RESEARCH AT THE CENTER
SCIENTIFIC PROGRAMS

The CNIC is organized into two departments, one focused on Basic Research and the other on Clinical Research. Research in these fields is fully interconnected through seven focused Programs.

NOVEL MECHANISMS
OF ATHEROSCLEROSIS

Coordinator: **Jose J. Fuster**

Clinical leaders: **Valentín Fuster, Inés García Lunar**

The Novel Mechanisms of Atherosclerosis Program aims to provide key insights into the pathophysiology of atherosclerosis, the underlying cause of the most frequent cardiovascular and cerebrovascular disorders. Despite the efficacy of interventions that target traditional cardiovascular risk factors, a substantial risk of atherosclerotic cardiovascular disease remains, even in individuals who achieve massive reductions in blood cholesterol and are apparently at low cardiovascular risk based on current risk scores. Therefore, while it remains imperative to target well-established cardiovascular risk factors, there is an evident need for a deep understanding of non-conventional risk factors and pathophysiological mechanisms that could lead to new strategies for the prediction, prevention, and treatment of atherosclerotic cardiovascular disease. In this context, the research groups in the program are working towards the identification and characterization of new inflammatory drivers of atherosclerosis.

Research during the past 30 years has clearly established that atherosclerosis is an inflammatory condition resulting from a maladaptive immune-inflammatory response to the chronic exposure to cardiovascular risk factors. Nevertheless, targeting inflammation in cardiovascular disease remains an unfulfilled promise, highlighting the need for a deep understanding of the intricacies of inflammatory responses in atherosclerosis. Several research groups in the Program are working towards this goal, building upon prior seminal work and combining human studies (based on existing and novel data from
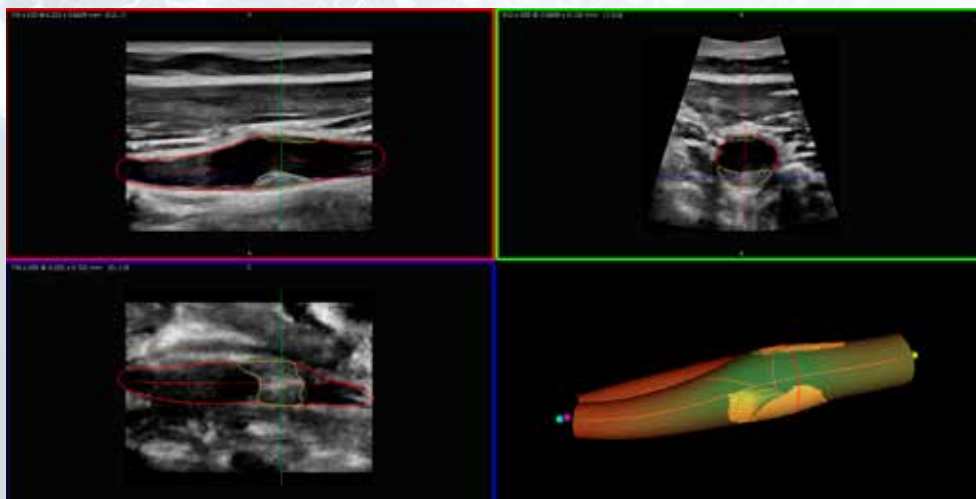

Standardized 3D vascular ultrasound images (multiplanar views and 3D reconstruction) from human atherosclerotic disease affecting one of the carotid arteries (taken from the PESA-HEALTH study using the CM2020 software).

RESEARCH GROUPS

- **Vicente Andrés**
  Molecular and Genetic Cardiovascular Pathophysiology

- **Jacob Fog Bentzon**
  Experimental Pathology of Atherosclerosis

- **Miguel A. del Pozo**
  Mechanoadaptation and Caveolae Biology

- **Jose J Fuster**
  Hematovascular Pathophysiology

- **Carlos Pérez-Medina**
  Nanomedicine and Molecular Imaging

- **Almudena Ramiro**
  B Lymphocyte Biology

- **Francisco Sánchez-Madrid**
  Intercellular Communication in the Inflammatory Response

- **David Sancho**
  Immunobiology

- **Jesús Vázquez**
  Cardiovascular Proteomics

the Progression of Early Subclinical Atherosclerosis (PESA) cohort (PI Dr. Valentin Fuster) and experiments in animal models. Ongoing research in this area is focused on the role of acquired mutations in hematopoietic cells, telomere dynamics, autoantibodies, and specific leukocyte subsets in atherosclerosis. Additional projects within the program are related to the biology of vascular smooth muscle cells in atherosclerotic plaques, the sensing of mechanical stress by the vascular wall, the effects of microbiota-derived metabolites, and the identification of circulating and imaging biomarkers of atherosclerosis development.

In 2022, among other research achievements, scientists in the Novel Mechanisms of Atherosclerosis Program provided evidence of the role of altered hematopoiesis as a link between traditional cardiometabolic risk factors and atherosclerosis development in humans. Program scientists also identified new mechanisms by which T lymphocytes can modulate atherosclerosis development. We also established a methodological framework for the identification of new autoantibodies and the evaluation of their effects on atherosclerosis, which may facilitate the future development of vaccines for the prevention or treatment of this condition. The quality and potential of these lines of research is attested by several successful applications for research funding in 2022, including two health research grants funded by La Caixa Foundation, which will fuel further developments in the scientific project of the program. Among other honors, several researchers within the program were elected to join prestigious academic and scientific societies, such as the Academia Europaea.
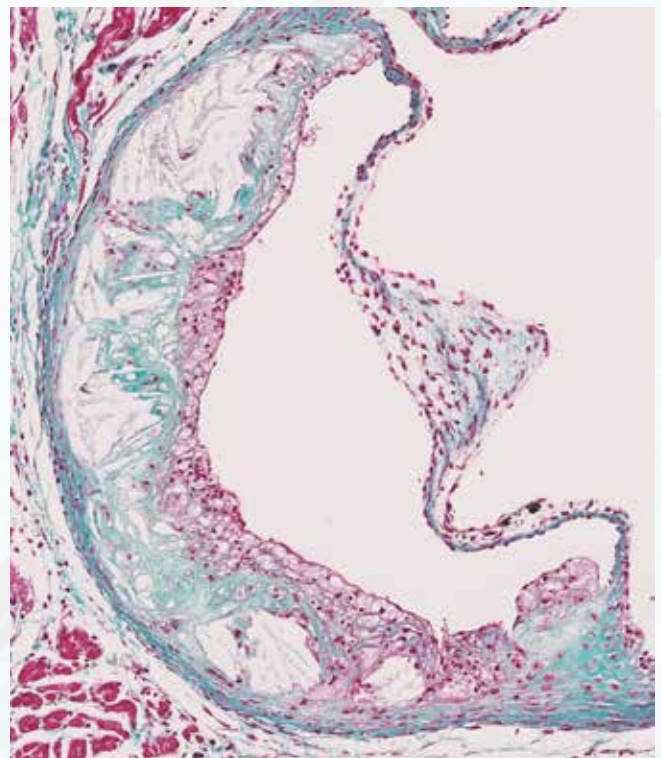
Atherosclerotic plaque in a mouse model of atherosclerosis

MYOCARDIAL HOMEOSTASIS AND CARDIAC INJURY

Coordinator: Enrique Lara-Pezzi

Clinical leader: Borja Ibáñez

The research groups forming the Myocardial Homeostasis and Cardiac Injury (MERCURY) Program investigate the genetic, molecular, and biomechanical mechanisms underlying myocardial injury and the development of inherited cardiomyopathies. MERCURY groups also investigate the development of new therapies based on these mechanisms.

Despite the development of diverse cancer therapies, for many cancers the first line treatment remains chemotherapy with anthracyclines. One of the most feared side effects of these drugs is irreversible cardiac injury, which affects many patients. Alternative treatments include immune checkpoint inhibitors (ICIs), which are monoclonal antibodies that target host negative immune regulatory receptors. While effective for cancer treatment, this approach can also be cardiotoxic, inducing myocarditis, which is associated with high mortality. Understanding remains limited about the mechanisms by which anthracyclines and ICIs induce cardiac damage, as well as the factors that determine variable interindividual vulnerability to these cytotoxic effects. This knowledge deficit translates into a lack of effective therapies able to prevent or reverse this cardiac pathology.

A major goal of the MERCURY Program is therefore to define the pathways and mechanisms underlying the cardiotoxic effects triggered by anthracyclines and ICIs used to treat cancer. We aim to identify the main determinants of this type of myocardial injury and then to develop new therapeutic approaches based on the inhibition of these pathways.

A second main area of interest of the MERCURY Program investigators is the genetic basis of inherited cardiomyopathies (CMs). Although genetic testing has evolved rapidly over the last decade and is now an established element of the clinical management of patients and their families, the current yield of genetic testing, even in familial cases (with two or more family members affected), is around 40%, and most cases remain unexplained. Furthermore, most genetic heart conditions are treated with drugs developed for generic cardiac pathologies, such as heart failure or cardiac arrhythmias. For most CMs, there are no specific disease-modifying treatments.

Our researchers are working to identify new disease-causing mutations in noncoding regions, chiefly introns, and are investigating the molecular basis of genetic cardiomyopathies. We are also developing large animal models of hypertrophic and arrhythmogenic cardiomyopathies, based on the success of our previous mouse models, and we aim to use these models to develop new gene therapy tools and identify small molecules with the potential to improve cardiac function.

The MERCURY Program relies on the combination of our research teams' strong complementary expertise in biomechanics, molecular biology, physiology, immunology, and genetics. This complementary approach will provide each of the tasks with additional granularity. Importantly, the whole project has a clearly translational orientation, aimed at developing new diagnostic and therapeutic tools.

MERCURY PROGRAM ACHIEVEMENTS IN 2022

- First demonstration that anthracycline therapy is associated with progressive and irreversible damage to the microcirculation, even in the absence of cardiac contractile deficits.

- Description of how the stiffness of the giant protein Titin is regulated by oxidation of conserved cysteines.

- Development of a new risk score to predict pathogenic genotypes in patients with dilated cardiomyopathy. The combination of this genetic testing with late gadolinium enhancement cardiac magnetic resonance imaging improves diagnosis and provides more precise patient selection criteria for primary prevention with an implantable cardioverter-defibrillator.

- New insights into dilated cardiomyopathy caused by mutations in MYH7, which is characterized by an early age of onset, high phenotypic expression, low left ventricular reverse remodeling, and frequent progression to heart failure.
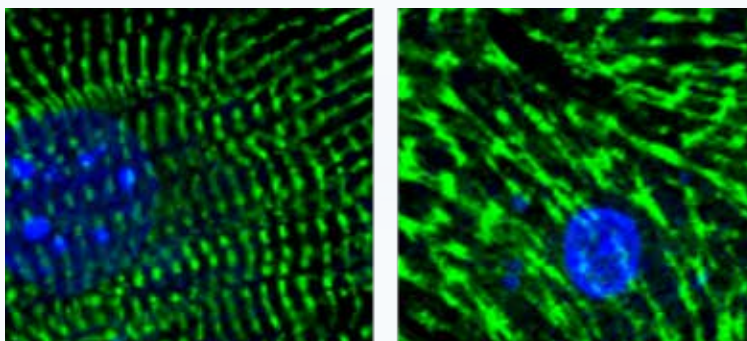
Sarcomere disarray in heart disease. Side-by-side comparison of a healthy cardiomyocyte with an intact sarcomere pattern (left) and a sick cardiomyocyte (right). Credit: Maria Rosaria-Pricolo.

RESEARCH GROUPS

- **Jorge Alegre-Cebollada**
  Molecular Mechanics of the
  Cardiovascular System

- **Pablo García-Pavía**
  Inherited Cardiomyopathies

- **Borja Ibáñez**
  Translational Laboratory for
  Cardiovascular Imaging and Therapy

- **Enrique Lara-Pezzi**
  Molecular Regulation of Heart Failure

Collaborator:
Juan A. Bernal
Viral Vectors Unit

Loss of sarcomere structure in a dying cardio-myocyte. A sick cardiomyocyte (center) with severely deteriorated sarcomere structure. Credit: Miguel López-Unzu.
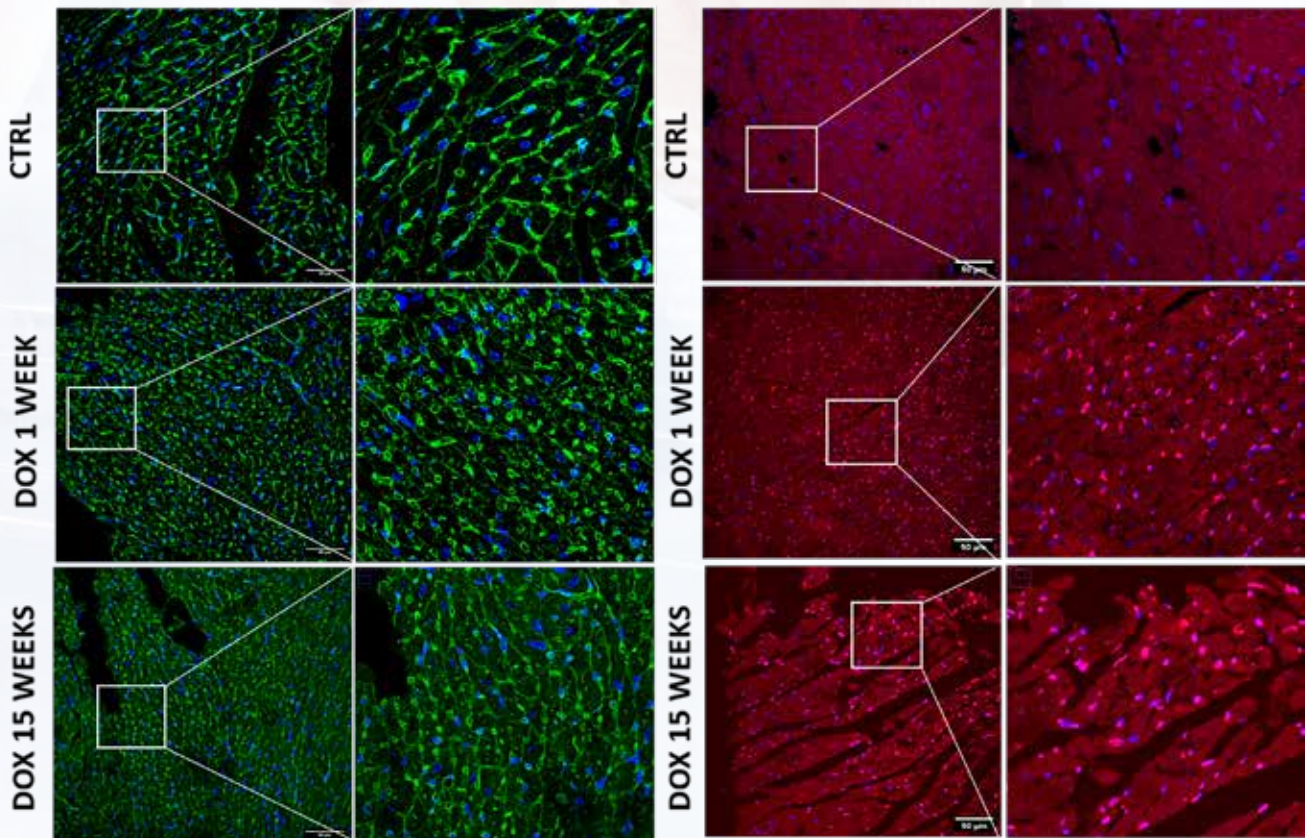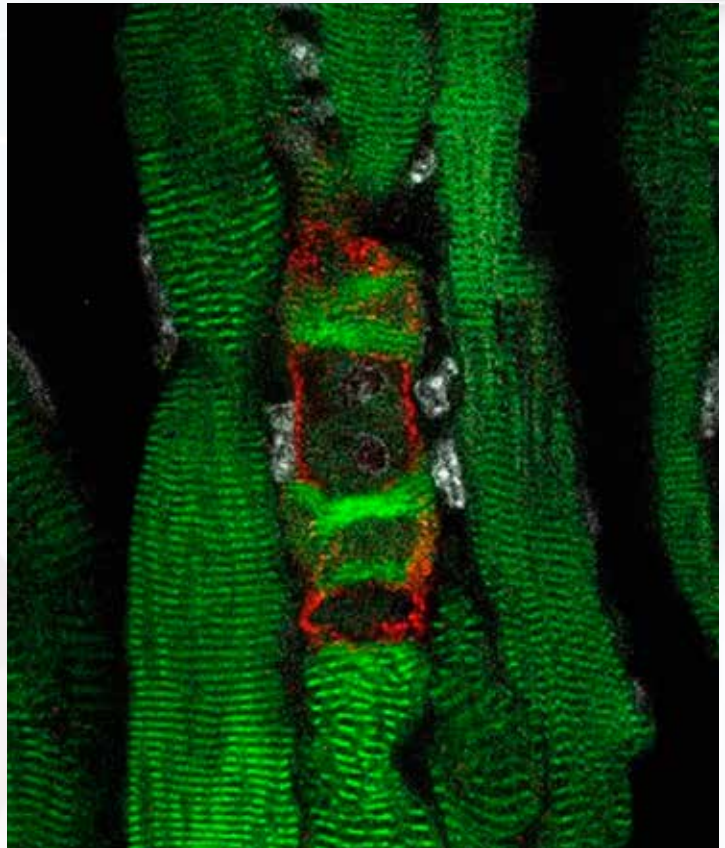
Anthracycline-induced cardiotoxicity. Adult CD1 male mice received 5 weekly intraperitoneal injections of 5 mg/kg doxo-rubicin (DOX) (25 mg/kg cumulative dose). Cardiomyocyte area was reduced and apoptosis increased in mice at 1 and 15 weeks after DOX treatment. Credit: Laura Cádiz.

CARDIOVASCULAR REGENERATION

Coordinator: Miguel Torres

Clinical leader: Hesham Sadek

Heart failure is a major worldwide epidemic that has an immense societal impact in avoidable deaths, morbidity, and an unsustainable economic burden. Several end-stage heart conditions are linked to the irreversible loss of myocardial tissue. This inability to restore the lost myocardium reflects the poor regenerative response of the adult human heart and frequently leads to fatal heart failure. The Cardiovascular Regeneration Program explores ways to activate heart regeneration as a therapeutic strategy. New knowledge about myocardial tissue growth during heart development and the mechanisms of natural heart regeneration in fish and neonatal mammals has identified pro-regenerative cellular and molecular pathways. Based on this knowledge, we are designing new strategies to activate adult mammalian heart regeneration. Our main translational goal is to develop new therapies for heart remuscularization, thereby reverting the conditions that lead to heart failure. To achieve our goals, we are currently concentrating our efforts in 3 main areas: 1) discovering molecular pathways and cellular functions that promote cardiovascular regeneration; 2) identifying small molecules and the design of biotechnological products that efficiently target cardiovascular pro-regenerative pathways in small experimental animals; and 3) promoting the translation of identified therapeutic strategies to clinical applications.

In 2022, the Cardiovascular Regeneration Program consolidated its faculty, recruiting Prof. Hesham Sadek as a new PI and Clinical Leader of the Program.

The Program has developed strong collaborative projects, and the results of these coordinated efforts have started to yield important results.

In the field of cardiac development, Dr Mercader identified a molecular pathway involved in cardiomyocyte lineage specification in the zebrafish. While the cardiomyocyte lineage is believed to be fully specified after gastrulation, Dr Mercader's group showed that the transcription factor WT1 was able to derail cardiomyocytes from their lineage, transforming them into epicardial cells. These findings challenge the established view on how the cardiomyocyte lineage is specified and maintained within its correct fate (Development, 10.1242/dev.200375, 2022). Also working on cardiac development but in the mouse model, Dr Torres' team generated the first 3D+t Atlas of mouse heart-tube formation. This new Atlas allows the quantitative study of evolving heart morphology and the comparison of mutant and normal development. Using these tools, the Torres' team was able to identify the first left-right asymmetry in the developing mouse heart and to determine the genetic basis of this asymmetry (Nature Cardiovascular Research, 1:504-517, 2022)

In the field of regenerative biology, the groups led by Drs Muñoz-Cánoves and Enriquez have collaborated to identify how metabolic regulation and mitochondrial dynamics regulate muscle regeneration in the mouse (Cell Stem Cell 29:1298-1314, 2022). The group led by Dr Hidalgo developed a highly innovative classification of innate immune cells based on their motility patterns in vivo. This approach identified a population of neutrophils associated with damaging inflammatory responses to injury. The inactivation of this population led to improved recovery after experimental myocardial infarction in mice (Nature 601:415-421, 2022), thus identifying new routes to intervention in acute myocardial infarction.
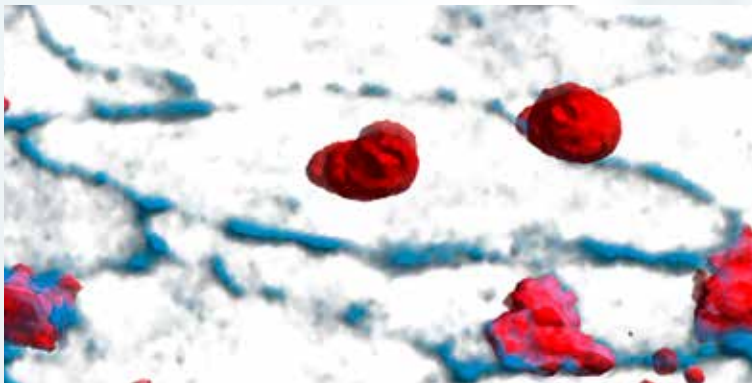
Neutrophils moving on an inflamed vascular bed. Each immune cell displays unique morphokinetic patterns that can be used to classify them. (Nature 601:415-421, 2022)
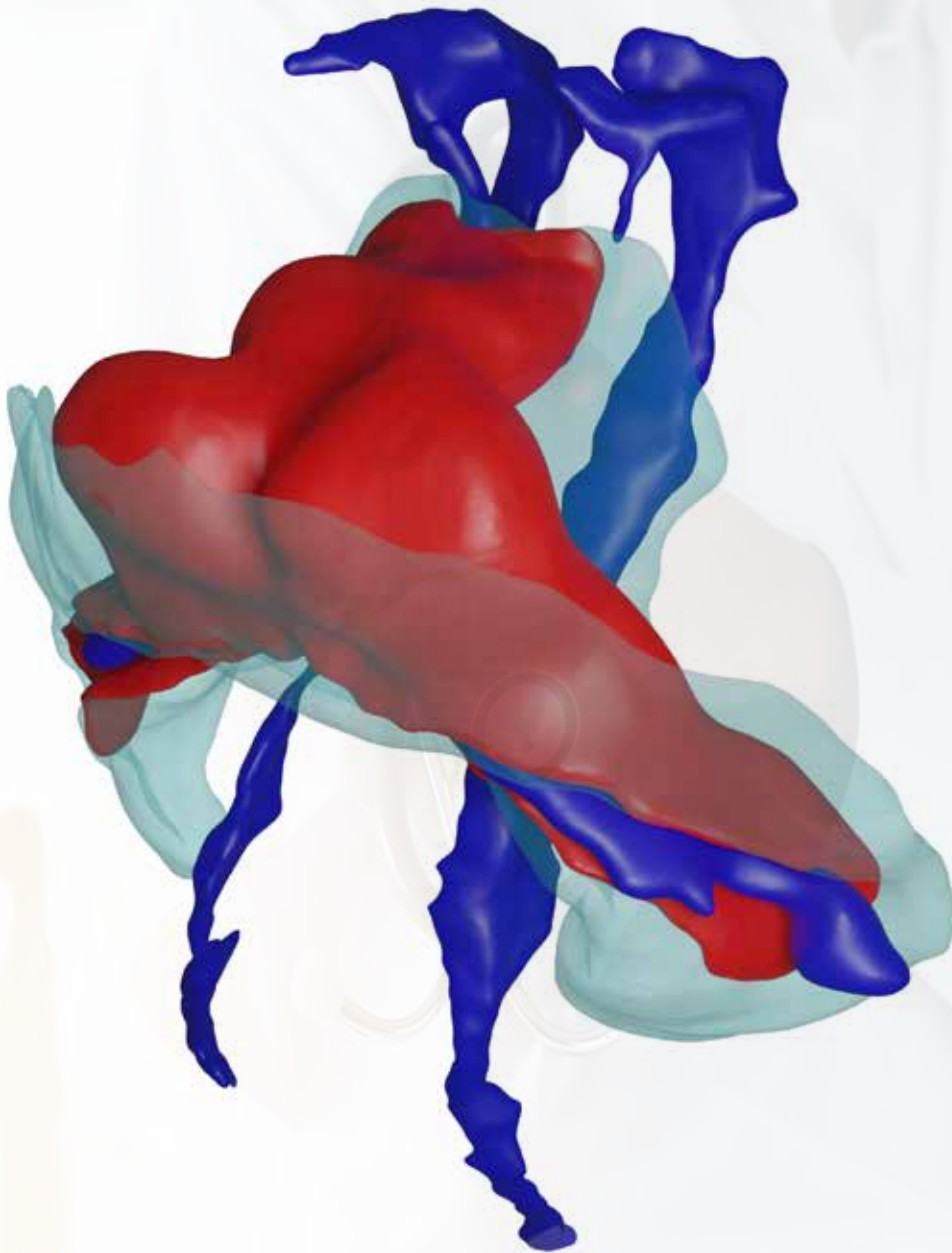
Rendering of myocardial tissue (red), splanchnic mesoderm (transparent blue), and aortic and endocardial endothelium (blue) at a specific stage of heart-tube formation in the mouse (Nature Cardiovascular Research 1:504-517, 2022)

RESEARCH GROUPS

- **Rui Benedito**
Molecular Genetics of Angiogenesis

- **Jose Luis de la Pompa**
Intercellular Signaling in Cardiovascular Development and Disease

- **Jose Antonio Enríquez**
Functional Genetics of the Oxidative Phosphorilation System (GENOPHOS)

- **Andrés Hidalgo**
Imaging the Cardiovascular Inflammation and the Immune Response

- **Nadia Mercader**
Development of the epicardium and its role during regeneration

- **Pura Muñoz**
Tissue Regeneration

- **Mercedes Ricote**
Nuclear Receptor Signaling

- **Hesham Sadek**
Myocardial regeneration via cardiomyocyte cell cycle regulation

- **Miguel Torres**
Genetic Control of Organ Development and Regeneration

# NOVEL ARRHYTHMOGENIC MECHANISMS

Coordinator: Silvia Priori

Clinical leader: David Filgueiras

Arrhythmia research has historically been performed by scientists specialized in recording electrical signals in hearts and isolated cardiomyocytes. The electrophysiological properties of single channels have been dissected and in silico models devised to gain a mechanistic understanding of arrhythmogenesis in highly controlled experimental settings. But this specialization has prevented integration of electrophysiological findings with major advances in cell biology, genomics, epigenetics, and systems biology, and this integrated knowledge is essential for understanding arrhythmogenesis in more complex scenarios in vivo. Under the leadership of recently recruited world authorities in arrhythmia research, the CNIC Novel Arrhythmogenic Mechanisms program studies electrical properties and arrhythmogenesis in the context of cardiac energetics and ion-channel plasticity and pleiotropy by bringing electrophysiologists to work together with molecular biologists, geneticists, and experts in metabolism, energetics, and cell signaling. Program scientists currently investigate inherited and acquired arrhythmias, with a primary focus on the cell pathways

and cardiac remodeling in each disease that are associated with arrhythmia maintenance and the development of potentially lethal ventricular arrhythmias.

The Novel Arrhythmogenic Mechanisms program aims to integrate biological and computational data from a multidisciplinary perspective to achieve novel understanding of the mechanisms associated with complex cardiac arrhythmias. This will enable us to develop more advanced and personalized predictive models for risk stratification of the arrhythmogenic substrate and lethal ventricular arrhythmia associated with sudden cardiac death.

Program investigators have already implemented highly translational animal models to study the phenotype and proarrhythmic substrate of pigs with dilated cardiomyopathy, ischemic cardiomyopathy (Figure 1), and long-QT syndrome. Arrhythmogenic mechanisms have been investigated from subcellular analysis to the whole organ in isolated heart preparations using computational models and advanced optical
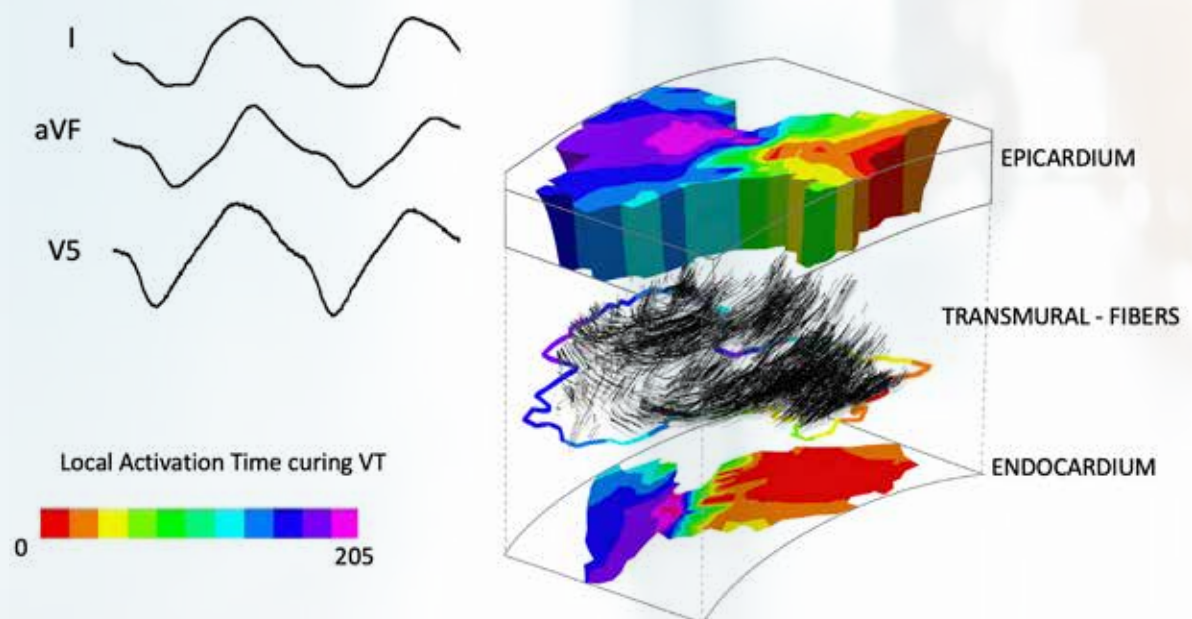

Figure 1. Visualization of the 3D transmural myocardial fiber substrate associated with ventricular tachycardia (VT) maintenance in the pig model of ischemic cardiomyopathy and inducible ventricular arrhythmia. Top left, VT morphology on the surface ECG. Right, color-coded activation map of the epicardial and endocardial surface during VT. The 3D fiber distribution across the myocardial wall in the region associated VT maintenance shows disorganized myocardial fibers.

mapping (Figure 2). Ongoing studies in patient populations are aimed at validating our experimental results.

Some of our most important results have shown that time-course changes in cardiac electrical parameters can predict lethal ventricular arrhythmia in heart failure substrates associated with ischemic or non-ischemic cardiomyopathy. Moreover, novel antiarrhythmic approaches have been tested in the long-QT syndrome pig model, opening the possibility for novel clinical breakthroughs to prevent sudden cardiac death in patients with channelopathies. In vivo endocardial and epicardial mapping in the pig knock-in model of LQT8 has allowed us to identify a novel arrhythmogenic mechanism underpinning the observed 30% rate of sudden death (Figure 3).

RESEARCH GROUPS

- **David Filgueiras**
  Advanced Development in Arrhythmia Mechanisms and Therapy

- **Silvia Priori**
  Molecular Cardiology
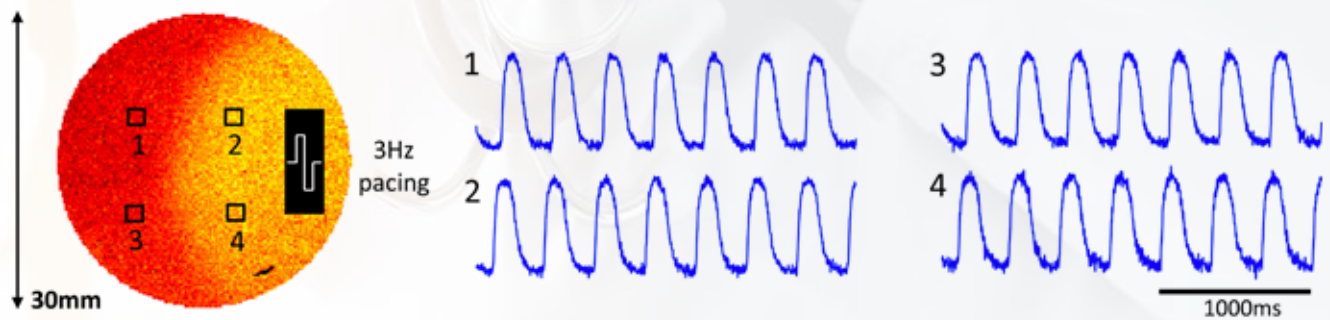
Figure 2. Imaging action potentials using a genetically encoded voltage indicator in human induced pluripotent stem-cell-derived cardiomyocytes. Sample action potentials (normalized signals) recorded in 4 locations in a monolayer during 3 Hz electrical pacing. The stimulation site is indicated by the black rectangle. (Data obtained in collaboration with Dr. Michael Laflamme, McEwen Stem Cell Institute, University Health Network, Toronto, Canada)
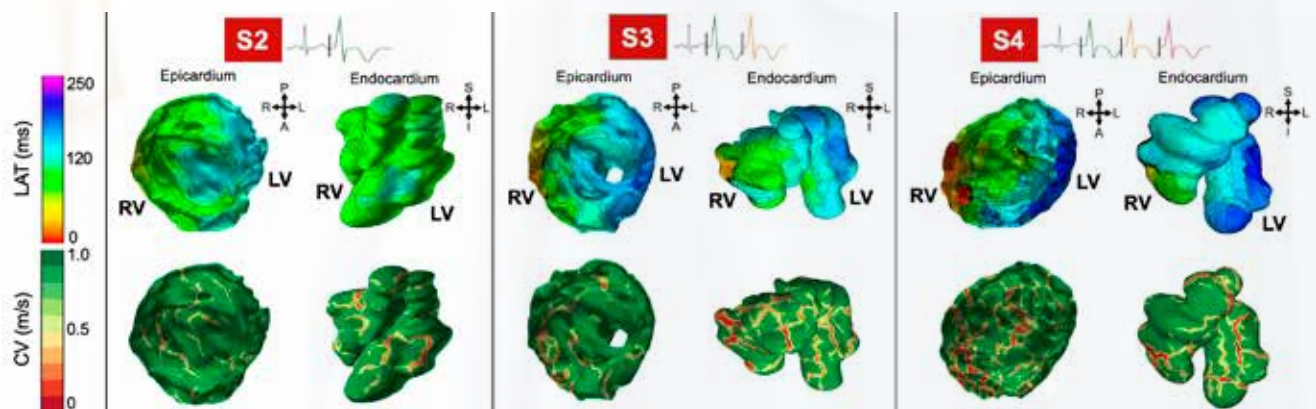
Figure 3: Electroanatomic mapping in a Long QT Syndrome type 8 (LQT8) pig model.
This figure illustrates high-density electroanatomic mapping of both the epicardial and endocardial surfaces (LV = left ventricle, RV = right ventricle) in a genetically engineered pig model of LQT8 (also known as Timothy Syndrome type 1). The maps display key electrophysiological parameters, including local activation time (LAT) and conduction velocity (CV). The progressive delivery of premature ventricular extrasystoles (shown as S2 to S4) results in the gradual elongation of activation times, culminating in the emergence of conduction blocks, highlighted by red areas on the CV maps. These findings suggest the presence of a functional arrhythmogenic substrate in this LQT8 model.

CARDIOVASCULAR
RISK FACTORS AND BRAIN FUNCTION

Coordinator: María Ángeles Moro

Clinical leader: Valentín Fuster

The principal cause of the escalating epidemic of cardiovascular disease is the increasing prevalence of modifiable cardiovascular risk factors. Of particular concern is the alarming increase among young people of obesity and its detrimental consequences, such as cardiometabolic syndrome. Even at subclinical stages of atherosclerosis, cardiovascular and cardiometabolic risk factors (CVMRFs), together with the progressive aging of the population, significantly contribute to the development of cerebrovascular diseases, including cognitive decline, a growing concern worldwide.

The Cardiovascular Risk Factors and Brain Function Program is a collaborative multidisciplinary effort of six research groups with complementary expertise, dedicated to elucidating the mechanisms underlying cardiovascular-driven brain dysfunction. The Program's scientific activities are optimally supported by the state-of-the-art technology provided by the Technological Development Program. A key area of interest in the Program is in understanding how subclinical atherosclerosis and CVMRFs impact the integrity of the cerebral vasculature and disrupt the homeostasis of neuroimmune interfaces involved in brain clearance mechanisms. These consequences ultimately compromise brain function, metabolism, and structure, leading to cerebrovascular pathology, cognitive decline, and other brain disorders. The ultimate goal of the Program is to develop preventive strategies that promote healthy brain aging.

This overarching goal is addressed through three structured research areas:

1) The association between atherosclerosis and Alzheimer's disease (AD) at preclinical stages.

2) The impact of CVMRF burden on cerebral vasculature, including the intravascular compartment.

3) The mechanisms leading to CVMRF-induced impairment of neuroimmune interfaces and brain clearance mechanisms.

RESEARCH HIGHLIGHTS

Researchers in the Cardiovascular Risk Factors and Brain Function Program in collaboration with Marta Cortés Canteli (CNIC and IIS-FJD), have investigated the link between AD and vascular changes. Similar to cardiovascular disease, AD has a long preclinical stage, and cardiovascular disease and AD share many risk factors, including obesity, smoking, hypertension, sedentary lifestyle, and elevated blood cholesterol and glucose. Clinical interventions targeting these risk factors have shown cognitive benefits. Our scientists have shown that subclinical atherosclerosis and cardiovascular risk are associated with brain hypometabolism in asymptomatic individuals in their 50's enrolled in the Progression of Early Subclinical Atherosclerosis study. We are currently analyzing longitudinal changes in brain metabolism associated with subclinical atherosclerosis and cardiovascular risk and
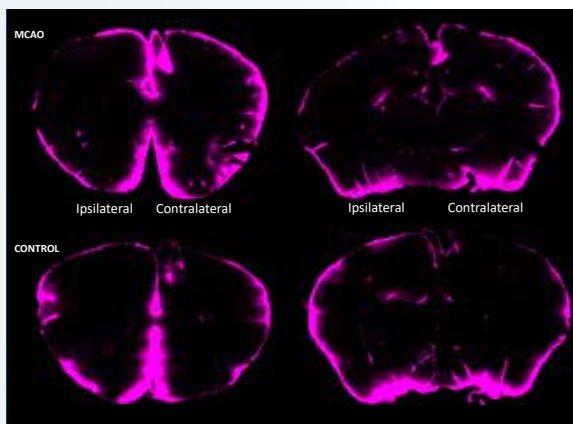
Stroke-induced glymphatic dysfunction. Brain-wide trace distribution of a CSF tracer (BSA, Alexa Fluor 647 labeled) in mouse brain sections of control (BOTTOM) and ischemic (MCAO; TOP) mice, showing stroke-induced glymphatic dysfunction
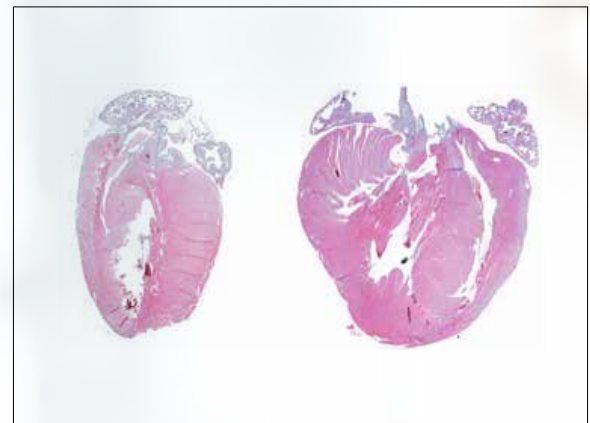
Histology comparing the size of the heart of a normal wild type mouse (left) and a mouse deficient for MKK6 (right).

RESEARCH GROUPS

- **Héctor Bueno**
  Multidisciplinary Translational Cardiovascular Research (MTCR)

- **Valentín Fuster**
  Cardiovascular Imaging and Population Studies

- **Pilar Martín**
  Regulatory Molecules of Inflammatory Processes

- **María Ángeles Moro**
  Neurovascular Pathophysiology

- **Juan Miguel Redondo**
  Gene regulation in Cardiovascular Remodelling and Inflammation

- **Guadalupe Sabio**
 Stress kinases in Diabetes, Cancer and Cardiovascular Disease

quantifying blood-based biomarkers of axonal injury, astrocytosis, and AD. In addition, Program scientists are developing plasma and neuroimaging biomarkers of AD based on disease factors such as procoagulant and immunothrombotic states identified in the disease.

The role of immunothrombosis in brain cognitive impairment driven by vascular dysfunction is one of the main interests of the Program. Our scientists have unraveled different roles of immune cells in cerebrovascular disease, as well as mechanisms of neutrophil-mediated immunothrombosis, including the generation of neutrophil extracellular traps (NETs) in stroke and vascular cognitive impairment, and have developed a novel TLR4 inhibitor, ApTOLL, for the treatment of acute stroke. Program scientists also investigate how neural substrates of cognition, specifically adult hippocampal neurogenesis, are damaged in stroke and vascular-driven dementia.

In the heart, a longitudinal study has demonstrated the crucial role of the MKK3/6-p38γ/δ pathway in cardiac hypertrophy, urging caution regarding the potential cardiotoxicity of the long-term clinical use of p38α inhibitors. Program scientists are now studying the role of this pathway in brain physiology and disease.

Using mouse models of aortic disease and advanced complementary approaches, one of our teams has identified novel mediators and signaling pathways involved in pathological vascular wall remodeling in syndromic and nonsyndromic aortic diseases and hypertension. Some of these mediators have been validated in humans and are potential therapeutic targets and disease biomarkers. A novel mouse model developed by the group demonstrates resistance to hypertension through specific knockdown of newly identified mediators of angiotensin II signaling in smooth muscle cells. Program scientists are currently investigating the role of these mediators and vascular smooth muscle cells in hypertensive brain dysfunction, a study that may contribute to the identification of new biomarkers and therapeutic targets for hypertension, as well as the prevention and treatment of brain dysfunction in vascular cognitive impairment.

The study of immune receptors by Program members has revealed that the expression of CD69 in regulatory T cells plays a key role in the regulation of inflammation after a cardiac ischemic event and in myocardial remodeling. High expression of this receptor in peripheral blood leukocytes after a heart attack is associated with a lower risk of hospitalization due to heart failure at 2.5 years. Immune changes after a cardiovascular event are also controlled by microRNAs, and Program members are studying the involvement of certain miRNAs in the impairment of cognitive function in a high-salt diet model.
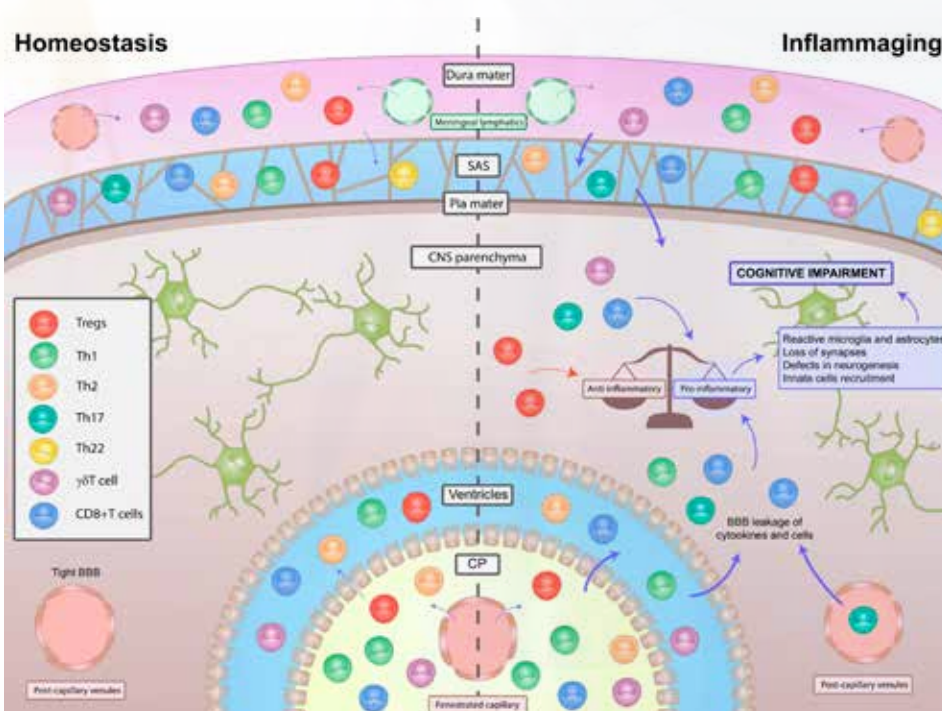
Role and location of T cell subsets in homeostasis and inflammaging in different brain compartments. In homeostatic conditions (left), the vascular blood-brain barrier, the blood-CSF barrier, and the meningeal barrier limit the access of the T cell population to the CNS. In the context of aging (right), these barriers are compromised by increased pro-inflammatory cytokine release, allowing the entry of mostly CD8+ T cells, T regulatory cells, and other effector T cells into the parenchyma. If the contribution of the different cytokine signatures results in a pro-inflammatory microenvironment, the effects on resident immune cells, glia, and neurons can induce cognitive impairment.

CARDIOVASCULAR HEALTH PROMOTION

Coordinator: Rodrigo Fernández-Jiménez

Clinical leader: Valentín Fuster

Cardiovascular disease is one of the leading causes of death and disability worldwide, and it high prevalence and impact are largely the result of risk factors that are modifiable by changes in behaviour (smoking, unhealthy diet, physical inactivity, etc.). The problem is expected to deteriorate in the near future due to the disturbing increase in the prevalence of unhealthy lifestyles and obesity, particularly among children.

The Cardiovascular Health Promotion Program research teams work on multidisciplinary studies and clinical trials in close collaboration with schools and communities, targeting both children and adults, and developing research applications and strategies for noninvasive technologies to support translational research and population studies on preclinical atherosclerosis.

The ultimate goal of the Program is the implementation of health promotion and prevention strategies as an effective means to reduce the burden of cardiovascular disease in individuals and society, and potentially increase life expectancy free of other diseases such as dementia or cancer. The key objectives of the Program are as follows:

1) To refine primordial prevention strategies in children and adolescents.

2) To improve global primary prevention by impacting on subclinical development and progression of atherosclerosis in young adults.

3) To translate initiatives for health promotion to society.

The Program includes two principal research groups: the Cardiovascular Imaging and Population Studies group (PI: Valentin Fuster) and the Cardiovascular Health and Imaging Lab (PI: Rodrigo Fernández-Jiménez). Projects and activities developed during 2022 generated relevant scientific advances, some of which are highlighted below.

CNIC researchers from the Cardiovascular Health Promotion Program led the H2020-funded SECURE trial. This multinational
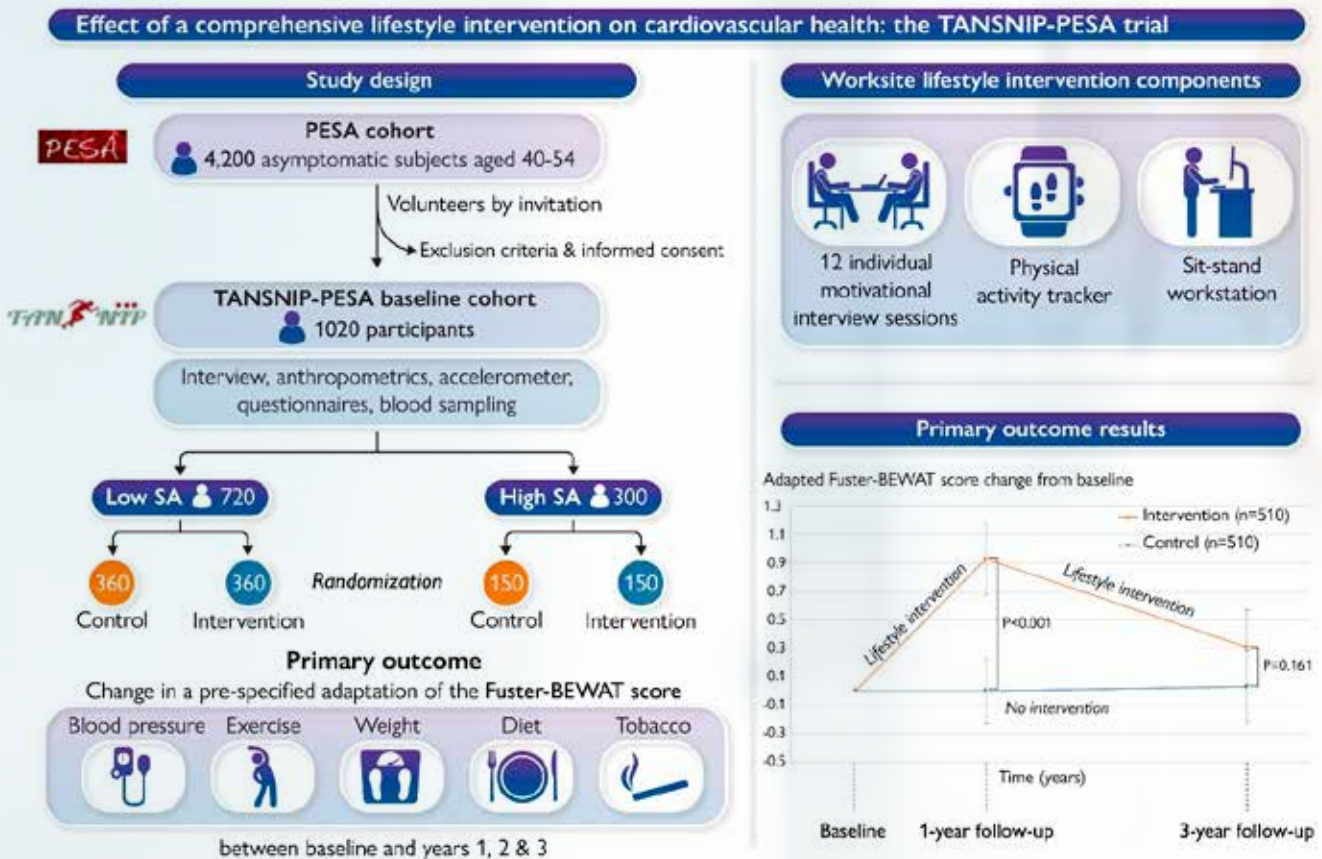
Figure 1. Summary of the design and primary outcome results of the TANSNIP-PESA trial [Eur Heart J. 2022;43(38):3732-3745].

randomized clinical trial tested the hypothesis that the CNIC-Ferrer polypill would improve patient adherence to secondary cardiovascular prevention medications. The primary results of the trial demonstrated that treatment with this polypill after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care [N Engl J Med. 2022;387(11):967-977. doi: 10.1056/NEJMoa2208275].

In the TANSNIP-PESA randomized control trial, we demonstrated that a worksite-based lifestyle program to promote cardiovascular health in middle-aged bank employees was associated with a significant improvement in cardiovascular health and behavioral metrics, although the effect attenuated after 1 year as the intensity of the intervention was reduced [Eur Heart J. 2022;43(38):3732-3745. doi: 10.1093/eurheartj/ehac378]. (**Figure 1**)

Taking advantage of the PESA cohort and using state-of-the-art whole body vascular 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging, we demonstrated that bone marrow activation is associated with early atherosclerosis [Eur Heart J. 2022;43(19):1809-1828. doi: 10.1093/eurheartj/ehac102]. We also validated a new 3-dimensional volumetric ultrasound method for accurate volume quantification of atherosclerotic plaques located in the carotid and femoral arteries [JACC Cardiovasc Imaging. 2022;15(6):1124-1135. doi: 10.1016/j.jcmg.2022.01.005]. (**Figure 2**)

Also we outlined the key lessons learned over 10 years of experience in implementing the SI! Program (Salud Integral–Comprehensive Health) for cardiovascular health promotion in preschool settings in 3 different countries: Colombia, Spain, and the United States [J Am Coll Cardiol. 2022;79(3):283-298. doi: 10.1016/j.jacc.2021.10.046. In addition, researchers from the Program acted as expert advisors for the Spanish High Commission Against Childhood Poverty (*Alto Comisionado de Lucha contra la Pobreza Infantil*) to elaborate the National Plan for the Reduction of Obesity in Children and Adolescents 2022-2030 (*Plan Nacional para la Reducción de la Obesidad Infantil 2022-2030*).

RESEARCH GROUPS

- **Rodrigo Fernández-Jiménez**
  Cardiovascular Health and Imaging

- **Valentín Fuster**
  Cardiovascular Imaging and Population Studies
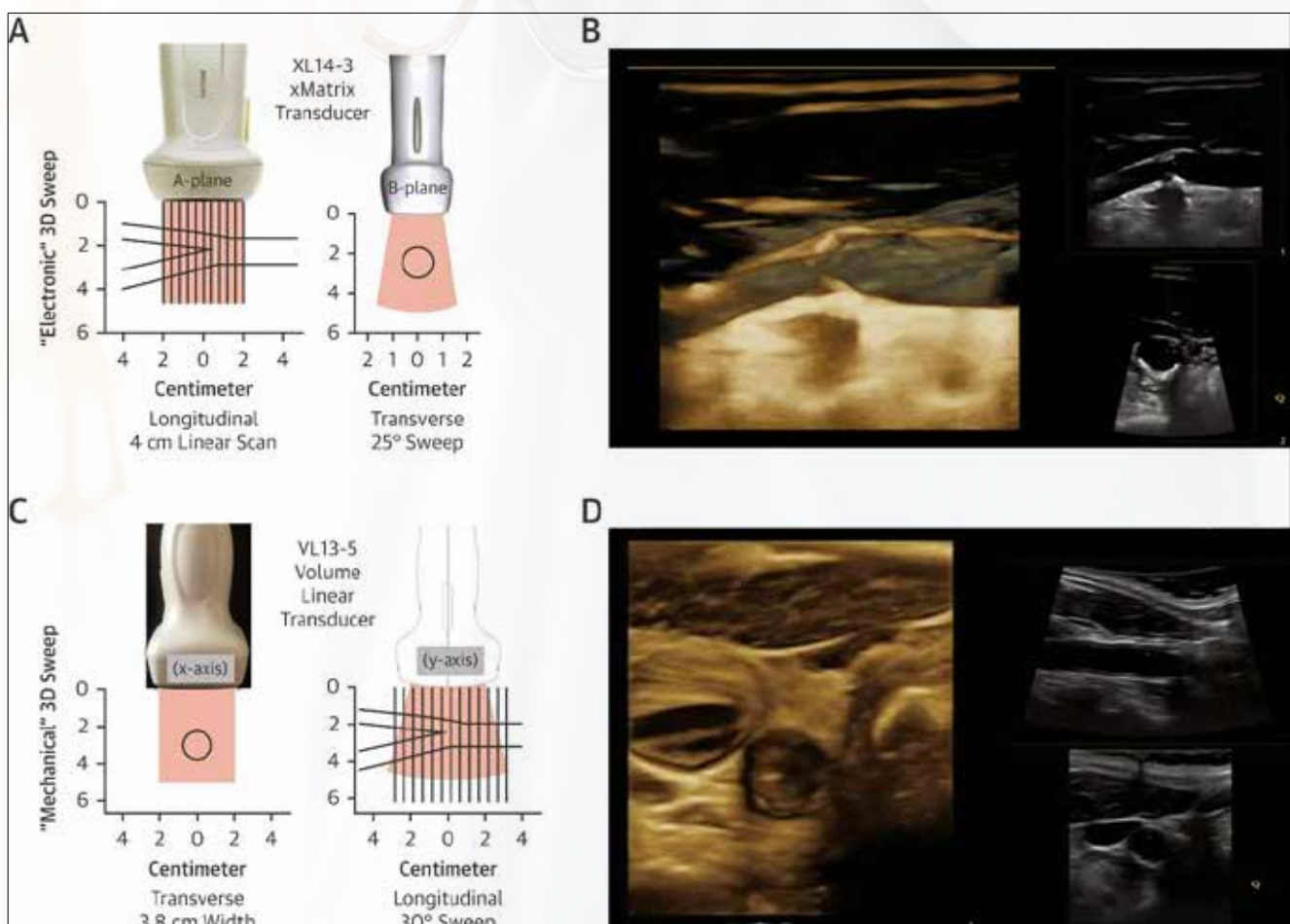
Figure 2. Technical features and examples of electronic and mechanical 3D-sweep acquisitions for the clinical evaluation of carotid atherosclerotic burden [JACC Cardiovasc Imaging. 2022;15(6):1124-1135].
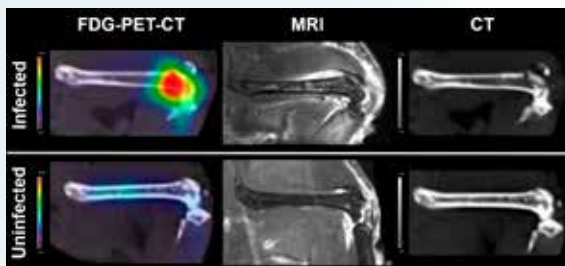
2.1.7
TECHNOLOGY
DEVELOPMENT

Coordinator: Beatriz Álvarez

The 11 Technical Units work to keep the CNIC at the forefront of cardiovascular research by developing and implementing cutting-edge biomedical technologies, providing internal and external services, and engaging in training and scientific collaborations in funded projects (https://www.cnic.es/en/investigacion/unidades-tecnicas).

Our work falls into 4 key areas:

1. Contributing to the strategical plans of the center by aligning our activities and vision to the ongoing Scientific Programs

2. Examining the latest technological advances relevant to the CNIC Scientific Programs for upgrading and innovation

3. Improving communication and protocol flows in coordination with the CNIC Direction, Administration, Governance Committees (Infrastructure, Computing, Innovation, etc.), and Research Groups

4. Guaranteeing ISO quality and reliability to infrastructure support and service

In 2022, we unified the organization of the Units, introducing standardized yearly user satisfaction surveys, an ISO certification process with the recruitment of a quality laboratory manager, and measures to configure the OTRS incident management system and channel the Units' needs in the committee advisory groups.

TECHNICAL UNITS

- Bioinformatics
  Fátima Sánchez Cabo

- Clinical Trial Coordination
  Antonio J. Quesada

- Comparative Medicine

- Flow Cytometry
  Beatriz Álvarez

- Genomics
  Ana Dopazo

- Imaging
  Manuel Desco

- Microscopy
  Valeria Caiolfa

- Pluripotent Cell Technology
  Gionanna Giovinazzo

- Proteomics
  Juan Antonio López

- Transgenesis
  Juan De Dios Hourcade

- Viral Vectors
  Juan A. Bernal

Study of infected and inflammatory (uninfected) lesions in mice using preclinical molecular imaging techniques
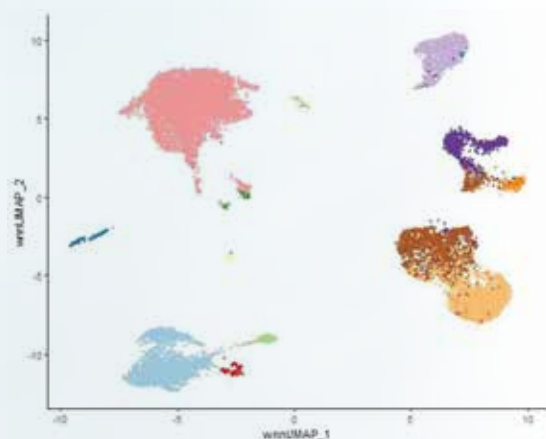
Single-cell Data Analysis and VISualization scDAVIS
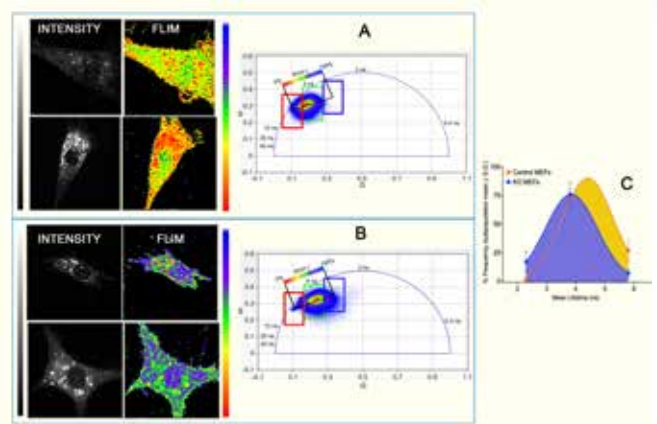
Phasor-fluorescence lifetime imaging (flim) analysis in living cells.

Expanded and hatched pig blastocyst developed after in vitro fertilization and in vitro culture for 6 days

Spectral Cell Sorter Cytometer

Purified hiPSC-derived cardiomyocytes

Cardiac disease model generated by Adeno-associated virus (AAV) transduction.

NovaSeq 6000 Sequencing System

2.2 CLINICAL STUDIES

EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS, DISEASE PROGRESSION, AND CARDIOVASCULAR HEALTH

(PESA-HEALTH-CNIC-SANTANDER STUDY)

Principal Investigator: *Valentín Fuster*

The PESA-Health-CNIC-Santander study is the natural continuation of the long-term endeavor started in 2010 with the PESA Study, carried out by the CNIC in collaboration with Santander Bank. Within PESA-Health, the PESA participants enrolled in 2010 (4184 asymptomatic individuals between the ages of 40 and 55 years at enrollment) are being actively followed up over an additional 10 years.

The original aim of the study was to identify the presence of subclinical atherosclerosis (SA) long before symptoms appear and to understand the cues leading to its development and progression. PESA-Health expands these objectives to new areas, such as the correlation of SA with Alzheimer's and cognitive diseases, the acquisition of somatic mutations during aging, and the correlation of these mutations with increasing cardiovascular event rates and SA progression. PESA-Health continues to take advantage of multiple state-of-the-art imaging technologies, including 3D

vascular ultrasound of the carotid arteries and aorta, coronary artery calcium quantification by computed tomography, cardiac magnetic resonance, AngioTC, PET, and PET-amyloid analysis, as well as biosampling for omics analysis. In addition, new state-of-the-art substudies have been added, including an investigation into the relationship between sleep apnea and SA.

PESA-Health is the CNIC's flagship study, and several CNIC clinical and basic research groups participate in it. The PESA study is already making seminal contributions to our understanding of the origin and progression of atherosclerosis.

The PESA-Health-CNIC-Santander study welcomed its first participant in February 2020, taking advantage of the follow-up of the PESA cohort to continue and expand the scientific approaches performed. By the end of 2022, 3481 participants had agreed to continue their participation, and more than 2000 participants had completed their first PESA-Health visit.

SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE ELDERLY POPULATION

(SECURE)

Principal Investigator: *Valentín Fuster*
H2020 Grant# 633765

Adherence to treatment after acute myocardial infarction (MI) is essential for efficient secondary prevention. Despite this, many post-MI patients abandon prescribed medication. To address this issue, CNIC researchers and FERRER laboratories developed a "polypill" including three key drugs prescribed to post-MI patients (aspirin, an ACE-inhibitor, and a statin). Having demonstrated that prescription of the CNIC Polypill significantly increases treatment adherence among post-MI patients (J Am Coll Cardiol. 2014; 64:2071-82), CNIC researchers led a multinational randomized

clinical trial supported by the H2020 program. The SECURE trial (trial identifier NCT02596126) enrolled patients in 7 European countries (Spain, Italy, Germany, Czech Republic, France, Poland, and Hungary).

In this phase 3, randomized, controlled clinical trial, we assigned patients with myocardial infarction within the previous 6 months to a polypill-based strategy or usual care. The polypill treatment consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary composite outcome

REMOTE ISCHEMIC CONDITIONING IN LYMPHOMA PATIENTS RECEIVING ANTHRACYCLINES

(RESILIENCE)

Principal Investigator: *Borja Ibáñez*
H2020 Grant# 945118

Anthracyclines are a class of anticancer drugs that are widely used to treat many cancers. Of the 4 million new cancer cases diagnosed in Europe every year, >3 million receive anthracyclines (alone or in combination with other treatments). Very recent data show that >35% of patients receiving anthracyclines develop some form of cardiotoxicity. The trade-off between cancer and chronic heart failure (HF) places an immense psychological burden on cancer survivors, and for healthcare systems the growing incidence of chronic HF is a devastating consequence of cancer treatment.

Remote ischemic pre-conditioning (RIPC) is a process in which brief, reversible episodes of ischemia followed by reperfusion in one region (e.g. an arm) render remote tissues and organs resistant to injury. RIPC is safe and effective, noninvasive, feasible, and inexpensive. There is abundant experimental evidence that individuals undergoing 3 to 5 cycles of brief (5 min) limb ischemia followed by 5 min reperfusion have a degree of protection against subsequent induced myocardial infarction, having smaller infarcts than animals undergoing myocardial infarction without preceding cycles of RIPC. Recent evidence suggests that, to be protective, RIPC needs to be initiated before the index insult. Anthracycline-induced cardiopathy provides an ideal setting for testing this hypothesis because the chemotherapy is a planned procedure.

RESILIENCE is a multinational prospective proof-of-concept phase II, double-blind, sham-controlled, randomized controlled trial aimed at evaluating the efficacy and safety of RIPC in non-Hodgkin lymphoma (NHL) patients receiving anthracyclines. Patients scheduled to undergo ≥3 chemotherapy cycles and fulfilling all inclusion and no exclusion criteria will be enrolled and undergo baseline cardiac magnetic resonance (CMR) imaging and a high sensitivity troponin (hsTn) and NT-proBNP blood test. Patients with confirmed LVEF >40% by CMR will be randomized 1:1 to RIPC or simulated RIPC (Sham).

Nine weeks after finishing chemotherapy, a final CMR+ hsTn/NT-proBNP text will be performed. All patients will be followed up for clinical events at 12, 18, 30, and 42 months until the last patient undergoes the final CMR.

The RESILIENCE Trial aims to recruit 608 patients in 6 European countries (Spain, Portugal, France, Germany, The Netherlands, and Denmark) and is funded by the European Commission (Grant Agreement-945118-RESILIENCE). The grant period began in June 2021, and in 2022 patient recruitment began at 11 sites, with 46 participants enrolled so far.

was cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization. The key secondary endpoint was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke. The trial completed its follow-up phase by the end of October 2021, and the grant period came to an end in December 2021. A total of 2499 patients underwent randomization and were followed for a median of 36 months. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.60 to 0.96; P = 0.02). A key secondary-outcome event occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P = 0.005). The results were consistent across prespecified subgroups. Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group. Adverse events were similar between groups.

These results, published in the New England Journal of Medicine, demonstrate that treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction results in a significantly lower risk of major adverse cardiovascular events than usual care. (N Engl J Med. 2022 Sep 15;387(11):967-977. doi: 10.1056/NEJMoa2208275)

THE TANSNIP-PESA RANDOMIZED CONTROL TRIAL: A 30-MONTH WORKSITE-BASED LIFESTYLE PROGRAM TO PROMOTE CARDIOVASCULAR HEALTH IN MIDDLE-AGED BANK EMPLOYEES

Principal Investigator: *Valentín Fuster*

Existing tools for characterizing atherosclerosis and determining the risk of its complications are inadequate. These deficiencies limit effective management across the spectrum of this disease, and therefore opportunities are lost for early, cost-effective interventions in subclinical disease, while high-risk populations with manifest disease are administered treatments almost indiscriminately. This leads to high 'numbers needed-to-treat' (NNT), unnecessary patient risk, wasted resources, and unsustainable costs for healthcare purchasers. In a relatively low-risk population (the PESA-CNIC cohort), we studied whether a personalized worksite-based lifestyle intervention driven by imaging data (2D and 3D-ultrasound of the carotid and iliofemoral arteries and coronary artery calcification) resulted in changes in behavior, improved control of risk factors, and reduced progression of subclinical atherosclerosis plaque burden (SAPB). TANSNIP was a randomized control trial including middle-aged bank employees from the PESA cohort stratified by SAPB (high SAPB n=260; low SAPB n= 590). Within each stratum, participants were randomized 1:1 to join a lifestyle program or receive standard care. The program consisted of three elements: (1) 12 personalized lifestyle counseling sessions using motivational interviewing over a 30-month period; (2) a wrist-worn physical activity tracker; and (3) a sit-stand workstation. The primary outcome measure was a composite score of blood pressure, physical activity, sedentary time, body weight, diet, and smoking (the adapted FUSTER-BEWAT score) measured at baseline and at 1-, 2-, and 3-year follow-up. Secondary outcomes were individual changes in lifestyle behaviors and specific changes in anthropometric measures, blood biomarkers, self-rated health, work-related outcomes (including work productivity and absenteeism), health care consumption, program process measures, and cost measures at different measurement points.

We have analyzed the primary outcome between baseline and follow-up years 1–3. The baseline adapted Fuster-BEWAT score was 16.2±3.7 points in the intervention group and 16.5± 3.5 points in the control group. At year 1, the score improved significantly in intervention participants compared with controls [estimate 0.83 (95% CI 0.52–1.15) points]. However, intervention effectiveness decreased to non-significant levels at year 3 [0.24 (95% CI −0.10 to 0.59) points]. Over the 3-year period, the intervention was effective in participants having low baseline SAPB [0.61 (95% CI 0.30–0.93) points] but not in those with high baseline SAPB [0.19 (95% CI −0.26 to 0.64) points].

Thus, the lifestyle intervention in middle-aged asymptomatic adults was associated with a significant improvement in cardiovascular health and behavioral metrics. The effect attenuated after 1 year as the intensity of the intervention was reduced. (Eur Heart J. 2022 Oct 7; 43(38): 3732–3745. DOI: 10.1093/eurheartj/ehac378)
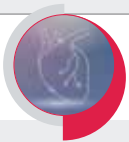
TREATMENT WITH BETA-BLOCKERS AFTER MYOCARDIAL INFARCTION WITHOUT REDUCED EJECTION FRACTION (REBOOT)

Principal Investigator: *Borja Ibáñez*

The prescription of beta-blockers to patients after a myocardial infarction (MI) is based on evidence from trials performed in the pre-reperfusion era. While there is solid evidence for the benefit of these drugs in post-MI patients with reduced ejection fraction, evidence is lacking for patients with a preserved ejection fraction. Despite this, more than 80% of post-MI patients in this category are prescribed beta-blockers for the rest of their lives. REBOOT is a multinational trial that will enroll 8600 post-MI patients with a left ventricular ejection fraction >40%. Patients are randomized to beta-blocker therapy (type and dose decided by the attending physician) or to no treatment. The primary endpoint is the composite of all-cause death, reinfarction, or heart failure admission during 3-year follow-up. This trial is coordinated by the CNIC Clinical Trials Coordination Unit and is run in close collaboration with the Mario Negri Institute of Research in Milan. In total, 77 hospitals in Spain and 29 in Italy are participating in this large-scale project, which will have a major impact on clinical practice.

The first patients were enrolled in October 2018, and 7650 had been recruited by the end of March 2023. The trial will finish enrollment during 2023.

NOVEL MITOCHONDRIA-TARGETED THERAPIES FOR CANCER TREATMENT-INDUCED CARDIOTOXICITY
(MATRIX)

Principal Investigator: *Borja Ibáñez*
ERC Consolidator Grant#819775

The MATRIX Project aims to develop new and innovative treatments for the cardiotoxicity associated with some cancer treatments. MATRIX will be jointly run by the CNIC and Fundación Jiménez Díaz (FJD) University Hospital within a collaborative framework established in 2015 to study myocardial diseases.

Great advances in the treatment of cancer—a disease with 4 million new diagnoses every year in Europe—sometimes come with a 'toll' to pay in the form of major adverse effects. One of the most common adverse effects is myocardial toxicity, which affects up to 25% of patients treated with the common anticancer drugs anthracyclines or trastuzumab. The cardiotoxic effects of these drugs can be very serious and condemn the cancer survivor to chronic heart failure or even death from this complication.

Cancer treatment-induced cardiotoxicity (CTiCT) can result in severe heart failure. The trade-off between cancer and chronic heart failure places an immense personal burden on patients, with physical and psychological consequences. Current therapies for CTiCT are suboptimal, featuring poor early detection algorithms and nonspecific heart failure treatments. Our recently published results and additional preliminary data indicate that CTiCT is associated with altered mitochondrial dynamics, triggering cardiomyocyte metabolic reprogramming. MATRIX adopts a holistic approach to tackling mitochondrial dysfunction in CTiCT. We propose that early-stage CTiCT could be reverted by metabolic reprogramming to shift mitochondrial substrate utilization. By refining a novel imaging-based algorithm recently developed by our group, we will achieve very early detection of myocardial damage in patients treated with commonly prescribed cancer therapies, long before clinically used parameters become abnormal. Such early detection, not available currently, is crucial for early therapeutic intervention. We also hypothesize that in end-stage CTiCT, mitochondrial dysfunction has passed a no-return point, and the failing heart will only be rescued by a strategy to replenish the myocardium with fresh healthy mitochondria. This can be achieved with the radical new therapeutic option of in-vivo mitochondrial transplant. The MATRIX project has broad translational potential, including a new therapeutic approach to a clinically relevant condition, the development of technology for early diagnosis, and advances in knowledge of basic disease mechanisms.

Patient recruitment began in 2020, and by the end of March 2023 we had already hosted 41 participants.

EFFECT OF REMOTE ISCHEMIC PRECONDITIONING ON COGNITIVE FUNCTION AND CEREBRAL VASCULATURE
(PRECOGNITIVE)

Principal Investigator: *Gonzalo Pizarro Sánchez*

Arterial hypertension can damage the cerebral vascular system, even when blood pressure values are normalized. All current therapies are aimed at controlling blood pressure values and avoiding damage to target organs, such as the brain. Thirty years ago, remote ischemic preconditioning (RIPC) was shown to protect organs such as the heart and brain in animal models, and the procedure has subsequently been used in human patients. RIPC consists of inflating and deflating a tension cuff on the arm for periods of 5 minutes, in a total of 4 cycles. This procedure creates ischemia in the arm, and this can protect distant organs, such as the brain. Our group has made important contributions in this area, and our recent studies have shown that RIPC can improve the cognitive level and cerebral vascular function in patients with dementia of vascular origin.

The PRECOGNITIVE study is a proof-of-concept randomized trial in which a total of 45 women with hypertension and evidence of target organ involvement (such as left ventricular hypertrophy) will be randomized into three groups. The RIPC group patients will receive RIPC (blood pressure increased by 20 mmHg above their systolic blood pressure). The RIPC-Sham group will undergo the same procedure, but the cuff will not be inflated enough to induce ischemia (50 mmHg). The control group participants will not undergo cuff therapy.

The goal is to determine if RIPC has a significant effect on the cerebral vasculature in patients with hypertension without significant cognitive impairment. The effect of the treatment will be assessed through comprehensive neurocognitive tests, noninvasive imaging tests such as echocardiography, noncontrast brain magnetic resonance imaging, and trans-cranial Doppler ultrasound.

So far, we have recruited 12 patients.

EARLY IMAGING MARKERS OF UNHEALTHY LIFESTYLES IN ADOLESCENTS

(ENIGMA)

Principal Investigator: *Rodrigo Fernández Jiménez*

The alarming increase of unhealthy lifestyles in adolescents is a societal threat. Early and effective health promotion strategies are desperately needed, as well as noninvasive tools to detect individuals showing very early stages of subclinical disease who may benefit from more intensive prevention approaches. The EnIGMA project has 3 main goals: 1) to identify early adverse vascular and cardiac subclinical changes in adolescents by cardiovascular magnetic resonance (CMR) and relate these changes to lifestyle patterns; 2) to assess the efficacy of a school-based intervention to promote cardiovascular health among adolescents and improve vascular and cardiac imaging parameters; and 3) to use CMR data to provide reference ranges for cardiac and vascular structure and function in adolescents.

The EnIGMA project, funded by the Fondo de Investigación Sanitaria of the Instituto de Salud Carlos III (PI19/01704), takes advantage of an already running cluster-randomized controlled trial in which we successfully recruited 24 Spanish public secondary schools (n=1326 adolescents) in 2017 to perform state-of-the-art CMR imaging of the heart and thoracic aorta in adolescents aged 15-17 years. In this trial, schools were 1:1:1 randomized to receive a short-term (2-year) educational program to promote health, a long-term (4-year) health-promotion program, or the usual curriculum (control). Participant assessment scheduled at baseline and at 2- and 4-year follow-up includes anthropometry, bioelectrical impedance, blood pressure, glucose and lipid profile, accelerometry, and the completion of lifestyle questionnaires.

For the EnIGMA project, a subset of 123 participants have undergone a multi-territory multi-parameter CMR imaging study. Based on this, we have recently provided overall and sex-stratified CMR reference values for cardiac dimensions and function, and myocardial tissue properties, in adolescents (eClinicalMedicine, https://doi.org/10.1016/j.eclinm.2023.101885). This information has direct implications for clinical practice and may help in the differential diagnosis of cardiac diseases in this population. Furthermore, this unique setting will allow us to study associations between health factors, behaviors, and early imaging markers of subclinical disease.

PROSPECTIVE REGISTRY TO VALIDATE A NEW DIAGNOSTIC MARKER IN PATIENTS WITH CLINICAL SUSPECT OF MYOCARDITIS

(MYOCARDITIS-CNIC)

Principal Investigator: *Mª Pilar Martín Fernández*
Co-Principal Investigator: *Domingo Pascual Figar*

Acute myocarditis is difficult to diagnose because of its varied clinical presentation and the lack of rapid, accessible, and accurate diagnostic methods. The nonspecific symptoms of acute myocarditis include atypical chest pain, suggesting pericarditis or angina, dyspnea, asthenia, palpitations, syncope, and even sudden death or shock. The difficulty of reaching an early diagnosis of myocarditis results from its heterogeneous presentation and the variability and lack of specificity of the findings in the usual tests (ECG, echocardiography, and laboratory tests).

Diagnosis of acute myocarditis typically requires either endomyocardial biopsy, which is invasive, or cardiovascular magnetic resonance imaging, which is not universally available, so there is a clear need for additional approaches. Dr. Martín Fernández's group has identified a novel microRNA in mice and humans with myocarditis; the team's research shows that the human homolog (hsa-miR-Chr8:96) can be used to distinguish patients with myocarditis from those with myocardial infarction (N Engl J Med. 2021 May 27;384(21):2014-2027).

In the MYOCARDITIS-CNIC Registry, run by the CNIC in collaboration with the Hospital Virgen de la Arrixaca, several Spanish hospitals (including Hospital de la Princesa and Clínica Universitaria de Navarra) will collect clinical data and biological samples from patients attending the emergency department with clinical signs of myocarditis. These data will provide valuable information on the early onset of myocarditis and will help in the validation of early clinical biomarkers. So far, 34 participants have been enrolled.

CHARACTERIZATION OF CARDIAC METABOLISM USING MULTIMODAL IMAGING IN IDIOPATHIC CARDIOMYOPATHY: MACADAMIA (MACADAMIA)

Principal Investigator: *Borja Ibáñez*

Heart failure (HF) is one of the main health problems in our society and a major consumer of medical resources. In order to develop new therapies, it is crucial to identify new mechanisms involved in the development and maintenance of HF.

The heart is the most energy-consuming organ in the body by weight. The primary energy source for the heart under physiological conditions is beta-oxidation of fatty acids, which generates approximately 60% of the total ATP consumed by the heart. The second most used substrate source is carbohydrates through the Krebs cycle, while other nutrients such as amino acids contribute less than 1%.

In the altered physiological conditions of HF, there is a shift in nutrient consumption by the cardiac muscle, which begins to consume more glucose instead of fatty acids, making carbohydrates the main energy substrate. This change is known as the "metabolic switch." Initially, this metabolic switch was considered a protective defense mechanism rather than a deleterious effect. However, recent data from animal and human models indicate that glucose metabolism produces 4-5 times less ATP than that of fatty acids, indicating that this metabolic switch, far from being beneficial, is harmful and increases the drop in cardiac contractile capacity.

Our group has demonstrated that the metabolic switch in HF secondary to idiopathic dilated cardiomyopathy (IDCM) is involved in the deterioration of ventricular function. We initially demonstrated this in a mouse model, where a diet rich in fatty acids was able to reverse the metabolic switch and the IDCM phenotype. Moreover, this ability of a fatty diet to reverse deteriorated ventricular function in IDCM is also seen in pigs, which have a similar metabolism to humans.

The first step before performing a clinical trial in patients with IDCM is to study the incidence of the metabolic switch in this patient group. This is the objective of the MACADAMIA study. MACADAMIA is an observational study with a small number of patients diagnosed with IDCM. The study aims to characterize this population, without any intervention, using cardiac imaging techniques, including transthoracic ultrasound (TTE, including myocardial strain), cardiac magnetic resonance (CMR), and a metabolic study by positron emission tomography/computed tomography (PET/CT) using the radiotracer 18FDG.

So far we have recruited 21 patients. Our medium–long-term goal is to conduct a clinical trial in IDCM patients with a metabolic switch demonstrated using these imaging techniques. These patients will be randomized to receive a diet rich in fatty acids or a normal diet, and we will assess changes in cardiac function (by CMR) and cardiac metabolism (by PET/CT) as a function of this dietary intervention.

CLINICAL TRIAL COORDINATION UNIT