CNIC Cicerone Program

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

List of Scientists and Research Lines 2022

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 has been proposed based on indirect observations. Here, we plan 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 muscle elasticity. This is an interdisciplinary project involving instrument development, protein biochemistry, polymer physics, single-molecule methods, and material science.

More information at:

https://www.cnic.es/en/investigacion/molecular-mechanicscardiovascular-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-mechanicscardiovascular-system

Research line 3: Mechanical modulation of titin in living cardiomyocytes

Research Group: Molecular Mechanics of the Cardiovascular System

Supervisor: **Jorge Alegre-Cebollada**

Summary: The giant protein titin is key to the force-generating and mechanosensing properties of cardiomyocytes. However, the study of its mechanical contribution without interfering with other properties of the protein is challenging. We have developed a first-of-its-kind tool to specifically and

acutely induce mechanical loss of function (mLOF) of titin in living cardiomyocytes. The project, funded by a recently awarded ERC Consolidator grant, involves cardiomyocyte isolation, virus-mediated protein expression, imaging, and molecular and cell biology techniques.
More information at: https://www.cnic.es/en/investigacion/molecular-mechanics-cardiovascular-system

Research line 4: 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 5: 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 using transgenic mice to understand the function of specific genes during the development of the cardiovascular system. The work will involve mouse genetics, state-of-the-art imaging techniques, as well as advanced molecular and cell biology techniques.
More information at: http://www.cnic.es/en/desarrollo/angiogenesis/index.php

Research line 6: Studying the association between atherosclerosis and Alzheimer´s disease in preclinical stages
Research Group: Cardiovascular Imaging and Population Studies
Supervisors: **Marta Cortés Canteli, Juan Domingo Gispert, Valentín Fuster**
Summary: The project aims at studying the association between subclinical atherosclerosis and brain changes present in preclinical Alzheimer´s disease and other types of dementia. The CICERONE student will participate in the development and optimization of neuroimaging scripts and pipelines to analyze images obtained by brain magnetic resonance imaging and positron emission tomography of healthy middle-aged participants of the Progression of Early Subclinical Atherosclerosis cohort (PESA-Brain sub-study).

Research line 7: **Cellular dynamics in ventricular wall maturation, cardiomyopathy & regeneration**

Research Group: Intercellular Signalling in Cardiovascular Development & Disease

Supervisors: **José Luis de la Pompa, Alejandro Salguero**

Summary: Alteration of the signals and effectors regulating cardiomyocyte cytoskeleton dynamics and proliferation disrupts ventricular maturation and cause cardiomyopathy. Some of these signals can be reactivated to drive myocardial regeneration. The highly motivated Cicerone student will work with genetically modified mouse models and carry out clonal, confocal microscopy, and ISH analysis.

More information:

https://www.cnic.es/en/investigacion/intercellular-signaling-cardiovascular-development-and-disease

Research line 8: **Mechanisms linking inflammation with arterial wall remodeling in cardiovascular disease**

Research Group: Mechanoadaptation and Caveolae Biology

Supervisors: **Miguel Ángel del Pozo, Miguel Sánchez-Álvarez**

Summary: Inflammation alters extracellular matrix (ECM) architecture, stiffness and composition; these in turn further promote inflammation and ECM remodelling, creating feedback loops that underlie disorders such as atherogenesis and tissue fibrosis. Using state-of-the-art molecular and cell biology, omics and *in vivo* disease models, we aim to understand this "reciprocal dialog" between ECM remodelling and inflammation, and study how they influence the response of endothelium to blood flow and atherogenesis.

More information at: https://www.cnic.es/en/investigacion/mechanoadaptation-and- caveolae-biology

Research line 9: **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 10: **Cardiovascular health promotion and Imaging in adolescents**

Research Group: Cardiovascular Health and Imaging Laboratory
Supervisors: **Rodrigo Fernández Jiménez, Jesús Martínez Gómez**
Summary: Our group focuses on health promotion and cardiovascular disease prevention. The CICERONE student granted in our group will work on school-based health promotion programs targeting children and adolescents in Spain, including but not limited to longitudinally collected health data and magnetic resonance imaging analysis. The student will have the opportunity to collaborate with the research team on ongoing research tasks and to formulate his/her own research ideas.

Research line 11: 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 remodeling 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 AF that resembles clinical progression of the arrhythmia.
More information at:
https://www.cnic.es/es/investigacion/desarrollo-avanzado-sobre-mecanismos-terapias-arritmias

Research line 12: 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 hematopoietic stem cells is an inevitable consequence of the aging process, which frequently leads to a process called clonal hematopoiesis. This phenomenon is an important modulator of inflammation and a shared risk factor for cardiovascular disease, cancer and other age-related conditions. The CICERONE student will contribute to experimental studies in mouse models and cultured cells to examine the interplay between clonal hematopoiesis, inflammation and vascular disease.
More information at:
https://www.cnic.es/en/investigacion/hematovascular-pathophysiology

Research line 13: Novel mitochondria-targeted therapies for cancer therapy-induced cardiotoxicity (MATRIX)
Research Group: Translational Laboratory for Cardiovascular Imaging and Therapy

Supervisor: **Borja Ibáñez**

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 14: Macromolecular Ion Channel Complexes and Inheritable Arrhythmogenic Cardiac Diseases

Research Group: Cardiac Arrhythmia Mechanisms

Supervisor: **José Jalife**

Summary: We aim to understand the role of macromolecular complexes in the mechanisms of arrhythmias and sudden cardiac death (SCD). Specifically, we focus on the interaction between the main cardiac sodium channel (NaV1.5) and the inward rectifying potassium channel (Kir2.1), with several other partner proteins, to define the molecular basis of SCD. Thus, we use mice- and iPSC-derived cardiomyocyte models of inherited cardiac diseases involving these ion channels including Andersen-Tawil Syndrome and Short QT Syndrome-type 3.

More information at: https://www.cnic.es/en/investigacion/cardiac-arrhythmia

Research line 15: 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 the molecular mechanisms underlying HFpEF progression associated with each 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 16: Early diagnosis of Immune Checkpoint Inhibitor myocarditis

Research Group: Regulatory Molecules of Inflammatory Processes

Supervisor: **Pilar Martín**

Summary: Cytotoxic chemotherapy and novel cancer therapies have various cardiotoxicities, ranging from heart failure to arrhythmias. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target the host immune negative regulation receptors, such as CTLA-4 (cytotoxic T-lymphocyte–associated protein 4) and programmed cell death receptor 1 (PD-1). The most common fatal immune-related adverse event (IRAE) is ICI-related myocarditis, which is associated with a high reported mortality (50%). There is a need for increased awareness to suspect, diagnose, and treat ICI-related myocarditis. Our group studies the potential of miR-721 in the treatment and early diagnosis of ICI-myocarditis both in animal models and in patient samples from the Spanish Registry of Immunotherapy-Cardiotoxicity (SIR-CVT).
More information at: http://www.cnic.es/es/inflamacion/moleculas/index.php

Research line 17: Effect of experimental global cerebral hypoperfusion on pathological parameters of Alzheimer's disease
Research Group: Neurovascular Pathophysiology
Supervisor: **Mª Ángeles Moro, Enrique Fraga**
Summary: Neuroscience has somehow neglected the vascular component of dementia described by Alois Alzheimer in recent decades. However, recent findings show that most dementias have associated vascular factors. In order to explore the contribution of cardiovascular risk factors to Alzheimer's disease (AD), different neuropathological AD-associated markers will be studied in a model of chronic cerebral hypoperfusion using bilateral common carotid artery stenosis (BCCAS).
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: Antibodies in 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
Supervisors: **Juan Miguel Redondo, Marta Toral**
Summary: We have identified new genes and mechanisms that mediate aortic diseases including Marfan syndrome 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 and pharmacological strategies to induce or regress disease, and to validate mediators, biomarkers and potential therapeutic targets identified in the human disease by proteomics and transcriptomics.
More information and articles of the group can be found at:
https://www.cnic.es/es/investigacion/1/3679/publicaciones

Research line 21: Nitric oxide (NO) in Aortic diseases
Research Group: Gene regulation in Cardiovascular Remodelling and Inflammation
Supervisors: **Juan Miguel Redondo, María Jesús Ruiz**
Summary: Marfan syndrome (MFS) is an inherited disease caused by pathogenic variants of the *FBN1* gene encoding fibrillin-1. We have shown that nitric oxide signaling is overactivated in MFS and dysregulates actin cytoskeleton dynamics in MFS muscle cells. We are using mouse models of MFS, omics, and biochemical approaches to elucidate the upstream signaling components that connect disease-causing *FBN1* mutations with overactivation of NO, a signature of MFS disease whose inhibition reverses the disease in animal models.
More information and articles of the group can be found at:
https://www.cnic.es/es/investigacion/1/3679/publicaciones

Research line 22: Role of nuclear receptors in cardiac homeostasis, regeneration and repair
Research Group: Nuclear Receptor Signaling
Scientist/Supervisor: **Mercedes Ricote**
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.
More information at: https://www.cnic.es/en/investigacion/nuclear-receptor-signalingResearch

Research line 23: Role of adipose tissue controling whole body homeostasis
Research Group: Stress kinases in Diabetes, Cancer and Cardiovascular Disease
Supervisor: **Guadalupe Sabio**
Summary: Cardiometabolic diseases (CMDs)—e.g., diabetes, steatohepatitis, and cardiomyopathy— are the leading cause of death worldwide. Adipose tissue (AT) heterogeneity and dysfunction might be involved in the CMD pathogenesis. We have recently demonstrated that i) AT regulates whole-body metabolism independently of obesity and predisposes to hepatic cancer in mice and humans; and ii) molecules secreted by AT trigger liver steatosis and insulin resistance. Our studies suggest that dysfunctional AT communicates with other organs and induces pathogenic adaptive responses through evolutionarily conserved mechanisms (rodent to humans). Our preliminary results show that AT dysfunction caused by mitochondrial alteration induces cardiomyopathy in lean mice, reinforcing that AT has a central role in controlling heart functionality.
More information at: https://www.cnic.es/en/investigacion/stress-kinases-diabetes-cancer-and-cardiovascular-disease

Research line 24: Stress in the brain, metabolic effects
Research Group: Stress kinases in Diabetes, Cancer and Cardiovascular Disease
Supervisor: **Guadalupe Sabio**
Summary: Obesity has become a new pandemic. It is known that obesity induces molecular changes in the brain that are fundamental for the development of diseases and for maintaining excess energy intake. However, little is known about how these changes appear and the molecular mechanisms that mediate them.We will study how modulating stress in the central nervous system induced by high fat diet affects the development of cardiometabolic diseases. For this purpose, genetically modified animals will be used and whole organism metabolism will be evaluated, and how the signalling of this stress in the brain affects the response of distant organs through inter-tissue communication.
More information at: https://www.cnic.es/en/investigacion/stress-kinases-diabetes-cancer-and-cardiovascular-disease

Research line 25: Mitochondria and lipid droplet reorganization during inflammatory T cell responses
Research Group: Intercellular Communication in the Inflammatory Response
Supervisors: **Francisco Sánchez-Madrid, Noa Martin Cofreces**
Summary: Our proposal aims to find the differential organization of metabolic related organelles in T cells to identify a specific signature allowing recognizing activated cells. We will analyze the

reciprocal organization of lipid droplets and mitochondria during inflammatory T cell responses. These studies may be complemented with measures of mitochondrial respiration and glycolysis. Our study may contribute to understand the relationship between these organelles and the dynamics of the cytoskeleton. These results will unveil the molecular mechanisms regulating the cell biology of T cells, leading to full activation during immune responses.
More information at:
https://www.cnic.es/en/investigacion/intercellular-communicationinflammatory-response

Research line 26: Gut microbiota sensing in the induction of cardiovascular disease
Research Group: Immunobiology
Supervisor: **David Sancho**
Summary: Our results show that sensing of gut microbiota and their metabolites by myeloid cells can drive cardiovascular disease. We use a combination of approaches at the cellular, biochemical and in vivo level, including analysis of cardiovascular disease models (atherosclerosis, heart damage) in animals deficient on myeloid receptors and signaling pathways. The student will learn many techniques working in vitro (cell culture, molecular biology, biochemistry and Immunology techniques) and will analyze models of disease in vivo.
More information at: https://www.cnic.es/es/investigacion/inmunobiologia

Research line 27: Metabolic plasticity instructs immune cell function
Research Group: Immunobiology
Supervisor: **David Sancho**
Summary: The student will help to explore how mitochondrial metabolism drives T cell, dendritic cell and macrophage function. This can offer new targets to treat immune-mediated diseases including infection, cancer, metabolic syndrome and cardiovascular diseases. The student will learn many techniques working in vitro (cell culture, biochemistry, cell metabolic assays, flow cytometry 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 28: Tissue engineering in Cardiac Regeneration
Research Group: Genetic Control of Organ Development and Regeneration
Supervisors: **Miguel Torres, Pura Muñoz, Oscar Ocaña, Joan Isern**
Summary: The student will be trained on redirecting Skeletal Muscle Stem Cells towards the Cardiomyocyte lineage and in bioengineering approaches to engraft such cells in wounded hearts. The project will involve isolation, culture and differentiation of Muscle Stem Cells and the exploration of procedures for their successful reintroduction in the mammalian heart.
More information at: https://www.cnic.es/en/investigacion/genetic-control-organ-development-and-regeneration

Research line 29: Metabolic control of Cardiomyocyte Cell Competition
Research Group: Genetic Control of Organ Development and Regeneration
Supervisors: **Miguel Torres, Lorena Esteban**
Summary: The student will be trained in cardiomyocyte in vivo en ex vivo characterisation. Genetic models of cell competition will be used in combination with cell biological and metabolic analysis of Cardiomyocyte performance in homeostasis and regeneration
More information at: https://www.cnic.es/en/investigacion/genetic-control-organ-development-and-regeneration

Research line 30: 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