List of Researchers and Research Lines (CICERONE 2017)

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/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
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/molecular-mechanics-cardiovascular-system
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: Summary: Aging is the main cardiovascular risk factor. Cardiovascular disease (CVD) and aging are much accelerated in Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder featuring premature aging and death (average lifespan: 14.6 yr) which is caused by progerin. This mutant form of lamin A is also expressed in aged tissues of non-HGPS individuals, suggesting a role in normal aging. The CICERONE student will learn about mechanisms through which A-type lamins regulate CVD and aging. More information in:.
https://www.cnic.es/en/investigacion/molecular-and-genetic-cardiovascular-pathophysiology
and http://www.progeriaresearch.org

04: Scientist/Supervisor: **Bernal, Juan Antonio**
Research Line: **Role of endurance training in early disease development in arrhythmogenic right ventricular cardiomyopathy (ARVC).**
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.

05: Scientist/Supervisor: **Cortés Cantelli, Marta**
Research Line: **Imaging the vasculature of the Alzheimer's disease brain**
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 such as high quality Magnetic Resonance Angiography, Positron Emission Tomography and different Molecular Biology techniques will be performed on AD animal models to show when and where the cerebral vessel obstructions start in vivo in the AD braination.

06: Scientist/Supervisor: **de la Pompa, Jose Luís**
Research Line: **Molecular and cellular mechanisms underlying cardiovascular development: Impact in congenital heart disease**
Summary: The student will be involved in live imaging and functional studies on how the mouse ventricles, cardiac valves and coronary vessels form and mature to give rise to the adult functional heart. Developmental techniques and organ/explant cultures will be instrumental. Global gene expression and proteomics analyses will be carried out to identify new candidate disease markers (cardiomyopathy: LVNC and HCM, and valve disease) that will be validated in human samples, using next generation sequencing. Special emphasis will be made on the Notch, Ephrin, Semaphorins and Bmp signaling pathways. Mouse/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: **del Pozo, Miguel Ángel**
Research Line: **Understanding how mechanical signals are propagated into the cell**
Summary: In mechanically stressed cells, such as cardiomyocytes or endothelial cells, the plasma membrane contains small invaginations, named caveolae, that protect cells from mechanical stress, preventing cardiovascular pathologies. The mechanical stress induces major changes at the plasma membrane, actin filaments and even at the genome structure. How these complex changes are coordinated and interconnected is not well understood. The student will focus on understanding how cells receive mechanical signals by caveolae at the plasma membrane and how these signals are propagated throughout cell.
Some recent publications of the group:
*Sala-Vila **Sci Rep** 2016, Echarri and Del Pozo, **JCS** 2015, Navarro-Lérida, **Dev Cell** 2015, Strippoli, **Embo Mol Med,** 2015, Parton & del Pozo, **Nature Reviews Mol Cell Biol** 2013, Echarri **J Cell Sci** 2012, Echarri & del Pozo, **Curr Biol** 2012, Navarro-Lérida **EMBO J** 2012, Goetz **Cell** 2011, Muriel **J Cell Sci** 2011, Strippoli **J Cell Sci** 2010, Cerezo **Mol Cell Biol**. 2009, Grande **J. Cell Biol**. 2007, del Pozo **Nature Cell Biol** 2005 & **Science** 2004.*
More information on the group: http://www.cnic.es/es/inflamacion/integrinas/index.php The scientific report of the group can be downloaded from http://www.cnic.es/es/cnic/scientific_report.php

08: Scientist/Supervisor: **Dos Santos Benedito, Rui Miguel**
Research Line: ***In vivo* analysis of vascular development in mice**
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 on the group: http://www.cnic.es/en/desarrollo/angiogenesis/index.php

09: Scientist/Supervisor: **Enríquez, Jose Antonio**
Research Line: **Mitochondrial supercomplex reorganization in metabolism**
Summary: The main aim of the project is the understanding of the mechanism by which the oxidative phosphorylation complex reorganizes in response to different fuel source to optimize ATP production

10: Scientist/Supervisor: **Filgueiras, David**
Research Line: **Spatial and Temporal Characterization of Ventricular Fibrillation and its Relationship with the Underlying Three-dimensional Substrate**
Summary: The main objective of this project aims at integrating electrical wave propagation dynamics with the underlying myocardial substrate using clinically relevant experimental and computational models of cardiac fibrillation. The highly innovative and novel experimental, clinical and technological approaches aim to be a foundation for increased understanding of cardiac fibrillation maintenance, while attempting translational applicability in order to define new and robust therapeutic strategies to prevent ventricular fibrillation.

11: Scientist/Supervisor: **García Arroyo, Alicia**
Research Line: **Cellular and molecular players in inflammation-induced angiogenesis**
Summary: The vasculature delivers nutrients and oxygen throughout the body, and for that, it must constantly adapt to varying tissue needs. Focused on the actions of membrane-type matrix metalloproteinases (MT-MMPs) in vascular endothelial and smooth muscle cells, and in macrophages, our group is dedicated to elucidating the cellular and molecular mechanisms that govern vascular responses during inflammation and how they can contribute to tissue repair. We use 2D and 3D angiogenic models, high-resolution microscopy, 3D image analysis, proteomics, bioinformatics, protein modeling, lentiviral strategies, and genetically modified mouse lines with the ultimate aim of developing novel therapies to improve tissue perfusion and/or modulate inflammation in disease.

12: Scientist/Supervisor: **Hidalgo, Andrés**
Research Line: **Circadian properties of immunity**
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.

13: Scientist/Supervisor: **Ibáñez, Borja**
Research line: **Ischemia reperfusion injury and the effect of the beta-adrenergic system**
Summary: 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.

14: 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.

15: 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.

16: 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.

17: 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.

18: Scientist/Supervisor: **Martín, Pilar**
Research line: **Study of heart 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 and diagnostic tools. Our group seeks to identify new regulatory cells and miRNAs involved in the treatment and diagnosis of these diseases.

19: Scientist/Supervisor: **Martín, Pilar**
Research line: **Novel biomarkers for cardiovascular diseases**
Summary: Recent studies estimate the prevalence of myocarditis in about. 22 of 100.000 patients annually. Moreover, between 1-5% of patients with acute viral infection develop myocarditis. The diagnosis of myocarditis made based on clinical, laboratory, ECG, and Echo findings is not always easy. Myocarditis is therefore a diagnostic challenge that does not have a solution in clinical practice. Our group is working in the development of new diagnostic tools related to these diseases.

20: Scientist/Supervisor: **Muñoz, 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: **Molecular mechanisms regulating germinal center B lymphocytes**
Summary: B lymphocytes elicit protective immune responses through the generation of highly specific antibodies. However antibodies and their diversification in germinal centers are also involved in autoimmune disease and cancer. Our lab studies the molecular mechanisms regulating these events, making use of animal models and state-of-the-art molecular biology approaches.

22: 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

23: 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

24: 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.

25: 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.

26: Scientist/Supervisor: **Sabio, Guadalupe**
Research Line: **Role of p38MAPK in metabolic diseases**
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.

27: Scientist/Supervisor: **Sabio, Guadalupe**
Research Line: **p38MAPK in heart phisiology**
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.

28: Scientist/Supervisor: **Sánchez-Madrid, Francisco**
Research line: **The Immunological Synapse as a Mechanism for ImmunoTraining of the Innnate response.**
Summary: We are exploring precise roles of Exosomes as immuno-shuttles of metabolic signals and programmers through the Immunological synapse. In addition, the role of post-translational modifications, miRNAs and mitochondrial components in the biogenesis and secretion of exosomes and their impact on macrophage and dendritic cell function will be analysed.
References:
Blas-Rus N, . ….and Sánchez-Madrid F. Aurora A drives early signalling and vesicle dynamics during T-cell activation. Nat Commun. 2016 Apr 19;7:1138;
Villarroya-Beltri C, ……. and Sánchez-Madrid F. ISGylation controls exosome secretion by promoting lysosomal degradation of MVB proteins. Nat Commun. 2016. Nov 24;7:13588;
Cibrian D, …….. and Sánchez-Madrid F. CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis. Nat Immunol. 2016 Aug;17(8):985-96

29: 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

30: 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

31: Scientist/Supervisor: **Torres, Miguel**
Research Line: **Live analysis of cardiac development in the mouse embryo**
Summary: Using a novel system of mouse embryo culture and multiphoton imaging, the project aims to understand the cellular basis of mammalian heart development in live analysis. The work involves learning mouse embryology, embryo culture, advanced microscopy and image analysis.

32: Scientist/Supervisor: **Torres, Miguel**
Research Line: **The role of Meis transcription factors in the cardiovascular system**
Summary: The project analyzes the role of Meis factors in the formation of the heart and its functioning during adult life. The work involves training in molecular biology of transcription factor activity and the characterization of cardiovascular mutant phenotypes in mouse embryos and adults.

33: Scientist/Supervisor: **Jesús Vázquez**

Research line: **Regulation of mitochondrial supercomplexome assembly/degradation by Data-independent-Scanning mass spectrometry (DiS-MS).**

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 mitochondrial protein associations in animals and human models. A wide variety of proteins (including the proteins involved in electron transport chain) associate in supercomplexes. How do these proteins interact remains poorly understood. The main goal in this project is to determine on one hand the super-assembly factors that mediate the protein-protein interactions, and on the other hand to deeply characterize the posttranslational modifications that can be attached to this proteins to regulate both, the assembly and the degradation processes. Since the proteins assembly pattern changes under specific pathological situations and disorders (e. g. hypoxia-reperfusion processes), these results will help to better understand the molecular basis of protein associations and how can it be regulated in mitochondrial dysfunction or damage.