CNIC Cicerone Program:

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

List of Scientists and Research Lines 2018

1. **Mechanical protein unfolding as a main contributor to the elasticity of the myocardium and muscle-mimicking biomaterials**

Supervisor: Alegre, Jorge
Group: Molecular Mechanics of the Cardiovascular System

Abstract: 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.

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

2. **Molecular events leading to the development of familial cardiomyopathies**

Supervisor: Alegre, Jorge
Group: Molecular Mechanics of the Cardiovascular System

Abstract: 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.

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

3. **Redox control of protein mechanics**

Supervisor: Alegre, Jorge
Group: Molecular Mechanics of the Cardiovascular System

Abstract: Over the last 10 years, we have pioneered the concept that redox posttranslational modifications are efficient modulators of the mechanical properties of proteins. In particular, we have measured how S-glutathionylation of cryptic cysteines in titin domains soften the protein while disulfide formation leads to stiffer domains. In our group, we are developing biochemistry and mass spectrometry techniques to be able to follow redox posttranslational

modifications in native tissues. Using these approaches, we have obtained the first evidence that titin is oxidized in vivo. The student will work towards molecular and mechanical characterization by Atomic Force Microscopy of titin's redox modifications.

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

4. Role of A-type lamins in aging and associated cardiovascular disease

Supervisor: Andrés, Vicente
Group: Molecular and Genetic Cardiovascular Pathophysiology

Abstract: 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). The disease is caused by progerin, a mutant form of lamin A which 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

https://www.cnic.es/en/investigacion/molecular-and-genetic-cardiovascular-pathophysiology

5. In vivo analysis of vascular development in mice

Supervisor: Benedito, Rui
Group: Molecular Genetics of Angiogenesis

Abstract: 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.

http://www.cnic.es/en/desarrollo/angiogenesis/index.php

6. Determinants of LDL uptake in the atherosclerotic plaque.

Supervisor: Bentzon, Jacob Fog
Group: Experimental Pathology of Atherosclerosis

Abstract: Uptake of low-density lipoprotein (LDL) in the atherosclerotic plaque is the driving force of atherosclerosis, but the processes by which LDL uptake is determined by different risk factors of atherosclerosis has only been partly explored. The student will use gene modified mouse models and fluorescently labeled LDL to monitor LDL uptake under different conditions. The student will also be introduced to imaging and alternative atherosclerosis models in gene-modified minipigs.

https://www.cnic.es/en/investigacion/experimental-pathology-atherosclerosis

7. **Plakophilin-2 (PKP2) mutations as a cause of arrhythmogenic right ventricular cardiomyopathy (ARVC): progress toward linking structural with functional changes (Metabolism).**

Supervisor: Bernal, Juan A
Group: Inherited Cardiomyopathies

Abstract: Exercise is universally considered a healthy practice in the general population. However, our recent data from plakophilin-2 (PKP2) mutant indicate that endurance training significantly increase the probability of developing arrhythmogenic right ventricular cardiomyopathy (ARVC). We hypothesize that genomic rearrangement precedes structural and functional cardiac remodeling during endurance exercise and consequent disease progression. We have generated a model of cardiac tissue-specific transgenic-like mice based on adeno associated virus (AAV) gene transfer to test and study the potential combination of a human PKP2 mutation (R735X) and endurance training to trigger ARVC.

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

8. **Plakophilin-2 (PKP2) mutations as a cause of arrhythmogenic right ventricular cardiomyopathy (ARVC): progress toward linking structural with functional changes (Biomechanics).**

Supervisor: Bernal, Juan A
Group: Inherited Cardiomyopathies

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

9. **Understanding how mechanical signals are propagated into the cell**

Supervisor: del Pozo, Miguel Ángel / Echarri, Asier
Group: Mechanoadaptation and Caveolae Biology

Abstract: 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.

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

10. Mitochondrial performance in heart disease

Supervisor: Enríquez, José Antonio
Group: Functional Genetics of the Oxidative Phosphorilation System (GENOPHOS)

Abstract: 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.

https://www.cnic.es/en/investigacion/functional-genetics-oxidative-phosphorilation-system-genophos

11. Magnetic Resonance Imaging-based 3D Modeling of Ventricular Substrate for

Supervisor: Filgueiras, David
Group: Advanced Development in Arrhythmia Mechanisms and Therapy

Abstract: Advanced Development in Arrhythmia Mechanisms and Therapy Accurate Characterization of In Vivo Scar-Related Monomorphic Ventricular Tachycardia: Translational Study From Pigs to Humans Radiofrequency catheter ablation has become the first line treatment for a number of cardiac arrhythmias including ventricular reentrant tachycardia (VT). Precise information about the arrhythmogenic substrate and its functional behavior during the ablation procedure may improve the success of ablation of ischemic scar-related VTs. The objective of this proposal is to generate realistic and interactive, Magnetic Resonance Imaging (MRI)-based 3D electro-anatomical models of the ventricles, which will be used to predict successful ablation strategies aimed at terminating VT.

https://www.cnic.es/en/investigacion/advanced-development-arrhythmia-mechanisms-and-therapy

12. Role of ubiquitin-specific proteases in cardiovascular development and disease.

Supervisor: Grego-Bessa, Joaquím
Group: Intercellular Signaling in Cardiovascular Development and Disease

Abstract: We will characterize the cellular and molecular mechanisms by which the UBPY/ubiquitin-specific protease 8 (USP8) regulates cardiovascular development. We will carry out: 1) Cellular and molecular characterization of specific cardiac and vascular -derived cell lineages after USP8 deletion, including advanced imaging techniques, gene expression analysis, and proteomics; 2) USP8 genetic interactions analysis with the Notch and Nrg1 signaling pathways; 3) high-resolution live imaging by genetically labelling mutant cells with specific fluorophores.

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

13. Molecular and cellular defects in human induced pluripotent stem cell derived cardiomyocytes from patients with inheritable cardiac diseases

Supervisor: Jalife, José
Group: Cardiac Arrhythmia

Abstract: The objective of this project is to determine cell-type specific mechanisms that underlie 3-dimensional (3D) human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) micro-tissue self-assembly and maturation. The lab has developed a novel cell culture platform for high content production of 3D hiPSC-CM cardiac micro-tissues. We have also generated preliminary data showing the essential role of non-myocytes for hiPSC-CM 3D cardiac micro-tissue development. Cardiac directed differentiation techniques direct stem cells through various developmental stages including mesodermal progenitors, cardiac progenitors to eventually create functional CMs and fibroblasts. However, the precise role of each of these developmental stage specific non-myocyte cell types in the development of human 3D cardiac micro-tissues is unexplored. We will generate 3D cardiac micro-tissues utilizing cells of each developmental state to determine cellular mechanisms of 3D hiPSC-CM micro-tissue self-assembly and maturation. Time lapse microscopy will be used to quantify the effect of cell type on kinetics of micro-tissue formation. Structural (sarcomere structure, t-tubules, intercalated disc, etc.) and functional phenotypes (force generation and electrophysiology) will be quantified using high resolution imaging and molecular biology approaches, as well as RNA-sec, proteomics and optical mapping with voltage sensitive dyes. This will be done using control and specific hiPSC-CMs from patients with inheritable cardiac diseased.

https://www.ncbi.nlm.nih.gov/pubmed/?term=Jalife+J

14. A mouse model of hypertrophy induced arrhythmias and sudden cardiac death

Supervisor: Jalife, José
Group: Cardiac Arrhythmia

Abstract: Cardiac hypertrophy is a risk factor for QT-prolongation, ventricular arrhythmias and sudden cardiac death (SCD), but the molecular link between hypertrophy, arrhythmia and SCD has not been demonstrated. The p38-MAPK signaling pathway is critical in stress-induced cardiac hypertrophy. In addition, p38□/□ regulates the localization of synapse-associated protein 97 (SAP97) in relation with the cytoskeleton by modulating its interaction with guanylate kinase-associated protein (GKAP). SAP97 is a scaffolding protein that forms a macromolecular complex with the α subunit of the cardiac sodium channel ($Na_V1.5$) carrying I_{Na}, the strong inward rectifier potassium channel (Kir2.1) carrying IK1 and the transient outward current ITo. These are important ion channels controlling cardiac excitability, action potential duration (APD) and the mechanisms of complex arrhythmias. The main p38 upstream activators are the MAPK kinases MKK3 and MKK6, which are highly selective for p38 MAPKs. Preliminary data shows that, in the mouse heart, lack of Mkk6 results in Mkk3 hyperphosphorylation leading to hyperactivation of the p38-MAPK signaling cascade, and resulting in cardiac hypertrophy, QT prolongation and SCD. In addition, cardiomyocytes from Mkk6-/- mice have SAP97 hyperphosphorylation and ion channel dysfunction, including decreased I_{To} but increased INa density with consequent APD prolongation. In human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) from a patient with the R403Q mutation in the β-myosin heavy

chain (MyH7 gene) motor protein, hypertrophic cardiomyopathy is associated with increased phosphorylation of p38γ-MAPK. Altogether, we demonstrate a new paradigm for the role of the p38-MAPK pathway in the mechanism of cardiac hypertrophy and arrhythmogenesis.

https://www.ncbi.nlm.nih.gov/pubmed/?term=Jalife+J

15. Innovative therapies for the treatment of cardiomyopathies

Supervisor: Lara Pezzi, Enrique
Group: Molecular regulation of heart failure

Abstract: 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.

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

16. Alternative splicing in subclinical atherosclerosis

Supervisor: Lara Pezzi, Enrique
Group: Molecular regulation of heart failure

Abstract: 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.

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

17. Understanding the Role of the Endocardium in Cardiac Disease

Supervisor: Luna Zurita, Luis
Group: Intercellular Signaling in Cardiovascular Development and Disease

Abstract: The endocardium plays crucial signaling roles both in cardiac development and in disease; Notch is one essential endocardial signalling pathway. We will develop the following objectives: 1) To understand the ligand–dependent Notch1 control of gene expression during cardiogenesis; 2) To identify N1ICD/RBPJ-dependent transcriptional active enhancers in endocardial cells. We will use ChIP-seq and ATAC sec technologies to identify candidate regulatory elements, whose function will be assessed in mice.

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

18. Reprogramming pluripotency in development and disease

Supervisor: Manzanares, Miguel
Group: Functional Genomics

Abstract: 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. In this Cicerone project, the student will study how pluripotency factors mediate cellular reprogramming at different developmental stages and how this can contribute to recovery of failing hearts.

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

19. Bioinformatic analysis of the regulatory basis of cardiovascular disease.

Supervisor: Manzanares, Miguel
Group: Functional Genomics

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.

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

20. Heart inflammation and cardiovascular disease

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

Abstract: 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.

https://www.cnic.es/en/investigacion/regulatory-molecules-inflammatory-processes

21. Tissue Regeneration

Supervisor: Muñoz, Pura
Group: Tissue Regeneration laboratory

Abstract: 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.

https://www.cnic.es/en/investigacion/tissue-regeneration-laboratory

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

Supervisor: Oliver, Eduardo
Group: Translational Laboratory for Cardiovascular Imaging and Therapy

Abstract: 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.

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

23. Somatic hypermutation of antibody genes

Supervisor: Ramiro, Almudena R
Group: B Lymphocyte Biology lab

Abstract: 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

https://www.cnic.es/en/investigacion/b-lymphocyte-biology

24. Identification of new pathophysiological mediators and mechanisms in aortic diseases.

Supervisor: Redondo, Juan Miguel
Group: Gene regulation in Cardiovascular Remodelling and Inflammation

Abstract: 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 (MCB 2015; Nat Med 2017a and Nat Med 2017b). 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 using samples from TAAD patients.

https://www.cnic.es/en/investigacion/gene-regulation-cardiovascular-remodelling-and-inflammation-0

25. Role of calcineurin (CN) in cardiovascular remodeling

Supervisor: Redondo, Juan Miguel
Group: Gene regulation in Cardiovascular Remodelling and Inflammation

Abstract: 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.

https://www.cnic.es/en/investigacion/gene-regulation-cardiovascular-remodelling-and-inflammation-0

26. Role of macrophage nuclear receptors in cardiac homeostasis and injury.

Supervisor: Ricote, Mercedes
Group: Nuclear Receptor Signaling

Abstract: 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.

https://www.cnic.es/en/investigacion/nuclear-receptor-signaling

27. Bioinformatic analysis of the transcriptional regulation of nuclear receptors in macrophages.

Supervisor: Ricote, Mercedes
Group: Nuclear Receptor Signaling

Abstract: 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.

https://www.cnic.es/en/investigacion/nuclear-receptor-signaling

28. Role of p38MAPK in metabolic diseases

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

Abstract: 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.

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

29. Post-Translational Modifications in the Inflammatory Response

Supervisor: Sanchez Madrid, Francisco
Group: Cell-Cell Communication in the Inflammatory Response

Abstract: The functionality of proteins can be regulated in cells beyond gene regulation; post-translational modifications (PTM) fine-tune catalytic activities, protein-protein interactions, sorting and degradation. PTM are regulated during inflammatory processes and immune response. We investigate the enzymes responsible of these modifications, such as acetylation, controlled cleavage and conjugation to proteins such as Ubiquitin, ISG or Sumo, as well as the enzymes in charge of reversion these PTM to unveil their role in exosome biogenesis and the regulation of immune cells in inflammatory disease.

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

30. Immune receptors sensing tissue damage in inflammation and immunity

Supervisor: Sancho, David
Group: Immunobiology

Abstract: 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.

https://www.cnic.es/en/investigacion/immunobiology

31. Metabolic plasticity instructs immune cell function

Supervisor: Sancho, David
Group: Immunobiology

Abstract: 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.

https://www.cnic.es/en/investigacion/immunobiology

32. Mechanisms of heart regeneration

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

Abstract: 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.

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

33. Regulation of mitochondrial supercomplexome assembly/degradation by Data-independent-Scanning mass spectrometry (DiS-MS).

Supervisor: Vázquez, Jesús
Group: Cardiovascular Proteomics

Abstract: 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.

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