CNIC Cicerone Program
Laboratory internships at the CNIC for university students during the summer months

List of Scientists and Research Lines 2021

Research line 1: Mechanical protein unfolding as a main contributor to the elasticity of the myocardium and muscle-mimicking biomaterials
Research Group: Molecular Mechanics of the Cardiovascular System
Supervisor: **Jorge Alegre-Cebollada**
Summary: The new concept that mechanical protein unfolding is behind the elasticity of tissues such as the myocardium has been proposed based only on indirect observations. Here, we plan to use a combination of techniques to observe, for the first time, protein unfolding as a main contributor to the elasticity of muscle tissue. Our new approach will also be applied to the design of smart biomaterials that mimic the elasticity of muscle tissue. This is an interdisciplinary project that borrows concepts and techniques from fields such as instrument development, protein biochemistry, polymer physics, single-molecule methods, and material science.
More information at: https://www.cnic.es/en/investigacion/molecular-mechanics-cardiovascular-system

Research line 2: Molecular events leading to the development of familial cardiomyopathies
Research Group: Molecular Mechanics of the Cardiovascular System
Supervisor: **Jorge Alegre-Cebollada**
Summary: The human heart is a formidable mechanical machine that pumps thousands of liters of blood every day. We are far from understanding how the heart works at the molecular level, and much less so how diseases of the heart develop. Following an interdisciplinary approach that includes protein biochemistry, biophysics, animal models and human clinical research, we plan to uncover how point mutations in cardiac proteins lead to life-threatening cardiomyopathy.
More information at: https://www.cnic.es/en/investigacion/molecular-mechanics-cardiovascular-system

Research line 3: Role of A-type lamins and progerin in aging and cardiovascular disease
Research Group: Molecular and Genetic Cardiovascular Pathophysiology
Supervisor: **Vicente Andrés**
Summary: Cardiovascular disease (CVD) is the main cause of morbimortality, in part due to the progressive aging of our societies. CVD and aging are much accelerated in Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder caused by the expression of progerin, a mutant form of lamin A which is also expressed at low level in tissues of non-HGPS individuals. The CICERONE student will learn about mechanisms through which A-type lamins and progerin regulate CVD and aging.

More information at: https://www.cnic.es/en/investigacion/molecular-and-genetic-cardiovascular-pathophysiology

Research line 4: In vivo analysis of vascular development in mice
Researh Group: Molecular Genetics of Angiogenesis
Supervisor: **Rui Benedito**
Summary: The group investigates different aspects of vascular biology using advanced mouse models and imaging technologies. We generated several new mouse lines that will allow us to induce precise genetic modifications during angiogenesis. The Cicerone student will be involved in a project to identify the best transgenic animals and do a pre-evaluation of the function of specific genes during the cardiovascular system development. The work will involve handling of mice and dissection, state-of-the-art imaging techniques, as well as molecular and cell biology techniques.
More information at: http://www.cnic.es/en/desarrollo/angiogenesis/index.php

Research line 5: Cellular dynamics in ventricular wall development and cardiomyopathy
Research Group: Intercellular Signaling in Cardiovascular Development & Disease
Supervisor: **José Luis de la Pompa / Joaquim Grego-Bessa**
Summary: Zebrafish, mouse and human genetics and imaging data indicate that alteration of cytoskeletal actin dynamics impairs trabeculation and compaction during ventricular development and cause cardiomyopathy. The highly motivated Cicerone student will work with mouse embryos, and carry out clonal, confocal microscopy and ISH analysis.
More information:
https://pubmed.ncbi.nlm.nih.gov/?term=de+la+pompa+JL&sort=date&filter=datesearch.y_10
https://www.cnic.es/en/investigacion/intercellular-signaling-cardiovascular-development-and-disease

Research line 6: Understanding how mechanical signals are propagated into the cell
Research Group: Mechanoadaptation and Caveolae Biology
Supervisors: **Miguel Ángel del Pozo / Asier Echarri**
Summary: In mechanically stressed cells, such as cardiomyocytes or endothelial cells, the plasma membrane contains small invaginations, named caveolae, that protect cells from mechanical stress, preventing cardiovascular pathologies. The mechanical stress induces major changes at the plasma membrane, actin filaments and even at the genome structure. How these complex changes are coordinated and interconnected is not well understood. The student will focus on understanding how cells receive mechanical signals by caveolae at the plasma membrane and how these signals are propagated throughout cell, up to the nucleus, and reprogram the cell structure and function.
More information at: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology
scientific report of the group can be downloaded from:
https://www.cnic.es/sites/default/files/files/attachments/2019/06/scientific_report_2018_lo.pdf

Research line 7: Mechanisms integrating blood flow sensing and arterial wall remodeling in atherosclerosis
Research Group: Mechanoadaptation and Caveolae Biology
Supervisor: **Miguel Ángel del Pozo / Miguel Sánchez-Álvarez**

Summary: While most cardiovascular risk factors (CVRF) known act systemically, atherosclerotic lesions develop at arterial regions subjected to disturbed flow patterns (typically, inner curvatures and bifurcations), which promote atherogenic wall remodeling, eliciting LDL retention and further inflammatory infiltration to sustain disease progression. Conversely, regions subjected to fast, laminar blood flow patterns are protected from lesion development. The student will study *in vitro* and *in vivo* novel molecular mechanisms as candidate regulators of local blood flow transduction and atherogenic arterial wall remodeling. This project will be carried out in the context of an international consortium, recently funded by the La Caixa Health Research programme (*AtheroConvergence*, https://fundacionlacaixa.org/en/therapeutic-targets-atherosclerosis).
More information at: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology
Scientific report of the group can be downloaded
from: https://www.cnic.es/sites/default/files/files/attachments/2019/06/scientific_report_2018_lo.pdf

Research line 8: Mitochondrial performance in heart disease
Research Group: Functional Genetics of the Oxidative Phosphorilation System (GENOPHOS)
Supervisor: **José Antonio Enríquez**
Summary: Our laboratory researches the mammalian mitochondrial electron transport chain (MtETC) and H+-ATP synthase, which together constitute the oxidative phosphorylation (OXPHOS) system.
We view this system as a functional entity, and use a range of approaches aimed at determining its role in health and disease. We are particularly interested in the role of the OXPHOS system in the development of the cardiovascular system, its relevance to ischemia-reperfusion, and its influence on microvascular blood flow.
More information at: https://www.cnic.es/en/investigacion/functional-genetics-oxidative-phosphorilation-system-genophos

Research line 9: Cardiovascular health promotion in adolescents
Research Group: Cardiovascular Health and Imaging
Supervisor: **Rodrigo Fernández Jiménez**
Summary: Our group focuses on health promotion and cardiovascular disease prevention. Specifically, the CICERONE student granted in our group will learn about school-based health promotion programs targeting adolescents in Spain, including but not limited to cardiovascular magnetic resonance imaging analysis and data management aspects. The student will have the opportunity to collaborate with the research team on ongoing research tasks and to formulate his/her own research ideas.
More information at: https://www.cnic.es/en/investigacion/cardiovascular-health-and-imaging

Research line 10: Structural Characterization and Wave Propagation Dynamics during Atrial Fibrillation.
Research Group: Advanced Development in Arrhythmia Mechanisms and Therapy Laboratory.
Supervisor: **David Filgueiras Rama**
Summary: The main objective of the project is to characterize wave propagation dynamics generated by reentrant patterns of activation (rotors), and the structural and functional changes that enable atrial fibrillation (AF) to persist at different progression stages. The objective involves the identification and analysis of functional and structural parameters, bringing

together experimental and clinical tools for interpretation and decision-making. The multidisciplinary and translational design of the project includes the study of an *in vivo* model of that resembles clinical progression of the arrhythmia.

More information at: https://www.cnic.es/en/investigacion/advanced-development-arrhythmia-mechanisms-and-therapy

Research line 11: Environmental factors as modulators of the effects of acquired mutations on inflammation and atherosclerosis

Research Group: Hematovascular Pathophysiology Laboratory

Supervisor: **José J. Fuster**

Summary: The accumulation of acquired mutations in blood and immune cells is an inevitable consequence of the aging process. A few of these mutations confer a competitive advantage to the mutant cell, leading to its clonal expansion, a process called clonal hematopoiesis. This phenomenon is an important modulator of inflammation and a shared risk factor for cardiovascular disease and cancer. Virtually everyone acquires clonal hematopoiesis-inducing mutations, but the clonal expansion of the mutant cells occurs only in some individuals, due to mechanisms that remain unknown. The CICERONE student will contribute to experimental studies that will examine how environmental factors (e.g. diet, pollutants, drugs) modulate the clonal expansion of cells carrying specific mutations and their impact on inflammation and atherosclerosis. By doing this, he/she will be exposed to many basic research techniques (e.g. histology, immunofluorescent staining, flow cytometry, immune cell culture), and will also be introduced to the use of mouse models in cardiovascular and hematological research.

More information at:

https://www.cnic.es/en/investigacion/hematovascular-pathophysiology

https://www.ncbi.nlm.nih.gov/pubmed/29420212

https://pubmed.ncbi.nlm.nih.gov/32109665/

Research line 12: Novel mitochondria-targeted therapies for cancer therapy-induced cardiotoxicity (MATRIX)

Research Group: Translational Laboratory for Cardiovascular Imaging and Therapy

Supervisors: **Borja Ibáñez / Eduardo Oliver**

Summary: Cancer therapy-induced cardiac toxicity is affecting up to 30% of cancer treated patients thus resulting in severe heart failure and premature death. We have recently demonstrated that imbalanced mitochondrial dynamics in cardiomyocytes results in a phenotype recapitulating cardiac toxicity induced by cancer treatment, including metabolic reprogramming and ultimately heart failure. Building on these data, we will study the mechanisms leading to mitochondrial failure in cardiac toxicity and use the knowledge obtained to develop novel therapies.

More information at:

https://www.cnic.es/en/investigacion/translational-laboratory-cardiovascular-imaging-and-therapy

Research line 13: Innovative therapies for the treatment of cardiomyopathies

Research Group: Molecular regulation of heart failure

Supervisor: **Enrique Lara-Pezzi**

Summary: Arrithmogenic cardiomyopathy type 5 (ACM5) is a rare and devastating disease for which there is no cure. It is caused by the p.S358L mutation in the gene TMEM43. We have developed an ACM5 mouse model that expresses the mutant protein and faithfully reproduces

the human disease (Padrón-Barthe, Circulation 2019). In this new translational project, we will use the acquired knowledge to develop new gene therapy tools to tackle this disease.
More information at: https://www.cnic.es/en/investigacion/molecular-regulation-heart-failure

Research line 14: Disentangling heart failure to improve diagnosis, prevention and treatment
Research Group: Molecular regulation of heart failure
Supervisor: **Enrique Lara-Pezzi**
Summary: Heart failure with preserved ejection fraction (HFpEF) is a major public health problem affecting 13 M patients worldwide, especially among the elderly. Patients often present several simultaneous comorbidities and it is virtually impossible to identify the specific contribution of each of them. The available diagnostic tools are inaccurate at best and treatment is still largely based on "one-size-fits-all", which is ineffective once HF manifests with clinical symptoms. The aim of the project is to disentangle the HFpEF mesh, to deepen our understanding of HFpEF progression associated with each underlying comorbidity, and to develop precise diagnostic and therapeutic tools that will prevent or reverse HFpEF symptoms.
More information at: https://www.cnic.es/en/investigacion/molecular-regulation-heart-failure

Research line 15 T cells as precision cardiovascular medicine
Research Group: Regulatory Molecules of Inflammatory Processes
Supervisor: **Pilar Martín**
Summary: T lymphocytes are pivotal in the development of cardiovascular disease (CVD) and have been shown to be altered in blood and cardiovascular tissues during their progression. Regulatory T (Treg) cells have a protective role in the development of atherosclerosis, acute myocardial infarction and myocarditis, being CD4$^+$ Th17 cells critical for the development of these CVD. Our group studies the therapeutic and diagnostic performance of these cells, and derived microRNAs, in the management of CVD.
More information at: http://www.cnic.es/es/inflamacion/moleculas/index.php

Research line 16: Role of AhR in Alzheimer's disease progression
Research Group: Neurovascular Pathophysiology
Supervisor: **Mª Angeles Moro**
Summary: Aging reduces cerebral perfusion and increases susceptibility to cerebral vascular failure. The aryl hydrocarbon receptor (AhR) is known for its role in xenobiotic metabolism as well as its role as a regulator of inflammation. Recent evidence supports the existence of a link between AhR and aging. The student will participate in a project aimed to ascertain whether AhR is involved in the progression of Alzheimer's disease. The student will thus be exposed to a wide array of experimental techniques as well as to the use of animal models in neurovascular research.
More information at: https://www.cnic.es/en/investigacion/neurovascular-pathophysiology

Research line 17: Dual role of neutrophils in stroke
Research Group: Neurovascular Pathophysiology
Supervisor: **Mª Angeles Moro**
Summary: After stroke, neutrophils are rapidly mobilized from the bone marrow to the injury site, where they rapidly infiltrate into the ischemic brain. Whereas this process has been traditionally associated with expansion of the lesion, it is now believed that there are neutrophil subpopulations able to exert different effects. The student will participate in a study aimed to investigate the full range of mechanisms and factors responsible for neutrophil reprogramming toward different phenotypes in cerebrovascular diseases. The student will be exposed to a wide

array of experimental techniques and will also be introduced to the use of animal models in neurovascular research.

More information at: https://www.cnic.es/en/investigacion/neurovascular-pathophysiology

Research line 18: Targeted pro-resolving nanoimmunotherapy to treat atherosclerosis
Research Group: Nanomedicine and Molecular Imaging
Supervisor: **Carlos Pérez Medina**
Summary: Our research integrates molecular imaging into nanomedicine development, both for evaluating in vivo behavior and non-invasively monitoring treatment and efficacy. We exploit the natural ability of our nanoplatforms to interact with myeloid immune cells to selectively deliver inflammation pro-resolving drugs and promote atherosclerosis regression. You will be involved in the generation of a library of pro-resolving nanoformulations as well as in their *in vitro* characterization and *in vivo* evaluation in a mouse model of atherosclerosis.

More information at: https://www.cnic.es/en/investigacion/nanomedicine-and-molecular-imaging

Research line 19: The antibody immune response during atherosclerosis
Research Group: B Lymphocyte Lab
Supervisor: **Almudena R Ramiro**
Summary: In our lab we are interested in the mechanisms regulating the generation of antibodies and their functional relevance during the immune response as well as in pathological contexts, including cancer and autoimmunity. Here, we aim at getting insights into the role of the antibody immune response during atherosclerosis, with the ultimate goal to find new biomarkers and therapeutic avenues.

More information at:

https://www.cnic.es/es/investigacion/biologia-linfocitos-b

Research line 20: Molecular basis of aortic diseases: Mouse models, omics and gene therapy approaches.
Research Group: Gene regulation in Cardiovascular Remodelling and Inflammation
Supervisor: **Juan Miguel Redondo / Andrea de la Fuente / Sara Martinez**
Summary: We have identified new genes and mechanisms that mediate aortic diseases including Marfan syndrome (Nature Communications 2018 ; 2021 Nature Medicine 2017a; Nature Medicine 2017b). We have generated a number of mouse models to characterize gene expression programs implicated in aortic disease. We are using approaches based on lentiviral delivery *in vivo* to induce or regress disease (Trends Mol Med 2018), and to validate mediators identified in the human disease by proteomics and transcriptomics.

More information on the cited articles and other articles of the group can be found at: https://www.cnic.es/en/investigacion/1/3680/publicaciones

Research line 21: Role of nuclear receptors in cardiac homeostasis, regeneration and repair
Research Group: Nuclear Receptor Signaling
Supervisor: **Mercedes Ricote / Ana Paredes**
Summary: Cardiomyocytes are considered as quiescent cells with limited capacity to proliferate, which highly restricts the regenerative ability of the mammalian heart upon injury (e.g., myocardial infarction). Growing evidences suggest that the modulation of cardiac metabolic environment and the activation of the immune system may be good candidates for triggering tissue repair. In this project, we aim to characterize the transcriptional and epigenomic mechanisms control by nuclear receptors that drive cardiac homeostasis and regeneration after

myocardial infarction, decoding the functional impact of metabolism and macrophage-driven inflammatory signals. We will use tissue-specific knockouts, transcriptomics, epigenomics and *in vivo* imaging to unravel the role of nuclear receptors in heart regeneration. The student will need some prior knowledge of R and/or Python programming.
More information at: https://www.cnic.es/en/investigacion/nuclear-receptor-signaling

Research line 22: Interorgan communication as a modulator of cardiovascular diseases
Research Group: Stress kinases in Diabetes, Cancer and Cardiovascular Disease
Scientist/Supervisor: **Guadalupe Sabio**
Summary: Obesity is involved in the development and progression of cardiovascular disease (CVD), diabetes, and cancer. Communication among different metabolic organs is essential for coordinating whole-body energy homeostasis and the alteration in this organ crosstalk leads to the development of obesity-related diseases.
We will investigate how alterations in one tissue could affect the development of disease in others. We will identify metabolites that control this crosstalk and molecular mechanisms implicated in the effects. We will use animal models, adipose tissue transplantation, and state of the art technology (tissue-specific adeno-associated viruses, omics, and imaging techniques) to reveal the mechanisms driving adipose tissue dysfunction and related organ crosstalk.
We will validate our findings human samples. In addition, we will develop a novel reporter system for *in vivo* identification, tracking and extraction of endogenous specific adipose tissue microvesicles.
More information at: https://www.cnic.es/en/investigacion/stress-kinases-diabetes-cancer-and-cardiovascular-disease

Research line 23: miRNAs and immune regulation of COVID-19 inflammatory response
Research Group: Intercellular Communication in the Inflammatory Response
Supervisor: **Francisco Sánchez-Madrid**
Summary: Our proposal aims to find miRNAs differentially expressed in plasma from mild versus severe COVID19 patients; and to identify a miRNA signature specific for COVID19 pneumonia versus other pre-COVID19 Community-Acquired pneumonias (CAP). Our study may contribute to increase the number of relevant biomarkers capable of correctly stratifying patients and may also shed light on the mechanisms that drive the worsening of COVID19 patients. A deep target analysis of our candidate miRNAs will be performed in order to identify genes than could be directly involved in the pathogenesis of the disease, more specifically, those related with their associated angiogenesis and fibrosis processes.
More information at: https://www.cnic.es/en/investigacion/intercellular-communication-inflammatory-response

Research line 24: Immune receptors sensing tissue damage in inflammation and immunity
Research Group: Immunobiology
Supervisor: **David Sancho**
Summary: We are analyzing the role of specific dendritic cell receptors sensing tissue damage in models of infection, inflammation and cancer. We use a combination of approaches at the cellular, biochemical and in vivo level, including analysis of disease models in animals deficient on the receptors. The student will learn many techniques working in vitro (cell culture, molecular biology, biochemistry, flow cytometry and Immunology techniques) and will learn to analyze models of disease in vivo.
More information at: https://www.cnic.es/es/investigacion/inmunobiologia

Research line 25: **Metabolic plasticity instructs immune cell function**
Research Group: Immunobiology
Supervisor: **David Sancho**
Summary: The student will help to explore how sensing infection and tissue damage affects the metabolism on dendritic cells and macrophages. Moreover, we are exploring how mitochondrial metabolism drives T cell, dendritic cell and macrophage function. The student will learn many techniques working in vitro (cell culture, biochemistry, flow cytometry, cell metabolic assays, and Immunology techniques) and will learn about the in vivo models that we are developing in the lab to address this problem.
More information at: https://www.cnic.es/es/investigacion/inmunobiologia

Research line 26: **Application of Advanced computational methods for the analysis of post-translational modifications to Cardiovascular Biology**
Research Group: Cardiovascular Proteomics
Supervisor: **Jesús Vázquez**
Summary: We are developing "open search" algorithms that allow true hypothesis-free identification and quantification of any post-translational modification from high-throughput mass spectrometrybased proteomics. In this project, we aim to further extend the development of semisupervised approaches to the interpretation of the data and to integrate the quantitative information in large-scale experiments. We will also apply these developments to study molecular mechanisms underlying cardiovascular diseases, including subclinical atherosclerosis and other diseases related to vascular-remodelling.
More information at: https://www.cnic.es/en/investigacion/cardiovascular-proteomics