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CURE HEART & BRAIN

CNIC Research Lines

CNIC Program	page
<u>Myocardial homeostasis & cardiac injury</u>	2
<u>Cardiovascular risk factors & brain function</u>	4
<u>Novel mechanisms of atherosclerosis</u>	6
<u>Cardiovascular regeneration</u>	9
<u>Novel arrhythmogenic mechanisms</u>	12
<u>Cardiovascular health promotion</u>	12

CNIC Program: Myocardial homeostasis & cardiac injury

Coordinator: Enrique Lara Pezzi – Clinical leader: Borja Ibáñez

CNIC Group 1: Molecular Regulation of Heart Failure

PI: Enrique Lara-Pezzi

Research Line: New translational approaches in dilated cardiomyopathy and heart failure: from molecular mechanisms to therapy

Description: The group investigates the molecular mechanisms that underlie inherited cardiomyopathies and heart failure by combining expertise in advanced non-invasive imaging, pathophysiology and molecular biology in translational animal models. Dilated cardiomyopathy (DCM) is a heart disease characterized by thinning and stretching of the ventricles, which grow larger, making it harder for the heart to pump blood. The mechanisms leading to dilatation of the left ventricle are not completely understood. Furthermore, current therapies are inefficient, as they follow a ‘one-size-fits-all’ approach, disregarding the specific pathology of the disease. The research in our group focuses on the identification of cellular and molecular mechanisms driving ventricular dilatation, cardiac dysfunction and heart failure in pig and mouse models of dilated cardiomyopathy. More specifically, the group investigates the contribution of different immune cell populations to DCM, based on recent single-nuclei RNA-seq analyses in our laboratory. Following the identification of potential targets, the group will develop new gene therapy products for the treatment of this disease.

CNIC Group 2: Translational Laboratory for Cardiovascular Imaging and Therapy

PI: Borja Ibáñez

Research Line: Novel metabolic interventions to prevent cancer therapy related cardiovascular toxicities

Description: By combining complementary experimental approaches in small and large animal models, our aim is to identify novel therapies able to prevent/treat cardiac metabolic alterations occurring in patients with cancer treated with cytotoxic agents. Within several tools, cardiac magnetic resonance will be key across the execution of this research.

CNIC Group 3: Molecular Mechanics of the Cardiovascular System

PI: Jorge Alegre-Cebollada

Research Line: Integrated sarcomere mechanics in familial and acquired cardiomyopathy

Description: The group Molecular Mechanics of the Cardiovascular System specializes in the multiscale characterization of myocardial mechanics, from the single-protein to the tissue levels. The research of the group focuses on understanding how the dysfunction of sarcomeres contributes to heart failure including the crosstalk with defective activity of other organelles like the mitochondria or adhesion complexes.

CNIC Group 4: Heart Failure and Pulmonary Hypertension translational research

PI: Ana García

Research Line: Heart failure and pulmonary hypertension translational research

Description: Our laboratory focuses on the study of myocardial diseases leading to heart failure (HF) and pulmonary hypertension (PH) from a translational perspective ranging from molecular studies and experimental models to multicenter clinical trials. We are a multidisciplinary team that includes cardiologists and cardiac surgeons and closely collaborate with experts in molecular biology, proteomics, metabolomics and genetics. We have developed and deeply characterized four different models of PH or RV pressure overload in pigs, induced by different mechanisms. These models have been used for the development of new diagnostic algorithms based on cardiac magnetic resonance, to identify early RV involvement, and to evaluate the mechanisms underlying the beneficial effects of current and novel treatments. Some of these investigations have been carried forward to the clinical arena and evaluated as multicenter clinical trials. In the last years, our efforts are centered on understanding the underlying mechanisms of RV dysfunction in PH through the integration of advanced imaging and omics (proteomics, metabolomics and genomics), from studies in our experimental models and in patients with various types of PH. The research seeks to decipher the mechanisms that lead to RV dysfunction in the presence of PH and various cardiomyopathies with a translational vision that moves from basic research to the clinics and vice versa, all with an open and friendly dialogue between professionals with different scientific background.

CNIC Group 5: Inherited Cardiomyopathies

PI: Pablo García-Pavía

Research Line: Identification of genetic mechanisms and new biomarkers in cardiomyopathies

Description: The group is focused on the study of the genetic mechanisms involved in the development of inherited heart diseases and in the identification of new biomarkers in TTR cardiac amyloidosis. It is intriguing why despite the advances in genetic field, a genetic cause is still only detected in less than 40% of the families with Hypertrophic cardiomyopathy (HCM) and Dilated cardiomyopathy (DCM), the two main types of cardiomyopathies. Therefore, our research is focused on the identification of new genes and new mutations that could explain the cause of the disease in the unsolved group of patients. Furthermore, the group has a strong interest in TTR cardiac amyloidosis, a progressive and often fatal disease that is a frequent cause of heart failure. In this area, the group is conducting several studies to understand how patients with this disease respond to available therapies along with studies to identify new diagnostic and prognostic biomarkers that would improve the diagnosis and the follow-up of these patients.

CNIC Programme: Cardiovascular risk factors & brain function

Coordinator: María Ángeles Moro - Clinical leader: Valentín Fuster

CNIC Group 6: Neurovascular Pathophysiology

PI: María Ángeles Moro

Research Line: Neurovascular Pathophysiology

Description: The Neurovascular Pathophysiology Group, led by Dr. María Ángeles Moro, is devoted to the study of the cerebrovascular disease, one of the leading causes of death and disability, with an increasing prevalence due to the ageing of the population. A major focus of the group is the investigation of stroke and vascular cognitive impairment, among the most devastating disorders and a major socio-economic problem for societies and health-care systems worldwide because of their enormous costs. Specifically, the research lines of the Neurovascular Pathophysiology group aim to unravel the mechanisms of vascular-driven cognitive impairment and dementia, including the participation and role of immunothrombosis, neuroimmune interfaces and perivascular spaces, glymphatic system/meningeal lymphatics, and blood-brain barrier and cerebral vasculature, among others. The research applies dedicated animal models and multidisciplinary cutting-edge technologies. Preclinical findings will be validated in human samples from ongoing collaborations with clinical groups. In addition to the mechanistical insight provided, our research serves to deliver a framework to improve prevention, diagnosis, and treatment of VCID.

CNIC Group 7: Cardiovascular Imaging and Population Studies

PI: Valentin Fuster

Research Line: Cardiovascular Imaging and Population Studies

Description: The Cardiovascular Imaging and Population Studies Group, led by Dr. Valentin Fuster, has developed research applications for non-invasive, high-resolution and high-sensitivity imaging technologies to support translational research and population studies in preclinical atherosclerosis.

Among their main studies, the group is performing a longitudinal study to evaluate their trajectories very early in their courses (i.e. in asymptomatic stages) in order to understand the interrelationship between brain and cardiovascular disease at the preclinical level. The Progression of Early Subclinical Atherosclerosis (PESA), led by Dr. Valentin Fuster, is a prospective ongoing study that included over 4,000 middle-aged asymptomatic participants back in 2010 with the aim of tracking the trajectories of atherosclerosis and associated disorders from early stages to symptomatic phases. The group also runs the PESA-Brain sub-study, led by Dr. Marta Cortes-Canteli. In this study 1000 PESA participants are currently undergoing a thorough neurocognitive testing together with amyloid-PET and a highly comprehensive brain magnetic resonance imaging protocol to study brain morphology, connectivity and perfusion, vascular lesions and intracranial atherosclerosis.

CNIC Group 8: Multidisciplinary Translational Cardiovascular Research

PI: Héctor Bueno

Research Line: Multidisciplinary Translational Cardiovascular Research (MTCR)

Description: The Multidisciplinary Translational Research (MTCR) Group, led by Dr. Héctor Bueno, is a platform for innovative knowledge generation in cardiovascular health and disease. The mission of the MTCR Group is to promote the generation of disruptive knowledge and innovation with a humanitarian perspective to foster, prevent or improve the health or quality of life of citizens and patients, increasing the efficiency/safety of the healthcare system. The research lines offered by the MTCR group include

- Mental health and cardiovascular risk
- Social determinants of cardiovascular health and disease
- Cardiovascular epidemiology, quality of care and outcomes
- Impact of gender on cardiovascular health and disease

CNIC Group 9: Regulatory Molecules of Inflammatory Processes

PI: Pilar Martín

Research Line: Regulatory Molecules of Inflammatory Processes

Description: The Regulatory Molecules of Inflammatory Processes group, led by Dr. Pilar Martín, seeks to study the therapeutic and diagnostic potential of T cells, their immunomodulatory receptors and microRNAs, in the management of cardiovascular disease (CVD) and in the development of precision

medicine tools. T lymphocytes are pivotal in the development of CVD and, together with certain microRNAs have been shown to be altered in blood and cardiovascular tissues during their progression. In this context, the research of the group encompasses a holistic approach to understand the full spectrum of cognitive impairments, whether they stem from neurodegenerative diseases, immune-related factors, or the natural aging process. We also explore the intricate intersections between immune system disturbances induced by cardiovascular risk factors, such as diet or vascular remodelling, and cognitive dysfunction. Part of our studies is aimed to assess cognitive impairments through behavioural tests, complemented by state-of-the-art molecular biology techniques, including single-cell RNA sequencing and advanced imaging modalities like magnetic resonance imaging (MRI) and PET-CT scans. These cutting-edge methods will enable us to track and analyze changes in both animal models and human subjects, providing valuable insights into the complex relationship between neuroinflammation and cognitive deficits.

CNIC Program: Novel mechanisms of atherosclerosis

Coordinator: José Javier Fuster – **Clinical leaders:** Valentín Fuster and Inés García Lunar

CNIC Group 10: Hematovascular Pathophysiology

PI: José Javier Fuster

Research Line: Pathophysiological effects and dynamics of age-related clonal hematopoiesis

Description: Clonal hematopoiesis has recently emerged as a novel risk factor for atherosclerotic cardiovascular disease (CVD), with significant implications for personalized medicine. This condition is typically driven by the acquisition of certain somatic mutations in the hematopoietic system, which lead to the clonal expansion of the mutant cell and the subsequent propagation of the mutation throughout the immune system. Our prior human and mouse studies support the direct contribution of some of these mutations to atherosclerotic CVD through the exacerbation of specific inflammatory responses (e.g. Science 2017, JACC 2021, Nature CVR 2023). In this context, one of our current objectives is to understand the factors that modulate the dynamics of clonal hematopoiesis and its impact on atherosclerosis. To achieve this, we will employ both bulk and single-cell omics analysis on deeply characterized human cohorts and conduct innovative experiments using mice and cultured cells. This interdisciplinary research may be of interest to investigators across multiple fields, including genomics, bioinformatics, experimental hematology, immunology, and cardiovascular pathophysiology.

More information:

<https://scholar.google.com/citations?user=9c-E-YAAAAJ&hl=en> ; <https://atheroclonal.com/>

CNIC Groups 11: Cardiovascular prevention through non-invasive imaging and Hematovascular Pathophysiology

PI: Inés García Lunar and José Javier Fuster

Research Line: New inflammatory drivers of human atherosclerosis

Description: Despite the efficacy of interventions targeting traditional cardiovascular risk factors like cholesterol-lowering drugs, atherosclerotic cardiovascular disease (CVD) remains the leading global cause of death. In this context, there is a gaping hole in our approach to CVD prevention. It is widely recognized that atherosclerosis, the primary cause of most CVD events, results from a maladaptive inflammatory response to the chronic exposure to various CVD risk factors. Yet, targeting inflammation for CVD prevention remains an unfulfilled promise due to the scarce understanding of the specific inflammatory factors that drive human atherosclerosis development across the disease continuum. In this context, this collaborative research is aimed at identifying the inflammatory drivers of the development of atherosclerosis during its preclinical stages. At the core of this endeavor are several human cohorts that are tracking subclinical atherosclerosis development in apparently healthy individuals through longitudinal non-invasive imaging. Using these unique resources and advanced omics analyses, we seek to identify the specific immunomodulatory mechanisms that, when dysregulated, drive human atherosclerosis development.

CNIC Group 12: Molecular and Genetic Cardiovascular Pathophysiology

PI: Vicente Andrés

Research Line: A-type lamin-dependent control of atherosclerosis during physiological and premature aging

Description: We are broadly interested in identifying mechanisms that control age-related atherosclerosis because: a) the world population is undergoing a profound demographic change due to progressive aging; b) aging is the main risk factor for atherosclerotic cardiovascular disease (aCVD), which is the number one killer in developed countries and is expected to become soon the leading cause of morbi-mortality worldwide; c) most aCVD-related deaths are considered premature and preventable. Our laboratory has made seminal contributions into the role of nuclear A-type lamins in pathophysiological processes, and has led research into Hutchinson-Gilford progeria syndrome (HGPS), a rare premature aging syndrome caused by progerin, a mutant form of lamin A that provokes exaggerated aCVD and premature death. Moreover, progerin has been detected at low level in aged tissues of non-HGPS individuals, suggesting a role in normal aging. Understanding how progerin causes CVD and premature aging may therefore shed light on normal aging, and viceversa. In this research we will use animal models and analysis of human samples to unravel new cellular and molecular mechanisms through which nuclear A-type lamins and progerin regulate aCVD and aging.

CNIC Group 13: Mechanoadaptation and Caveolae Biology

PI: Miguel Ángel del Pozo

Research Line: Mechanisms integrating blood flow sensing, arterial wall remodeling and inflammation during atherogenesis

Description: 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. Combining advanced in vitro microfluidics, quantitative proteomics, scRNAseq and animal disease models. Our group studies molecular mechanisms regulating blood flow sensing and transduction, cell-cell communication, LDL transcytosis & retention, and arterial matrix remodeling under atherogenic conditions. This research falls within the context of the AtheroConvergence international consortium funded by La Caixa among other grants. More information: Pubmed EMBO

CNIC Group 14: Nanomedicine & Molecular Imaging

PI: Carlos Pérez-Medina

Research Line: Human antibody-enabled cardiovascular personalized theragnosis

Description: The ultimate goal of our research is to develop fully human antibodies (HuAbs) into diagnostic tools and personalized therapeutic agents to treat atherosclerosis. Specifically, we are isolating promising candidates from a macrolibrary of HuAbs selected in vivo from atherosclerotic samples. These candidates subsequently are characterized and produced in different formats suitable for therapeutic purposes or imaging with positron emission tomography (PET). In vivo testing of HuAb-based therapies and PET radiotracers is carried out in mouse and pig models of atherosclerosis.

CNIC Group 15: B Lymphocyte Biology

PI: Almudena Ramiro

Research Line: Antibody-mediated atheroprotection: novel perspectives to immunotherapeutic approaches in cardiovascular disease

Description: Atherosclerosis progression involves various arms of the adaptive immune response, whose role in the disease is still poorly understood. For the last years we have been studying the antibody adaptive immune response in atherosclerosis and we have identified atherosclerosis-associated antibodies that can have a protective function in this disease. Our research focuses on

understanding the mechanisms of atheroprotection mediated by antibodies, with the ultimate aim of designing novel immunomodulatory approaches of therapeutic interest.

CNIC Group 16: Immunobiology

PI: David Sancho

Research Line: Gut microbiota-derived metabolites in atherosclerosis diagnosis, prognosis and therapy

Description: The gut microbiota influences our metabolism and may affect atherosclerosis (AT) progression. However, how the specific products from microbiota (metabolites) can modulate AT is poorly known. Our group studies the association of gut microbiota and their metabolites with AT, focusing on mechanisms driving inflammation and on their connection with macrophages. We assess the potential of microbial metabolites to identify AT in groups of human volunteers with early AT, and their potential to predict future AT by studying patients with more advanced AT. We also investigate the mechanism of action of these promising metabolites in order to find new targets with potential to treat AT. Our research can result in new diagnostic/prognostic tools for AT and can unveil novel strategies for the prevention and/or therapy of AT.

CNIC Program: Cardiovascular regeneration

Coordinator: Miguel Torres – Clinical leader: Hesham Sadek

CNIC Group 17: Genetic Control of Organ Development and Regeneration

PI: Miguel Torres

Research Line: The role of autophagy in heart homeostasis and regeneration

Description: Autophagy is an essential pathway to ensure cardiomyocyte physiology, however, how autophagy modulation affects cardiac function and regenerative ability remains unknown. Our research uses genetic models developed in our laboratory to conditionally activate or inactivate macro-autophagy in cardiomyocytes and study the impact of these interventions on heart physiology and regenerative ability.

CNIC Group 18: Myocardial regeneration via cardiomyocyte cell cycle regulation

PI: Hesham Sadek

Research Line: Myocardial regeneration via cardiomyocyte cell cycle regulation

Description: The long-term goal of Sadek Lab research program is to find a cure for heart failure through the discovery of key mechanisms that regulate endogenous heart regeneration in mammals. Specifically, my laboratory is interested in understanding how the endogenous regenerative properties of the

mammalian myocardium are regulated by intrinsic cardiomyocyte mechanisms as well as by signals in the intrauterine and postnatal environment. Ultimately, we aim to leverage these findings to identify therapeutic targets that can reactivate cardiomyocyte proliferation and induce myocardial regeneration in humans.

CNIC Group 19: Molecular Genetics of Angiogenesis

PI: Rui Bedito

Research Line: Mechanisms and therapies to promote endothelial protection against reperfusion injury

Description: Reperfusion of vessels with oxygen rich blood after an ischemic event exacerbates the endothelial damage caused by hypoxia, leading to the further loss of blood vessels and surrounding tissue damage. Our lab has identified that arterialized endothelial cells are protected against the transition from hypoxia to normoxia caused by the reperfusion. Our research aims at genetically and pharmacologically arterializing capillary ECs, in order to protect blood vessels and the surrounding tissue against the damaging effects of reperfusion.

CNIC Group 20: Intercellular Signaling in Cardiovascular Development and Disease

PI: José Luis de la Pompa

Exploring the molecular mechanisms regulating cardiomyocyte maturation. **Description:** Ventricles power the heart's beat. The signaling molecule Neuregulin-1 (Nrg1) is vital for trabecular growth and ventricular wall maturation, orchestrating cardiomyocyte processes like migration, adhesion, and cell cycle progression. We have identified a set of Nrg1-dependent genes which appear to be involved in cardiomyocyte differentiation and ventricular maturation (PMID: 37846569).

Phenotypic transitions in genetic cardiomyopathies. **Description:** Genetic cardiomyopathies are heart muscle disorders caused by genetic mutations. Mouse modelling of disease-causing mutations identified in families with mixed cardiomyopathy phenotypes (HCM+LVNC), indicates that there is a developmental transition involving the transcription factor Prdm16, in which an early fetal-neonate hypertrabeculation evolves postnatally into hypertrophic cardiomyopathy. We characterize the underlying molecular mechanisms with the ultimate goal to generate fundamental knowledge with translational implications for CHD (PMID: 36325906, 37405741).

CNIC Group 21: Functional Genetics of the Oxidative Phosphorilation System (GENOXPHOS)

PI: José Antonio Enríquez

In silico design of pharmacological targets for heart regeneration. **Description:** Identification of novel therapeutics in heart regeneration is demanded. This research aims to discover potent therapeutic drugs

based on the expression profile of heart-specific genes involved in regeneration by comprehensively analyzing sequencing data exclusively.

Deciphering of the mitochondrial complexes behind heart regeneration. **Description:** The supramolecular structures of complex IV have different metabolic and physiological functions, ranging from metabolic maturation necessary for correct tissue physiology, to plasticity and adaptation to different metabolic requirements. Using different genetic approaches, the research aims to understand the supramolecular organization behind the heart regeneration.

Preclinical model of heart regeneration therapy based on mitochondrial performance. **Description:** OMA1 is a mitochondrial protease that participates in various processes: the regulation of mitochondrial structure, the activation of the integrated stress response and, eventually, the cell's entry to apoptosis. Current efforts are focused in proving the therapeutic potential of this target in heart regeneration, exploring the possible adverse effects that the absence of this protein might have, due to the marked translational nature of this research.

CNIC Group 22: Development of the epicardium and its role during regeneration

PI: Nadia Mercader

Research Line: Medaka as a model to test genes and molecules promoting heart regeneration

Description: The natural capacity of zebrafish for heart regeneration is not shared by a second teleost fish, namely Medaka. **This research aims at using this latter model for a small molecules and genetic screening of pro-regenerative compounds and genes.**

CNIC Group 23: Cardiac tissue engineering and regenerative therapies

PI: Florian Weinberger

Research Line: Harnessing anti-fibrotic strategies to improve cardiomyocyte transplantation

Description: The research aims to combine cardiomyocyte differentiation from human iPSCs with different pharmacological and genetic anti-fibrotic strategies to improve in vivo cardiomyocyte transplantation in animal models. We hypothesize that this approach will allow cardiomyocytes to better invade the fibrotic scar tissue and replenish the injured area with more new muscle following injury. Combining different genetic (i.e. genetic modifications of iPSC), molecular, and imaging tools with tissue engineering and physiological analysis of cardiac function, we will study the functional consequences of anti-fibrotic strategies on cardiomyocyte transplantation success. The goal is to eventually develop strategies to improve cardiomyocyte transplantation.

CNIC Program: Novel arrhythmogenic mechanisms

Coordinator: Silvia Priori – Clinical leader: David Filgueiras

CNIC Group 24: Molecular Cardiology

PI: Silvia Priori

Research Line: DNA and RNA Therapies for the management of ventricular arrhythmias and prevention of sudden cardiac death

Description: The research is focused on two severe inherited arrhythmogenic diseases: catecholaminergic polymorphic ventricular tachycardia (CPVT) and Long QT syndrome type 8 (LQT8). The group is currently working on two existing mice models for the dominant and the recessive forms of CPVT with the objective of investigating the effects of gene therapy strategies developed by the Molecular Cardiology Laboratories at the ICS Maugeri Institute in Pavia (Italy) on intracellular calcium handling and cellular electrophysiology. A most ambitious effort of the group is the development of a knock-in pig to model LQT8.

CNIC Program: Cardiovascular health promotion

Coordinator: Rodrigo Fernández Jiménez – Clinical leader: Valentín Fuster

CNIC Group 25: Cardiovascular Health and Imaging

PI: Rodrigo Fernández Jiménez

Research Line: Health Promotion and Cardiovascular Prevention

Description: Our research line focuses on cardiovascular disease prevention and health promotion by working in multidisciplinary studies in close collaboration with schools and communities, targeting both children and adults. The ultimate goal of our research is the implementation of effective health promotion and prevention strategies to reduce the burden of cardiovascular disease in individuals and society