CNIC Cicerone Program:

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

List of Scientists and Research Lines 2019

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

References:
Alegre-Cebollada J, Kosuri P, Giganti D, Eckels E, Rivas-Pardo JA, Hamdani N, Warren CM, Solaro RJ, Linke WA, Fernández JM. **S-glutathionylation of cryptic cysteines enhances titin elasticity by blocking protein folding**. *Cell (*2014) 156:1234-46

(Preprint) Carolina Pimenta-Lopes, Carmen Suay-Corredera, Diana Velázquez-Carreras, David Sánchez-Ortiz, Jorge Alegre-Cebollada[#] (2019). Concurrent Atomic Force Spectroscopy. **BioRxiv** https://www.biorxiv.org/content/early/2018/11/06/293506

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

References:

Alegre-Cebollada J, Kosuri P, Giganti D, Eckels E, Rivas-Pardo JA, Hamdani N, Warren CM, Solaro RJ, Linke WA, Fernández JM. **S-glutathionylation of cryptic cysteines enhances titin elasticity by blocking protein folding**. *Cell* (2014) 156:1234-46

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

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

5. **Role of endurance training in early disease development in arrhythmogenic right ventricular cardiomyopathy (ARVC)**

Research Group: Inherited cardiomyopathies
Supervisor: Juan A. Bernal

Summary: Inherited cardiomyopathies are a major health problem. Our interest lies in defining the interaction between different disease-causing mutations (with arrhythmogenic right ventricular cardiomyopathy [ARVC] as a paradigm) and exercise as a factor that lead to disease progression. We have developed a method in which adeno-associated virus (AAV) vectors are used to generate cardiac disease models. To study the effect of exercise on mice carrying the most prevalent ARVC-associated mutated gene (*plakophilin-2, PKP2*), we expressed R735X mutant by a single injection of AAV carrying the mutation and the wild type. While the AAV-mediated R735X mutation expression does not result in overt ARVC phenotype in sedentary mice, exercise triggers the phenotype. Using this ARVC models we will analyze whether the myocardial abnormalities in animals expressing mutant PKP2 induce genetic changes in response to extreme exercise. To test these hypotheses, we will analyze and identify new genetic changes (heart tissue RNA sequencing) that could be used as biomarkers to predict adverse events during exercise. Finally, potential candidates will be validated.

More information at:
https://www.cnic.es/en/investigacion/inherited-cardiomyopathies

6. **Genetics basis of cardiomyopathies heterogeneity**

Research Group: Intercellular Signaling in Cardiovascular Development & Disease
Supervisor: José Luis de la Pompa

Summary: Cardiomyopathies are a heterogeneous group of genetic diseases that affect the cardiac muscle and may have a developmental basis, or manifest in adulthood. They are incurable and relatively frequent, and a major cause of morbidity and mortality. The goal of this project is to model cardiomyopathies in mice using genomic edition by Crispr-Cas9 of specific disease-causing genes identified in familial pedigrees, analyzing phenotypes using developmental (imagine, global gene expression, explants) and functional (ECHO, CMRI) approaches.

More information at:

https://www.ncbi.nlm.nih.gov/pubmed/30287945
https://www.ncbi.nlm.nih.gov/pubmed/26641715
https://www.ncbi.nlm.nih.gov/pubmed/23314057
https://www.cnic.es/en/investigacion/intercellular-signaling-cardiovascular-development-and-disease

7. Targeting Caveolin1-exosome trafficking for a novel Cancer Immunotherapy

Research Group: **Mechanoadaptation and Caveolae Biology**
Scientist Director/Supervisor: Miguel Ángel del Pozo / Inmaculada Navarro-Lérida

Summary: Among hallmarks of cancer, ***evasion from immune destruction*** is gaining increased attention. A critical target is the system operated by programmed cell death protein 1 (PD-1) and its ligands (PD-L1/2), but its regulatory principles are unknown. Caveolin-1 is a pleiotropic protein we have characterized as regulator of mechanosensing, stromal remodelling and exosome biogenesis. The candidate will explore how Cav1-dependent mechanotransduction regulates the incorporation of immunomodulators including PD-L1 into exosomes, promoting an immunosuppressive microenvironment.

More information at:
Some recent publications of the group: Moreno-Vicente ***Cell Rep*** 2018; Albacete ***bioRXiv*** 2018; Minguet, ***Nature Immunol*** 2017; Echarri & Del Pozo, **JCS** 2015, Navarro-Lérida ***Dev Cell*** 2015; Strippoli ***Embo Mol Med*** 2015; Parton & del Pozo ***Nature Reviews Mol Cell Biol*** 2013; Echarri & del Pozo, ***Curr Biol*** 2012, Navarro-Lérida ***EMBO J*** 2012; Goetz ***Cell*** 2011; Grande ***J. Cell Biol.*** 2007; del Pozo ***Nature Cell Biol*** 2005 & ***Science*** 2004.

More information at: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology
scientific report of the group can be downloaded from:
http://www.cnic.es/es/cnic/scientific_report.php

8. Mitochondrial performance in heart disease

Research Group: Functional Genetics of the Oxidative Phosphorilation System (GENOPHOS)
Supervisor: Jose A. 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

9. 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/es/investigacion/desarrollo-avanzado-sobre-mecanismos-terapias-arritmias

10. Imaging the vasculature of the Alzheimer's disease brain

Research Group: Cardiovascular Imaging and Population Studies
Scientist/Supervisor: Valentin Fuster/Marta Cortes Canteli

Summary: The vascular pathology present in Alzheimer's disease (AD) contributes to the neurodegeneration and subsequent cognitive decline found in this disorder. Our aim is to develop a non-invasive imaging technique that allows visualization of the altered cerebrovasculature and identification of the increased thrombosis present in the AD brain. Studies using Positron Emission Tomography will be performed on AD animal models to investigate when and where the cerebral vessel obstructions start in vivo in the AD brain.

More information at:
https://www.cnic.es/en/investigacion/cardiovascular-imaging-and-population-studies

11. Acquired mutations in immune cells as a driver of atherosclerotic cardiovascular disease

Research Group: Hematovascular Pathophysiology Laboratory
Supervisor: José J. Fuster

Summary: Age is the greatest risk factor for cardiovascular disease (CVD), the leading cause of death worldwide. Despite this, we have an incomplete understanding of how aging promotes CVD. In this regard, acquired mutations in blood and immune cells are emerging as a new risk factor for cardiovascular disease, and as a shared pathophysiologic mechanism of CVD and cancer. The CICERONE student will contribute to experimental studies that intend to examine how mutant immune cells contribute to atherosclerotic CVD. By doing this, he/she will get exposed to many research techniques (e.g. histology, flow cytometry, immune cell culture), and will also be introduced to the use of mouse models in cardiovascular research.

More information at:

https://www.cnic.es/en/investigacion/hematovascular-pathophysiology
https://www.ncbi.nlm.nih.gov/pubmed/29420212

12. Mechanisms linking vascular senescence to inflammation and cardiovascular disease

Research Group: Hematovascular Pathophysiology Laboratory
Supervisor: José J. Fuster

Summary: Upon aging and disease, the cardiovascular system accumulates senescent cells, which cannot replicate and exhibit an abnormal pro-inflammatory phenotype that contributes to cardiovascular disease (CVD). The specific molecular and cellular mechanisms that induce this senescence-associated pro-inflammatory phenotype remain largely unexplored. The CICERONE student will contribute to experimental studies aimed at examining a potential new molecular mechanism linking vascular senescence to inflammation and CVD. By doing this, he/she will get exposed to many research techniques (e.g. vascular cell culture, immunofluorescent staining, flow cytometry), and will also be introduced to the use of mouse models in cardiovascular research.

More information at:

https://www.cnic.es/en/investigacion/hematovascular-pathophysiology
https://www.ncbi.nlm.nih.gov/pubmed/29420212

13. Ischemia reperfusion injury and the effect of the beta-adrenergic system.

Research Group: Translational Laboratory for Cardiovascular Imaging and Therapy
Supervisor: Borja Ibáñez

Myocardial infarction is one of the leading causes of death in the developed countries. The extent of the irreversible injury, the infarct size, determines the outcome after the event. Nowadays the main treatment is a rapid reperfusion to restore the blood flow. Although this improves survival the reperfusion itself increases the inflammatory response associated with myocardial injury. Ischemia reperfusion injury is therefore a main contributor of the final infarct size. Our group is interested in how the modulation of the beta-adrenergic system is able to reduce the reperfusion injury. The group is composed of clinical cardiologist and basic researchers and covers translational research from bench to bedside.

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

14. Innovative therapies for the treatment of cardiomyopathies

Research Group: Molecular regulation of heart failure
Supervisor: Enrique Lara-Pezzi

Summary: Arrithmogenic right ventricular cardiomyopathy type 5 (ARVC5) is a rare and devastating disease for which there is no cure. ARVC5 is caused by the p.S358L mutation in the gene TMEM43. We have developed an ARVC5 mouse model that expresses the mutant protein and faithfully reproduces the human disease. Using this mouse, we have identified the major mechanisms of action of the mutant

protein. In this new translational project, we will use the acquired knowledge to develop new therapeutic tools to tackle this disease.

More information at: https://www.cnic.es/en/investigacion/molecular-regulation-heart-failure

15. Alternative splicing in subclinical atherosclerosis

Research Group: Molecular regulation of heart failure
Supervisor: Enrique Lara-Pezzi

Summary: As part of the PESA project, a flagship project at CNIC, we have unveiled that atherosclerosis appears subclinically (with no symptoms) much earlier than previously anticipated and with a very high prevalence. The molecular mechanisms and predictors of subclinical atherosclerosis are far from being completely understood. In particular, the role of different protein isoforms generated by alternative splicing (AS) and the role and regulation of AS itself in the disease are poorly understood. In this new project, we will analyse the association of AS with subclinical atherosclerosis and other determinants of the disease.

More information at: https://www.cnic.es/en/investigacion/molecular-regulation-heart-failure

16. Reprogramming and regeneration of the injured heart

Research Group: Functional Genomics
Supervisor: Miguel Manzanares

Summary: We have previously shown how pluripotency factors (Oct4 and Nanog) or the OSKM (Oct4-Sox2-Klf4-Myc) reprogramming cassette can elicit novel programs in committed cells in both the embryo and the adult. Preliminary results show how OSKM improves the effects of myocardial infarction in mice. In collaboration with the group of Dr. Borja Ibañez at CNIC, we are exploring this capacity of OSKM using tissue-specific and inducible transgenic approaches, and will analyze the molecular mechanism underlying the regenerative capacity of cardiomyocytes.

More information at:
https://www.cnic.es/en/investigacion/functional-genomics

Abad et al (2013). Reprogramming in vivo produces teratomas and iPSCs with totipotency features. **Nature** 502, 340-5.

Piazzolla et al (2014). Lineage-restricted function of the pluripotency factor NANOG in stratified epithelia. **Nat Commun** 5, 4226.

Sainz de Aja et al (2019). The pluripotency factor NANOG controls primitive hematopoiesis and directly regulates *Tal1*. **EMBO J** (*in press*).

17. Heart inflammation and cardiovascular disease

Research Group: Regulatory Molecules of Inflammatory Processes
Supervisor: Pilar Martín

Summary: Inflammation and autoimmune abnormalities play an important role in the progression of heart failure and vascular diseases. Understanding peripheral mechanisms operating in autoimmune and chronic inflammatory diseases is critical for the design and development of novel therapies and diagnostic tools. Our group seeks to identify new regulatory cells and miRNAs involved in the treatment and diagnosis of these diseases.

More information at: http://www.cnic.es/es/inflamacion/moleculas/index.php

18. Chromatin remodeling during antibody diversification in germinal centers

Research Group: B Lymphocyte Lab
Supervisor: Almudena R Ramiro

Summary: During the immune response, antibody genes can be somatically remodeled in germinal centers by the enzyme Activation Induced Deaminase, which promotes somatic hypermutation and class switch recombination. We are interested in understanding the regulation of these events by the remodeling of chromatin architecture. To approach this issue we use genetically modified mouse models and cell based protocols in combination with state-of-the-art next generation sequencing technologies.

More information at:

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

19. Molecular basis of aortic diseases

Research Group: Juan Miguel Redondo
Supervisor: Juan Miguel Redondo

Summary: We have identified new genes and mechanisms that mediate aortic diseases such as familial forms of thoracic aortic aneurysm and dissection (TAAD), including Marfan syndrome (Oller et al MCB 2015 and Nature Med 2017a, de Carcer et al Nature Med 2017b ; Villahoz et al Nature Communications 2018). We have generated a number of mouse models to characterize the major gene expression programs during the onset, establishment, and regression of aortic disease. We are also validating these mediators in the human disease by proteomics and transcriptomics using samples from TAAD patients.

More information and papers of the group can be found at: https://www.cnic.es/en/juan-miguel-redondo-moya https://www.cnic.es/en/investigacion/publicaciones/JMRedondo

20. Role of calcineurin (CN) in cardiovascular remodeling

Research Group: Juan Miguel Redondo
Supervisor: Juan Miguel Redondo

Summary: We have found that genes regulated by CN play a major role in cardiac hypertrophy, inflammation and vascular wall remodeling (*J Exp Med* 2001;*Mol Cell* 2009; *Blood* 2011; EMBO J 2014;*J Exp Med* 2011; *EMBO Mol Med* 2013; *JMCC* 2017). We plan to use mouse models of cardiovascular disease to study the mechanisms underlying cardiovascular remodeling, including mice conditionally deficient for CN and Rcan1 in the endothelial, vascular smooth muscle, and cardiomyocyte compartments.
More information and papers of the group can be found at: https://www.cnic.es/en/juan-miguel-redondo-moya https://www.cnic.es/en/investigacion/publicaciones/JMRedondo

21. **Bioinformatic analysis of the transcriptional regulation of nuclear receptors in macrophages.**

Research Group: Nuclear Receptor Signaling
Scientist/Supervisor: Mercedes Ricote

Summary: Our laboratory is using genome wide studies to decipher the contribution of nuclear receptors to the macrophage functions and the pathogenesis of human diseases. The project will focus on analysis of data derived from the application of chromatin immunoprecipitation coupled to massively parallel sequencing (ChIP-Seq) and high throughput transcriptomic data to build pathway models for differentially regulated genes that will help us to define the molecular mechanism of nuclear receptor actions in macrophage biology. The student will need some prior knowledge of R and/or Python programming.

22. Role of nuclear receptors in cardiac homeostasis and disease.

Research Group: Nuclear Receptor Signaling
Scientist/Supervisor: Mercedes Ricote

Summary: The heart needs a constant supply of energy to maintain cardiac contraction. It can oxidize a wide variety of substrates to produce ATP. However, the transcriptional mechanisms that control cardiac metabolism remain poorly understood. In this project, we will focus on the role of the nuclear receptor Retinoid X Receptor (RXR) in cardiac homeostasis. We will use tissue-specific knockouts, metabolomics, *in vivo* advance imaging, and the latest techniques in omics (RNA-seq, ChIP-seq and ATAC-seq) to unravel the role of this transcription factor in heart physiology.

23. Role of p38MAPK in metabolic diseases

Research Group: Stress kinases in Diabetes, Cancer and Cardiovascular Disease

Scientist/Supervisor: Guadalupe: Sabio

Summary: Metabolic syndrome is a medical disorder defined by the co-occurrence of obesity, impaired glucose tolerance, dyslipidemia and hypertension. Stress activated protein kinases have been shown to control both obesity by itself and diabetes associated to obesity. These stress kinases are activated by several MAPK activated kinases (MKK). We want to investigate the role of MKK3 in this process and the molecular mechanism by which this kinase could affect diabetes.

More information at:
https://www.cnic.es/en/investigacion/stress-kinases-diabetes-cancer-and-cardiovascular-disease

24. **p38MAPK in heart phisiology**

Research Group: Stress kinases in Diabetes, Cancer and Cardiovascular Disease
Scientist/Supervisor: Guadalupe: Sabio

Summary: The p38 MAPK pathway transduces a variety of extracellular signals regulating cellular responses to stress, being implicated in cell proliferation, differentiation and apoptosis. Its implication in the development of human diseases it is being deeply studied. Four p38 MAPK family members have been identified: p38α, β, γ and δ.

Preliminary data from our laboratory show that these kinases may control cytokine production during acute and chronic inflammatory processes. Moreover, studies with genetically modified mice made in our laboratory confirm that p38MAPKs have a role in the development of the heart. Our main objective is to determine if the regulation of the p38MAPK signaling pathway could have beneficial effects in the cardiac response to exercise.

More information at:
https://www.cnic.es/en/investigacion/stress-kinases-diabetes-cancer-and-cardiovascular-disease

25. miRNAs as Biomarkers in Inflammatory Diseases

Research Group: Intercellular Communication in the Inflammatory Response
Scientist / Supervisor: Francisco Sánchez-Madrid / Hortensia de la Fuente

Summary: Autoimmune and inflammatory diseases are very complex immune-mediated diseases where different cells and molecules participate in the initiation and maintenance of the inflammatory response. miRNAs modulate and fine-tune expression of key regulatory molecules involved in controlling the immune response and, thus affecting a plethora of inflammatory pathological processes. Our main objective is to analyze the expression of miRNAs in serum and tissue samples of coronary artery diseases and psoriasis patients and the putative correlation between miRNAs expression and therapeutic response or disease severity

More information at: https://www.cnic.es/en/investigacion/intercellular-communication-inflammatory-response

26. 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

27. Metabolic plasticity instructs immune cell function

Research Group: Immunobiology
Supervisor: David Sancho (dsancho@cnic.es)

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

28. Mechanisms of heart regeneration

Research Group: Genetic Control of Organ Development and Regeneration
Supervisor: Miguel Torres

Summary: the molecular and cellular mechanisms regulating cardiomyocyte spontaneous and induced proliferation and death will be studied in the mouse model. The impact of these mechanisms on heart regenerative ability will be explored.

More information at: https://www.cnic.es/en/investigacion/genetic-control-organ-development-and-regeneration

29. Advanced computational methods for the analysis of post-translational modifications

Research Group: Cardiovascular Proteomics
Supervisor: Jesús Vázquez

Summary: We are working in “open search” algorithms that allow true hypothesis-free identification and quantification of any post-translational modification from high-throughput mass spectrometry-based proteomics. In this project we aim to develop semisupervised approaches to the interpretation of the data and to integrate the quantitative information in large scale experiments.

More information at: https://www.cnic.es/en/investigacion/cardiovascular-proteomics