List of Researchers and Research Lines (CICERONE 2016)

01: Scientist/Supervisor: **Alegre-Cebollada, Jorge**
Research Line: **Mechanical protein unfolding as a main contributor to the elasticity of the myocardium and muscle-mimicking biomaterials**
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. For more information about our group, please visit:
https://www.cnic.es/en/investigacion/single-molecule-mechanobiochemistry
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
Saqlain, F., Popa, I., Fernandez, J. M. & Alegre-Cebollada, J. A novel strategy for utilizing voice coil servoactuators in tensile tests of low volume protein hydrogels. Macromolecular materials and engineering (2015) 300, 369-76.

02: Scientist/Supervisor: **Alegre-Cebollada, Jorge**
Research Line: **Molecular events leading to the development of familial cardiomyopathies**
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, proteomics and single-molecule manipulation techniques, we plan to uncover how point mutations in cardiac proteins lead to life-threatening cardiomyopathy. For more information about the group, please visit:
https://www.cnic.es/en/investigacion/single-molecule-mechanobiochemistry
Reference:
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

03: Scientist/Supervisor: **Andrés, Vicente**
Research Line: **Role of A-type lamins in aging and associated cardiovascular disease**
Summary: Aging is the main risk factor for cardiovascular disease (CVD), which is responsible for 1/3 of deaths in developed countries. By 2020, CVD is expected to become the main health problem worldwide, in part due to the progressive aging that the world is experiencing. CVD and aging are greatly accelerated in Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder characterized by premature aging and death (average lifespan: 13.5 yr) that is caused by the abnormal expression of progerin (see www.progeriaresearch.org). This mutant form of lamin A is also expressed in aged tissues of non-HGPS individuals, suggesting a role in normal aging. We have also evidence that wild-type lamin A/C regulate CVD. By analyzing cultured cells and genetically-modified mice using a variety of molecular and cellular biology techniques, the student will learn about mechanisms through which wild-type and mutant lamin A/C regulate CVD and aging.

04: Scientist/Supervisor: **Bentzon, Jacob Fog**
Research Line: **Clonal structure of neointimal SMCs**
Summary: After arterial injury, such as that inflicted by balloon opening of a coronary artery in heart attack, medial smooth muscle cells (SMCs) migrate and proliferate to form a neointima. It is thought that a large number of medial SMCs participate in the process, but we think this may not be true. Using a stochastically recombining fluorescent reporter transgene and arterial injury models in mice, the student will test the hypothesis that the neointima is derived from few SMCs.

05: Scientist/Supervisor: **Bentzon, Jacob Fog**
Research Line: **Dynamics of LDL uptake in the atherosclerotic plaque**
Summary: Uptake of low-density lipoprotein (LDL) in the atherosclerotic plaque is the driving force of atherosclerosis, but the processes by which LDL is retained at different stages of the disease has only been partly explored. The student will use serial injections of LDL labeled in different fluorescent colors and blocking of candidate LDL-binding receptors to provide new insight into the dynamics and pathways of LDL uptake in atherosclerosis.

06: Scientist/Supervisor: **de la Pompa, Jose Luís**
Research Line: **Mechanisms underlying ventricular chamber development and cardiomyopathy**
Summary: Study how ventricle differentiation is initiated with the appearance of trabeculae and the trabecular network is integrated in the compact myocardium and coronary vessel circulation established. Mouse/zebrafish, molecular/cell biological/image analysis of cardiac development/function. Cardiomyopathy samples/target validation. See: https://www.cnic.es/en/investigacion/1/824/publicaciones

07: Scientist/Supervisor: **de la Pompa, Jose Luís**
Research Line: **Signaling during cardiac valve morphogenesis and disease**
Summary: Defective cardiac valve development is one of the most common congenital heart disease. The molecular mechanisms regulating fusion of the primitive cushions to give rise to the mature valve leaflets is poorly understood. Mouse models, molecular/cell biological/image analysis of valve development/function. Valve disease samples/target validation. See: https://www.cnic.es/en/investigacion/1/824/publicaciones

08: Scientist/Supervisor: **Enríquez, Jose Antonio**
Research Line: **Functional genetics of the OXPHOS system related to cardiovascular diseases**
Summary: The student will be involved in the development of high-throughput strategies to catalogue the set of the genes whose products participate in the biogenesis and regulation of the OXPHOS system in heart performance. The molecular genetic studies of the mitochondrial OXPHOS system will be continued through a functional genetics approach involving both the nuclear and mtDNA-encoded genes. The main objectives are: (1) mouse mtDNA functional genetics. (2) The transfer of the characterized mutations from standard to ES cell lines to use them as cell models of OXPHOS deficiencies (3) Study of the mtDNA allelic variants with potential functional effects

09: Scientist/Supervisor: **Figueiras, David**
Research Line: **Biological and Computational Characterization of Mechanisms Underlying Paroxysmal and Persistent Atrial Fibrillation in a Pig Model that Resembles Clinical Progression of the Arrhythmia**

Summary: Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia. Some patients suffer paroxysmal AF indefinitely, but a large proportion progress to persistent or permanent AF. However, the precise mechanisms have not been established. The objective of this proposal is to test the hypothesis that sustained atrial fibrillation triggers an inflammatory response that activates signaling pathways which are common to the electrical and structural remodeling leading to sustained reentry with increased complexity and AF perpetuation.

10: Scientist/Supervisor: **García Arroyo, Alicia**
Research Line: **Cellular and molecular players in inflammation-induced angiogenesis**
Summary: Angiogenesis, the formation of new vessels from pre-existing ones, is essential for organ development but also for promotion and resolution of inflammatory responses. This process requires fine-tuned orchestration of cell-cell interactions together with coordination of defined molecular pathways such as membrane-type matrix metalloproteinases (MT-MMPs) and their substrates. We will use ex vivo and in vivo assays in genetically modified mice, mathematical and proteomics approaches, and state-of-the-art confocal microscopy and imaging analysis to elucidate molecular and cellular partners relevant to inflammation-induced angiogenesis.

11: Scientist/Supervisor: **González, Susana**
Research line: **Impact of epigenetic mechanisms on age-associated cardiovascular pathophysiology.**
Summary: We hypothesize that inadequate orchestration of epigenetic mechanisms play vital roles in age-related adult cardiomyopathies. Aided by conditional knockout models and parabiotic assays, this study has uncovered crucial role for epigenetic Polycomb regulator in the adult heart.

12: Scientist/Supervisor: **González, Susana**
Research line: **Epigenetic regulation of adult hematopoietic stem cells**
Summary: We are studying the role of the epigenetic Polycomb-mediated silencing mechanism in stemness maintenance, with particular emphasis on the self-renewal capacity and the microenvironment of haematopoietic stem cells (HSCs), a key adult stem cell population with diverse regenerative capacity.

13: Scientist/Supervisor: **Hidalgo, Andrés**
Research Line: **Defining the temporal properties of neutrophils**
Summary: Neutrophils are important to fight invasion by microbes but can at the same time damage tissues unintentionally yet irreversibly. Interestingly, disease associated with these functions (ex. stroke or myocardial infarction) is not constant, but rather changes during the day. The CICERONE student will participate in our studies aimed at understanding whether and how neutrophils perceive time, and how this in turn impacts their capacity to immigrate, to cause inflammation or to protect us against infections.

14: Scientist/Supervisor: Ibáñez, Borja
Research line: **Challenging Therapeutic Strategies and Imaging Technology in Myocardial Infarct**
Summary: The multidisciplinary "*Translational Laboratory for Cardiovascular Imaging and Therapy*" integrates a team of cardiologists, physicists, engineers and biologists aiming to translational research in the field of cardiovascular diseases.
The lab is looking for a Master or advanced undergraduate students studying towards a biomedicine-related university degree to participate in the project entitled "Challenging

Therapeutic Strategies and Imaging Technology in Myocardial Infarct" by the use of a pig model of myocardial infarction and state-of-the-art non-invasive imaging technology. During the last years the group has made significant contributions in the field of cardioprotection during myocardial infarction and the development of novel cardiac imaging modalities.
For more information about our group and related publications, please visit: https://www.cnic.es/en/investigacion/translational-laboratory-cardiovascular-imaging-and-therapy

15: Scientist/Supervisor: **Lara-Pezzi, Enrique**
Research line**: Gene therapy of myocardial infarction and heart failure**
Summary: Myocardial infarction leads to a massive loss of cardiomyocytes and a decline in contractile function. We have recently shown that overexpression of the calcineurin variant CnAbeta1 following myocardial infarction improves cardiac function and reduces remodelling. We have now generated a viral vector capable of overexpressing CnAbeta1 in cardiomyocytes. The Cicerone researcher will help investigate the potential benefit of this gene therapy approach to treat myocardial infarction in mice.

16: Scientist/Supervisor: **Lara-Pezzi, Enrique**
Research line**: Bioinformatic analysis of alternative splicing in the infarcted heart**
Summary: Although mortality associated to myocardial infarction (MI) has diminished, heart failure (HF) prevalence has not declined in the past 30 years and represents a heavy health and economic burden. Our knowledge of the molecular mechanisms that lead to ischemic HF is still very limited. We largely ignore the variety of isoforms that are generated for each gene by alternative splicing (AS) in the infarcted heart, how AS is regulated and how AS trans-regulatory factors impact the response to MI, remodelling and the development of HF. In this project we will investigate the changes in alternative splicing that take place after myocardial infarction. The student will need some prior knowledge of Perl and/or Python programming.

17: Scientist/Supervisor: **Manzanares, Miguel**
Research Line: **The role of genome structure in the regulation of gene expression**
Summary: In the lab we aim to understand how gene expression is regulated in a spatially and temporally controlled manner during development, and how this relates to the occurrence of cardiovascular disease (CVD). In this Cicerone project, the student will study how the genome acquires its 3D structure and its relationship with the control of gene expression, by a combination of deep sequencing and super-resolution imaging.

18: Scientist/Supervisor: **Manzanares, Miguel**
Research Line: **Bioinformatic analysis of the regulatory basis of cardiovascular disease**
Summary: The genome encompasses not only the instruction to build proteins, but also the instructions that determine when, where and how much each gene is expressed. Proximal and distal regulatory elements are present in the non-coding portion of the genome, but are difficult to find based on sequence alone. We are combining available gene expression, epigenetic and functional data in a genome-wide manner in order to construct a predictive score to find regulatory regions in the genome associated to cardiac disease. For this Cicerone project, it is necessary that the student has some prior knowledge and a keen interest in bioinformatics.

19: Scientist/Supervisor: **Martín, Pilar**
Research line: **Control of inflammation in cardiovascular diseases**
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. Our group seeks to identify new regulatory cells and miRNAs involved in the control of these diseases.

20: Scientist/Supervisor: **Muñoz Canoves, Pura**
Research line: **Tissue Regeneration**
Summary: Alternatively activated (aa) macrophages (a subset of inflammatory cells with profibrotic activity) increase age-dependently in muscle of Duchenne Muscular Dystrophy (DMD) patients. Whether aa contribute to the poor DMD muscle regenerative capacity and fibrosis is unknown. We aim to investigate the function of aa macrophages in DMD using mdx mice (animal model of DMD) in combination with specific aa targeting. Our results will show whether interfering with aa macrophages may ameliorate DMD.

21: Scientist/Supervisor: **Ramiro, Almudena**
Research line: **B cells in cardiovascular disease**
Summary: B cells play a fundamental role in the immune response through the generation of protective and highly specific antibodies. However antibodies and the mechanisms that diversify them are also involved in autoimmune disease and cancer. One interest of the lab is to understand the role of B cells in atherosclerosis, using animal models and a combination of molecular analyses, including next generation sequencing.

22: Scientist/Supervisor: **Ramiro, Almudena**
Research line: **Chromatin remodeling in germinal center B cells**
Summary: B cells play a fundamental role in the immune response through the generation of protective and highly specific antibodies. However antibodies and the mechanisms that diversify them are also involved in autoimmune disease and cancer. Our lab studies regulatory mechanisms of these events, including chromatin remodeling, using animal models and molecular biology.

23: Scientist/Supervisor: **Redondo, Juan Miguel**
Research line: **Vascular wall remodeling: Molecular and cellular mechanisms and in vivo animal models**
Summary: Extensive artery wall remodeling is a major feature of vascular diseases such as atherosclerosis, aneurysm and restenosis. We have set up in the lab animal modes of these three pathologies, and generated mice deficient in target molecules of the Angiotensin II signaling pathway that are resistant to these diseases. We plan to elucidate the molecular and cellular mechanisms that account for such protection.
https://www.cnic.es/es/investigacion/regulacion-genica-remodelado-vascular-e-inflamacion

24: Scientist/Supervisor: **Redondo, Juan Miguel**
Research line: **Role of calcineurin (CN) in cardiac remodeling**
Summary: Many biologically central processes including the regulation and development of the immune and cardiovascular systems are regulated by the Calcineurin. We plan to use mouse models of cardiac hypertrophy to define the time profile of cardiac remodeling processes during disease progression and will assess the impact of CN deletion using inducible CRE-mice in cardiomyocytes. We also plan to identify genes relevant to the development of CH by comparative whole genome analysis.
https://www.cnic.es/es/investigacion/regulacion-genica-remodelado-vascular-e-inflamacion

25: Scientist/Supervisor: **Ricote, Mercedes**

Research Line: **Bioinformatic analysis of the transcriptional regulation of nuclear receptors in macrophages**

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.

26: Scientist/Supervisor: **Ricote, Mercedes**

Research line: **Role of macrophage nuclear receptors in cardiac homeostasis and injury**

Summary: Activation of the immune system is a good candidate for triggering tissue regeneration; however the molecular pathways that directly link the immune system to myocardial regeneration remain poorly understood. In this project, we will focus on the role of macrophage nuclear receptors (NRs) in cardiac homeostasis, and in the inflammatory response after myocardial infarction. We will use tissue-specific knockouts, transcriptomics, in vivo imaging, and the latest techniques in cell-fate mapping to unravel the role of macrophages in cardiovascular physiology.

27: Scientist/Supervisor: **Sabio, Guadalupe**

Research Line: Role of muscle p38 Mapk signalling in metabolism

Summary: Obesity, a major health problem that has become pandemic, is characterized by fat accumulation, alteration of different metabolic pathways, and insulin resistance in peripheral tissues. Previous studies of the metabolism of obese patients showed the involvement of kinases such as JNK and ERK, but little is known about the role in obesity of the p38 MAPK family, a group of kinases that respond to stimuli such as metabolic and oxidative stress. We will investigate the role of p38 MAPK signaling in muscle using animals that lack this protein only in skeletal muscle

28: Scientist/Supervisor: **Sabio, Guadalupe**

Research Line: Role of p38gamma and delta in heart and liver metabolism

Summary: The alterations in myocardial energy substrate metabolism that occur in heart failure, and the causes and consequences of these abnormalities, are poorly understood. The high cardiovascular risk associated with metabolic syndrome and type 2 diabetes suggests that common mechanisms are involved in the etiology of these conditions, and that agents acting on the same therapeutic targets might improve disease parameters in both. Research suggests that one such target might be the stress activated protein kinases (SAPKs), an important family of kinases implicated in the transduction of stress signals into the cell.

We know that p38gamma and delta play an important role in heart growth and we will investigate how these kinases could affect heart metabolism.

29: Scientist/Supervisor: **Sánchez-Madrid, Francisco**

Research line: **Regulation of immune synapse formation and function.**

Summary: We are exploring protein multiplexing at the MTOC, specifically the role of MTOC folding complexes, and the post-translational modifications of Ser/Thr kinases and the tubulin deacetylase HDAC6. We address the molecular mechanisms that control mitochondria transport during leukocyte-endothelial adhesion and extravasation and maturation of the IS. We are also

analyzing the role of mitochondrial components in the biogenesis and secretion of exosomes and their impact on macrophage and dendritic cell function.

References:

Martín-Cófreces NB, Baixauli F, Sánchez-Madrid F. Immune synapse: conductor of orchestrated organelle movement. Trends Cell Biol (2014) 24:61-72.

Mittelbrunn M, Vicente-Manzanares M, Sánchez-Madrid F. Organizing polarized delivery of exosomes at synapses. Traffic (2015) 16: 327-37

30: Scientist/Supervisor: **Sánchez-Madrid, Francisco**

Research line: **Immunoregulatory molecules and miRNAs in inflammatory diseases.**

Summary: We are analyzing the role of miRNAs and immunoregulatory molecules such as CD69, galectins, aminoacid transporters and HDAC6 in animal models of atherosclerosis and psoriasis, and in human patients in order to identify the molecular basis of these inflammatory diseases.

References:

de la Fuente H, Cruz-Adalia A, Martinez Del Hoyo G, Cibrian-Vera D, Bonay P, Perez-Hernandez D, Vazquez J, Navarro P, Gutierrez-Gallego R, Ramirez-Huesca M, Martin P, Sanchez-Madrid F. The Leukocyte Activation Receptor CD69 Controls T Cell Differentiation through Its Interaction with Galectin-1. Mol Cell Biol (2014) 34: 2479-87.

Diaz-Gonzalez F, Sanchez-Madrid F. NSAIDs: Learning new tricks from old drugs. Eur J Immunol (2015) 45: 679-86

31: Scientist/Supervisor: **Sancho, David**

Research line: **Immune myeloid receptors sensing tissue damage in inflammation and immunity**

Summary: tissue damage sensing modulates inflammation and immunity. We are analyzing the role of specific myeloid receptors sensing tissue damage in models of infection, allergy, inflammation and cancer. We use a combination of approaches at the cellular, biochemical and in vivo level, including analysis of animals deficient on the receptors at the physiological level, transcriptomic analysis, and in vivo imaging. 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. The student will also be intellectually involved in the discussions and implications of this work for the treatment of these diseases and the design of better vaccines.

http://www.cnic.es/es/inflamacion/inmunobiologia/index.php

32: Scientist/Supervisor: **Sancho, David**

Research line: **Sensing infection and tissue damage affects myeloid cell metabolic plasticity**

Summary: The student will help to explore how sensing infection and cell death affects the metabolic status and mitochondrial metabolic plasticity on myeloid cells. Our preliminary data show that pathogen sensing affects the metabolism of the myeloid cell with possible implications on myeloid cell function as the basis for innate and adaptive immune responses. We hypothesize that the sensing of cargo´s nature upon phagocytosis dictates a metabolic switch in myeloid cells. 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. The student will also be intellectually involved in the discussions and implications of this work for opening new avenues in the modulation of inflammation, immunity and tolerance.

http://www.cnic.es/es/inflamacion/inmunobiologia/index.php

33: Scientist/Supervisor: **Torres, Miguel**

Research Line: **Role of transcription factors in cardiovascular development and regeneration**

Summary: We have generated gain- and loss-of-function mouse models of the homeodomain transcription factors Meis and Pbx, revealing new roles for these factors in cardiovascular development. These studies have identified a new morphogenetic role for platelets during lymph angiogenesis, and further suggest a general role for platelets in vascular morphogenesis and remodeling that might be relevant to vascular disease. Our work on heart regeneration focuses on the epicardium, the outermost layer of the vertebrate heart, which plays an important role during cardiac development as a source of progenitor cells and signals controlling myocardial proliferation. A role for the epicardium in regeneration has also been suggested, but its exact function here is still unknown. Using the zebrafish model system we are analyzing the formation of the epicardium in vivo and generating tools to study the fate of epicardium derived cells and their role during cardiac regeneration. More information about the group´s research:
https://www.cnic.es/es/investigacion/1/7265/publicaciones

34: Scientist/Supervisor: **Jesús Vázquez**

Research line: **The deep mitochondrial redox proteome in models of cardiovascular disease.**

Summary: Using front-end proteomics technologies, including gel separation of supercomplexes and a novel data-independent mass spectrometry scanning technique (DiS) that improves performance of conventional shotgun approaches, we plan to study different models of cardiac pathologies that increase oxidation of Cys sites of mitochondrial proteins. These models include ischemia-reperfusion, aging and maladaptative cardiac hypertrophy (EndoG KO model), where we have found that oxidation increases mainly in OxPhos complexes and Krebs cycle proteins. Different computational methods will be applied to perform an extremely detailed structural map of components of mitochondrial oxidative phosphorylation supercomplexes, including molecular determinants of assembly. These results will help to better understand the mechanisms underlying mitochondrial oxidative damage and their implications in mitochondrial functionality.