changes in holobionts; these theoretical advances will set the stage for future applied projects aiming at designing microbial consortia with biocontrol properties.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101039843	**CHIMERA**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Anouk Willemsen**
Host Institution:	Universitat Wien - AUT

The sympatric lifestyle of giant viruses: contact tracing and fitness through mobile genetic elements

Giant viruses appear to be ubiquitous in soil and aquatic environments, infecting a wide range of protist hosts. As lytic viruses, they are important regulators in nutrient and energy cycles and key influencers of microbial community composition. The recent discovery of giant viruses challenged previous assumptions and blurred the sharp division between viruses and cellular life. Besides large particle sizes, giant viruses possess complex "chimeric" genomes, including genes that were likely acquired from their hosts and bacteria that parasitise the same hosts. Unique is the presence of prokaryotic-like mobile genetic elements (MGEs) that are speculated to aid giant viruses in defence against the host immune system or in direct competition for resources with other viruses or bacteria. Contrarily, bacteria may use MGEs to help the hosts counteract viral infections. Our current knowledge on the factors promoting giant virus diversity and maintenance of the virus-host balance in nature, are largely unknown. In the proposed project, I will investigate the role of MGEs in the evolution and ecology of giant viruses. I postulate that the presence of MGEs plays a crucial role in the competition between giant viruses and other parasites infecting the same hosts. Using co-infection experiments, as well as cutting-edge molecular, microscopy, and sequencing techniques, I will investigate viral competitive fitness as well as physical and molecular interactions between selected partners. By developing a highly specific giant virus genome editing tool, I will rigorously test whether MGEs can provide giant viruses with higher fitness. Moreover, I will combine cell sorting with metagenome analysis of two selected habitats, to unravel how MGEs are distributed in a natural ecosystem. My overarching goal is to elucidate the molecular dialogue between viruses, bacteria, and their hosts, and to use MGEs as a tool to trace the evolutionary history of this unique group of viruses.

Link to the ERC project webpage: https://homepage.univie.ac.at/anouk.willemsen/?page_id=52

Keywords of the ERC project: virus evolution, virus interactions, giant viruses, fitness, competition. defense

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101039862	**VenomEvolvability**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Eivind Undheim**
Host Institution:	Universitetet I Oslo - NOR

Lacewing venom: Linking the molecular and phenotypic evolution of adaptive traits

Understanding the ability of species to adapt to their environment, or their evolvability, is central to evolutionary biology. Most traits are complex in that their phenotype results from the contributions of many genes with small, sometimes non-additive effects. While quantitative genetics has been instrumental in showing that short term evolvability depends on additive genetic variation, it ignores details of the molecular underpinnings of phenotypic characters that are crucial for the production and maintenance of additive genetic variation, and therefore evolvability at longer time scale. This impacts our understanding of evolvability and calls for model traits that enable the integration of quantitative and molecular genetics. Venoms are great model systems for this purpose. They are convergent sets of traits well-suited for comparative studies, and their phenotypes result from the combined actions of a relatively small number of secreted, functionally repurposed proteins, or toxins, that can be identified, characterised, and quantified. This project focuses on the venoms of Neuroptera, which venoms remain unstudied despite providing a unique opportunity among venomous animals to combine omics techniques, and comparative molecular and morphological evolution with evolutionary quantitative genetics. This multidisciplinary approach will elucidate the genetic and evolutionary mechanisms that underlie the emergence of venoms as complex evolutionary novelties and identify the molecular properties that facilitate or constrain their evolution across micro- and macroevolutionary timescales. Thus, the project will test central hypotheses about venom evolvability, but it is also likely to yield novel bioactive molecules with potential use as molecular tools and agrochemical leads. It will also establish venom as model systems that enable integration of quantitative and molecular genetics, thereby addressing a major methodological challenge in evolutionary biology.

Link to the ERC project webpage: https://www.mn.uio.no/cees/english/research/projects/103353/index.html

Keywords of the ERC project: venom, evolvability, evolution, toxin

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101040311	**Mechano-Wolbachia**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Ewa Chrostek**
Host Institution:	Uniwersytet Jagiellonski - POL

Uncovering the mechanisms of action of an antiviral bacterium

Animals and microbes interact in intricate ways. Wolbachia, a common intracellular insect symbiont, can manipulate reproduction and protect hosts from viruses. Thus, Wolbachia is an asset in the control of insect-borne diseases. However, as Wolbachia cannot be cultured outside of host cells or genetically manipulated, the mechanisms of its antiviral phenotype remain poorly understood, and this inhibits wider exploitation. I have been working to remedy these deficiencies, and now stand poised to discover the mechanisms of Wolbachia-conferred antiviral protection by answering the following questions: 1) Where does the protection originate? Up to now, mechanisms of protection have been studied in whole organisms, often lacking resolution, or in cultured cells, which lack emergent properties. I will identify tissues and cell types of the host where protection starts. To do this, I will: a) quantify titers of Wolbachia and virus at early time points post-viral infection in insect tissues, b) measure gene expression of host and microbes to identify candidates for further molecular characterisation, and c) test the extent of the utility of widely adopted, yet unvalidated, cell-culture models of antiviral protection. 2) Which Wolbachia genes effect protection? Wolbachia research has historically been impeded by a lack of tools to study gene function. Here, I will deploy antisense technology, which I have recently developed, to interrogate function of candidate Wolbachia genes in the native system. I will also engineer new methods to target Wolbachia genes and proteins, based on my data on cell-penetrating peptide-mediated delivery of bioactive cargo to Wolbachia. This project has two major outcomes: it will uncover Wolbachia factors responsible for Wolbachia-conferred antiviral protection, and it will transform Wolbachia and symbiosis research by creating tools to study symbiont gene function.

Link to the ERC project webpage: https://www.chrosteklab.com/

Keywords of the ERC project: intracellular bacteria, virus, insects, host-microbe interactions

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101040724	**SuPerSilk**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Jonas Wolff**
Host Institution:	Universitaet Greifswald - DEU

Melding behavioural ecology and biomaterials research to track the evolution of mechanical super- performance of spider silk composites

Many organisms assemble biological materials into architectures and tools that add and extend biological functions - with profound ecological effects, and inspiring human technologies. However, there is no general concept of how evolutionary bio-material innovation arises from both the physiological and the behavioural recombination of compounds. SuPerSilk aims to understand how mechanical super-performance evolves by disentangling the concerted effects of both physiological and behavioural factors on structure-function relationships, utilizing spiders and their silk products as a model system. Specifically, SuPerSilk will (1) determine if the diversification into different types of silk glands facilitated the evolvability of spider silk performance, (2) test if the behavioural combination of different spider silks into compound threads provides a fast track for the evolution of thread performance and an extension of performance limits, (3) test whether similar thread functions evolved via repeated or alternative pathways, and (4) establish a roadmap for the targeted bioprospecting of silk compounds with specific properties. Being the first project that will jointly track the evolution of base materials and their behaviourally assembled compound products, SuPerSilk will address a timely question in evolutionary biology: if and how the evolvability of physical traits can be modified by the evolution of novel behaviours and vice versa. The outcome will be a precedent for the integrative study of animal products that will establish a new line of research: evolutionary materials. In addition, by probing the structure-function relationship of behaviourally assembled silk composites, SuPerSilk will reinvigorate efforts to develop super-tough biofibres for industrial applications, a field that has stagnated in recent years, and enable the engineering of bio-fabrics with tailorable properties.

Link to the ERC project webpage:

Keywords of the ERC project: spider silk; biomaterials; biological materials; behavioural ecology; phylogenetics; biomimetics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101041354	**HOW2DOUBLE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Polina Novikova**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

The basic principles of polyploidy in plants and animals

Many eukaryotes have more than two sets of chromosomes due to whole-genome duplication (WGD) and are called polyploids. WGDs explain many cases of speciation bursts and evolutionary inventions. Some evidence suggests an adaptive advantage of polyploids: the origins of many ancient WGDs correspond to the times of extreme climate change, and contemporary polyploids often occupy harsher environments compared to their ancestors. However, most new polyploids are not as lucky and rarely survive. To explain the cause, predict and manipulate this process, we need to understand the basic principles of polyploidy: (1) how it is triggered, (2) what enables the initial survival of newly formed polyploids, and (3) how they stabilize a population and become successful. My program will comprehensively cover all these aspects, from the functional and genetic levels to the evolutionary forces driving the entire process. I propose a cross-disciplinary approach to identify common polyploidy principles in plant and animal diploid-tetraploid species complexes: Arabidopsis lyrata, widespread plant in Northern Hemisphere, and Neobatrachus, burrowing frogs living in the Australian desert. The approach combines classic genetics with the latest genomics technologies and population genetics analysis of natural herbarium and museum collections across broad geographies. I will (1) expose genetic and environmental predispositions to polyploidy formation by mapping natural variation of the unreduced gametes rates; (2) reveal mechanics and genetics stabilizing meiosis in polyploids, comparing recombination and selection across ploidies; (3) uncover polyploid populations recovery processes after bottlenecks accompanying their origin by reconstructing introgression patterns. Deciphering the mechanisms leading to successful polyploidization across the plant and animal kingdoms will deliver groundbreaking advances relevant across biology, agriculture, and medicine.

Link to the ERC project webpage:

Keywords of the ERC project: polyploidy, adaptation, genomics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101043548	**RECODYN**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Daniel Montoya**
Host Institution:	Asociacion Bc3 Basque Centre For Climate Change - Klima Aldaketa Ikergai - ESP

Ecosystem recovery dynamics and their response to climate change and habitat fragmentation

Global change degrades ecosystems worldwide. To mitigate its effects is the environmental challenge of our age, and restoration has emerged as the main strategy to stem the biodiversity crisis and repair damaged ecosystems. Despite substantial progress on the number of restoration studies and datasets, there is a fundamental gap in our understanding and prediction of the patterns and mechanisms underlying ecological restoration and how they are altered by global change. The goal of RECODYN is to determine the recovery rates and trajectories of biodiversity, community structure and ecosystem functioning in complex multitrophic communities, and how climate change and habitat fragmentation – two of the largest threats to biodiversity and ecosystems in terrestrial systems – influence those dynamics. To achieve this, I will use an integrative approach that combines the development of new theory on metacommunities and temperature-dependent food web dynamics in close dialogue with a unique long-term terrestrial mesocosm experiment. RECODYN is articulated around three objectives. First, I will investigate differences between natural assembly and recovery dynamics. Then, I will determine the effects of global change – i.e. climate change and fragmentation – on biodiversity, community structure, spatial and temporal stability, and key ecosystem functions of recovering ecosystems. Finally, I will provide creative solutions to restore ecosystems in a warmer and more fragmented world. RECODYN proposes an ambitious integrative and innovative research program that will provide a much-needed new perspective on ecological restoration in an era of global change. It will greatly contribute to bridging the gap between theoretical and empirical ecology, and to move restoration from an idiosyncratic discipline to a more predictive science. RECODYN will foster links with environmental policy by providing new restoration measures that derive from our theoretical and empirical findings.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101044424	**PlantSoilAdapt**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Marina Semchenko**
Host Institution:	Tartu Ulikool - EST

Eco-evolutionary dynamics in plant-soil interactions during land use transition: consequences for soil functioning and resilience to drought

European grasslands have been shaped by millennia of low-intensity management and are unique cultural and biodiversity hotspots providing critical ecosystem services. However, the area of traditionally-managed grassland has declined dramatically during the last century, with land-use intensification on productive soil and abandonment of unfertile land both causing species loss and deterioration of ecosystem services. Recent evidence suggests that land-use change also leads to genetic and phenotypic changes in plant populations. How population-level processes mediate the impact of land use on ecosystem functions and affect adaptive potential to future perturbations is entirely unknown. Filling this knowledge gap is urgent as grasslands face additional pressure from climate change, particularly an increasing frequency of droughts. I hypothesise that land use intensification and abandonment lead to evolutionary shifts in plant function away from resource conservation towards fast resource acquisition and low stress tolerance. Combined with the disruption of co-evolved mutualistic plant-microbial interactions, this has cascading effects on essential ecosystem services provided by soils and their resilience to drought-induced perturbation. The hypothesis will be tested using laboratory tests of the mechanisms underlying eco-evolutionary dynamics in plant-soil interactions during land-use change and community-level experiments to uncover the consequences of adaptation for soil functioning and resilience to drought. I will use the world's longest-running fertilization experiment and grassland networks in three European regions, representing different histories and contrasting management regimes. The project will provide a step-change in our understanding of the selective pressures imposed on plant-soil systems by human land use and will inform future policies for sustainable land management and maintenance of adaptive potential in the face of climate change.

Link to the ERC project webpage:

Keywords of the ERC project: plant-soil interactions, eco-evolutionary dynamics, local adaptation, mycorrhizal fungi, grasslands, land use

Keywords that characterize the scientific profile of the potential visiting researcher/s: plant-soil interactions, plant ecology, evolutionary ecology

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Project ID:	Project Acronym:	Evaluation Panel:
101044452	**BLOOMTOX**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Dedmer Van De Waal**
Host Institution:	Koninklijke Nederlandse Akademie Van Wetenschappen - Knaw - NLD

Global change impacts on cyanobacterial bloom toxicity

Harmful cyanobacterial blooms produce toxins that are a major threat to water quality and human health. Blooms increase with eutrophication and are expected to be amplified by climate change. Yet, we lack a mechanistic understanding on the toxicity of blooms, and their response to the complex interplay of multiple global change factors. Bloom toxicity is determined by a combination of mechanisms acting at different ecological scales, ranging from cyanobacterial biomass accumulation in the ecosystem, to the dominance of toxic species in the community, contribution of toxic genotypes in the population, and the amounts of toxins in cells. I will develop a fundamental understanding of bloom toxicity by revealing the combined effects of nutrients, elevated pCO2 and warming at each scale, and integrate these responses using a unique combination of ecological theory, technological advances, and methodological innovations. Specifically, I will use first principles to scale from cellular traits, like carbon and nutrient acquisition, cellular toxin synthesis and growth rates, to population and community dynamics. To enable rapid assessment of numerous cyanobacterial traits, I will set-up a high-throughput flow-cytometry pipeline. Also, I will develop a novel lab-on-a-chip experimental platform to allow massive parallel screening of key competitive traits in various phytoplankton species and cyanobacterial genotypes. To scale from these cellular traits to population and community interactions, I will study genotype selection and interspecific resource competition in state-of-the-art chemostats. I will further scale-up to natural communities in the field and in large-scale indoor mesocosms to assess global change impacts on the mechanisms underlying toxicity of (near) real-life blooms. With this unique combination of scaling approaches, I will provide a breakthrough in our mechanistic understanding on the toxicity of cyanobacterial blooms, and their response to global change.

Link to the ERC project webpage:

Keywords of the ERC project: Pnytoplankton, HABs, Ecology, cyanobacteria

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101044740	**BEAST**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Petr Keil**
Host Institution:	Ceska Zemedelska Univerzita V Praze - CZE

Biodiversity dynamics across a continuum of space, time, and their scales

We face an unprecedented threat from global alteration of nature and biodiversity, but we still lack rigorous estimates of how fast, where, and at which scales biodiversity changes. Studies report fragmented and seemingly contradictory results, suffer from mismatches in biodiversity metrics, mismatches in temporal and spatial grains, and are constrained by huge data gaps. Moreover, local loss and gain of biodiversity is decoupled from changes in countries or continents, with opposing directions at different scales being plausible. A quantitative synthesis that connects all this, and bridges the gaps, is needed. The objective of BEAST is to map and interpolate temporal biodiversity change in Europe, the US, and the world, across continuous space, time, and their grains, from locations as small as 1 m, to countries and continents, over the last ca 40 years, for birds, plants, and butterflies. To do this we will combine data from local time series with high-quality gridded atlas data from countries and continents. We will use a new cross-scale model to interpolate biodiversity change jointly across space and time, and across the data gaps. We will test if temporal change of diversity, distributions, and turnover can be estimated from: (i) static patterns of diversity and distributions, (ii) from data lacking temporal replication, (iii) from space-for-time substitution of spatial vs temporal species turnover, (iii) from spaceborne remotely sensed spectral diversity and turnover. These methods will enable integration of heterogeneous and messy biodiversity data, and they will improve estimates of change in data-poor regions of the global South. BEAST will deliver the first integrative statistical model revealing, for the first time, how multiple facets of biodiversity change across scales. It will show which regions, habitats, and biomes undergo the most pronounced change, which is critical for informed large-scale conservation policy.

Link to the ERC project webpage: https://petrkeil.github.io/

Keywords of the ERC project: biodiversity, scale, anthropocene, extinction

Keywords that characterize the scientific profile of the potential visiting researcher/s: statistics, biodiversity, ecology, geography

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Project ID:	Project Acronym:	Evaluation Panel:
101045309	**Time-lines**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Sandra Nogue**
Host Institution:	Universitat Autonoma De Barcelona - ESP

Island TIME-LINES to quantify biodiversity change

One of the most exciting and important research questions in ecology and palaeoecology is how fast, where, and why biodiversity is changing; heated debate on the topic within the scientific community reflects observations of apparently heterogeneous rates of change across the world. Biodiversity responses to different types of drivers of change remain underexplored, because to study these phenomena over the necessary span of years (often centuries to millennia) patterns and processes must be inferred from fossil records. There is also evidence that geographical attributes may mediate biodiversity responses to drivers of change, creating further complexity. That biodiversity change is spatially structured is the main hypothesis of TIME-LINES, which will examine ~5000 years of plant biodiversity change and the drivers of that change using a range of high-quality palaeoecological records derived from sedimentary sequences from islands worldwide. Islands are often described as hotspots of biodiversity and natural laboratories with legacies of relatively recent human impacts. For the first time, it is feasible to build palaeoecological networks at biogeographical scales. TIME-LINES will first establish the historical ranges of variability for both drivers of change and biodiversity. Aligning information on the magnitude of biodiversity change with the geographic properties of islands can then address whether change both at taxonomic and functional levels, is mediated by geographical context. The results will open new research horizons, bringing palaeoecology and biogeography together, and developing methods to quantify the effects of drivers of change—not only for islands but elsewhere, and in much greater depth than has been possible to date. From these findings, we can address to what degree historically informed baselines and change trajectories have utility for sustainable biodiversity management.

Link to the ERC project webpage:

Keywords of the ERC project: Biogeography, island biology, palaeoecology

Keywords that characterize the scientific profile of the potential visiting researcher/s: Macroecology, palaeoecology. Archaeology

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Project ID:	Project Acronym:	Evaluation Panel:
101052538	**NovoGenePop**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Mar Alba**
Host Institution:	Fundacio Institut Hospital Del Mar D Investigacions Mediques - ESP

Deciphering de novo gene birth in populations

Genes are fundamental units of life and their origin has fascinated researchers since the beginning of the molecular era. Many of the studies on the formation of new genes in genomes have focused on gene duplication and subsequent divergence of the two gene copies. But, in recent years, we have learnt that genes can also arise de novo from previously non-genic sequences. The discovery of de novo genes has become possible by the sequencing of complete genomes and the comparison of gene sets between closely related species. Here we wish to test a novel hypothesis, we propose that de novo gene formation dynamics in populations results in substantial differences in gene content between individuals. If they exist, these differences would be not be visible by the current methods to study gene variation, which are based on the comparison of the sequences of each individual to a common set of reference genes. To test our hypothesis, we will need to develop novel computational approaches to first obtain an accurate representation of all transcripts and translated open reading frames in each individual, and then integrate the information at the population level. We propose to apply these methods to two very distinct biological systems, a large collection of Saccharomyces cerevisiae world isolates and a human lymphoblastoid cell line (LCL) panel. For this, we will collect and generate RNA (RNA-Seq) and ribosome profiling (Ribo-Seq) sequencing data. In order to identify de novo originated events occurred within populations, as opposed to phylogenetically conserved genes that have been lost in some individuals, we will also generate similar data from a set of closely related species in each of the two systems. Combined with genomics data, we will identify the spectrum of mutations associated with de novo gene birth with an unprecedented level of detail and uncover footprints of adaptation linked to the birth of new genes.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101052538

Keywords of the ERC project: de novo gene birth, population genomics, protein evolution

Keywords that characterize the scientific profile of the potential visiting researcher/s: yeast genomics, protein sequence evolution

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Project ID:	Project Acronym:	Evaluation Panel:
101053543	**VIBES**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Assaf Vardi**
Host Institution:	Weizmann Institute Of Science - ISR

The impact of the viral shunt and its metabolic landscape on microbial lifestyles and the flow of carbon during algal blooms

The fate of carbon in marine environments is influenced by associations between heterotrophic bacteria and phytoplankton, mediated by chemical communication and metabolic exchange. Deciphering the nature of these associations is critical given the impact of marine plankton on biogeochemical cycling and climate regulation. Viral infection is a prevalent mortality agent of algal blooms in the ocean, leading to massive release of biomass to the dissolved organic matter (DOM) pool, one of the largest global inventories of carbon. This process, termed the 'viral shunt', is a key ecosystem process, but remains unquantifiable and mechanistically enigmatic. Furthermore, the metabolic composition of the DOM released following viral infection (vDOM) and its role in shaping microbial communities are largely unknown. In the VIBES project, we will disentangle the complexity of the viral shunt, and elucidate its impact on microbial lifestyles (mutualism and pathogenicity) during algal bloom demise. We will generate experimental approaches to study these bacterial lifestyles, and uncover the chemical language that mediates them. Our expertise in marine microbial chemical ecology, using single-cell transcriptomics to quantify host-pathogen interactions, and metabolomics to identify the chemical signals that govern microbial interactions, will pave the way for unprecedented quantification of the viral shunt. We will investigate the molecular and metabolic basis of virus-derived microbial lifestyles and their consequence for the flow of carbon in the ocean, both under controlled lab-based experiments and during complex interactions in the ocean. We will investigate how microbial lifestyles that specialize on vDOM can determine the partitioning of carbon between the dissolved and particulate fractions, representing carbon cycling and export, respectively. Ultimately, VIBES will enable to evaluate the importance of microscale interactions to the cycling of carbon in the ocean.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101076740	**STOIKOS**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Marcos Fernández-Martínez**
Host Institution:	Centro De Investigacion Ecologica Y Aplicaciones Forestales - ESP

Elemental Ecology: towards an element-based functional ecology

Life on Earth, as we have known it for millennia, is at stake. Human activities are putting all kinds of ecosystems under increased stress because of land-use change and the alteration of the biogeochemical cycles of nitrogen (N), phosphorus (P) and carbon (C), thus inducing climate warming. Functionally diverse ecosystems are more productive and stable than less diverse ones, and biogeochemical changes affect both biodiversity and the elemental composition of organisms (their elementome), changing how they and their ecosystems function. It is, therefore, imperative to provide evidence about how the interactions between elementomes, biodiversity, and climate drive ecosystem functioning if we are to avoid the serious threat of reducing essential resources for life within the context of global change. STOIKOS will achieve an in-depth understanding of the interaction between elementomes and biodiversity in determining ecosystem functioning by introducing the concept of elemental diversity, and moving functional ecology from using functional traits to elementomes, an easy and universal way to compare all sort of organisms. STOIKOS will particularly test the hypothesis that community-weighted elementomes and elemental diversity explain ecosystem functioning better than functional traits and their diversity. STOIKOS will integrate data from observations (field campaigns), long-term monitoring sites, microcosm experiments and theoretical modelling to provide synergies amongst their outputs to build the foundations of an elemental-based ecology. This will allow STOIKOS' hypotheses to be tested at the individual, species and community/ecosystem scales using new and game-changing methodologies and study systems. The cutting-edge science of STOIKOS will not only provide the foundations of an elemental-based ecology, but will also deliver new ecological theory and methodological tools that will help us predict the future of ecosystems and assess the fragility of our biosphere.

Link to the ERC project webpage: https://stoikos.creaf.cat/

Keywords of the ERC project: elements, ecosystem functioning, functional traits

Keywords that characterize the scientific profile of the potential visiting researcher/s: data analyst, modeller, ecologist, earth scientist, physicist

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Project ID:	Project Acronym:	Evaluation Panel:
101076837	**FutureNature**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Koenraad Van Meerbeek**
Host Institution:	Katholieke Universiteit Leuven - BEL

Shaping functional ecosystems of the future

Accelerating climate change is moving ecosystems rapidly beyond the bounds of historical variability. Many of the traditional conservation approaches trying to maintain a status quo are no longer effective. Rather than resisting change, we need to guide transforming ecosystems towards preferred ecological outcomes. Assisted migration, the active translocation of species to mimic range expansion under climate change, is a widely proposed adaptive management strategy. But it is also controversial, as it disrupts long-held views on biological conservation. Focusing on risks and ignoring benefits has hampered scientific research on assisted migration and halted necessary conservation innovation. Yet, the costs of inaction are too high and time is running out. In FUTURENATURE, I will approach the assisted migration of plant species from an innovative functional perspective, shifting the focus from minimising the impact of translocated species to maximising their contribution to the functioning of novel communities. I will advance our understanding of how assisted migration can safeguard functioning ecosystems by combining the wealth of large observational databases, state-of-the-art joint species distribution models and a cutting-edge climate change experiment. Specifically, I will (1) study the contribution of non-invasive alien species to ecosystem functioning; (2) incorporate species interactions and traits into species distribution modelling to simulate novel grassland communities; and (3) experimentally test the functionality of the best performing communities under future climate scenarios. With the knowledge gained, we will be able to shape ecosystems that will not only survive, but thrive under climate change. FUTURENATURE will provide a "greenprint" to study assisted migration across species groups and ecosystems, and, ideally, enable a paradigm shift in conservation thinking by lifting the psychological barriers preventing changes in natural ecosystems.

Link to the ERC project webpage:

Keywords of the ERC project: Assisted migration, plants, alien species, biodiversity conservation, modelling, grassland experiment

Keywords that characterize the scientific profile of the potential visiting researcher/s: Plant ecologist, modelling

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Project ID:	Project Acronym:	Evaluation Panel:
101077809	**HorizonGT**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Jeronimo Rodriguez-Beltran**
Host Institution:	Servicio Madrileno De Salud - ESP

Constraints and Opportunities for Horizontal Gene Transfer in Bacterial Evolution

Horizontal gene transfer (HGT) –the movement of genetic material between individuals– is a significant force fueling bacterial evolution. Through HGT, bacteria acquire new traits, develop new metabolic capabilities and learn to withstand harsh environmental conditions. However, in some cases, HGT brings genetic information that is not advantageous to its host. Despite its crucial relevance for bacterial ecology and evolution, understanding the selective forces that drive the success (or failure) of HGT remains a major challenge. Previous studies addressing this challenge ignored the fact that not all HGT events are alike: incoming DNA can be integrated into the host genome (e.g., transposons, integrons), or it can stand as a physically separated, autonomous DNA molecule (e.g., plasmids). This difference in genomic context poses several mechanistic constraints that are likely to alter the evolutionary outcome of HGT. Here, I will present a conceptually novel approach that explicitly considers genomic context to uncover the selective drivers of HGT in bacterial populations. First, I will develop a new genetic technology to obtain high-throughput fitness measurements of thousands of HGT events. Then, I will use these data to identify and quantify the constraints that determine the success of HGT, both considering the intrinsic effects of the transferred DNA and the role of genomic context on host fitness. Specifically, I will measure the fitness effects of genetic transfers mediated by plasmids (Obj. 1) or integrated into the chromosome and, in the latter case, in different regions of the chromosome (Obj. 2). Finally, I will leverage the rules derived from these analyses to reconstruct the role of HGT in the evolution of a relevant human pathogen (Obj. 3). This project will provide a quantitative and mechanistic understanding of the selective forces driving HGT, expanding horizons in evolutionary microbiology.

Link to the ERC project webpage: www.evodynamicslab.com

Keywords of the ERC project: Horizontal gene transfer, plasmid, bacteria, high throughput screening

Keywords that characterize the scientific profile of the potential visiting researcher/s: Horizontal gene transfer, bacterial evolution, antimicrobial resistance

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Project ID:	Project Acronym:	Evaluation Panel:
101077939	**ArcticEDGE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Anne Bjorkman**
Host Institution:	Goeteborgs Universitet - SWE

Consequences of warming-driven vegetation change for Arctic carbon cycling and feedbacks to the global climate system

ArcticEDGE will identify the consequences of warming-driven vegetation change for the functioning of Arctic ecosystems, particularly the cycling of carbon, and the impact on the global climate. The Arctic is the fastest-warming region on Earth, and Arctic soils contain more than double the amount of carbon currently in the atmosphere. Changes in the vegetation can influence whether this carbon is released into the atmosphere, thus contributing to additional climate warming, or stored in soils and plant biomass. Until now, we have lacked the ability to scale up from site-specific, local-scale studies to generalizable vegetation-function relationships relevant for the entire Arctic. ArcticEDGE will: 1) quantify the relationships between widely-measured plant functional and phenological traits and three key ecosystem processes related to global carbon cycling: litter decomposition, primary production, and fire dynamics, using field and laboratory experiments, 2) predict the rate with which these traits are likely to change in response to warming by identifying the relative contribution of turnover in species identity, shifts in abundance, phenotypic plasticity and genetic differentiation to trait variability and change over time, 3) determine the contribution of Arctic vegetation change to global-scale vegetation-climate feedbacks by combining knowledge from aims 1 and 2 with multi-decadal records of vegetation change and responses to experimental warming and precipitation at hundreds of locations across the Arctic, and 4) produce quantifiable outputs that will feed directly into Dynamic Global Vegetation and Earth System models to determine the consequences of Arctic vegetation change for the global climate. The knowledge generated by ArcticEDGE will contribute both to our theoretical understanding of how plants influence and are influenced by their environment as well as inform urgent efforts to project future changes in the global climate with greater precision.

Link to the ERC project webpage: https://edge-ecology.com

Keywords of the ERC project: plant ecology, vegetation change, Arctic, tundra, plant functional traits, ecosystem function, carbon cycling

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101078021	**SEXIPLANTS**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Jeanne Tonnabel**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

The scope for sexual selection in plants

The SEXIPLANTS project aims at providing a comprehensive empirical test for plants of the sexual selection theory, and decipher the mechanisms underlying sexual selection in plants. Sexual selection, acting through competition for the access to mates and their gametes, successfully explained numerous reproductive strategies in animals. Sexual selection typically emerges when females produce fewer numbers of larger gametes than males – a situation called anisogamy – which fosters competition among males for accessing the rare ovules. Sexual selection theory should thus be universally valid for all sexually reproducing anisogamous organisms encompassing plants. While the idea that sexual selection acts on plants is largely admitted, most predictions of the sexual selection theory remain untested in the plant kingdom. With a multi-method approach, including experimental evolution in the hermaphroditic plant Brassica rapa and comparative analyses in angiosperms, the SEXIPLANTS project asks: Q1. Testing the theory. Are fundamental predictions of sexual selection theory valid in the plant kingdom? We will empirically test key predictions of sexual selection theory regarding both male-male competition and female choice processes, and their demographical and genetic consequences. Q2. Specificity. Does the action of pollinators introduces specificity in the operation of sexual selection? We will empirically test how pollinator behaviour and density can alter sexual selection. Q3. Perception. Can plants perceive and respond to variation in their mating opportunities? We will empirically test whether plants can plastically adjust the reproductive strategies to variation in competition for access to mates. SEXIPLANTS will contribute to the development of a uniform and integrative theory of sexual selection valid for sexually-reproducing organisms including plants, and potentially reform our conceptual understanding of plant reproduction, with implications for conservation.

Link to the ERC project webpage:

Keywords of the ERC project: sexual selection, plant evolution, experimental evolution, pollinators

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101078303	**ERODE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Hernan Eduardo Morales Villegas**
Host Institution:	Kobenhavns Universitet - DNK

Evolutionary dynamics of genomic erosion and its application in biodiversity conservation

Reducing biodiversity loss is one of the most pressing societal challenges of our time. Population decline has put many species on the path of collapse and extinction. Reducing or reversing this decline is not enough to tackle the associated hidden evolutionary costs, most notably genomic erosion which compromises the long-term viability and resilience of species. ERODE will employ state-of-the-art approaches – (paleo)genomics, quantitative genomics, and evolutionary modelling – to assess the dynamics of genomic erosion on neutral, beneficial, and deleterious variation and understand its effects on organismal fitness, population viability, and extinction risk. I will perform one of the most comprehensive genome-fitness studies to date by examining the fitness effects of genomic erosion over time in 6,530 individuals of three iconic endangered bird species for which I have access to over 30 years of genetic samples and fitness data. Together with zooarchaeological and museum-preserved samples, I will draw a dynamic timeline of genomic erosion in response to population decline. Next, I will develop a modelling framework parametrized and validated with empirical data to predict the consequences of genomic erosion. I will use this framework to understand the efficacy of in-situ and ex-situ conservation strategies in collaboration with The European Association of Zoos and Aquaria (EAZA). The computer model will incorporate genomics into the Green Status of Species to evaluate species recovery and conservation impact, in collaboration with members of the International Union for Conservation of Nature (IUCN). ERODE will produce one of the largest genomic datasets for endangered species in the world and a robust modelling framework for conservation scientists and practitioners. The outputs will be disseminated in academic journals but also over a series of workshops, instruction videos and other outreach activities, which will support their practical application.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101078303

Keywords of the ERC project: genomics, biodiversity, conservation, evolutionary biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: quantitative genetics, bioinformatics, genomics, evolutionary biology

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Project ID:	Project Acronym:	Evaluation Panel:
101085894	**CarboCell**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Marian Yong-An Hu**
Host Institution:	Christian-Albrechts-Universitaet Zu Kiel - DEU

Vesicular mechanisms of carbon fixation in calcifying cells of marine animals

The process of biomineralization has profound impacts on the geology of our planet and is an integral part of the global carbon cycle by generating large amounts of CaCO3 bound in coral reefs, chalk mountains and deep sea sediments. Mounting evidence demonstrate that many marine calcifiers generate biominerals by the intracellular formation of CaCO3 from seawater Ca2+ and metabolic CO2. To date, the underlying mechanisms that control the carbonate chemistry in calcifying vesicles are unknown which however will provide ground-breaking insights into a biological process that is capable of transforming a metabolic waste product - CO2 - into a versatile construction material. In the past 5 years my group has developed a unique methodological expertise to study the cellular physiology of calcifying systems. Building on this expertise CarboCell will tackle the important but challenging task to identify and understand the mechanisms of vesicular calcification. The sea urchin larva will serve as a powerful model organism, that represents a prime example for the intracellular formation of CaCO3 and which allows us to employ specifically targeted molecular perturbations in combination with sub-cellular ion and pH recordings. CarboCell will take a stepwise strategy to systematically examine the mechanisms of vesicular calcification on the three main core subjects- carbonate chemistry (WP1), ion/CO2 transport mechanisms (WP2) and vesicular volume regulation and trafficking (WP3). CarboCell will provide a deep mechanistic understanding of the calcification process with strong implications for explaining and predicting responses of marine calcifiers to the global phenomenon of ocean acidification. More importantly, knowledge about the mechanisms that allow organisms to transform CO2 into a construction material will pave the ground for novel, biology-inspired solutions of CO2 capture and utilization – a basic science approach at the core of twenty-first century concerns.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101086771	**GorBEEa**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Ainhoa Magrach**
Host Institution:	Asociacion Bc3 Basque Centre For Climate Change - Klima Aldaketa Ikergai - ESP

Understanding biodiversity-ecosystem function and biodiversity-stability relationships across spatial and organizational scales

The role of biodiversity in shaping ecosystem functioning (EF) and stability (ES) is a fundamental question in ecology. The mechanisms underlying biodiversity-EF (BEF) and biodiversity-ES (BES) relations have been extensively studied, but they have been approached separately, and we thus lack an understanding of how EF and ES relate, a particularly urgent task in the face of global environmental change. Further, most research has been conducted within single trophic communities and relatively small spatial scales, and whether the types of relations observed are scalable and applicable to multi-trophic communities is unknown. To address these shortcomings, in GorBEEa I propose to merge BEF and BES research (i) within multi-trophic communities, in this case plant-pollinator interaction networks, (ii) across spatial and organizational scales (from local to regional scales, and from populations, to communities), (iii) taking a dynamic perspective that considers multiple temporal scales (within day, within season, between years), and (iv) following a multi-functional approach, analysing several functions on the resource side, but also considering the many times neglected impact on the consumer side. Further, (v) to understand aspects of stability beyond temporal invariability, I will introduce a perturbation to the system, to understand whether biodiversity in multi-trophic communities provides higher resistance and resilience values. GorBEEa represents an ambitious research programme at the intersect of population, community, ecosystem, and conservation ecology, that will deliver an understanding of how declining biodiversity levels influence natural ecosystem dynamics. But it will also offer an applied angle, through collaborations with stakeholders to develop scientifically-informed management practices.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101086900	**CONVERGENCE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Laszlo Nagy**
Host Institution:	Szegedi Biologiai Kutatokozpont - HUN

Major transitions made easy? In search of genetic preconditions that help the repeated evolution and loss of fungal multicellularity

In this project, we aim to study the genetic mechanisms of convergent evolution by uncovering the mechanistic details of two highly replicated transitions in organismal complexity. Convergent evolution is widespread in nature, even on macroevolutionary timescales. To explain its pervasiveness, recent studies have proposed the idea of predisposing precursor traits that, if easily co- or exapted for new functions, can increase the likelihood of convergence. However, most of these hypotheses remain untested because of the lack of tractable model systems. We identified two fungal case studies that offer optimal model systems to mechanistically test the hypothesis that precursor traits increase the likelihood of convergence: (i) 8-11 repeated origins of complex multicellularity in mushrooms and (ii) >14 losses of multicellularity in yeast-like fungi. We hypothesize that both of these occurred by the repeated exaptation of ancient morphogenetic programs and, in the case of yeasts, additionally, by the emergence of mechanisms for bypassing multicellular growth. Our hypotheses imply that both complex multicellular and yeast-like lifestyles are only a few mutations away for any filamentous fungus because precursor traits shorten the mutational path for evolution. Although these are bold hypotheses, we obtained promising preliminary results that support them. We designed an experimental plan involving phylogeny-aware comparative -omics, reverse genetics, and evo-devo, which, when combined with our preliminary results, will provide a robust entry point for testing the role of predisposition in convergent evolution and will ultimately allow us to “replay the tape of major fungal transitions” in the laboratory. We expect this project to contribute to uncovering the general principles of convergent evolution and to be one of the first to mechanistically test if certain precursor traits can promote convergence.

Link to the ERC project webpage:

Keywords of the ERC project: evolution, fungi, evo-devo, morphogenesis, wood-decay

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101087042	**MicroRescue**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Ashley Shade**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Resolving mechanisms of microbiome rescue to promote resilience to climate change

Earth's climate crisis threatens to disrupt ecosystem services and destabilize food security. Communities of microorganisms, called microbiomes, provide critical functions that feedback on climate and support soil and plant health. I propose a new framework, Microbiome Rescue, to recover microbial populations and lost functions after disturbances. With critical knowledge about the ecology of microbiomes and their contributions to creating resilient systems, I propose that we can achieve a paradigm shift in ecosystem management via directed microbiome interventions. Here, I focus on elaborating rescue strategies that leverage the selective reactivation of dormant microbes. Because microbial dormancy is extensive in soil and the rhizosphere, reactivation offers access to untapped biodiversity and provides immediate solutions for maintaining functions in ecosystems affected by climate change. My first objective is to understand and predict the capacity of dormant soil microorganisms to rescue microbiomes in a changing climate and discover reactivated bacteria that facilitate resilience. My second objective is to investigate and develop bacterial reactivation for rescue-based microbiome management to support plant resilience to climate change stressors and preserve plant-soil feedback. To achieve these goals, I will execute three multi-factor experiments to reactivate the dormant microbiome from soil and plant systems after exposure to heat and moisture stress. First I will perform a heat and moisture experiment for European soils, assess risk, and curate microbial collections that support functional rescue. Next I will perform two practical rescue experiments for the microbiomes of legumes exposed to heat and moisture stress: customized microbiological amendments and host-microbiome engineering. This work will provide unprecedented insights into microbiome rescue and identify targets for biological interventions to support soil and crop resilience to climate change.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/101087042

Keywords of the ERC project: environmental microbiology
microbial ecology
microbiome
climate change
soil microbiome
plant-microbiome interactions
resilience
disturbance ecology
community and population ecology
metagenomics
time series

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101087134	**ETHYLUTION**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Bram Van De Poel**
Host Institution:	Katholieke Universiteit Leuven - BEL

Revealing the ancient plant ethylene biosynthesis and ACC signaling pathway

When ancestral plants colonized the land 450 million years ago, they needed to adapt to harsh environmental conditions when giving up their aquatic lifestyle. I hypothesize that during this water-to-land transition, the volatile plant hormone ethylene became an important growth regulator to face terrestrial stressors. In fact, modern-day crops use ethylene to regulate stress responses, and perhaps ethylene served this role in pioneering land plants to cope with the harsh conditions coinciding with this habitat transition. During my postdoc, I showed that ethylene signaling was functionally assembled in ancestral Charophyte green algae, prior to land colonization. Now I question why and how early land plants produced ethylene. While seed plants make ethylene using ACC as precursor, non-seed plants follow a different, yet unknown ethylene biosynthesis pathway, which I want to reveal using the liverwort Marchantia polymorpha, a model species representing early life on earth. Our preliminary data indicate that KMBA might be the precursor of this hidden pathway. I also question why non-seed plants make ACC, but not use it for ethylene synthesis. Recent studies revealed that ACC itself can act as a signaling molecule, independent from ethylene, by an unknown signaling pathway to regulate plant development. Recently, my lab found some ACC insensitive mutants in Marchantia, which will allow us to reveal the ACC signaling pathway of plants. I also postulate that both the alternative ethylene biosynthesis and ACC signaling pathway might have an origin in ancient algae, prior to land colonization, and might be conserved in seed plants, possibly exerting important functions yet to be uncovered. Using functional genetics in representative species of algae and crops, ETHYLUTION will unravel the importance and role of ACC and ethylene that allowed plants to thrive on earth, perhaps one of the most impactful events in the evolutionary history of plants.

Link to the ERC project webpage:

Keywords of the ERC project: ethylene, ACC, Marchantia polymorpha, evolution, Arabidopsis, molecular biology, tomato, Arabidopsis, algae

Keywords that characterize the scientific profile of the potential visiting researcher/s: plant scientists, plant hormones, plant evolutionary biology, plant molecular biology, ethylene biosynthesis, ACC signaling, Marchantia polymorpha,

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Project ID:	Project Acronym:	Evaluation Panel:
101088581	**EPISTAT**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Ilkka Kronholm**
Host Institution:	Jyvaskylan Yliopisto - FIN

Role of epistatic interactions in evolution

The distribution of fitness effects of mutations is vital to our understanding of rates and patterns of adaptation. Population genetics and mutation accumulation experiments have given us insight into the distribution of fitness effects of single mutations. However, mutations often interact with each other. This is called epistasis. The role of epistatic interactions in adaptation has remained controversial. Yet, the distribution of epistatic effects is as fundamental as distribution of mutational effects themselves. Without knowing the distribution of epistatic effects, we can't calculate the average fitness effect of a given mutation across multiple genetic backgrounds. Moreover, if epistatic interactions tend to be positive or negative on average, this will have an important effect on evolutionary dynamics. Epistatic interactions are also known to play a role in speciation, but the proportion of mutations that exhibit incompatible interactions that can lead to speciation is unknown. I will investigate the properties of epistatic interactions among mutations with two complementary approaches. First, I will estimate the probability and distribution of effects of epistatic interactions among spontaneous mutations. I will cross mutation accumulation lines that I have developed for the fungus Neurospora crassa to produce a mapping population where spontaneous mutations are segregating, and use it to estimate the distribution of epistatic effects. Second, I will estimate the proportion of substitutions that cause reproductive incompatibilities between populations from the relationship between reproductive isolation and genetic divergence. This is achieved by an evolution experiment with fission yeast, with a design that will maximize the rate of genetic divergence with minimal change in mean phenotype. The elucidation of properties of epistatic interactions will be a major breakthrough for the field of evolutionary biology.

Link to the ERC project webpage:

Keywords of the ERC project: epistasis, experimental evolution, mutation accumulation, genomics, population genetics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101088709	**EcoEvoDiv**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator: **Dr Jan Hrcek**

Host Institution: Biologicke Centrum Akademie Vid Ceske Republiky Verejna Vyzkumna Instituce - CZE

Eco-evolutionary dynamics and the maintenance of organismal diversity

There is growing evidence of rapid evolution leading to entangled eco-evolutionary dynamics. However, we are only beginning to address what this implies for maintenance of biodiversity in nature. Community ecology studies how species diversity is maintained in communities despite negative interactions. Separately, population biology studies how phenotypic and genetic variation is maintained in populations despite selection and drift. These two questions are interlinked, but usually addressed independently, not considering the other level. Intriguingly, genetic variation could help maintain species diversity, and reciprocally, diversity could help maintain variation, forming a positive feedback loop. However, this hypothesis has not been empirically tested in complex ecological networks, because maintaining such networks in the laboratory is a major challenge. I propose to experimentally test this hypothesis using a uniquely tractable network of tropical rainforest Drosophila and their parasitoids (6 fly and 5 wasp species), that I developed to allow multigenerational microcosm experiments. We will manipulate species diversity and genetic variation of all species in a factorial design to test the hypothesis. We will then explore the mechanisms of interactions between diversity and variation, focusing on rapid evolution. To link the findings to natural eco-evolutionary dynamics, we will investigate mechanisms maintaining diversity and variation in the wild. Based on the empirical work we will advance eco-evolutionary concepts of organismal diversity and stability. This project will provide a causal test of the interaction between maintenance of diversity and variation, thus linking two key questions in ecology and evolutionary biology. Uncovering the specific coexistence mechanisms will allow us to predict the importance of diversity – variation feedbacks in other systems with important implications for conservation of biodiversity.

Link to the ERC project webpage: http://lab.hrcek.net

Keywords of the ERC project: rapid evolution, diversity, genetic variation, parasitism

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101115983	**EVOL-SV**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Claire Mérot**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

The role of structural genomic variants in eco-evolutionary processes

Genetic diversity is a fundamental level of biodiversity at a time of global change. It provides variation that underpins species persistence and their adaptation to changing environments. Variation in the direction or presence of DNA sequences has been largely overlooked until now. Yet, those structural variants (SVs) represent a key aspect of genetic diversity. SVs cover 3 to 10 times more of the genome than the well-studied single-nucleotide variants and have different properties (length, effect on recombination, mutation rate). Structural variation thus represents a quantitative and qualitative shift in our understanding of genetic diversity, with predicted, but understudied, implications for evolution. The project EVOL-SV calls for a reassessment of the genomic basis of eco-evolutionary processes. My ambition is to lead new research avenues on the impact of SVs in ecology and evolution and to determine the contribution of SVs to current biodiversity. I will combine cutting-edge genomics and powerful experimental approaches, developed throughout my career, to perform multidisciplinary research on a focal system, Coelopa flies, and then across taxa. First, I will investigate SVs within a population genetic framework in Coelopa spp. to determine how SV properties affect their distribution and effects on fitness. Second, I will assess the contribution of SVs to deleterious load in a case of range shift northwards. Third, I will examine how SVs contribute to phenotypic adaptation, focusing on parallel climatic gradients and rapid thermal variation. Fourth, at a broader phylogenetic level, I will draw general principles about the evolution of structural genetic diversity. EVOL-SV will have long-term impacts by providing the first comprehensive assessment of structural genetic diversity across the tree of life, developing the study of SVs in non-model species, and determining how genetic architecture contributes to evolutionary response in a rapidly changing world.

Link to the ERC project webpage:

Keywords of the ERC project: Evolution - Population Genomics - Adpatation - Structural variants - Insects - Genomes - Experiments

Keywords that characterize the scientific profile of the potential visiting researcher/s: Bioinformatician - Entomologist - Evolutionary biologist -

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Project ID:	Project Acronym:	Evaluation Panel:
101117204	**GIAPHAGE**	**LS8** Environmental Biology, Ecology and Evolution

Principal Investigator:	**Dr Elina Laanto**
Host Institution:	Jyvaskylan Yliopisto - FIN

Life of Giant Phages

Bacterial viruses, phages, are ubiquitous and most numerous entities in the biosphere. Development of sequencing techniques has increased our understanding on the diversity of phages that have not been isolated due to lack of cultivable hosts and/or suitable isolation methods. While sequence data enables a better view to the viral diversity, at the same time lack of functional data and biological connection increases. Recently, different studies have found megaphages (mainly phages with a genome over 600 kbp) by assembling metagenomes from various environmental samples. However, no such isolates have been obtained thus far meaning that their characteristics and host interactions are completely unknown. In this ERC project, I will enlighten the life of giant phages, the term I coined for both jumbo and megaphages. I will achieve this by using the first megaphage isolates that I have isolated from boreal freshwaters. During the project, evidence on the megaphage structure, the host interactions and symbiotic relationship with host will be provided. Using a unique set of different phage sizes infecting the same host I will determine the size correlation to different life history traits. I will provide insight to the mutualistic relationship between bacteria and their viruses and reveal new mechanisms behind phage competition. I will also determine the environmental preferences for the megaphage emergence and abundance in boreal freshwaters. In this proposal, I aim to understand How, Where and When megaphages are isolated. Consequently, results will aid in understanding the role of megaphages in other environments such as gut microbiome and potentially provide avenues for developing new genetic tools. This project will open new understanding for microbial ecology and especially phage ecology and the project will create a new field of study under phage biology.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
864117	**nbPTMs**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Ivan Matic**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

A multifaceted platform for exploring nucleotide-based post-translational modifications

Nucleotide-based post-translational modifications (nbPTMs) play key roles in health and disease, from bacterial pathogenesis to cancer. However, technical challenges of these versatile, but chemically complex protein modifications have constrained our fundamental understanding of even the most intensely studied nbPTMs for decades. The overarching aim of this proposal is to establish, apply and disseminate a methodology to unveil novel types of nbPTMs and allow site-specific proteomic analyses. The conceptual innovation lies in a strategy for turning the complex chemical structures of nbPTMs from a challenge to an advantage. First, shared chemical moieties will be exploited to develop pan-specific enrichment of multiple nbPTMs. For this purpose, we will generate the first nbPTMs-specific antibodies by converting specific signalling proteins into biotechnology tools for chemoenzymatic synthesis of challenging peptide antigens (aim 1). Second, we will take advantage of the chemical lability of nbPTMs to analyse modified peptides using a nucleobase-targeted mass spectrometry approach (aim 2). The unbiased scope of our methodology will make possible the discovery of as yet unknown forms of nbPTMs (aim 3) and nbPTM site mapping throughout eukaryotic proteomes (aim 4). These new materials, methods, discoveries and datasets will be made publicly available to allow future investigations of nbPTMs by the scientific community. The new substrates, sites and nbPTMs will provide starting points for biological characterization (aim 5). Poised at the interface of biology and technology, this interdisciplinary research project has the potential to explore new territories within established biomedical fields and to contribute to the knowledge base for improved treatment of diseases.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/864117/de

Keywords of the ERC project: Chemical biology, proteomics, biological chemistry, nucleotide-based post-translational modifications, nbPTMs, post-translational modifications, ADP-ribosylation, AMPylation, HPF1, histones

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
883687	**Multiorganelledesign**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Edward Lemke**
Host Institution:	Johannes Gutenberg-Universitat Mainz - DEU

Multiple Designer Organelles for Expanded Eukaryotic life

The emergence of organelles dedicated to specific cellular functions drove the evolution of more complex eukaryotic organisms. We recently created membraneless organelles inside eukaryotic cells dedicated to orthogonal translation, which opened a new path to residue-specific protein engineering using genetic code expansion. We now want to design novel organelles into eukaryotes that will internally enact the entire central dogma of molecular biology. This will supplement the complex eukaryotic cell with an additional simple and easily tailored orthogonal machinery that can also facilitate transcription and replication. This will enable us to create eukaryotes that have more than four additional expanded genetic codes, and we will explore the functional space occupied by these novel living systems. The organelles will be enhanced to process specific signals to e.g. modify RNA or degrade specific proteins. Besides these curiosity-driven goals, specific applications will allow us to road test our technology. We will directly use these approaches to advance protein engineering in eukaryotes to create proteins and artificial peptide polymers having multiple, noncanonical functionalities suitable for diverse biotechnological applications and new bioinspired materials. We will also develop organelle design into a truly universal and powerful labeling method fully compatible with eukaryotic host cell physiology that has single-residue precision and goes way beyond the state-of-the-art of any fluorescent labeling technology. The approaches will be general and truly flexible in how translation can be tailored in terms of protein, RNA and codon choice, including sense codons and type of new functionalities. Progress made in recent decades has shown that protein design and engineering can revolutionize biology. We can only imagine what can be achieved with designed functional organelles inside eukaryotic cells and how they might enable the creation of new living systems.

Link to the ERC project webpage: lemkelab.com

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
948588	**hOssicle**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Paul Bourgine**
Host Institution:	Lunds Universitet - SWE

Bioengineering of human ossicles as advanced in vivo hematopoietic model

hOssicle aims at developing miniaturized human bone organs in mice to be used as advanced model of healthy and malignant human hematopoiesis. In Europe, 80 million people are estimated to suffer from blood disorders. When at all existing, treatments are poorly effective: 92 % of new drugs successful in preclinical testing (animals and in vitro culture systems) fail in clinical trials. This urgently calls for the development of superior models, to refine our understanding of human hematopoiesis and better predict patient´ therapy efficacy. My laboratory has developed unique human mesenchymal lines capable of forming “human ossicles” by recapitulation of endochondral ossification -the developmental process of bone formation. These ossicles form subcutaneously in mice and display a similar structure and function to native mouse bones, but rely on human mesenchymal cells reconstituting a complex bone marrow environment specifically supporting the development of human hematopoiesis. hOssicle will offer the unprecedented custom engineering of human bones to understand the functional organization of its hematopoietic compartment. By genetic reprogramming of mesenchymal lines, I aim at controlling the molecular and cellular composition of the ossicles and study the corresponding impact on hematopoietic development. Finally, I envision the engineering of patient-specific ossicles with mesenchymal and leukemic blood cells from the same individual towards recapitulation of the disease setting. This will be a significant breakthrough, by offering the study of malignancy progression and drug-testing in a personalized in vivo context for cancer remission. By combining principles of bone development & tissue engineering, hOssicle proposes an “organ engineering” approach applied to hematopoiesis. The implications run from the identification of key factors controlling the production of blood cell types to the personalized modelling of leukemia and test of therapies.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
949080	**DEUSBIO**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Rodrigo Ledesma Amaro**
Host Institution:	Imperial College Of Science Technology And Medicine - GBR

Deciphering and Engineering the overlooked but Universal phenomenon of Subpopulations in BIOtechnology

Microbial bioproduction, despite being considered a paradigmatic sustainable alternative to petroleum-based chemistry, is often limited by low yields and productivities, which prevents commercialisation. It is generally known for all types of cells that genetically identical populations can form metabolically distinct subpopulations. This diversity strongly impairs bioproduction as the presence of low-producer or slow-grower cells reduces overall yields. However, the universal phenomenon of subpopulations emergence has been largely overlooked, especially in biotechnology, due to technical difficulties. Now, thanks to recent developments in single cell technologies, in molecular understanding of microbial communities and in synthetic biology tools, we can begin to address this widespread and impactful biological feature. I propose to explore the emergence of subpopulations in yeast and understand their implications in metabolism and bioproduction using and developing cutting edge synthetic biology tools. I aim to use that knowledge to develop novel engineered strains that lack the presence of undesired subpopulations and then use such homogeneous populations for bioproduction. The homogenised production will be investigated in both, monocultures and microbial communities. In DEUSBIO, I will set up an innovative framework to maximise the biosynthesis of high value molecules, with high potential to overcome current limitations. This project will shed light on the phenomenon of subpopulations, whose relevance goes beyond bioproduction, as for example, it has been associated with the origin of multicellularity. Increasing our knowledge about this matter will also have implications in biomedicine, as cell subpopulations are extremely important in the appearance of antimicrobial resistant, in cancer heterogeneity, and in microbiome complexity.

Link to the ERC project webpage:

Keywords of the ERC project: synthetic biology, metabolic engineering, heterogeneity, bioproduction, biotechnology

Keywords that characterize the scientific profile of the potential visiting researcher/s: synthetic biology, metabolic engineering, heterogeneity, bioproduction, biotechnology, systems biology, single cell

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Project ID:	Project Acronym:	Evaluation Panel:
950050	**PREDICT-CARE**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Pedro Miguel Mena Parreño**
Host Institution:	Universita Degli Studi Di Parma - ITA

Developing tools for the PREDICTion, at individual level, of the CArdiometabolic REsponse to the consumption of dietary (poly)phenols

Life on Earth, as we have known it for millennia, is at stake. Human activities are putting all kinds of ecosystems under increased stress because of land-use change and the alteration of the biogeochemical cycles of nitrogen (N), phosphorus (P) and carbon (C), thus inducing climate warming. Functionally diverse ecosystems are more productive and stable than less diverse ones, and biogeochemical changes affect both biodiversity and the elemental composition of organisms (their elementome), changing how they and their ecosystems function. It is, therefore, imperative to provide evidence about how the interactions between elementomes, biodiversity, and climate drive ecosystem functioning if we are to avoid the serious threat of reducing essential resources for life within the context of global change. STOIKOS will achieve an in-depth understanding of the interaction between elementomes and biodiversity in determining ecosystem functioning by introducing the concept of elemental diversity, and moving functional ecology from using functional traits to elementomes, an easy and universal way to compare all sort of organisms. STOIKOS will particularly test the hypothesis that community-weighted elementomes and elemental diversity explain ecosystem functioning better than functional traits and their diversity. STOIKOS will integrate data from observations (field campaigns), long-term monitoring sites, microcosm experiments and theoretical modelling to provide synergies amongst their outputs to build the foundations of an elemental-based ecology. This will allow STOIKOS' hypotheses to be tested at the individual, species and community/ecosystem scales using new and game-changing methodologies and study systems. The cutting-edge science of STOIKOS will not only provide the foundations of an elemental-based ecology, but will also deliver new ecological theory and methodological tools that will help us predict the future of ecosystems and assess the fragility of our biosphere.

Link to the ERC project webpage: https://hnu.unipr.it/en/predict-care/

Keywords of the ERC project: personalised nutrition, polyphenols, cardiometabolic response, metabotypes

Keywords that characterize the scientific profile of the potential visiting researcher/s: biostatistian, bioinformatic, data scientist

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101001905	**FORWARD**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Rupert Seidl**
Host Institution:	Technische Universitaet Muenchen - DEU

Causes and consequences of forest reorganization: Towards understanding forest change

ForeForest ecosystems around the globe are undergoing rapid reorganization. The unabated continuation of climate change, the accelerating rate of alien species introductions, and the precipitous loss of biological diversity are altering the structure and composition of forest ecosystems. As a consequence, novel ecosystems are emerging. However, the trajectories to novelty and the consequences thereof remain widely unknown. This limits the ability of forest policy and management to counteract undesired developments and safeguard the supply of ecosystem services to society. Here I will investigate the causes and consequences of reorganization in forest ecosystems. I will use a concerted combination of complementary methodological approaches to understand why reorganization takes place, when and where reorganization is likely to happen, and what impacts reorganization will have on biodiversity and ecosystem services. Replicated experiments will be conducted both in the field and in walk-in climate chambers to answer whether compounding climatic extremes could result in bottlenecks of forest regeneration. A next-generation forest landscape model will be developed to investigate how invasive alien species alter forest development. Based on these insights the FORWARD project will derive operational early warning indicators of reorganization, and test their generality and applicability in the field for landscapes on three continents. Subsequently, a machine-learning aided synthesis of big datasets will be used to compile the first map of global hotspots of forest reorganization. Finally, robust management strategies for addressing reorganization will be developed. Jointly studying the effects of global change on tree mortality and regeneration across scales, the FORWARD project will bring about a new level of understanding of forest change, and will provide the data, tools and strategies to tackle one of the most pressing challenges of current forest policy and management.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101002646	**Switch2See**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator: **Dr Andre C Stiel**

Host Institution: Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Genetically encoded reporters and sensors for whole animal imaging using photo-modulated Optoacoustics

In vivo imaging of cellular localization and function and visualization of the chemicals that drive life are key challenges for biological research. Current methods limit our insight into this "bigger picture" to either a glimpse (low penetration and small field of view) or a coarse overview (low resolution). Optoacoustic (OA) imaging has the physical means to overcome these limitations, but it lacks the necessary toolbox of genetically encoded reporters and sensors that allow specific probing of localizations and distributions. So far, all efforts to create such a toolbox were impeded by the strong tissue background inherent to OA. Recently, exploiting my longstanding expertise in reversibly switchable reporters I overcame this hurdle by introducing the concept of photo-modulation to OA. Switchable reporters allow modulation of the reporter signal to separate it from the background – making the latter virtually invisible ("Switch2See"). In parallel, the concept was used by a U.S. consortium in vivo, underpinning its validity. Hence, now is the time to combine my expertise in switching, protein-engineering, sensors, and OA imaging to create a toolbox that will allow to follow cells over time, visualize their interactions, and image the distributions of chemicals – all on the scale of the whole live organism with resolutions of 20 - 150 µm. With Switch2See, I will lay the foundations by building dedicated screening infrastructure, use it to develop a range of reporters (multiplexing) and sensors, and develop algorithms to convert the photo-modulation patterns into images. I will demonstrate the revolutionary impact on whole-animal imaging by visualizing localization, dynamics and interaction of immune cells in the tumor micro-environment (TME) and visualize aspects of its chemical heterogeneity. Beyond cancer research, this will impact all questions requiring a "bigger picture" – from developmental processes over neurobiology to the functioning of the immune system.

Link to the ERC project webpage:

Keywords of the ERC project: Protein engineering, Bioengineering, Optical Imaging, genetically encoded labels and sensors, signal processing

Keywords that characterize the scientific profile of the potential visiting researcher/s: directed evolution, protein biochemistry, AI, signal processing, cell biology

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101003111	**CPTarget**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Akane Kawamura**
Host Institution:	University Of Newcastle Upon Tyne - GBR

Cyclic Peptide Platform as an Approach to Target Validation

The current 'genomics' era is an exciting time for drug target discovery with considerable opportunities for therapeutic intervention. Whilst classical small molecules remain the reagents of choice as chemical probes for target validation, not all targets are tractable with small molecules. There is thus an urgent need to develop methods for more efficient target validation, not only of individual proteins but also of protein-protein and other complexes. Natural product like cyclic peptides have enormous potential as a chemical platform for target validation. Recent technological advances have enabled the efficient production and screening of large libraries containing non-proteinogenic residues. De novo cyclic peptides with high affinity and selectivity for target proteins can be readily generated, even for protein-protein interaction targets perceived as challenging. Development of this technology and their innovative applications as outlined in our proposal will provide a step-change in methodology, and transform the current approach for studying the biological function of the target / pathways, enabling new ways to investigate potential targets. We aim to develop innovative chemical and molecular techniques to explore the applications of natural product-like cyclic peptides in target validation for very challenging targets. Ultimately the work aims to enable the development of new therapeutic agents targeting multiple diseases.

Link to the ERC project webpage:

Keywords of the ERC project: chemical biology; cyclic peptides; chemistry; biotechnology

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatician, molecular biologist, chemists, cell biologists

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Project ID:	Project Acronym:	Evaluation Panel:
101041231	**HSC-CRISPR**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Rasmus Bak**
Host Institution:	Aarhus Universitet - DNK

Transcriptional Engineering of Hematopoietic Stem Cells using CRISPR

Hematopoietic stem cells (HSCs) reside in the bone marrow where they throughout life sustain continuous blood production through a controlled balance of differentiation and self-renewal. Transplantation of HSCs from a healthy person can replace a defective hematopoietic system of a patient thereby curing the patient for life. HSCs have found increasing therapeutic application, e.g. in hematologic malignancies and hematopoietic genetic disorders. This applies not only to the allogeneic transplantation setting but also to the autologous setting where advances in genetic engineering technologies have enabled autologous gene therapies. However, major challenges remain in both settings pertaining to the scarcity of HSCs, as well as the cells being partially refractory to precise gene correction. In this research proposal, I will address these challenges by leveraging the unique power of repurposed CRISPR/Cas systems for precise transcriptional manipulation of HSCs. In these systems, the normal DNA-cleaving ability of the Cas9 enzyme is disabled (dCas9) while transcriptional activators or inhibitors are fused to dCas9. By targeting the dCas9-effector proteins to transcriptional start site regions by sgRNA programming, gene transcription can be activated (CRISPRa) or inhibited (CRISPRi). Complex transcriptional engineering is readily achieved using multiple sgRNAs and orthogonal CRISPR systems for simultaneous CRISPRa and CRISPRi. I will apply these technologies to investigate and enhance therapeutically relevant HSC pathways, namely homologous recombination for precise gene editing, self-renewal, and bone marrow homing. These biological phenomena have previously been studied with techniques that do not have the same elegant properties and therapeutic relevance as CRISPRa/i. With this new state-of-the-art method for precisely controlling gene expression, I will study and manipulate genetic pathways to overcome long-standing challenges in HSC therapies.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: CRISPR Gene Therapy Genetic Engineering

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Project ID:	Project Acronym:	Evaluation Panel:
101041729	**LEAPHY**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Astrid Avellan**
Host Institution:	Centre National De La Recherche Scientifique Cnrs - FRA

Unravelling the behaviour of inorganic (nano)phases in leaves to optimize the foliar delivery of sustainable agrochemicals

Population growth and the expected-to-increase (a)biotic stresses due to climate change are putting the agro-ecosystems under pressure. The dependence on inorganic agrochemicals (IAs) for fertilization and plant protection will lead to an increase in their use. Yet, current IAs do not efficiently reach their target. They lead to waste of resources, pollutions, and environmental degradations. Foliar application of nanostructures is one of the proposed solutions to optimize IAs in order to better protect crops, but also their agro-ecosystem. Nano-IAs can exhibit reduced leaf leaching and increased bioavailability, allowing to strictly applying the right dose of IA at the right time. However, the lack of knowledge on IA behaviour at the leaf interface hinders our ability to predict optimized nanostructures. The LEAPHY project aims to establish a rationale for the design of such nano-IAs. Model nano-IAs with controlled morphologies and surface properties will be designed and exposed to isolated plant cells or model leaves characterized for their surface characteristics and interfacial functional groups. The pathways and associated rates of uptake, transformations, and in planta behaviour will be quantified. These results will be used to establish a predictive modelling framework for the biological and chemical interactions that govern IA adhesion, uptake, and translocation from leaves to other plant tissues. This knowledge will be leveraged to design and test bio- and geo-inspired copper-based fertilizers and pesticides with improved delivery. The team's expertise in tuning (in)organic reactivity at plant interfaces and studying the resulting interactions and speciation changes is the backbone of LEAPHY's state-of-the-art experimental strategy. This project will be a cornerstone in implementing solutions to contribute moving forward a better, safer rationale for foliar phytoprotection and fertilization strategies.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101044878	**DETOXPEST**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Simon Stael**
Host Institution:	Sveriges Lantbruksuniversitet - SWE

Towards increased biosafety for non-target insects - Damage-activated proteolysis to selectively enhance toxicity of pesticides

Insects numbers and diversity have rapidly declined in the EU and worldwide. Pesticides, and particularly the toxicity of insecticides to non-target insects (e.g. bees), are one of the major drivers of insect declines. Apart from destabilizing natural ecosystems, pollinator disappearance directly threatens food security. To help combat insect decline, I propose an innovative approach for the damage-activation of pro-pesticides (DAPP) by plant proteases that are activated in the gut of feeding caterpillars. Non-target beneficial insects that cause no damage, including pollinators and natural enemies of pests, are spared. My team pioneers the study of proteolysis in the plant wound response, following our recent discovery that physical damage activates a class of proteases, called metacaspases. I hypothesize that i) damage-activated plant proteolysis is a largely unrecognized but potential key player in the plant wound response to insect herbivores and ii) this knowledge can be used to enhance pesticide biosafety. We will study the impact of fall armyworm (Spodoptera frugiperda), an invasive insect pest and potential major threat to EU agriculture, on the model plant Arabidopsis thaliana and the economically important crop maize. A combination of advanced (N-terminomics) and novel (Proteome Integral Solubility Alteration) proteomics technologies will allow us to uncover unknown plant metacaspase substrates and damage-activated proteases and to assess their impact on insect herbivory. These fundamental studies will feed information into a pipeline of first-in-class DAPP development, where we will modify biological insecticides with newly-discovered protease cleavage sites. Finally, we will test toxicity against target (Spodoptera) and non-target insects. My early-stage and fundamental research on damage-activated proteolysis can have a tremendous positive impact on the increase of insecticide selectivity to help combat the escalating problem of insect decline.

Link to the ERC project webpage: https://staellab.com/

Keywords of the ERC project: proteolysis, plant-insect interaction, pesticide selectivity improvement

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101053857	**STEADY**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Wilfried Weber**
Host Institution:	Leibniz-Institut Fuer Neue Materialien Gemeinnuetzige Gmbh - DEU

Engineering homeostasis into living materials

Engineered Living Materials (ELMs) are dynamically emerging at the intersection of synthetic biology and materials sciences and are providing solutions in a rapidly growing number of application fields. Current areas of application comprise, for example, biomedicine, textiles, sensors, soft robotics, electronics, or construction materials. From a conceptual point of view, ELMs provide the opportunity of endowing materials with properties and functions long sought for in materials sciences, such as adaptivity and interactivity, evolvability, hierarchical design, self-reproduction, energy harvesting from the environment, synthesis from renewable resources, as well as biodegradability. Despite intensive research, however, a key defining property of life is largely missing in ELMs, that is homeostasis. Homeostasis is the ability of a system to maintain an inner steady state despite external fluctuations that impact this state. For example, mammals maintain a constant body temperature despite varying external temperatures. In STEADY, we will develop and test the concept of engineering homeostasis into living materials. To this aim, we will develop three genetically encoded modules, (i) a sensor to sense the actual state of a specific mechanical property of the material, (ii) a controller to process the sensor signal, and (iii) an actuator, that, based on the controller's output, steers the material towards the setpoint. The design of the homeostatic system will be highly modular, so that the sensor and actuator can be adapted in order to maintain homeostasis for other properties or functions of the material. The tools developed here are not restricted to ELMs but may also be used to confer homeostasis to polymer-based soft materials with regard to maintaining a desired feature. Thus, STEADY will open novel opportunities for engineering materials to be robust and resilient to changing environmental conditions.

Link to the ERC project webpage: https://www.leibniz-inm.de/en/research/research-groups/materials-synthetic-biology/

Keywords of the ERC project: Engineered living materials, synthetic biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: Synthetic Biology, Optogenetics, Biohybrid Materials, Programmable Materials, Biosensors

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Project ID:	Project Acronym:	Evaluation Panel:
101053972	**UNROPO**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Lieven De Veylder**
Host Institution:	Vib Vzw - BEL

Unlocking de novo Rooting Potential

Plants display an unparalleled regenerative capacity that is widely exploited in modern agriculture, where elite genotypes are asexually multiplied through stem cuttings. A critical point for this successful propagation entails the development of new roots. Unfortunately, the regenerative potential of plants is not universal as many economically and ecologically important species display poor de novo rooting. In my lab we demonstrated that the regenerative potential of plants is the result of a synergistic reaction of two independent wound responses: (1) the accumulation of the phytohormone auxin and (2) the transcriptional activation of stem cell-inducing transcription factors. Follow-up work showed that the latter are specifically activated by pectin-dependent cell wall changes, driving de novo root formation. In UNROPO, we will elucidate this process to UNlock the ROoting POtential of poorly regenerating trees to broaden the spectrum of plant species that can be propagated through cuttings. Through a systematic knockout of pectin modifying and degrading enzymes, combined with metabolic profiling, we aim to identify wound-induced, pectin-derived oligogalacturonides (OGs) that trigger a regeneration response. Downstream OG signal-transducing proteins will be identified through forward genetics experiments and an innovative in-house developed epitope-based single-cell sequencing method. Independently, we will link the regenerative potential of a collection of 250 poplar trees with their pectin metabolome and use genome-wide association studies to pinpoint the underlying pectin modifying, degrading and signaling genes. Ultimately, the obtained results will be used to modify in poorly regenerating tree species the genes involved in the production of regeneration-competent pectin variants, their derived wound-induced OG, and signaling molecules, to unlock the de novo rooting potential, in such manner contributing to the biodiversity of commercial plantations.

Link to the ERC project webpage:

Keywords of the ERC project: Poplar; regeneration; stem cells

Keywords that characterize the scientific profile of the potential visiting researcher/s: Poplar, GWAS, Genome analysis

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Project ID:	Project Acronym:	Evaluation Panel:
101076355	**AsexualEmbryo**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Charles Underwood**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

Asexual reproduction through clonal seeds: mechanisms to application

Some plant species have abandoned sex and produce clonal seeds by apomixis; here, we will explore how this occurs, and exploit these insights to develop novel breeding technologies. In contrast to most eukaryotic species in which reproduction is sexual, a minority of plants and animals have evolved alternative – asexual – reproductive strategies. In plants, apomixis allows clonal transmission of favorable, hybrid genotypes through seeds over unlimited generations. Hybrid crop varieties are stress-resistant and high-yielding due to hybrid vigor, yet they reproduce sexually. The introduction of apomixis in hybrid crops would allow stable inheritance of hybrid vigor through seeds, in perpetuity, and eradicate the need to continuously re-make hybrids by crossing. However, our knowledge of the genetic and molecular basis of apomixis remains incomplete, and blueprints for synthetic apomixis in crops must be established. This project will decipher the function and evolution of a novel PARTHENOGENESIS gene that I recently demonstrated causes asexual embryo formation in naturally apomictic dandelions. Harnessing and extending fundamental findings, synthetic apomixis systems will be developed in two important vegetable crops – hybrid lettuce and tomato – allowing the full complement of hybrid traits to be faithfully inherited through seeds. Ultimately, apomixis in crops could revolutionize the €22 billion hybrid seed industry, make hybrid seeds readily available for all, and facilitate sustainable, high-performance agriculture around the world. Specifically, this project will involve: 1) Deciphering how a PARTHENOGENESIS gene homologue functions during sexual reproduction 2) Optimizing the expression of PARTHENOGENESIS factors through evolutionary insights and mutagenesis 3) Engineering synthetic apomixis – a holy grail of plant breeding – in two important dicot crop species by skipping meiosis and triggering PARTHENOGENESIS

Link to the ERC project webpage: https://www.mpipz.mpg.de/underwood

Keywords of the ERC project: Plant reproduction, Plant genomics, Apomixis, Seed development, Bioinformatics, Developmental Biology

Keywords that characterize the scientific profile of the potential visiting researcher/s:

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Project ID:	Project Acronym:	Evaluation Panel:
101086483	**PRODIGEST**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Marta Martinez Sanz**
Host Institution:	Agencia Estatal Consejo Superior De Investigaciones Cientificas - ESP

Nanostructure formation during food protein digestion and influence on intestinal transport

The global food system is currently facing great challenges, which are mainly motivated by environmental and health-related concerns: (i) The existing food resources are not efficiently utilized; while some of them are overexploited, causing water/soil shortage, biodiversity losses, etc., others are not properly valorized (e.g. seaweeds). (ii) Moreover, the unhealthy dietary habits of modern societies are leading to a dramatic increase in the incidence of diet-related chronic diseases (e.g. obesity, diabetes, etc.). In this context, the food industry is actively looking for 'novel' food sources with added health benefits. However, to design strategies for a sustainable production of nutritious food products from alternative sources and to predict their potential metabolic responses (e.g. satiety, allergenicity, etc.), it is essential to understand how food structure, digestibility and bioavailability are correlated. PRODIGEST seeks to investigate this topic from a novel perspective, focusing on the mechanistic and structural aspects of the gastrointestinal digestion of food proteins and studying their implications on bioavailability. The type of structures formed by the assembly of the digestion products through intermolecular associations or by interactions with physiological medium components, as well as the effect of dietary fibres (which are abundant in alternative protein sources) will be studied and linked to their intestinal transport and susceptibility to trigger metabolic responses. To address this challenge, a set of advanced structural characterization tools (including X-ray and neutron scattering techniques, peptidomic analyses and rheology), as well as intestinal transport studies, will be combined through a multi-disciplinary approach, interconnecting structural characterization, food science and biotechnology. The project outcomes will find potential applications to diverse research areas, such as nutrition, food technology, pharmacology and medicine.

Link to the ERC project webpage:

Keywords of the ERC project: alternative proteins, gastrointestinal digestion, nanostructure, intestinal transport

Keywords that characterize the scientific profile of the potential visiting researcher/s: nanostructural characterization, digestion, scattering, proteins

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101095736	**NectarGland**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator: **Dr Abdelhafid Bendahmane**

Host Institution: Institut National De Recherche Pour L'Agriculture, L'Alimentation Et L'Environnement - FRA

Improving flower attractiveness for pollinators: Study of developmental, morphological and chemical cues in relation to bee foraging

Animal pollinators are vital for life on earth. While human population keeps growing, pollinator populations are dropping, thus threatening food security. In agriculture, the main insect pollinators are bees, by far. The lack of knowledge on how domesticated plants attract and reward bees has hampered the selection of varieties with improved and mutually beneficial crop-pollinator relationships. We propose to investigate flower features, including developmental, morphological and chemical cues, in relation with bee foraging. Elucidating the molecular basis of these processes would not only help sustain yields, but it is key to understand the co-evolution of plants and pollinators. We chose melon as a model system, because it is a strictly entomophilous crop, and because it provides all flower sexual morphs useful to probe plant-insect interactions. ForBees is a multidisciplinary project that integrates molecular genetic analysis and precise phenotyping. First, we will study melon genetic biodiversity with the aim to identify alleles that control nectar-related traits and bee attraction. The comparative analysis of wild accessions, landraces and breeding lines will further test whether domestication led to the loss of useful traits affecting insect visits. Second, we will analyse the gene networks that drive nectar gland development and nectar production. Finally, potential key regulators will be validated genetically. Through this work, we aim to develop a toolbox to tailor the morphology and chemistry of the flowers towards improved bee foraging activities. In addition to research in melon, results from this project, and from previous works, will be translated into neglected crops of the Cucurbitaceae family. These are major food crops in many developing countries, ensuring food security and generating income for poor farmers. Yet, these crops suffer from low fruit set because of partial pollination and would greatly benefit from enhanced breeding tools.

Link to the ERC project webpage:

Keywords of the ERC project: Bees; Cucurbitaceae; Nectar Gland; GWAS; Population genetics; Metabomomics; OMICS; Machine learning

Keywords that characterize the scientific profile of the potential visiting researcher/s: Bees; Cucurbitaceae; Nectar Gland; GWAS; Population genetics; Metabomomics; OMICS; Machine learning

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Project ID:	Project Acronym:	Evaluation Panel:
101096163	**glossi**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr An Martel**
Host Institution:	Universiteit Gent - BEL

Targeting skin glycosylation patterns to protect threatened salamanders from disease driven extinction

Disease driven amphibian declines are frequently compared to the extinction of dinosaurs and have become an icon of the global biodiversity crisis. The deadly skin disease chytridiomycosis is causing the greatest recorded loss of biodiversity attributable to a disease. The recently introduced chytrid fungus Batrachochytrium salamandrivorans (Bsal) is expanding its range in Europe, remains unmitigated and thus poses an imminent threat to western Palearctic urodele (= salamanders and newts) diversity. While hypersusceptible species invariably die after exposure, other species show a much more variable, individual and dose dependent response, ranging from self-limiting infections with self-cure to lethal disease. My group recently discovered that host susceptibility correlates with the skin glycosylation pattern of salamanders, with cutaneous galactose content predicting variation in intensity of Bsal colonization. The variability of the skin glycosylation pattern offers a unique opportunity for marker directed selection of disease resistant salamanders. The overarching hypothesis of GLOSSI (Glycosylation in Salamander Skin Infection) is that variability of hereditary glycosylation patterns in the salamander skin underpins differential Bsal colonization and allows the selection of colonization resistant host lineages. To study the contribution of skin glycosylation patterns towards the development of salamander resistance against the Bsal epidemic, GLOSSI will combine laboratory and field trials to study 1) the temporal dynamics and heritability of glycosylation patterns and associated susceptibility to Bsal infection in urodeles, 2) the potential of natural selection towards increased resistance in infected, natural urodele populations and its impact on population dynamics, 3) the host genetics that underpin the epidermal glycosylation pattern and implications for disease resistance. GLOSSI will lead to novel strategies for curbing disease driven loss of biodiversity.

Link to the ERC project webpage:

Keywords of the ERC project: glycoproteins - skin transcriptome - glycosylation pathway - Crispr - salamander

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics - biotechnology - proteoglycomics

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101096548	**INTETOOLS**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Guillermo Montoya**
Host Institution:	Kobenhavns Universitet - DNK

Repurposing of CAST Systems as Next-Generation Tools for Genome Engineering of Mammalian Cells

Genome editing using RNA-guided CRISPR-Cas nucleases (Clustered Regularly Interspaced Short Palindromic Repeats that associate with CRISPR associated proteins) has radically altered life sciences, enabling genome manipulation in living organisms. However, their use is limited by dependence on DNA Damage Response (DDR), which restricts genome editing to dividing cells. Further, these nucleases cannot handle DNA cargos large enough to harbour regulatory DNA circuitry, thus precluding genome engineering. In INTETOOLS, I will overcome these limitations by dissecting and repurposing CRISPR Associated Transposon (CAST) systems into genome engineering tools. CASTs are naturally occurring prokaryotic protein–RNA machineries consisting of an inactive CRISPR effector complex, which associate with Tn7 family transposons to insert large DNA cargos. Knowledge of their molecular mechanisms is scarce, which prevents their practical application in genome engineering. Accordingly, in Objective 1, I will investigate the architecture of different CASTs to obtain fundamental knowledge of their RNA-guided integration. I will then use this knowledge in Objective 2, to dissect their mechanism underpinnings whereby CRISPR-Cas complexes associate with transposition complexes to insert with nucleotide accuracy DNA cargos. This will inform Objective 3, where I will design new CAST tools that will allow RNA-guided transposition in eukaryotic genomes. These revamped CASTs will be capable of inserting large DNAs with high precision, harbouring regulatory regions into eukaryotic genomes, enabling genome engineering in eukaryotes. I will test the redesigned CASTs in mammalian cell lines and at the organismal level by rescuing the eyeless mutant phenotype in Drosophila melanogaster. INTETOOLS will catalyse a conceptual leap propelling the field into a new era of genome engineering, with major biomedical and biotechnological applications especially in synthetic biology.

Link to the ERC project webpage:

Keywords of the ERC project: genome editing CRISPR-Cas, transposons structural biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: cell biology, genome editing, cryo-EM, bioinformatics. structural biology, DNA repair

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101097367	**qScope**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Björn Högberg**
Host Institution:	Karolinska Institutet - SWE

The sequencing microscope - a path to look at the molecules of biology

The goal of biological research is to understand how life works. Although progress is fast, there seems to be an infinity of things we do not understand. When it comes to understanding tissue from the bottom up, our knowledge leaves much to desire. Feynman claimed that "It is very easy to answer many of these fundamental biological questions; you just look at the thing!" well the problem is that looking at the thing is the problem. Microscopy might never give us the possibility to directly see DNA- or RNA-sequence. For this, the community has evolved extraordinarily powerful sequencers. Today one man can routinely read millions of sequences on a weekly basis. And likely soon, we will read billions of sequences daily in small labs. But this, in itself, will not allow us to just look at the thing. We argue in this proposal, that by using the sequencer itself as a microscope, we will get that much closer to actually see what is going on in biological systems. Researchers have started in this direction by coupling microscopy- and sequencing-data from the same sample, but that is a temporary solution. Here, we propose a technology for inferring images using sequencing data alone, bypassing the need for advanced microscopy and leveraging the potential of the exponential growth of sequencing technology. We use random DNA barcodes as initial seeds and perform a reaction in-situ that allow these seeds to copy themselves locally. This is analogous to phylogenetic reconstruction, but instead of inferring ancestry, we infer relations of amplicons to spatial locations in tissue. By using a unique two-layer approach, one to provide a network for geometrical reconstruction and one for coupling measurements of RNA transcripts to this network, we allow for a non-targeted spatial transcriptomics technique that is as simple as running a PCR. When successful, this approach will then enable us, and others, to learn the inner secrets of biological system at a significantly faster rate.

Link to the ERC project webpage: hogberglab.net

Keywords of the ERC project: DNA Nanotechnology, DNA Molecular Tools, Transcriptomics

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101114948	**NAD-ART**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Katharina Höfer**
Host Institution:	Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften Ev - DEU

Conjugation of NAD-capped RNAs to proteins by ADP-ribosyltransferases to generate RNA therapeutics

Background: We discovered that NAD-capped RNAs can be covalently attached to specific target proteins by the phage T4 ADP-ribosyltransferase (ART) ModB, which we term RNAylation. Scientific problem: RNA therapy has almost limitless yet unexplored potential. Its translation into the clinics, however, requires optimal RNA delivery with high RNA stability, efficient cellular internalisation and precise target affinity. Hypothesis: Protein-RNA interactions are ubiquitous and central in biological control. I hypothesise that conjugating a NAD-capped nucleic acid to a protein catalysed by an ART generates a novel biomolecule – the RNAylated protein – with unique functionalities. The covalently linked protein or nucleic acid can trigger a directed intracellular delivery, where both, the protein and the nucleic acid, can become functionally active. This allows targeted modulation of translation or transcription, or editing. RNAylated proteins may provide a platform to engineer the cell and represent a starting point for the creation of next generation RNA therapeutics. Objectives: This project aims to establish RNAylated proteins as a fundamentally novel tool to regulate cellular processes. In objective 1, we will define the design principles for RNAylated proteins, allowing to control cellular processes. In objective 2, we will develop delivery strategies to transfer RNAylated proteins in specific cell types and allow for precise cellular localisation. In objective 3, we will combine the design and delivery principles for RNAylated proteins and apply them to target the tumour suppressor protein p53 by regulating translation, transcription or by editing. Impact: This project will develop RNAylated proteins as next generation RNA therapeutics and deepen our understanding of how a fundamental scientific discovery –the RNAylation of proteins, catalysed by the T4 ART ModB – can be translated into an application.

Link to the ERC project webpage: https://www.mpi-marburg.mpg.de/mprg/katharina-hoefer

Keywords of the ERC project: RNA, RNA Modifications, RNA therapeutics, Post-translational Protein Modifications, RNAylation

Keywords that characterize the scientific profile of the potential visiting researcher/s: RNA biochemistry, Bacterial Epitranscriptomics; Bacteriophage-Host interactions, NAD-capped RNA, ADP-ribosylation and RNAylation, Biorthogonal chemistry, Synthetic biology, RNA therapeutics

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Project ID:	Project Acronym:	Evaluation Panel:
101115323	**REINCARNATION**	**LS9** Biotechnology and Biosystems Engineering

Principal Investigator:	**Dr Lea Rems**
Host Institution:	Univerza V Ljubljani - SVN

Reversible and irreversible cardiac electroporation: Establishing the fundamentals to advance cardiac treatments

Cardiovascular diseases are the No. 1 healthcare challenge in the world, among which ischemic heart disease and atrial fibrillation are the most prevalent. Better treatment strategies are greatly needed to reduce the medical, economic, and social burden of these conditions. Electroporation (application of intense pulsed electric field) is showing tremendous potential for treatment of atrial fibrillation, enabling a safer and shorter treatment procedure compared with existing thermal ablation approaches. Moreover, recent pioneering studies provide evidence that electroporation can also be used as a nonviral vector for intracellular delivery of therapeutic nucleic acids that promote cardiac regeneration, potentially offering a way to cure the so-far incurable ischemic heart disease. For treatment of atrial fibrillation, electroporation must be irreversible, resulting in the death of cardiac muscle cells, to locally destroy (ablate) the arrhythmogenic cardiac tissue. Conversely, for treatment of ischemic heart disease electroporation must be reversible, meaning that the pulsed electric field transiently enhances cellular uptake of nucleic acids while the cells are able to survive and express the delivered transgene(s). Due to a lack of fundamental understanding of cardiac electroporation, there are currently no reliable methods able to ensure electroporation (ir)reversibility and the desired treatment outcome. This project is designed to decipher the biophysical mechanisms of cardiac electroporation at the molecular, cellular and tissue level as to develop methodologies that will enable optimal implementation of both irreversible and reversible electroporation. By combining bottom-up experiments in primary cardiac cells and tissue slices with computational modeling and advanced data analysis I will create the foundations needed to streamline further (pre)clinical research and realize the potential of electroporation to advance cardiac treatments.

Link to the ERC project webpage:

Keywords of the ERC project: electroporation, electric pulses, pulsed field ablation, cardiac arrhythmias, cardiac regeneration, nonviral nucleic acid delivery, computational modeling, fluorescence microscopy, primary cardiomyocytes, cardiac slices

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
810377	**ConnectToBrain**	**SYG** Synergy

Principal Investigator:	**Dr Ulf Ziemann**
Host Institution:	Eberhard Karls Universitaet Tuebingen - DEU

Connecting to the Networks of the Human Brain

ConnectToBrain will introduce whole-brain multi-locus transcranial magnetic stimulation (mTMS), in which the brain-stimulating electric-field location, direction, magnitude and timing are controlled electronically based on real-time high-density electroencephalography (hdEEG) information of activity and connectivity in brain networks. The final mTMS apparatus will consist of 50 coils. Superpositions of electric fields produced by the different overlapping coils allow spatiotemporally millimeter- and millisecond-precise stimulus sequences to arbitrary cortical sites without physical movements of the coil set. Spatial targeting of mTMS will be further improved by measuring individual brain conductivity distributions with ultra-low-field MRI. The proposed hdEEG methodology uses a brain–computer interface (BCI) and a computer–brain interface (CBI) in a closed, algorithmically-controlled loop. BCI receives real-time information about brain activity and connectivity from hdEEG, while CBI adapts mTMS to drive brain activity and connectivity into desired directions. ConnectToBrain will allow unprecedented tracking of dynamic changes and reorganization of brain networks in real-time, and network-targeted closed-loop stimulation. This radically novel technology will cause a paradigm shift from current open-loop practice that is only moderately effective in therapy. We will apply ConnectToBrain to reach new levels of efficacy of therapeutic applications. Patients after stroke and with Alzheimer's disease will be tested and treated as models of network disorders. Our high-risk, high-gain endeavor will reach the ambitious goals only through the Synergy of the 3 PIs, world leaders in their complementary areas of expertise (instrumentation, algorithms, translation). If the project succeeds, we expect the value of societal, health and industrial benefits in Europe to exceed €1 billion annually, not to mention the immense value of alleviating human suffering from brain disorders.

Link to the ERC project webpage: https://www.connecttobrain.eu/#news

Keywords of the ERC project: Individualized non-invasive therapeutic brain stimulation; transcranial magnetic stimulation; EEG; closed-loop-stimulation; brain state; stroke; Alzheimer's disease

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
854126	**PhotoRedesign**	**SYG** Synergy

Principal Investigator:	**Dr Dario Leister**
Host Institution:	LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN - DEU

Redesigning the Photosynthetic Light Reactions

Oxygenic photosynthesis uses the energy of sunlight to generate the oxygen we breathe and the food we eat, but the vast majority of the received solar energy is not converted to biomass. Enhancing photosynthesis to improve the production of food, energy and high value compounds is a compellingly important challenge that has not been taken up yet, because it requires the modification and exchange of large ensembles of interacting photosynthesis components from different organisms. For the first time, we will undertake the comprehensive redesign of photosynthesis to enhance its capacity to harvest and safely convert solar energy. To achieve this, we combine in our team unique and complementary expertise in genetics, biochemistry and biophysics in the full range of bacterial and plant photosynthetic organisms. We will combine genetic engineering with new approaches from synthetic biology and adaptive evolution to create a novel enhanced variant of photosynthesis in the model cyanobacterium Synechocystis as chassis. The ground-breaking overall objective is to combine photosystems from different photoautotrophic organisms, including de novo-designed antennas in reimagined photosystems. By employing a multidisciplinary approach for combining different natural and de novo-designed photosynthesis modules in one adaptable bacterial chassis with the goal to create a novel enhanced type of photosynthesis, PhotoRedesign goes far beyond conventional applied and fundamental photosynthesis research. PhotoRedesign will establish new model systems and toolkits for the next generation of photosynthesis researchers, and it develops a novel concept for modifying complex processes, hitherto considered to be immutable. In consequence, PhotoRedesign will advance photosynthesis research and create the basis for improving the productivity of economically-relevant photosynthetic organisms.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
855923	**ASTRA**	**SYG** Synergy

Principal Investigator:	**Dr Giancarlo Ruocco**
Host Institution:	FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA - ITA

ASsembly and phase Transitions of Ribonucleoprotein Aggregates in neurons: from physiology to pathology.

Recent works indicate the pathogenic relevance of altered RNA metabolism and aberrant ribonucleoprotein (RNP) assembly in several neurodegenerative diseases, such as Amyotrophic lateral sclerosis. How defective RNPs form, what are their integral components and which events trigger their appearance late in life are still unsolved issues. While emerging evidence indicates that mutations and post-translational modifications of specific RNA-binding proteins (RBPs) induce liquid-solid phase transition in vitro, much less is known about the in vivo properties of RNP assemblies and which role RNA plays in their formation. ASTRA will combine sophisticated imaging-derived RNP complex purification with innovative computational approaches and powerful genetic tools to unravel the biophysical properties and composition of RBP complexes and how they are modified in disease conditions. Through the development of new imaging and optical methods we plan to study how RNPs separate in liquid and solid phases in cells, in tissues (retina) and animal models and to characterize their RNA and protein components in physiological and pathological states. Exploiting the novel finding that non-coding RNAs act as scaffolding molecules for RNP assembly, we will investigate how such RNAs control the dynamic link between RNP formation, intracellular sorting and function. In a genuine interdisciplinary team effort, we will reveal how the architecture and localization of cytoplasmic RNP complexes are controlled in motor neurons and affected in neurodegeneration. We plan to develop novel advanced microscopy methods to monitor formation of aberrant RNPs in vivo and we will explore new molecules to impede pathological cascades driven by RNP assemblies. In conclusion, ASTRA will allow us to gain a comprehensive understanding of RNP function and dysfunction; we will use this knowledge to develop new therapeutic strategies that will impact on several protein-misfolding neurodegenerative diseases.

Link to the ERC project webpage:

Keywords of the ERC project: imaging, Brillouin microscopy, mechanobiology

Keywords that characterize the scientific profile of the potential visiting researcher/s: imaging, Brillouin microscopy, mechanobiology

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
856404	**SPHERES**	**SYG** Synergy

Principal Investigator:	**Dr Dominique Langin**
Host Institution:	UNIVERSITE PAUL SABATIER TOULOUSE III - FRA

Lipid droplet hypertrophy : the link between adipocyte dysfunction and cardiometabolic diseases

The goal of SPHERES is to understand the dynamics and consequences of adipocyte hypertrophy (enlargement) through investigation of its large lipid droplet (LD). The adipocyte LD is a unique organelle specialized in storing energy in triglycerides (TGs). Its surface is composed of a phospholipid monolayer and specific LD-associated proteins (such as perilipins, CIDEs and lipases), which jointly regulate LD stability and TG turnover. Adipocyte hypertrophy due to an increase in LD size may, irrespective of body fat mass, cause a wide range of pathological conditions, notably cardiometabolic diseases. SPHERES PIs (Langin, Rydén, Antonny) postulate that disturbances in the interactions between LD proteins and LD lipid composition lead to adipocyte hypertrophy and its deleterious consequences. We have identified three fundamental unanswered questions: what determines the unique structure and dynamics of large LD; why does increased LD size alter the functional phenotype of the adipocyte; which factors cause inter-individual variations in LD size. To address these questions, SPHERES gathers expertise in clinical and cellular studies on human adipocytes, in/ex vivo investigations in mouse models, and biophysical analyses of LDs. At the core of this application is the development of beyond-state-of-the-art models and methods (spheroid cultures, native large LD preparation and reconstitution, proximity labelling of LD proteins, gene editing in cell and mouse models, and advanced LD imaging), only achievable through joint integrated effort of the PIs and co-workers. Spanning from molecular, cellular to the whole-body level, SPHERES will link new knowledge on the formation and maintenance of large adipocyte LDs to the deleterious impact of adipocyte hypertrophy. Altogether, SPHERES has a strong potential to discover novel pathogenic mechanisms, leading to a better understanding of highly prevalent diseases and identification of therapeutic strategies targeting adipocytes.

Link to the ERC project webpage: https://erc-spheres.univ-tlse3.fr/

Keywords of the ERC project: adipocyte, lipid droplet, lipase, lipolysis, adipose tissue, obesity, diabetes

Keywords that characterize the scientific profile of the potential visiting researcher/s: mouse metabolic phenotyping, protein-protein interactions, cell biology, cell imaging, adipose tissue biology, chronic metabolic diseases

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
856421	**LeibnizDream**	**SYG** Synergy

Principal Investigator:	**Dr Artemis Alexiadou**
Host Institution:	GEISTESWISSENSCHAFTLICHE ZENTREN BERLIN EV - DEU

Realizing Leibniz's Dream: Child Languages as a Mirror of the Mind

Children around the globe acquire language and with it the human ability to communicate complex thoughts. This project develops a new linguistic theory to explain language and its acquisition. Our central hypothesis is that language radically compresses thought structures to sound or sign. While current theories assume a parallel between thought and language or meaning-preserving transformations, we assume that thought is mapped to language by only realizing some pieces of conceptual representations. Adult language is hyper-efficient at compressing information. For this reason, Leibniz and many others over the last 300 years have been unable to agree on the primitives of human thought. We predict that child languages are a better mirror of the human mind. Our initial evidence suggests that children are not able to compress conceptual representations as efficiently as adults. Sometimes children produce more material than adults, leading to so-called commission errors, which have never been systematically investigated. Furthermore, comprehension is easier for children when there is a one-to-one match between language and thought. To test our central hypothesis and specify how conceptual structure is compressed into language, we carry out a series of at least twelve targeted language acquisition studies on a global scale. We have recruited collaborators for more than 50 languages from 21 different language families, two sign languages and two creoles to carry out our studies. With this data, we can formulate a complete formal model of the semantic primitives, their combination into conceptual structures, the morphological compression mechanism, and the acquisition process within our model. To accomplish these goals, we rely on insights from formal semantics, generative syntax, distributed morphology, and several other linguistic frameworks. As part of our work, we also create the first open, global research collaboration to conduct language acquisition studies.

Link to the ERC project webpage: https://leibnizdream.eu

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
856488	**SEACHANGE**	**SYG** Synergy

Principal Investigator:	**Dr James Scourse**
Host Institution:	THE UNIVERSITY OF EXETER - GBR

Quantifying the impact of major cultural transitions on marine ecosystem functioning and biodiversity

The seas are changing. Marine conservation seeks to protect valuable habitats but the pristine state of marine ecosystem functioning and biodiversity – that is, the system as it operated before there was any large scale human impact – is conjectural. Conservation management strategies are often based on highly altered ecosystems where the degree of human-induced change is unknown. In SEACHANGE, we propose a structured and systematic approach to the reconstruction of marine ecosystem baselines to quantify the impact of anthropogenic cultural transitions on marine biodiversity and ecosystem functioning. SEACHANGE will address two key questions: 1) What was the nature of long-term changes in prehistoric marine biodiversity and ecosystem functioning over a 3000-year period in NW Europe and the degree of human impact associated with major socioeconomic changes across the Mesolithic-Neolithic boundary? 2) What has been the scale and rate of marine biodiversity loss and changes to ecosystem functioning as a result of fishing intensity and marine habitat loss during the last 2000 years (including the Industrial Transition) in the North Sea and around Iceland, eastern Australia and the west Antarctic Peninsula? To address these questions we will analyse: 1) absolutely-dated annually-resolved bivalve shell series ("sclerochronologies"); 2) marine sediment cores; 3) archaeological midden (waste) materials including shells and bones. We will date these samples precisely and undertake zooarchaeological and palaeoecological, stable isotope geochemical and environmental DNA/DNA metabarcoding analyses. We will compare the data with historical and archival sources, and we will generate numerical ecosystem simulations. We will identify how depleted the current marine environment is compared with that before large scale human impact and what measures are needed, and how long will it take, for marine biodiversity to recover.

Link to the ERC project webpage: https://seachange-erc.eu/

Keywords of the ERC project: Sclerochronology; environmental DNA; marine history, ecosystem modelling; marine conservation; middens

Keywords that characterize the scientific profile of the potential visiting researcher/s: Archaeology; Environmental Sciences; Marine Sciences; Earth Sciences; Geography; Geology; Ecology; Molecular Biology

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
856506	**LIFEPLAN**	**SYG** Synergy

Principal Investigator:	**Dr David Dunson**
Host Institution:	DUKE UNIVERSITY - USA

A Planetary Inventory of Life – a New Synthesis Built on Big Data Combined with Novel Statistical Methods

Biodiversity underlies ecosystem functioning. To achieve the basis for a sustainable management of natural resources under current environmental change, we thus need a unified theory of the forces structuring vast sets of ecosystems and taxonomical groups on Earth. For the first time, such a synthesis is now within reach, based on a recent revolution in sampling methodology, globally relevant ecological data, and advances in statistical methods for linking immense data to community ecological theory. In LIFEPLAN, we bring together the key expertise needed to generate and interpret Big Ecological Data for a global synthesis of biotic patterning across our planet: world leaders in community ecology, methods for automated species recognition, and Bayesian statistics for immense data. Our objectives are to generate a new understanding of biodiversity patterns and dynamics by developing fundamentally new methods for big data statistics. To this end, we will generate fully standardized, global big data on a range of species groups, thus allowing quantification of variation in ecological communities at spatial scales covering six orders of magnitude (from 0.1 km to 10000 km), across tens of thousands of species. The resulting data motivate the development of transformative big data statistics, in particular highly scalable algorithms for spatio-temporal data, as well as methods for automated species identification from DNA, audio and image samples. As a key deliverable, we will develop global joint species distribution models describing the spatio-temporal structure of life on Earth. Working together will allow each of us to tackle what we regard as the ultimate challenges in our own fields, while simultaneously collaborating around solutions changing the face of modern biodiversity science. Now is the time for this project, as the big data and big methods emerging today coincide with a great need for global understanding of biodiversity structure and dynamics.

Link to the ERC project webpage:

Keywords of the ERC project: Statistical methods, machine learning, Bayesian, ecology, biodiversity, statistical modeling

Keywords that characterize the scientific profile of the potential visiting researcher/s: Statistics, Bayesian, latent variables, hierarchical models

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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951146	**LiquOrg**	**SYG** Synergy

Principal Investigator:	**Dr Ivan Lopez Montero**
Host Institution:	UNIVERSIDAD COMPLUTENSE DE MADRID - ESP

Do liquid crystal-like phases of proteins organize membrane compartments?

We are in the midst of a revolution in our understanding of the internal organization of cells. In the 1950s we learned that lipid bilayer-based membranes serve as containers (organelles) within the cytoplasm. Now we are learning that liquid-like "membrane-less" organelles i.e. without any container, self-assemble based on "liquid-liquid" phase separations. We propose the seemingly radical idea that membrane-bounded organelles– like their membrane-less counterparts- are stabilized or even templated by analogous phase separations of their surface proteins into largely planar liquids akin to liquid crystals. Our unique Synergy team is organized specifically to test this "liquid crystal hypothesis" on the cell's secretory compartments - ER exit sites (ERES) and the Golgi stack - by employing our complementary skills in physics, physical chemistry, biochemistry and cell biology. We hypothesize based on pilot experiments evidence that the ERES and Golgi self-organize as a multi-layered series of adherent liquid crystal-like phases of "golgin" and similar proteins which surround and enclose their membranes. Their differential adhesion and repulsion would specify the topology and dynamics of the membrane compartments. If this is true, it will literally rewrite the history of cell biology. We will test the 'liquid crystal' hypothesis directly, systematically, and quantitatively on an unprecedented scale to either modify/disprove it or place it on a firm rigorous footing. Experiments (Aim 1) with 13 pure golgins in cis and trans pairwise combinations will establish their foundational physical chemistry. Surgically engineered changes in golgins/ERES proteins will alter the rank order (hierarchy) of their affinities for each other and link phase separation physics to cell biology (Aim 2) and be used to establish the structural basis of phase separations and their specificity, and the potential for self-assembly of wholly synthetic biological organelles (Aim 3).

Link to the ERC project webpage:

Keywords of the ERC project: Golgins, AFM, lipid membranes, protein reconstitution, TR-fluorescence microscopy

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951224	**TOMATTO**	**SYG** Synergy

Principal Investigator:	**Dr Fernando Martin**
Host Institution:	FUNDACION IMDEA NANOCIENCIA - ESP

The ultimate Time scale in Organic Molecular opto-electronics, the ATTOsecond

Photoinduced electron transfer (ET) and charge transfer (CT) processes occurring in organic materials are the cornerstone of technologies aiming at the conversion of solar energy into electrical energy and at its efficient transport. Thus, investigations of ET/CT induced by visible (VIS) and ultraviolet (UV) light are fundamental for the development of more efficient organic opto-electronic materials. The usual strategy to improve efficiency is chemical modification, which is based on chemical intuition and try-and-error approaches, with no control on the ultrafast electron dynamics induced by light. Achieving the latter is not easy, as the natural time scale for electronic motion is the attosecond (10-18 seconds), which is much shorter than the duration of laser pulses produced in femtochemistry laboratories. With femtosecond pulses, one can image and control “slower” processes, such as isomerization, nuclear vibrations, hydrogen migration, etc., which certainly affect ET and CT at “longer” time scales. However, real-time imaging of electronic motion is possibly the only way to fully understand and control the early stages of ET and CT, and by extension the coupled electron-nuclear dynamics that come later and lead (or not) to an efficient electric current. In this project we propose to overcome the fs time-scale bottleneck and get direct information on the early stages of ET/CT generated by VIS and UV light absorption on organic opto-electronic systems by extending the tools of attosecond science beyond the state of the art and combining them with the most advanced methods of organic synthesis and computational modelling. The objective is to provide clear-cut movies of ET/CT with unprecedented time resolution and with the ultimate goal of engineering the molecular response to optimize the light driven processes leading to the desired opto-electronic behavior. To this end, synergic efforts between laser physicists, organic chemists and theoreticians is compulsory.

Link to the ERC project webpage: https://tomatto.eu/

Keywords of the ERC project: Theoretical attosecond science, computational modeling, theoretical attosecond chemistry

Keywords that characterize the scientific profile of the potential visiting researcher/s: Theoretician working in attosecond science, quantum chemistry of excited states, theoretical modeling of ionization

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951284	**ENSEMBLE**	**SYG** Synergy

Principal Investigator:	**Dr Erwan Bezard**
Host Institution:	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE - FRA

Structure and functions of the brain extracellular space

Brain research has made tremendous progress over the last few decades in nearly all areas of investigation with the exception of one: the extracellular space (ECS). It is however a key compartment defined as the web-like space between brain cells, filled with a myriad of molecules that enable brain functions and homeostasis. How molecules navigate in the ECS is a very important, yet unsolved, challenge that precludes conceptual advance in brain science and innovation in therapeutics (e.g. immunotherapy). The lack of knowledge is mainly due to the absence of dedicated investigation strategies for such a complex and finely structured biological entity. Our ground-breaking project (ENSEMBLE) will shed light on the conceptual and methodological roadblocks that have prevented us from understanding the fine architecture of the ECS and how molecules navigate within it throughout the brain. We posit that molecular diffusion in the ECS is locally regulated by the properties of the ECS, which is essential for brain functions. Four world-class scientists, L. Groc (molecular neuroscience, CNRS), E. Bezard (systems neuroscience, INSERM), L. Cognet (optics & nanoscience, CNRS), and U.V. Nägerl (neurophotonics, Univ. Bordeaux), team up to develop and apply unconventional investigation approaches, based on original nano-imaging strategies (super-resolution microscopy and carbon nanotube/nanoparticle tracking), to the in vivo brain. Yet, to consider and achieve such an experimental and multidisciplinary tour de force a side-by-side and daily interactive effort is necessary. Thanks to our complementary expertise and geographical proximity, ENSEMBLE will provide a unique opportunity to unveil in vivo the structure and functions of this crucial brain compartment and will offer a new theoretical and experimental framework to manipulate molecule navigation. The ENSEMBLE project will also cross-fertilize the fields of nanoscience, optical imaging, organ pathophysiology and immunotherapy.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951292	**Sympore**	**SYG** Synergy

Principal Investigator:	**Dr Wolf Frommer**
Host Institution:	HEINRICH-HEINE-UNIVERSITAET DUESSELDORF - DEU

Plasmodesmata, Symplasmic pores for plant cell-to-cell communication

During evolution of multicellularity, cells differentiated to become specialized and interdependent. Multicellular organisms invented channels for nutrient exchange and communication between cells. Plants uniquely developed plasmodesmata, complex cell-cell connections traversing the cell wall. Roles ascribed to plasmodesmata include selective transport of signals, ions, metabolites, RNAs and proteins. Due to technical hurdles, composition, structure and regulation of plasmodesmatal conductance remain enigmatic. Genetic approaches to study plasmodesmata were hampered by lethality or redundancy. Novel technologies now set the stage for resolving roles of plasmodesmata in transport and signaling in an interdisciplinary approach. We will use proximity labeling proteomics to obtain plasmodesmatal composition, and PAINT and cryo electron tomography (cryoET) for near atomic structures. Models of plasmodesmata will be built from bottom up and top down approaches and combined with quantitative assessment of plasmodesmatal activity. Novel biosensor approaches together with knock down by genome editing will permit quantitation of transport of the diverse cargo. Single cell sequencing helps fine-tuning mutant selection and targeting of subtypes. Four labs will join forces: highly recognized experts in biophysics and cryoET (WB), advanced imaging and developmental signaling (RS), high-end proteomics and lipidomics (WS), and interactomics, transporters and cutting-edge biosensor technology (WF). We will iteratively address: (1) systematic quantitative identification of components, (2) their localization and dynamics, (3) structures and molecular building blocks of diverse plasmodesmatal types, and (4) transport and signaling mechanisms. We expect breakthrough discoveries and completely new understanding of plasmodesmatal function and evolution. Since plasmodesmata play key roles in nutrient allocation and virus spread, we lay the basis for novel biotech solutions in agriculture.

Link to the ERC project webpage: https://www.sympore.org

Keywords of the ERC project: intercellular transport, cell cell communication

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951324	**R2-Tension**	**SYG** Synergy

Principal Investigator:	**Dr Aurelien Roux**
Host Institution:	UNIVERSITE DE GENEVE - CHE

In-situ spatiotemporal imaging of membrane hydration, electrostatics, tension and curvature to understand cell response to osmotic shocks and cell migration.

Lipid membranes compartmentalize and protect cells from the environment, and selectively permit transport. This functionality derives from unique membrane properties: 5 nm thick, yet fluid, deformable, resistant to stress and chemically complex. The physicochemical properties of membranes are expected to have a major impact on cell life, but the tools to measure the relevant multiscale and dynamic parameters in-vitro and, more importantly, in-vivo membranes are lacking. An essential property of membranes, their hydration and charge state, both needed for membrane integrity and playing a vital role in cell survival is not understood beyond the level of continuum theory. To enable quantitative physics, and physical chemistry for biology Roux and Roke, R^2, will join their expertise on molecular biology & biophysics and physics & interfacial chemistry & optics to create tools to measure membrane water and ion fluxes, and image 3D fields of electrostatic free energy, membrane tension and curvature. We will understand how molecular factors, such as the influence of the aqueous phase and interfacial electrostatics, are coupled to tension and curvature under dynamic conditions such as osmosis in artificial and cellular membranes. Obtaining the first temporally resolved, 3D maps of hydration, free energy, tension and curvature at the nanoscale in migrating cells and cells experiencing osmotic shocks we will quantify membrane physical parameters in two processes essential for cell survival, for which currently no data is available: Osmotic shock response and cell migration. Osmotic shock response plays an important role in infections, kidney and intestine function. Cell migration is essential to many cell processes, for example the spreading of cancer, wound repair and the immunological response, as well as food search in unicellular organisms.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
951459	**HiSCORE**	**SYG** Synergy

Principal Investigator:	**Dr Jan Korvink**
Host Institution:	KARLSRUHER INSTITUT FUER TECHNOLOGIE - DEU

Highly Informative Drug Screening by Overcoming NMR Restrictions

The need for drug screening with increasingly higher throughput is dictated both by the increasing number of drug targets made available through genomics and the increasing number of chemical molecules generated through combinatorial chemistry. Merely Boolean high-throughput screening techniques today can scan large compound libraries, but the ever increasing throughput has not translated into a significant increase in late-phase drug candidates. HiSCORE presents a synergistic approach to high-throughput, high-information drug screening that builds on the complementary skills of four laboratories supported by two external experts of drug screening: (i) Research and build innovative magnetic resonance instrumentation (Kentgens, IMM/RU) that can provide small, hyperpolarized solid samples on a seconds timescale, transfer and dissolve or liquefy these samples with minimum dilution, and acquire multiple high-resolution NMR spectra of the liquefied samples in parallel (Meier, IBG/KIT), using complementary contrast-enhancement methods, in up to 1000 massively parallelized microfluidic detectors (Korvink, IMT/KIT). (ii) Use this instrumentation for binding assays and measure the dissociation constants in the nano to micromolar range, and determine kinetic rates of the association and dissociation for a large number of complexes of putative drug compounds and protein targets (Bodenhausen, ENS) (iii) Use this instrumentation for functional assays, in particular for systems that comprise multiple enzyme steps with intermediate products, and to determine the efficacy of potential inhibitors, while fully exploiting the rich information that can be obtained by fluorine-19 NMR. (iv) Use this instrumentation for metabonomic assays to observe the metabolism of the compounds in cultures of living cells in view of identifying potentially toxic side-products. The contrast between compounds that bind to targets and those that fail to bind will be boosted by exploiting long-lived states

Link to the ERC project webpage:

Keywords of the ERC project: NMR drug screening. Miniaturized NMR technology.

Keywords that characterize the scientific profile of the potential visiting researcher/s: Interest in NMR upscaling.

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Project ID:	Project Acronym:	Evaluation Panel:
101071386	**GlycanSwitch**	**SYG** Synergy

Principal Investigator:	**Dr Gordan Lauc**
Host Institution:	GENOS DOO ZA VJESTACENJE I ANALIZU - HRV

Glycans as Master Switches of B Cell Activity in Autoimmunity

Autoimmune diseases including rheumatoid arthritis (RA) are often life-threatening disorders with increasing disability having a negative impact on patients' quality of life. Mechanisms leading to the breach of tolerance in development of autoimmunity are still largely unknown. Protein glycosylation is an essential regulatory mechanism in the immune system. We recently demonstrated that N-glycosylation of the variable region (Fab) of autoantibodies is a hallmark of RA development and progression. We also demonstrated that autoantibodies acquire these Fab glycosylation signatures already many years before disease onset. We herein hypothesize that Fab glycosylation at the level of the B cell receptor is a key molecular switch promoting the selection, activation and proliferation of autoreactive B cells leading to the concomitant breach of immunotolerance. Within GlycanSwitch, we will map the Fab glycome of various types of RA autoantibodies and autoreactive B cells. We will study the factors and underlying cellular mechanisms that regulate Fab glycosylation of B cell receptors and autoantibodies. We will investigate the immunological effects of Fab glycosylation and the impact in B cells signalling and activation in the context of molecular and cellular interacting partners in the immune microenvironment. Finally, we will test in relevant mouse models how Fab glycosylation of autoantibodies and autoreactive B cells contributes to the breach of tolerance. We expect that the obtained insights into the role of glycans as key checkpoint for the selection of autoreactive B cells and the rise of autoimmunity will provide leads for targeted therapeutic interventions as well as rationales for the early detection of RA and autoimmune diseases in general. We foresee that the knowledge generated will allow us to embark on a targeted prevention clinical study in patients at risk for RA to turn off the GlycanSwitch leading to chronic RA.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101071386	**GlycanSwitch**	**SYG** Synergy

Principal Investigator:	**Dr Salomé Pinho**
Host Institution:	Universidade de Porto - PRT

Glycans as Master Switches of B Cell Activity in Autoimmunity

Autoimmune diseases including rheumatoid arthritis (RA) are often life-threatening disorders with increasing disability having a negative impact on patients' quality of life. Mechanisms leading to the breach of tolerance in development of autoimmunity are still largely unknown. Protein glycosylation is an essential regulatory mechanism in the immune system. We recently demonstrated that N-glycosylation of the variable region (Fab) of autoantibodies is a hallmark of RA development and progression. We also demonstrated that autoantibodies acquire these Fab glycosylation signatures already many years before disease onset. We herein hypothesize that Fab glycosylation at the level of the B cell receptor is a key molecular switch promoting the selection, activation and proliferation of autoreactive B cells leading to the concomitant breach of immunotolerance. Within GlycanSwitch, we will map the Fab glycome of various types of RA autoantibodies and autoreactive B cells. We will study the factors and underlying cellular mechanisms that regulate Fab glycosylation of B cell receptors and autoantibodies. We will investigate the immunological effects of Fab glycosylation and the impact in B cells signalling and activation in the context of molecular and cellular interacting partners in the immune microenvironment. Finally, we will test in relevant mouse models how Fab glycosylation of autoantibodies and autoreactive B cells contributes to the breach of tolerance. We expect that the obtained insights into the role of glycans as key checkpoint for the selection of autoreactive B cells and the rise of autoimmunity will provide leads for targeted therapeutic interventions as well as rationales for the early detection of RA and autoimmune diseases in general. We foresee that the knowledge generated will allow us to embark on a targeted prevention clinical study in patients at risk for RA to turn off the GlycanSwitch leading to chronic RA.

Link to the ERC project webpage: https://pinholab.i3s.up.pt/

Keywords of the ERC project: Immunology; Glycobiology; Autoimmunity; B cells; T cells; glycans

Keywords that characterize the scientific profile of the potential visiting researcher/s: Know how in: immunology; animal experimentation; bioinformatics/computational biology; molecular biology techniques

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Project ID:	Project Acronym:	Evaluation Panel:
101071583	**TubulinCode**	**SYG** Synergy

Principal Investigator:	**Dr Filippo Del Bene**
Host Institution:	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE - FRA

Uncovering the molecular effects of the tubulin code and their impact on organism-wide functions

Microtubules (MT) are core components of the eukaryotic cytoskeleton with essential roles in cell division, cell shape, intracellular transport, and motility. Despite their functional divergence, MTs have highly conserved structures made from almost identical molecular building blocks – tubulin proteins. A variety of posttranslational modifications (PTMs) diversifies these building blocks, which is thought to control most of the properties and functions of the MT cytoskeleton, a concept referred to as the 'tubulin code'. While they appear to have subtle effects at the molecular level, tubulin PTMs are essential for maintaining cellular functions of MTs over large spatial and temporal scales. Yet, a comprehensive knowledge of the principles of the tubulin code, connecting its functions across the molecular, cellular and organismal levels, is almost entirely lacking. Our project aims to obtain a novel molecular and mechanistic understanding of how tubulin PTMs control long-term cellular function and homeostasis. Our unique approach bridges all relevant scales of biology and relies on a synergy between our powerful experimental models and expertise in biochemistry, structural biology, single-molecule assays, systems-biophysics, cell biology, and physiology. Specifically, we will: (1) Determine how different tubulin PTMs affect biophysical and structural properties of MTs and their interactions with associated proteins; (2) Define the impact of tubulin PTMs on overall MT cytoskeleton behaviour and the resulting physiological implications in neurons; (3) Combine zebrafish and mouse models and develop a novel fish model for lifelong in-vivo imaging to determine how the tubulin PTMs control lifelong MT-based functions. Our work will define the importance of tubulin PTMs by revealing their critical molecular functions over the lifetime of an organism. The project has the potential to substantially change our perception of the cytoskeleton's role in homeostasis and disease.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
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Project ID:	Project Acronym:	Evaluation Panel:
101071793	**PushingCell**	**SYG** Synergy

Principal Investigator:	**Dr Anna Akhmanova**
Host Institution:	UNIVERSITEIT UTRECHT - NLD

Pushing from within: Control of cell shape, integrity and motility by cytoskeletal pushing forces

The ability of cells to sense environmental cues and respond to them by adjusting their shape and motion is fundamental for biological processes ranging from animal development to disease. Much is known about how cells sense and respond to the geometry and mechanics of their environment by adhering to and pulling on the substrate. However, recent studies demonstrated that cells also strongly depend on non-adhesive interactions with the environment and that they probe, sense and deform their surroundings by pushing into them. The goal of this project is to address the mechanisms controlling cell shape and cell-substrate interactions via pushing forces. We will focus on three levels of cell organization: 1. Nanoscale pushing: We will investigate how cells locally sense and respond to obstacles without adhering to them and quantify the associated forces. Using micro-engineered substrates and tissue mimics, we will molecularly and biophysically dissect, biochemically reconstitute and theoretically model the interface between an obstacle, the plasma membrane and the actin cortex. 2. Mesoscale cell mechanics: We will investigate how actin, microtubules and intermediate filaments collaborate to generate and extend mesoscopic cell protrusions that push by adhesion-independent mechanisms. We will combine cell biological experiments and optogenetics with modeling and bottom-up reconstitutions. 3. Global force balance: We will examine adhesion-independent mechanisms that allow a cell to coordinate competing protrusions, maintain its integrity and translocate in complex environments. Using biophysical measurements and local molecular perturbations, we will test models of long-range communication within cells. Our work will provide new fundamental insights into biological and physical principles underlying the control of cell shape, integrity and motility, which are key to most physiological processes from development and homeostasis to cancer, immune responses and regeneration.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101071836	**KARST**	**SYG** Synergy

Principal Investigator:	**Dr Bojan Mohar**
Host Institution:	Univerze v Ljubljani - SVN

KARST: Predicting flow and transport in complex Karst systems

Karst aquifers are a treasure and a threat: while up to 25% of the world population depends on them for drinking water, they also have capabilities for extremely fast conduction of water and contaminants. In the light of climate change, we need to prepare for extreme flooding and understand the consequences for karst aquifers. Despite their socio-economic importance, decades of research, and high-profile disasters, karst structures and processes remain notoriously difficult to assess. Because of the complexity of karst and its lack of accessibility, the foundations of flow and transport modeling in karst systems are weak. Key phenomena related to extreme events such as flash floods and heavy tails in tracer recovery are still beyond current modeling capabilities. KARST will establish the next generation of coupled stochastic modeling frameworks to predict karst processes, assess the vulnerability of karst aquifers, and forecast their response to extreme events. Our approach will bridge structures and processes on all scales, far beyond the capabilities of current theories and computer simulations. This will be achieved by targeting three key objec- tives: (i) Identification and quantification of flow and transport dynamics at the conduit scale. (ii) Characterization and modeling of karst network structure at the catchment scale. (iii) Derivation of a new upscaled approach to predict karst processes at different resolution scales. Together, this will result in an unprecedented multiscale modeling framework for the prediction of flow and transport in karst. Solving this long-standing problem is possible thanks to the synergy of the KARST PI team combining the set of skills and knowledge (hydrogeology, physics, mathematics) required to make a ground-breaking step in this field. Beyond that, the new approach is expected to impact other real-world systems in medicine (capillary networks), neuroscience (brain microcirculation) or glaciology (meltwater flow in glaciers).

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: Fracture networks, Geometric graph theory, Topological graph theory

European Research Council
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Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101071936	**UNLEASH**	**SYG** Synergy

Principal Investigator:	**Dr Juan Valcarcel**
Host Institution:	FUNDACIO CENTRE DE REGULACIO GENOMICA - ESP

Harnessing the splicing code for targeted control of gene expression

Alternative splicing (AS) of mRNA precursors plays important roles in tissue-specific gene regulation and biological regulatory mechanisms, as it can radically alter protein expression, cell phenotypes and physiological responses. Altered splicing also contributes to disease mechanisms, ranging from neurodegeneration to cancer. Drugs modulating AS have recently provided the first therapy for Spinal Muscular Atrophy, a common genetic disorder, illustrating the huge potential for treating many other diseases of unmet need, if only we understood the mechanisms controlling splice site selection and how to regulate them with small molecules. Unfortunately, despite decades of research, a comprehensive understanding of the mechanisms that control specificity of AS is lacking. This gap in basic knowledge prevents opportunities to harness splicing modulators as tools to study gene function, novel therapeutics or other biotech applications. This Project addresses head-on the major technical challenges that have limited progress in the AS field. Building on extensive preliminary data, we will use a multidisciplinary approach that combines chemical, structural, cellular, systems biology and machine learning to characterize mechanisms of splice site selection and identify targets for modulating these mechanisms using tool compounds. The outcomes will define key regulatory sequences, splicing factors and molecular interactions involved, thereby illuminating how the splicing machinery efficiently accommodates, yet also discriminates between, a wide range of splice site sequences. This will enable future applications harnessing splice site selection. Our primary goal is to answer the central question, 'Is it generally possible to modulate splicing with high specificity using small molecules?' Success will transform our basic understanding of human gene expression and unleash major opportunities for Pharma to develop new therapeutics.

Link to the ERC project webpage:

Keywords of the ERC project: RNA splicing, small molecule

Keywords that characterize the scientific profile of the potential visiting researcher/s:

European Research Council
Executive Agency

Established by the European Commission

Project ID:	Project Acronym:	Evaluation Panel:
101072047	**CoTransComplex**	**SYG** Synergy

Principal Investigator:	**Dr Bernd Bukau**
Host Institution:	RUPRECHT-KARLS-UNIVERSITAET HEIDELBERG - DEU

Mechanisms of co-translational assembly of multi-protein complexes

Most proteins function within larger complexes. How these intricate structures are correctly formed is poorly understood, yet critical to all cellular processes and pathological conditions. Recent breakthroughs suggest that multi-protein complexes form co-translationally, by super-assemblies of multiple ribosomes and other cofactors that are coordinated in time and space. This striking notion contrasts starkly with textbook models and is key to the possibilities and failures of complex formation. However, owing to technical limitations, the mechanisms and scope of actively coordinated protein assembly are poorly understood. Elucidating how these large and transient co-translational formations produce protein complexes throughout the genome is a next-level challenge that cannot be addressed by a single discipline. We propose a unique merging of cutting-edge approaches: 1) Ribosomal profiling to detect interactions between ribosomes engaged in assembly and cofactors genome-wide, 2) Single-molecule force spectroscopy and super-resolution imaging to reveal ribosome movements and nascent chain assembly. 3) Cryo-EM and tomography to elucidate the structural basis of ribosome interactions that enable direct assembly. Our program addresses 1) the coordination of multiple ribosomes in time and space, 2) the folding and assembly of nascent chains, and guidance by chaperones and novel cofactors, 3) the major protein complexes classes of homo-dimers, higher-order oligomers, hetero-dimers, and complexes formed at membranes. This ambitious program will provide insight of unprecedented detail and scope, spanning from the cellular to the atomic level, from in vivo to in vitro, from genome-wide patterns to molecular mechanisms, and from bacteria to human cells. It will impact a vast spectrum of protein complexes, reveal unknown layers of control in protein biogenesis, with implications for ribosome quality control, artificial protein design, and mechanisms of disease.

Link to the ERC project webpage:

Keywords of the ERC project: Co-translational folding and assembly of protein complexes, chaperones, translation, ribosome profiling

Keywords that characterize the scientific profile of the potential visiting researcher/s: translation, protein folding, bioinformatics, protein biochemistry