CNIC Cicerone Program

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

List of Scientists and Research Lines 2023

1. **Research line: Effect of posttranslational modifications on mechanical protein unfolding as a main contributor to the elasticity of the myocardium**

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 and determine the effect of posttranslational modifications of constituent proteins on the mechanical response of cardiomyocytes and skeletal muscle. This is an interdisciplinary project involving instrument development, protein biochemistry, polymer physics and single-molecule methods.

More information at:

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

2. **Research line: 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

3. **Research line: 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

4. **Research line: Multiscale mechanics of cell nuclei in diabetes**

Research Group: Molecular Mechanics of the Cardiovascular System
Supervisor: **Jorge Alegre-Cebollada**
Defective molecular, cellular and tissue mechanics are emerging hallmarks of diabetes mellitus (DM), a chronic metabolic disease characterized by hyperglycemia. We will focus on mechanical fingerprints of DM using a multiscale approach that combines single-molecule biophysical techniques with protein biochemistry, cell mechanics and animal models. Cell nuclei will be studied as relevant targets for glycation due to their role as central hub in cell cellular mechanotransduction, both structurally and biochemically, with important implications in physiology and disease. The CICERONE student will learn about mechanical profiling of cells and single protein nanomechanics in pathological states.
More information at: https://www.cnic.es/en/investigacion/molecular-mechanics-cardiovascular-system

5. **Research line: 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

6. **Research line: 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

7. **Research line: Functional analysis of genes involved in cytoskeleton dynamics, ventricular wall maturation, cardiomyopathy & regeneration**

Research Group: Intercellular Signalling in Cardiovascular Development & Disease
Supervisors: **José Luis de la Pompa, Marcos Siguero-Álvarez**
Summary: We are interested in the signals and effectors that regulate heart development and how their alteration may lead to congenital heart disease and cardiomyopathy. The highly motivated Cicerone student will work with newly generated genetically modified mouse models and study if and how cardiomyocyte maturation is affected, using confocal microscopy, in situ hybridization, and global gene expression analyses.
More information at : https://www.cnic.es/en/investigacion/intercellular-signaling-cardiovascular-development-and-disease

8. **Research line: Mechanisms integrating blood flow sensing, arterial wall remodeling and inflammation during atherogenesis**

Research Group: Mechanoadaptation and Caveolae Biology
Supervisors: **Miguel Ángel del Pozo, Fidel Lolo**
Summary: While most cardiovascular risk factors act systemically, atherosclerotic lesions develop at arterial regions subjected to disturbed flow (typically, inner curvatures and bifurcations), which promote atherogenic wall remodeling, eliciting LDL retention and immune cells-infiltration, driving disease progression. Conversely, regions subjected to laminar blood flow are protected from atherosclerosis. The student will study in vitro and in vivo molecular mechanisms regulating blood flow sensing and transduction, LDL transcytosis & retention, and arterial matrix remodeling under atherogenic conditions. This project falls within the context of the AtheroConvergence international consortium funded by La Caixa https://fundacionlacaixa.org/en/therapeutic-targets-atherosclerosis.
More information: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology

9. **Research line: Mechanically-driven signaling networks determining myocardial homeostasis and cardiac hypertrophy**

Research Group: Mechanoadaptation and Caveolae Biology
Supervisors: **Miguel Ángel del Pozo, Victor Jiménez, Miguel Sánchez**

Summary: The molecular mechanisms by which Cardiac Hypertrophy and Dilated Cardiomyopathy occur are not completely understood. Our previous systems-level cardio-physiopathology bioinformatics studies identified candidate signaling networks feeding from mechanotransduction and governed by specific chemoquines and receptors. The student will experimentally address in vitro (with molecular and cell biology state-of-the-art techniques) and in vivo (with specific genetically engineered mouse models, including myocardium-specific) the association of these networks with cardiovascular disease, and the molecular mechanisms behind.
More information: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology

10. **Research line: 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 phisyopathology.
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. We also investigate the relevance of mitochondria on inflammation, obesity and vascular physiopathology.
More information at: https://www.cnic.es/en/investigacion/functional-genetics-oxidative-phosphorilation-system-genophos

11. **Research line: Functional Genetics of the Mitochondrial Electron Transport Chain**

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 are determining the factors that regulate the structural organization of the electron transport chain and the role that this superstructural organization plays in the production of reactive oxygen species (ROS). This area is linked to our interest in the role of ROS as mitochondrial second messengers and to our aim to deconstruct the mammalian OXPHOS system into its functional components (electron transport, proton pumping and ATP synthesis). With the knowledge that we are acquiring, we aim to identify and modulate molecular targets and regulatory pathways to protect the cardiovascular system against disease by increasing its robustness and its regenerative capacity.
More information at: https://www.cnic.es/en/investigacion/mechanoadaptation-and-caveolae-biology

12. **Research line: Cardiovascular health promotion and Imaging in adolescents**

Research Group: Cardiovascular Health and Imaging Laboratory

Supervisors: **Rodrigo Fernández Jiménez, Jesús Martínez Gómez, Juan Miguel Fernández**

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.

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

13. **Research line: 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

14. **Research Line: 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. However, we have an incomplete understanding of how aging promotes CVD. In this regard, age-related acquired mutations in blood and immune cells are emerging as a new risk factor for CVD. The CICERONE student will contribute to the investigation of how mutant immune cells contribute to atherosclerosis, the ultimate cause of the most frequent cardiovascular disorders. Depending on the student's interests and experience, he/she will analyze sequencing data from different human cohorts or participate in experimental studies in mouse models of CVD. This will

expose him/her to many research techniques (e.g. genomic approaches, histology, flow cytometry, immune cell culture) and introduce him/her to the use of mouse models in cardiovascular research. More information at: https://www.cnic.es/en/investigacion/hematovascular-pathophysiology

15. **Research Line: The role of sex chromosomes in inflammation and cardiovascular disease**

Research Group: Hematovascular Pathophysiology Laboratory

Supervisor: **José J. Fuster**

Summary: Women and men tend to have different rates of several cardiovascular disorders, with some conditions affecting women more frequently, whereas others are more frequent in men. Although these differences are traditionally linked to sex hormones, emerging evidence suggests that sex chromosomes may also play a major role in this context. To investigate this possibility, the CICERONE student will contribute to the analysis of new mouse models that have different dosages of sex chromosomes, recently generated in the lab. This will expose the student to many basic research techniques (e.g. immunofluorescent staining, flow cytometry, immune cell culture) and introduce him/her to the use of mouse models in biomedical research.

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

16. **Research line: Dissecting Tailored Therapies in Mouse Models of Dilated Cardiomyopathy.**

Research Group: Inherited Cardiomyopathies

Supervisors: **Pablo Garcia Pavia, Manuel A. Fernandez-Rojo**

Summary: Dilated cardiomyopathy (DCM) is caused by genetic variants in >40 genes & associated with significant morbidity and mortality, including heart failure (HF) and sudden cardiac death (SCD). Consequently, genetic DCM subtypes are different diseases and, as such, their appropriate management requires a tailored approach. We will mice animal studies to challenge and push the current uniform “one-fits-all” standard pharmacological treatment of DCM towards a personalized therapeutic approach.

More information at: https://www.cnic.es/en/investigacion/inherited-cardiomyopathies-0

17. **Research line: 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

18. Research Line: **Post-transcriptional regulation mechanisms in heart failure**

Research Group: Molecular regulation of heart failure
Supervisor: **Enrique Lara-Pezzi**
Summary: Heart failure (HF) is the ultimate consequence of defects in the contraction or relaxation capacity of the heart. Although the changes in gene expression that accompany the development of HF are reasonably well known, the role of post-transcriptional regulation is very poorly understood. In this project, we will investigate the role of the RNA-binding protein SRSF6 in the development of heart failure using mouse models and adeno-associated viral vectors.
More information at: https://www.cnic.es/en/investigacion/molecular-regulation-heart-failure

19. Research line: **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

20. Research line: **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

21. **Research line: Characterization of maladaptive neurogenesis and post-stroke cognitive impairment**

Research Group: Neurovascular Pathophysiology
Supervisor: **Mª Ángeles Moro, Francisco. Javier de Castro**
Summary: Stroke is the second leading cause of death in the world, according to the World Health Organization. Due to better strategies in prevention and healthcare is now considered as a chronic disease, being the principal cause of vascular cognitive impairment and dementia (VCID). Recent findings show a neurogenic response taking place at the subgranular zone in the hippocampus linked to aberrant morphology of post-stroke newborn neurons and cognitive deficits in spatial and contextual memory. To further investigate this process, we are currently exploring the hippocampal neurogenic response after focal cerebral ischemia in a mouse model of stroke with a permanent occlusion of the middle cerebral artery induced by the topic application of FeCl3.
More information at: https://www.cnic.es/en/investigacion/neurovascular-pathophysiology

22. **Research line: Neutrophil circadian oscillations and ischemic stroke outcome.**

Research Group: Neurovascular Pathophysiology
Supervisor: **Mª Ángeles Moro, Sandra Vázquez Reyes**
Summary: Stroke is the second leading cause of death and disability worldwide. After blood interruption, several inflammation events will be triggered in the brain. One of them is the infiltration of inmune cells in the brain parenchyma. Neutrophils are key players in this neuroinflammation process and the first cells to be infiltrated. Several studies support that neutrophil number and phenotype oscillations are circadian-dependent. These oscillations can influence ischemic stroke outcome. Infarct volume, density of infiltration and NETosis are some of the characteristics observed in our studies. The main objetive of this project is to characterize these mechanisms and their influence in stroke outcome.
More information at: https://www.cnic.es/en/investigacion/neurovascular-pathophysiology

23. **Research line: 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

24. Research line: 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

25. Research line: 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

26. Research line: 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

27. Research line: Human-based tools and strategies for cardiac regeneration studies

Research Group: Myocardial regeneration via cardiomyocyte cell cycle regulation
Supervisor: **Hesham Sadek, Mª Piedad Menéndez Gutiérrez**
Summary: Our group focused on understanding the basis of heart regeneration in neonatal mammals to identify methods to re-activate endogenous cardiomyocyte proliferation in adult hearts. For example, we identified Meis1 and Hoxb13 as critical regulators of cardiomyocyte cell cycle. Thus, we aim to modulate some of the molecules that play significant roles in cardiomyocyte hyperplastic versus hypertrophyc growth in human iPSC-derived cardiomyocytes to obtain high yields of mature cardyomjyocytes for in vitro screening of candidate drugs.
More information at: https://www.cnic.es/en/investigacion/myocardial-regeneration-cardiomyocyte-cell-cycle-regulation

28. Research line: Generation of bispecific antibodies for immunotherapy

Research Group: Immunobiology
Supervisor: **David Sancho**
Summary: We are generating and characterizing a new generation of bispecific antibodies designed to boost immunotherapy. The initial characterization in vitro and in vivo in models of immunization will determine whether we obtain an immunogenic or tolerogenic effect that will guide our in vivo efforts to cancer or cardiovascular immunotherapy respectively. 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

29. Research line: Metabolic plasticity instructs immune cell function

Research Group: Immunobiology
Supervisor: **David Sancho**

Summary: The student will help to explore new "gain-of-function" strategies to manipulate mitochondrial metabolism and determine how it controls dendritic cell and macrophage function. This can offer new therapies for immune-mediated diseases including: infection, cancer and cardiovascular diseases. The student will learn many techniques working in vitro (cell culture, biochemistry, metabolic assays, flow cytometry and Immunology techniques) and will learn about the in vivo models that we are developing to address this problem.
More information at: https://www.cnic.es/es/investigacion/inmunobiologia

30. **Research line: Characterization of coronary vasculature development**

Research Group: Genetic Control of Organ Development and Regeneration
Supervisors: **Miguel Torres, Morena Raiola**
Summary: The student will train on segmenting complex 3D data-sets and in extracting and analyzing quantitative data thereof. A background in computer science and programming abilities is required.
More information at: https://www.cnic.es/en/investigacion/genetic-control-organ-development-and-regeneration

31. **Research line: Characterization of coronary vasculature development**

Research Group: Genetic Control of Organ Development and Regeneration
Supervisors: **Miguel Torres, Cristina Villa**
Summary: The student will train on the phenotypic characterization of mutant mice that affect coronary vasculature formation. Advanced microscopy, advanced mouse genetics and immunophenotping of cell lineages will be used to characterize the mutant phenotypes
More information at: https://www.cnic.es/en/investigacion/genetic-control-organ-development-and-regeneration

32. **Research line: 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