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Call for Expression of Interest
2020

Project ID:	Project Acronym:	Evaluation Panel:
759661	**SPOCkS MS**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr Charlotte Uetrecht**
Host Institution:	Heinrich-Pette Institut Leibniz Institut Fuer Experimentelle Virologie - DEU

Sampling Protein cOmplex Conformational Space with native top down Mass Spectrometry

The main question to be addressed by SPOCk'S MS is how protein complex conformation adapts to local changes, such as processing of polyproteins, protein phosphorylation or conversion of substrates. While labelling strategies combined with mass spectrometry (MS), such as hydrogen deuterium exchange and hydroxyl footprinting, are very versatile in studying protein structure, these techniques are employed on bulk samples averaging over all species present. SPOCk'S MS will remedy these by studying the footprinting and therefore exposed surface area on conformation and mass selected species. Labelling still happens in solution avoiding gas phase associated artefacts. The labelling positions are then read out using newly developed top-down MS technology. Ultra-violet and free-electron lasers will be employed to fragment the protein complexes in the gas phase. In order to achieve the highest possible sequence and thus structural coverage, lasers will be complemented by additional dissociation and separation stages to allow MS^N. SPOCk'S MS will allow sampling conformational space of proteins and protein complexes and especially report about the transient nature of protein interfaces. Constraints derived in MS will be fed into a dedicated software pipeline to derive atomistic models. SPOCk'S MS will be used to study intracellular viral protein complexes, especially coronaviral replication/transcription complexes, which are highly flexible and often resist crystallisation and are barely accessible by conventional structural biology techniques.

Objectives:

- Integrate labelling with complex species selective native MS for time-resolved structural studies
- Combine fragmentation techniques to maximise information content from MS
- Develop software suite to analyse data and model protein complex structures based on MS constraints
- Apply SPOCk'S MS to protein complexes of human pathogenic viruses

Link to the ERC project webpage:

Keywords of the ERC project: native mass spectrometry, structural virology, structural proteomics, coronavirus replication/transcription complex

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

Principal Investigator:	**Dr Sharon Tooze**
Host Institution:	The Francis Crick Institute Limited - GBR

In vitro high resolution reconstitution of autophagosome nucleation and expansion catalyzed by ATG9

Autophagy is a conserved, lysosomal-mediated pathway required for cell homeostasis and survival. It is controlled by the master regulators of energy (AMPK) and growth (TORC1) and mediated by the ATG (autophagy) proteins. Deregulation of autophagy is implicated in cancer, immunity, infection, aging and neurodegeneration. Autophagosomes form and expand using membranes from the secretory and endocytic pathways but how this occurs is not understood. ATG9, the only transmembrane ATG protein traffics through the cell in vesicles, and is essential for rapid initiation and expansion of the membranes which form the autophagosome. Crucially, how ATG9 functions is unknown. I will determine how ATG9 initiates the formation and expansion of the autophagosome by amino acid starvation through a molecular dissection of proteins resident in ATG9 vesicles which modulate the composition and property of the initiating membrane. I will employ high resolution light and electron microscopy to characterize the nucleation of the autophagosome, proximity-specific biotinylation and quantitative Mass Spectrometry to uncover the proteome required for the function of the ATG9, and optogenetic tools to acutely regulate signaling lipids. Lastly, with our tools and knowledge I will develop an in vitro reconstitution system to define at a molecular level how ATG9 vesicle proteins, membranes that interact with ATG9 vesicles, and other accessory ATG components nucleate and form an autophagosome. In vitro reconstitution of autophagosomes will be assayed biochemically, and by correlative light and cryo-EM and cryo-EM tomography, while functional reconstitution of autophagy will be tested by selective cargo recruitment. The development of a reconstituted system and identification proteins and lipids which are key components for autophagosome formation will provide a means to identify a new generation of targets for translational work leading to manipulation of autophagy for disease related therapies.

Link to the ERC project webpage:

Keywords of the ERC project: ATG9, autophagy, autophagosome, protein trafficking

Keywords that characterize the scientific profile of the potential visiting researcher/s: biochemistry, cell biology, structural biology, cryoEM, proteomics, proximity labelling, HDX, native mass spec, light and electron microscopy

	Project ID:	Project Acronym:	Evaluation Panel:
	789121	**EditMHC**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr Robert Tampé**
Host Institution:	Johann Wolfgang Goethe Universitaet Frankfurt Am Main - DEU

How MHC-I editing complexes shape the hierarchical immune response

Our body constantly encounters pathogens or malignant transformation. Consequently, the adaptive immune system is in place to eliminate infected or cancerous cells. Specific immune reactions are triggered by selected peptide epitopes presented on major histocompatibility complex class I (MHC-I) molecules, which are scanned by cytotoxic T lymphocytes.

Intracellular transport, loading, and editing of antigenic peptides onto MHC-I are coordinated by a highly dynamic multisubunit peptide-loading complex (PLC) in the ER membrane. This multitasking machinery orchestrates the translocation of proteasomal degradation products into the ER as well as the loading and proofreading of MHC-I molecules.

Sampling of myriads of different peptide/MHC-I allomorphs requires a precisely coordinated quality control network in a single macromolecular assembly, including the transporter associated with antigen processing TAP1/2, the MHC-I heterodimer, the oxidoreductase ERp57, and the ER chaperones tapasin and calreticulin. Proofreading by MHC-I editing complexes guarantees that only very stable peptide/MHC-I complexes are released to the cell surface.

This proposal aims to gain a holistic understanding of the PLC and MHC-I proofreading complexes, which are essential for cellular immunity. We strive to elucidate the mechanistic basis of the antigen translocation complex TAP as well as the MHC-I chaperone complexes within the PLC. This high-risk/high-gain project will define the inner working of the PLC, which constitutes the central machinery of immune surveillance in health and diseases. The results will provide detailed insights into the architecture and dynamics of the PLC and will ultimately pave the way for unraveling general principles of intracellular membrane-embedded multiprotein assemblies in the human body. Furthermore, we will deliver a detailed understanding of mechanisms at work in viral immune evasion.

Link to the ERC project webpage: https://biochem.uni-frankfurt.de/index.php?id=10

Keywords of the ERC project: antigen processing, MHC chaperone, qualtiy control complexes, ABC transporters, T-cell receptor, MHC I complexes

Keywords that characterize the scientific profile of the potential visiting researcher/s: cellular structural biology, cell biology, biochemistry, immunology, virology, membranbe biology, molecular machineries

Repurposing small RNA from ciliates for genome editing: single-molecule study

Genome editing is an essential tool for life sciences. Recent ground-breaking discovery in microbiology drew our attention to the genome editing ability of bacteria (CRISPR). Since its discovery, CRISPR has revolutionized the way of editing a genome. Despite its wide use, CRISPR-genome editing has limitations, especially in the use for medical applications. Numerous studies have shown that it suffers from the off-target effect. Its use is also restricted by its particular sequence requirement and its poor accessibility to a structured genome. Furthermore, recent studies suggested that it might act as a virulence factor within human cells. These limitations demand new genome editing tools.

This proposal sets out to understand the molecular mechanism of Tetrahymena DNA elimination. This naturally occuring genome editing is mediated by a eukaryotic RNA system (Twi1). This system uses an entirely different mechanism from CRISPR and has potential to perform more effectively. I will first investigate how small RNA-loaded Twi1 ("target searcher") recognizes its target and whether its performance exceeds other target searchers including CRISPR/Cas9. I will use single-molecule fluorescence for high resolution observations and develop a high-throughput single-molecule method for transcriptome-wide understanding. Second, I aim to identify a Twi1-related DNA nuclease(s) that carries out DNA elimination. I will use cutting-edge tools of single-molecule pull-down and multi-color FRET together with mass spectrometry. The nanoscopic understanding of a searcher (Twi1) and the identification of a nuclease will help create a new genome editing tool (e.g. a fusion of Twi1 and the nuclease) that potentially perform better than Cas9. Thereby, this fundamental study on "mighty RNA" will make a long-term impact for applications in science and technology. To realize this ambitious project, I will utilize my experience of studying small RNAs (funded by ERC Starting Grant).

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
820187	**EXCHANGE**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr David Drew**
Host Institution:	Stockholms Universitet - SWE

Dynamic Complexes and Allosteric Regulation of Small Molecule Transporters

Solute Carrier (SLC) transporters mediate the translocation of substrates across membranes and after GPCRs represent the second-largest fraction of the human membrane proteome. SLC transporters are critical to cell homeostasis, which is reflected in the fact that more than a quarter is associated with Mendelian disease. Despite a few exceptions, however, they have been under-utilized as drug targets and most of the mechanistic understanding has been derived from bacterial homologues of these medically important proteins. In addition to subtle differences, bacterial homologues will not enable us to establish how the activities of many SLC transporters are allosterically regulated through the binding of accessory factors, e.g., hormones, to their non-membranous globular domains. Understanding the mechanisms by which their activities can be allosterically regulated through these complex and dynamic assembles is critical to human physiology and important for future drug design.

Our model system is a family of transporters known as sodium/proton exchangers (NHEs), which exchange sodium for protons across membranes to aid many fundamental processes in the cell. NHEs are important to the cell cycle, cell proliferation, cell migration and vesicle trafficking and are associated with a wide-spectrum of diseases. Their diverse portfolio is connected to the importance of pH homeostasis, and the binding of many different factors to a large, globular cytosolic domain exquisitely regulates them. To date, we have no structural information for any of the NHE's, functional assays in liposomes are lacking, and many interaction partners are yet to be validated by in vitro studies. Determining the structure, dynamics, and allosteric regulation of NHEs will be an enormous challenge. However, we envisage that by achieving our objectives, we will reveal important mechanistic insights relevant not just to NHEs, but to many types of SLC transporters.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
852798	**ConflictResolution**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr Stephan Hamperl**
Host Institution:	Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Transcription-replication conflicts in disease and development

Genetic and epigenetic instability contribute to cancers, aging, developmental disorders, and neurological diseases, so in-depth understanding how this instability arises is an important question affecting millions in Europe. Physical conflicts between the transcription and DNA replication machineries are a potent endogenous source of this instability.

My preliminary data indicate that a single collision can trigger long-term epigenetic changes and affect the normal expression state of genes. I hypothesize that collisions can rewire gene expression networks and lead to cellular transformations relevant to disease and development. Unfortunately, this mechanism is largely understudied owing to the lack of suitable cellular systems to characterize collisions in molecular detail. My proposal will address this key gap in knowledge.

I recently pioneered a unique human cell-based episomal system to analyse collisions in an inducible and localized fashion. Using this highly tractable system, we will molecularly characterize the (epi)genetic consequences and identify novel factors that prevent or resolve collisions (Aim 1).

To address the relevance of collisions in disease, we will establish a novel proximity-labelling system (Split-APEX2) to map collision sites and identify their associated genetic and chromatin changes in a breast cancer cell model. This cutting-edge technology will decipher their role in pathological transformations observed in breast cancer genomes (Aim 2).

To link collisions to developmental transformations, we will determine their potential to induce local epigenetic changes during zygotic genome activation in mouse embryonic cells. This approach can shift the paradigm how cells in development first start to differ from each other and reprogram their genome into different cell types (Aim 3).

Uncovering the key principles of collisions may implement highly innovative approaches to avoid or establish cellular transformations in disease and development.

Link to the ERC project webpage: https://www.helmholtz-muenchen.de/ies/research/chromosome-dynamics-and-genome-stability/research/index.html

Keywords of the ERC project: Transcription-Replication Conflicts, Genome Integrity, Epigenetic Instability

Keywords that characterize the scientific profile of the potential visiting researcher/s: Cellular Decision Making, Epigenetics, Chromatin, Genome Stability,

	Project ID:	Project Acronym:	Evaluation Panel:
	866011	**MemDense**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr Robert Ernst**
Host Institution:	Universitaet Des Saarlandes - DEU

Cellular control of membrane protein density in the endoplasmic reticulum via the unfolded protein response

All cells must balance the production of proteins and lipids to maintain membrane functions. Imbalances in protein folding and lipid metabolism cause endoplasmic reticulum (ER) stress associated with a wide range of complex diseases including diabetes, neurodegeneration, and viral infections. The central homeostatic program of the ER is the unfolded protein response (UPR), which senses unfolded proteins in the ER to control protein synthesis, chaperone abundance, and lipid metabolism. Through these mechanisms, the UPR centrally controls decisions between cell survival, adaptation, and apoptosis. The field has focused almost exclusively on soluble proteins as triggers of the UPR, while the more abundant membrane proteins have been neglected. Our finding of UPR activation by membrane aberrancies provides a radically new perspective and allows us to address central questions in membrane and cell biology: How is the density of ER membrane proteins sensed and controlled? How are misfolded membrane proteins recognized to mount adaptive responses? Focusing on the conceptual advance that UPR transducers sense signals from the membrane, we will 1) establish and reconstitute the machinery for sensing membrane protein crowding, 2) identify mechanisms coordinating protein and lipid homeostasis between organelles, 3) study the molecular recognition of misfolded membrane proteins by the UPR.

Key to this endeavor is our unique combination of genetic, biochemical, and biophysical tools for parallel characterization of the UPR in vivo and in vitro. Combining this framework with novel strategies for an immuno-isolation of organelles, we are primed to answer how membrane aberrancies cause chronic ER stress. By establishing the UPR as a quality control system for membrane proteins, and providing novel tools and valuable resources to the community, MemDense will have wide impact on our molecular and cellular understanding of ER homeostasis and the many diseases related to ER stress.

Link to the ERC project webpage:

Keywords of the ERC project: membrane homeostasis; protein-to-lipid ratio; membrane protein crowding; chronic ER stress

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

	Project ID:	Project Acronym:	Evaluation Panel:
	866250	**mARs**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr Orsolya Barabas**
Host Institution:	European Molecular Biology Laboratory - DEU

mARs: Mobile DNA driven antibiotic resistance spreading: molecular strategies, control and evolution for broad distribution

Antibiotic resistance (AR) is spreading rapidly, leading to the development of highly virulent pathogens and multidrug-resistant 'superbugs', a major health concern of our era. Mobile DNA elements, transposons and integrons, effectively drive the spread of AR genes in microbial interaction hotspots, such as bacterial communities in humans and natural environments. Yet, our knowledge of their mechanisms remains very sparse. It is unclear how DNA movement occurs on the molecular level and how it is controlled in cells and communities; biochemical and structural data are rare and our view on their diversity and evolution is limited. Here I propose an integrated approach combining bioinformatics, genetics, microbiology, biochemistry, and structural biology to elucidate the mechanisms and diversity of mobile DNA driven resistance spreading. I want to (a) investigate the molecular mechanisms and regulation of AR gene movement in vitro, in model bacteria and in gut bacterial communities; (b) dissect the structure of the underlying molecular machineries to reveal how protein-DNA interplay promotes gene transfer; and (c) characterize the diversity, evolution and functional success of distinct molecular pathways. Mechanistic work will focus on selected mobile elements that confer resistance to last resort drugs and promiscuous gene carriers with high prevalence in health care. Bioinformatic quests will draw on recent (meta)genomic data to chart the clinical significance of molecular insights in situ. By bridging disciplines, I want to provide functionally annotated molecular movies of gene movement and explain how specific molecular strategies evolved to enable broad dissemination of resistance determinants. The insights gained in this research will provide in-depth knowledge on major AR transfer pathways and will have key implications for the development of novel intervention strategies and preventive measures aimed at reducing dissemination of drug resistance in bacteria.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
883240	**monochrome**	**LS1** Molecular and Structural Biology and Biochemistry

Principal Investigator:	**Dr gijs wuite**
Host Institution:	Stichting Vu - NLD

Disentangling metaphase chromosome organisation one chromosome at a time

Chromosomes assume their most compact state during metaphase just before they are separated. In this process of cell division the chromosomes experience high forces and genomic defects can occur then. Many techniques have built considerable understanding of metaphase chromosome structure and a multitude of models have been put forward how cells organize their chromosomes during metaphase. Yet, given the complexity of the process and limitations of the methods to study them, it is far from being fully understood. The breakthrough opportunity in this regard is the development of tools that allow real-time, 3D, super-resolution imaging and manipulation of entire non-fixed metaphase chromosomes under nearphysiological conditions.

Here I propose to quantitatively image the proteins that establish the architecture of metaphase chromosomes and disentangle the connection between its architecture, internal protein dynamics and mechanics at the multi-protein as well as the single-molecule level. For this project I plan to expand the combination of optical manipulation and fluorescent microscopy by introducing force-induced expansion microscopy together with advanced labeling and imaging techniques that ultimately will permit real-time, 3D, super-resolution quantitative analysis of complex (protein) structures within native non-fixed metaphase chromosomes. With this kind of instrument it becomes possible to validate and/or challenge the current models of metaphase organization as well as explore the physical properties of chromosomes but also study chromosome separation dynamics.

My extensive experience handling biological systems and pushing instrumental boundaries gives me an excellent starting point to address key research questions with regards to metaphase chromosomes. In doing so I can improve our understanding of chromosome organization which is important because chromosome defects can have devastating consequences leading to for example cancer or fragile X syndrome.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
	947709	**HyDegronomics**	**LS1** Molecular and Structural Biology and Biochemistry

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 degradation; Protein quality control; degrons; E3 ubiquitin ligase; Ubiquitination

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

Pervasive Upstream Non-Coding Transcription Underpinning Adaptation

Genomic DNA represents the blueprint of life: it instructs solutions to challenges during life cycles of organisms. Curiously DNA in higher organisms is mostly non-protein coding (e.g. 97% in human). The popular "junk-DNA" hypothesis postulates that this non-coding DNA is non-functional. However, high-throughput transcriptomics indicates that this may be an over-simplification as most non-coding DNA is transcribed. This pervasive transcription yields two molecular events that may be functional: 1.) resulting long non-coding RNA (lncRNA) molecules, and 2.) the act of pervasive transcription itself. Whereas lncRNA sequences and functions differ on a case-by-case basis, RNA polymerase II (Pol II) transcribes most lncRNA. Pol II activity leaves molecular marks that specify transcription stages. The profiles of stage-specific activities instruct separation and fidelity of transcription units (genomic punctuation). Pervasive transcription affects genomic punctuation: upstream lncRNA transcription over gene promoters can repress downstream gene expression, also referred to as tandem Transcriptional Interference (tTI). Even though tTI was first reported decades ago a systematic characterization of tTI is lacking. Guided by my expertise in lncRNA transcription I recently identified the genetic material to dissect tTI in plants as an independent group leader. My planned research promises to reveal the genetic architecture and the molecular hallmarks defining tTI in higher organisms. Environmental lncRNA transcription variability may trigger tTI to promote organismal responses to changing conditions. We will address the roles of tTI in plant cold response to test this hypothesis. I anticipate our findings to inform on the fraction of pervasive transcription engaging in tTI. My proposal promises to advance our understanding of genomes by reconciling how the transcription of variable non-coding DNA sequences can elicit equivalent functions.

Link to the ERC project webpage: https://cpsc.ku.dk/meet-the-scientists-page/sebastian-marquardts-group/

Keywords of the ERC project: Epigenetics, RNA, non-coding Genome, Gene Expression, Genomics, Plant-environment

Keywords that characterize the scientific profile of the potential visiting researcher/s: Epigenetics, RNA, non-coding Genome, Gene Expression, Genomics, computational biology

	Project ID:	Project Acronym:	Evaluation Panel:
			LS2
	758397	**miRCell**	Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Marc Friedländer**
Host Institution:	Stockholms Universitet - SWE

MicroRNA functions in single cells

It is now becoming apparent that genes are regulated not only by transcription, but also by thousands of post-transcriptional regulators that can stabilize or degrade mRNAs. Some of the most important regulators are miRNAs, short RNA molecules that are deeply conserved in sequence and are involved in numerous biological processes, including human disease. Surprisingly, transcriptomic and proteomic studies show that most miRNAs only have subtle silencing effects on their targets, suggesting additional important, but yet undiscovered functions. Thus the question is raised: if the main function of miRNAs is not to silence targets, what is it?

I will test two novel hypotheses about miRNA function. The first hypothesis proposes that miRNAs can buffer gene expression noise. The second hypothesis is inspired by my preliminary results and proposes that miRNAs can synchronize expression of genes. If I validate either hypothesis, it would mean that miRNA functions can be investigated in entirely new ways, yielding important new biological insights relevant to both basic research and human health. However, these hypotheses can only be tested in individual cells, and the necessary single-cell technologies and computational tools are only maturing now.

I will apply my expertise in miRNA biology and in combined wet-lab and computational methods to design, develop and apply miRCell-seq to test these two hypotheses in cell cultures and in animals. This new method will for the first time measure miRNAs, their targets, and the interactions between them in single cells and transcriptome-wide. We will use mutant cells devoid of miRNAs and time course experiments to generate sufficient data to develop detailed models of the miRNA impact on their targets. We will then validate our findings with single cell proteomics. This project thus has the potential to reveal novel functions of miRNAs and substantially improve our general understanding of gene regulation.

Link to the ERC project webpage: https://friedlanderlab.org/

Keywords of the ERC project: miRNA, microRNA, single-cell transcriptomics, single-cell proteomics

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**759154**	**Cellkarma**	**LS2** Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Davide Cacchiarelli**
Host Institution:	Fondazione Telethon - ITA

Dissecting the regulatory logic of cell fate reprogramming through integrative and single cell genomics

The concept that any cell type, upon delivery of the right "cocktail" of transcription factors, can acquire an identity that otherwise it would never achieve, revolutionized the way we approach the study of developmental biology. In light of this, the discovery of induced pluripotent stem cells (IPSCs) and cell fate conversion approaches stimulated new research directions into human regenerative biology. However, the chance to successfully develop patient-tailored therapies is still very limited because reprogramming technologies are applied without a comprehensive understanding of the molecular processes involved.

Here, I propose a multifaceted approach that combines a wide range of cutting-edge integrative genomic strategies to significantly advance our understanding of the regulatory logic driving cell fate decisions during human reprogramming to pluripotency.

To this end, I will utilize single cell transcriptomics to isolate reprogramming intermediates, reconstruct their lineage relationships and define transcriptional regulators responsible for the observed transitions (AIM 1). Then, I will dissect the rules by which transcription factors modulate the activity of promoters and enhancer regions during reprogramming transitions, by applying synthetic biology and genome editing approaches (AIM 2). Then, I will adopt an alternative approach to identify reprogramming modulators by the analysis of reprogramming-induced mutagenesis events (AIM 3). Finally, I will explore my findings in multiple primary reprogramming approaches to pluripotency, with the ultimate goal of improving the quality of IPSC derivation (Aim 4).

In summary, this project will expose novel determinants and yet unidentified molecular barriers of reprogramming to pluripotency and will be essential to unlock the full potential of reprogramming technologies for shaping cellular identity in vitro and to address pressing challenges of regenerative medicine.

Link to the ERC project webpage: https://armeniseharvard.org/scientists/davide-cacchiarelli/

Keywords of the ERC project: pluripotency, ipsc, reprogramming, genomics, bioinformatics, computational biology, stem cells, transcription factors, cell fate conversion

Keywords that characterize the scientific profile of the potential visiting researcher/s: genomics, bioinformatics, computational biology, cell fate conversion

Principal Investigator:	**Dr Karoline Faust**
Host Institution:	Katholieke Universiteit Leuven - BEL

Ecosystem in a box: Dissecting the dynamics of a defined microbial community in vitro

The dynamics of microbial communities may be driven by the interactions between community members, controlled by the environment, shaped by immigration or random events, influenced by evolutionary processes or result from an interplay of all these factors. This project aims to improve our understanding of how community structure and the environment impact community dynamics. Towards this aim, a defined in vitro community of human gut bacteria will be assembled, since their genomes are available and their metabolism is comparatively well resolved.

In the first step, we will quantify the intrinsic variability of community dynamics and look for alternative stable states. Next, we will systematically vary community structure as well as nutrient supply and monitor their effects on the dynamics. Finally, we will measure model parameters, evaluate to what extent different community models predict observed community dynamics and validate the models by identifying and experimentally validating keystone species.

Studies of microbial community dynamics are hampered by the cost of obtaining densely sampled time series in replicates and by the difficulty of community manipulation. We will address these challenges by setting up an in vitro system for parallel and automated cultivation in well-controlled conditions and by working with defined communities, where every community member is known.

The proposed project will discern how external factors and community structure drive community dynamics and encode this knowledge in mathematical models. Moreover, the project has the potential to transform our view on alternative microbial communities and their interpretation. In addition, the project will extend our knowledge of human gut microorganisms and their interactions. These insights will ease the design of defined gut communities optimized for therapeutic purposes.

Link to the ERC project webpage:

Keywords of the ERC project: microbial community dynamics, population models, metabolic models, human gut bacteria

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

Homologous recombination and its application in manipulating animal mitochondrial DNA

Mitochondrial DNA (mtDNA) is a multi-copy genome that works with the nuclear genome to control energy production and various cellular processes. To date, disorders associated with mutations in mtDNA are among the most common genetically inherited metabolic diseases1. However, our knowledge regarding many aspects of mtDNA biology remains limited, and we know even less about how it influences development and organismal traits. This is largely due to our inability to manipulate mtDNA. Recently, a colleague and I developed novel genetic tools in Drosophila that allowed us to isolate animal mitochondrial mutants for the first time, and to create heteroplasmic organisms containing two mitochondrial genotypes2,3. These advances make Drosophila a powerful system for mtDNA studies. Importantly, I showed that Drosophila mtDNA could undergo homologous recombination. Furthermore, I established a system to induce recombination at specific sites and select for progeny containing only the recombinant genome4. Thus, my work has demonstrated the existence of recombination in animal mitochondria, and opens up the possibility of developing a recombination system for functional mapping and manipulating animal mtDNA. Here I propose to 1) identify components of the mitochondrial recombination machinery by a candidate RNAi screen; 2) develop a recombination toolkit to map trait-associated mtDNA sequences/SNPs; and 3) build a site-directed mutagenesis system by establishing robust ways to deliver DNA into fly mitochondria. Given the essential functions of mitochondria and their involvement in incurable diseases, the genetic tools developed in this proposal will transform the field by making it possible to link mtDNA variations to phenotypic differences and introduce specific mutations into mtDNA for functional studies at organismal level. These advances will open many possibilities to accelerate our understanding on how mtDNA impacts health, disease and evolution.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
		LS2
819941	**EpiRIME**	Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Nicola Iovino**
Host Institution:	Max Planck Gesellschaft Zur Foerderung Der Wissenschaften E.V. - DEU

Epigenetic Reprogramming, Inheritance and Memory: Dissect epigenetic transitions at fertilisation and early embryogenesis

During gametogenesis, germ cells undergo profound chromatin reorganisation, condensation and transcriptional shutdown. Upon fertilization, gamete chromatin is epigenetically reprogrammed, generating a totipotent zygote that can give rise to all cell types of the adult organism. The maternal factors that reprogram gametes to totipotency are unknown. The current dogma suggests that the parental epigenetic information must be erased in order to establish totipotency.

In contrast, we have recently discovered that maternal gametes transmit the epigenetic H3K27me3 histone modification to the next generation (Zenk et al., Science, 2017) adding to increasing evidence suggesting that gametes convey more than just DNA to the offspring. Nevertheless, the underlying mechanisms and the impact of epigenetic inheritance through the gametes are not yet fully resolved. Critically, the mechanisms and impact of (i) paternal gamete reprogramming, (ii) paternal epigenetic inheritance and (iii) de novo establishment of the zygotic epigenome remain essentially unknown.

The objective of this proposal is to unravel the fundamental principles underlying these three major epigenetic transitions in vivo in Drosophila.

We will achieve our objective via three aims: (i) We will investigate the mechanisms underlying the reprogramming of sperm chromatin at fertilization. Specifically, we will determine the nature and extent of the contributions of two proteins essential for sperm chromatin reprogramming (ii) We will examine the mechanism of histone H3K27me3 inheritance through the paternal germline (iii) We will genetically dissect the de novo establishment of constitutive heterochromatin in the newly formed zygote.

Our investigations of these epigenetic transitions are expected to reveal novel insights into the first steps in the formation of life, and to ultimately advance reproductive and regenerative medicine.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
850405	CHROMREP	**LS2** Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Aniek Janssen**
Host Institution:	Universitair Medisch Centrum Utrecht - NLD

Dissecting the chromatin response to DNA damage in silenced heterochromatin regions

Cells are continuously exposed to insults that can break or chemically modify their DNA. To protect the DNA, cells have acquired an arsenal of repair mechanisms. Proper repair of DNA damage is essential for organismal viability and disease prevention. What is often overlooked is the fact that the eukaryotic nucleus contains many different chromatin domains that can each influence the dynamic response to DNA damage. Different chromatin environments are defined by specific molecular and biophysical properties, which could necessitate distinct chromatin responses to ensure safe DNA damage repair.

The aim of this proposal is to understand how diverse chromatin domains, and in particular the dense heterochromatin environment, shape the dynamic chromatin response to DNA damage.

I recently developed locus-specific DNA damage systems that allow for in-depth analysis of chromatin domain-specific repair responses in Drosophila tissue. I will employ these systems and develop new ones to directly observe heterochromatin-specific dynamics and repair responses. I will combine these systems and state-of-the art chromatin analysis with high-resolution live imaging to dissect the DNA damage-associated heterochromatin changes to determine their function in repair -kinetics, -dynamics and -pathway choice.

Deciphering the chromatin dynamics that regulate DNA damage repair in heterochromatin will have broad conceptual implications for understanding the role of these dynamics in other essential nuclear processes, such as replication and transcription. More importantly, understanding how chromatin proteins promote repair will be important in determining how cancer-associated mutations in these chromatin proteins impact genetic instability in tumours in the long run.

Link to the ERC project webpage:

Keywords of the ERC project: chromatin, drosophila, DNA damage repair, heterochromatin

Keywords that characterize the scientific profile of the potential visiting researcher/s: cell biologist and/or computational biologist

	Project ID:	Project Acronym:	Evaluation Panel:
			LS2
	852451	**DecodeDegRNA**	Genetics, Genomics, Bioinformatics and Systems Biology

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

Post-transcriptional regulation of RNA degradation in early zebrafish development

Regulation of gene expression lies at the heart of fundamental biological processes, such as the formation of different cell types inside an embryo or responses to environmental stimuli. Living cells ensure that the right genes are expressed at the right time and place by carefully controlling every RNA molecule inside a cell from its 'birth' by transcription to its final 'death' by degradation. While vast efforts strive to understand the first part of this process – transcription, studies of RNA degradation have been more limited. Current knowledge largely relies on small-scale investigation of key – but anecdotal – cases, while technical and experimental difficulties limit its large-scale analysis. Therefore, we still lack a systematic and predictive understanding of RNA degradation: technologies to globally measure it, the molecular mechanisms involved, its functional and physiological implications and models to decode and predict it. Transcriptional silencing makes early embryos an ideal system to study RNA degradation and uncover its basic concepts, as I propose here. Aim 1 will decipher how genomic information within native RNA sequences determines their degradation in embryos. Aim 2 will develop the technology to investigate RNA degradation at single-cell resolution, and uncover its regulation within arising embryonic cell populations. Aim 3 will reveal the molecular implementation of the regulatory code of RNA degradation and determine its physiological roles that underlie the massive degradation of maternal mRNAs – a key regulatory event and a main developmental transition in early embryos of all animals. This work will uncover new principles of RNA degradation in early development and elicit its mechanisms and functions using the zebrafish as an in vivo model system. The assays and models to be developed will be broadly applicable to study RNA degradation in diverse contexts, ranging from disease mechanisms to engineering of RNA- protein interactions.

Link to the ERC project webpage:

Keywords of the ERC project: RNA degradation zebrafish maternal to zygotic transition post transcriptional regulation

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS2
	852786	**TYPEWIRE**	Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Amit Zeisel**
Host Institution:	Technion - Israel Institute Of Technology - ISR

Reconstructing wiring rules of in vivo neural networks using simultaneous single-cell connectomics and transcriptomics

The brain performs sophisticated functions and complex behaviours, orchestrated by highly specialized cells. Neurons are at the core of the nervous system's computational capabilities. In recent years, we and others have advanced single-cell RNAseq to reveal their extraordinary molecular diversity in transcriptome-based cell-type taxonomies. It is the unique combinations of circuits that these different neuronal types form – within a practically unlimited space of possible implementations – that encode the large functional repertoire of the nervous system. Although critical, little is known about the basic organizational principles of cells within the circuits – the 'wiring rules'. This highlights the conceptual challenge to measure connectivity on a systematic and synaptic, single-cell level. What is the topology of networks? What is the relation between network topology and function? How do cell types and gene expression determine wiring? Answering these questions will help resolve nervous system computation at the level of its cellular building blocks. The vision of this proposal is to provide and apply a novel approach that will allow us to investigate neuronal connectivity at large-scale. Two key requirements for such measurements are the ability to measure true synaptic connections, and obtain tens of thousands of datapoints. Further, the concept of cell types is crucial for addressing the connectivity problem, as it allows us to distinguish the network elements and thus assemble a global picture even from fragmented, partial measurements. For this purpose, we will combine transcriptomics and connectomics measurements at the single cell level.

The proposed project has enormous potential to systematically (re)address basic functional questions in neuroscience. It can expand our understanding of neural circuits to an unprecedented resolution, with conceivable impact on computational research, such as in vivo inspired neural networks and artificial intelligence.

Link to the ERC project webpage:

Keywords of the ERC project: single cell, synaptic connectivity

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS2
	852865	**EmbryoMethFunc**	Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Yonatan Stelzer**
Host Institution:	Weizmann Institute Of Science - ISR

Cell-Type Specific DNA Methylation Changes During Mammalian Development: Beyond Mapping

DNA methylation is essential for normal mammalian development. While seminal work has provided tremendous insight into the dynamic regulation of DNA methylation throughout embryogenesis, comprehensive understanding of how cell-specific methylation programs are established and maintained, and how they are involved in defining cell states in vivo through regulation of target genes, remains a formidable task. Revolutionary technologies now offer unprecedented opportunities for understanding the function of DNA methylation in specifying, memorizing and modulating embryonic programs. These powerful tools motivate further development of novel experimental systems, to integrate single-cell monitoring with flexible engineering of markers, reporters and perturbations. This will make it possible to precisely target key rare embryonic cell populations for in-depth analysis.

Here, combining cutting-edge methods for single cell mapping of DNA methylation and gene expression, and by developing a novel approach for inferring spatial information from single cell genomic data, we propose to comprehensively chart the post-implantation embryo, at unprecedented resolution. To move to functional studies, we will implement our recently established reporter system that enables monitoring and isolation of cells based on endogenous locus-specific changes in DNA methylation. Together with site-specific methylation editing tools, mouse genetics, and in vitro differentiation of pluripotent stem cells, we will study the developmental potential of rare epiblast cells that we identified that exhibit lower-than-expected genome-wide methylation levels. We will further study the effects of cell-specific methylation changes at an imprinted control region on gene dosage by genetic and epigenetic perturbation, during mouse development. Our combined approach will open new avenues for elucidating the contribution of cell-specific DNA methylation changes to cell-state and function following implantation

Link to the ERC project webpage:

Keywords of the ERC project: Epigenetics, Embryonic Development, Single Cell Genomics, Genome Editing, Mouse Genetics, Parental Imprinting

Keywords that characterize the scientific profile of the potential visiting researcher/s: Epigenetics, Embryonic Development, Single Cell Genomics, Genome Editing, Mouse Genetics, Parental Imprinting

Project ID:	Project Acronym:	Evaluation Panel:
947803	**FIND-seq**	**LS2** Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Davide Seruggia**
Host Institution:	St. Anna Kinderkrebsforschung - AUT

Functional Interrogation of Non-coding DNA Sequences in leukemia development and drug resistance

Functional non-coding regions of the genome play a fundamental role in gene expression and are enriched for disease associated variants. Perturbation of non-coding regions harbouring disease-associated variants is now the rationale of ongoing clinical trials (e.g. NCT03432364), highlighting the translational potential of basic research in the non-coding space. However, our ability to systematically identify disease-associated functional elements in the non-coding genome, understand its grammar, and subsequently develop new therapies is limited. CRISPR-based pooled screens targeting non-coding elements in situ have been successful in uncovering complex gene regulatory architecture in a variety of biological systems. However, these approaches are limited to a few loci, lack of direct genotype-phenotype correlation, and do not target large chromatin structures that determine gene expression programs. To overcome these limitations, I propose a multi-scale approach platform that is generalizable to different cell types and phenotypes. Under this proposal, I will focus on the role of non-coding sequences in the context of blood malignancies. I will investigate non-coding sequences whose change in chromatin state (activation or repression) is associated with drug resistance in Chronic Myelogenous Leukemia (CML). I will study alterations in the chromatin structure (i.e. at chromatin loops or topologically associated domains) that are causal to imatinib resistance in CML. Finally, to learn enhancer grammar and mechanistically link non-coding variants to disease, I will focus on non-coding sequence variation in leukemia and dissect non-coding sequences at base pair resolution using dense mutagenesis coupled with long-reads sequencing. A deeper understanding of the non-coding regulatory architecture in diseases will provide the basis for development of innovative therapies targeting the non-coding genome.

Link to the ERC project webpage:

Keywords of the ERC project: hematopoiesis; enhancers; chromatin biology; 3Dgenome; CRISPR

Keywords that characterize the scientific profile of the potential visiting researcher/s: hematopoiesis; leukemia; epigenetics

	Project ID:	Project Acronym:	Evaluation Panel:
	948770	**DECIPHER**	**LS2** Genetics, Genomics, Bioinformatics and Systems Biology

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: natural products, microbiomes, metagenomics, bioinformatics, computational biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics, cheminformatics, computational biology, metagenomics

Project ID:	Project Acronym:	Evaluation Panel:
		LS2
949990	**BrainBreaks**	Genetics, Genomics, Bioinformatics and Systems Biology

Principal Investigator:	**Dr Pei-Chi Wei**
Host Institution:	Deutsches Krebsforschungszentrum - DEU

DNA Breaks Shape Neural Genome Heterogeneity

Neural progenitor cells undergo tens of thousands of cell divisions to generate the 80 billion neurons in a human brain. In neural progenitor cells, replication stress can lead to recurrent DNA break clusters (RDCs). Joining of two RDC breaks may introduce somatic genomic diversity. On the other hand, unbalanced genomic mosaicism in neural progenitor cells may lead to brain cancer and neuropsychiatric disorders. This proposal will test whether cell-autonomous DNA lesions that accumulate during rapid progenitor division contribute to the genetic heterogeneity found across neuronal cell populations.

Aim 1 will elucidate how replication stress drives recurrent break clusters in the neural progenitor cell genome. We will evaluate whether chromatin loop extrusion mechanistically contributes to breakage repairs, and thus helps shape genomic structure variations.

Aim 2 will quantify the extent and impact of tissue-specific recurrent break clusters in the embryonic brain. I will create a mouse model to identify DNA breaks in temporal and cell-type-specific manner across the entire population of neuronal progenitor cells.

Aim 3 will evaluate whether replicative stress drives the recurrent genomic alteration in the RDC-containing gene during embryonic neurogenesis. We will investigate one of the RDC-containing gene Neurexin 1, where deletion or truncation results in neurological disorders.

By combining a powerful in vitro cell line-based tool, versatile in vivo mouse models, and cutting-edge multi-omics approaches, we will uncover the mechanisms that are critical to the fields of genomics and developmental neuroscience and may also provide valuable new insights into neuropsychiatric disorders and tumor biology.

Link to the ERC project webpage:

Keywords of the ERC project: Brain development, DNA damage

Keywords that characterize the scientific profile of the potential visiting researcher/s: Single cell transcriptomics, lineage tracing

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency *Established by the European Commission*	**742138**	**LOGNEURODEV**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr James Briscoe**
Host Institution:	The Francis Crick Institute Limited - GBR

The molecular and cellular logic of vertebrate neural development

A central problem in biology and key to realising the potential of regenerative medicine is understanding the mechanisms that produce and organize cells in the complex tissues of an embryo. In broad terms, initially uncommitted progenitors acquire their fate in response to signals that control transcriptional programmes. These programmes drive cells through spatial and temporal successions of states that gradually refine cell identity. How these states are established and cell fate decisions implemented is poorly understood. To address this we use an experimentally tractable system – the formation of defined populations of progenitors in the vertebrate spinal cord. We take an interdisciplinary approach that combines our in vivo expertise with three recent advances in our group. First, we have developed in vitro differentiation systems and microfluidic devices that use embryonic stem cells to recapitulate development processes. Second, we have embraced new technologies that provide unprecedented ability to manipulate and assay single cells. Finally, we have established interdisciplinary collaborations to develop computational tools and construct data driven mathematical models. Using these approaches, alongside established embryological methods, we will establish a platform for manipulating and analysing mechanisms by which the multipotent progenitors that form the spinal cord acquire specific identities. We will identify the rules by which cells make decisions and we will define the design logic and network architectures that lead to distinct cell fate choices. The ability to: (i) follow the trajectory of a cell as it transitions to a specific neuronal subtype in vivo; (ii) manipulate the process in vitro and in vivo; and (iii) model it in silico, offers a unique system for understanding organogenesis. Together these approaches will provide the knowledge and technical foundations for rational, predictive tissue engineering of the spinal cord.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency — Established by the European Commission	**757557**	**MECHABLASTO**	**LS3** Cellular and Developmental Biology

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

Morphogenesis during pre-implantation development: molecular and mechanical regulation

During the first days of mammalian development, blastomeres organize themselves into the blastocyst, which implants the embryo into the maternal uterus. Failure to build the blastocyst will result in a miscarriage and yet the mechanisms underlying the construction of the blastocyst are mostly unknown. The blastocyst is sculpted by forces generated by its constituent cells. Without a tool to study the mechanics of the mammalian embryo, it is challenging to identify the molecules and cellular processes controlling morphogenetic forces. Using biophysical methods, I have recently measured the forces shaping the mouse blastocyst and identified cellular processes generating and controlling them. This approach enables the identification of the molecules controlling morphogenesis and constitutes the first step towards a complete theoretical modelling of blastocyst morphogenesis.

The aim of this project is to understand the molecular and mechanical aspects of blastocyst morphogenesis. By developing novel biophysical tools for the developing blastocyst, we will measure uncharacterized mechanical properties such as cytoplasmic and luminal pressure, adhesion strength and viscosity. The resulting mechanical map of the blastocyst will help understand the mechanisms of action of genes involved in its morphogenesis. To identify novel candidate genes involved in blastocyst morphogenesis, we will carry out a screen using live high-resolution confocal microscopy of mouse embryos injected with siRNA. Together, this will reveal the molecular, cellular and mechanical processes controlling blastocyst morphogenesis. I expect this to shed light on how blastomeres self-organize into the blastocyst and to reveal the physical laws underlying morphogenesis in general. Importantly, the knowledge and non-invasive biophysical techniques that we will develop will help developing Assisted Reproduction Technologies, which will be greatly beneficial to the fertility of the ageing European population.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
	788363	**HITSCIL**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Erwin Peterman**
Host Institution:	Stichting Vu - NLD

How intraflagellar transport shapes the cilium: a single-molecule systems study

Sensory cilia are organelles extending like antennas from many eukaryotic cells, with crucial functions in sensing and signalling. Cilia consist of an axoneme built of microtubules, enveloped by a specialized membrane. Ciliary development and maintenance depend critically on a specific, microtubule-based intracellular transport mechanism, intraflagellar transport (IFT). In my laboratory, we study the chemosensory cilia of C. elegans, which sense water-soluble molecules in the animal's environment for chemotaxis. Over the past years, we have developed a unique set of quantitative, single-molecule fluorescence microscopy tools that allow us to visualize and quantify IFT dynamics with unprecedented detail in living animals. So far, our focus has been on the cooperation of the motor proteins driving IFT. The overall objective of my current proposal is to zoom out and shed light on the connection between ciliary structure, chemosensory function and IFT, from a systems perspective. Recent work has indicated that axoneme length is controlled by IFT. Preliminary results from my laboratory show that axoneme length changes dynamically in response to perturbations of IFT or cilia. Furthermore, we have shown that IFT is substantially affected upon exposure of animals to known repellent solutions. The four major aims in my proposal are to:

• determine how directional changes in IFT are regulated and are affected by external disturbances,

• understand the dynamics of the axonemal microtubules and how IFT affects these dynamics and vice versa,

• study how sensory ciliary function affects IFT and ciliary structure,

• further develop our (single-molecule) fluorescence microscopy toolbox by improving instrumentation and using better fluorescent probes and sensors.

These experiments will place my lab in a unique position to push forward our understanding of the relationship between structure, function and dynamics of transport of this fascinating and fundamental organelle.

Link to the ERC project webpage: www.nat.vu.nl/~erwinp

Keywords of the ERC project: C. elegans, cilia, intraflagellar transport, single-molecule fluorescence microscopy, in vivo imaging, quantitative imaging

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency. Established by the European Commission	**803952**	**MCS-MD**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Stefano Vanni**
Host Institution:	Universite De Fribourg - CHE

The Molecular Dynamics of Membrane Contact Sites

The goal of this project is to obtain an atomistic structural and dynamical characterization of the inner workings of membrane contact sites (MCS) between intracellular organelles, in order to understand how molecular processes such as non-vesicular lipid transport at MCS might modulate lipid homeostatic processes at the whole-cell scale.

Investigation of the mechanisms taking place at MCS has emerged as a central topic in cellular biology in the last few years, and it has led to a large amount of novel cellular, biochemical and structural data that has drastically revolutionized our general understanding of lipid homeostasis in the cell. Yet, due to limitations of experimental methods, a high-resolution understanding of how MCS proteins work is still limited, and the specific molecular details of these mechanisms are still under intense debate, and especially concerning the specificity of lipid transport or the discrimination between lipid sensing and lipid transport.

To understand these processes with unprecedented molecular detail, I will develop high-throughput protocols based on atomistic and coarse-grain molecular dynamics simulations that leverage and take advantage of all the available, yet often scattered, experimental data. With these approaches, that have not been used so far to investigate MCS because of the extreme complexity of these cellular machineries, I will obtain a detailed understanding of key molecular processes taking place at MCS, including the specificity of membrane binding, the mechanism of lipid uptake and release, the influence of confinement on protein activity, and the role of membrane lipid composition in the regulation of lipid transport.

This approach will drive forward our perception of the limits of structure-based in-silico methods, and it will contribute to our mechanistic understanding of key cellular biology processes by providing new quantitative results that are beyond the current possibilities of experimental approaches.

Link to the ERC project webpage:

Keywords of the ERC project: lipid, membrane, lipid transport, membrane contact sites, molecular dynamics

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

	Project ID:	Project Acronym:	Evaluation Panel:
	819314	**DCRIDDLE**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Sophie janssens**
Host Institution:	Vib - BEL

A novel physiological role for IRE1 and RIDD..., maintaining the balance between tolerance and immunity?

Dendritic cells (DCs) play a crucial role as gatekeepers of the immune system, coordinating the balance between protective immunity and tolerance to self antigens. What determines the switch between immunogenic versus tolerogenic antigen presentation remains one of the most puzzling questions in immunology. My team recently discovered an unanticipated link between a conserved stress response in the endoplasmic reticulum (ER) and tolerogenic DC maturation, thereby setting the stage for new insights in this fundamental branch in immunology.

Specifically, we found that one of the branches of the unfolded protein response (UPR), the IRE1/XBP1 signaling axis, is constitutively active in murine dendritic cells (cDC1s), without any signs of an overt UPR gene signature. Based on preliminary data we hypothesize that IRE1 is activated by apoptotic cell uptake, orchestrating a metabolic response from the ER to ensure tolerogenic antigen presentation. This entirely novel physiological function for IRE1 entails a paradigm shift in the UPR field, as it reveals that IRE1's functions might stretch far from its well-established function induced by chronic ER stress. The aim of my research program is to establish whether IRE1 in DCs is the hitherto illusive switch between tolerogenic and immunogenic maturation. To this end, we will dissect its function in vivo both in steady-state conditions and in conditions of danger (viral infection models). In line with our data, IRE1 has recently been identified as a candidate gene for autoimmune disease based on Genome Wide Association Studies (GWAS). Therefore, I envisage that my research program will not only have a large impact on the field of DC biology and apoptotic cell clearance, but will also yield new insights in diseases like autoimmunity, graft versus host disease or tumor immunology, all associated with disturbed balances between tolerogenic and immunogenic responses.

Link to the ERC project webpage:

Keywords of the ERC project:

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

ChaperoneRegulome: Understanding cell-type-specificity of chaperone regulation

Protein misfolding causes devastating health conditions such as neurodegeneration. Although the disease-causing protein is widely expressed, its misfolding occurs only in certain cell-types such as neurons. What governs the susceptibility of some tissues to misfolding is a fundamental question with biomedical relevance.

Molecular chaperones help cellular proteins fold into their native conformation. Despite the generality of their function, chaperones are differentially expressed across various tissues. Moreover exposure to misfolding stress changes chaperone expression in a cell-type-dependent manner. Thus cell-type-specific regulation of chaperones is a major determinant of susceptibility to misfolding. The molecular mechanisms governing chaperone levels in different cell-types are not understood, forming the basis of this proposal. We will take a multidisciplinary approach to address two key questions: (1) How are chaperone levels co-ordinated with tissue-specific demands on protein folding? (2) How do different cell-types regulate chaperone genes when exposed to the same misfolding stress?

Cellular chaperone levels and their response to misfolding stress are both driven by transcriptional changes and influenced by chromatin. The proposed work will bring the conceptual, technological and computational advances of chromatin/ transcription field to understand chaperone biology and misfolding diseases. Using in vivo mouse model and in vitro differentiation model, we will investigate molecular mechanisms that control chaperone levels in relevant tissues. Our work will provide insights into functional specialization of chaperones driven by tissue-specific folding demands. We will develop a novel and ambitious approach to assess protein-folding capacity in single cells moving the chaperone field beyond state-of-the-art. Thus by implementing genetic, computational and biochemical approaches, we aim to understand cell-type-specificity of chaperone regulation.

| Principal Investigator: | **Dr Jens Stougaard** |
| Host Institution: | Aarhus Universitet - DNK |

The Roots of Infection

Plant roots and soil microbes have been associated since the emergence of plants on land. Nevertheless the mechanisms that have coevolved to control these commensal and mutualistic associations are currently unknown. RINFEC will identify both plant and bacterial genes involved in root colonization by commensal and mutualistic bacteria with an approach that would be transformative in the field. The ambitious challenge is to identify and functionally characterize the central genes controlling root cells competence for infection. RINFEC´s central hypothesis is that key components of ancient pathways for bacterial colonization of the root surface (rhizosphere) and root interior (endosphere) were adapted during evolution of mechanism(s) controlling colonization of legume roots by symbiotic rhizobia. RINFEC will uncover the genetics and biochemistry of these shared mechanisms by characterizing a novel, unexplored intercellular infection mode observed for certain rhizobia that act as endophytes in non-legume plants and are able to infect the model legume Lotus japonicus. The unique biological feature exploited in RINFEC is the capacity of Lotus to support either intercellular entry (conserved mode) or legume specific infection thread entry, dependent on the rhizobia encountered. This allows comparative investigations of these two infection modes in simple binary interactions with the same host. Given the exceptional ability of different rhizobia for intercellular endophytic colonization of non-legume roots this provides an unprecedented platform to identify mechanisms by which plants selectively enable a subset of bacteria to infect roots. RINFEC will build on my considerable expertise with Lotus and pioneers novel plant and bacterial genetic methods, cell-layer transcriptomics, phospho-proteomics and advanced biochemistry to break new ground in understanding infection and soil microbe influences on plant performance under environmental stress conditions.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**835322**	**CENGIN**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Pierre Gönczy**
Host Institution:	Ecole Polytechnique Federale De Lausanne - CHE

Deciphering and engineering centriole assembly

Deciphering and engineering the assembly of cellular organelles is a key pursuit in biology. The centriole is an evolutionarily conserved organelle well suited for this goal, and which is crucial for cell signaling, motility and division. The centriole exhibits a striking 9-fold radial symmetry of microtubules around a likewise symmetrical cartwheel containing stacked ring-bearing structures. Components essential for generating this remarkable architecture from alga to man have been identified. A next critical step is to engineer assays to probe the dynamics of centriole assembly with molecular precision to fully understand how these components together build a functional organelle. Our ambitious research proposal aims at taking groundbreaking steps in this direction through four specific aims:

1) Reconstituting cartwheel ring assembly dynamics. We will use high-speed AFM (HS-AFM) to dissect the biophysics of SAS-6 ring polymer dynamics at the root of cartwheel assembly. We will also use HS-AFM to analyze monobodies against SAS-6, as well as engineer surfaces and DNA origamis to further dissect ring assembly.

2) Deciphering ring stacking mechanisms. We will use cryo-ET to identify SAS-6 features that direct stacking of ring structures and set cartwheel height. Moreover, we will develop an HS-AFM stacking assay and a reconstituted stacking assay from human cells.

3) Understanding peripheral element contributions to centriole biogenesis. We will dissect the function of the peripheral centriole pinhead protein Cep135/Bld10p, as well as identify and likewise dissect peripheral A-C linker proteins. Furthermore, we will further engineer the HS-AFM assay to include such peripheral components.

4) Dissecting de novo centriole assembly mechanisms. We will dissect de novo centriole formation in human cells and water fern. We will also explore whether de novo formation involves a phase separation mechanism and repurpose the HS-AFM assay to probe de novo organelle biogenes

Link to the ERC project webpage:

Keywords of the ERC project: centriole, assembly, de novo

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**949717**	**RNAloc**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Andreas Moor**
Host Institution:	Eidgenoessische Technische Hochschule Zurich - CHE

Epithelial mRNA localization in homeostasis and pathophysiology

Asymmetric subcellular mRNA distributions have been observed in a variety of polar cell types and organisms. RNA polarization is instrumental at the beginning of life and determines the morphogen gradients needed for embryo patterning. In highly polar neurons, subcellular transcript localization and translation are thought to enhance cellular efficiency and timely responses to extrinsic cues. However, the functional consequence of mRNA localization has, in most cases, not been elucidated. We have shown that a large fraction of an epithelial transcriptome is localized, yet the role(s) of mRNA localization in adult tissue homeostasis and function are unknown. Moreover, we still do not know how the transcript sorting machinery works, and we lack insights into the molecular composition of the membrane-less compartments that may maintain RNA segregation in the cytoplasm.

We will address these gaps by combining RNA microscopy and subcellular proximity proteomics to study the functional contribution of RNA localization in digestive epithelia. Our project will comprehensively map the subcellular space across three adult epithelial tissues – liver, jejunum, and colon. To elucidate the mechanisms that mediate sequence-specific mRNA transport and maintain localization, we will develop a system to tether a construct for proximity proteomics to localized RNAs. We will functionally test the contribution of RNA localization to tissue homeostasis and disease development by disrupting the localizing elements and machinery.

Our novel toolkit will enable the spatial mapping of RNA and proteins in parallel, allowing us to annotate the subcellular space and subsequently probe the biological significance of this fundamental process in adult epithelia. This novel technology can be extended to the subcellular study of all epithelia and tissues in general; it will ultimately lead to a more comprehensive understanding of tissue function in homeostasis and disease.

Link to the ERC project webpage:

Keywords of the ERC project: Systems biology, RNA localization, smFISH, proximity biotinylation, spatial transcriptomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: Computational biologist, bioinformatician, microscopy expert

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**949808**	**COSI**	**LS3** Cellular and Developmental Biology

Principal Investigator:	**Dr Inge De Clercq**
Host Institution:	Vib - BEL

Understanding organelle communication through contact sites in plant stress responses

To be able to suTo be able to survive constantly changing and often harmful environmental conditions, plants must continuously adapt. Therefore, plants have complex mechanisms that sense and transduce environmental stimuli into adaptive responses. Organelles within the cell are thought to be important sensors and due to their tight integration into whole-cell metabolic and signalling networks, they are in a prime position to communicate stress signals and trigger adaptive responses. However, the mechanisms on how organelles convey stress signals remain poorly understood, especially in plants: "Which is the nature of the signals, how are they propagated and how are they perceived by other organelles?"

I have revealed a novel mechanism how mitochondria, chloroplasts, and the endoplasmic reticulum communicate stress signals to coordinate stress signal transduction into adaptive responses in the nucleus. My recent data provide novel leads that this coordination is mediated by organellar re-positioning and close association with each other. Therefore, I hypothesize that these organelles can associate directly through contact sites to enable fast and efficient communication of stress signals. Although inter-organellar contact sites have been studied in animal and yeast systems, mainly in the context of lipid transfer and calcium exchange, nearly nothing is known on their existence and mode of action in plants.

Understanding the mechanisms and functions of inter-organellar contact sites induced by stress is key in plant stress signalling research. To tackle this question, the COSI project will first identify stress-induced inter-organellar contact sites (SOCS) by means of high-end live-cell imaging and proteomics approaches, followed by their functional characterisation in plant stress responses.

The outcome of COSI is will be a better understanding, and potentially re-evaluation, of the fundamental mechanisms by which plants respond and adapt to stresses.

Link to the ERC project webpage: https://cordis.europa.eu/project/id/949808

Keywords of the ERC project: plant stress signaling, inter-organelle communication, pathogens, cell biology, proteomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: microscopy, cell biology, proteomics, organelle biology

Project ID:	Project Acronym:	Evaluation Panel:
		LS4
714922	**iGBMavatars**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Gaetano Gargiulo**
Host Institution:	Max Delbrueck Centrum Fuer Molekulare Medizin In Der Helmholtz-Gemeinschaft (Mdc) - DEU

Glioblastoma Subtype Avatar models for Target Discovery and Biology

The Glioblastoma Multiforme (GBM) is the most common primary brain tumor and it is incurable. Two major challenges affect GBM clinical management: its heterogeneity (which treatment will best fit this very patient?) and its resistance to available treatments (will the patient benefit in any way from the chosen therapy?). Here we approach these questions with a personalized entry point. First, we aim to create "humanized" experimental models of GBM accurately reflecting patients at molecular level. These GBM Subtype Avatars models (GSA) will be exploited as "targeted patients" in personalized biology and intervention studies. Since GBM exists as molecular subtypes with similar histopathology but mutually exclusive genetic lesions and molecular features, we will generate GSA by targeting mutations recurrently associated with Proneural, Classical or Mesenchymal GBM subtypes into adult human neural stem cells (NSC). Evidence supports that these cells can give rise to high-grade gliomas when engineered with the appropriate genetic lesions. Next, engineered NSC will be orthotopically implanted into immunocompromised rats and the resulting tumors profiled for gene expression, DNA methylation and copy number aberrations. These profiles will be compared to those generated in patient-derived xenografts and biopsies. Second, to identify drug targets favoring patients' response to the current standard of care, we will exploit GSA for state-of-art genetic screens in vivo. Specifically, we will seek for synthetic lethal interactions between DNA damaging agents and the GSA transcriptome using an in vivo CRISPRi screening approach. Third, to investigate the molecular basis of GBM heterogeneity in GSA models, we will combine genetic and immunophenotypic tracing with gene expression and epigenomic profiling. Identifying tumor-specific vulnerabilities in a dismal disease urging for effective therapies and its molecular fingerprinting convey conceivably rapid Translation in Oncology.

Link to the ERC project webpage:

Keywords of the ERC project: animal models fidelity, integrative data analysis, transcriptional states, functional genomics, synthetic biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: computational biology, bioinformatics, omics, scRNA-seq, integrative data analysis, dimensionality reduction

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency — Established by the European Commission	**759006**	**TRANSREG**	**LS4** Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Ataman Sendoel**
Host Institution:	Universitaet Zuerich - CHE

Dissecting the role of Translational Regulation in Tumorigenesis

The control of translation is a key determinant of protein abundance, which in turn defines cellular states. The impact of translational regulation may be even greater during the transition from homeostasis to malignancy, as revealed by the surprisingly low correlations between mRNA and protein levels in human cancer databases. This raises the intriguing possibility that through an ability to generate aberrant downstream networks of translational regulators, oncogenic drivers might impose altered protein synthesis programs that become the driving force for tumor formation and malignant progression.

We recently unveiled a hitherto unappreciated role for upstream open reading frame (uORF) translation in tumorigenesis and unearthed a novel switch from conventional EIF2 initiation factor-mediated to alternative EIF2A-mediated uORF translation. These observations suggest that uORFs constitute an exciting new frontier in the field of translational regulation with the potential to fundamentally impact cellular fate.

Here, I propose to systematically analyze the function of uORFs during tumorigenesis. First, we will conduct an in vivo CRISPR/CAS9-based screen in mice to elucidate the role of thousands of uORFs in development, differentiation and upon oncogenic transformation. Second, focusing on select uORFs surfacing in the screen, we will document their role during tumor initiation and progression. Third, we will develop novel tools to detect uORF translation in vivo, exploit them to monitor uORF translation during different stages of tumorigenesis, gain mechanistic insight into their function and finally test the relevance of these findings in human cancer. Collectively, these approaches will provide unprecedented and comprehensive insight into the function of uORFs, unravel new paradigms in the control of gene expression and expose novel strategies for cancer diagnostics and treatment.

Link to the ERC project webpage:

Keywords of the ERC project: translational control, cancer, stem cells, CRISPR screening

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS4
	759248	**MODVASC**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Konstantinos Stellos**
Host Institution:	University Of Newcastle Upon Tyne - GBR

Endothelial RNA Modifications in Vascular Homeostasis and Disease

Endothelial cells cover the entire arterial and venous tree, and play a pivotal role in vascular and organ homeostasis. In general, cardiovascular risk factors induce endothelial cell activation towards a pro-inflammatory phenotype leading to atherosclerosis, a major cause of mortality in the Western world. Understanding the mechanisms that orchestrate endothelial cell functions and response to environmental stimuli is essential for the discovery and development of novel biomarkers and therapeutic strategies in vascular disease.

RNA base modifications increase the RNA alphabet from the 4 canonical nucleotides to more than 140. Adenosine methylation at the N6 position (m6A) is the most prevalent RNA modification in eukaryotic mRNA and is catalyzed by a multiprotein methyltransferase complex. Accumulating recent evidence suggests that m6A RNA methylation is a critical posttranscriptional regulator of RNA metabolism. In preliminary unpublished work we have identified methylated RNA targets, which may critically regulate endothelial cell functions. Since the impact of m6A RNA methylation on vascular function is completely unknown, MODVASC aims to explore the role of m6A RNA methylation in vascular growth, homeostasis and disease. By m6A-RNA immunoprecipitation followed by RNA-sequencing we will identify the transcriptome-wide m6A RNA methylation in endothelial cells under basal and stress conditions. With the help of advanced molecular biology and biochemical methods, we will describe in single nucleotide level the impact of m6A RNA methylation on mRNA fate and RNA-protein interactions and define its functional consequences in endothelial cell functions. In vivo studies will consolidate the impact of endothelial RNA methylation on vascular growth and homeostasis as well as its contribution to atherosclerosis. Finally, MODVASC will evaluate the clinical relevance of our findings in patients with cardiovascular disease.

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

Keywords of the ERC project: RNA modifications, endothelial cell biology, cardiovascular disease, atherosclerosis, RNA metabolism

Keywords that characterize the scientific profile of the potential visiting researcher/s: RNA biology or vascular biology

	Project ID:	Project Acronym:	Evaluation Panel:
			LS4
	773208	**ImmunoFit**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Massimiliano Mazzone**
Host Institution:	Vib - BEL

Harnessing tumor metabolism to overcome immunosupression

Anti-cancer immunotherapy has provided patients with a promising treatment. Yet, it has also unveiled that the immunosuppressive tumor microenvironment (TME) hampers the efficiency of this therapeutic option and limits its success. The concept that metabolism is able to shape the immune response has gained general acceptance. Nonetheless, little is known on how the metabolic crosstalk between different tumor compartments contributes to the harsh TME and ultimately impairs T cell fitness within the tumor.

This proposal aims to decipher which metabolic changes in the TME impede proper anti-tumor immunity. Starting from the meta-analysis of public human datasets, corroborated by metabolomics and transcriptomics data from several mouse tumors, we ranked clinically relevant and altered metabolic pathways that correlate with resistance to immunotherapy. Using a CRISPR/Cas9 platform for their functional in vivo selection, we want to identify cancer cell intrinsic metabolic mediators and, indirectly, distinguish those belonging specifically to the stroma. By means of genetic tools and small molecules, we will modify promising metabolic pathways in cancer cells and stromal cells (particularly in tumor-associated macrophages) to harness tumor immunosuppression. In a mirroring approach, we will apply a similar screening tool on cytotoxic T cells to identify metabolic targets that enhance their fitness under adverse growth conditions. This will allow us to manipulate T cells ex vivo and to therapeutically intervene via adoptive T cell transfer. By analyzing the metabolic network and crosstalk within the tumor, this project will shed light on how metabolism contributes to the immunosuppressive TME and T cell maladaptation. The overall goal is to identify druggable metabolic targets that i) reinforce the intrinsic anti-tumor immune response by breaking immunosuppression and ii) promote T cell function in immunotherapeutic settings by rewiring either the TME or the T cell itself.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS4
	787171	**Police**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Andreas Villunger**
Host Institution:	Medizinische Universitat Innsbruck - AUT

The PIDDosome in Centrosome and Ploidy-Surveillance

Tight control of the number of chromosome sets in a cell (ploidy) is fundamental for normal development and organismal health. Most cells in our body are diploid, yet, some cells, including cardiomyocytes or hepatocytes require a balanced increase in ploidy for proper function. Polyploidization is accompanied by an accumulation of centrosomes, structures needed for nucleating the mitotic spindle and ciliogenesis. Extra centrosomes, however, promote aneuploidy in proliferating cells by causing errors in chromosome segregation, underlying a series of human pathologies, most notably cancer and premature ageing. How polyploidization is controlled in organogenesis and how errors in ploidy control contribute to disease is poorly understood.

We recently demonstrated that the "PIDDosome" complex polices centrosome numbers in mammalian cells, alerting the tumor suppressor p53 in response to extra centrosomes. This is achieved by inactivating MDM2, the key-inhibitor of p53, by targeted proteolysis. MDM2-processing is mediated by caspase-2, a neglected member in a protease family that controls cell death and inflammation, activated in the PIDDosome.

This exciting finding allows examining the consequences of deregulated ploidy and centrosome number in development and disease without interfering with p53, nor the cell fusion or cytokinesis machineries. This puts us in pole position to carry out an integrative study that aims to develop the PIDDosome as a new therapeutic target in cancer, related inflammation and in regenerative medicine. To meet this aim, we will define

(i) the relevance of the PIDDosome in aneuploidy tolerance of cancer

(ii) the role of the PIDDosome in controlling sterile inflammation and immunity

(iii) the PIDDosome as a key-regulator of organ development and regeneration

POLICE will open new lines of research at the interface of cell cycle, cell death & inflammation control and promote the PIDDosome as new target in our efforts to improve human health.

Link to the ERC project webpage:

Keywords of the ERC project:

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

SIGNALING PROPENSITY IN THE MICROENVIRONMENT OF B CELL CHRONIC LYMPHOCYTIC LEUKEMIA

B cell chronic lymphocytic leukemia (CLL) is the most frequent leukemia in adults. CLL cells are characterized by their universal dependency on pro-survival and pro-proliferative signals from immune niches. To achieve this they constantly re-circulate between blood and lymph nodes, which is inhibited by novel microenvironment-targeting therapies such as "BCR inhibitors". We aim to reveal how the malignant B cells change the propensity of their signalling pathways in response to the different microenvironments such as peripheral blood vs lymph node to obtain the proliferative signals. This is of major relevance for CLL, but also transferable to the biology of some other B cell malignancies and/or normal B cells. We analyzed the "finger print" of microenvironmental interactions in many CLL samples at various times during the disease course or during therapy. The obtained data led us to hypothesize on the mechanisms of regulation of signalling propensity of two pathways that are responsible for proliferation and survival of CLL cells, namely B Cell Receptor (BCR) signalling and signals from T-cells mediated by CD40/IL4. In aim 1 we hypothesize that CD20 is one of the key proteins involved in CLL cell activation, and influences BCR and interleukin signalling (see figure). This has important therapeutic implication since CD20 is used as a therapeutic target for 20 years (rituximab), but its function in CLL/normal B cells is unknown. In aim 2 we hypothesize that miR-29 acts a key regulator of T-cell signalling from CD40 and down-stream NFkB activation (see figure). This represents the first example of miRNAs' role in the propensity of T-cell interaction, and could be also utilized therapeutically. In aim 3 we will integrate our data on microenvironmental signaling (aim 1+2) and develop a first mouse model for PDX that would allow stable engraftment of primary CLL cells. Currently, CLL is non-transplantable to any animal model which complicates studies of its biology.

Link to the ERC project webpage:

Keywords of the ERC project: CLL, BCR signalling, T cell signalling, microRNA, ncRNA, B cells

Keywords that characterize the scientific profile of the potential visiting researcher/s: CLL, BCR signalling, T cell signalling, microRNA, ncRNA, B cells

Project ID:	Project Acronym:	Evaluation Panel:
		LS4
802825	**EnDeCAD**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Minna Kaikkonen-Määttä**
Host Institution:	Ita-Suomen Yliopisto - FIN

Enhancers Decoding the Mechanisms Underlying CAD Risk

In recent years, genome-wide association studies (GWAS) have discovered hundreds of single nucleotide polymorphisms (SNPs) which are significantly associated with coronary artery disease (CAD). However, the SNPs identified by GWAS explain typically only small portion of the trait heritability and vast majority of variants do not have known biological roles. This is explained by variants lying within noncoding regions such as in cell type specific enhancers and additionally 'the lead SNP' identified in GWAS may not be the 'the causal SNP' but only linked with a trait associated SNP. Therefore, a major priority for understanding disease mechanisms is to understand at the molecular level the function of each CAD loci. In this study we aim to bring the functional characterization of SNPs associated with CAD risk to date by focusing our search for causal SNPs to enhancers of disease relevant cell types, namely endothelial cells, macrophages and smooth muscle cells of the vessel wall, hepatocytes and adipocytes. By combination of massively parallel enhancer activity measurements, collection of novel eQTL data throughout cell types under disease relevant stimuli, identification of the target genes in physical interaction with the candidate enhancers and establishment of correlative relationships between enhancer activity and gene expression we hope to identify causal enhancer variants and link them with target genes to obtain a more complete picture of the gene regulatory events driving disease progression and the genetic basis of CAD. Linking these findings with our deep phenotypic data for cardiovascular risk factors, gene expression and metabolomics has the potential to improve risk prediction, biomarker identification and treatment selection in clinical practice. Ultimately, this research strives for fundamental discoveries and breakthrough that advance our knowledge of CAD and provides pioneering steps towards taking the growing array of GWAS for translatable results.

Link to the ERC project webpage:

Keywords of the ERC project: cardiovascular, gene regulation, atherosclerosis, enhancer, genetics

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

Project ID:	Project Acronym:	Evaluation Panel:
		LS4
803526	**Barinafld**	Physiology, Pathophysiology and Endocrinology

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

Using Bariatric Surgery to Discover Weight-Loss Independent Mechanisms Leading to the Reversal of Fatty Liver Disease

Non-Alcoholic Fatty Liver Disease (NAFLD), a disease characterized by accumulation of lipid droplets in the liver, is the major precursor for liver failure and liver cancer, and constitutes a global health challenge. An estimated 25% of the adult population suffers from NAFLD, but no FDA approved drugs are available to treat this condition. Obesity is a major NAFLD risk factor and weight-loss improves disease severity in obese patients. Bariatric surgeries are an effective treatment for obesity when lifestyle modifications fail and often lead to improvement in NAFLD and type 2 diabetes.

The overreaching objective of this proposal is to combine bariatric surgery in mice and humans with advanced molecular and computational analyses to discover novel, weight-loss independent mechanisms that lead to NAFLD alleviation, and harness them to treat NAFLD.

In preliminary studies, I discovered that bariatric surgery clears lipid droplets from the livers of obese db/db mice without inducing weight-loss. Using metabolic and computational analysis, I found that bariatric surgery shifts hepatic gene expression and blood metabolome of post-bariatric patients to a new trajectory, distinct from lean or sick patients. Data analysis revealed the transcription factor Egr1 and one-carbon and choline metabolism to be key drivers of weight-loss independent effects of bariatric surgery.

I will use two NAFLD mouse models that do not lose weight after bariatric surgery to characterize livers of mice post-surgery. Human patients do lose weight following surgery, therefore I will use computational methods to elucidate weight-independent pathways induced by surgery, by comparing livers of lean patients to those of NAFLD patients before and shortly after bariatric surgery. Candidate pathways will be studied by metabolic flux analysis and manipulated genetically, with the ultimate goal of reaching systems-levels understanding of NAFLD and identifying surgery-mimetic therapies for this disease.

<u>Link to the ERC project webpage:</u>

<u>Keywords of the ERC project:</u> Obesity, nafld, systems

<u>Keywords that characterize the scientific profile of the potential visiting researcher/s:</u> Obesity, nafld, systems

	Project ID:	Project Acronym:	Evaluation Panel:
	804135	**INVADERS**	**LS4** Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Benoit Chassaing**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale (Inserm) - FRA

Mucus-Penetrating Microbiota: Characterization, Mechanism and Therapeutic in Metabolic Disease

Mucus-Penetrating Microbiota: Characterization, Mechanism and Therapeutic in Metabolic Disease

Humanity is facing an epidemic of inter-related metabolic disorders, including obesity, insulin resistance, hyperglycemia, hyperlipidemia, and hepatic steatosis, that altogether have major impact on the promotion of cardiovascular diseases. The increasing incidence of these complex metabolic disorders and their highly morbid, chronic and costly downstream diseases threatens to overwhelm the world's health care systems and economies, making it a top public health priority in dire need of investigation.

The intestinal tract is inhabited by a large and diverse community of bacteria, collectively referred to as the intestinal microbiota. When stably maintained at an appropriately safe distance from the epithelial cell monolayer, the microbiota provides important benefits to its host. However, disturbance of the microbiota-host relationship, promoted by genetic or non-genetic factors, can alter intestinal homeostasis and drive chronic low-grade intestinal inflammation, ultimately leading to metabolic abnormalities. We previously reported that a ubiquitous class of food additives, emulsifiers, detrimentally impact the microbiota resulting in its encroachment into the mucus layer that associated with low-grade inflammation and development of metabolic disorders.

The central goal of this proposal is to investigate the hypothesis that bacteria that penetrate the inner part of the mucus layer, referred as invaders, promote development of metabolic alterations.

We herein propose to identify mucus-invaders, in preclinical models and clinical conditions, and investigate mechanisms by which they promote inflammatory and metabolic abnormalities. Furthermore, we propose to define original approaches to modulate the intestinal microbiota in order to counteract microbiota encroachment and protect against associated metabolic abnormalities.

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

Keywords of the ERC project: Microbiota, Inflammation, Mucus

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

	Project ID:	Project Acronym:	Evaluation Panel:
	805225	**VESSEL CO-COPTION**	**LS4** Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Giorgio Seano**
Host Institution:	Institut Curie - FRA

Vessel co-option and radioresistance in glioblastoma

Glioblastoma (GBM) is one of the deadliest types of human cancer. Despite a very aggressive treatment regime – including resection of the tumor, radiation and chemotherapy – its estimated recurrence rate is more than 90%. Recurrence is mostly caused by the regrowth of highly invasive cells spreading from the tumor bulk, which are not removed by resection. To develop an effective therapeutic approach, we need to better understand the underlying molecular mechanism of radiation resistance and tumor spreading in GBM.

Radioresistance in GBM is attributed to glioma stem cells (GSCs), a fraction of perivascular, self-renewing, multipotent and tumor-initiating cells. Growing evidence highlights the perivascular space as a niche for GSC survival, resistance to therapy, progression and dissemination. The unknown factor is the dynamics of GSCs, how they end up in the vascular niche and how this impacts on radioresistance.

My overall hypothesis is that GSCs reach the perivascular niche through vessel co-option - the directional migration of tumor cells towards vessels - and that targeting vessel co-option has the potential to radiosensitize GBM.

With this project, we aim to uncover the exact molecular and cellular connections among vessel co-option, GSCs, the vascular niche and radioresistance. Using multiple strategies, such as multiphoton intravital microscopy, orthotopic models of GBM, organotypic cultures, screenings and survival studies, we will investigate and mechanistically change the dynamics of GSC and differentiated GBM cells in order to understand the role of their interaction with brain vessels and whether this confers resistance to radiotherapy.

These studies will provide clinically relevant insights into the involvement of GSCs, the vascular niche and vessel co-option in the resistance of GBM to therapy. Since all GBM patients receive radiotherapy, many would benefit from therapeutic strategies aimed at increasing its efficacy.

Link to the ERC project webpage:

Keywords of the ERC project: Glioblastoma; tumor vasculature; plasticity; vessel co-option; resistance mechanisms

Keywords that characterize the scientific profile of the potential visiting researcher/s: Glioblastoma; tumor vasculature; plasticity; vessel co-option; resistance mechanisms

	Project ID:	Project Acronym:	Evaluation Panel:
	819543	**MetaboSENS**	**LS4** Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Ganna Panasyuk**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale (Inserm) - 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, metabolism, signal transduction, rare diseases

Keywords that characterize the scientific profile of the potential visiting researcher/s: open to all passionate scientists, interdisciplinary knowledge, insatiable curriosity, expertise in codding and omics analyses (optional)

Project ID:	Project Acronym:	Evaluation Panel:
		LS4
819600	**FIRM**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Michelangelo Campanella**
Host Institution:	The Royal Veterinary College - GBR

Form and Function of the Mitochondrial Retrograde Response

The molecular communication between mitochondria and nucleus is an integrated bi-directional crosstalk - anterograde (nucleus to mitochondria) and retrograde (mitochondria to nucleus) signalling pathways. The mitochondrial retrograde response (MRR) is driven by defective mitochondrial function, which increases cytosolic reactive oxygen species (ROS) and Ca2+. Metabolic reprogramming is a key feature in highly proliferative cells to meet the energy needs for rapid growth by generating substrates for cellular biogenesis. In these mitochondria retro-communicate with the nucleus to induce wide-ranging cytoprotective effects exploited to develop resistance against treatment and sustain uncontrolled growth. Recently, the mitochondrial management of cholesterol-derived intermediates for the synthesis of steroids has been demonstrated as a determinant in the oncogenic reprogramming of cellular environment.

We hypothesise that cholesterol-enriched domains facilitate the communication between remodelled mitochondria and nucleus to expedite MRR. This mechanism may be exploited during abnormal cell growth in which cholesterol metabolism and associated molecules are increased.

This application capitalizes on expertise in cell signalling and metabolism to interrogate core pathways and unveil molecular sensors and effectors that define form and function of the MRR by:

I. Elucidating the mechanism of metabolic regulation of MRR, describing the role exerted by cholesterol trafficking;

II. Unveiling microdomains for mito-nuclear communication established by remodelled, autophagy escaped, mitochondria;

III. Validating protocols to modulate and target MRR for diagnostic and therapeutic benefit;

The experimental plan will (i) define a molecular signalling axis that currently stands uncharacterized, (ii) provide mechanistic knowledge for preventive, and (iii) therapeutic applications to counteract deficiencies associated with stressed, dysregulated mitochondria.

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

Keywords of the ERC project: Mitochondria, Nucleus, Autophagy, Cholesterol and Contact Sites

Keywords that characterize the scientific profile of the potential visiting researcher/s: Dynamic, Enthusiastic, Daring in challenging the status quo of biomedicine

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: Ion channel, electrophysiology, cardiac arrhythmia

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**852742**	**PROTEOFIT**	**LS4** Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Alexander Bartelt**
Host Institution:	Ludwig-Maximilians-Universitaet Muenchen - DEU

Adapting protein fate for muscle function and fitness

Muscle function is essential for motion, exercise, and shivering, whereas physical inactivity is causally related to reduced metabolic fitness in animal models and humans. A critical requirement for muscle function is that proteins are properly produced and, if necessary, degraded to adapt the proteome to meet metabolic demands. However, there is a fundamental, open gap in understanding how challenges to muscle proteostasis are sensed and how protein fate is subsequently adapted to enhance muscle function in exercise or, conversely, how it is compromised in obesity. I hypothesize that protein fate is highly adaptive and can be fine-tuned to promote proteostasis, the integrity of muscle cells, and metabolic health. Identifying novel key regulators of these mechanisms in muscle may hold great therapeutic promise for targeting metabolic fitness to combat obesity and associated disorders. In this innovative project I want to define new mechanisms of muscle adaptation in humans and preclinical mouse models, with the ultimate goal of using this knowledge to improve muscle function and fitness in obesity. I will identify exercise- and obesity-specific substrates of the proteasome by ubiquitomics in human and mouse muscle and define how the ubiquitination and turnover of these proteins dictates muscle cell function. In a complementary approach, I will use novel loss- and gain-of-function mouse models allowing for precise muscle-specific manipulation of Nfe2l1, an adaptive regulator of proteasomal protein degradation, to define the biological and therapeutic significance of this pathway for muscle function in exercise and obesity. In summary, this novel work will provide a transformative molecular understanding of muscle adaption to metabolic challenges and provide insight into how this translates into metabolic fitness and the development of obesity and associated disorders in humans.

Link to the ERC project webpage: www.kreislaufinstitut.de

Keywords of the ERC project: Proteostasis, energy metabolism, exercise, obesity

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

Project ID:	Project Acronym:	Evaluation Panel:
852761	**ONco-Energetics_OFF**	**LS4** Physiology, Pathophysiology and Endocrinology

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:

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

Project ID:	Project Acronym:	Evaluation Panel:
		LS4
864522	**Retina Rhythm**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Matthew Campbell**
Host Institution:	The Provost, Fellows, Foundation Scholars & The Other Members Of Board Of The College Of The Holy & Undivided Trinity Of Queen Elizabeth Near Dublin - IRL

Investigating the role of the inner retina in age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is the leading cause of irreversible central blindness in the world. The number of people with AMD is predicted to be 196 million by 2020, with an estimated 1 in 10 people over the age of 55 already showing early signs of the condition. Identifying those individuals at greater risk of disease progression is challenging and robust animal models of disease are delaying the development of therapeutics.

We have recently discovered that the blood vessels of the inner retina are highly dynamic and our data suggest that they play a central role in AMD development. I hypothesize, in contrast to studies to date, that the inner retina may be critical to the early stages of AMD onset. We have discovered that circadian regulation of the inner blood-retina barrier (iBRB) allows for replenishment and renewal of components of photoreceptor outer segments on a daily basis by a process we have termed Retinal Interstitial Kinesis (RIK).

Here, I propose that circadian mediated regulation of the inner retinal blood vessels is paramount in the early stages of AMD pathology. Our preliminary data suggests that circadian-mediated changes in the permeability of the iBRB can lead to an AMD-like phenotype in mice and non-human primates. I propose that re-establishing the dynamic cycling of the iBRB may represent a novel therapeutic strategy for the prevention and treatment of AMD.

Over the next 5 years, the central aims of Retina-Rhythm are to:

1. Develop and characterize newly established mouse and non-human primate models of AMD by disrupting circadian cycling of the iBRB.

2. Develop a novel AAV based vector with the ability to re-establish dynamic circadian cycling of the iBRB and treat AMD.

3. Prove that dysregulated circadian-mediated iBRB cycling mediates AMD pathology in human subjects.

Our goal: To determine the key early initiators of AMD and to develop the next generation of therapies for this devastating form of blindne

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS4
	866240	**EXPLOSIA**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Jacob Fog 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: bentzonlab.org

Keywords of the ERC project: atherosclerosis, smooth muscle cells

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS4
	949017	**StopWaste**	Physiology, Pathophysiology and Endocrinology

Principal Investigator:	**Dr Maria Rohm**
Host Institution:	Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Targeting the crosstalk of lipid and glucose metabolism to stop cancer-associated wasting

Cachexia is the deadly outcome of many late stage cancers. It is characterized by severe wasting of adipose tissue and muscle mass, cardiac dysfunction and systemic inflammation. To date, no prognostic biomarker or efficient treatment against wasting is available, and ultimately 30% of all patients with cancer will die of cachexia. Hence, we have the critical unmet and urgent medical need of developing novel biomarkers and treatment options.

Until now, research has focused on targeting either tumor-derived secreted proteins or specific aspects of organ dysfunction such as muscle atrophy. StopWaste builds on recent advances of my group in targeting adipose tissue malfunction in cachexia. My current data support the new concept that tumors activate futile substrate cycling in adipocytes, which leads to an energy crisis that drives systemic metabolic dysfunction. Interestingly, similar to obesity, perturbed adipose tissue in cachexia causes the increased release of bioreactive signaling lipids such as C16:0 ceramides which appear before any wasting occurs. My recently established state-of-the-art multi-omics workflow to trace substrate cycling paired with the functional and clinical readouts of cachexia present in my lab now enable me to identify the molecular origin of these cycles and their impact on systemic metabolism. Using my established cell culture systems and multiple cachexia mouse models as well as patient samples, I will investigate (1) the origin of the altered circulating lipids and their potential as early cachexia biomarkers, (2) if they derive from perturbed adipocytes by futile cycling, and (3) if they drive insulin resistance which, in combination with the as-yet unknown tumor-islet axis I have identified, aggravates catabolism by lack of insulin anabolic signaling. In summary, StopWaste addresses the interplay of glucose and lipid metabolic pathways that lead to cachexia, providing for the first time a holistic signature of wasting metabolism.

Link to the ERC project webpage:

Keywords of the ERC project: cachexia, metabolism, tissue crosstalk

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**758604**	**ENTRAINER**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Rafael Polania**
Host Institution:	Eidgenoessische Technische Hochschule Zurich - CHE

Enhancing brain function and cognition via artificial entrainment of neural oscillations

Neural oscillations are ubiquitous in the human brain and have been implicated in diverse cognitive functions to support both neural communication and plasticity. Their functional relevance is further supported by a large number of studies linking various cognitive deficits (e.g., attention deficit hyperactivity disorder, ADHD) with abnormal neural oscillations. However, this field of research faces two important problems: First, there is only correlative, but no causal evidence linking cognitive deficits to abnormal neural oscillations in humans. Second, there is virtually no theory-driven mechanistic approach that generates insights into how oscillations within and across neural networks are linked to human behavior. In this project, I propose to take decisive steps to provide a long-needed neurophysiological characterization—via (1) computational modelling, (2) electrophysiological measures, and (3) novel non-invasive manipulations of cortical rhythms—on how neural oscillations contribute to two types of cognitive processes that are fundamental for many aspects of human behavior: attention and short-term memory. I will go a step further by demonstrating that it is possible to augment performance in these cognitive functions with the design of non-invasive brain stimulation protocols individually tailored to the theory-driven neurocomputational characterizations and electrophysiological signatures of each individual. This will result in the applied goal of deriving new neuro-computational assays that can detect deviant network interactions causally related to cognitive functions, which is key for then renormalizing those functions in neuropsychological conditions such as ADHD. Thus, if successful, my proposed work will ultimately result in novel, low-cost, and painless non-invasive neural interventions for a wide range of neuropsychological disorders tied to abnormal neural oscillations.

Link to the ERC project webpage: https://decision.ethz.ch/

Keywords of the ERC project: Decision making, computational neuroscience, brain stimulation

Keywords that characterize the scientific profile of the potential visiting researcher/s: Decision making, computational neuroscience, brain stimulation

Project ID:	Project Acronym:	Evaluation Panel:
770244	**CMTaaRS**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Erik Storkebaum**
Host Institution:	Stichting Katholieke Universiteit - NLD

Defective protein translation as a pathogenic mechanism of peripheral neuropathy

Familial forms of neurodegenerative diseases are caused by mutations in a single gene. It is unknown whether distinct mutations in the same gene or in functionally related genes cause disease through similar or disparate mechanisms. Furthermore, the precise molecular mechanisms underlying virtually all neurodegenerative disorders are poorly understood, and effective treatments are typically lacking.

This is also the case for Charcot-Marie-Tooth (CMT) peripheral neuropathy caused by mutations in five distinct tRNA synthetase (aaRS) genes. We previously generated Drosophila CMT-aaRS models and used a novel method for cell-type-specific labeling of newly synthesized proteins in vivo to show that impaired protein translation may represent a common pathogenic mechanism.

In this proposal, I aim to determine whether translation is also inhibited in CMT-aaRS mouse models, and whether all mutations cause disease through gain-of-toxic-function, or alternatively, whether some mutations act through a dominant-negative mechanism. In addition, I will evaluate whether all CMT-aaRS mutant proteins inhibit translation, and I will test the hypothesis, raised by our unpublished preliminary data shown here, that a defect in the transfer of the (aminoacylated) tRNA from the mutant synthetase to elongation factor eEF1A is the molecular mechanism underlying CMT-aaRS. Finally, I will validate the identified molecular mechanism in CMT-aaRS mouse models, as the most disease-relevant mammalian model.

I expect to elucidate whether all CMT-aaRS mutations cause disease through a common molecular mechanism that involves inhibition of translation. This is of key importance from a therapeutic perspective, as a common pathogenic mechanism allows for a unified therapeutic approach. Furthermore, this proposal has the potential to unravel the detailed molecular mechanism underlying CMT-aaRS, what would constitute a breakthrough and a requirement for rational drug design for this incurable disease.

Link to the ERC project webpage: https://www.ru.nl/donders/research/theme-2-perception-action-control/research-groups-theme-2/molecular-neurobiology

Keywords of the ERC project: motor neuron degeneration; mRNA translation; peripheral neuropathy; Drosophila and mouse genetics

Keywords that characterize the scientific profile of the potential visiting researcher/s: interest in motor neuron degeneration; experience with Drosophila and/or mouse genetics

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

Deciphering deep architectures underlying structured perception in auditory networks

The principles of sensory perception are still a large experimental and theoretical puzzle. A strong difficulty is that perception emerges from networks of recurrently connected brain areas whose activity and function are poorly approximated by current generic mathematical models. These models also fail to explain many of the fundamental structures effortlessly identified by the brain (shapes, objects, auditory or tactile categories). I here propose to establish a new approach combining high-throughput population recoding methods with a tailored theoretical framework to derive computational principles operating throughout sensory systems and leading to biologically structured perception. This approach follows on the recent mathematical proposal, suggested by Deep Machine Learning methods, that complex perceptual objects emerge through series of simple nonlinear operations combining increasingly complex sensory features along the sensory pathways. Starting with the mouse auditory system as a model pathway, we will recursively extract, with model-free methods, the main nonlinear sensory features encoded in genetically tagged output and local neurons at different processing stages, using optical and electrophysiological high density recording techniques in awake animals. The role of these features in perception will be identified with behavioural assays. Specific intra- and interareal feedback connections, typically not included in Deep Leaning models, will be opto- and chemogenetically perturbed to assess their contribution to precise nonlinearities of the system and their role in the emergence of complex perceptual structures. Based on these structural, functional and perturbation data, a new generation of well-constrained and predictive sensory processing models will be built, serving as a platform to extract general computational principles missing to link neural activity to perception and to fuel artificial neural networks technologies.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**770951**	**CLAUSTRUM**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Ami Citri**
Host Institution:	The Hebrew University Of Jerusalem. - ISR

The Claustrum: A Circuit Hub for Attention

Our senses face a constant barrage of information. Hence, understanding how our brain enables us to attend to relevant stimuli, while ignoring distractions, is of increasing biomedical importance. Recently, I discovered that the claustrum, a multi-sensory hub and recipient of extensive neuromodulatory input, enables resilience to distraction.

In my ERC project, I will explore the mechanisms underlying claustral mediation of resilience to distraction and develop novel approaches for assessing and modulating attention in mice, with implications for humans. Transgenic mouse models that I identified as enabling selective access to claustral neurons overcome its limiting anatomy, making the claustrum accessible to functional investigation. Using this novel genetic access, I obtained preliminary results strongly suggesting that the claustrum functions to filter distractions by adjusting cortical sensory gain.

My specific aims are: 1) To delineate the mechanisms whereby the claustrum achieves sensory gain control, by applying in-vivo cell-attached, multi-unit and fiber photometry recordings from claustral and cortical neurons during attention-demanding tasks. 2) To discriminate between the functions of the claustrum in multi-sensory integration and implementation of attention strategies, by employing multi-sensory behavioral paradigms while modulating claustral function. 3) To develop validated complementary physiological and behavioral protocols for adjusting claustral mediation of attention via neuromodulation.

This study is unique in its focus and aims: it will provide a stringent neurophysiological framework for defining a key mechanism underlying cognitive concepts of attention, and establish a novel platform for studying the function of the claustrum and manipulating its activity. The project is designed to achieve breakthroughs of fundamental nature and potentially lead to diagnostic and therapeutic advances relevant to attention disorders.

Link to the ERC project webpage: citrilab.com

Keywords of the ERC project: Claustrum, systems neuroscience, attention

Keywords that characterize the scientific profile of the potential visiting researcher/s: systems neuroscience, slice physiology

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**772395**	**Acclimatize**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Jan Siemens**
Host Institution:	Universitatsklinikum Heidelberg - DEU

Hypothalamic mechanisms of thermal homeostasis and adaptation

Mammalian organisms possess the remarkable ability to maintain internal body temperature (Tcore) within a narrow range close to 37°C despite wide environmental temperature variations. The brain's neural "thermostat" is made up by central circuits in the hypothalamic preoptic area (POA), which orchestrate peripheral thermoregulatory responses to maintain Tcore. Thermogenesis requires metabolic fuel, suggesting intricate connections between the thermoregulatory centre and hypothalamic circuits controlling energy balance. How the POA detects and integrates temperature and metabolic information to achieve thermal balance is largely unknown. A major question is whether this circuitry could be harnessed therapeutically to treat obesity.

We have recently identified the first known molecular temperature sensor in thermoregulatory neurons of the POA, transient receptor potential melastatin 2 (TRPM2), a thermo-sensitive ion channel. I aim to use TRPM2 as a molecular marker to gain access to and probe the function of thermoregulatory neurons in vivo. I propose a multidisciplinary approach, combining local, in vivo POA temperature stimulation with optogenetic circuit-mapping to uncover the molecular and cellular logic of the hypothalamic thermoregulatory centre and to assess its medical potential to counteract metabolic syndrome.

Acclimation is a beneficial adaptive process that fortifies thermal responses upon environmental temperature challenges. Thermoregulatory neuron plasticity is thought to mediate acclimation. Conversely, maladaptive thermoregulatory changes affect obesity. The cell-type-specific neuronal plasticity mechanisms underlying these changes within the POA, however, are unknown.

Using ex-vivo slice electrophysiology and in vivo imaging, I propose to characterize acclimation- and obesity-induced plasticity of thermoregulatory neurons. Ultimately, I aim to manipulate thermoregulatory neuron plasticity to test its potential counter-balancing effect on obesity.

Link to the ERC project webpage: http://siemenslab.de/research/thermoregulation/

Keywords of the ERC project: neuroscience, hypothalamus, acclimatization, neuronal plasticity thermoregulation, homeostasis

Keywords that characterize the scientific profile of the potential visiting researcher/s: interest and expertise in: neuroscience, computational neuroscience, modeling, neuronal plasticity, synaptic physiology, circuit analysis

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**772452**	**nanoAXON**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr János Szabadics**
Host Institution:	Kirserleti Orvostudomanyi Kutatointezet - HUN

Nano-physiology of small glutamatergic axon terminals

We will reveal the neuronal mechanisms of fundamental hippocampal and axonal functions using direct patch clamp recordings from the small axon terminals of the major glutamatergic afferent and efferent pathways of the dentate gyrus region. Specifically, we will investigate the intrinsic axonal properties and unitary synaptic functions of the axons in the dentate gyrus that originate from the entorhinal cortex, the hilar mossy cells and the hypothalamic supramammillary nucleus. The fully controlled access to the activity of individual neuronal projections allows us to address the crucial questions how upstream regions of the dentate gyrus convey physiologically relevant spike activities and how these activities are translated to unitary synaptic responses in individual dentate gyrus neurons. The successful information transfers by these mechanisms ultimately generate specific dentate gyrus cell activity that contributes to hippocampal memory functions. Comprehensive mechanistic insights are essential to understand the impacts of the activity patterns associated with fundamental physiological functions and attainable with the necessary details only with direct recordings from individual axons. For example, these knowledge are necessary to understand how single cell activities in the entorhinal cortex (carrying primary spatial information) contribute to spatial representation in the dentate (i.e. place fields). Furthermore, because the size of these recorded axon terminals matches that of the majority of cortical synapses, our discoveries will demonstrate basic biophysical and neuronal principles of axonal signaling that are relevant for universal neuronal functions throughout the CNS. Thus, an exceptional repertoire of methods, including recording from anatomically identified individual small axon terminals, voltage- and calcium imaging and computational simulations, places us in an advantaged position for revealing unprecedented information about neuronal circuits.

Link to the ERC project webpage: http://szabadicslab.koki.hu/

Keywords of the ERC project: hippocampal circuit, voltage imaging, patch clamp, neurons, axons, action potentials, synaptic responses

Keywords that characterize the scientific profile of the potential visiting researcher/s: Voltron, GEVI, dentate gyrus

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency — Established by the European Commission	**786467**	**MiCaBra**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Giovanni Marsicano**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale (Inserm) - FRA

Mitochondrial Cannabinoid Receptors in the Brain

Brain activity critically depends on the high energetic support provided by mitochondria, the cell organelles transforming energy sources into molecularly usable ATP. The pathological effects of chronic mitochondrial dysfunctions in the brain are under scrutiny, but the impact of physiological modulation of mitochondrial activity on ongoing brain functions is almost unknown. Cannabinoid type-1 receptors (CB1) are amongst the G Protein-Coupled receptors (GPCR) expressed at highest levels in the brain, and they are key regulators of behaviour. We recently showed that CB1 receptors are present at brain mitochondrial membranes (mtCB1), where they regulate bioenergetic processes, thereby mediating amnesic effects of cannabinoids. Thus, the physiological roles of the brain endocannabinoid system formed by CB1 receptors and endogenous

ligands, and the pharmacological effects of cannabinoid drugs (e.g. the psychotropic compound of the plant cannabis sativa, Δ9-tetrahydrocannabinol) partially rely on the regulation of brain mitochondrial activity. Using a bottom-up approach at micro-, meso- and macro-scale levels, MiCaBra will reveal cell biological features, signalling properties and behavioural impact of mtCB1 receptors in the brain. First, we will address the cell biology of mtCB1 receptors, determining the structural and molecular requirements for their mitochondrial trafficking. To define how this GPCR modulate mitochondrial activity and what are the functional consequences of these effects, we will study downstream intra-mitochondrial signalling of mtCB1 receptors and the eventual impact on cellular processes controlled by the organelle. Finally, we will tackle the role of mtCB1 receptors in the (endo)cannabinoid control of brain circuits and behaviour. Thus, MiCaBra has the ambitious aim to understand the impact of regulation of bioenergetic processes on ongoing brain functions, thereby determining a novel framework in the study of behavioural pathophysiology.

Link to the ERC project webpage:

Keywords of the ERC project: Brain Mitochondria Cannabinoid Receptors Behavior Biochemistry, Electrophysiology, Brain Metabolism and Bioenergetics

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

	Project ID:	Project Acronym:	Evaluation Panel:
	789128	**Sensational Tethers**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Gary Lewin**
Host Institution:	Max Delbrueck Centrum Fuer Molekulare Medizin In Der Helmholtz-Gemeinschaft (Mdc) - DEU

Tethers for sensory mechanotransduction: from molecules to perception

Touch sensation is built upon the ability of sensory neurons to detect and transduce nanometer scale mechanical displacements. The underlying process has been termed mechanotransduction: the high sensitivity and speed of which is enabled by direct gating (opening) of ion channels by mechanical force. Force detection is functionally compartmentalized and only takes place at the peripheral endings of sensory neurons in vivo. Two molecules are known to be genetically necessary for touch in many sensory neurons, the force gated ion channel PIEZO2 and its modulator STOML3. However, mechanotransduction complexes in all touch receptors absolutely require tethering to the extracellular matrix for function. Tethering is dependent on large extracellular proteins that are sensitive to site-specific proteases. Here we will not only identify the nature of these tethers, but will develop technology to acutely and reversibly abolish tethers and other mechanotransducer components. We will use genome engineering to tag tether and mechanotranduction components in order to visualize and manipulate these proteins at their in vivo sites of action. By engineering de novo cleavage sites for site-specific proteases we will render tethers and ion channels newly sensitive to normally ineffective proteases in the skin. We will engineer mutations into candidate ion channels that dramatically alter biophysical properties to physiologgcally "mark" function in vivo. Finally we will develop new behavioural paradigms in mice that allow us to measure touch perception from the forepaw. Psychometric curves for different vibrotactile tasks can then be precisely compared between humans and mice. Furthermore, the impact of acute and reversible manipulation of mechanotransduction on touch perception can be measured. Understanding how molecules assemble to function in a mechanotransduction complex in the skin will open up avenues to develop therapeutic strategies to modulate touch.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Neural drivers of functional disconnectivity in brain disorders

A rapidly expanding approach to understanding neural organization is to map patterns of spontaneous neural activity as an index of functional communication and connectivity across brain regions. Fostered by the advent of neuroimaging methods like resting-state fMRI (rsfMRI), this approach has revealed that functional connectivity is almost invariably disrupted in severe psychiatric disorders, such as autism or schizophrenia. However, the neural basis of such functional disconnectivity remains mysterious. What drives brain-wide functional synchronization? And are there shared pathophysiological mechanisms leading to impaired large-scale neural coupling?

This project aims to elucidate the neural drivers of macroscale functional connectivity, as well as its breakdown in brain connectopathies. To achieve this goal, I propose a multi-scale perturbational approach to establish causal relationships between specific neural events and brain-wide functional connectivity via a novel combination of rsfMRI and advanced neural manipulations and recordings in the awake mouse.

By directionally silencing functional hubs as well as more peripheral cortical regions, I will provide a hierarchical description of spontaneous network organization that will uncover regional substrates vulnerable to network disruption. I will also manipulate physiologically-distinct excitatory or inhibitory populations to probe a unifying mechanistic link between excitatory/inhibitory imbalances and aberrant functional connectivity. Finally, to account for the hallmark co-occurrence of synaptic deficits and functional disconnectivity in developmental disorders, I will link cellular mechanisms of synaptic plasticity and learning to the generation of canonical and aberrant spontaneous activity patterns. These studies will pave the way to a back-translation of aberrant functional connectivity into interpretable neurophysiological events and models that can help understand, diagnose or treat brain disorders.

Link to the ERC project webpage:

Keywords of the ERC project: fMRI, mouse, optogenetics, chemogenetics, connectivity

Keywords that characterize the scientific profile of the potential visiting researcher/s: MRI, fMRI, computational neuroscience

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**802531**	**EvolutioNeuroCircuit**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Lucia Prieto Godino**
Host Institution:	The Francis Crick Institute Limited - GBR

Cellular and genetic bases of neural circuits evolution

Sensory systems encode the world around us to produce context-dependent appropriate behaviours. However, we know little about the way new sensory evoked behaviours arise as neural circuits are re-shaped during evolution. Tackling this question requires a deep understanding of the circuits underlying specific behaviours and integration of this knowledge with tools from other fields, including evolutionary and developmental biology. Recent technological advancements on neural circuit interrogation and genome editing have put progress on this fundamental biological question within reach.

The olfactory system of the larval stage of the fly Drosophila melanogaster and related species is an ideal model for investigating these questions because (i) D. melanogaster has pioneered both the fields of population genetics and neurogenetics and (ii) its olfactory system is one of the best-characterised neural circuits. We will address the question of how olfactory circuits evolve by studying four species with divergent odour-guided behaviours through the following multidisciplinary aims:

1. Which olfactory pathways are targeted in the evolution of ecological specialisation? – Combining high-throughput behavioural assays, optogenetics and calcium imaging in the larva of all four species we will determine whether/which olfactory pathways have switched valences or sensitivity.

2. How have central neural circuits diverged? – We will address this question at unprecedented resolution through whole-brain calcium imaging and serial electron microscopy reconstruction.

3. What are the molecular and genetic bases of neural circuits rewiring during evolution? – Using transcriptomic profiling we will identify differentially expressed genes in conserved and divergent circuits across species, and functionally probe selected candidates to establish causality.

4. How do evolutionary forces shape olfactory circuits? – We will investigate this question using field studies and population genetics

Link to the ERC project webpage: https://prietogodinolab.org/

Keywords of the ERC project: neural circuit, evolution, sensory ecology, behaviour, connectomics, live imaging

Keywords that characterize the scientific profile of the potential visiting researcher/s: neural circuit, evolution, sensory ecology, behaviour, connectomics, live imaging

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**803714**	**iGluRs - A New View**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Timothy Lynagh**
Host Institution:	Universitetet I Bergen - NOR

Exposing nature's view of ligand recognition in ionotropic glutamate receptors

Molecular biology strives for the prediction of function, based on the genetic code. Within neuroscience, this is reflected in the intense study of the molecular basis for ligand recognition by neurotransmitter receptors. Consequently, structural and functional studies have rendered a profoundly high-resolution view of ionotropic glutamate receptors (iGluRs), the archetypal excitatory receptor in the brain. But even this view is obsolete: we don't know why some receptors recognize glutamate yet others recognize other ligands; and we have been unable to functionally test the underlying chemical interactions. In other words, our view differs substantially from nature's own view of ligand recognition. I plan to lead a workgroup attacking this problem on three fronts. First, bioinformatic identification and electrophysiological characterization of a broad and representative sample of iGluRs from across the spectrum of life will unveil the diversity of ligand recognition in iGluRs. Second, phylogenetic analyses combined with functional experiments will reveal the molecular changes that nature employed in arriving at existing means of ligand recognition in iGluRs. Finally, chemical-scale mutagenesis will be employed to overcome previous technical limitations and dissect the precise chemical interactions that determine the specific recognition of certain ligands. With my experience in combining phylogenetics and functional experiments and in the use of chemical-scale mutagenesis, the objectives are within reach. Together, they form a unique approach that will expose nature's own view of ligand recognition in iGluRs, revealing the molecular blueprint for protein function in the nervous system.

Link to the ERC project webpage:

Keywords of the ERC project: Neurotransmitter Receptors, Ligand-gated Ion Channels

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

Principal Investigator:	**Dr Jan Gründemann**
Host Institution:	Universitaet Basel - CHE

Deep brain imaging of cellular mechanisms of sensory processing and learning

Learning and memory are the basis of our behaviour and mental well-being. Understanding the mechanisms of structural and cellular plasticity in defined neuronal circuits in vivo will be crucial to elucidate principles of circuit-specific memory formation and their relation to changes in neuronal ensemble dynamics.

Structural plasticity studies were technically limited to cortex, excluding deep brain areas like the amygdala, and mainly focussed on the input site (dendritic spines), whilst the plasticity of the axon initial segment (AIS), a neuron's site of output generation, was so far not studied in vivo. Length and location of the AIS are plastic and strongly affects a neurons spike output. However, it remains unknown if AIS plasticity regulates neuronal activity upon learning in vivo.

We will combine viral expression of AIS live markers and genetically-encoded $Ca2+$-sensors with novel deep brain imaging techniques via gradient index (GRIN) lenses to investigate how AIS location and length are regulated upon associative learning in amygdala circuits in vivo. Two-photon time-lapse imaging of the AIS of amygdala neurons upon fear conditioning will help us to track learning-driven AIS location dynamics. Next, we will combine miniature microscope imaging of neuronal activity in freely moving animals with two-photon imaging to link AIS location, length and plasticity to the intrinsic activity as well as learning-related response plasticity of amygdala neurons during fear learning and extinction in vivo. Finally, we will test if AIS plasticity is a general cellular plasticity mechanisms in brain areas afferent to the amygdala, e.g. thalamus.

Using a combination of two-photon and miniature microscopy imaging to map structural dynamics of defined neural circuits in the amygdala and its thalamic input areas will provide fundamental insights into the cellular mechanisms underlying sensory processing upon learning and relate network level plasticity with the cellular level.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**818996**	**DEVMEM**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Francesca Cacucci**
Host Institution:	University College London - GBR

Learning to remember: the development of the neural mechanisms supporting memory processing.

The ability to form and store memories allows organisms to learn from the past and imagine the future: it is a crucial mechanism underlying flexible and adaptive behaviour. The aim of this proposal is to identify the circuit mechanisms underlying our ability to learn and remember, by tracking the ontogenesis of memory processing. Importantly, we are not born with a fully functioning memory system: generally, adults cannot recollect any events from before their third birthday ('infantile amnesia'). There are several accounts as to the source of this mnemonic deficit, each placing emphasis on impairments of specific processes (encoding, consolidation, retrieval). However, a general weakness in the study of memory ontogeny is the lack of neural data describing the activity of memory-related circuits during development. To directly address this knowledge gap, we propose to study the ontogeny of brain-wide hippocampus-centred memory networks in the rat. We will study to which extent memory expression relies on spatial signalling, delineate the role of sleep in memory consolidation, determine how hippocampal planning-related neuronal activity influences memory processing, understand whether the rapid forgetting observed in development is due to interference, and explore interactions between the hippocampus, pre-frontal and striatal circuits in orchestrating memory emergence. We are best placed to deliver this ambitious experimental plan due to our extensive experience of in vivo recording in developing rats which we will couple with the application of recently emerged technologies (2-photon imaging, high density electrophysiology, chemogenetic manipulation of neural activity). As our studies of the development of hippocampal spatial representations have delivered powerful insights into their adult function, we expect the work outlined here to critically advance our understanding not only of development, but also of healthy memory processing in adulthood.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
819814	**RememberEx**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Bryan Strange**
Host Institution:	Universidad Politecnica De Madrid - ESP

Human Subcortical-Cortical Circuit Dynamics for Remembering the Exceptional

Our memory system is optimised for remembering the exceptional over the mundane. We remember better those events that violate predictions generated by the prevailing context, particularly because of surprise or emotional impact. Understanding how we form and retrieve long-term memories for important or salient events is critical for combating the rapidly growing incidence of pathologies associated with memory dysfunction with huge socio-econonomic burden. Human lesion and non-invasive functional imaging data, motivated by findings from animal models, have identified subcortical structures that are critical for upregulating hippocampal function during salient event memory. However, mechanistic understanding of these processes in humans remains scarce, and requires better experimental approaches such as direct intracranial recordings from, and focal electrical stimulation of, these subcortical structures.

This project will characterise human subcortico-cortical neuronal circuit dynamics associated with enhanced episodic memory for salient stimuli by studying direct recordings from human hippocampus, amygdala, nucleus accumbens, ventral midbrain and cortex. Within this framework, I will elucidate the electrophysiological mechanisms underlying amygdala-hippocampal-cortical coupling that lead to better memory for emotional stimuli, extend the hippocampal role in detecting unpredicted stimuli to define its role in orchestrating cortical dynamics in unpredictable contexts, and discover the neuronal response profile of the human mesolimbic dopamine system during salient stimulus encoding. The predicted results, based on my own preliminary data, will offer several conceptual breakthroughs, particularly regarding hippocampal function and the role of dopaminergic ventral midbrain in memory. The knowledge gained from this project is a fundamental requirement for designing therapeutic interventions for patients with memory deficits and other neuropsychiatric disorders.

Link to the ERC project webpage: www.thestrangelab.org/erc-cog-rememberex/

Keywords of the ERC project: human, memory, emotion, salience, MRI, intracranial EEG, MEG, deep brain stimulation (DBS)

Keywords that characterize the scientific profile of the potential visiting researcher/s: electrophysiology, oscillations, single-units, MRI, cognitive neuroscience

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**851257**	**Nanoglia**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Elvira Mass**
Host Institution:	Rheinische Friedrich-Wilhelms-Universitat Bonn - DEU

Understanding the impact of nanoplastics on the development of neurological disorders

An omnipresent but understudied environmental risk for our immune system is pollution by nano-sized plastics. Plastic particles have been detected in a wide variety of ecosystems and are speculated to enter and spread in the food web all the way to humans. Ingested nanoplastics can translocate from the gut to the lymph and circulatory systems and have the capacity to cross the blood-brain barrier in mammals. It has been recently shown that nanoplastics cause behavioural disorders in fish, and thus may also represent a risk for human health, in particular for brain function. However, the long-term bioavailability and toxicity of nanoplastics in the brain are unknown. Microglia as the main neuroimmune cells have not only a defence function required during inflammatory conditions, but constantly sense and response to environmental changes as part of their housekeeping functions that are essential for neuronal homeostasis. This places microglia at the interface between normal and abnormal brain development and function. In line with this, we have recently discovered that chronic microglial activation causes neurodegeneration. As highly phagocytic cells, microglia internalize nanoplastics reaching the brain. This process might in turn lead to their acute or chronic activation, thereby triggering neurological disorders. In NanoGlia, we will use rodent animal models to investigate behavioural as well as cellular and molecular changes in the brain that occur upon ingestion of nanoplastics. We will further determine nanoplastics-induced developmental reprogramming events in fetal microglia that may influence brain organogenesis and function. Understanding how nanoplastics triggers microglial activation during embryogenesis and postnatal stages and whether this immune activation leads to permanent changes in brain development and function will reveal ground-breaking mechanistic insights into the environmentally triggered pathogenesis of neurological disorders.

Link to the ERC project webpage:

Keywords of the ERC project: Microglia, Macrophage, Neurodevelopment, Neurodegeneration

Keywords that characterize the scientific profile of the potential visiting researcher/s: Neuroscience, Neuroinflammation, Immunology

Principal Investigator:	**Dr Jerome Mertens**
Host Institution:	Universitaet Innsbruck - AUT

Age-dependent mechanisms of sporadic Alzheimer's Disease in patient-derived neurons

Sporadic Alzheimer's Disease (AD) accounts for the overwhelming majority of all AD cases and exclusively affects people at old age. However, mechanistic links between aging and AD pathology remain elusive. We recently discovered that in contrast to iPSC models, direct conversion of human fibroblasts into induced neurons (iNs) preserves signatures of aging, and we have started to develop a patient-based iN model system for AD. Our preliminary data suggests that AD iNs show a neuronal but de-differentiated transcriptome signature. In this project, we first combine cellular neuroscience assays and epigenetic landscape profiling to understand how neurons in AD fail to maintain their fully mature differentiated state, which might be key in permitting disease development. Next, using metabolome analysis including mass spec metabolite assessment, we explore a profound metabolic switch in AD iNs that shows surprisingly many aspects of aerobic glycolysis observed also in cancer. While this link might represent an interesting connection between two age-dependent and de-differentiation-associated diseases, it also opens new avenues to harness knowledge from the cancer field to better understand sporadic AD. We further focus on identifying and manipulating key metabolic regulators that appear to malfunction in an age-dependent manner, with the ultimate goal to define potential targets and treatment strategies. Finally, we will focus on early AD mechanisms by extending our model to mild cognitive impairment (MCI) patients. An agnostic transcriptome and epigenetic landscape approach of glutamatergic and serotonergic iNs will help to determine the earliest and probably most treatable disease mechanisms of AD, and to better understand the contribution of neuropsychiatric risk factors. We anticipate that this project will help to illuminate the mechanistic interface of cellular aging and the development of AD, and help to define new strategies for AD.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**865634**	**PreSynPlast**	**LS5** Neurosciences and Neural Disorders

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: Learning and memory; Synaptic plasticity; Electrophysiology; Super-resolution microscopy

Keywords that characterize the scientific profile of the potential visiting researcher/s: Curiosity; Team player; Expertise in synaptic biology/pathophysiology, electrophysiology, or super-resolution microscopy

	Project ID:	Project Acronym:	Evaluation Panel:
	866237	**LOCOLEARN**	**LS5** Neurosciences and Neural Disorders

European Research Council
Executive Agency
Established by the European Commission

Principal Investigator:	**Dr Megan Carey**
Host Institution:	Fundacao D. Anna Sommer Champalimaud E Dr. Carlos Montez Champalimaud - PRT

Cerebellar circuits for locomotor learning in space and time

Every movement we make requires us to coordinate our actions precisely in space and time. This proposal aims to understand how that remarkable coordination is achieved by neural circuits controlling movement. The cerebellum plays a critical role in keeping movements calibrated and coordinated, and it is thought to do this in part through a motor learning process in which predictable perturbations of movement are gradually compensated. Cerebellum-dependent forms of motor learning have been identified for a variety of behaviors, including locomotion, and locomotor learning is used as a rehabilitative therapy in human patients. We recently established locomotor learning in mice, using a custom-built, transparent split-belt treadmill that controls the speeds of the two sides of the body independently and allows for high-resolution behavioral readouts. Here, we will combine quantitative analysis of locomotor behavior with genetic circuit dissection to answer two fundamental questions: How are cerebellar outputs read out by downstream circuits, to calibrate spatial and temporal components of movement? and How are instructive signals for spatial and temporal learning encoded by cerebellar inputs? Specifically, we will: 1) Use circuit tracing combined with manipulation of specific cerebellar outputs to identify downstream pathways for spatial and temporal locomotor learning, 2) Investigate the role of error signals for cerebellar learning via optogenetic perturbation of climbing fiber inputs to the cerebellum, and 3) Image complex spike activity from populations of Purkinje cells during locomotion and learning, to ask how spatial and temporal error signals are encoded within the cerebellum. These studies will allow us to bridge levels of analysis to understand how cerebellar learning mechanisms convert behaviorally-relevant sensorimotor error signals into calibration signals that ensure accurate and coordinated movements in space and time for a wide range of behaviors.

Link to the ERC project webpage: careylab.org

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency	**882673**	**OrganellenanoComp**	**LS5** Neurosciences and Neural Disorders

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

Computational methods and modeling to decipher organelle nanophysiology

Neuronal and glial physiology in nanodomains remains poorly understood due to the spatio-temporal limitation of direct unperturbed in vivo measurements. Yet, it is the scale of voltage regulation, ionic, proteins and molecular trafficking, metabolism control and local signal transduction. The goal of this proposal is to determine how the flow of ions and molecules is regulated in the cytoplasm in relation with organelles, such as the endoplasmic reticulum and mitochondria in various physiological conditions such as steady-state, induction of plastic changes or ionic depletion. The approach is based on mathematical modeling, large data analysis, simulation methods, and developing the associated fast and efficient algorithms. We developed in the past 15 years computational tools such as molecular modeling, stochastic simulations and data analysis at a molecular level to study various signals such as voltage recordings or super-resolution microscopy single particle trajectories (SPTs). However, these theoretical approaches are not sufficient today to face the novel data revolution coming from SPTs, but also voltage dyes, voltage recorded by nanopipettes, or photoconversion in nanocompartments. The aim of the project is to develop physical models of molecular diffusion and electro-diffusion. These models will be applied to reconstruct and interpret the local transport, which is not homogeneous because molecules or receptors could aggregate in some specific nano-regions. We will explore the mechanisms underlying this heterogeneity. Second, we will apply these modeling and numerical simulations to analyze data about flux regulation inside the cytoplasm but also in organelles, such as the ER and mitochondria.Third, we analyze calcium fluorescent data (photoactivation, local uncaging) to study how calcium is exchanged in nanodomains during synaptic transmission in dendrites and dendritic spines.

Link to the ERC project webpage:

Keywords of the ERC project: Data analysis; modeling; cell biology; neuroscience; numerical simulations

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

	Project ID:	Project Acronym:	Evaluation Panel:
	884281	**SynapseBuild**	**LS5** Neurosciences and Neural Disorders

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:

Keywords of the ERC project: presynaptic development; axonal transport; mammalian neurons; advanced imaging (light and electron microscopy); knockout mice; electrophysiology

Keywords that characterize the scientific profile of the potential visiting researcher/s: synaptic physiologist or cell biologist; researchers with interest or expertise in iPS derived neurons and/ or correlative light and electron microscopy or genome engineering

	Project ID:	Project Acronym:	Evaluation Panel:
	885090	**HOLOVIS**	**LS5** Neurosciences and Neural Disorders

European Research Council
Executive Agency
Established by the European Commission

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

Holographic control of visual circuits

The aim of this research program is to produce novel all-optical technologies to explore brain functions at the mesoscopic scale with cellular resolution opening a new phase in optogenetics that I named circuit optogenetics.

Revealing the neural codes supporting specific mammalian brain functions is a daunting task demanding to relate in vivo the individual activities of large numbers of neurons recorded jointly within collectives that form distinct nodes of a network and to perform precisely targeted and calibrated interventions in the spatiotemporal dynamics of neural circuits on the scale of naturalistic patterns of activity. Despite recent technical advances, these experiments remain out of reach because we lack a comprehensive approach for large-scale, multi-region, in depth, single cell and millisecond precise manipulation of neural circuits. HOLOVIS will tackle these limitations through the construction of an innovative paradigm combining optogenetics with cutting-edge technology of wave front shaping, compressed sensing, microendoscopy, wave-guide probes, laser developments and opsin engineering.

My lab has pioneered the use of wave front shaping for neuroscience and developed in the past years a number of new optical methods, for patterned optogenetic neuronal stimulation. Here, we will push forward this technology and first demonstrate the performances of these breakthrough systems to reveal how inter, intra-laminar and cortical/sub-cortical wiring construct and refine visual orientation selectivity in mice.

We will focus on the visual system of mice, whose input-output responses to controlled sensory stimulations have been characterized in decades of studies. However, we are persuaded that our approach can be used to reveal the connectivity rules that underlie specific patterns of activity of any neuronal circuit, thus defining the functional building blocks of distinct brain areas.

Link to the ERC project webpage:

Keywords of the ERC project: optical microscopy; optogenetics; in vivo imaging; visual circuits (mice and zebrafish larvae)

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

Project ID:	Project Acronym:	Evaluation Panel:
948716	**AllOptHIPP**	**LS5** Neurosciences and Neural Disorders

Principal Investigator:	**Dr Yoav Adam**
Host Institution:	The Hebrew University Of Jerusalem. - ISR

All-Optical Dissection of Hippocampal Circuits Using Voltage Imaging

The hippocampus is critical for the storage of episodic memories and has been extensively studied on its role in spatial memory. The hippocampus is also a central model for in vitro studies on the molecular, cellular and microcircuit basis for learning and memory. I propose to use a new technology that I developed to record and manipulate the membrane potential of multiple neurons, simultaneously, in behaving animals to reveal the mechanisms by which hippocampal circuits process spatial information. This research will bridge the gap between the in vitro mechanistic studies and the in vivo efforts to describe the spatial representations.

I first propose to employ the voltage imaging technology for detailed mechanistic studies of the function and plasticity of hippocampal microcircuits during place cell formation (Objective 1). To this end, we will combine voltage imaging with Optogenetics in head-fixed mice performing virtual navigation in familiar and novel environments. To expand to a 'systems' view on hippocampal plasticity, we will next establish a method for optical selection of single neurons based on their functional profile (Objective 2). We will use this technology to trace the long-range projections and the pre- and postsynaptic landscape of photo-selected CA1 neurons. In the last objective, we will combine both technologies to dissect the contribution of different entorhinal cell types (i.e. grid cells, border cells, and speed cells) to place cell formation in CA1 (objective 3). To this end, we will image the entorhinal cortex and photo-select cells based on their functional profiles. We will then image CA1 while manipulating the activity of the selected entorhinal cells. Our work will provide new discoveries on the mechanistic basis for spatial memory and will comprise a first step towards broader understanding of how the brain stores and retrieves episodic memories.

Link to the ERC project webpage:

Keywords of the ERC project:

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

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.

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**716718**	**ALLERGUT**	**LS6** Immunity and Infection

Principal Investigator:	**Dr Caspar Ohnmacht**
Host Institution:	Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Mucosal Tolerance and Allergic Predisposition: Does it all start in the gut?

Currently, more than 30% of all Europeans suffer from one or more allergic disorder but treatment is still mostly symptomatic due to a lack of understanding the underlying causality. Allergies are caused by type 2 immune responses triggered by recognition of harmless antigens. Both genetic and environmental factors have been proposed to favour allergic predisposition and both factors have a huge impact on the symbiotic microbiota and the intestinal immune system. Recently we and others showed that the transcription factor ROR(γt) seems to play a key role in mucosal tolerance in the gut and also regulates intestinal type 2 immune responses.

Based on these results I postulate two major events in the gut for the development of an allergy in the lifetime of an individual: First, a failure to establish mucosal tolerance or anergy constitutes a necessity for the outbreak of allergic symptoms and allergic disease. Second, a certain 'core' microbiome or pathway of the intestinal microbiota predispose certain individuals for the later development of allergic disorders. Therefore, I will address the following aims:

1) Influence of ROR(γt) on mucosal tolerance induction and allergic disorders

2) Elucidate the T cell receptor repertoire of intestinal Th2 and ROR(γt)+ Tregs and assess the role of alternative NFκB pathway for induction of mucosal tolerance

3) Identification of 'core' microbiome signatures or metabolic pathways that favour allergic predisposition

ALLERGUT will provide ground-breaking knowledge on molecular mechanisms of the failure of mucosal tolerance in the gut and will prove if the resident ROR(γt)+ T(reg) cells can function as a mechanistic starting point for molecular intervention strategies on the background of the hygiene hypothesis. The vision of ALLERGUT is to diagnose mucosal disbalance, prevent and treat allergic disorders even before outbreak and thereby promote Public Health initiative for better living.

Link to the ERC project webpage:

Keywords of the ERC project: mucosal immunology, intestinal tolerance, microbiome, alternative NFkB

Keywords that characterize the scientific profile of the potential visiting researcher/s: knowledge in immunology, molecular biology and bioinformatics, interest in microbiome-host symbiosis

Novel mechanisms of early defense against virus infections

Virus-induced type I interferons (IFN) have classically been considered to constitute the first line of defense against virus infections However, recent work by us and others has identified early antiviral actions that occur independently of inducible type I and III IFN expression and sometimes even prior to IFN action (e.g. Iversen,...., Paludan. Nature Immunology, 2016; Paludan. Trends in Immunology, 2016). These discoveries challenge the current thinking in the field that IFNs constitute the first line of defense. Hence, there is an urgent need for more detailed understanding of the immediate antiviral defense mechanisms. Most importantly, we remain to identify key players in IFN-independent antiviral responses, we completely lack insight into the mechanisms that govern these responses, and we also lack information on the importance of this layer of defense in mice and humans. In accord with this, my proposal follows four aims: (i) Identification of mechanisms of virus detection at epithelial surfaces, (ii) elucidation of the role of tonic IFN signaling in antiviral defense, (iii) identification and characterization of novel restriction factors, and (iv) deciphering the mechanisms that govern induction of the first wave of IFNs at epithelial surfaces. In addition, I will also explore the interactions between the early antiviral actions. To achieve the goals, I will combine unbiased genome-wide screens with hypothesis-driven approaches, and will integrate molecular biology/genetics/biochemistry with advanced cell culture systems, animal science and analysis of patient material. Strong preliminary data have been generated for all four aims, and world-leading collaborations are in place, hence minimizing the risks, and allowing fast progress. Our findings will (i) change the thinking in innate immunology by uncovering a novel layer of antiviral defense and (ii) provide new avenues for therapeutic modulation of immune responses.

Link to the ERC project webpage:

Keywords of the ERC project: Innate immunity; interferon; virus infections; signaling

Keywords that characterize the scientific profile of the potential visiting researcher/s: Innate immunity; interferon; virus infections; signaling

Functional Diversity of T cells

T cells have a central role in most adaptive immune responses, including immunity to infection, cancer, and autoimmunity. Increasing evidence shows that even resting steady-state T cells form many different subsets with unique functions. Variable level of self-reactivity and previous antigenic exposure are most likely two major determinants of the T-cell diversity. However, the number, identity, and biological function of steady-state T-cell subsets are still very incompletely understood. Receptors to ligands from TNF and B7 families exhibit variable expression among T-cell subsets and are important regulators of T-cell fate decisions. We hypothesize that pathways triggered by these receptors substantially contribute to the functional diversity of T cells.The FunDiT project uses a set of novel tools to systematically identify steady-state CD8+ T cell subsets and characterize their biological roles. The project has three complementary objectives.

(1) Identification of CD8+ T cell subsets. We will identify subsets based on single cell gene expression profiling. We will determine the role of self and foreign antigens in the formation of these subsets and match corresponding subsets between mice and humans.

(2) Role of particular subsets in the immune response. We will compare antigenic responses of particular subsets using our novel model allowing inducible expression of a defined TCR. The activity of T-cell subsets in three disease models (infection, cancer, autoimmunity) will be characterized.

(3) Characterization of key costimulatory/inhibitory pathways. We will use our novel mass spectrometry-based approach to identify receptors and signaling molecules involved in the signaling by ligands from TNF and B7 families in T cells.

The results will provide understanding of the adaptive immunity in particular disease context and resolve long-standing questions concerning the roles of T-cell diversity in protective immunity and tolerance to healthy tissues and tumors.

Link to the ERC project webpage:

Keywords of the ERC project: T cells, tolerance, signaling, diversity, immunity

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

	Project ID:	Project Acronym:	Evaluation Panel:
	802899	**VIRUSES AND RNA**	**LS6** Immunity and Infection

Principal Investigator:	**Dr Troels Scheel**
Host Institution:	Kobenhavns Universitet - DNK

RNA regulation during viral infection

Viral infections are responsible for significant morbidity and mortality and frequency and impact of epidemics are expected to increase. Thorough understanding of basic virology is critical for informed development of prevention and control. Most systematic studies of virus-host interactions have focused on proteins, however, with recent methodological advances the intersecting fields of viral infection and RNA biology hold great promise for basic and therapeutic exploration. The goal of this application therefore is to discover and dissect RNA-based virus-host interactions and related regulatory mechanisms of gene expression.

Micro-RNAs (miRNAs) fine-tune gene expression by repressing mRNA targets. However, cellular miRNAs increase translation and replication of certain viruses. Thus, hepatitis C virus (HCV) critically depends on the liver specific miR-122, which emerged as a therapeutic target. Further, HCV sequesters enough miR-122 to indirectly regulate cellular gene expression. I hypothesize that this RNA-based mechanism contributes to virus induced liver cancer, and aim to address this using our recently developed rodent model for HCV infection (Aim 1). Better understanding of viral RNA (vRNA) interactions could significantly contribute to basic infection biology and novel therapeutics. I therefore aim to systematically identify vRNA interactions with other cellular RNAs and proteins (Aim 2). I expect to identify interactions of value for functional regulation and therapeutic targeting. I finally hypothesize that translation of certain cellular mRNAs – similarly to viruses – increase upon miRNA binding, and aim to systematically screen for such virus-like alternative regulation, with potential to change understanding of post-transcriptional regulation (Aim 3).

In conclusion, this high-risk high-gain project has potential to shape novel dogmas for virus and RNA biology and to identify novel RNA-based therapeutic targets; a promising upcoming field of discovery.

Link to the ERC project webpage: https://isim.ku.dk/staff/vip/?pure=en/persons/221047

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

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

	Project ID:	Project Acronym:	Evaluation Panel:
	805500	**Riboinflam**	**LS6** Immunity and Infection

Principal Investigator:	**Dr Emiliano Ricci**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale (Inserm) - FRA

Assessing the role of ribosomes and mRNA translation in shaping the inflammatory response

Inflammation is a highly regulated process that acts as a first line of defense against pathogens infections. Triggered by cellular pattern recognition receptors (PRRs) that recognize specific microbial components and endogenous or exogenous non-microbial components, activation of inflammation induces a dynamic and coordinated gene expression program that leads to the production of cytokines and chemokines to attract effector cells to the site of infection. Although a robust inflammatory response is required for efficient clearance of pathogens, uncontrolled or prolonged inflammation can lead to inflammatory disorders such as septic shocks or to autoimmune diseases like lupus.

Most studies have focused so far on the transcriptional control of the inflammatory gene expression program. However, post-transcriptional regulatory mechanisms involving mRNA splicing, mRNA decay or translation have also been described to control the inflammatory response. Among these, regulation of mRNA translation allows for rapid and reversible modulation of gene expression but its precise role and control mechanisms in the inflammatory response remain poorly understood.

Using innovative technologies, our project aims at characterizing the role of ribosomes and mRNA translation in regulating the inflammatory response. In particular, we propose to identify the complete set of of ribosome accessory proteins and to determine their role in the context of "specialized ribosomes" with specific regulatory activities. We will also study the cross-talks between ribosomes and other cellular processes such as mRNA decay and uncover the role of mRNA editing in regulating translation during the inflammatory response.

From this work, we expect to identify new regulatory mechanisms that orchestrate inflammation as well as cellular factors that could represent new therapeutic targets for the design of drugs modulating inflammation.

Link to the ERC project webpage:

Keywords of the ERC project: ribosome, RNA, mRNA, translation, immunity, innate immunity, RNA degradation, RNA turnover

Keywords that characterize the scientific profile of the potential visiting researcher/s: ribosome, mRNA, turnover, translation

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**850638**	**B-DOMINANCE**	**LS6** Immunity and Infection

Principal Investigator:	**Dr Davide Angeletti**
Host Institution:	Goeteborgs Universitet - SWE

B Cell Immunodominance in Antiviral Immunity

This proposal aims at understanding how B cell specificity and immunodominance shape primary and secondary humoral responses to influenza A virus. Influenza A virus is a relevant human pathogen causing a considerable yearly death toll and economic burden to society. Immunodominance is a major driving force of adaptive immunity and defines the hierarchical recognition of epitopes on the same antigen. Previous studies analysing B cell dynamics in primary and secondary responses have been mainly focusing on simple antigens and competition between B cell clones of the same family. Investigation using complex antigens and examining interclonal competition are surprisingly scarce. Influenza hemagglutinin (HA) is a prime candidate to study immunodominance in B cells. I have generated a set of mutant viruses that will allow for an unprecedented investigation into immunodominance and B cell interclonal competition in primary and secondary responses. These viruses can be used to isolate and enumerate antibody and B cells specific for different epitopes on the same complex antigen (HA). I will use these unique tools in combination with state-of-the-art immunological methods, multi-colour flow cytometry and single cells RNA sequencing paired with B cell receptor sequencing to gain fundamental insights into B cell regulation and anti-viral humoral responses. I will i) study the link between B cell receptor characteristics, specificity and B cell fate decisions in primary responses, ii) characterize the relative contribution of pre-existing B cells, serum antibodies and CD4 T cells for immunodominance of secondary responses, iii) define immunodominance in human individuals, repeatedly exposed to influenza virus. I expect this project to critically improve our understanding of basic B cell biology with the long-term benefit of improving current vaccination against variable viral pathogens.

Link to the ERC project webpage:

Keywords of the ERC project: immunodominance, B cell, influenza, antibodies, vaccines

Keywords that characterize the scientific profile of the potential visiting researcher/s: immunodominance, B cell, influenza, antibodies, vaccines

	Project ID:	Project Acronym:	Evaluation Panel:
	853608	**VIROME**	**LS6**
European Research Council Executive Agency			Immunity and Infection
Established by the European Commission			

Principal Investigator:	**Dr Bénédicte Machiels**
Host Institution:	Universite De Liege - BEL

Shaping of long term innate immunity by viral education of bone marrow monocytes

Symbiotic and pathogenic microbes are major environmental factors that play fundamental roles in shaping host immunity. Such dynamic interactions between commensals or pathogens and the host must be finely regulated to balance protective immune responses and induction of regulatory pathways. While frequently underestimated, immune imprinting by viruses is a key determinant for variation in disease susceptibility. Numerous evidence shows that a history of infections trains the innate immune system for the long term. Amongst the cells that are trained, monocytes are highly heterogeneous and are involved in essential biological processes such as anti-microbial activity, immunomodulation or macrophage-niche replenishment. While the current paradigm states that monocyte fate and function are driven by the local microenvironment, a recent study has shown that monocytes are primed in the bone marrow for functional properties. Here, we want to explore how and where monocyte development and function are educated by symbiotic (Murid herpesvirus 4) or pathogenic (Pneumonia Virus of Mice) viruses and with which potential outcomes for long-term immunity. To this end, we have devised three main aims. First, following infections, we will characterize monocytes and their progenitors by classical immunophenotyping, functional assays and unbiased single-cell RNA-seq in combination with ATAC-seq, to investigate in-depth how and where viruses shape monocytes and monocyte-derived cells. Second, molecular mechanism(s) underlying monocyte priming after infections will be assessed. In particular, based on literature and preliminary results, we postulate that bone marrow CD169+ macrophages could play a key role in early monocyte priming. Third, the consequences of virus-driven monocyte training will be investigated at steady state and upon heterologous challenges. Such research could provide the proof of concept that viral education of bone marrow monocytes shapes long-term innate immunity.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Principal Investigator:	**Dr David Courtney**
Host Institution:	The Queen'S University Of Belfast - GBR

Post-transcriptional regulation of influenza A virus RNA

This research proposal aims to significantly alter our understanding of the critical role post-transcriptional processes play in the influenza A virus (IAV) life cycle. Post-transcriptional regulation of cellular mRNAs has seen a lot of research interest in recent years, including projects looking at the effects of RNA modifications and ribosome specialisation. However, much less attention has been paid to the effects these processes have on the viral life cycle. This project focuses on the post-transcriptional regulation of both IAV mRNAs and negative strand vRNAs. However, outcomes of this work will have a profound effect on our perceptions of the regulatory processes affecting a wide range of viral RNAs. In fact, by better understanding the roles of these processes on viral RNAs, such as IAV, we can also uncover novel functions on cellular mRNAs.

This project comprises 5 work packages with 11 intermediate goals. We will first identify the locations of various modifications present on IAV RNAs across multiple strains in both human and avian infected cells, significantly expanding on our current understanding, while exploring the potential for species-specific adaptions. Through mutagenesis and RNA capture techniques, we will evaluate how these modifications affect RNA characteristics and what effector proteins are involved in these processes. We will also use this information to determine the composition of ribosomes actively translating IAV mRNAs and evaluate whether specialised ribosomes are involved in the normal IAV life cycle. Finally, we will focus on the roles of RNA modifications on vRNAs, which should be quite distinct from mRNAs, and the host proteins that specifically bind, or are blocked from binding, sites of modification. This is an ambitious, multifaceted project that will have a direct impact on our understanding of IAV biology, and also provide novel insights of value to multiple disciplines including virology, RNA biology and protein translation.

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

Keywords of the ERC project: influenza RNA modification epitranscriptomics trafficking

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

	Project ID:	Project Acronym:	Evaluation Panel:
	671231	**HEPCIR**	**LS7** Diagnostic Tools, Therapies and Public Health

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

Cell circuits as targets and biomarkers for liver disease and cancer prevention

Chronic liver diseases such as liver cirrhosis and hepatocellular carcinoma (HCC) are major challenges for global health. HCC is the second leading and fastest rising cause of cancer death worldwide. The limited availability of therapeutic options reflects our poor understanding of the molecular and clinical mechanisms involved in progression of liver disease. Chronic hepatitis C virus (HCV) infection is a main risk factor for HCC. Although HCC may be avoided by addressing the underlying cause in early stage disease, strategies to prevent HCC in patients with established cirrhosis and advanced fibrosis, in which the risk of HCC persists despite treatment of the underlying cause are lacking. Indeed, even HCV cure does not eliminate the risk of HCC development when advanced fibrosis is already present. Since fibrosis/cirrhosis-driven carcinogenesis is the mechanism of HCC development common to all major etiologies, we propose to use HCV-induced liver disease as a model to decipher the pan-etiology sequence of molecular events underlying disease progression and HCC. Our own data provide solid evidence that HCV infection alters pathways implicated in liver disease progression, including cirrhosis deterioration, HCC development, and overall and liver-specific death. Thus, the molecular investigation of these pathways will identify key cell circuits for the understanding of the pathogenesis of liver disease and HCC in general, and as broadly applicable pan-etiology diagnostic and therapeutic targets. Using a novel patient-derived cell culture model system for liver disease biology combined with advanced functional genomics, novel animal models and clinical investigation, we aim to uncover the cell circuits that are of clinical relevance for liver disease progression and cancer. By providing novel targets and biomarkers for liver disease and HCC prevention, this proposal will have a marked impact on the management and prognosis of patients with liver disease and HCC.

Link to the ERC project webpage: https://www.u1110.inserm.fr/en/content/erc-advanced-grant-hepcir

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: Cell biologist, virologist, hepatologist, MD, bioinformatician

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	725229	**EVICARE**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Joost Sluijter**
Host Institution:	Universitair Medisch Centrum Utrecht - NLD

Extracellular Vesicle-Inspired CArdiac Repair

More than 3.5 million people are newly diagnosed with heart failure every year in Europe with a long-term prognosis of 50% mortality within 4 years. There is a major need for more innovative, regenerative therapies that have the potential to change the course of disease. My hypothesis is that we can recondition heart failure by stimulating cardiac repair with extracellular vesicles that are derived from progenitor cells. In my laboratory, extracellular released vesicles containing a cocktail of stimulating factors, are amongst the most potent vectors for cardiac repair.

To achieve a sustainable and long-term therapeutic effect of these vesicles and enhance cardiac function by stimulating myocardial repair, we will 1) improve local cardiac delivery of progenitor cell-derived extracellular vesicles, 2) understand the mechanism of action of extracellular vesicles, and 3) stimulate extracellular vesicles release and/or production by progenitor cells.

These questions form the rationale for the current proposal in which we will co-inject extracellular vesicles and slow-release biomaterials into the damaged myocardium. By subsequent genetic tracing, we will determine fate mapping of injected vesicles in vivo, and perform further mechanistic understanding in in vitro culture models of targeted and identified myocardial cell types. Moreover, we will upscale the vesicles production by progenitor cells further via bioreactor culturing and medium-throughput screening on factors that stimulate vesicles release.

The use of stem cell-derived extracellular vesicles to stimulate cardiac repair will potentially allow for an off-the shelf approach, including mechanistic understanding and future clinical use. Additionally, since these vesicles act as a natural carrier system outperforming current artificial drug delivery, we might understand and mimic their characteristics to enhance local (RNA-based) drug delivery systems for cardiovascular application.

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

Keywords of the ERC project: Extracellular vesicles, cardiac therapy, targeting, heart failure

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**740230**	**TREAT-NPM1-AML**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Brunangelo Falini**
Host Institution:	Universita Degli Studi Di Perugia - ITA

Improving therapy of NPM1-mutated AML

Acute myeloid leukemia (AML) is the most common acute leukemia in adults accounting for approximately 15,000 new cases/year in Europe and 20,000 new cases/year in US. Currently, 40-50% of AML patients (age 18-60 years) and only 5-10% of older patients (who are usually more frequently affected by the disease) can be cured using conventional chemotherapy +/- allogeneic hematopoietic stem cell transplantation. Thus, AML still remains an urgent medical need which calls for new forms of molecular targeted therapies (similarly to those available for acute promyelocytic leukemia). The P.I. previously discovered the nucleophosmin (NPM1) mutations, the most common genetic lesion in AML (about one-third of cases) and gave fundamental contributions in the translation of this seminal discovery into the clinic (improved classification of myeloid neoplasms according to WHO, genetic-based risk- stratification of AML patients, monitoring of minimal residual disease and first demonstration of the anti-leukemic activity of actinomycin D). The present research proposal is focused on improving therapy of NPM1-mutated AML. Specifically, it is aimed to: i) identify novel chemical tools interfering with NPM1 functions by interacting with the N-terminal portion of the protein (objective 1); ii) conduct a clinical trial (AML-PG02; Eudract 2014-003490-41) with actinomycin D in older untreated and/or unfit patients with NPM1-mutated AML and to better understand in vitro and in mice models the mechanisms of action of this drug, used alone or in combination with other agents (objective 2); iii) develop compound mouse models aimed to investigate how NPM1 mutations cooperate with FLT3-ITD or DNMT3A mutations in promoting AML with the goal to better understand the characteristics of relapsed cases and to design new therapeutic strategies (objectives 3 and 4): and iv) generate a murine model for testing the feasibility of "in situ" vaccination in AML, especially in NPM1-mutated AML (objective 5).

Link to the ERC project webpage: http://erc.falinigroup.eu

Keywords of the ERC project: Acute myeloid leukemia (AML), NPM1 Mutations, NPM1 Cytoplasmic dislocation, AML targeted therapy, mouse models, cell cultures, CRISPR gene editing.

Keywords that characterize the scientific profile of the potential visiting researcher/s: hematology, AML, CRISPR gene editing, bioinformatics, NGS, RNA-seq, proteomics

	Project ID:	Project Acronym:	Evaluation Panel:
	757398	**NanOnc**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Stefaan Soenen**
Host Institution:	Katholieke Universiteit Leuven - BEL

Nanomaterials in Oncology: Exploiting the Intrinsic Cancer-Specific Toxicity of Nanoparticles.

In our current society, therapeutic strategies against cancer suffer from dose-limiting toxicity, lack of specificity and high morbidity. To overcome this, the use of nanomaterials (NMs) is rising, where several NM formulations are undergoing clinical trials or are used in clinics where the NMs are used as drug delivery vehicles or as mediators in physical anticancer methods (e.g. hyperthermia), where to date, the success rate is limited due to low tumor targeting efficacy, lack of specificity and frequent re-use of classical toxicity mechanisms.

To overcome these issues, this research program aims to exploit the intrinsic toxicity of certain types of metal-based, degradation-prone NMs (Fe-doped ZnO, Fe-doped CuO and Ag of different sizes and coatings) towards only cancer cells as a novel and generic anti-cancer tool with 1) improved efficacy against difficult to treat cancers such as multidrug-resistant cancer cells, 2) enhanced specificity and selectivity of the treatment by the intrinsic cancer cell-specific toxicity of NMs towards cancer cells. To overcome the issues related to selective delivery of the NMs, tumor-homing cells will be used that have been shown to efficiently home to primary tumors and their metastases. In practice, the NMs used show distinct degradation kinetics that primarily induce cancer-selective toxicity. To obtain efficient tumor targeting, suicide gene-expressing tumor-homing cells will be loaded with the NMs in their cytoplasm, hereby impeding premature NM degradation. The tumor homing efficacy of these cells will be monitored via optical imaging and once at the target site these cells will be chemically destroyed using the suicide gene strategy. This will release the NMs into the tumor site, where they can selectively destroy the cancer cells. This research program will be the first to explore the full potential of cancer-specific toxicity of NMs and the use of cytoplasmic loading of cells as biological carriers for efficient delivery.

Link to the ERC project webpage:

Keywords of the ERC project: nanomedicine, optical imaging, cancer therapy

Keywords that characterize the scientific profile of the potential visiting researcher/s: nanomedicine, cancer therapy, preclinical optical imaging

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	758151	**CHIPS**	Diagnostic Tools, Therapies and Public Health

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: Acrylamide biomarkers diet early life epidemiology

Keywords that characterize the scientific profile of the potential visiting researcher/s: Dietary/Nutritient epidemiology, Psychology, Analytical Chemistry

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
European Research Council Executive Agency			Diagnostic Tools,
Established by the European Commission	**758657**	**ImPRESS**	Therapies and Public Health

Principal Investigator:	**Dr Kyrre E. Emblem**
Host Institution:	Oslo Universitetssykehus Hf - NOR

Imaging Perfusion Restrictions from Extracellular Solid Stress

Even the perfect cancer drug must reach its target to have an effect. The ImPRESS project main objective is to develop a novel imaging paradigm coined Restricted Perfusion Imaging (RPI) to reveal - for the first time in humans - vascular restrictions in solid cancers caused by mechanical solid stress, and use RPI to demonstrate that alleviating this force will repair the cancerous microenvironment and improve therapeutic response. Delivery of anti-cancer drugs to the tumor is critically dependent on a functional vascular bed. Developing biomarkers that can measure how mechanical forces in a solid tumor impair perfusion and promotes therapy resistance is essential for treatment of disease.

The ImPRESS project is based on the following observations; (I) pre-clinical work suggests that therapies targeting the tumor microenvironment and extracellular matrix may enhance drug delivery by decompressing tumor vessels; (II) results from animal models may not be transferable because compressive forces in human tumors in vivo can be many times higher; and (III) there are no available imaging technologies for medical diagnostics of solid stress in human cancers. Using RPI, ImPRESS will conduct a comprehensive series of innovative studies in brain cancer patients to answer three key questions: (Q1) Can we image vascular restrictions in human cancers and map how the vasculature changes with tumor growth or treatment? (Q2) Can we use medical engineering to image solid stress in vivo? (Q3) Can RPI show that matrix-depleting drugs improve patient response to conventional chemo- and radiation therapy as well as new targeted therapies?

The ImPRESS project holds a unique position to answer these questions by our unrivaled experience with advanced imaging of cancer patients. With successful delivery, ImPRESS will have a direct impact on patient treatment and establish an imaging paradigm that will pave the way for new scientific knowledge on how to revitalize cancer therapies.

Link to the ERC project webpage: https://www.ous-research.no/emblem/

Keywords of the ERC project: MRI, glioma, treatment, perfusion, extracellular matrix

Keywords that characterize the scientific profile of the potential visiting researcher/s: Image analysis, artificial intelligence, neuroimaging, brain tumors

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	759585	**ToMeTuM**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Vojtech Adam**
Host Institution:	Vysoke Uceni Technicke V Brne - CZE

Towards the Understanding a Metal-Tumour-Metabolism

A tumour cell uses both genetic and protein weapons in its development. Gaining a greater understanding of these lethal mechanisms is a key step towards developing novel and more effective treatments. Because the metal ion metabolism of a tumour cell is not fully understood, we will address the challenge of explaining the mechanisms of how a tumour cell copes both with essential metal ions and platinum based drugs. The metal-based mechanisms help a tumour to grow on one side and to protect itself against commonly used metal-based drugs. On the other side, the exact description of these mechanisms, which are being associated with multi-drug resistance occurrence and failure of a treatment, still remains unclear. We will reveal the mechanism of the as yet not understood biochemical and molecularly-biological relationships and correlations between metal ions and proteins in a tumour development revealing the way how to suppress the growth and development of a tumour and to markedly enhance the effectiveness of a treatment.

To achieve this goal, we will focus on metallothionein and its interactions with essential metals and metal-containing anticancer drugs (cisplatin, carboplatin, and oxaliplatin). Their actions will be monitored both in vitro and in vivo. For this purpose, we will optimize electrochemical, mass spectrometric and immune-based methods. Based on processing of data obtained, new carcinogenetic pathways will be sought on cell level and proved by genetic modifications of target genes. The discovered processes and the pathways found will then be tested on two animal experimental models mice bearing breast tumours (MCF-7 and 4T1) and MeLiM minipigs bearing melanomas.

The precise description of the tumour related pathways coping with metal ions based on metallothioneins will direct new highly effective treatment strategies. Moreover, the discovery of new carcinogenetic pathways will open a window for understanding of cancer formation and development.

Link to the ERC project webpage: https://www.ceitec.eu/towards-the-understanding-a-metal-tumour-metabolism-tometum/t10110

Keywords of the ERC project: Metallothionein; Isoforms; Oligomers; Cancer Treatment; Metal Based Cytostatics; Resistance; CRISPR; Bioanalytical Methods, In vitro, In vivo

Keywords that characterize the scientific profile of the potential visiting researcher/s: Metallomics, Clinical Medicine; Molecular Biology; Biochemistry; Bioanalytical Chemistry

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	772970	**MicroC**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr FRANCESCA , BUFFA**
Host Institution:	The Chancellor, Masters And Scholars Of The University Of Oxford - GBR

Agent-Based Modelling of Gene Networks to model clonal selection in the tumour microenvironment and predict therapeutic resistance

The occurrence of therapeutic resistance is a major cause for the small effect on overall survival showed by targeted cancer therapies. Whilst experimental strategies to evaluate available treatments have been faced by an ever increasing number of possible combinations, computational approaches have been challenged by the lack of a framework able to model the multiple interactions encompassed by the three major factors affecting therapeutic resistance: selection of resistant clones, adaptability of gene signalling networks, and a protective and hypoxic tumour microenvironment.

Here I propose a novel modelling framework, Agent-Based Modelling of Gene Networks, which brings together powerful computational modelling techniques and gene networks. This combination allows biological hypotheses to be tested in a controlled stepwise fashion, and it lends itself naturally to model a heterogeneous population of cells acting and evolving in a dynamic microenvironment, which is needed to predict therapeutic resistance and guide effective treatment selection.

Using triple negative breast cancer (TNBC) as a testing case (15% of breast cancers, lacks validated), I propose to:

1. Develop a computational model of the TNBC tumour microenvironment using in-vitro and in-vivo, including patient-derived, models and data from clinical samples. 2. Validate the ability of the model to predict driver genes conferring a survival advantage to cancer cells in a hypoxic microenvironment. 3. Predict combinations of druggable targets to tackle TNBC therapeutic resistance. 4. Select most effective drug combinations and validate pre-clinically.

This project will deliver pre-clinically validated drug combinations, new therapeutic targets and a virtual environment to study individual tumours and predict therapeutic resistance. Complementing and empowering experimental models and assays, microC will offer a new powerful tool for diagnosis and therapy.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	786462	**HOPE**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Gottfried Baier**
Host Institution:	Medizinische Universitat Innsbruck - AUT

Host Protective Engineering of Cancer Immunity by Targeting the Intracellular Immune Checkpoint NR2F6

Because of its biological complexity, cancer is still poorly understood. Chronic inflammation has been shown, both experimentally and epidemiologically, to be a predisposition to, and also an inseparable aspect of clinically prevalent cancer entities. Therefore, a detailed understanding of both tumour and immune cell functions in cancer progression is a prerequisite for more successful therapeutic startegies. My team was the first to reveal the lymphocyte-intrinsic PKC/NR2F6 axis as an essential signalling node at the crossroads between inflammation and cancer. It is the mission of this project to identify molecular signatures that influence the risk of developing tumours employing established research tools and state-of-the-art genetic, biochemical, proteomic and transcriptomic as well as large scale CRISPR/Cas9 perturbation screening-based functional genomic technologies. Defining this as yet poorly elucidated effector pathway with its profoundly relevant role would enable development of preventive and immune-therapeutic strategies against NSCLC lung cancer and potentially also against other entities. Our three-pronged approach to achieve this goal is to: (i) delineate biological and clinical properties of the immunological PKC/NR2F6 network, (ii) validate NR2F6 as an immune-oncology combination target needed to overcome limitations to "first generation anti-PD-1 checkpoint inhibitors" rendering T cells capable of rejecting tumours and their metastases at distal organs and (iii) exploit human combinatorial T cell therapy concepts for prevention of immune-related adverse events as well as of tumour recurrence by reducing opportunities for the tumour to develop resistance in the clinic. Insight into the functions of NR2F6 pathway and involved mechanisms is a prerequisite for understanding how the microenvironment at the tumour site either supports tumour growth and spread or prevents tumour initiation and progression, the latter by host-protective cancer immunity.

Link to the ERC project webpage: http://www.baierlab.com/

Keywords of the ERC project: Non-small cell lung cancer, NSCLC; CD8 T lymphocytes; T cell signaling; nuclear orphan receptor NR2F6; CD8 T cell stemness maintenance; induced CD8 T cell exhaustion resistance; gene editing technology; immune checkpoint blockade therapy; CAR-T therapy.

Keywords that characterize the scientific profile of the potential visiting researcher/s: Experience with mouse tumor models or mouse immunology

Understanding the influence of human and organizational factors on surgeon performance to enhance patient outcomes: experimental evaluation of a customized coaching program

Individual performance of surgeon is a core element of successful surgery that can vary greatly over career for poorly understood reasons. Solutions to optimize physical and mental condition of surgeon during operation have not been thoroughly explored so far, while this may represent basic foundation for delivering high quality surgery. This surgeon-centred outcome research pursues three successive goals: 1-Identifying the key determinants related to surgeon's human factor and operating room organization influencing his/her performance in terms of patient safety and care efficiency; 2-Developing a customized coaching program for surgeons based on the human and organizational factors previously discovered, which includes a charting system for individual parameters and surgical outcomes feedback, profiling of individual surgeon, and standardized modules of improvement; 3-Implementing and measuring the impact of this program on surgical outcomes of a randomized group of surgeons against a control group of non-exposed surgeons. Inspired from previous experiences in the aeronautic and sport arena to improve pilots and athletes performance, our approach will take place in real time at the point of care in close collaboration with front-line personnel. A particular attention will be paid to quantify the influence of several factors that may affect how the surgeon operates every day (physiological stress, sleep quality, physical activities, workload, team composition and unplanned events in operating room). Generated knowledge on these factors will be exploited for identifying deficiencies that, if corrected, could improve surgeon's functional capacity. Solutions to control these factors and achieve optimal outcomes will then be experimentally tested to establish evidence-based standards of surgical practice. Those standards will be adapted to each surgeon's needs and preferences, potentially leading to a certification model for surgeons complying with excellence criteria.

Link to the ERC project webpage: https://topsurgeons.univ-lyon1.fr/en/accueil-english/

Keywords of the ERC project: surgeon ; public health ; health service research

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	803077	**PHARMS**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Li Deng**
Host Institution:	Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Bacteriophage inhibition of antibiotic-resistant pathogenic microbes and founding for novel therapeutic strategies

Emergence of antimicrobial resistance (AMR) is a grand scientific challenge of our time that has killed more than 700,000 people worldwide. Phage therapy, a promising complement to antibiotics, utilizes viruses of bacteria (bacteriophages) or phage-derived inhibitors as natural ways to fight AMR. The main obstacles in the clinical application of phage-based AMR therapy are the limited number of phage isolates and the unknown molecular mechanisms of phage-delivered bactericidal action. Building on the recent advances of my group in high-throughput, culture-independent but host-targeted methodologies, PHARMS aims to deploy a revolutionary approach: to screen for all possible phages of a resistant bacterial isolate, characterize multiple lines of their bactericidal functions, and use this information for the design of a whole battery of phage-based therapies that employ multifaceted modes of action.

Using an interdisciplinary research plan, PHARMS will discover phage-specific bactericidal action modes at all possible levels ranging from nucleotide sequence and transcription to translation, in order to elucidate the molecular mechanisms driving phage-mediated inhibition of AMR Acinetobacter baumannii, Helicobacter pylori, & Haemophilus influenzae (WP1). These discoveries, together with novel synthetic biology tools, will enable us to engineer an array of phage vectors that mimic phage-deployed bactericidal modes discovered under WP1, including transport of alien genes to deliver bactericidal effects (WP2). PHARMS will provide molecular confirmation and in vitro & in vivo validation of the functions of phage-encoded bactericidal peptides and enzymes (WP3). By elucidating universal and specific mechanisms of phage-delivered inhibition of AMR pathogens, PHARMS is positioned to provide the rational framework for the design of novel therapeutic strategies aimed at treating common and life-threatening infectious diseases.

Link to the ERC project webpage: https://web.med.tum.de/en/virologie/research-groups-tum/li-deng/research-topics/
https://www.helmholtz-muenchen.de/viro/research/emmy-noether-research-group-virus-in-nature-and-health/research-topics/index.html

Keywords of the ERC project: microbiome/phageome/virome/phage therapy/synthetic biology/bioinformatics

Keywords that characterize the scientific profile of the potential visiting researcher/s: microbiome/phageome/virome/phage therapy/synthetic biology/bioinformatics

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	804199	**BRuSH**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Randi J Bertelsen**
Host Institution:	Universitetet I Bergen - NOR

Oral bacteria as determinants for respiratory health

The oral cavity is the gateway to the lower respiratory tract, and oral bacteria are likely to play a role in lung health. This may be the case for pathogens as well as commensal bacteria and the balance between species. The oral bacterial community of patients with periodontitis is dominated by gram-negative bacteria and a higher lipopolysaccharide (LPS) activity than in healthy microbiota. Furthermore, bacteria with especially potent pro-inflammatory LPS have been shown to be more common in the lungs of asthmatic than in healthy individuals. The working hypothesis of BRuSH is that microbiome communities dominated by LPS-producing bacteria which induce a particularly strong pro-inflammatory immune response in the host, will have a negative effect on respiratory health. I will test this hypothesis in two longitudinally designed population-based lung health studies. I aim to identify whether specific bacterial composition and types of LPS producing bacteria in oral and dust samples predict lung function and respiratory health over time; and if the different types of LPS-producing bacteria affect LPS in saliva saliva and dust. BRuSH will apply functional genome annotation that can assign biological significance to raw bacterial DNA sequences. With this bioinformatics tool I will cluster microbiome data into various LPS-producers: bacteria with LPS with strong inflammatory effects and others with weak- or antagonistic effects. The epidemiological studies will be supported by mice-models of asthma and cell assays of human bronchial epithelial cells, by exposing mice and bronchial cells to chemically synthesized Lipid A (the component that drive the LPS-induced immune responses) of various potency. The goal of BRuSH is to prove a causal relationship between oral microbiome and lung health, and gain knowledge that will enable us to make oral health a feasible target for intervention programs aimed at optimizing lung health and preventing respiratory disease.

Link to the ERC project webpage: https://www.uib.no/en/rg/respiratorygroup/130718/brush

Keywords of the ERC project: human, respiratory, oral, microbiome, endotoxin

Keywords that characterize the scientific profile of the potential visiting researcher/s: biostatistics, bioinformatics, statistics, programming

	Project ID:	Project Acronym:	Evaluation Panel:
	817884	**ViroPedTher**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Marta Alonso**
Host Institution:	Universidad De Navarra - ESP

Oncolytic viruses for the treatment of pediatric brain tumors: An integrated clinical and lab approach

The overreaching goal of my lab is to improve the prognosis of patients with high-risk pediatric brain tumors. To this end, I propose to integrate clinical and lab-based research to develop tumor-targeted oncolytic adenoviruses with the capacity to elicit a therapeutic immune response in those tumors. Our research will use novel and relevant models to accomplish the experimental aims. We have previously worked with Delta-24-RGD (DNX-2401) a replication-competent adenovirus that has been translated to the clinical scenario. In 2017, the first clinical trial phase I with DNX-2401 for newly diagnosed Diffuse Intrinsic Pontine Gliomas (DIPG; a lethal pediatric brain tumor) opened propelled by my team. Preliminary results from the first trials revealed that the intratumoral injection of the virus instigated an initial phase of oncolysis followed by a delayed inflammatory response that ultimately resulted in complete regression in a subset of the patients without associated toxicities. I hypothesized that enhancement of the immune component of the DNX-2401-based therapy will result in the complete regression of the vast majority of pediatric brain tumors. In our specific approach, we propose to understand the immune microenvironment of DIPGs and the response to viral therapy in the context of the trial. Moreover, that knowledge will leverage the design of Delta-24-based adenoviruses to recruit lymphocytes to the tumor with the competence of different type of ligands to activate the tumor infiltrating lymphocytes. I expect that this combinatorial innovative treatment will efficiently challenge the profound and inherent tumor immunosuppression and, in turn, will elicit a robust anti-tumor immune response resulting in the significant improvement of the prognosis and quality of life of patients with pediatric brain tumors. This project has the potential to produce a vertical advance in the field of pediatric oncology.

Link to the ERC project webpage:

Keywords of the ERC project: pediatric brain tumors, oncolytic virus, therapies, immunetherapies, AT/RTs, DIPGs, pHGG, humanized mice models

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**817938**	**ImmunoBioSynth**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Bruno De Geest**
Host Institution:	Universiteit Gent - BEL

Synergistic engineering of anti-tumor immunity by synthetic biomaterials

Immunotherapy holds the potential to dramatically improve the curative prognosis of cancer patients. However, despite significant progress, a huge gap remains to be bridged to gain board success in the clinic. A first limiting factor in cancer immunotherapy is the low response rate in large fraction of the patients and an unmet need exists for more efficient - potentially synergistic - immunotherapies that improve upon or complement existing strategies. The second limiting factor is immune-related toxicity that can cause live-threatening situations as well as seriously impair the quality of life of patients. Therefore, there is an urgent need for safer immunotherapies that allow for a more target-specific engineering of the immune system. Strategies to engineer the immune system via a materials chemistry approach, i.e. immuno-engineering, have gathered major attention over the past decade and could complement or replace biologicals, and holds promise to contribute to resolving the current issues faced by the immunotherapy field. I hypothesize that synthetic biomaterials can play an important role in anti-cancer immunotherapy with regard to synergistic, safe, but potent, instruction of innate and adaptive anti-cancer immunity and to revert the tumor microenvironment from an immune-suppressive into an immune-susceptible state. Hereto, the overall scientific objective of this proposal is to fully embrace the potential of immuno-engineering and develop several highly synergistic biomaterials strategies to engineer the immune system to fight cancer. I will develop a series of biomaterials and address a number of fundamental questions with regard to optimal biomaterial design for immuno-engineering. Based on these findings, I will elucidate those therapeutic strategies that lead to synergistic engineering of innate and adaptive immunity in combination with remodeling the tumor microenvironment from an immune-suppressive into an immune-susceptible state.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
818170	**Epi4MS**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Maja Jagodic**
Host Institution:	Karolinska Institutet - SWE

Targeting the epigenome: towards a better understanding of disease pathogenesis and novel therapeutic strategies in Multiple Sclerosis

Multiple Sclerosis (MS) is a leading cause of unpredictable and incurable progressive disability in young adults. Although the exact cause remains unknown, this immune-mediated disease is likely triggered by environmental factors in genetically predisposed individuals. I propose that epigenetic mechanisms, which regulate gene expression without affecting the genetic code, mediate the processes that cause MS and that aberrant epigenetic states can be corrected, spearheading the development of alternative therapies. We will exploit the stable and reversible nature of epigenetic marks, in particular DNA methylation, to gain insights into the novel modifiable disease mechanisms by studying the target organ in a way that has not been possible before. This highly ambitious project comprises three synergistic facets formulated in specific aims to: (i) identify epigenetic states that characterize the pathogenesis of MS, (ii) prioritize functional epigenetic states using high-throughput epigenome-screens, and (iii) develop novel approaches for precision medicine based on correcting causal epigenetic states. Our unique MS biobank combined with cutting-edge methodologies to capture pathogenic cells and measure their functional states provides a rational starting point to identify MS targets. I will complement this approach with studies of the functional impact of MS targets using innovative in vitro screens, with the added value of unbiased discovery of robust regulators of specific MS pathways. Finally, my laboratory has extensive experience with animal models of MS and I will utilize these powerful systems to dissect molecular mechanisms of MS targets and test the therapeutic potential of targeted epigenome editing in vivo. Our findings will set the stage for a paradigm-shift in studying and treating chronic inflammatory diseases based on preventing and modulating aggressive immune responses by inducing self-sustained reversal of aberrant epigenetic states.

Link to the ERC project webpage: https://www.cmm.ki.se/web/guest/maja-jagodic-group

Keywords of the ERC project: multiple sclerosis, epigenetics, DNA methylation, epigenome-editing, epigenome screens

Keywords that characterize the scientific profile of the potential visiting researcher/s: epigenome-editing, dCas9 screens, bioinformatics, multi-omics

	Project ID:	Project Acronym:	Evaluation Panel:
	818715	**SECRETE-HF**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Rudolf de Boer**
Host Institution:	Academisch Ziekenhuis Groningen - NLD

SECRETED FACTORS IN CARDIAC REMODELING PROVOKE TUMORIGENESIS AND END ORGAN DAMAGE IN HEART FAILURE

The objective of SECRETE-HF is to demonstrate the effects of secreted factors from failing hearts to explain the etiology of multimorbidity in heart failure (HF). The project focuses on two co-morbid patterns: 1) the emerging susceptibility of HF patients for incident cancer, 2) the more established co-morbid conditions of renal, liver and pulmonary disease in HF. The rationale is:

• HF treatment has improved, yet morbidity and mortality remain high, which can be attributed to co-morbid conditions rather than pump failure alone.

• HF treatment is heart-oriented, neglecting the systemic effects that come with HF, and the associated morbidity and mortality.

• Using innovative experimental approaches such as organ transplant models, target finding, and deep phenotyping of clinical databases I will dissect HF-derived effects on tumor growth and organ damage.

OBJECTIVES

1. To establish the effects of HF, due to different etiologies, using the state-of-the-art heart transplantation murine model with (spontaneous) formation of colon and renal tumors, and phenotype tumor growth, as well as the main HF-affected organs: kidney, liver and lungs.

2. Identification of the cardiac secretome using unbiased approaches.

3. Integrate the results and identify overlapping and diverse factors from different HF forms, and their consequences for tumor growth and kidney/liver/lung remodeling.

4. Validate discoveries in human cohorts with data on incident HF, cancer and organ function.

5. Create clinical algorithms to detect, monitor and act on extra-cardiac disease.

WORKPACKAGES

WP 1: Create HF, murine heart transplantation models; phenotype tumor growth and organ involvement.

WP 2: Explore the proteomic, metabolomic and extracellular vesicle profiles from HF subforms.

WP 3: Validate secreted factors in vitro and in vivo.

WP 4: Validate human relevance in large population-based cohorts with unique phenotyping.

WP 5: Describe added value of novel markers and design clinical

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

Keywords of the ERC project: cardio-oncology; oncology; heart failure; biomarkers

Keywords that characterize the scientific profile of the potential visiting researcher/s: systems biology; molecular biology; cardiology

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	835286	**SCOPE**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Pierangelo Geppetti**
Host Institution:	Universita Degli Studi Di Firenze - ITA

Schwann Cell Options for chronic Pain Eradication

Chronic pain, characterized by increased sensitivity to innocuous/mild stimuli (allodynia), afflicts 25% of the European adult population. Efficacy and/or safety of analgesic medicines is limited, and the treatment of chronic pain associated with inflammation, peripheral and central neuropathies and cancer remains unsatisfactory. Thus, identification of novel targets for better and safer analgesics is a major medical need. Transient receptor potential ankyrin 1 (TRPA1) channel, expressed by a subpopulation of primary sensory neurons (nociceptors), has been proposed as a major transducer of acute pain. We have, recently, identified that TRPA1 is expressed in Schwann cells that ensheath peripheral nerve fibres. In a prototypical model of neuropathic pain (sciatic nerve ligation in mice), we discovered that Schwann cell-TRPA1 exerts a hitherto unknown role that, via amplification of the oxidative stress message, sustains neuroinflammation and chronic pain (allodynia). Thus, Schwann cells, through their own repertoire of channels and enzymes orchestrate in the injured/inflamed tissue an autocrine/paracrine signalling pathway to sustain chronic pain. The purpose of the present project is to extend this observation to other models of inflammatory, neuropathic and cancer pain to identify a general paradigm based on Schwann cell/TRPA1/oxidative stress as the pathway that sustains chronic pain. We aim also at identifying in oligodendrocytes (the Schwann cells of the brain) whether the TRPA1/oxidative stress pathway sustains pain in the central nervous system. In mouse, rat and human Schwann cells/oligodendrocytes we aim at identifying biomarkers and combine them into biosignatures predictive of the susceptibility to the development of chronic pain. We anticipate that each molecular step that entails the TRPA1/oxidative stress pathway in Schwann cell lineages is an eligible target for discovering new effective and safer medicines for the treatment of chronic pain.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	850896	**E4I**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Pascal Geldsetzer**
Host Institution:	Universitatsklinikum Heidelberg - DEU

Improving health services to prevent heart attacks and strokes: Evidence for interventions (E4I) in large middle-income countries

Largely due to the ageing of their populations and changing lifestyles, middle-income countries (MICs) are facing a rapidly increasing burden of heart attacks and strokes. Most of these cardio- and cerebrovascular disease (CCVD) events are preventable through successful treatment of three major risk factors: diabetes, dyslipidaemia, and hypertension. Yet despite the existence of inexpensive and effective medications, only a small minority of adults with these risk factors in MICs successfully transition through the care continuum from screening to effective treatment. There is currently little to no evidence from these settings on what health services interventions are most effective in reducing the loss of patients along the CCVD risk factor care continuum. Focussing on the four most populous MICs – which jointly account for 43% of the world's population – E4I thus aims to i) determine at which of the main steps in the care continuum – screening, linkage to care, and retention in care – the greatest loss of patients occurs; ii) establish which health services interventions have been most effective in reducing the loss of patients at each of these three care steps; and iii) ascertain the causal effect of reducing the loss of patients along the care continuum on individuals' health and economic outcomes. To do so, E4I will use novel causal inference techniques from different academic disciplines on large population-based cross-sectional and cohort datasets with jointly over seven million participants, challenging the frequently-held beliefs in public health that only randomised trials can provide causal effect estimates and that cohort data's principal value is the study of disease aetiology. By generating urgently needed knowledge on how to more effectively deliver proven treatments for a major public health problem in MICs, E4I will decisively advance public health research and has the potential to have an important impact on population health globally.

Link to the ERC project webpage:

Keywords of the ERC project: global health; epidemiology; health policy; health services research; cardiovascular disease; chronic diseases; causal inference

Keywords that characterize the scientific profile of the potential visiting researcher/s: epidemiology; statistics; econometrics; machine learning; deep learning; data science

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7 Diagnostic Tools, Therapies and Public Health
	850974	**MABSTER**	

European Research Council
Executive Agency
Established by the European Commission

Principal Investigator:	**Dr Andreas Laustsen**
Host Institution:	Danmarks Tekniske Universitet - DNK

Monoclonal Antibodies with Binding Sensitive To Environmental Regulation

Snakebite envenoming is a Neglected Tropical Disease (NTD) that each year affects 2.5 million victims and kills >100,000, unless they are treated with antivenom. Conventional antivenoms, derived from immunized animals, inflict serum sickness and anaphylaxis in patients, and are costly to manufacture. Monoclonal human antibodies with special toxin-binding properties that are sensitive towards regulation by their microenvironment (e.g. pH), which may be discovered using phage display selection, may solve this issue, providing significant societal impact by enabling the development of cost-effective antivenoms to victims in low and middle-income countries. In this project, phage display selection, high-density peptide microarray technology, and antibody engineering techniques will in three scientific objectives be harnessed in the pursuit of developing novel methodologies for discovery of therapeutic human monoclonal antibodies that are recyclable (can neutralize more than one snake toxin per antibody), broadly cross-reactive (can neutralize different types of snake toxins), and that are both broadly cross-reactive and recyclable at the same time. This will open up for entirely new ways of designing biotherapeutics against complex indications, such snakebite envenoming, but also cancer, infectious, and parasitic diseases, where the targets can be elusive due to hyper-mutability. The ERC Starting Grant offers a unique opportunity to consolidate me as an international key scientific researcher in this field of antibody discovery and NTDs. I have already independently led a research group in this area for 2 years, I have in-depth experience with toxin-targeted antibody discovery (my dr.tech dissertation similar to the German "habilitation" will be submitted during fall 2018), and I am already involved in high level policy in the field of snakebite envenoming via my role as a scientific advisor for the World Health Organization.

Link to the ERC project webpage: https://mabstertpl.wordpress.com

Keywords of the ERC project: antibody; toxin; phage display

Keywords that characterize the scientific profile of the potential visiting researcher/s: antibody; toxin; phage display

	Project ID:	Project Acronym:	Evaluation Panel:
	851231	**Therautism**	**LS7** Diagnostic Tools, Therapies and Public Health

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

New molecular targets and proof-of-concept therapies for Autism Spectrum Disorders

Autism is the major neurodevelopmental health public issue, affecting 1/100 child births worldwide. These disorders are diagnosed before the age of 3, based on behavioural cues: deficits in social interaction and communication as well as stereotyped and restrained behaviours. There is no medication to improve this condition. Most recent molecular targets identified within narrow frameworks (unspecific molecule, single tissue targeted, single disease model used) have failed in clinical trials. My first objective aims at thwarting this autism research gap, unravelling the common molecular and cellular dysfunctions underlying autism-related behaviours across several preclinical models and neuronal circuits. In particular, setting up translatomic analyses in these paradigms will identify and validate new molecular therapeutic targets. I recently deciphered one such molecular substrate, involving the loss of oxytocin transcripts in oxytocinergic axon terminals thus demonstrating the feasibility of this global approach. The second major objective of my project is to hijack the properties of a newly identified protein function to restore this new target and rescue social deficits in different preclinical models of autism. This would yield a novel and safe gene therapy vector which has never been explored before. Altogether, my research project will deliver strategic resources to the scientific and medical communities that will spur the development of new treatment options for autistic patients.

Link to the ERC project webpage:

Keywords of the ERC project: mRNAs, autism, social interaction, therapeutic

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	852373	**MultiSeroSurv**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Michael White**
Host Institution:	Institut Pasteur - FRA

Algorithms and multiplex assays for integrated serological surveillance of malaria and neglected tropical diseases

Malaria and neglected tropical diseases (NTDs) such as lymphatic filariasis, onchocerciasis, trachoma and schistosomiasis affect almost 2 billion people every year. Coordinated targeting of these diseases will aid future control and elimination campaigns, but this will require integrated surveillance strategies. Malaria surveillance is routinely implemented through cross-sectional surveys where blood samples are tested for parasites. A major barrier to routine NTD surveillance is the range of samples required for parasite diagnosis: stool, urine, blood, eye swabs and skin snips. Instead of direct detection of parasites, there is an opportunity to implement serological surveillance by measuring antibodies to multiple pathogens in blood samples collected for malaria surveillance.

This proposal has four aims: (i) Characterise the sero-epidemiology of malaria and NTDs in longitudinal cohort studies in Senegal, Ethiopia, Cambodia and Papua New Guinea; (ii) Measure antibodies to 34 antigens from 12 pathogens from single blood samples; (iii) Model antibody kinetics and validate the use of serology for detecting infections; and (iv) Demonstrate how a population's concurrent and past exposure to multiple parasites can be estimated by analysing multiplex data from cross-sectional surveys.

These aims will be achieved through innovative epidemiological studies, new technologies, and especially developed analytic methods, including: (1) utilisation of multiplex bead-based Luminex assays; (2) mixed-effects models in a Bayesian framework with data augmentation to identify serologically suspected infections, with validation against confirmed infections; and (3) statistical algorithms for reconstructing long-term and recent transmission trends. This interdisciplinary project will undertake fundamental research in analytic methods for processing complex multiplex data and converting it to the actionable information needed for integrated serological surveillance of malaria and NTDs.

Link to the ERC project webpage:

Keywords of the ERC project: malaria; neglected tropical diseases; serology; modelling

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	852832	**RARITY**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Noel de Miranda**
Host Institution:	Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum - NLD

RAtional design of canceR ImmunoTherapY: one size does not fit all

Checkpoint blockade immunotherapies have revolutionized cancer treatment. However, this immunotherapy only benefits a minority of patients (< 15%), mainly those diagnosed with cancers having many mutations. Furthermore, checkpoint blockade therapy does not selectively activate cancer-reactive T cells.

RARITY responds to these shortcomings, aiming to provide innovative solutions for the development of effective immunotherapies for patients who do not benefit from current treatments. The ground-breaking preliminary data included in this application demonstrates that cancer-reactive T cells can be naturally present in so-called non-immunogenic cancers and that they acquire distinctive phenotypes. RARITY will apply state-of-the-art technologies to fingerprint these phenotypes. This will allow the isolation of cancer-reactive T cells from tumour tissues and their employment as highly-effective therapies. Therapeutic vaccination with cancer antigens can also be used to induce T cell responses in patients where natural activation of cancer-specific T cells is not detectable. However, the applicability of vaccination is compromised by the lack of specific targets, particularly in malignancies with few mutations. RARITY will address this problem by deploying a novel class of cancer antigens. An unprecedented screening of non-exomic genomic regions will be done to detect unannotated proteins that arise from de novo transcription and translation events. These proteins can then be targeted by personalized immunotherapies. Finally, thought-provoking findings included in RARITY suggest that immune cell subsets other than T cells play a major role in anti-tumour immune responses. These subsets need to be fully inventoried and categorised so that complementary strategies to T cell immunotherapies can be developed. RARITY will do so by conducting multidimensional analysis of cancer microenvironments using imaging mass cytometry and ex vivo modulation of immune responses.

Link to the ERC project webpage: https://www.lumc.nl/over-het-lumc/nieuws/2019/September/erc-immuuntherapie/?setlanguage=English&setcountry=en

Keywords of the ERC project: Cancer immunotherapy; mass cytometry; neoantigens; innate lymphoid cells.

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

	Project ID:	Project Acronym:	Evaluation Panel:
	864180	**QUANTUM**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Teun Bousema**
Host Institution:	Stichting Katholieke Universiteit - NLD

Quantifying the spread of P. falciparum malaria

Background: A major challenge for malaria elimination is its phenomenally efficient spread through sexual stage parasites (gametocytes). Many individuals in endemic settings harbour low but transmissible gametocyte densities. It is currently unclear how gametocyte density translates into the likelihood that an infected mosquito gives rise to secondary infections, who drive malaria transmission at population level and how anti-gametocyte immunity affects gametocyte production and infectivity.

I hypothesize that secondary infections can arise from low-density infections but that higher gametocyte densities result in comparatively more infectious mosquitoes and an increased number of secondary infections. I further hypothesize that malaria transmission efficiency and changes therein can only be accurately predicted if anti-gametocyte immunity is thoroughly understood and that the rapid loss of gametocyte immunity during effective control results in increased transmission efficiency.

Aims and approach: I will perform the first-ever direct assessment of numbers of malaria parasites ejected by mosquitoes in relation to natural gametocyte densities. Using novel genotyping approaches, longitudinal sampling of infections at unsurpassed resolution and state-of-the art analytical approaches, I will perform the most comprehensive molecular evaluation of malaria transmission in a real community ever performed. Lastly, I will quantify the impact of immune responses that reduce gametocyte density and infectivity by novel immune-profiling approaches and mathematical transmission models.

Importance and innovation: this project will profoundly improve understanding of the production and infectivity of gametocytes and the epidemiological impact of human immune responses that influence these processes. The work in different African settings will provide a major leap forward in understanding the human infectious reservoir for malaria and has direct implications for elimination

Link to the ERC project webpage:

Keywords of the ERC project: malaria, gametocyte, transmission, anopheles, elimination

Keywords that characterize the scientific profile of the potential visiting researcher/s: complementing interest in transmission from vector or parasite side, epidemiology, bioinformatics, molecular biology, diagnostics,

	Project ID:	Project Acronym:	Evaluation Panel:
	865797	**DITSB**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Annarita Miccio**
Host Institution:	Institut National De La Sante Et De La Recherche Medicale (Inserm) - FRA

Development of Innovative Therapeutic Strategies for beta-hemoglobinopathies

Beta-thalassemia and sickle cell disease (SCD) are caused by mutations affecting the synthesis or the structure of the adult hemoglobin (Hb) beta-chain. The only definitive cure is transplantation of allogeneic hematopoietic stem cells (HSCs) from an HLA-matched donor, an option available to <30% of the patients. The clinical severity of beta-hemoglobinopathies is alleviated by the co-inheritance of mutations causing expression of fetal gamma-globin in adult life - a condition termed hereditary persistence of fetal hemoglobin (HPFH). Transplantation of autologous, genetically modified HSCs is an attractive therapeutic option for patients lacking a suitable donor. To this aim, genome editing approaches based on the use of site-specific nucleases have been explored by many groups, including ours. These approaches may either revert the single point mutation causing SCD or reactivate fetal globin expression, by mimicking HPFH mutations or by decreasing the level of BCL11A, a master repressor of fetal Hb synthesis. Site-specific nucleases, however, generate double-strand breaks (DSBs) in the genome and raise safety concerns for clinical applications, particularly when used in DSB-sensitive HSCs. In this proposal, we aim at exploiting targeted base-editing to develop novel, efficacious and safe strategies for beta-hemoglobinopathies without generating DSBs. This will be attempted by (i) correcting the SCD-causing mutation, (ii) mimicking HPFH mutations in the gamma-globin promoters, or (iii) modulating the activity of a BCL11A erythroid-specific enhancer. These approaches will be tested in human adult erythroid cell lines and patient HSCs, differentiated in vitro and in vivo into mature red cells to evaluate editing efficiency, fetal Hb expression, phenotypic cell correction and biosafety. The ultimate goal of the project is to provide sufficient proof of efficacy and safety to enable the clinical development of base-edited HSCs for the therapy of beta-hemoglobinopathies.

Link to the ERC project webpage:

Keywords of the ERC project: gene therapy hemoglobinopathies transcription epigenetics

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	866411	**CompHematoPathology**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Carsten Marr**
Host Institution:	Helmholtz Zentrum Muenchen Deutsches Forschungszentrum Fuer Gesundheit Und Umwelt Gmbh - DEU

Computational Hematopathology for Improved Diagnostics

Identifying hematologic malignancies still relies on the time-consuming and subjective visual assessment of images. Every day, cytologists and pathologists are confronted with rare diagnostic cells, ever-increasing image data, and heterogeneous disease manifestations. Although we understand blood better than any other human tissue, we are unable to quantitatively predict a patient's blood dynamics from a measurement. Diagnosis thus depends on rough staging schemes and the expertise and intuition of the clinician.

In my proposal, I address these challenges by establishing computational hematopathology, a combination of artificial intelligence algorithms and mathematical models that will boost the currently prevailing manual assessment. Based on my experience in using these methods for scrutinizing stem cell differentiation I will combine the power of deep learning and mathematical modeling with digitized and expertly annotated image data. My unique approach enables me to design and parametrize a data-driven model to predict hematopoietic dynamics in health and disease. Since the interpretation of digitized slides is becoming the clinical standard, novel algorithms for standardized disease classification and improved diagnosis are critically needed now.

This interdisciplinary project merges methods from digital pathology, machine learning, image processing, and mathematical modeling. ComHematoPathology will provide novel approaches and software tools for automated classification of hematopathology image data, allowing for reproducible and precise diagnosis at an unprecedented level. This will increase throughput and standardize the diagnosis of blood diseases and will thus improve the treatment of patients suffering from hematologic malignancies.

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**866448**	**TrojanDC**	**LS7** Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr Filipe 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.

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	866504	**CANCER-RADIOMICS**	Diagnostic Tools, Therapies and Public Health

Principal Investigator:	**Dr HUGO AERTS**
Host Institution:	Universiteit Maastricht - NLD

Deep Learning for Automated Quantification of Radiographic Tumor Phenotypes

Artificial Intelligence (AI), deep-learning in particular, is propelling the field of radiology forward at a rapid pace. In oncology, AI can characterize the radiomic phenotype of the entire tumor and provide a non-invasive window into the internal growth patterns of a cancer lesion. This is especially important for patients treated with immunotherapy as, despite the remarkable success of these novel therapies, the clinical benefit remains limited to a subset. As immunotherapy is expensive and could bring unnecessary toxicity there is a direct need to identify beneficial patients, but this remains difficult in clinical practice today. Radiomic biomarkers could address this, as, unlike biopsies that only represent a sample within the tumor, radiomics can depict a full picture of each cancer lesion with a single non-invasive examination. Previous work found significant connections between radiomic data, molecular pathways, and clinical outcomes. However, a direct link between radiomics and immunotherapy response has not yet been established. This project will address this problem by analyzing unique multicentre clinical data, including non-invasive imaging, clinical outcomes, and extensive biologic characterization, of over 3200 patients with lung or melanoma cancer. Specifically, I will develop deep-learning radiomic biomarkers to predict immunotherapy response using baseline (WP1) and follow-up imaging (WP2). I will also investigate if radiomics can characterize underlying biological factors, and, in turn, can be used to improve response predictions (WP3). Successful completion of this proposal will demonstrate the potential of radiomics to help physicians in selecting patients who will likely benefit from immunotherapy, while sparing this expensive and potentially toxic treatment for patients who don't. This work has implications for the use of imaging-based biomarkers in the clinic, as they can be applied noninvasively, repeatedly, and at low additional cost.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS7
	866510	**TRANSLATIONAL**	Diagnostic Tools, Therapies and Public Health

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:

Keywords of the ERC project: Diabetes type 2, RNA sequencing, single-cell, pancreatic islets, insulin secretion

Keywords that characterize the scientific profile of the potential visiting researcher/s: Diabetes type 2, RNA sequencing, single-cell, pancreatic islets, insulin secretion

Toxin mimetics of human peptides as novel tools for drug discovery and design

Venomous animals use a myriad of toxins to specifically disrupt the physiology and behavior of their prey. Because of their high stability, potency, and specificity, toxins are important tools for biomedical research and have been developed as therapeutics for various human diseases. However, contributions to date pale in comparison to future prospects. We hypothesize that a small and essentially overlooked group of toxins, "ToxMims", represent the most promising candidates for drug discovery and development. ToxMims potently disrupt the prey's physiology by specifically mimicking the action of endogenous signaling peptides. Because many of these signaling peptides are critical players in human health and disease, ToxMims are exceptionally promising drug leads. Proof-of-concept is provided by our recent discovery of a toxin mimetic of insulin that is used by a marine cone snail to induce dangerously low blood sugar in fish prey. Because of its advantageous properties over human insulin, the venom insulin has rapidly become a novel drug lead for the treatment of diabetes. Despite their significant biomedical potential, ToxMims are rare and difficult to systematically detect using currently available methodologies. By leveraging recent advances in next-generation sequencing combined with our proven expertise in computational and experimental venom discovery and pharmacology, this project aims to develop a set of tools to enable the systematic identification and characterization of any ToxMim of the ~350 human signaling peptides with an emphasis on those implicated in disease. If successful, this research will not only identify a set of unique drug leads with profound impact on human health but elucidate previously unknown mechanisms of receptor activation, inhibition and signaling. Furthermore, this project will foster European excellence in venom research and develop scientific leadership competences for an independent, early-career researcher returning to Europe.

Link to the ERC project webpage:

Keywords of the ERC project: venom, discovery, computational, hormones, toxins, GPCR, biomedicine

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatician, biochemist, pharmacologist, GPCR pharmacology

Project ID:	Project Acronym:	Evaluation Panel:
		LS8
724324	**macroevolution.abc**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Lee Hsiang Liow**
Host Institution:	Universitetet I Oslo - NOR

Abiota, Biota, Constraints in Macroevolutionary Processes

To what degree do microevolutionary processes that happen on a generational time scale matter for macroevolutionary patterns recorded on time scales of millions of years in the fossil record? To answer this fundamental question in evolutionary biology, we need a model system in which we can overcome the conceptual and empirical boundaries imposed by disparate timescales. macroevolution.abc will develop bryozoans as the Drosophila of macroevolution, integrating molecular, fossil, phenotypic, ecological and environmental data to shed light on the currently inaccessible "Dark Time Scale" (thousands, to tens of thousands of years), spanning the chasm between microevolution studied by population geneticists and evolutionary ecologists and macroevolution studied by paleontologists and comparative phylogeneticists. Using bryozoans, a little-known but uniquely ideal study group for evolutionary questions, I will generate, then cross-integrate, (i) empirical time series of intra- and interspecific biotic interactions; (ii) phenotypic data describing variation within genetic individuals, variation among contemporaneous individuals in both extinct and living populations; (iii) robust estimates of abundance shifts in fossil populations; and (iv) speciation and extinction rate estimates from molecular phylogenies and the fossil record. The new bryozoan model evolutionary system will provide answers to previously intractable questions such as "do ecological interactions crucial for individual survival matter for group diversification patterns observed on geological time scales" and "why do we have to wait a million years for bursts of phenotypic change"?

Link to the ERC project webpage:

Keywords of the ERC project: macroevolution, evolutionary biology, paleoecology, bryozoa, biotic interactions, life history traits

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	725848	**CORALASSIST**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr James Guest**
Host Institution:	University Of Newcastle Upon Tyne - GBR

Assisting Coral Reef Survival in the Face of Climate Change

CORALASSIST spans the disciplines of evolutionary biology, restoration ecology and proteomics and examines the role assisted gene flow (AGF) can play in sustaining biodiversity and ecosystem services in the face of climate change. AGF involves the deliberate movement of individuals or gametes within their natural range to facilitate adaptation to environmental change. Corals reefs provide an excellent model for testing AGF as a conservation tool because reef building corals are foundation species and are highly vulnerable to thermal stress. Selective breeding and translocation of thermotolerant individuals may lead to reductions in recipient population fitness due to resource trade-offs with other fitness traits, such as growth and fecundity. The overall aim of CORALASSIST is to establish the feasibility of implementing AGF in coral reef ecosystems using a combination of selective breeding, proteomics and innovative translocation techniques. CORALASSIST will address four primary questions: 1) Are there resource trade-offs between increased thermotolerance and other fitness traits in corals? 2) Which physiological and proteomic traits correlate with increased individual thermotolerance in corals? 3) Are phenotypic traits for thermotolerance heritable? 4) Can AGF and selective breeding lead to persistent shifts in thermotolerance in recipient populations? Phenotypic traits will be measured in permanently tagged individuals within selected coral populations to examine the relationships between thermotolerance and key fitness attributes. For the first time, state of the art proteomic approaches will be used to elucidate the physiological basis for increased levels of thermotolerance in corals. Innovative translocation methods will be used in tandem with selective breeding techniques to carry out the first long term assessment of heritability of thermotolerance and to test the feasibility of large scale AGF to assist conservation of coral reef ecosystems.

Link to the ERC project webpage: www.coralassistlab.org

Keywords of the ERC project: Coral reefs, climate change, assisted evolution, selective breeding, restoration

Keywords that characterize the scientific profile of the potential visiting researcher/s: Ecology, molecular ecology, coral reefs, restoration

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	741298	**MagneticMoth**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Eric Warrant**
Host Institution:	Lunds Universitet - SWE

Hunting for the elusive "sixth" sense: navigation and magnetic sensation in a nocturnal migratory moth

Many animals – including birds, sea turtles and insects – perform spectacular long-distance migrations across the surface of the Earth. Remarkably some, like birds, can accurately migrate between highly specific locations thousands of kilometres apart, a navigational feat that requires an external compass cue and a robust sensory system to detect it. The Earth's magnetic field is one such compass cue. But exactly how the magnetic field is sensed, and which receptor cells are involved, remains a mystery and its discovery is one of the greatest "holy grails" in modern sensory physiology, and also the main aim of this proposal. Fortuitously, I have made a pioneering discovery that a migratory insect – the Australian Bogong moth – relies on the Earth's magnetic field to navigate at night. Due to its tractable nervous system, this insect may thus hold the key to uncovering the identity of the enigmatic magnetosensor. By tethering flying migrating moths in a flight simulator, I will dissect for the first time how insects use magnetic cues to navigate, isolating which of the two current (contentious) hypotheses for magnetic sensation apply. The most likely of these involves the action of photoreceptor-based cryptochrome (Cry) molecules in the eyes. Having cloned genes for 4 visual opsins and 2 Cry in Bogong moths, I will use in situ hybridisation to localise putative magnetoreceptors in the eyes, targeting them with intracellular electrophysiology and magnetic stimulation in an attempt to describe the physiology of these elusive sensors for the first time. The project is ground breaking since it will elucidate how a migratory insect, despite its small eyes and brain, detects and uses the Earth's magnetic field for navigation. The discovery of the enigmatic magnetoreceptor would be a sensation, opening the floodgates for international research on this little understood sense.

Link to the ERC project webpage:

Keywords of the ERC project: Magnetic sense, nocturnal vision, animal navigation, migration, insects, Bogong moth, Agrotis infusa

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency *Established by the European Commission*	**742312**	**MATURATION**	**LS8** Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Craig Primmer**
Host Institution:	Helsingin Yliopisto - FIN

Age at maturity in Atlantic salmon: molecular and ecological dissection of an adaptive trait

Life history is the nexus of biology, because various biological questions ultimately revolve around the causes and consequences of variation in reproduction and survival, i.e. fitness. Traditionally, a major tool in life-history research has been quantitative genetics because it provides an important statistical link between phenotype and genotype. However, the mechanisms by which evolution occurs may remain unclear unless such traditional approaches are combined with molecular investigations. Another complicating factor is that the fitness of male vs female life histories do not always align, and hence life history traits may be shaped by sexual conflict. This is why life-history approaches focusing on both quantifying the conflict and understanding its resolution at the genetic level are needed.

As in many species, age at maturity in Atlantic salmon is tightly linked with size at maturity and thus represents a classic evolutionary trade-off: later maturing individuals spend more time at sea before returning to freshwater to spawn and have higher reproductive success due to their larger size but also have a higher risk of dying prior to first reproduction. Our recent cover paper in Nature reported a large-effect gene explaining 40% of the variation in this key life history trait. Remarkably, the locus exhibits sex-dependent dominance and this resolves a potential intra-locus sexual conflict in the species. The relatively simple genetic architecture of this trait combined with the features of Atlantic salmon as a model system offer an ideal opportunity to better understand the molecular mechanisms and ecological drivers underlying a locally adapted life history trait.

In MATURATION I will i) characterize age at maturity candidate gene functions and allelic effects on phenotypes ii) elucidate fitness effects of these phenotypes and GxE interactions iii) develop a mechanistic model for the sex-dependent dominance and validate intra-locus sexual conflict resolution

Link to the ERC project webpage:

Keywords of the ERC project: sexual conflict, functional genomics, ecology, evolutionary biology, ecological genetics, population genetics

Keywords that characterize the scientific profile of the potential visiting researcher/s: sexual conflict, functional genomics, ecology, evolutionary biology, ecological genetics, population genetics

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	755876	**Ca2Coral**	Evolutionary, Population and Environmental Biology

European Research Council
Executive Agency
Established by the European Commission

Principal Investigator:	**Dr Tali Mass**
Host Institution:	University Of Haifa - ISR

Elucidating the molecular and biophysical mechanism of coral calcification in view of the future acidified ocean

Although various aspects of biomineralisation in corals have been studied for decades, the basic mechanism of precipitation of the aragonite skeleton remains enigmatic. Two parallel lines of inquiry have emerged: geochemist models of calcification that are directly related to seawater carbonate chemistry at thermodynamic equilibrium. Here, the role of the organisms in the precipitation reaction is largely ignored. The second line is based on biological considerations of the biomineralisation process, which focuses on models of biophysical processes far from thermodynamic equilibrium that concentrate calcium ions, anions and proteins responsible for nucleation in specific compartments. Recently, I identified and cloned a group of highly acidic proteins derived the common stony coral, Stylophora pistillata. All of the cloned proteins precipitate aragonite in seawater at pH 8.2 and 7.6 in-vitro. However, it is not at all clear if the expression of these proteins in-vivo is sufficient for the formation of an aragonite skeleton at seawater pH values below ~7.8. Here using a combination of molecular, biophysical, genomic, and cell biological approaches, we proposed to test the core hypothesis that, unless wounded or otherwise having skeletal material exposed directly to seawater, stony zooxanthellate corals will continue to calcify at pH values projected for the CO2 emissions scenarios for 2100.

Specifically, the objectives of Ca2Coral are to:

1) Use functional genomics to identify the key genes and proteins involved both in the organic matrix and skeleton formation in the adult holobiont and during its larval development.

2) Use a genetics approach to elucidate the roles of specific proteins in the biomineralisation process.

3) Use ultra-high resolution imaging and spectroscopic analysis at different pH levels to elucidate the biomineralisation pathways and mineral precursor in corals in the adult holobiont and during its larval development.

Link to the ERC project webpage: http://marsci.haifa.ac.il/labs/cbp

Keywords of the ERC project: Biomineralization, Coral, climate change, photosynthesis, proteomic, genomic

Keywords that characterize the scientific profile of the potential visiting researcher/s: Biomineralization, Coral, climate change, photosynthesis, proteomic, genomic

Project ID:	Project Acronym:	Evaluation Panel:
		LS8
758161	**Multicellularity**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Laszlo Nagy**
Host Institution:	Szegedi Biologiai Kutatokozpont - HUN

The genetic basis of the convergent evolution of fungal multicellularity

The evolution of multicellularity (MC) has been one of the major transitions in the history of life. Despite immense interest in its evolutionary origins, the genomic changes leading to the emergence of MC, especially that of complex MC (differentiated 3-dimensional structures) are poorly known. Previous comparative genomics projects aiming to understand the genetic bases of MC in one way or another relied on gene content-based analyses. However, a pattern emerging from these studies is that gene content provides only an incomplete explanation for the evolution of MC even at ancient timescales. We hypothesize that besides gene duplications, changes to cis-regulatory elements and gene expression patterns (including protein isoforms) have significantly contributed to the evolution of MC. To test this hypothesis, we will deploy a combination of computational methods, phylogenomics, comparative transcriptomics and genome-wide assays of regulatory elements. Our research focuses on fungi as a model system, where complex MC evolved convergently and in subsequent two steps. Fungi are ideal models to tackle this question for several reasons: a) multicellularity in fungi evolved multiple times, b) there are rich genomic resources (>500 complete genomes), c) complex multicellular structures can be routinely grown in the lab and d) genetic manipulations are feasible for several cornerstone species. We set out to examine which genes participate in the building of simple and complex multicellular structures and whether the evolution of regulome complexity and gene expression patterns can explain the evolution of MC better than can traditionally assayed sources of genetic innovations (e.g. gene duplications). Ultimately, our goal is to reach a general synthesis on the genetic bases of the evolution of MC and that of organismal complexity.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	758382	**GUPPYCon**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Bonnie Fraser**
Host Institution:	The University Of Exeter - GBR

Genomic basis of convergent evolution in the Trinidadian Guppy

Many species have independently evolved similar phenotypes in response to similar environmental challenges. This phenomenon, termed convergent evolution, reflects both the power and the limits of adaptation. However, we often do not know at what scale evolution has repeated itself: did selection act on the same genes in different populations or species, or did convergence result from selection on different genes? This is because, until recently, it has not been possible to investigate the genomic basis of evolution in most systems, limiting our understanding of the factors that facilitate or inhibit convergence and adaptation. To fully understand convergent evolution we need to query the genomic response to selection and determine genotype-phenotype links in systems where convergent adaptation is well established. The Trinidadian guppy (Poecilia reticulata) is a system that offers the opportunity to test the roles of multiple factors in convergent evolution: this species includes multiple natural and experimentally established populations that have repeatedly evolved similar phenotypes under similar predation environments. I propose to fully characterize the genomic-basis of repeated adaptive evolution in guppies. Aim 1 will identify regions that repeatedly show signatures of selection, and will contrast the nature of selection in natural and experimental populations that differ in age and levels of founding genetic diversity. Aim 2 will identify genomic regions associated with phenotypes that are known to play a significant role in local adaptation in the guppy using quantitative genetics approaches. I will then directly test the effects of candidate genes using novel functional genomic approaches, as detailed in Aim 3. Overall, this project will test whether repeated selection led to convergence at the genomic level, determine the genetic basis of convergent adaptations, and ultimately understand how convergent evolution has occurred in an important wild system.

Link to the ERC project webpage:

Keywords of the ERC project: population genetics, genomics, convergent evolution, guppy

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	758873	**TreeMort**	Evolutionary, Population and Environmental Biology

European Research Council
Executive Agency
Established by the European Commission

Principal Investigator:	**Dr Thomas Pugh**
Host Institution:	The University Of Birmingham - GBR

Redefining the carbon sink capacity of global forests: The driving role of tree mortality

Everything that lives must die. Yet when it comes to the world's forests, we know much more about the processes governing their life than those governing their death. Global forests hold enormous amounts of carbon in their biomass, which has absorbed about 20% of anthropogenic carbon dioxide emissions over recent decades. Whether the size of this sink will persist, intensify, decrease or even become a source is highly uncertain, yet knowing this is crucial to the calculation of carbon emission budgets consistent with limiting global temperature rise. One of the most compelling explanations for this uncertainty is a lack of knowledge of how tree mortality affects forest carbon storage on a global scale. Mortality rates and mechanisms are closely tied to forest structure and composition, and thus the storage of carbon in biomass, but mechanistic complexity and the difficulty of measurement have hindered understanding, resulting in a striking lack of consensus in existing assessments. TreeMort will remedy this, combining newly available sources of data with appropriate conceptualisation and innovative modelling, to provide quantifications of the rates and causes of tree death, and their relation to environmental drivers, that set new standards for robustness, comprehensiveness and consistency at the global scale. This breaking-out of the narrower foci of previous work will be a game-changer, finally enabling globally-comprehensive investigation of the extent to which whole forest structure and function are governed by and interact with mortality, and their likely evolution under environmental change. TreeMort will assess this using state-of-the-art ecosystem modelling, which will then be employed to make a fundamental reassessment of the current and future carbon storage capacity of global forests. TreeMort will thus bring us significantly closer to understanding fully how forests interact with the global carbon cycle, assisting efforts to mitigate climate change.

Link to the ERC project webpage: more.bham.ac.uk/treemort

Keywords of the ERC project: Forest, tree mortality, carbon cycle, climate change, ecology, earth system modelling

Keywords that characterize the scientific profile of the potential visiting researcher/s: Forest ecology, modelling

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	771419	**DOUBLE EXPRESS**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Aoife McLysaght**
Host Institution:	The Provost, Fellows, Foundation Scholars & The Other Members Of Board Of The College Of The Holy & Undivided Trinity Of Queen Elizabeth Near Dublin - IRL

Gene expression level as a keystone to understanding gene duplication: evolutionary constraints, opportunities, and disease

Duplicate genes are important in disease, are a hugely important source of evolutionary novelty, and for many years we thought we understood them. We thought that duplication relieved selective constraints. We thought that gene knockout neutrality was due to redundancy. We thought that a duplicate is a duplicate is a duplicate. Evidence is accumulating challenging each of these views. Rather than being the result of an unbiased process, the genes that tend to duplicate in our genome and others are quickly evolving, non-essential genes, irrespective of current duplication status. Conversely, genes retained after whole genome duplication (WGD) are slowly evolving, important genes.

I propose that different resolution of the evolutionary constraints imposed by the demands of gene expression can explain these contrasting relationships. I propose that the opposing constraints on gene-by-gene duplications as compared to WGD channel these different sets of genes into remarkably different evolutionary trajectories. In particular, in much the same way that individual gene duplication creates an opportunity for the evolution of a new gene, the co-evolution of expression of sets of interacting genes after WGD creates an opportunity for the evolution of new biochemical pathways and protein complexes. Furthermore, I suggest a common mechanism of pathogenicity for many duplication events independent of the biochemical function of the encoded genes.

With the availability of abundant high-quality genomics data, now is an opportune time to address these questions. Primarily through computational and statistical analysis I will reveal the relationship between gene duplication and expression and test a model that the indirect costs of gene expression are a major determinant of the outcome of gene duplication. I will explore the effects this has on gene and genome evolution. Finally, I will link the patterns of gene expression and duplicability to pathogenic effects.

Link to the ERC project webpage:

Keywords of the ERC project: Comparative genomics

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

	Project ID:	Project Acronym:	Evaluation Panel:
	771592	**Amitochondriates**	**LS8** Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Vladimir Hampl**
Host Institution:	Univerzita Karlova - CZE

Life without mitochondrion

Mitochondria are often referred to as the "power houses" of eukaryotic cells. All eukaryotes were thought to have mitochondria of some form until 2016, when the first eukaryote thriving without mitochondria was discovered by our laboratory – a flagellate Monocercomonoides. Understanding cellular functions of these cells, which represent a new functional type of eukaryotes, and understanding the circumstances of the unique event of mitochondrial loss are motivations for this proposal. The first objective focuses on the cell physiology. We will perform a metabolomic study revealing major metabolic pathways and concentrate further on elucidating its unique system of iron-sulphur cluster assembly. In the second objective, we will investigate in details the unique case of mitochondrial loss. We will examine two additional potentially amitochondriate lineages by means of genomics and transcriptomics, conduct experiments simulating the moments of mitochondrial loss and try to induce the mitochondrial loss in vitro by knocking out or down genes for mitochondrial biogenesis. We have chosen Giardia intestinalis and Entamoeba histolytica as models for the latter experiments, because their mitochondria are already reduced to minimalistic "mitosomes" and because some genetic tools are already available for them. Successful mitochondrial knock-outs would enable us to study mitochondrial loss in 'real time' and in vivo. In the third objective, we will focus on transforming Monocercomonoides into a tractable laboratory model by developing methods of axenic cultivation and genetic manipulation. This will open new possibilities in the studies of this organism and create a cell culture representing an amitochondriate model for cell biological studies enabling the dissection of mitochondrial effects from those of other compartments. The team is composed of the laboratory of PI and eight invited experts and we hope it has the ability to address these challenging questions.

Link to the ERC project webpage: https://www.biocev.eu/en/about/projects/erc-consolidator-grant.6

Keywords of the ERC project: Protists, mitochondrion, evolution, endosymbiosis, iron-sulphur clusters, anaerobes

Keywords that characterize the scientific profile of the potential visiting researcher/s: Protists, endosymbiosis, mitochondrion, plastid, anaerobes, phylogenetics, euglenids, oxymonads, horisontal gene transfer

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	772284	**IceCommunities**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Gentile Francesco Ficetola**
Host Institution:	Universita Degli Studi Di Milano - ITA

Reconstructing community dynamics and ecosystem functioning after glacial retreat

Glaciers show a pattern of retreat at the global scale. Increasing areas are exposed and colonized by multiple organisms, but lack of global studies hampers a complete understanding of the future of recently deglaciated terrains. What will be the fate of these areas? How do animals, plants and microorganisms colonize them? How do they interact to perform successful colonization? Which are the climatic, geological and biogeographical processes determining colonization patterns? How does ecosystem functioning evolves through time? Until now, the complete reconstruction of soil communities was hampered by the complexity of identification of organisms, thus analyses at broad geographical and taxonomic scale have been so far impossible. IceCommunities will combine innovative methods and a global approach to boost our understanding of the evolution of ecosystems in recently deglaciated areas. I will investigate chronosequences ranging from recently deglaciated terrains to late successional stages of soil pedogenesis. Through environmental DNA metabarcoding I will identify species from multiple taxonomic groups (bacteria, fungi, protists, soil invertebrates, plants), to obtain a complete reconstruction of biotic communities along glacier forelands over multiple mountain areas across the globe. This will allow measuring the rate of colonization at an unprecedented detail. Information on assemblages will be combined with analyses of soil, landscape and climate to identify the drivers of community changes. I will also identify the impact of eco-geographical factors (climate, regional pool of potential colonizers) on colonization. Analysis of functional traits will allow reconstructing how functional diversity emerges during community formation, and how it scales to the functioning of food webs. IceCommunities will help to predict the future development of these increasingly important ecosystems, providing a supported rationale for the appropriate management of these areas

Link to the ERC project webpage:

Keywords of the ERC project: environmental DNA; climate change; biodiversity; soil; functional ecology; macroecology; DNA metabarcoding

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics; macroecology; functional ecology; food webs; biogeography; numerical ecology; DNA metabarcoding

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	789037	**EPICLINES**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Magnus Nordborg**
Host Institution:	Gregor Mendel Institut Fur Molekulare Pflanzenbiologie Gmbh - AUT

Elucidating the causes and consequences of the global pattern of epigenetic variation in Arabidopsis thaliana

Epigenetics continues to fascinate, especially the notion that it blurs the line between "nature and nurture" and could make Lamarckian adaptation via the inheritance of acquired characteristics possible. That this is in principle possible is clear: in the model plant Arabidopsis thaliana (Thale cress), experimentally induced DNA methylation variation can be inherited and affect important traits. The question is whether this is important in nature. Recent studies of A. thaliana have revealed a pattern of correlation between levels of methylation and climate variables that strongly suggests that methylation is important in adaptation. However, somewhat paradoxically, the experiments also showed that much of the variation for this epigenetic trait appears to have a genetic rather than an epigenetic basis. This suggest that epigenetics may indeed be important for adaptation, but as part of a genetic mechanism that is currently not understood. The goal of this project is to determine whether the global pattern of methylation has a genetic or an epigenetic basis, and to use this information to elucidate the ultimate basis for the global pattern of variation: natural selection.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
		LS8
801669	**EVOCELFATE**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Jose M Martin Duran**
Host Institution:	Queen Mary University Of London - GBR

Evolution of cell fate specification modes in spiral cleavage

Spiral cleavage is a highly stereotypical early embryonic program, and the ancestral, defining feature to Spiralia, a major phylogenetic clade including almost half of the animal phyla. Remarkably, spiral-cleaving embryos specify homologous cell fates (e.g. the progenitor cell of posterodorsal structures) conditionally –via cell interactions– or autonomously –via segregation of maternal inputs. This variation occurs naturally, even between closely related species, and has been related to the precocious formation of adult characters (adultation) in larvae of autonomous spiral-cleaving species. How spiralian lineages repeatedly shifted between these two cell fate specification modes is largely unexplored, because the mechanisms controlling spiral cleavage are still poorly characterized.

This project tests the hypothesis that maternal chromatin and transcriptional regulators differentially incorporated in oocytes with autonomous spiral cleavage explain the evolution of this mode of cell fate specification. Through a comparative and phylogenetic-guided approach, we will combine bioinformatics, live imaging, and molecular and experimental techniques to: (i) Comprehensively identify differentially supplied maternal factors among spiral cleaving oocytes with distinct cell fate specification modes using comparative RNA-seq and proteomics; (ii) Uncover the developmental mechanisms driving conditional spiral cleavage, which is the ancestral embryonic mode; and (iii) Investigate how maternal chromatin and transcriptional regulators define early cell fates, and whether these factors account for the repeated evolution of autonomous specification modes.

Our results will fill a large gap of knowledge in our understanding of spiral cleavage and its evolution. In a broader context, this project will deliver fundamental insights into two core questions in evolutionary developmental biology: how early embryonic programs evolve, and how they contribute to phenotypic change.

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

Keywords of the ERC project: animal development, epigenomics, evolutionary developmental biology (Evo-Devo)

Keywords that characterize the scientific profile of the potential visiting researcher/s: animal development, epigenomics, evolutionary developmental biology (Evo-Devo), genomics, modelling

	Project ID:	Project Acronym:	Evaluation Panel:
	804569	**FIT2GO**	**LS8** Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Claudia Bank**
Host Institution:	Universitaet Bern - CHE

A toolbox for fitness landscapes in evolution

A major challenge in evolutionary biology is to quantify the processes and mechanisms by which populations adapt to new environments. In particular, the role of epistasis, which is the genetic-background dependent effect of mutations, and the constraints it imposes on adaptation, has been contentious for decades. This question can be approached using the concept of a fitness landscape: a map of genotypes or phenotypes to fitness, which dictates the dynamics and the possible paths towards increased reproductive success. This analogy has inspired a large body of theoretical work, in which various models of fitness landscapes have been proposed and analysed. Only recently, novel experimental approaches and advances in sequencing technologies have provided us with large empirical fitness landscapes at impressive resolution, which call for the evaluation of the related theory.

The aim of this proposal is to build on the theory of fitness landscapes to quantify epistasis across levels of biological organization and across environments, and to study its impact on the population genetics of adaptation and hybridization. Each work package involves classical theoretical modelling, statistical inference and method development, and data analysis and interpretation; a combination of approaches for which my research group has strong expertise. In addition, we will perform experimental evolution in Escherichia coli and influenza to test hypotheses related to the change of fitness effects across environments, and to adaptation by means of highly epistatic mutations. We will specifically apply our methods to evaluate the potential for predicting routes to drug resistance in pathogens. The long-term goal lies in the development of a modeling and inference framework that utilizes fitness landscape theory to infer the ecological history of a genome, which may ultimately allow for a prediction of its future adaptive potential.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: ecological modeling, experimental evolution, population genomics

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	804673	**sEEIngDOM**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Andrew Tanentzap**
Host Institution:	The Chancellor, Masters And Scholars Of The University Of Cambridge - GBR

Ecological and Evolutionary Importance of Molecular Diversity in Dissolved Organic Matter

Dissolved organic matter (DOM) is central to the functioning of freshwater ecosystems that support life on Earth. For example, DOM has a major role in global carbon (C) cycling by helping to bury four times more C in the bottom of lakes and rivers than across all of the world's oceans. DOM also majorly influences the growth of aquatic organisms and impedes drinking water treatment for millions of people, such as by increasing microbial growth. Yet, despite its importance, DOM remains poorly understood because it has been measured with little resolution for nearly 200 years. Recent technological advances have now shown that a handful of lake water can contain at least 2,000 different molecules of varying origin and composition. But the role of all these different molecules in aquatic ecosystems largely remains a mystery.

This project will discover the importance of the tremendous diversity of molecules – termed chemodiversity – found in DOM for lake functioning and human wellbeing. It will do so by combining cutting-edge techniques in analytical chemistry, genomics, and statistical modelling with careful lab-based studies, proven field experiments, and large-scale observational surveys. By thinking about species of molecules as we would species of organisms, this project will draw upon rich theory and methods developed for the study of biodiversity. The work will allow us to learn how variation in chemodiversity across lakes is driven by associations with different microbes and how these microbes reciprocally adapt and evolve to different DOM. In the process, we will improve predictions of how important functions and services provided by lakes, such as C cycling and drinking water, vary with chemodiversity. An exciting application of this work is to improve emerging technologies for water purification by identifying microbial consortia that can consume chemodiversity and make water clearer.

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

Keywords of the ERC project: ecology, evolution, biogeochemistry, microbial ecology, genomics, carbon cycling, analytical chemistry, metabolomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: ecology, evolution, biogeochemistry, microbial ecology, genomics, carbon cycling, analytical chemistry, metabolomics

	Project ID:	Project Acronym:	Evaluation Panel:
	819952	**Mari.Time**	**LS8** Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Kristin Tessmar-Raible**
Host Institution:	Universitaet Wien - AUT

Dissecting the mechanistic basis of moon-controlled monthly timing mechanisms in marine environments

The correct timing of biological processes is crucial for organisms. The moon is an important timing cue for numerous marine species, ranging from brown and green algae to corals, worms and fishes. It acts either directly or via the synchronization of monthly (circalunar) inner clocks. Such lunar timing mechanisms typically control the gonadal maturation and behavioral changes associated with reproductive rhythms, including spectacular mass-spawning events. Despite their biological importance, the mechanisms underlying circalunar clocks, as well as their responses to naturalistic stimuli are unknown.

My lab has spearheaded research into the mechanisms underlying circalunar timing systems, establishing tools and resources for two well-suited, complementary animal models: Platynereis dumerilii and Clunio marinus. We unraveled first principles of the circalunar clock, e.g. its continuous function in the absence of oscillation of the daily (circadian) clock. Recent unpublished work revealed the first gene that functionally impacts on circalunar rhythms.

By capitalizing on these powerful tools and key findings, my lab is in a leading position to dissect the mechanisms of circalunar clocks and their interaction with other rhythms and the environment via three objectives:

(1) A reverse genetic approach to unravel how nocturnal light sets the phase of the monthly clock.

(2) A forward genetic screen to identify molecules involved in the circalunar clock, an experimental strategy that was the key to unravel the principles of animal circadian clocks.

(3) By growing animals in outside tanks and subjecting them to established analyses, we will test our lab-based results in more naturalistic conditions.

This project will substantially deepen our mechanistic insight into marine rhythms – ecologically important phenomena – and provide a first basis to predict how environmental changes might impact on timing systems of crucial importance to many marine species and likely beyond.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Principal Investigator:	**Dr Richard Merrill**
Host Institution:	Ludwig-Maximilians-Universitaet Muenchen - DEU

The genetic and neural basis of reproductive isolation

Speciation is a fundamental evolutionary process, which relies on the accumulation of reproductive barriers. These barriers often act before mating, and many taxa remain separate not because they fail to produce viable offspring, but because they 'choose' not to mate in the first place. Although the significance of behavioural barriers has long been recognized, an integrated understanding remains elusive: How is behavioural isolation mediated through changes in the sensory systems? Are these changes driven by selection? And what is the genetic and developmental basis of behavioural divergence in natural populations?

My research will address these questions to understand how behavioural barriers are generated, both during development and across evolutionary time. This project will be novel in uniting genomic and neurosensory data, with ecological and behavioural studies across a single radiation. Heliconius butterflies offer an excellent opportunity to achieve this as they are a group of closely related species with well-characterised ecologies, high-quality genomic resources, and are emerging as a model of evolutionary neurobiology.

These attributes will allow me to address the enduring problem of how natural selection and genetics interact to drive divergence in behavioural preferences. I will determine how components of behavioural isolation vary with ecology, both within and between species; and then explicitly test whether changes in sensory perception and processing in the brain are driven by selection imposed by the external environment. Genetic mapping will allow me to test for a link between changes in the sensory systems and mate choice. By combining these data with expression and functional analyses I will identify genes strongly implicated in the divergence of behavioural preferences. This will lead to novel insights into the developmental and neurological bases of behavioural isolation, a process fundamental to biodiversity.

Link to the ERC project webpage:

Keywords of the ERC project: Speciation Behaviour Heliconius Evolution

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

	Project ID:	Project Acronym:	Evaluation Panel:
	851678	**SHIFTFEEDBACK**	**LS8** Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Franciska de Vries**
Host Institution:	Universiteit Van Amsterdam - NLD

Ecosystem response to drought: unravelling the unexplored role of plant-soil feedback

Drought is severely threatening our ecosystems and their functioning: it causes strong shifts in plant community composition that are difficult to revert. Positive feedbacks often underlie these dramatic shifts, but in many ecosystems drought causes fast-growing species to increase. These species are not only vulnerable to drought, but they also suffer negative plant-soil feedback, i.e. they change the soil microbial community in a way that keeps their own abundance in check. Thus, drought-induced shifts in plant communities do not result from positive feedbacks, unless drought changes plant-soil feedback. We know that plant-soil feedback drives plant community succession, but its role in community response to drought has never been explored. Here, I will unravel whether and how changes in plant-soil feedback underlie strong shifts in plant community composition following drought. This knowledge is crucial for mitigating the effects of drought on terrestrial ecosystems.

My objectives are:

1. Examining how drought affects plant community and soil microbial community composition and the implications for plant-soil feedback

2. Quantifying the effects of plant-plant and plant-microbial interactions on plant growth and subsequent shifts in plant community composition in response to drought

3. Disentangling the mechanisms underlying drought-induced changes in plant-soil feedback

I will address these objectives in a novel set of approaches. I will identify general patterns in plant-soil feedback across European drought experiments, and assess the role of plant-plant and plant-microbial interactions across a Dutch secondary successional gradient. In a set of targeted mesocosm experiments, I will elucidate the mechanisms underlying changes in plant-soil feedback and the consequences for plant community composition. These approaches will result in a step-change in understanding the dynamics of plant-soil interactions under drought and the consequences for ecosystem change.

Link to the ERC project webpage:

Keywords of the ERC project: drought, plant-soil interactions, climate change, soil microbial communities, ecosystems, ecology

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	852725	**TerreStriAL**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Jan de Vries**
Host Institution:	Georg-August-Universitat Gottingen Stiftung Offentlichen Rechts - DEU

Terrestrialization: Stress Signalling Dynamics in the Algal Progenitors of Land Plants

Land plants abound on Earth's surface. All of this diversity arose in a singular event. The algal progenitor of land plants was a streptophyte alga and only recent phylogenomic analyses have specified the particular algal lineage that is most closely related to land plants. But why did land plants evolve only once? And what properties did the ancestors of these terrestrial organisms possess that allowed them to conquer land? Life on land involves rapid and drastic shifts in temperature, light or water availability. Hence, a prime candidate property is the ability to deal with these terrestrial stressors by dynamically responding to shifting environmental cues. My recent data highlight that the streptophyte algae closest to land plants have the genetic makeup for land plant-like stress response signalling circuits—including genes for sensing the major stress phytohormone abscisic acid (ABA). This provides us with testable candidates. To shed light on the early evolution of one of land plants' key properties, I, here, propose to combine in-depth molecular biological analyses of these candidate stress signalling and response pathways with large-scale systems biology approaches. For this, my team and I will develop streptophyte algal model systems. We will dissect the regulatory hierarchy employed during stress signalling and the response pathways it is regulating in real-time in vivo and across evolutionary time in silico. These approaches will go beyond a view of gene evolution that is based on presence/absence to address if land plant stress dynamics have evolved from algal stress regulatory networks that became hardwired into land plant biology. The aim of this work is to infer the biology of the earliest land plants by investigating their closest algal relatives and interrogating a candidate mechanism used to deal with the challenges of life on land. Understanding this mechanism means understanding a key player that paved the way for the success of plants on land.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	865694	**DiversiPHI**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Bas E. Dutilh**
Host Institution:	Universiteit Utrecht - NLD

Predicting the evolution of complex phage-host interactions

What determines if a phage can infect a host? This question arises as we work to understand the ecological roles of the hundreds of thousands of unknown viruses that I and others have discovered around the world. Phages are the most abundant life forms on Earth with important applications in medicine and biotechnology and far-ranging effects on microbial community functioning in all environments. Phage-host interactions (PHI) are an emergent trait that depends on the complex integration of factors like their taxonomic identity, the environment, and phage- and host-encoded proteins. With DiversiPHI, I propose a research program to unravel PHI by 1) measuring, 2) modelling, and 3) experimentally testing these diverse factors to develop a predictive understanding of host-range evolution.

I will first measure a range of evolutionary, ecological, and molecular factors contributing to PHI at high resolution using newly developed computational tools that exploit high-throughput datasets from thousands of natural environments around the world. Next, I will apply deep learning to integrate these measurements to simultaneously (i) quantify the relative importance and complex inter-dependencies of the different factors, and (ii) create a unique predictive model of host-range evolution. To complement these in silico predictions, I will develop an experimental evolution setup that tests the effect of the different PHI factors on host-range evolution in vitro.

Little is known about the abundant phages and their role in shaping our microbial world. DiversiPHI will vastly elevate this understanding and contribute new fundamental knowledge on how species-species interactions evolve in complex environments. Moreover, I will provide valuable new analysis tools to the community and consolidate my strong international reputation as a pioneering researcher in the cross-disciplinary field encompassing microbial ecology, virology, metagenomics, bioinformatics, and computer learning.

Link to the ERC project webpage: https://tbb.bio.uu.nl/dutilh/

Keywords of the ERC project: bioinformatics, genomics, microbiology, bacteriophages, computational modelling, artificial intelligence, machine learning, virus-host interactions, metagenomics, host-range

Keywords that characterize the scientific profile of the potential visiting researcher/s: bioinformatics, genomics, microbiology, bacteriophages, computational modelling, artificial intelligence, machine learning, virus-host interactions, metagenomics, host-range

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	865787	**GLOBAL**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Thomas Couvreur**
Host Institution:	Institut De Recherche Pour Le Developpement - FRA

Tropical rain forest diversification: a GLOBAL approach

Tropical rain forests (TRF) are the most species rich yet highly threatened ecosystems on Earth. They play pivotal roles as global climate regulators and for human wellbeing. Their long term conservation is central for global climate mitigation and biodiversity conservation. Elucidating the evolutionary processes that underpin this immense diversity is critical for improved conservation actions. What evolutionary processes determine TRF diversity? How will human-induced species losses impact the evolutionary history of TRF? Time calibrated phylogenies retain the fingerprint of these patterns and are fundamental prerequisites to maximize the conservation of evolutionary history. However, global densely sampled robust phylogenies are lacking for TRF plants, significantly limiting our ability to properly address these questions. I will generate the largest most comprehensive datasets ever assembled for a major, ecologically important and species-rich pantropical model plant family: Annonaceae (~2500 species). First, I will test major hypotheses about TRF evolution at a global scale and what biotic and abiotic factors drove their diversification. Then, I will predict the impact of plant species extinction on the evolutionary history of TRF. Using the extensive network of European herbaria, I will reconstruct a robust time-calibrated complete species level phylogenomic tree of Annonaceae. I will compile massive morphological, chemical and geographical datasets for all species. Novel paleoclimatic data will be modelled through space at ten discrete periods over the last 100 million years. These data will then be integrated using innovative statistical macroevolutionary comparative approaches to answer the above questions at never achieved levels of precision. GLOBAL will provide improved predictions of TRF evolution informing conservation policies, and set the new standard for next generation evolutionary studies of TRF evolution applicable to other key tropical groups.

Link to the ERC project webpage: http://www.couvreurlab.org/erc-global.html

Keywords of the ERC project: phylogeny, biodiversity, evolution, tropical rain forest, Annonaceae

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

Project ID:	Project Acronym:	Evaluation Panel:
		LS8
945026	**METASCALE**	Evolutionary, Population and Environmental Biology

Principal Investigator:	**Dr Oleg Simakov**
Host Institution:	Universitaet 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:

Keywords of the ERC project: genomics, evolution, cephalopods

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS8
	948465	**ROCKS-PARADOX**	Evolutionary, Population and Environmental Biology

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:

Keywords of the ERC project:

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

Principal Investigator:	**Dr Sónia 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: Not yet available

Keywords of the ERC project: kleptoplasty, sacoglossa, lipidomic, light-stress, photosynthesis, kleptoplasts

Keywords that characterize the scientific profile of the potential visiting researcher/s: transcriptomic, metabolomic, stress response, isotopes

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	695078	**noMAGIC**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr anna moroni**
Host Institution:	Universita Degli Studi Di Milano - ITA

Noninvasive Manipulation of Gating in Ion Channels

noMAGIC has the visionary goal of engineering genetically encoded ion channels, which can be remotely controlled (gated) by stimuli that penetrate deep into human tissue without negative side effects. The control over ion channel activity by deep penetrating stimuli will revolutionize research in neurobiology and physiology as it paves the way for remote and genuine non-invasive control of cell activity in vivo. Synthetic channels, which can be gated by magnetic fields (MF), near infrared (NIR) radiation or ultrasound (US) will be engineered in the frame of noMAGIC by three complementary work packages (WP1-3). Design and engineering of the channels will be performed in WP1 by reiterated steps of rational and irrational design, high throughput screening and in vitro and in vivo functional testing. We have identified two sensor modules for MF and NIR radiation, respectively, which will be functionally connected to a channel pore for a remote control of gating. For the US-gated channel we will engineer a channel pore that is maximally responding to local changes in the lipid environment induced by US. Design and engineering of channels will be complemented by a computational approach (WP2), which analyses, from elastic network models, the mechanical connections in the channel pore and which extracts information on the forces, which are required to gate a channel by the three stimuli. The outcome of WP2 will provide general design rules for synthetic channels with implications much beyond the present project. WP3 also contributes to the engineering effort in WP1 by a spectrum of avant-garde spectroscopic methods, which resolve structural changes of the channel proteins under the influence of remote stimuli. These structural insights will greatly advance our understanding of structure/function correlates in composite ion channels and it will inspire the design and engineering of channels, which respond to remote stimuli.

Link to the ERC project webpage: https://nomagicproject.eu/

Keywords of the ERC project: synthetic ion channels

Keywords that characterize the scientific profile of the potential visiting researcher/s: membrane proteins, structural biology, ion channels

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**743165**	**BLASTOFF**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Sophien Kamoun**
Host Institution:	The Sainsbury Laboratory - GBR

Retooling plant immunity for resistance to blast fungi

Plant NLR-type immune receptors tend to have a narrow spectrum of pathogen recognition, which is currently limiting their value in agriculture. NLRs can recognize pathogen effectors through unconventional domains that have evolved by duplication of an effector target followed by fusion into the NLR. One NLR with an integrated domain is the rice resistance protein Pik-1, which binds an effector of the blast fungus Magnaporthe oryzae via its Heavy-Metal Associated (HMA) domain. We solved the crystal structure of the HMA domain of Pik-1 in complex with a blast fungus effector and gained an unprecedented level of detail of the molecular interactions that define pathogen recognition. This led to the overall aim of this proposal to generate a complete picture of the biophysical interactions between blast fungus effectors and HMA-containing cereal proteins to guide the retooling of the plant immune system towards resistance to blast diseases. M. oryzae is a general cereal killer that infects wheat, barley and rice, which are staple food for a majority of the world population. The central hypothesis of the proposed research is that mutations in cereal HMA-containing proteins will result in broad-spectrum resistance to blast fungi.

To achieve our goal, we will pursue the following objectives:

1. BIOPHYSICS. Define the biophysical properties that underpin binding of M. oryzae effectors to HMA-containing proteins of cereal crops.

2. RECEPTOR ENGINEERING. Develop Pik-1 receptors that respond to a wide-spectrum of M. oryzae effectors.

3. GENOME EDITING. Mutate HMA domain-containing genes in cereal genomes to confer broad-spectrum blast resistance.

At the completion of this project, we will generate a thorough understanding of the biophysical properties of pathogen effector binding to cereal HMA proteins, and deliver traits and non-transgenic cultivars for breeding blast disease resistance in cereal crops.

Link to the ERC project webpage: http://www.kamounlab.net

Keywords of the ERC project: genomics, immunity, immune receptors, NLR

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	757833	**FORMICA**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Pieter De Frenne**
Host Institution:	Universiteit Gent - BEL

Microclimatic buffering of plant responses to macroclimate warming in temperate forests

Recent global warming is acting across ecosystems and threatening biodiversity. Yet, due to slow responses, many biological communities are lagging behind warming of the macroclimate (the climate of a large geographic region). The buffering of microclimates near the ground measured in localized areas, arising from terrain features such as vegetation and topography, can explain why many species are lagging behind macroclimate warming. However, almost all studies ignore the effects of microclimatic buffering and key uncertainties still exist about this mechanism. Microclimates are particularly evident in forests, where understorey habitats are buffered by overstorey trees. In temperate forests, the understorey contains the vast majority of plant diversity and plays an essential role in driving ecosystem processes.

The overall goal of FORMICA (FORest MICroclimate Assessment) is to quantify and understand the role of microclimatic buffering in modulating forest understorey plant responses to macroclimate warming. We will perform the best assessment to date of the effects of microclimates on plants by applying microtemperature loggers, experimental heating, fluorescent tubes and a large-scale transplant experiment in temperate forests across Europe. For the first time, plant data from the individual to ecosystem level will be related to microclimate along wide temperature gradients and forest management regimes. The empirical results will then be integrated in cutting-edge demographic distribution models to forecast plant diversity in temperate forests as macroclimate warms.

FORMICA will provide the first integrative study on microclimatic buffering of macroclimate warming in forests. Interdisciplinary concepts and methods will be applied, including from climatology, forestry and ecology. FORMICA will reshape our current understanding of the impacts of climate change on forests and help land managers and policy makers to develop urgently needed adaptation strategies.

Link to the ERC project webpage: www.formica.ugent.be

Keywords of the ERC project: climate change, forests, microclimate

Keywords that characterize the scientific profile of the potential visiting researcher/s: climate change, forests, microclimate

	Project ID:	Project Acronym:	Evaluation Panel:
	770835	**SynBioBrain**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Chris Barnes**
Host Institution:	University College London - GBR

Building biological computers from bacterial populations

Biosensors detect compounds using a biological component combined with a physio-chemical detector. Using synthetic biology, we can now engineer bacteria into whole-cell biosensors where sensing, transduction and output occur within the living cell. Applications include the detection of harmful environmental agents, bioprocess monitoring, and detecting medically relevant biomarkers. As we move towards more sophisticated applications, single channel read-out will be replaced with sensors that have multiple inputs and more complex information processing capabilities. Whilst digital logic within a single strain of bacteria can be implemented, consortia offer a powerful alternative, where information is integrated and processed in a distributed fashion. This proposal sets out a research project that will construct biological computers formed from engineered bacterial populations that communicate using quorum sensing molecules. Information from multiple biosensor inputs will be integrated and processed by the biocomputer, the output of which will be spatial patterning. The architecture will be based on cellular automata, which can perform any computation, including logic and temporal logic operations, memory and counting, all of which can be used to distinguish states in complex biological and chemical environments. Our biocomputers will be housed in microfluidic devices using hydrogel structures to create two and three dimensional regular arrangements. As a proof-of-concept, we will develop a biocomputer for the analysis and monitoring of intestinal and microbiota health through stool samples. Sensors for inflammation, pH and short chain fatty acids will be combined into a device that can indicate whether an individual has inflammatory bowel disease or irritable bowel syndrome. A low-cost device for use at home, which distinguishes between these conditions, could potentially save the global health care industry billions of dollars in unnecessary diagnostic treatments.

Link to the ERC project webpage: https://ucl-cssb.github.io/

Keywords of the ERC project: synthetic biology; biological computation; biosensors

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	771035	**conVIRgens**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Gunther Doehlemann**
Host Institution:	Universitaet Zu Koeln - DEU

De- and reconstructing virulence strategies of fungal plant pathogens

Fungal pathogens are enormous threats to plants, causing tremendous losses in worldwide crop production. Mechanistic understanding of fungal virulence is crucial to developing novel plant protection strategies in sustainable agriculture.

Biotrophic pathogens colonize living plant tissue and reprogram their hosts to stimulate proliferation and development of infection structures. To promote infection, fungal pathogens secrete sets of virulence proteins termed "effectors" in a spatiotemporal program. Many economically relevant biotrophs like rusts and powdery mildew fungi are obligate pathogens. These organisms cannot be grown in culture and are not amenable to reverse genetics, which is a severe constraint for current research. In contrast, the biotrophic smut fungi have a haploid yeast stage, which allows simple cultivation and genetic modification. The causal agent of corn smut disease, Ustilago maydis, is one of the best-established model organisms for fungal genetics.

This project aims to utilize the excellent genetic accessibility of U. maydis to approach a previously impossible, pioneering enterprise: the synthetic reconstruction of eukaryotic plant pathogens. In a first step, fungal virulence will be deconstructed by consecutive deletion of the U. maydis effector repertoire to generate disarmed mutants. These strains will serve as chassis for subsequent reconstruction of fungal pathogenicity from different sources. A combination of transcriptomics and comparative genomics will help to define synthetic effector modules to reconstruct virulence in the chassis strains.

Deconstruction of U. maydis virulence will identify a complete arsenal of fungal virulence factors. Reconstruction of virulence will show how effector modules determine fungal virulence, including those of the previously not accessible obligate biotrophs. conVIRgens will thereby provide fundamentally new insights and novel functional tools towards the understanding of microbial virulence.

Link to the ERC project webpage:

Keywords of the ERC project: fungal effectors, fungal genomics, CRISPR-Cas9, host specificity, synthetic biology,

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	787115	**MaCChines**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Roman Jerala**
Host Institution:	Kemijski Institut - SVN

Molecular machines based on coiled-coil protein origami

Proteins are the most versatile and complex smart nanomaterials, forming molecular machines and performing numerous functions from structure building, recognition, catalysis to locomotion. Nature however explored only a tiny fraction of possible protein sequences and structures. Design of proteins with new, in nature unseen shapes and features, offers high rewards for medicine, technology and science. In 2013 my group pioneered the design of a new type of modular coiled-coil protein origami (CCPO) folds. This type of de novo designed proteins are defined by the sequence of coiled-coil (CC) dimer-forming modules that are concatenated by flexible linkers into a single polypeptide chain that self-assembles into a polyhedral cage based on pairwise CC interactions. This is in contrast to naturally evolved proteins where their fold is defined by a compact hydrophobic core. We recently demonstrated the robustness of this strategy by the largest de novo designed single chain protein, construction of tetrahedral, pyramid, trigonal prism and bipyramid cages that self-assemble in vivo.

This proposal builds on unique advantages of CCPOs and represents a new frontier of this branch of protein design science. I propose to introduce functional domains into selected positions of CCPO cages, implement new types of building modules that will enable regulated CCPO assembly and disassembly, test new strategies of caging and release of cargo molecules for targeted delivery, design knotted and crosslinked protein cages and introduce toehold displacement for the regulated structural rearrangement of CCPOs required for designed molecular machines, which will be demonstrated on protein nanotweezers. Technology for the positional combinatorial library-based single pot assembly of CCPO genes will provide high throughput of CCPO variants. Project will result in new methodology, understanding of potentials of CCPOs for designed molecular machines and in demonstration of different applications.

Link to the ERC project webpage:

Keywords of the ERC project: molecular machines, designed protein, nanotechnology, synthetic biology

Keywords that characterize the scientific profile of the potential visiting researcher/s: synthetic biology, structural biology, molecular modeling, protein engineering,

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency Established by the European Commission	**802629**	**INTERACT**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Korbinian Schneeberger**
Host Institution:	Ludwig-Maximilians-Universitaet Muenchen - DEU

Phylogenetic association mapping and its application to secondary metabolite variation in Brassicaceae species

During the past years, great progress has been made in connecting phenotypes to genotypes based on within-species variation. However, the more dramatic variation that can be found between species has not been explored for phenotype/genotype associations so-far. Using classical genetics to mine between-species variation is mostly impossible, because crosses between distinct species hardly work and their genomes are usually highly rearranged.

The goal of this project is to develop unprecedented genomics-based methods for inter-species (phylogenetic) association mapping, which can find signals even in highly re-arranged genomes of different species. To ensure that these methods are also useful in practice, we will apply them to the variation in secondary metabolites within the Brassicaceae plant family. Secondary metabolites are highly variable, genetically controlled, easy to measure and have broad application in cancer prevention, pest control and food design. Given the great potential of phylogenetic association mapping in general and secondary metabolites in particular, our work promises to be ground-breaking and have profound impact on many different fields of genetic research.

Specifically, our work plan includes the following points:

I) We will develop strategies for phylogenetic association mapping and implement them in publicly-available software.

II) We will establish a panel of inbred lines from ~200 Brassicaceae species and generate whole-genome assemblies for each of them.

III) We will exemplify the usefulness of phylogenetic association mapping by correlating the diversity of secondary metabolites to the differences in the respective genomes and validate the results by transforming or mutating candidate genes in appropriate species.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	802736	**MORPHEUS**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Christine Beemelmanns**
Host Institution:	Leibniz-Institut Fur Naturstoff-Forschung Und Infektionsbiologie Ev Hans-Knoll-Istitut - DEU

Deciphering Bacteria-induced Morphogenesis and Protection in marine Eukaryotes

Symbiotic bacteria play critical roles in animal evolution, development and metabolism. The molecular and cellular mechanisms underlying these fundamental interactions, however, are largely unknown.

To fill this major knowledge gap, I will establish the bacteria-Hydractinia symbiosis as a new model system to fully characterize key cross-kingdom signalling molecules and response mechanisms. The results of my ERC proposal (MORPHEUS) will lead to ground-breaking insights into molecular drivers of eukaryotic morphogenesis, illuminate the evolutionary history of developmental signals for animals – including humans – and provide new chemical scaffolds with intrinsic biological activities that are urgently needed for drug discovery.

The marine colonial hydroid Hydractinia belongs to an early branching metazoan lineage, dating back more than 500 million years. The organism reproduces through a larval stage, which upon perception of yet unidentified bacterial morphogenic signals, produced within marine bacterial biofilms, undergoes transformation into the mature organism. In the absence of the bacterial signals, the larva fails to settle and eventually dies. This fundamental process is the basis of this proposal. Capitalizing from my recent pioneering work, I will address the following pressing research questions: Which bacterial signals ensure larval recruitment and metamorphosis? How are bacterial signalling molecules perceived? How is the system protected against alien species? I will apply an innovative combination of state-of-the-art methodologies developed within the fields of natural product and synthetic organic chemistry, microbiology and molecular biology to pursue an in-depth biochemical analysis of this paradigmatic system. Results of MORPHEUS will be transformative for many scientific branches across biological and chemical disciplines, and directly impact the development of sustainable anti-biofouling and drug discovery strategies.

Link to the ERC project webpage:

Keywords of the ERC project: chemical ecology, natural product chemistry, microbiology, marine science, symbiosis

Keywords that characterize the scientific profile of the potential visiting researcher/s: organic chemistry, natural products, metabolomics, microbiology, Cnidaria, symbiosis

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency			**LS9**
	803363	**FuncMab**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Klaus Eyer**
Host Institution:	Eidgenoessische Technische Hochschule Zurich - CHE

High-throughput single-cell phenotypic analysis of functional antibody repertoires

Antibodies play an important role ensuring successful protection after vaccination. Upon injection, antigen-binding antibodies are generated to prime the host's immune system for future encounters with the threat. These responses are highly heterogeneous, with each cell contributing with a single antibody variant to the complexity. Each antibody variant furthermore can recognize a different antigen/epitope with varying specificity and affinity. The immunological function induced is related to those parameters.

Depending on the nature of the threat, required protective functional antibodies vary. Therefore, also each vaccination against those threads needs to trigger a specific functional antibody repertoire. Presently, induced functional antibody repertoires have not yet been studied sufficiently, mostly due to the lack of technologies that enable analysing these repertoires with high enough throughput and resolution. Consequently, the mechanisms behind the evolution of these functional repertoires, and the influence of vaccination on these repertoires remain poorly understood.

An innovative technology combined with a methodical approach to vaccinations will enable the FuncMab research team to generate data sets needed for the understanding of immunological processes that result in different functional antibody repertoires. Herein, antibodies are analysed on the individual cell level in high-throughput using specific bioassays that target various antibody functions and their biophysical parameters, generating high-resolution data. These functional repertoires are followed over time and evolutionary changes can be linked to introduced vaccine variations, allowing a quantitative approach to study the changes within the repertoires. These in-depth data sets will not only allow understanding interactions between vaccine components and their generated immune responses, but also propels this project to the forefront of creating a new generation of successful vaccines

Link to the ERC project webpage: https://eyergroup.ethz.ch/

Keywords of the ERC project: Single-cell analysis, antibody-secreting cells, antibodies

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

	Project ID:	Project Acronym:	Evaluation Panel:
	805094	**GRASP**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Charles Melnyk**
Host Institution:	Sveriges Lantbruksuniversitet - SWE

Overcoming plant graft incompatibility by modifying signalling and perception

For millennia, people have cut and joined together different plants through a process known as grafting. Plants tissues from different genotypes fuse, vasculature connects and a chimeric organism forms that combines desirable characteristics from different plants such as high yields or disease resistance. However, plants can only be grafted to closely related species and in some instances, they cannot be grafted to themselves. This phenomenon is referred to as graft incompatibility and the mechanistic basis is completely unknown. Our previous work on graft formation in Arabidopsis thaliana has uncovered genes that rapidly activate in grafted tissues to signal the presence of adjoining tissue and initiate a vascular reconnection process. These genes activate around the cut only during graft formation and present a powerful tool to screen large numbers of chemicals and genes that could promote tissue perception and vascular formation. With these sensors and our previously established grafting tools in the model plant Arabidopsis, we can address fundamental questions about grafting biology that have direct relevance to improving graft formation through:

1. Identifying genes required for the recognition response using forward and reverse genetic screens.
2. Determining and characterising signals that activate vascular induction using a chemical genetics screen.
3. Characterising the transcriptional basis for compatibility and incompatibility by analysing
tissues and species that graft and comparing these to tissues and species that do not graft.
4. Overcoming graft incompatibility and improving graft formation by applying the knowledge obtained from the three previous objectives.

We thus aim to broaden our fundamental understanding of the processes associated with grafting including wound healing, vascular formation and tissue regeneration, while at the same time, use this information to improve graft formation and expand the range of grafted species.

Link to the ERC project webpage:

Keywords of the ERC project: Plant grafting

Keywords that characterize the scientific profile of the potential visiting researcher/s: Plant biology, plant development

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	819934	**ProMiDis**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Georgios Skretas**
Host Institution:	Ethniko Idryma Erevnon - GRC

A unified drug discovery platform for protein misfolding diseases

It is now widely recognized that a variety of major diseases, such as Alzheimer's disease, Huntington's disease, systemic amyloidosis, cystic fibrosis, type 2 diabetes etc., are characterized by a common molecular origin: the misfolding of specific proteins. These disorders have been termed protein misfolding diseases (PMDs) and the vast majority of them remain incurable. Here, I propose the development of a unified approach for the discovery of potential therapeutics against PMDs. I will generate engineered bacterial cells that function as a broadly applicable discovery platform for compounds that rescue the misfolding of PMD-associated proteins (MisPs). These compounds will be selected from libraries of drug-like molecules biosynthesized in engineered bacteria using a technology that allows the facile production of billions of different test molecules. These libraries will then be screened in the same bacterial cells that produce them and the rare molecules that rescue MisP misfolding effectively will be selected using an ultrahigh-throughput genetic screen. The effect of the selected compounds on MisP folding will then be evaluated by biochemical and biophysical methods, while their ability to inhibit MisP-induced pathogenicity will be tested in appropriate mammalian cell assays and in established animal models of the associated PMD. The molecules that rescue the misfolding of the target MisPs and antagonize their associated pathogenicity both in vitro and in vivo, will become drug candidates against the corresponding diseases. This procedure will be applied for different MisPs to identify potential therapeutics for four major PMDs: Huntington's disease, cardiotoxic light chain amyloidosis, dialysis-related amyloidosis and retinitis pigmentosa. Successful realization of ProMiDis will provide invaluable therapeutic leads against major diseases and a unified framework for anti-PMD drug discovery.

Link to the ERC project webpage:

Keywords of the ERC project: biomolecular engineering, directed evolution, synthetic biology, protein misfolding and aggregation

Keywords that characterize the scientific profile of the potential visiting researcher/s: biomolecular engineering, directed evolution, synthetic biology, protein misfolding and aggregation, protein folding, protein biochemistry,   protein   biophysics,   cell   and   c.   elegans   biology

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	849029	**EpigeneticScars**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Debira Toiber**
Host Institution:	Ben-Gurion University Of The Negev - ISR

Understanding DSB repair from pathway choice to long term effects and their consequences.

DNA safekeeping is one of the most important functions of the cell. Since DNA damage occurs in the context of chromatin, it affects both the DNA itself, but also the epigenetic landscape. While the repair mechanism of the DNA has been extensively studied, questions abound regarding the restoration of the epigenetic landscape, and the long-term effects that damage leaves in the region. In this proposal I aim to address these questions using modified DSBs repair sensors from different pathways such as "homologous recombination" and "non-homologous end joining" to map the repair process. Our method will allow us to investigate the influence of the natural epigenetic landscape on pathway choice, the dynamic process of repair and the restoration of the region. Moreover, we will investigate whether certain repair processes leave long- lasting effects at the site of damage or even "epigenetic scars". The advantage of our method is that it allows us to map each sensor repair time-line in an unbiased and high throughput manner over extended periods of time, even once the damage is already repaired. These questions are especially important for our understanding of ageing, and age-related diseases that are driven by DNA damage. Last, we will test the long-lasting effects of past damage in two different contexts: animal models of neurodegeneration, where DNA damage accumulates, and in the efficiency of reprograming to produce healthy induced pluripotent stem cells (IPCs).

Link to the ERC project webpage:

Keywords of the ERC project: DNA damage, sensors, epigenetic signatures, neurodegeneration

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

	Project ID:	Project Acronym:	Evaluation Panel:
	852600	**Lacto-Be**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Sarah Lebeer**
Host Institution:	Universiteit Antwerpen - BEL

Advancing Lactobacillus' beneficial potential

Lactobacillus bacteria have a strong, but underexplored potential as sustainable bio-based solutions for many food and health-related problems. Since Nobel-laureate Eli Metchnikoff hypothesized that lactic acid bacteria can promote human health in the gut, the research on lactobacilli and probiotics has mainly focused on the human gut and fermented dairy foods. However, a major knowledge gap exists on the beneficial potential of Lactobacillus species in other human body sites (vagina, skin, upper respiratory tract), animals (e.g. chickens, honey bees), plants, crops, and even on abiotic surfaces. In addition, lactobacilli play a key role in many plant- and vegetable-based fermentations, where they promote the shelf life and nutritional value of food and feed. Yet, why and how Lactobacillus species can be beneficial in such a wide variety of niches is currently underexplored. Therefore, the core aim of this project is a systematic and integrated analysis of the evolutionary history, ecology, and beneficial functions of Lactobacillus species. I propose an unconventional approach situated at the intersections of molecular microbiology (focusing on a single microbe), molecular ecology (focusing on microbial communities) and comparative genomics with an evolutionary perspective on niche adaptation of lactobacilli. By looking deeper into Lactobacillus biology, a paradigm shift can be made moving from a classical ad hoc base to a unique knowledge-based framework for strain selection and analysis of fitness and performance.

Link to the ERC project webpage: lebeerlab.com

Keywords of the ERC project: probiotics, lactobacilli, microbiome

Keywords that characterize the scientific profile of the potential visiting researcher/s: microbiologist, bio-informatician, immunologist

	Project ID:	Project Acronym:	Evaluation Panel:
	853272	**PALAEOFARM**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Laurent Frantz**
Host Institution:	Ludwig-Maximilians-Universitaet Muenchen - DEU

Linking livestock genetic diversity with three thousand years of agricultural crises and resilience

Over the last 50 years, chiOver the last 50 years, chicken production has increased fivefold, chicken growth rate has tripled, and milk production per cow has doubled. Yet, many of the biotechnological tools responsible for this accelerated trend are now under threat of becoming obsolete. While the causes are numerous, one significant driver is a dramatic reduction of genetic diversity in livestock populations.

Cycles of agricultural productivity growth and decline have occurred throughout European history, spurred by major historical forces such as the spread of empires and continent-wide epidemics. For example, productivity crashed between the 4th-13th centuries, only to rebound during the Agricultural Revolution of the 13-18th centuries. Fluctuating levels of genetic diversity were likely both cause and remedy to these cycles. Genetic diversity acts as a fuel for selection: the lower it is, the more difficult it is to improve traits, and the more likely that epidemics will develop and spread. Given this importance, maintaining diversity amongst livestock is recognised as one of the UN's Sustainable Development Goals. Despite this, we lack any understanding of how much genetic variability was present, and subsequently lost, before, during, and after either the Green or Agricultural Revolutions, nor do we understand how efficiently it was utilised.

PALAEOFARM will assess the long-term sustainability of modern breeding practices by unravelling how genetic variability was leveraged across major agricultural transitions in European history. Using an innovative combination of ancient DNA, archaeozoology, and experimental immunology, I will explore how livestock populations withstood epidemics and selective breeding in a world without antibiotics or quantitative genetic techniques. This will provide a novel perspective on how a multi-billion euro industry, responsible for feeding billions of people, can be sustained in the face of major biotechnological obsolescence.

Link to the ERC project webpage: https://www.animal-palaeogenomics.com/

Keywords of the ERC project: evolutionary genomics, livestock, ancient DNA, archeology, conservation biology

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	864117	**nbPTMs**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Ivan Matic**
Host Institution:	Max Planck Gesellschaft Zur Foerderung Der Wissenschaften E.V. - 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:

Keywords of the ERC project: ADP-ribosylation; mono-ADP-ribosylation; MARylation; HFP1; PARP1; DNA damage; histones; chemical biology; antibodies; AMPylation; proteomics

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	864528	**PArtCell**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Arnold Boersma**
Host Institution:	Dwi Leibniz-Institut Fur Interaktive Materialien Ev - DEU

Physiologically Crowded Artificial Cells for Relevant Drug Screens

In the crowded cell, nonspecific interactions between biomolecules alter biochemical equilibria. This matrix of weak nonspecific interactions is composed of hydrophobic, electrostatic, H-bonding, van der Waals, and steric interactions, and is "the dark matter of biology".

Inaccurate prediction of the behaviour of biomolecules inside cells hampers drug discovery: A high throughput drug screen against a purified target protein in dilute buffer ignores the presence of these weak interactions and results are less relevant. High throughput screens directly in cells are however more difficult to control, interpret and measure.

PArtCell provides a key advance by combining the high level of control and ease of high-throughput screening on purified proteins, with the relevance of screening in the native environment.

The aim is to construct artificial cells that provide a physiologically relevant drug-screening platform.

We will achieve this aim by constructing artificial cells with a matrix of weak nonspecific interactions akin living cells as verified with newly engineered fluorescent probes. The probes measure hydrophobicity, electrostatics and steric effects, as well as the physicochemical state of pathogenic condensates, in healthy and stressed living cells. With this information, we will benchmark artificial cells. Drug screens are applied against pathogenic oligomers that we now can observe in these well-characterized artificial cells.

This research will update textbook knowledge and provide the molecular origin of the matrix of weak nonspecific interactions in living cells. It provides a platform that allows screening against targets under native-like conditions not achievable with other methods. This research thus provides a new opportunity to screen drugs against diseases for which we have no cure yet.

Link to the ERC project webpage:

Keywords of the ERC project: synthetic cells, crowding, FRET

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	864669	**e-MICROBe**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Miriam Rosenbaum**
Host Institution:	Leibniz-Institut Fur Naturstoff-Forschung Und Infektionsbiologie Ev Hans-Knoll-Istitut - DEU

Energizing microbes with redox mediators for new bioproductions

In many bioprocesses a broad bioproduct portfolio can currently only be obtained when microorganisms can access oxygen as an electron acceptor. For numerous target substances, however, oxygen is detrimental to product stability and the bioprocess operation. The central aim of e-MICROBe is to innately couple microbial metabolism and electrochemistry via a self-secreted soluble electron mediator to achieve efficient oxygen independent energy metabolism and to directly steer and control metabolism and product formation. This will require creating entirely new physiological traits for production and utilization of redox mediators to generate cellular energy. Thereby, mediators can either act as electron discharge shuttle to enable electro-respiration at an anode or they are employed as inorganic energy donor to deliver electrons from a cathode into the metabolism. We will clarify the underlying reaction pathways in known environmental microorganisms and re-engineer the energy metabolism of common biotech hosts. Thereby, we will switch cellular energy generation from aerobic respiration to anaerobic anodic electro-respiration or from hydrogen consumption as autotrophic electron donor to cathodic electron consumption. The latter process will provide a mechanism to store electrical energy in microbial products. For a new level of in situ insight into microbial energy metabolism, a novel micro-scale bioelectrochemical reactor coupled to microscopic observation and high performance analysis will be developed. With this technique two fundamental concepts for future mediator-based bioprocesses will be evaluated: An all-in-one strategy where one cell is generating the mediators and the targeted product as well as a co-culture system, whereby one cell produces the mediators and a partner cell utilizes them for electro-respiration and product formation. This concept will lay the foundation for a plug-and-play exchange of biotech strains in a mediator-producing co-culture system.

Link to the ERC project webpage:

Keywords of the ERC project:

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

Principal Investigator:	**Dr Chase Beisel**
Host Institution:	Helmholtz-Zentrum Fur Infektionsforschung Gmbh - DEU

Interrogating native CRISPR arrays to achieve scalable combinatorial screens and dissect genetic redundancy

A ubiquitous yet poorly understood theme pervading biology is redundancy, wherein seemingly equivalent components drive shared processes. In cases from development to pathogenesis, untangling the ensuing web of potential genetic interactions can be virtually impossible with conventional techniques. CRISPR technologies, with their propensity for multiplexing, are well poised to address this challenge. However, current CRISPR-based screens have not exceeded more than two targets at a time. Here, I will achieve a major leap forward for CRISPR-based screens and dissecting redundancy by harnessing a core yet underexplored part of CRISPR: CRISPR arrays. CRISPR arrays naturally form the immunological memory of CRISPR-Cas systems and produce multiple targeting gRNAs processed from a single transcript. The arrays are highly compact, genetically stable, and can encode hundreds of gRNAs. However, the repetitive "repeats" within each array have hampered their construction and widespread adoption. My group recently made a breakthrough with the modular one-pot assembly of long arrays and array libraries. This capability grants us the unique opportunity to develop the first high-throughput, CRISPR-based screens that readily scale to many gene targets at a time. In parallel, our first assembled arrays highlighted technical constraints to designing robust and highly active arrays. I posit that native CRISPR arrays have faced similar limitations and thus can inform the design of array libraries. I thus propose to

1)   Develop design rules for CRISPR arrays yielding only intended and uniformly abundant guide RNAs.

2)   Elucidate and exploit why CRISPR arrays are genetically stable.

3)   Perform scalable combinatorial screens using redundancy by small RNAs in E. coli as a compelling case study.

If successful, this project will reveal unexplored properties of CRISPR arrays and, for the first time, achieve scalable combinatorial screens for interrogating redundancy throughout biology.

Link to the ERC project webpage:

Keywords of the ERC project: CRISPR, genome editing, bacteria, Cas9, genetic screens

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

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	883687	**MultiOrganelleDesign**	Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Edward Lemke**
Host Institution:	Johannes Gutenberg Universitaet 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: www.lemkelab,com

Keywords of the ERC project:

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

Project ID:	Project Acronym:	Evaluation Panel:
946192	**HUMYCO**	**LS9** Applied life Sciences and Non-Medical Biotechnology

Principal Investigator:	**Dr Marthe De Boevre**
Host Institution:	Universiteit Gent - BEL

Investigating the Human Mycobolome through Uniting Large-scale Epidemiological and Mechanistic Poly-omic Designs

Mycotoxins, toxic fungal secondary metabolites, known to be the most hazardous of all food contaminants in terms of chronic toxicity, have the potential to contribute to a diversity of adverse health effects in humans, and are unfortunately ubiquitously present in our daily diet. Chronic low-dose intake of multiple mycotoxins are hypothesized to be associated with an increased risk of developing human renal, colorectal and hepatocellular carcinomas. HUMYCO refers to a unique, holistic & multi(cross)-disciplinary research field, aiming at comprehensively investigating the human mycobolome through uniting large-scale epidemiological & mechanistic designs using a poly-omic approach. Focus is set to generate newly hypotheses-driven insights into the role of multiple mycotoxin exposure in the aetiology of human carcinomas. The capability of conducting accurate exposure assessments of mycotoxins at the individual-level is required to fully understand the potential health consequences in humans, therefore, mycotoxin biomarkers of exposure will be primarily identified in vitro, and validated using human intervention studies by elucidating human mycotoxicokinetic profiles via metabolomics. The nature and extent of associations between estimated external and internal dietary multiple mycotoxin exposures and developing renal, colorectal and hepatocellular carcinomas will be investigated through large-scale epidemiological bio-cohorts, established in both Europe and Africa. To further disentangle possible associative mycotoxin-induced cancer development, causal relations will be verified through an innovative mechanistic arm applying advanced cutting-edged technologies. For the first time, genome-wide mutation spectra associated with multi-exposure to putatively carcinogenic mycotoxins will be experimentally determined. HUMYCO contributes to dietary-based human health prevention by identification of specific cancer risks related to multiple mycotoxins exposure.

Link to the ERC project webpage:

Keywords of the ERC project: food safety - mycotoxins - human health - cancer

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

Stem cell isolation and transplantation in Hexacorallia: Toward cell-therapy for corals

Reef corals are the foundation of ecosystems that host much of the ocean's biodiversity, making them a significant component of economies and communities around the world. They are under severe threat from anthropogenic stressors, particularly global warming. Some parts of the world's oceans have already lost the majority of their corals.

Efforts to mitigate the damage are informed by research on understanding and transferring naturally-occurring resilient genotypes. This has a direct parallel in medicine; cell- or gene-therapy, which is founded on an ability to isolate and then transplant progenitor/stem cells. This technology does not exist for any coral species.

In this research program we will develop robust tools for the isolation, characterization, and transplantation of coral progenitor cells. The tools will be species non-specific, and therefore widely applicable.

We will develop generalized strategies for isolating cell-type enriched cell populations, especially progenitor cells, in four species of anemones and stony corals. We will develop cell transplantation techniques for engraftment in non-model species. We will then characterize the engraftment potentials of candidate progenitor cell populations in these species.

This technology will have an impact on basic and applied research. Because of the broad applicability, it will become a valuable tool for researchers seeking a more complete cell biology in non-classical invertebrate species. Being able to isolate, manipulate, and replace progenitor cells in diverse species will assist in efforts to understand how the developmental programs that construct or regenerate an organism function and change during evolution. Being able to transfer progenitor cells from a stress-resilient coral to a sensitive one will assist in understanding the mechanisms governing stress tolerance. With this research, and using the tools developed here, it may become possible to confer resilience in the wild.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
	948588	**hOssicle**	**LS9** Applied life Sciences and Non-Medical Biotechnology

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: www.bourginelab.com

Keywords of the ERC project: human hematopoiesis - stem cell niche - mesenchymal stem cells

Keywords that characterize the scientific profile of the potential visiting researcher/s: single cell transcriptomics - humanized mouse models - human hematopoiesis - stem cell niche

	Project ID:	Project Acronym:	Evaluation Panel:
			LS9
	949080	**DEUSBIO**	Applied life Sciences and Non-Medical Biotechnology

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: www.rlalab.org

Keywords of the ERC project: synthetic biology, metabolic engineering, industrial microbiology, heterogeneity, metabolic subpopulations

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

Project ID:	Project Acronym:	Evaluation Panel:
810131	**PlaMorf**	**SYG**
		Synergy

Principal Investigator:	**Dr Richard Morris**
Host Institution:	JOHN INNES CENTRE - GBR

Plant Mobile RNAs: Function, Transport and Features

An essential consequence of multi-cellularity is the need for intercellular and tissue wide communication. As seen with animals, higher plants coordinate metabolic and developmental processes via signals transferred to different body parts. Plants use a dual vascular system consisting of phloem and xylem for long-distance transfer of metabolites and signalling molecules. In contrast to circular systems in animals, transport in flowering plants occurs in the phloem via the cytoplasm of connected cells devoid of nuclei. In addition to small molecules, a remarkably large number of so-called mobile micro RNAs (miRNAs), messenger RNAs (mRNAs), and phloem RNA-binding proteins (RBPs) were identified in the phloem and in chimeric plants. Mobile RNAs and RBPs move through plasmodesmata into and through the phloem to distinct tissues. Thus, mobile RNAs represent an additional class of signalling molecules, raising important questions in the field of intercellular signalling. This project combines the expertise of three research groups in the fields of cell biology/macromolecular transport, mathematical modelling/bioinformatics and phloem function/protein biochemistry. It addresses the questions: How are mobile miRNAs and mRNAs selected for transport? Is this process specific and regulated by RBPs and motifs? What determines their destination? And importantly, how are these signals processed in the destination cells? To address these questions, we will develop predictive models, using novel single cell transcriptomics pipelines to establish cell-type specific RNA transport and motifs (WP1), and studying the structure, affinity, and functions of phloem RBPs to gain insights in the RNA delivery mechanism (WP2). We will combine the advantages of the agronomically important plant oilseed rape to identify phloem RNAs and RBPs with the well-established A. thaliana model that allows us to identify and test cell-specific transported RNA signals and RBPs in a time-efficient manner.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: mathematical modelling; bioinformatics; computational biology; RNA transport;

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency *Established by the European Commission*	**810186**	**BacterialCORE**	**SYG** Synergy

Principal Investigator:	**Dr Sigal Ben-Yehuda**
Host Institution:	THE HEBREW UNIVERSITY OF JERUSALEM - ISR

Widespread Bacterial CORE Complex Executes Intra- and Inter-Kingdom Cytoplasmic Molecular Trade

The enormous versatility of bacteria enables the formation of multi-species communities that colonize nearly every niche on earth, making them the dominant life form and a major component of the biomass. Exchange of molecular information among neighboring bacteria in such communities, as well as between bacteria and proximal eukaryotic cells, is key for bacterial success. Yet, the principles controlling these multicellular interactions are poorly defined. Here we describe the identification of a bacterial protein complex, herein termed CORE, whose function is to traffic cytoplasmic molecules among different bacterial species, and between pathogenic bacteria and their human host cells. The CORE is composed of five membrane proteins, highly conserved across the entire bacterial kingdom, providing a ubiquitous platform that facilitates both intra- and inter-kingdom crosstalk. Our preliminary data support the idea that the CORE acts as a shared module for the assembly of larger apparatuses, executing this universal molecular flow among organisms. We propose to elucidate components, structure and biogenesis of the CORE machinery, operating during bacteria-bacteria and pathogen-host interactions. We further aim to provide an unbiased-global view of the extent and identity of cytoplasmic molecules traded via CORE including metabolites, proteins and RNA, and to reveal the criteria determining the specificity of the transported cargo. Furthermore, we intend to decipher the impact of CORE-mediated molecular exchange on bacterial physiology and virulence, and devise anti-CORE compounds to combat pathogenic bacteria. This study is expected to transform the way we currently view bacterial communities and host-pathogen interactions. We anticipate these findings to lead to the development of creative strategies to modulate, predict and even design bacterial communities, and lay the foundation for new and innovative approaches to fight bacterial diseases.

	Project ID:	Project Acronym:	Evaluation Panel:
	810207	**ArpComplexity**	**SYG** Synergy

Principal Investigator:	**Dr Edgar Gomes**
Host Institution:	Institute of Molecular Medicine - PRT

Defining the role of Arp2/3 complex diversity at multiple scales of biology

The actin cytoskeleton of the cell is critical for the complex, integrated processes associated with development, operation and sustainability of the human body. The Arp2/3 complex consisting of seven protein subunits is essential to stimulate dynamic branched actin networks needed for multiple cellular processes. The Arp2/3 complex has always been considered as a single entity, but in humans and other mammals, three of the Arp2/3 complex subunits are encoded by two isoforms, thus allowing the formation of eight distinct Arp2/3 complexes. The Way lab has shown that Arp2/3 subunit composition dramatically affects the formation and stability of branched actin networks. The Way and Gomes labs have shown how specific Arp2/3 isoforms are essential for muscle development. Our synergistic, high-risk, high-gain goal is to define the role of Arp2/3 complex diversity at three hierarchies of biology: 1. Molecular basis of Arp2/3 diversification With purified isoform-specific complexes we will perform cryo-electron microscopy and single molecule fluorescence microscopy to reveal the structural variations and influence of Arp2/3 diversity on actin networks in vitro. 2. Cellular function of different Arp2/3 complexes With cells expressing specific Arp2/3 isoforms, we will use quantitative live cell imaging and cryoelectron tomography to reveal the dependence of cellular actin networks on Arp2/3 diversity and its functional consequences. 3. Developmental and physiological role of individual Arp2/3 complexes. With genetically modified cultured myofibers and transgenic mice, we will use an array of imaging approaches to reveal the contribution of different Arp2/3 family members to muscle development, structure and physiology. Our interdisciplinary plan builds on the strengths of our three labs, takes advantage of unique reagents and powerful model systems, and will allow us to determine how Arp2/3 diversity contributes to biological complexity at multiple scales.

Link to the ERC project webpage: https://imm.medicina.ulisboa.pt/investigation/laboratories/edgar-gomes-lab/#intro

Keywords of the ERC project: cytoskeleton, cell biology, skeletal muscle, arp 2/3, actin

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

	Project ID:	Project Acronym:	Evaluation Panel:
	810296	**DECODE**	**SYG** Synergy

Principal Investigator:	**Dr Michael Boutros**
Host Institution:	Deutsches Krebsforschungszentrum - DEU

Decoding Context-Dependent Genetic Networks in vivo

The evolutionary success of multicellular organisms is based on the division of labor between cells. While some of the molecular determinants for cell fate specification have been identified, a fundamental understanding of which genetic activities are required in each cell of a developing tissue is still outstanding. The DECODE project will develop and apply leading-edge system genetics methods to Arabidopsis and Drosophila, two major model systems from the plant and animal kingdoms to decode context-dependent genetic networks in vivo. To achieve this, DECODE will bring together experimental and theoretical groups with complementary expertise in model organism genetics and cellular phenotyping, single-cell genomics, statistics and computational biology. Building on our combined expertise, we will create functional genetic maps using conditional CRISPR/Cas9-based single- and higher order knockout perturbations in vivo combined with single-cell expression profiling and imaging. Coupled with powerful computational analysis, this project will not only define, predict and rigorously test the unique genetic repertoire of each cell, but also unravel how genetic networks adapt their topology and function across cell types and external stimuli. With more than 3000 conditional knockouts, characterized by at least six million single-cell transcriptome profiles and high-resolution imaging this project will create the largest single-cell perturbation map in any model organism and will provide fundamental insights into the genetic architecture of complex tissues. Analyzing two tissues with divergent organization and regulatory repertoire will enable us to uncover general principles in the genetic circuits controlling context dependent cell behavior. Consequently, we expect that the DECODE project in model organisms will lay the conceptual and methodological foundation for perturbation-based functional atlases in other tissues or species.

Link to the ERC project webpage: https://www.dkfz.de/signaling

Keywords of the ERC project: Genomics, Systems Genetics; Single-cell genomics

Keywords that characterize the scientific profile of the potential visiting researcher/s: New computational approaches, single cell technologies

	Project ID:	Project Acronym:	Evaluation Panel:
	810331	**WATCH**	**SYG** Synergy

Principal Investigator:	**Dr Markus Schwaninger**
Host Institution:	UNIVERSITAET zu LUEBECK - DEU

Well-Aging and the Tanycytic Control of Health

The survival of an organism depends on energy homeostasis, involving the control of neuroendocrine functions that integrate metabolic feedback and adapt the response of the organism to physiological demands. Tanycytes, specialized glial cells lining the floor of the third ventricle in the median eminence of the hypothalamus, act as linchpins of these processes, dynamically controlling the secretion of neuropeptides by hypothalamic neurons into the pituitary portal circulation and regulating blood-brain and blood-cerebrospinal fluid exchanges, both processes that depend on their morphological plasticity in response to the physiological state. In addition to their barrier properties, they actively shuttle circulating metabolic signals to hypothalamic neurons that control food intake. The overarching goal of WATCH is to synergistically employ state-of-the-art technologies in systems neuroscience, mouse genetics and bench-to-bedside research, to explore the role of these unique and versatile cells, providing new directions in biomarker research and new therapeutic approaches for a variety of disorders that impair well-aging. Our specific aims are:

1. Genetic dissection of the in vivo regulation, pathophysiological function and molecular markers of tanycytes classified according to their anatomical location.

2. Identification of novel heterogeneous, molecularly distinct tanycytes and associated endothelial cells and determining how these characteristics evolve under distinct physiological and pathological conditions.

3. Functional validation of newly classified subgroups of tanycytes and the specific modulation of the activity of these subgroups at the experimental level.

4. Exploration of the functional consequences of pharmacologically activating pathways required for the tanycytic shuttling of metabolic signals on their CSF levels of these factors, hypothalamic activity and cognition in animal models and patients with morbid obesity or age-related cognitive deficits.

Link to the ERC project webpage:

Keywords of the ERC project: blood-brain barrier, tanycytes, capillaries, mass spectrometry

Keywords that characterize the scientific profile of the potential visiting researcher/s: single cell mass spectrometry, AAV techniques, single cell RNA seq

	Project ID:	Project Acronym:	Evaluation Panel:
	855158	**ANEUPLOIDY**	**SYG** Synergy

Principal Investigator:	**Dr Nenad Pavin**
Host Institution:	FACULTY OF SCIENCE UNIVERSITY OF ZAGREB - HRV

Molecular origins of aneuploidies in healthy and diseased human tissues

Chromosome segregation errors cause aneuploidy, a state of karyotype imbalance that accelerates tumor formation and impairs embryonic development. Even though mitotic errors have been studied extensively in cell cultures, the mechanisms generating various errors, their propagation and effects on genome integrity are not well understood. Moreover, very little is known about mitotic errors in complex tissues. The main goal of this project is to uncover the molecular origins of mitotic errors and their contribution to karyotype aberrations in healthy and diseased tissues. To achieve our goal, we have assembled an interdisciplinary team of experts in molecular and cell biology, cell biophysics, chromosomal instability in cancer, and theoretical physics. Our team will introduce novel approaches to study aneuploidy (superresolution microscopy, optogenetics, laser ablation, single cell karyotype sequencing) and apply them to state-of-the-art tissue cultures (mammalian organoids and tumoroids). In close collaboration, Tolić will establish assays to detect and quantify error types in cells, and Kops and Amon will use the assays on various healthy and cancer tissues. Tolić and Kops will uncover the molecular origins of errors, their propagation and impact on genome integrity, while Amon will lead the investigation of the mechanisms that ensure high chromosome segregation fidelity in healthy tissues. Interwoven in these collaborations are the efforts of Pavin, who will develop a theoretical model to describe the origin of errors and to quantitatively link chromosome segregation fidelity in single cells and tissues. Model and experiment will continuously inspire each other, to achieve deep understanding of how mitotic errors arise, how they propagate and how they impact on cell populations. Thus, the extensive sets of expertise present in our team will be combined and expanded with novel technologies to tackle the big challenge of the origins of aneuploidy in humans.

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency *Established by the European Commission*	**855158**	**Aneuploidy**	**SYG** Synergy

Principal Investigator:	**Dr Iva Tolić**
Host Institution:	Ruder Boskovic Institute - HRV

Molecular origins of aneuploidies in healthy and diseased human tissues

Chromosome segregation errors cause aneuploidy, a state of karyotype imbalance that accelerates tumor formation and impairs embryonic development. Even though mitotic errors have been studied extensively in cell cultures, the mechanisms generating various errors, their propagation and effects on genome integrity are not well understood. Moreover, very little is known about mitotic errors in complex tissues. The main goal of this project is to uncover the molecular origins of mitotic errors and their contribution to karyotype aberrations in healthy and diseased tissues. To achieve our goal, we have assembled an interdisciplinary team of experts in molecular and cell biology, cell biophysics, chromosomal instability in cancer, and theoretical physics. Our team will introduce novel approaches to study aneuploidy (superresolution microscopy, optogenetics, laser ablation, single cell karyotype sequencing) and apply them to state-of-the-art tissue cultures (mammalian organoids and tumoroids). In close collaboration, Tolić will establish assays to detect and quantify error types in cells, and Kops and Amon will use the assays on various healthy and cancer tissues. Tolić and Kops will uncover the molecular origins of errors, their propagation and impact on genome integrity, while Amon will lead the investigation of the mechanisms that ensure high chromosome segregation fidelity in healthy tissues. Interwoven in these collaborations are the efforts of Pavin, who will develop a theoretical model to describe the origin of errors and to quantitatively link chromosome segregation fidelity in single cells and tissues. Model and experiment will continuously inspire each other, to achieve deep understanding of how mitotic errors arise, how they propagate and how they impact on cell populations. Thus, the extensive sets of expertise present in our team will be combined and expanded with novel technologies to tackle the big challenge of the origins of aneuploidy in humans.

Link to the ERC project webpage: http://tolic.irb.hr/erc-synergy

Keywords of the ERC project: chromosome segregation, aneuploidy, mitotic spindle, organoids, laser microsurgery,
modeling

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

	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: protein aggregation, mechanical properties, mechanical microscopy

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

	Project ID:	Project Acronym:	Evaluation Panel:
European Research Council Executive Agency *Established by the European Commission*	**856432**	**HyperQ**	**SYG** Synergy

Principal Investigator:	**Dr Jan Ardenkjaer-Larsen**
Host Institution:	DANMARKS TEKNISKE UNIVERSITET - DNK

Quantum hyperpolarisation for ultrasensitive nuclear magnetic resonance and imaging

Many of the most remarkable contributions of modern science to society have arisen from the interdisciplinary work of scientists enabling novel methods of imaging and sensing. Outstanding examples are nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) which have enabled fundamental insights in a broad range of sciences extending from Chemistry to the Life Sciences. However, the key challenge of NMR and MRI is their very low inherent sensitivity due to the weak nuclear spin polarisation under ambient conditions. This makes the extension of magnetic resonance to the nanoscale (small volumes) and to the observation of metabolic processes (low concentrations) impossible.

HyperQ will address this challenge with the development of room-temperature quantum control of solid-state spins to increase nuclear spin polarisation several orders of magnitude above thermal equilibrium and thereby revolutionise the state-of-the-art of magnetic resonance. Essential for this development is the synergy of an interdisciplinary team of world leaders in quantum control and hyperpolarised magnetic resonance to enable the development of quantum control theory ("Quantum Software"), quantum materials ("Quantum Hardware"), their integration ("Quantum Devices") and applications to biological and medical imaging ("Medical Quantum Applications"). HyperQ will target major breakthroughs in the field of magnetic resonance, which include chip-integrated hyperpolarisation devices designed to operate in combination with portable magnetic resonance quantum sensors, unprecedented sensitivity of bio-NMR at the nanoscale, and biomarkers of deranged cellular metabolism.

The HyperQ technology will provide access to metabolic processes from the micron to the nanoscale and thereby insights into metabolic signatures of a broad range of disease such as cancer, Alzheimer and the mechanisms behind neurodegenerative disease. This will enable fundamentally new insights into the Life Sciences.

Link to the ERC project webpage:

Keywords of the ERC project:

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

	Project ID:	Project Acronym:	Evaluation Panel:
	856432	**HyperQ**	**SYG** Synergy

Principal Investigator:	**Dr Martin Plenio**
Host Institution:	Universitaet Ulm - DEU

Quantum hyperpolarisation for ultrasensitive nuclear magnetic resonance and imaging

Many of the most remarkable contributions of modern science to society have arisen from the interdisciplinary work of scientists enabling novel methods of imaging and sensing. Outstanding examples are nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) which have enabled fundamental insights in a broad range of sciences extending from Chemistry to the Life Sciences. However, the key challenge of NMR and MRI is their very low inherent sensitivity due to the weak nuclear spin polarisation under ambient conditions. This makes the extension of magnetic resonance to the nanoscale (small volumes) and to the observation of metabolic processes (low concentrations) impossible.

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	Project ID:	Project Acronym:	Evaluation Panel:
	856487	**AgingTimer**	**SYG** Synergy

Principal Investigator:	**Dr Valery Krizhanovsky**
Host Institution:	Weizmann Institute Of Science - ISR

Systems biology of the individual stochastic timer of aging

Aging is the biggest risk factor for frailty and death. However, we lack basic understanding of a fundamental question: Why do genetically identical organisms raised in the same conditions get sick and die at different times? If we understood the stochastic timer that drives aging in each individual, we could devise ways to turn back the timer and treat age-related diseases, extending the healthy lifespan. This requires addressing both molecular and social factors that vary between individuals, such as socioeconomic status in humans and social ranking in mice, which impact every aspect of aging. This synergy program aims to identify the stochastic timer of aging and develop methods to read the timer and turn it back. We use mice as a tractable organism relevant to human aging, and combine three disciplines: 1) systems biology to mathematically define the stochastic timer of aging and the basic concepts needed to understand its production, removal and noise processes; 2) neurobiology of behavioral individuality; and 3) biology of cellular senescence, which studies the most promising candidate for the timer: senescent cells that accumulate with age, causing chronic inflammation and whose removal delays age-related decline. To pinpoint the timer, we will follow the natural variability of large cohorts of genetically identical mice, tracked across the lifespan by video and RFID tags. We will measure a battery of behavioral, physiological and molecular parameters, as well as senescent cells in multiple organs throughout life. We will use new mouse models that allow us to visualize, pull down and ablate senescent cells, to provide full molecular profiles of senescent cells in different organs and to characterize their immune-surveillance mechanisms. This study will provide basic understanding of the timer of aging and provide ways to read the timer. Moreover, we will offer new ways to set back the timer in order to address age-related diseases and functional decline.

Link to the ERC project webpage:

Keywords of the ERC project: aging, senescence, behavior, immune system

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

	Project ID:	Project Acronym:	Evaluation Panel:
	856495	**Relevance**	**SYG** Synergy

Principal Investigator:	**Dr Beatrice de Gelder**
Host Institution:	UNIVERSITEIT MAASTRICHT - BEL

How body relevance drives brain organization

Social species, and specifically human and nonhuman primates, rely heavily on conspecifics for survival. Considerable time is spent watching each other's behavior because this is often the most relevant source of information for preparing adaptive social responses. The project RELEVANCE aims to understand how the brain evolved special structures to process highly relevant social stimuli like bodies and to reveal how social vision sustains adaptive behaviour.

This requires a novel way of thinking about biological information processing, currently among the brains' most distinctive and least understood characteristic that accounts for the biggest difference between brains and computers.

The project will develop a mechanistic and computational understanding of the visual processing of bodies and interactions and show how this processing sustains higher abilities such as understanding intention, action and emotion. Relevance will accomplish this by integrating advanced methods from multiple disciplines: psychophysics and high-field functional imaging in combination with virtual reality and neural stimulation in humans; electrophysiology with optogenetics and laminar recordings in monkeys.

Crosstalk between human and monkey methods will establish homologies between the species, revealing cornerstones of the theory. In a radical departure from current practice, we will develop novel deep neural network models that unify the data. These models will not only capture detailed mechanisms of neural processing of complex social stimuli and its dynamics, but also reproduce the modulation of brain activity during active behavior.

RELEVANCE will reveal novel ways of understanding and diagnosing social communication deficits in neuropsychiatry, and suggest novel hypotheses about their genetic basis. It will motivate novel principles and architectures for processing of socially relevant information in computer and robotic systems.

Link to the ERC project webpage:

Keywords of the ERC project:

Keywords that characterize the scientific profile of the potential visiting researcher/s: systems neuroscience, fMRI 7T, computational methods

Principal Investigator:	**Dr Yohei Yamauchi**
Host Institution:	UNIVERSITY OF BRISTOL - GBR

Ubiquitin Chains in Viral Infections

Viruses such as Influenza A (IAV) and others remain one of the greatest threats to human health and society. Despite their danger and widespread prevalence, the molecular mechanisms of how they infect mammalian hosts and evade the immune system remains poorly understood. Recent studies from our team implicate two common proteins – HDAC6 and unanchored ubiquitin chains – in host cells as key mediators of viral entry via the aggresome processing pathway. This discovery offers a new line of investigation for understanding and preventing viral infections.

By identifying the pathways and interactions involved in this infection process, we will provide new molecular targets for the development of broad-spectrum antiviral compounds. Multidisciplinary studies by a team consisting of a molecular biologist, a virologist, and a chemical biologist will use a diverse set of tools to validate these pathways and gain fundamental knowledge about their regulation. To achieve this, detailed studies on the exact nature of the ubiquitin chains needed to activate HDAC6 will allow the development of biochemical and cellular assays of Influenza A infection and enable the determination of the precise mechanism and the downstream cellular pathways necessary for viral infection. The chemical synthesis of labeled ubiquitin chains will support detailed structural studies and a clear understanding of how they are formed and packaged into infectious viral particles. The strong possibility that numerous other virus types also utilize this pathway will be tested with life-threatening agents of current concern including Zika, Dengue, Ebola, and MERS viruses.

By demonstrating – with both biological approaches and small molecule compounds – that blocking these cellular processes in cells and animal models reduces viral infection, this project will provide a wealth a novel insights and the basis for the development of a new generation of anti-viral therapies.

Link to the ERC project webpage:

Keywords of the ERC project: Viral entry, Virus-host interaction, broad band antiviral, cellular processes

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