WHRI-ACADEMY

International Fellowship Programme

5th Call for Proposals

CATALOGUE OF PROJECTS

Preamble

This catalogue presents projects co-financed by WHRI-ACADEMY International Fellowship Programme in the frame of its third Call for proposals.

WHRI-ACADEMY is a FP7 COFUND Marie Curie action[1].

In total 7 projects were retained for funding, from which:

N. of projects	Research Area (RA)
0	**RA1** – Molecular and Structural Biology and Biochemistry
0	**RA2** – Physiology, Pathophysiology, Cardiovascular Diseases and Endocrinology
2	**RA3** – Genetics, Genomics, Bioinformatics and Systems Biology
0	**RA4** – Cellular and Development Biology
1	**RA5** – Neurosciences and Neural Disorders
2	**RA6** – Immunity and Infection
2	**RA7** – Diagnostic Tools, Therapies and Public Health

The present version is intended to be disseminated.

In case successful projects believe that this document harms in any way IPR held by them as a person or as a representative of an entity, please do notify us immediately.

[1] http://ec.europa.eu/research/mariecurieactions/about-mca/actions/cofund/index_en.htm


Research Area 3:
Genetics, Genomics,
Bioinformatics and
Systems Biology

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Marek Wojciechowski	01/12/2016	18	Incoming

Host Institution
School of Biological and Chemical Sciences, Queen Mary University of London, United Kingdom.

Acronym: ---

Project Title: Functional analysis of chromatin modifications in honeybee caste determination.

Free keywords: Honeybee, Chromatin, Epigenetics.

Abstract
Honeybees are ecologically and economically important eusocial insects. They live in structured societies in which there are two female castes: the queen, which is unique in the hive and is the only female with the capacity to lay fertilised eggs, and thousands of facultatively sterile female workers. Although the queen and the workers are genetically identical, their differential nutrition during larval development leads to two castes that are physiologically, morphologically and behaviorally distinct. During the first days of larval development workers and queens are both fed glandular secretions (royal jelly and workers jelly), which mainly differ in their sugar concentrations. From the third/fourth day onward diets diverge; worker larvae receive a mix of glandular secretions, royal jelly, and pollen, while queen larvae continue to receive large quantities of royal jelly. Extensive transcriptional studies have been carried out to determine which genes are differentially expressed in worker versus queen tissues. However, although functions for DNA methylation and hormonal signals have been found to be important for caste determination, crucially a direct link between these mechanisms and differential nutrition and gene expression remains elusive. In particular, the function of histone post-translational modifications (PTMs) has not been determined. In order to explore this fundamentally important and unresolved question, we propose to conduct chromatin immunoprecipitation experiments on histone PTMs that are catalysed by the highly conserved Polycomb group complexes, in order to determine the genome-wide location and enrichment of these specific histone PTMs during development of the two female castes. In particular, we will examine larval tissues that ultimately become fundamentally different caste-specific adult structures. These studies will yield the first insights into the role of histone PTMs in caste development in honeybees and help to explain how the honeybee genome has the ability to encode more than one distinct organism.

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Weini Huang	01/12/2016	24	Incoming

Host Institution
Barts Cancer Institute, Queen Mary University of London, United Kingdom.

Acronym: ---

Project Title: Mathematical modeling on the evolution of drug resistance in ovarian cancer.

Free keywords: Evolutionary theory, Drug resistance, Ovarian cancer.

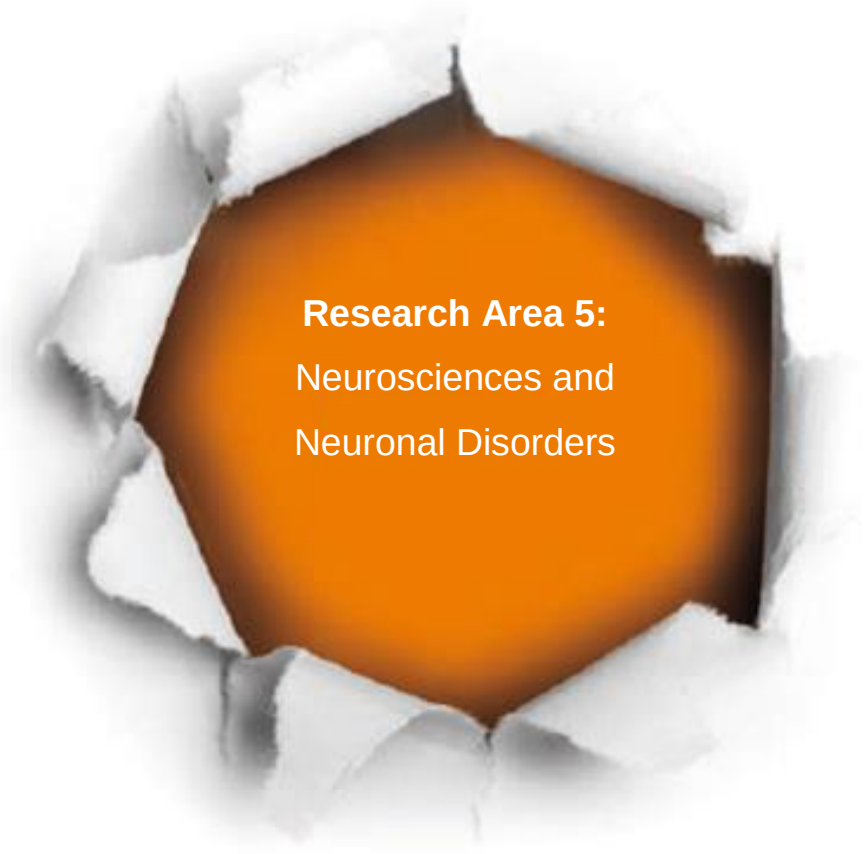
Abstract
We aim to reveal the evolutionary process of chemo-resistance by a combined approach with evolutionary theory, experimental and clinical data. Tumour dynamics is an evolutionary process, where mutation causes heterogeneity and selection reforms the population composition. Chemotherapy resistance is one of the biggest challenges in cancer treatment, and is due to the selection of pre-existing resistant sub-clones. In high-grade serious ovarian cancer (HGSOC) 70% of patients will develop chemo-resistant disease following treatment. We will build mathematical models to describe of the evolution of competitions between resistant and sensitive tumour cells, and parameterise these models using data from in vitro experiments measuring the growth of drug-sensitive and drug-resistant cell-lines. Mathematical optimization of the model will reveal how to dose chemotherapy to minimise the abundance of resistant clones. To overcome the limit of in vitro experiments, we will evaluate and adjust our models with clinical data from circulating tumour cells in blood samples, ascites and solid tissue biopsies of patients with HGSOC. The ultimate goal of our project is to improve the efficacy of chemotherapy by predicting treatment regimens that suppress the evolution of resistance.

WHRI-ACADEMY

International Fellowship Programme

5th Call for Proposals

CATALOGUE OF PROJECTS



Research Area 5:

Neurosciences and

Neuronal Disorders

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Maite Ogueta Gutierrez	01/01/2017	24	Incoming

Host Institution
Institute for Neuro- and Behavioural Biology, University of Münster, Germany.

Acronym: ---

Project Title: How light synchronizes the daily oscillations in circadian clock neurons.

Free keywords: Circadian Clock, Photoreception, Functional neuronal imaging.

Abstract
Circadian clocks are perhaps the best example of how genes give rise to complex physiology and behaviour. They reveal how the environment influences gene expression, which in turn alters the behaviour of the organism. Circadian clocks therefore demonstrate that the interplay between genetic and external factors determine the overt behaviour of an organism.
The extensive exposure to artificial light has permitted modern societies to escape the temporal limits usually imposed by the natural environment. These mis-timed activities provide conflicting signals to the circadian clock, perturbing its synchrony with the external world and provoking serious physiological consequences. Sleep deprivation building up during regular working weeks due to social activities, TV or computers at night, and work/school schedules, challenge our internal clock, causing what is generally referred to as “social jetlag”. Social jetlag, and more extreme forms of de-synchronizing our internal clocks has led to an alarming increase in health risks, and has causatively been linked to physical and mental diseases.
To understand and mitigate these problems, full comprehension of the molecular and neuronal mechanisms underlying circadian clock synchronization to daily light/dark cycles is required. In *Drosophila*, the blue light photoreceptor Cryptochrome (Cry), in combination with canonical rhodopsin photoreception operating in the compound eyes, are responsible for the main light-input to the circadian clock. Nevertheless, because light-dependent synchronization of key circadian clock proteins, which is the crucial step in molecular resetting of the clock, also occurs independently of Cry and canonical rhodopsin signalling, it is clear that other photoreceptors and signalling mechanisms are important for light-synchronization. This means we are currently lacking fundamental knowledge about circadian photoreception, both in terms of the photoreceptors involved and light signalling mechanisms to the clock. In this project I plan to identify and characterize these novel components.

Research Area 6:

Immunity and Infection

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Loïc Rolas	01/12/2016	24	Incoming

Host Institution
Centre for Microvascular Research, William Harvey Research Institute, Queen Mary University of London, United Kingdom.

Acronym: Neut-rTEM.

Project Title: Neutrophil reverse transendothelial cell migration: Phenotype, pathogenic potential and impact of age.

Free keywords: Neutrophil, Transendothelial cell migration, Inflammation.

Abstract
Neutrophil migration through blood vessel walls is a key step in innate immunity, but if inappropriately triggered or aberrant in nature, it can induce vascular/tissue damage. One such example is the novel phenomenon of neutrophil reverse migration through endothelial cells (ECs). Although transendothelial cell migration (TEM) commonly occurs in a luminal-to-abluminal direction, through the application of advanced confocal intravital microscopy (IVM), the laboratory of my proposed supervisor, Prof. Nourshargh (Queen Marry, University of London), provided evidence for the occurrence of neutrophil TEM in reverse direction *in vivo*, i.e.: abluminal-to-luminal (rTEM). This enigmatic response has been associated with dissemination of a local inflammatory response to distant organs but there remain many unanswered questions about this reaction. Here I aim to investigate the specific and original hypothesis that the aberrant nature of neutrophil rTEM dynamics is the underlying cause of inappropriate neutrophil activation at the level of the endothelium leading to both local vascular/tissue & remote organ injury. As such, I will use numerous novel and specialized *in vivo* techniques, most notably confocal IVM to determine the following within inflammatory settings: (i) the molecular signature of rTEM neutrophils, (ii) the activation state of rTEM neutrophils, (iii) the pathogenic properties of rTEM neutrophils, & (iv) the impact of vascular aging on the prevalence of neutrophil rTEM.
Through engaging with this exciting project, the COFUND fellowship will provide me with increased scientific independence and ability to explore challenging objectives. This will include opportunities for developing novel tools (e.g. unique mouse models) and technologies (e.g. enhancement of existing IVM platforms). Collectively the requested funds will significantly improve the scientific strength of my project, enhance my training, facilitate the establishment of international collaborative links and as such provide a strong platform for launching my independent career.

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Bonnie van Wilgenburg	01/01/2017	24	Outgoing

Host Institution
Department of Microbiology and Immunology, The University of Melbourne, Australia.

Acronym: ---

Project Title: Characterisation of Mucosal Associated Invariant T-cells in viral infections.

Free keywords: Mucosal Associated Invariant T (MAIT) cells, Viral immunity, Influenza

Abstract
Mucosal Associated Invariant T (MAIT) cells, a recently identified innate-like T cell subset, likely play an important role in controlling viral infections. MAIT cells exist in a very diverse range of vertebrate species and are abundant, comprising around 10% of human peripheral T cells and enriched in the lungs, intestine and liver, representing 10-50% of CD8+ T cells. The laboratory of my Scientist in Charge showed that MAIT cells react to bacteria through their semi-invariant T cell receptor, which is restricted by the conserved MR1 molecule; it can present ligands derived from the riboflavin synthesis pathway. More recently, we discovered that human MAIT cells also become activated, and are lost from the blood, during viral infections, notably Influenza infection. Our findings are correlative. More definitive experiments in animal models are not straightforward, as mice have infrequent MAIT cells and a MR1 tetramer is required for detection. However, these technical hurdles have been overcome by my Scientist in Charge, who not only developed the first MR1 MAIT-specific tetramers, but also developed unique, novel methods to boost MAIT cells in mice. Access to these experimental models will allow me to answer fundamental questions as to the protective and pathogenic functions of MAIT cells in viral infections. The critical aim addressed by my proposal is to define the function and regulation of MAIT cells in response to viral challenges. This, in turn, might identify novel therapeutic targets to modulate the host defenses.


Research Area 7:
Diagnostic Tools,
Therapies and Public
Health

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Angad Malhotra	01/01/2017	24	Incoming

Host Institution
Laboratory for Bone Biomechanics, Institute for Biomechanics, ETH Zurich (Swiss Federal Institute of Technology), Switzerland.

Acronym: CaP+MECHLOAD.

Project Title: Enhanced bone revascularization through biomaterials, mechanical loading, and computational biomechanics.

Free keywords: Bone vascularity, Biomechanics, Biomaterials.

Abstract
The management of bone defects continues to present surgical challenges, motivating bone regeneration research. With a chemical similarity to bone mineral, calcium phosphates (CaP) is the most obvious choice for bone graft substitutes, despite that they remain inferior to autograft. This project explores how to bridge the large gap in bone healing through mechanical loading and vascularity.
Mechanical regulation has a well-known relation to vascular growth, though this insight is poorly utilized within the bone-biomaterial realm. Here, the hypothesis is that combining mechanical loading with CaPs will induce a synergistic effect that enhances healing, driven by changes in the angiogenic responses.
A focus is on vascularity, as a lack of revascularization is a major contributor to bone healing complications. Therefore, this project focuses on revascularization via two factors: the localized mechanical strain conditions, and the CaP biomaterial. One of the major difficulties with current techniques is to match the developing vascularity with the local strain history of the region. This complexity is compounded by a changing stiffness from bone matrix deposition and CaP degradation. To address this, time-lapse μCT will be used to visualize vascularity, bone formation, and CaP degradation.
Using existing computational methods, the localized strain conditions can be modeled. To dig further into the molecular mechanisms, laser capture microdissection will be used to study the endothelial cell gene expression at 4 weeks, and these will be correlated to revascularization outcomes.
This fresh approach will provide massive insight into how biomaterials, mechanical loading, and vascularity relate to bone biomechanics and regeneration. Most importantly, this study will answer whether mechanical loading and CaPs have a synergistic effect on revascularization and bone regeneration, and whether this focus on biomaterials and vascularity can reduce the clinical reliance on autograft. Overall, this project will provide an advanced treatment options by combining the fields of computational biomechanics, biomaterials, and regenerative medicine.

CATALOGUE OF PROJECTS

Fellow	Starting date	Duration	Mobility
Dr. Francesco Ursini	01/01/2017	18	Incoming

Host Institution
Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, United Kingdom.

Acronym: TAIRA.

Project Title: Therapeutic Antibodies ImmunoPET in Rheumatoid Arthritis: Defining in vivo Diverse Molecular Pathology and Therapeutic Response.

Free keywords: Rheumatoid arthritis, PET/CT, Personalized medicine.

Abstract
Despite the advent of powerful DMARD-biologic therapies, including monoclonal antibodies (mAbs), ~40% of patients with rheumatoid arthritis (RA) fail to respond to treatment. The lack of biomarkers predictive of response means that drugs are still used on a "trial-and-error" basis. Thus, the search for predictive biomarkers is intense, and while antibody status, gene-expression and cytokine profiles have shown an association, they are not predictive. However, it is clear that target expression levels in the disease tissue influence clinical response. For example, high synovial TNFα levels pre-treatment associate with responsiveness to TNF-inhibitors (TNF-i). Reciprocally, we have demonstrated (unpublished) that low/absence CD20+B cells, the target of the mAb Rituximab (RTX), is associated with poor response - notably, 40-60% of patients have no/few B-cells in the joint. On this basis, we hypothesize that low TNFα or B cells levels in the disease tissue would predict nonresponse.
This hypothesis is being tested in two MRC/NIHR funded, biopsy-driven randomised clinical trials. However, recruitment has been difficult, as though we have pioneered the use of ultrasound-guided biopsy as a minimally-invasive, well-tolerated procedure, this is still relatively complex and not in routine use in most hospitals.
In this project, therefore, we propose to test the ability of Positron Emission Tomography/Computed Tomography (PET/CT) to image non-invasively the joint for TNFα and B cells levels (immunoPET) employing a small dose of radiolabelled mAbs that patients are planned to receive e.g. the TNFi Adalimumab (ADA) or RTX. This approach has been successfully applied in oncology for personalized medicine.
We will test this hypothesis first in a proof of concept (POC) study in the human-synovium/SCID mouse transplantation model developed at the Centre for Experimental Medicine and Rheumatology at William Harvey Research Institute (EMR – WHRI). Second, in collaboration with Rome University, we will carry out a pilot study in RA patients.