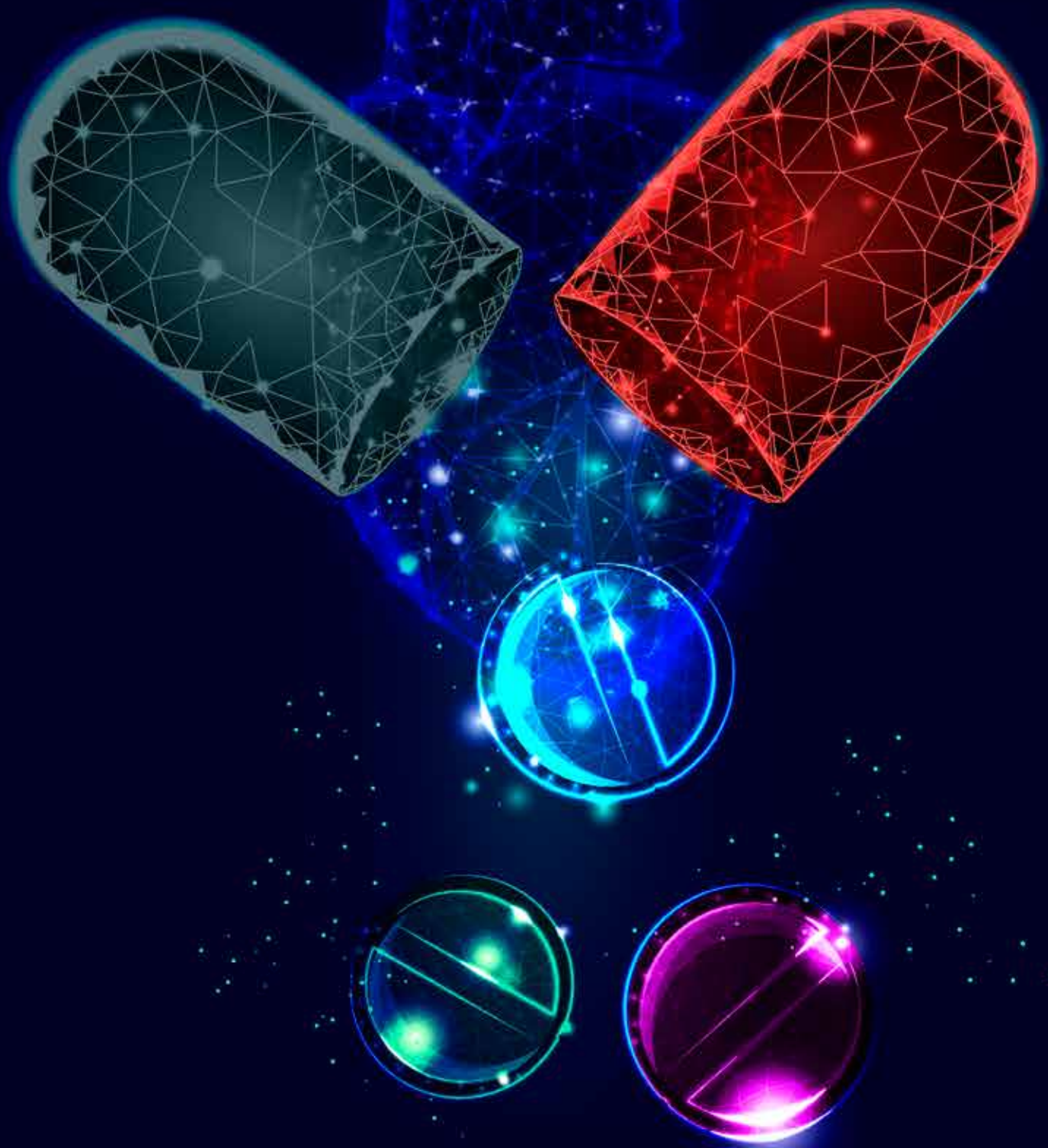




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The Pro CNIC Foundation brings together 11 of the most important Spanish companies and foundations: Acciona, Santander Bank, Endesa, the Mapfre Foundation, the Mutua Madrileña Foundation, the Ramón Areces Foundation, the Repsol Foundation, Inditex, la Caixa, Prisa, and Telefónica.

This innovative public-private financing formula has allowed the CNIC to reach a very high level of excellence, as recognized in the Severo Ochoa accreditation and other international awards.

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1

FOREWORD AND CNIC MISSION

Valentín Fuster, General Director

Borja Ibáñez, Scientific Director and Clinical Research Director

Vicente Andrés, Basic Research Director

The Centro Nacional de Investigaciones Cardiovasculares (CNIC) is a biomedical research center funded through a pioneering public-private partnership between the Spanish Government and the Pro CNIC Foundation (composed of eleven Spanish companies unrelated to the biomedical sector). The CNIC is a Severo Ochoa Center of Excellence of the Spanish Ministry of Science and Innovation. The Center also benefits from the external support of its Scientific Advisory Board, composed of leading international experts who provide guidance on strategy and regularly assess the performance of the Center and its program projects and group leaders.

Cardiovascular disease (CVD) is the principal cause of death worldwide, and the exponential increase in the cost of treating CVD in its symptomatic phase places an insurmountable burden on patients, families, and health systems. In response to this challenge, the CNIC has defined three major goals: to increase the understanding of cardiovascular health, to improve disease prevention, and to generate treatment advances for the prevalent manifestations of CVD. These goals require mechanistic studies to gain insight into the molecular and cellular processes underlying disease, coupled to the translation of these findings into improvements in health promotion, diagnosis, and disease management.

To meet these challenges, the CNIC has four pillars: excellence in basic and clinical research, technology, networking and training.

CNIC scientific area is organized into two departments focused on Basic Research and Clinical Research, fully interconnected through seven highly focused and integrated programs: (1) novel mechanisms of atherosclerosis, (2) myocardial homeostasis & cardiac injury, (3) cardiovascular regeneration, (4) novel arrhythmogenic mechanisms, (5) CVD, risk factors & cognitive function, (6) cardiovascular health promotion, and (7) technology development. These programs span from basic research to advanced health-changing clinical

trials and build on the CNIC's deep-rooted and proven expertise in state-of-the-art technology, cellular and animal models, imaging modalities, and large-scale data gathering and analysis.

In 2022, CNIC recruited two Group Leaders, Dr Pablo García Pavia in the myocardial homeostasis & cardiac injury Program and Dr Hesham Sadek as Clinical Leader of the cardiovascular regeneration Program.

The Center's translational studies, including several large randomized clinical trials, have already changed clinical practice worldwide. These studies bear testimony to the enthusiastic commitment of researchers, healthy volunteers, patients, and emergency service personnel to defining the causes and risk factors of CVD. This commitment of citizens and professionals outside the research community is making essential contributions to advancing the use of noninvasive imaging technology for diagnosis and research.

A major discovery in 2022 was the result of the H2020-funded SECURE trial, a multinational randomized clinical trial with the CNIC-Ferrer polypill that demonstrated that treatment with this polypill after myocardial infarction reduces cardiovascular mortality by 33%. Other important findings in basic, translational and clinical research are included in the section of Scientific Highlights.

As we move forward, the CNIC will maintain the drive and focus established in its initial phases and ensure that the Center's basic and clinical scientists continue to work closely together to devise innovative projects that help reduce the health and socioeconomic burden associated with CVD and to train the researchers of the future.



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.

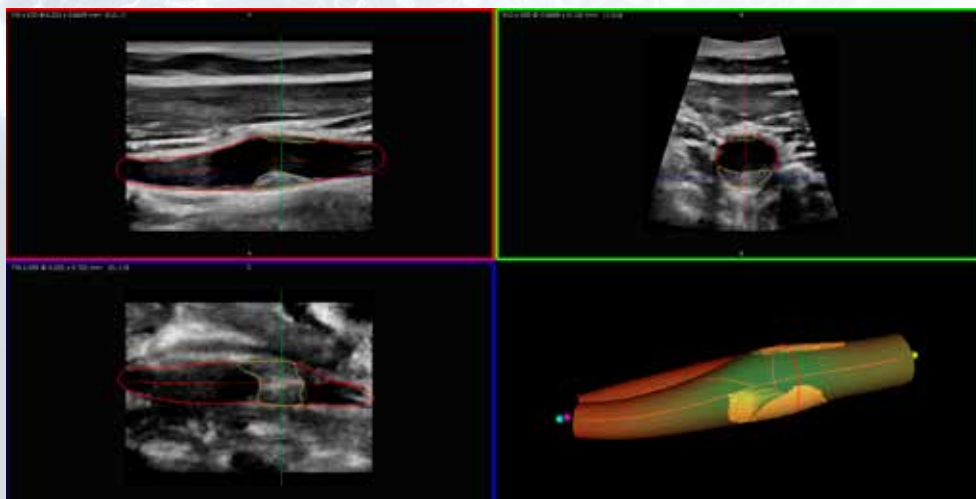
NOVEL MECHANISMS OF ATHEROSCLEROSIS

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



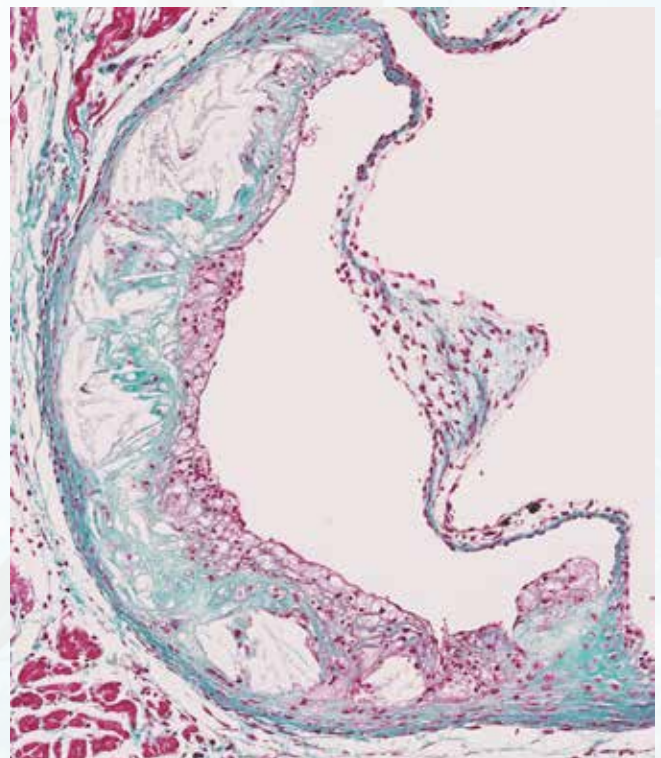
Standardized 3D vascular ultrasound images (multiplanar views and 3D reconstruction) from human atherosclerotic disease affecting one of the carotid arteries (taken from the PESA-HEALTH study using the CM2020 software).

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

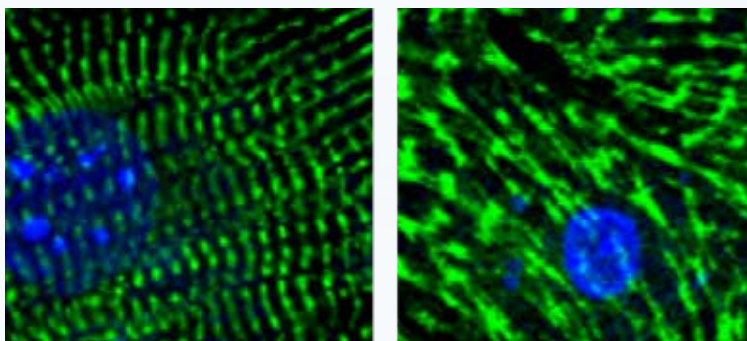
treated with drugs developed for generic cardiac pathologies, such as heart failure or cardiac arrhythmias. For most CMs, there are no specific disease-modifying treatments.

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.



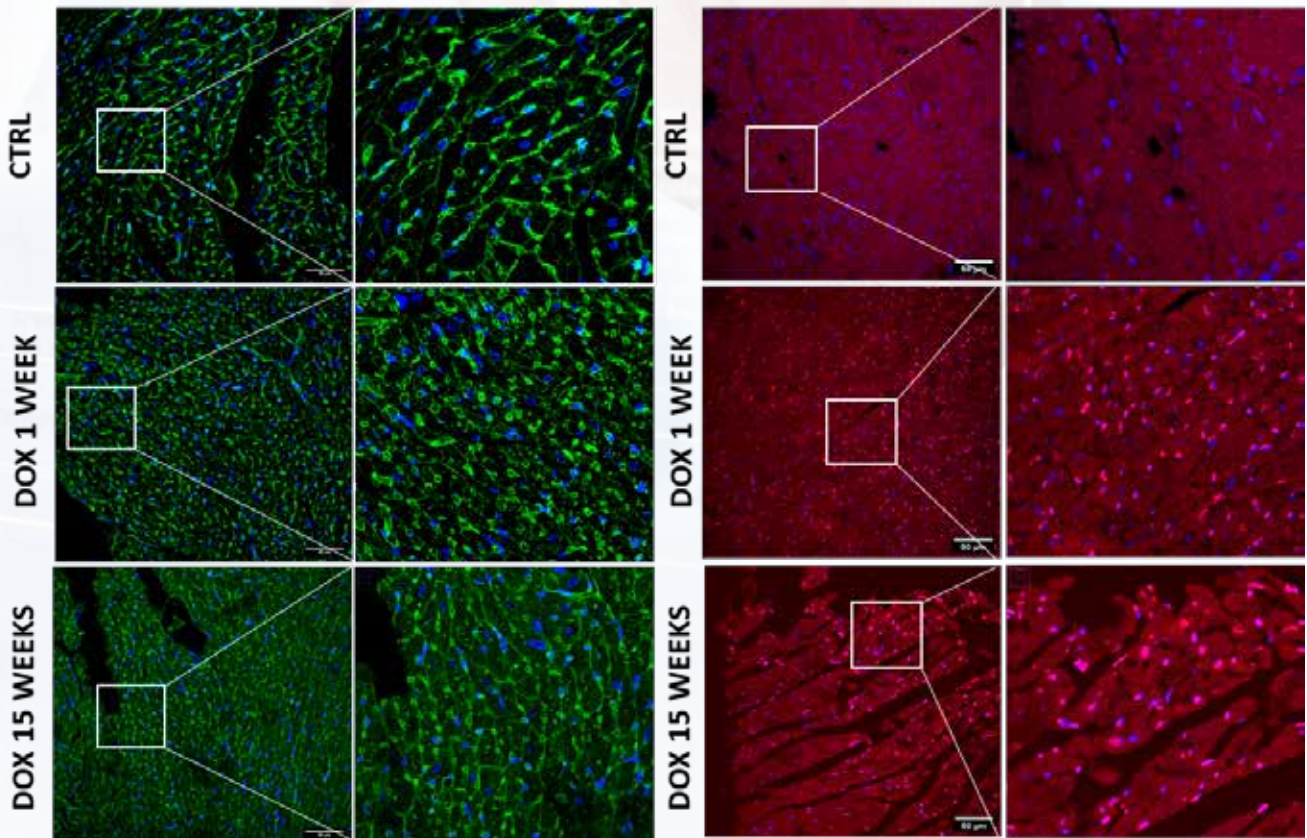
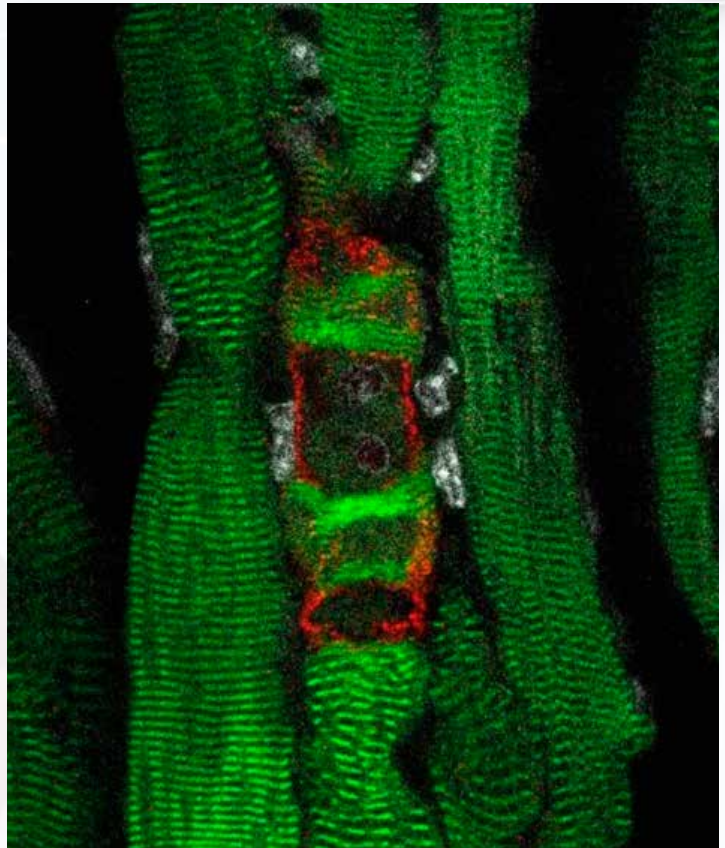
Sarcomere disarray in heart disease. Side-by-side comparison of a healthy cardiomyocyte with an intact sarcomere pattern (left) and a sick cardiomyocyte (right). Credit: Maria Rosaria-Pricolo.

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 cardiomyocyte. 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 doxorubicin (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.

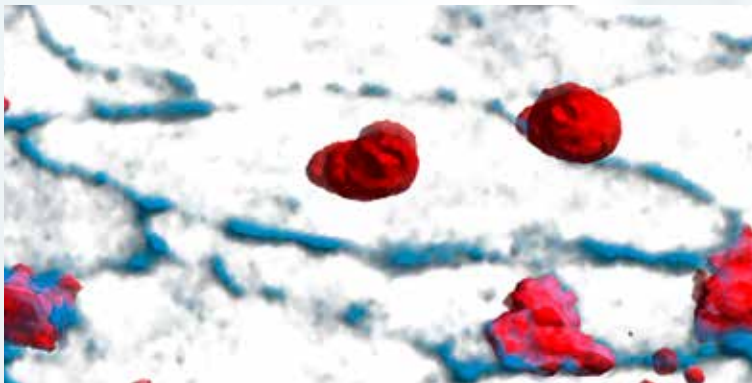
In 2022, the Cardiovascular Regeneration Program consolidated its faculty, recruiting Prof. Hesham Sadek as a new PI and Clinical Leader of the Program.

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

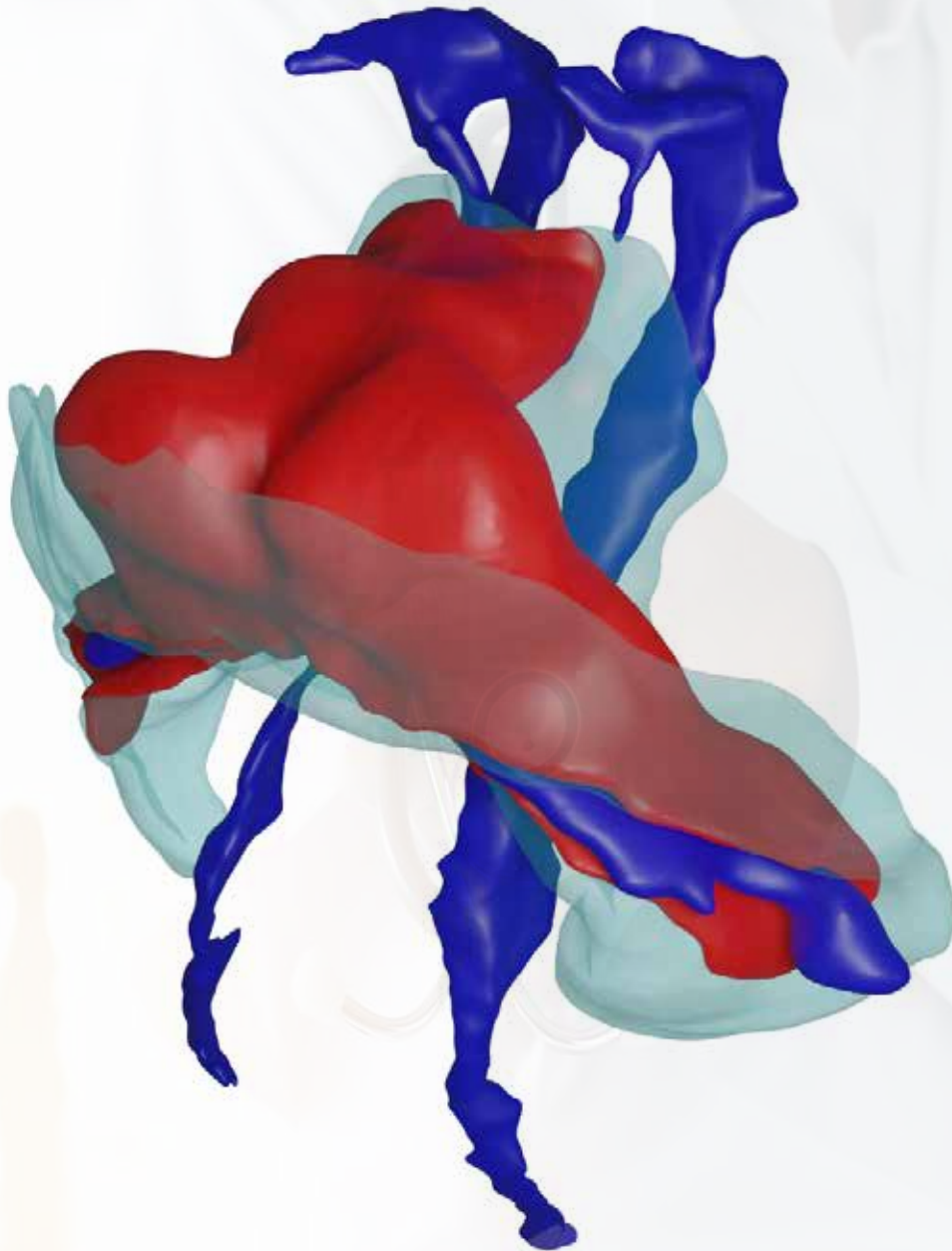
In the field of cardiac development, Dr Mercader identified a molecular pathway involved in cardiomyocyte lineage

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 Phosphorylation 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

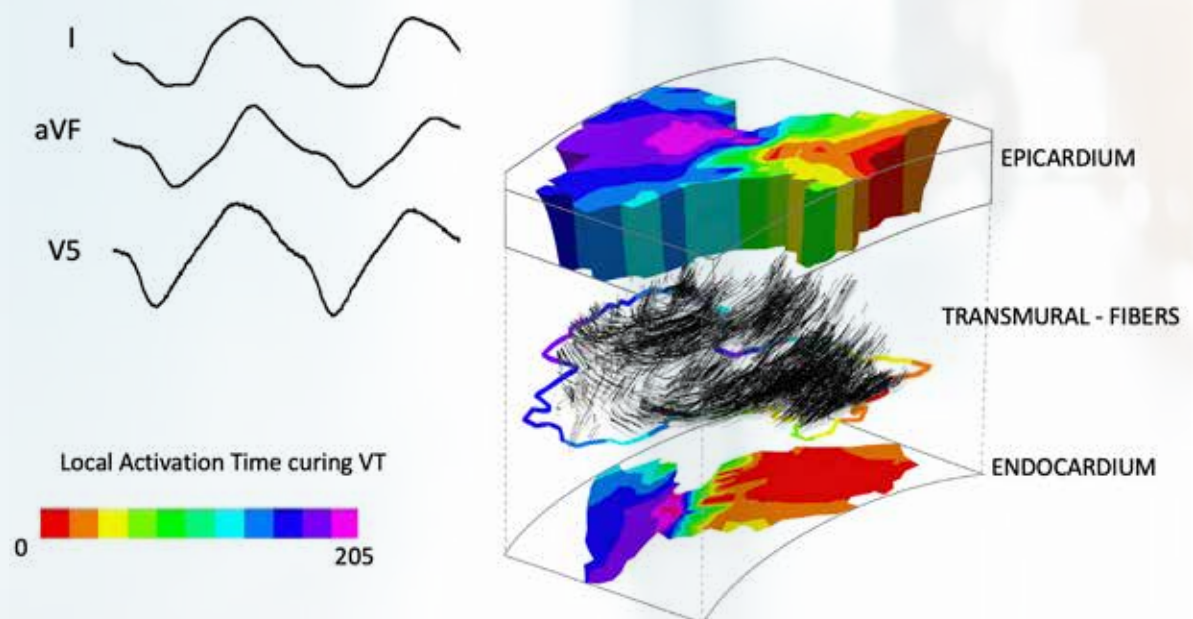


Figure 1. Visualization of the 3D transmural myocardial fiber substrate associated with ventricular tachycardia (VT) maintenance in the pig model of ischemic cardiomyopathy and inducible ventricular arrhythmia. Top left, VT morphology on the surface ECG. Right, color-coded activation map of the epicardial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

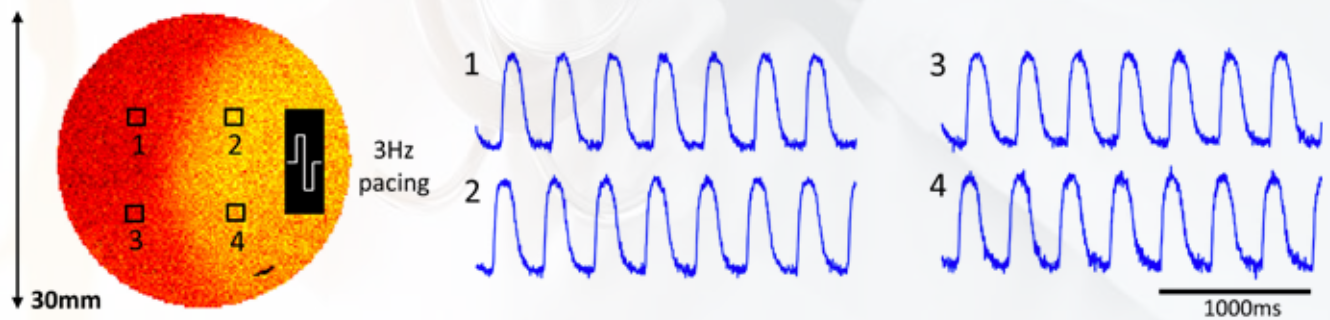


Figure 2. Imaging action potentials using a genetically encoded voltage indicator in human induced pluripotent stem-cell-derived cardiomyocytes. Sample action potentials (normalized signals) recorded in 4 locations in a monolayer during 3 Hz electrical pacing. The stimulation site is indicated by the black rectangle. (Data obtained in collaboration with Dr. Michael Laflamme, McEwen Stem Cell Institute, University Health Network, Toronto, Canada)

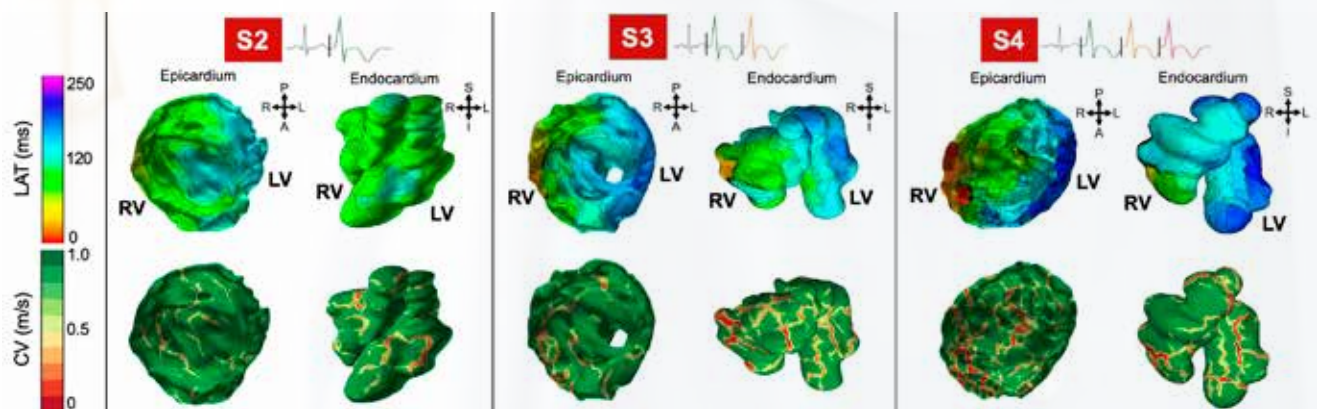


Figure 3: Electroanatomic mapping in a Long QT Syndrome type 8 (LQT8) pig model. This figure illustrates high-density electroanatomic mapping of both the epicardial and endocardial surfaces (LV = left ventricle, RV = right ventricle) in a genetically engineered pig model of LQT8 (also known as Timothy 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.

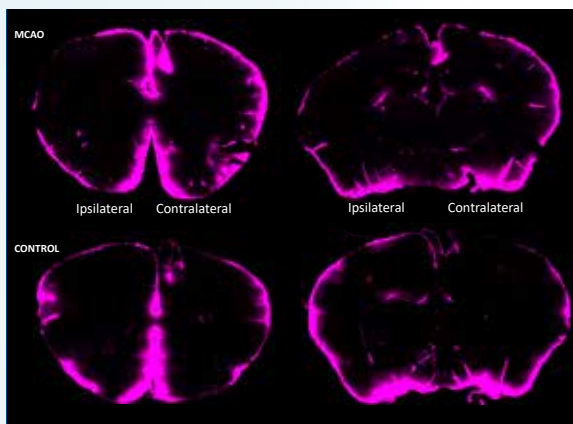
The Cardiovascular Risk Factors and Brain Function Program is a collaborative multidisciplinary effort of six research groups with complementary expertise, dedicated to elucidating the mechanisms underlying cardiovascular-driven brain dysfunction. The Program's scientific activities are optimally supported 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:

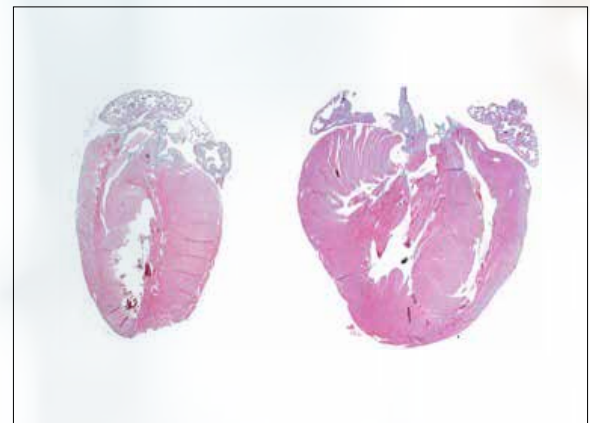
- 1) The association between atherosclerosis and Alzheimer's disease (AD) at preclinical stages.
- 2) The impact of CVMRF burden on cerebral vasculature, including the intravascular compartment.
- 3) The mechanisms leading to CVMRF-induced impairment of neuroimmune interfaces and brain clearance mechanisms.

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

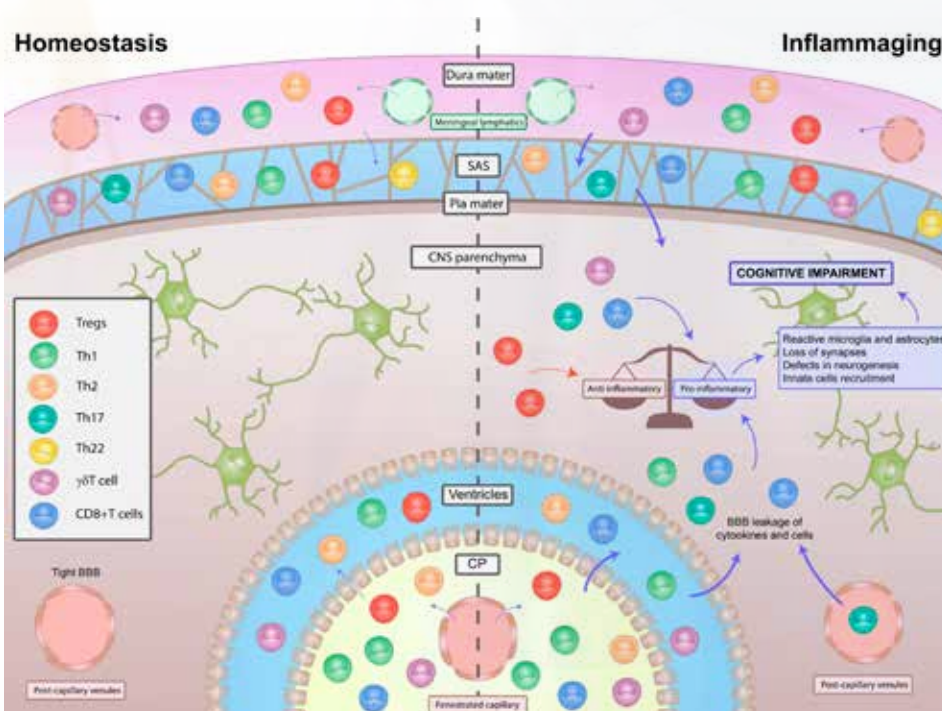
quantifying blood-based biomarkers of axonal injury, astrocytosis, and AD. In addition, Program scientists are developing plasma and neuroimaging biomarkers of AD based on disease factors such as procoagulant and immunothrombotic states identified in the disease.

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-p38 γ / δ pathway in cardiac hypertrophy, urging caution regarding the potential cardiotoxicity of the long-term clinical use of p38 α 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 its 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: Valentín 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

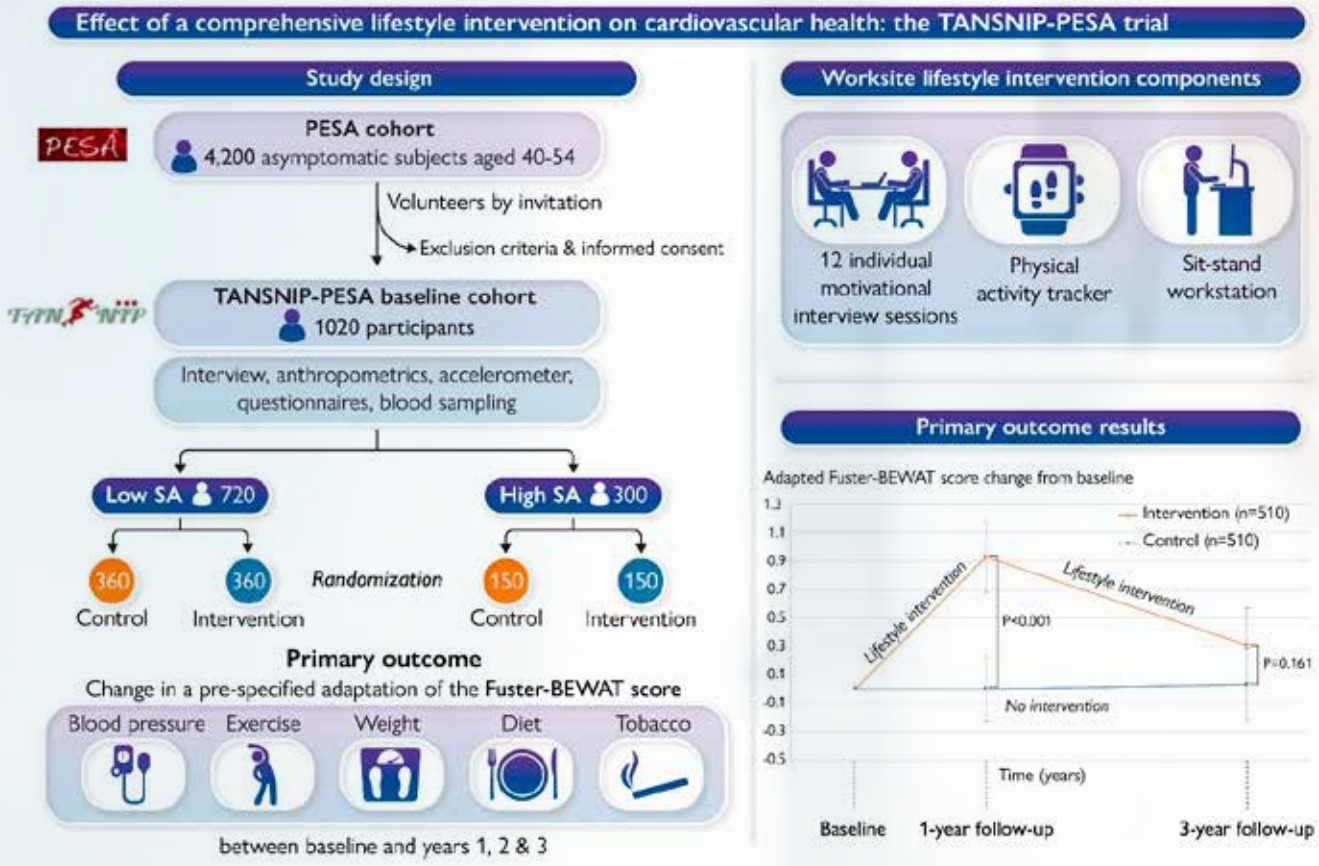


Figure 1. Summary of the design and primary outcome results of the TANSNIP-PESA trial [Eur Heart J. 2022;43(38):3732-3745].

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 SII 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

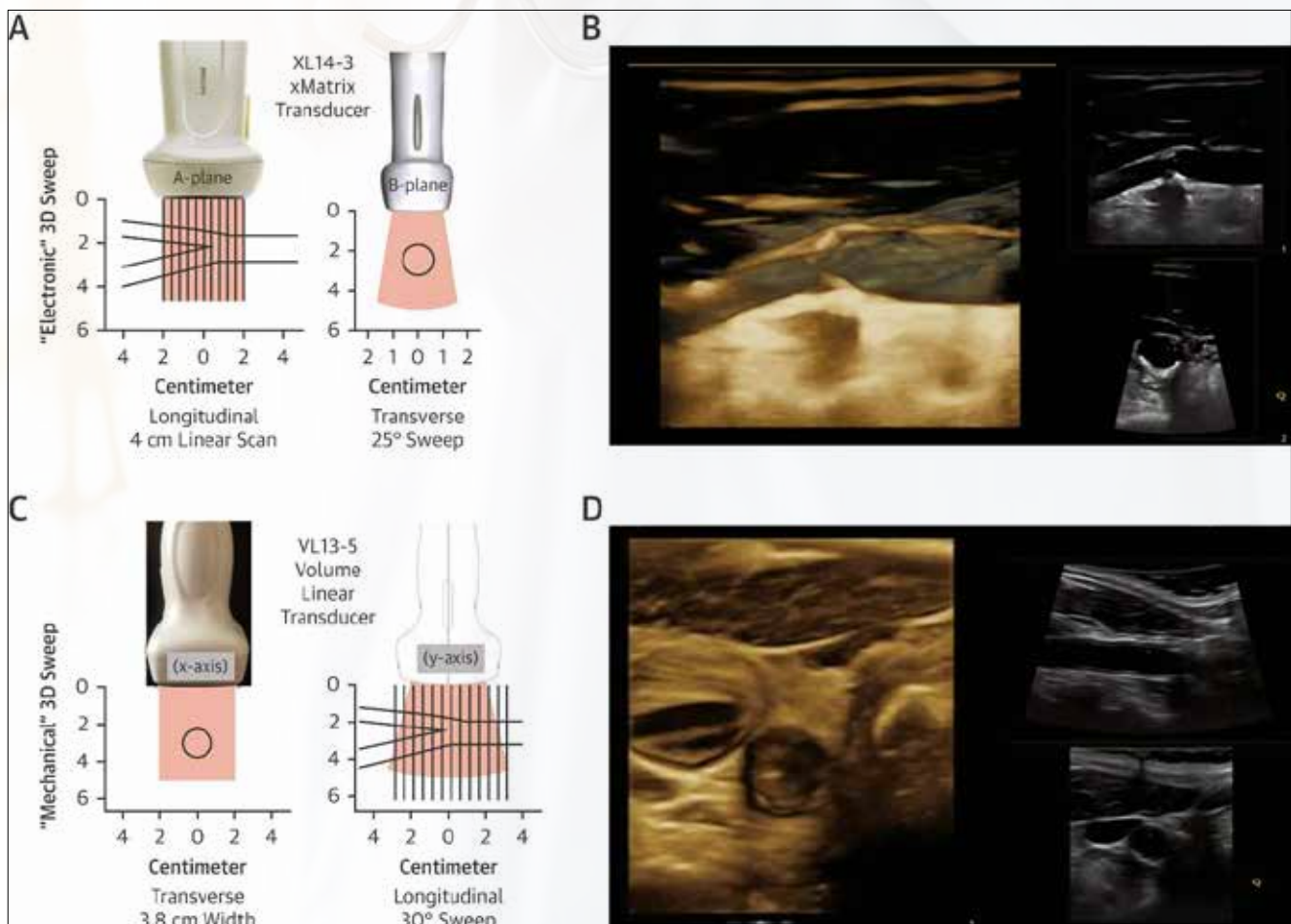


Figure 2. Technical features and examples of electronic and mechanical 3D-sweep acquisitions for the clinical evaluation of carotid atherosclerotic burden [JACC Cardiovasc Imaging. 2022;15(6):1124-1135].

TECHNOLOGY DEVELOPMENT

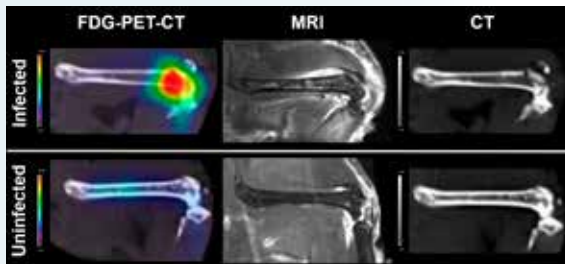
Coordinator: **Beatriz Álvarez**

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>).

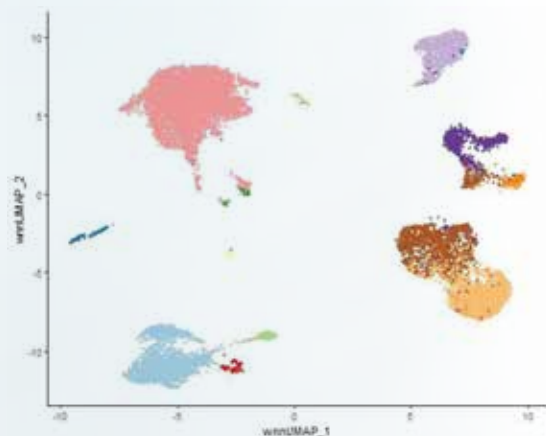
Our work falls into 4 key areas:

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.



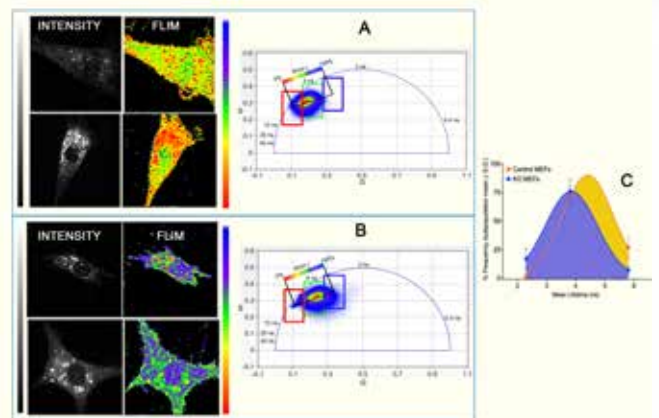
Study of infected and inflammatory (uninfected) lesions in mice using preclinical molecular imaging techniques



Single-cell Data Analysis and Visualization scDAVIS

TECHNICAL UNITS

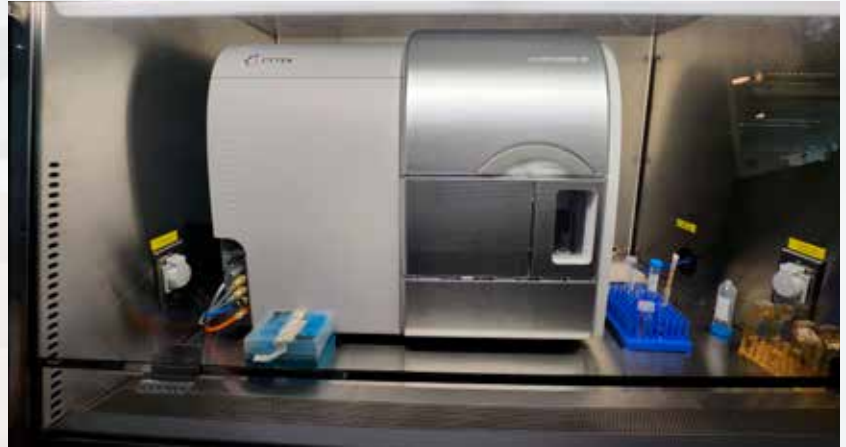
- Bioinformatics
Fátima Sánchez Cabo
- Clinical Trial Coordination
Antonio J. Quesada
- Comparative Medicine
- Flow Cytometry
Beatriz Álvarez
- Genomics
Ana Dopazo
- Imaging
Manuel Desco
- Microscopy
Valeria Caiolfa
- Pluripotent Cell Technology
Gionanna Giovinnazzo
- Proteomics
Juan Antonio López
- Transgenesis
Juan De Dios Hourcade
- Viral Vectors
Juan A. Bernal



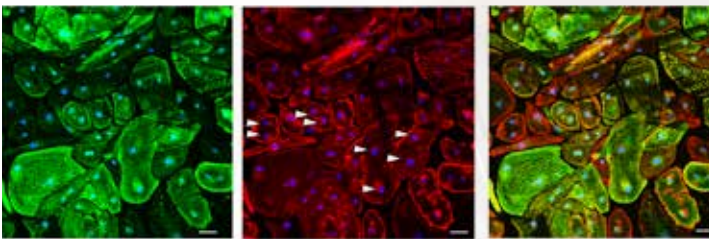
Phasor-fluorescence lifetime imaging (flim) analysis in living cells.



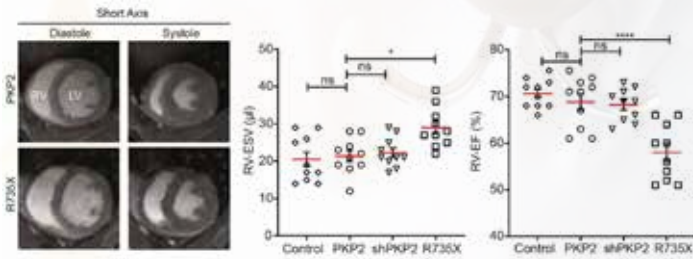
Expanded and hatched pig blastocyst developed after in vitro fertilization and in vitro culture for 6 days



Spectral Cell Sorter Cytometer



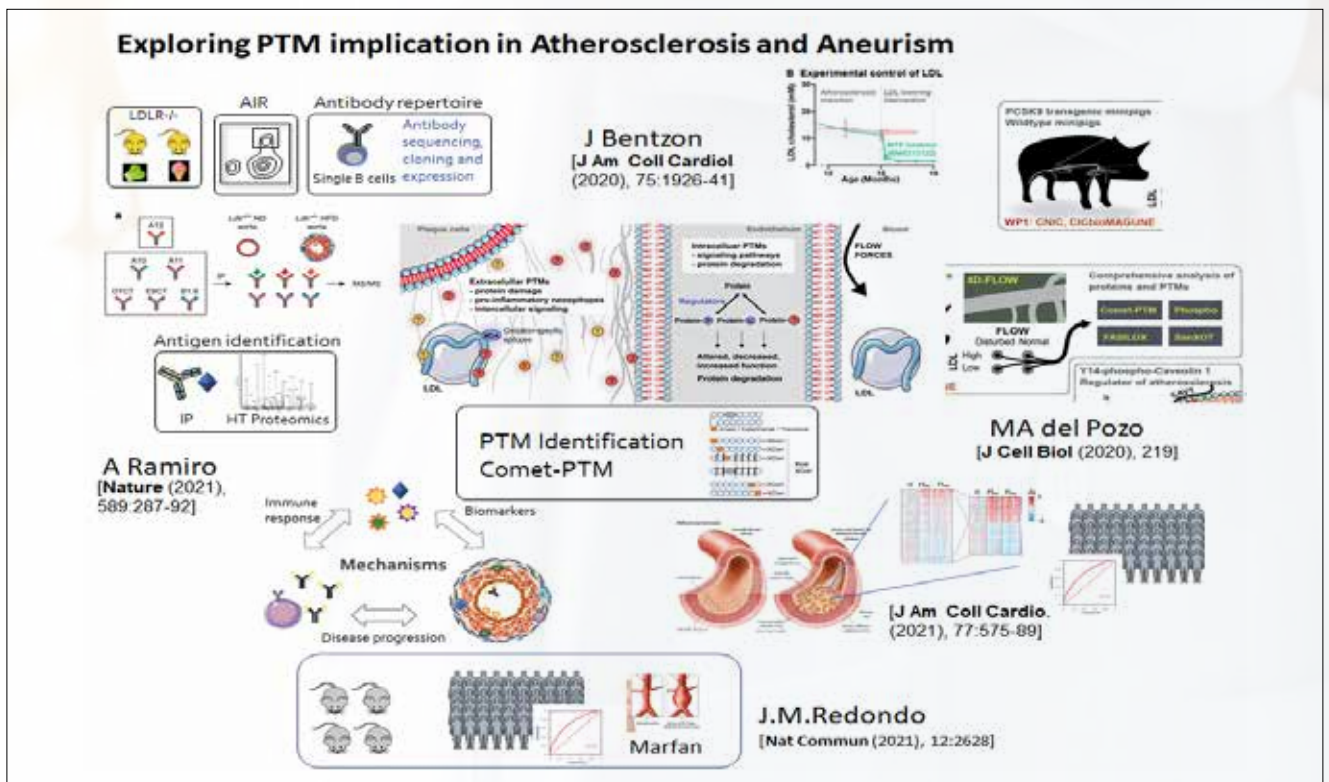
Purified hiPSC-derived cardiomyocytes



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



NovaSeq 6000 Sequencing System



2.2 CLINICAL STUDIES



PESA Health
Initiative

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: **M^a 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.

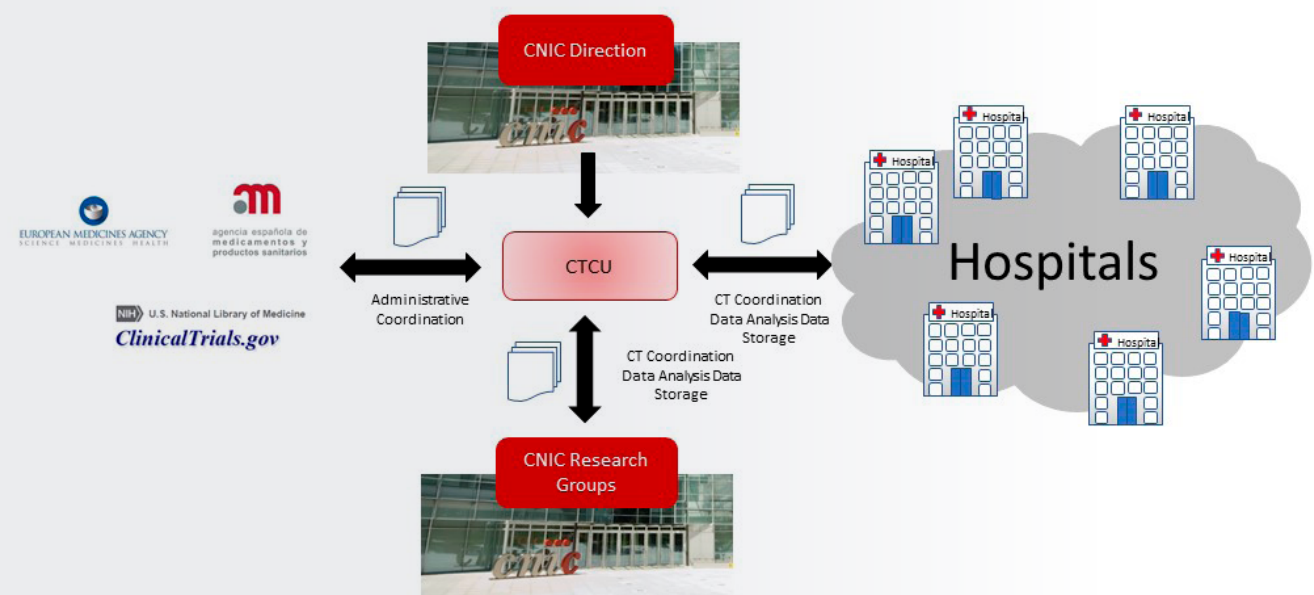
Our group has demonstrated that the metabolic switch in HF secondary to idiopathic dilated cardiomyopathy (IDCM) is involved in the deterioration

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 ¹⁸F-FDG.

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



3

SCIENTIFIC HIGHLIGHTS BY PUBLICATION DATE

NATURE CNIC SCIENTISTS DISCOVER A CELL BEHAVIOR PATTERN THAT PREDICTS CARDIOVASCULAR DISEASE

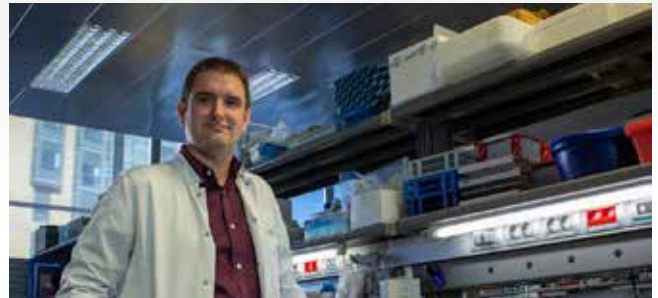
Scientists led by Dr. Andrés Hidalgo at the CNIC have discovered that circulating neutrophils acquire different behavior patterns during inflammatory processes. The study, published in *Nature*, identifies a harmful neutrophil behavior associated with cardiovascular disease.



Crainiciuc G, Palomino-Segura M, Molina-Moreno M, Sicilia J, Aragones DG, Li JLY, Madurga R, Adrover JM, Aroca-Crevillén A, Martin-Salamanca S, Del Valle AS, Castillo SD, Welch HCE, Soehnlein O, Graupera M, Sánchez-Cabo F, Zarbock A, Smithgall TE, Di Pilato M, Mempel TR, Tharaux PL, González SF, Ayuso-Sacido A, Ng LG, Calvo GF, González-Díaz I, Díaz-de-María F, Hidalgo A. Behavioural immune landscapes of inflammation. *Nature*. 2022 Jan;601(7893):415-421. <https://doi.org/10.1038/s41586-021-04263-y>

NATURE CARDIOVASCULAR RESEARCH MUTATIONS ACQUIRED BY BLOOD CELLS ARE AN INDICATOR OF CARDIOVASCULAR RISK

Scientists at the CNIC and Columbia University, New York have published a review article in *Nature Cardiovascular Research* examining the role of acquired mutations linked to clonal hematopoiesis in cardiovascular disease.



Tall AR, Fuster JJ. Clonal hematopoiesis in cardiovascular disease and therapeutic implications. *Nat Cardiovasc Res*. 2022 Feb;1(2):116-124. <https://doi.org/10.1038/s44161-021-00015-3>

NATURE COMMUNICATIONS CNIC SCIENTISTS IDENTIFY A SHUTTLE PROTEIN REQUIRED FOR THE NUCLEAR IMPORT OF PROTEINS ESSENTIAL FOR ORGAN GROWTH AND DEVELOPMENT

Organ growth and regeneration require the entry into the cell nucleus of proteins that activate essential genes for these processes. This process is the subject of a new study by CNIC scientists, led by Dr. Miguel Ángel del Pozo, who heads the Mechanoadaptation and Caveolae Biology group, and group member Dr. Asier Echarri. The scientists have identified the mechanism that controls the nuclear import of these proteins in response to mechanical stimuli, such as



the hemodynamic forces generated by arterial blood flow, tumor rigidity, or locomotory movements during routine activities like walking or sports.

García-García M, Sánchez-Perales S, Jarabo P, Calvo E, Huyton T, Fu L, Ng SC, Sotodosos-Alonso L, Vázquez J, Casas-Tintó S, Görlich D, Echarri A, Del Pozo MA. Mechanical control of nuclear import by Importin-7 is regulated by its dominant cargo YAP. *Nat Commun*. 2022 Mar 4;13(1):1174. <https://doi.org/10.1038/s41467-022-28693-y>

CIRCULATION

A CNIC STUDY HIGHLIGHTS THE RISKS OF MITOCHONDRIAL THERAPEUTIC INTERVENTIONS

Research carried out at the CNIC has demonstrated that mixing mitochondrial DNAs (mtDNAs) of different origins can have damaging effects over the medium and long term. mtDNA is a component of the genetic material that is transmitted exclusively from mothers to their children.

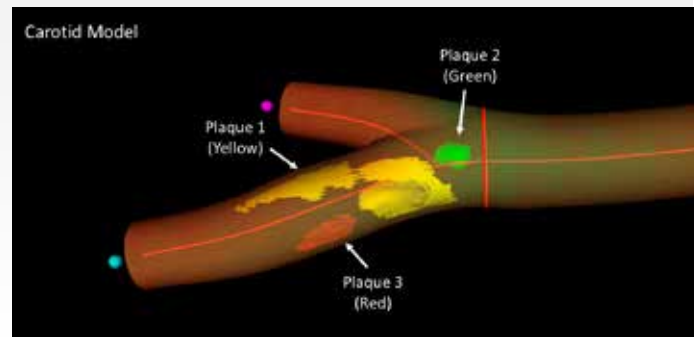


Lechuga-Vieco AV, Latorre-Pellicer A, Calvo E, Torroja C, Pellico J, Acín-Pérez R, García-Gil ML, Santos A, Bagwan N, Bonzon-Kulichenko E, Magni R, Benito M, Justo-Méndez R, Simon AK, Sánchez-Cabo F, Vázquez J, Ruíz-Cabello J, Enríquez JA. Heteroplasmy of Wild-Type Mitochondrial DNA Variants in Mice Causes Metabolic Heart Disease With Pulmonary Hypertension and Frailty. *Circulation*. 2022 Apr 5;145(14):1084-1101. <https://doi.org/10.1161/CIRCULATIONAHA.121.056286>

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY: CARDIOVASCULAR IMAGING

3D MATRIX ULTRASOUND ACCURATELY IDENTIFIES CARDIOVASCULAR INJURY IN HEALTHY INDIVIDUALS

A new imaging technique for real 3D vascular ultrasound could become a key tool in strategies aimed at preventing cardiovascular disease in apparently healthy persons, complementing traditional risk parameters such as cholesterol and high blood pressure. The



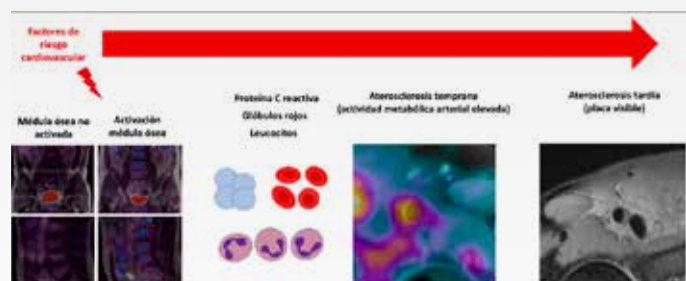
new results, published in *JACC: Cardiovascular Imaging*, show that real 3D vascular ultrasound is reliable, accurate, and faster than previous methods for the assessment of plaque volume in the carotid and femoral arteries.

López-Melgar B, Mass V, Nogales P, Sánchez-González J, Entrekin R, Collet-Billon A, Rossello X, Fernández-Friera L, Fernández-Ortiz A, Sanz J, Bentzon JF, Bueno H, Ibáñez B, Fuster V. New 3-Dimensional Volumetric Ultrasound Method for Accurate Quantification of Atherosclerotic Plaque Volume. *JACC Cardiovasc Imaging*. 2022 Jun;15(6):1124-1135. <https://doi.org/10.1016/j.jcmg.2022.01.005>

EUROPEAN HEART JOURNAL

BONE MARROW CONTRIBUTES TO THE DEVELOPMENT OF ATHEROSCLEROSIS

The activation of the bone marrow appears to play a key role in the origin and development of atherosclerosis, the pathological process underlying cardiovascular conditions such as myocardial infarction and stroke. A study carried out by scientists at the CNIC and led by cardiologists Drs. Valentín Fuster and Borja Ibáñez suggests that the bone marrow is activated in response to known cardiovascular risk factors. In the study, published in the *European Heart Journal*, the researchers show that these risk factors lead to an increase in the number of circulating inflammatory cells, which go on to trigger the initiation and subsequent progression of atherosclerotic disease.

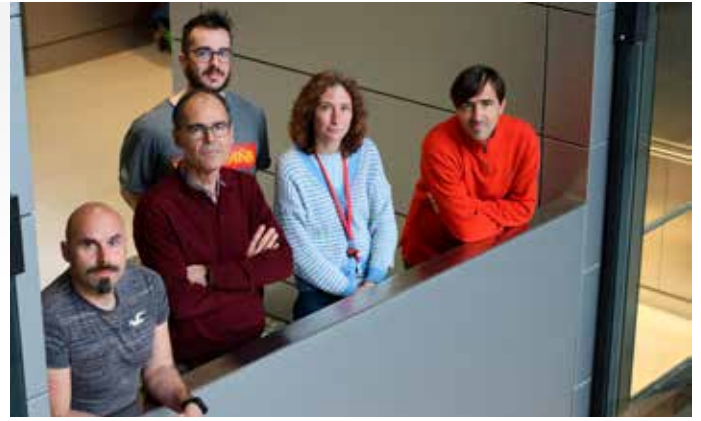


Devesa A, Lobo-González M, Martínez-Milla J, Oliva B, García-Lunar I, Mastrangelo A, España S, Sanz J, Mendiguren JM, Bueno H, Fuster JJ, Andrés V, Fernández-Ortiz A, Sancho D, Fernández-Friera L, Sanchez-Gonzalez J, Rossello X, Ibanez B, Fuster V. Bone marrow activation in response to metabolic syndrome and early atherosclerosis. *Eur Heart J*. 2022 May 14;43(19):1809-1828. <https://doi.org/10.1093/eurheartj/ehac102>

eBIOMEDICINE

SCIENTISTS DISCOVER A NEW METHOD FOR THE EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS

A study published in the journal *eBioMedicine* identifies new biomarkers that predict the presence of subclinical atherosclerosis. The study was carried out by scientists from the Spanish Cardiovascular Research Network (CIBERCV) working at the CNIC and the Instituto de Investigación Sanitaria-Fundación Jiménez Díaz-Universidad Autónoma de Madrid (IIS-FJD-UAM), in partnership with other institutions.



Núñez E, Fuster V, Gómez-Serrano M, Valdivielso JM, Fernández-Alvira JM, Martínez-López D, Rodríguez JM, Bonzon-Kulichenko E, Calvo E, Alfayate A, Bermudez-Lopez M, Escola-Gil JC, Fernández-Friera L, Cerro-Pardo I, Mendiguren JM, Sánchez-Cabo F, Sanz J, Ordovás JM, Blanco-Colio LM, García-Ruiz JM, Ibáñez B, Lara-Pezzi E, Fernández-Ortiz A, Martín-Ventura JL, Vázquez J. Unbiased plasma proteomics discovery of biomarkers for improved detection of subclinical atherosclerosis. *EBioMedicine*. 2022 Feb;76:103874. <https://doi.org/10.1016/j.ebiom.2022.103874>

REDOX BIOLOGY

CNIC SCIENTISTS DISCOVER A NEW MECHANISM INVOLVED IN THE MODULATION OF HEART MUSCLE ELASTICITY

Scientists at the CNIC, in collaboration with an international scientific team, have described a new mechanism of modulation of the mechanical properties of the heart, based on the oxidation of the protein titin, which is the main protein responsible for the passive elasticity of the heart muscle.



Herrero-Galán E, Martínez-Martín I, Sánchez-González C, Vicente N, Bonzón-Kulichenko E, Calvo E, Suay-Corredera C, Pricolo MR, Fernández-Trasancos Á, Velázquez-Carreras D, Careaga CB, Abdellatif M, Sedej S, Rainer PP, Giganti D, Pérez-Jiménez R, Vázquez J, Alegre-Cebollada J. Basal oxidation of conserved cysteines modulates cardiac titin stiffness and dynamics. *Redox Biol*. 2022 Jun;52:102306. <https://doi.org/10.1016/j.redox.2022.102306>

NATURE CARDIOVASCULAR RESEARCH

A CNIC TEAM CREATES A DYNAMIC 3D ATLAS OF THE FORMATION OF THE EMBRYONIC HEART

Scientists at the CNIC have used a collection of mouse tissue samples to create a 3D atlas of the formation of the heart during embryonic and fetal development. The 3D atlas has allowed the scientists to identify the first appearance of left–right asymmetry in the heart. The study, published today in *Nature Cardiovascular Research*, provides important information on the development of congenital heart malformations.



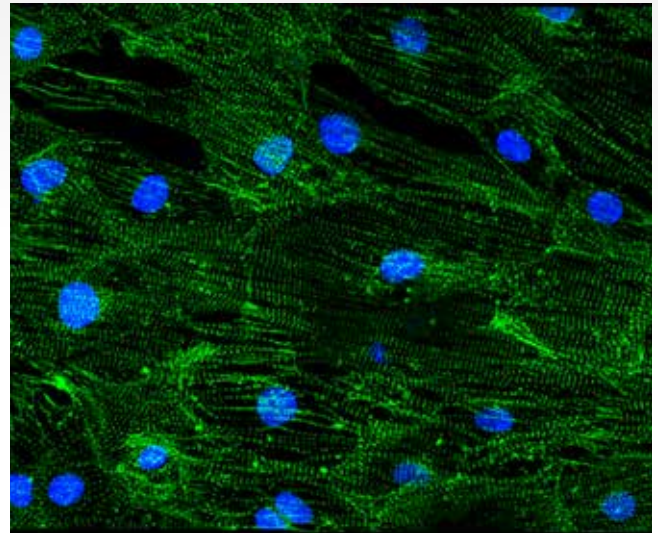
Esteban I, Schmidt P, Desgrange A, Raiola M, Temiño S, Meilhac SM, Kobbelt L, Torres M. Pseudodynamic analysis of heart tube formation in the mouse reveals strong regional variability and early left–right asymmetry. *Nat Cardiovasc Res*. 2022 May;1: 504-517. <https://doi.org/10.1038/s44161-022-00065-1>

ELIFE

STUDY REVEALS HOW DUCHENNE MUSCULAR DYSTROPHY CAUSES HEART RHYTHM PROBLEMS

Abnormalities in the proteins responsible for transmitting electrical signals in the heart likely cause abnormal heart rhythms in patients with Duchenne muscular dystrophy (DMD), shows a study published in *eLife*.

Jimenez-Vazquez EN, Arad M, Macías Á, Vera-Pedrosa ML, Cruz FM, Gutierrez LK, Cuttita AJ, Monteiro da Rocha A, Herron TJ, Ponce-Balbuena D, Guerrero-Serna G, Binah O, Michele DE, Jalife J. SNTA1 gene rescues ion channel function and is antiarrhythmic in cardiomyocytes derived from induced pluripotent stem cells from muscular dystrophy patients. Elife. 2022 Jun 28;11:e76576. <https://doi.org/10.7554/eLife.76576>



HEPATOLOGY

IMMUNE CELLS IN THE LIVER REGULATE BODY TEMPERATURE

A study published in *Hepatology* demonstrates that the activation of thermogenesis in the livers of obese mice contributes to weight loss and improves diabetes symptoms.

Crespo M, Nikolic I, Mora A, Rodríguez E, Leiva-Vega L, Pintor-Chocano A, Horrillo D, Hernández-Cosido L, Torres JL, Novoa E, Nogueiras R, Medina-Gómez G, Marcos M, Leiva M, Sabio G. Myeloid p38 activation maintains macrophage-liver crosstalk and BAT thermogenesis through IL-12-FGF21 axis. Hepatology. Epub 2022. Hepatology. 2023 Mar 1;77(3):874-887. <https://doi.org/10.1002/hep.32581>



EUROPEAN JOURNAL OF HEART FAILURE

SPANISH SCIENTISTS COMBINE GENETIC AND IMAGING DATA TO IMPROVE THE TREATMENT OF DILATED CARDIOMYOPATHY

Combining a person's genetic profile with imaging data obtained by cardiac magnetic resonance accurately predicts the prognosis of patients with dilated cardiomyopathy, the most frequent cause of heart failure.



Mirelis JG, Escobar-Lopez L, Ochoa JP, Espinosa MÁ, Villacorta E, Navarro M, Casas G, Mora-Ayestarán N, Barriales-Villa R, Mogollón-Jiménez MV, García-Pinilla JM, García-Granja PE, Climent V, Palomino-Doza J, García-Álvarez A, Álvarez-Barredo M, Cabrera-Borrego E, Ripoll-Vera T, Peña-Peña ML, Rodríguez-González E, Gallego-Delgado M, Gonzalez-Carrillo J, Fernández-Ávila A, Rodríguez-Palomares JF, Brugada R, Bayes-Genis A, Dominguez F, García-Pavía P. Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaeamic dilated cardiomyopathy. Eur J Heart Fail. 2022 Jul;24(7):1183-1196. <https://doi.org/10.1002/ejhf.2514>

EUROPEAN HEART JOURNAL

ONE CHANGE A DAY MAKES 365 CHANGES IN A YEAR

Many cardiovascular disorders can be prevented by taking action to reduce risk factors. Making even small behavioral changes and sticking with them over the long term can help to preserve cardiovascular health. This is the conclusion of a study conducted at the CNIC and published in the European Heart Journal. The study also demonstrates that the workplace is an ideal setting for programs promoting the adoption of heart-healthy habits and producing major health benefits.



García-Lunar I, van der Ploeg HP, Fernández Alvira JM, van Nassau F, Castellano Vázquez JM, van der Beek AJ, Rossello X, Fernández-Ortiz A, Coffeng J, van Dongen JM, Mendiguren JM, Ibáñez B, van Mechelen W, Fuster V. Effects of a comprehensive lifestyle intervention on cardiovascular health: the TANSNIP-PESA trial. *Eur Heart J.* 2022 Oct 11;43(38):3732-3745. <https://doi.org/10.1093/eurheartj/ehac378>

ELIFE

CNIC SCIENTISTS UNCOVER OPPOSING ROLES OF P38 PROTEINS IN CARDIAC HYPERTROPHY

A study carried out by scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and led by Dr. Guadalupe Sabio has identified a key role for the MKK3/6–p38 γ/δ signaling pathway in the development of cardiac hypertrophy. The results, published in the journal eLife, suggest that inhibition of p38 γ/δ could be a useful therapeutic strategy for diseases such as hypertrophic cardiomyopathy; however, this avenue remains unexplored because of the lack of specific inhibitors



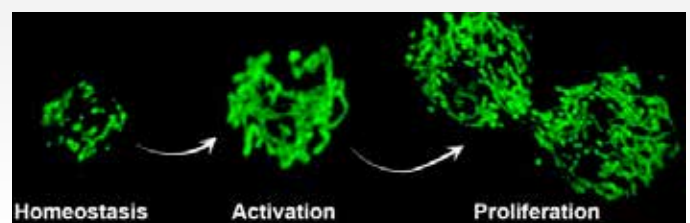
for these kinase enzymes. The study also shows the opposite effect upon inhibition of another member of this protein family, p38 α , indicating that long-term clinical use of p38 α inhibitors to treat chronic disease risks damage to the heart.

Romero-Becerra R, Mora A, Manieri E, Nikolic I, Santamans AM, Montalvo-Romeral V, Cruz FM, Rodríguez E, León M, Leiva-Vega L, Sanz L, Bondía V, Filgueiras-Rama D, Jiménez-Borreguero LJ, Jalife J, Gonzalez-Teran B, Sabio G. MKK6 deficiency promotes cardiac dysfunction through MKK3-p38 γ/δ -mTOR hyperactivation. *Elife.* 2022 Aug 16;11:e75250. <https://doi.org/10.7554/eLife.75250>

CELL STEM CELL

RESEARCHERS AT CNIC, UPF, ICREA, CIBERNED AND CIBERFES IDENTIFY A MECHANISM THAT MAINTAINS MITOCHONDRIA FUNCTION IN MUSCLE STEM CELLS AND THAT CAN BE STIMULATED IN OLD AGE

Researchers at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), Universidad Pompeu Fabra, ICREA, Centro de Investigación Biomédica de Enfermedades Neurodegenerativas (CIBERNED) and Centro de Investigación Biomédica en Red Fra-



gilidad y Envejecimiento Saludable (CIBERFES) have identified a physiological mechanism that sustains the regenerative capacity of muscle stem cells, and that fails at old age. This failure can be overcome genetically and pharmacologically, hence restoring old stem cell regenerative functions.

Hong X, Isern J, Campanario S, Perdiguero E, Ramírez-Pardo I, Segalés J, Hernansanz-Agustín P, Curtabbi A, Deryagin O, Pollán A, González-Reyes JA, Villalba JM, Sandri M, Serrano AL, Enríquez JA, Muñoz-Cánoves P. Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy. *Cell Stem Cell.* 2022 Sep 1;29(9):1298-1314.e10. <https://doi.org/10.1016/j.stem.2022.07.009>

THE NEW ENGLAND JOURNAL OF MEDICINE

THE POLYPILL REDUCES CARDIOVASCULAR MORTALITY BY 33% IN PATIENTS TREATED AFTER MYOCARDIAL INFARCTION

The polypill developed by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Ferrer, which includes three drugs (aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin), is effective at preventing secondary adverse cardiovascular events in people who have previously had a heart attack. The polypill reduces mortality from cardiovascular causes in this population by 33%.



Castellano JM, Pocock SJ, Bhatt DL, Quesada AJ, Owen R, Fernandez-Ortiz A, Sanchez PL, Marin Ortuño F, Vazquez Rodríguez JM, Domingo-Fernández A, Lozano I, Roncaglioni MC, Baviera M, Foresta A, Ojeda-Fernandez L, Colivicchi F, Di Fusco SA, Doehner W, Meyer A, Schiele F, Ecamot F, Linhart A, Lubanda JC, Barczi G, Merkely B, Ponikowski P, Kasprzak M, Fernandez Alvira JM, Andres V, Bueno H, Collier T, Van de Werf F, Perel P, Rodriguez-Manero M, Alonso Garcia A, Proietti M, Schoos MM, Simon T, Fernandez Ferro J, Lopez N, Beghi E, Bejot Y, Vivas D, Cordero A, Ibañez B, Fuster V; SECURE Investigators. Polypill Strategy in Secondary Cardiovascular Prevention. *N Engl J Med.* 2022 Sep 15;387(11):967-977. <https://doi.org/10.1056/NEJMoa2208275>

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

SCIENTISTS AT THE CNIC AND HOSPITAL PUERTA DE HIERRO DEVELOP A TOOL TO DETERMINE IF DILATED CARDIOMYOPATHY HAS A GENETIC ORIGIN

Scientists at the CNIC and Hospital Universitario Puerta de Hierro Majadahonda have developed a software application that predicts the likelihood that a case of dilated cardiomyopathy is caused by a genetic mutation. The research was carried out in collaboration with hospitals in Spain, Italy, and the Netherlands. The findings, published in the *Journal of the American College of Cardiology (JACC)*, will



allow physicians to adjust the treatment of dilated cardiomyopathy patients appropriately and to identify family members who have also inherited the disease. The software application is available online at www.madriddcmscore.com.

Escobar-Lopez L, Ochoa JP, Royuela A, Verdonschot JAJ, Dal Ferro M, Espinosa MA, Sabater-Molina M, Gallego-Delgado M, Larrañaga-Moreira JM, Garcia-Pinilla JM, Basurte-Elorz MT, Rodríguez-Palomares JF, Climent V, Bermudez-Jimenez FJ, Mogollón-Jiménez MV, Lopez J, Peña-Peña ML, Garcia-Alvarez A, López-Abel B, Ripoll-Vera T, Palomino-Doza J, Bayes-Genis A, Brugada R, Idiazabal U, Mirelis JG, Dominguez F, Henkens MTHM, Krapels IPC, Brunner HG, Paldino A, Zaffalon D, Mestroni L, Sinagra G, Heymans SRB, Merlo M, Garcia-Pavia P. Clinical Risk Score to Predict Pathogenic Genotypes in Patients With Dilated Cardiomyopathy. *J Am Coll Cardiol.* 2022 Sep 20;80(12):1115-1126. <https://doi.org/10.1016/j.jacc.2022.06.040>

CELLULAR AND MOLECULAR LIFE SCIENCES

NEW MECHANISM LINKING INFLAMMATION AND PATHOLOGIC CARDIOVASCULAR REMODELING

The immune-inflammatory response contributes to the pathological remodeling of arteries in various cardiovascular diseases. Research published in *CMLS* has shed new light on one of the mechanisms



linking the immune-inflammatory response to vascular disease by describing the key role played by the early lymphocyte activation antigen CD69.

Jiménez-Fernández M, Rodríguez-Sinovas C, Cañes L, Ballester-Servera C, Vara A, Requena S, de la Fuente H, Martínez-González J, Sánchez-Madrid F. CD69-oxLDL ligand engagement induces Programmed Cell Death 1 (PD-1) expression in human CD4+ T lymphocytes. *Cell Mol Life Sci.* 2022 Aug 5;79(8):468. <https://doi.org/10.1007/s00018-022-04481-1>

BRITISH JOURNAL OF PHARMACOLOGY

CNIC SCIENTISTS IDENTIFY A NEUROPROTECTIVE ACTION OF METOPROLOL AFTER A STROKE

A drug costing just €2 a shot can protect the brain during a stroke and greatly reduce long-term incapacity. Metoprolol, a beta-blocker in routine use in cardiology for more than 40 years, has now been shown to have a specific neuroprotective effect.

Clemente-Moragón A, Oliver E, Calle D, Cussó L, Gómez M, Pradillo JM, Castejón R, Rallón N, Benito JM, Fernández-Ferro JC, Carneado-Ruiz J, Moro MA, Sánchez-González J, Fuster V, Cortés-Canteli M, Desco M, Ibáñez B. Neutrophil β 1 adrenoceptor blockade blunts stroke-associated neuroinflammation. Br J Pharmacol. Epub 2022 Nov 20. Br J Pharmacol. 2023 Feb;180(4):459-478. <https://doi.org/10.1111/bph.15963>



JOURNAL OF CLINICAL INVESTIGATION

CNIC SCIENTISTS IDENTIFY A FACTOR THAT PROTECTS THE HEART AGAINST DAMAGE AFTER A HEART ATTACK

A study carried out at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has identified a key factor that protects the heart after a heart attack. The study, led by Dr. Pilar Martín, who heads the Regulatory Molecules of Inflammatory Processes group at the CNIC, was published in the Journal of Clinical Investigation. The study shows that the expression of the receptor CD69 on regulatory T lymphocytes confers protection after a myocardial infarction by acting as a checkpoint for the exacerbated inflammation that causes medium-term cardiac injury.



Blanco-Domínguez R, de la Fuente H, Rodríguez C, Martín-Aguado L, Sánchez-Díaz R, Jiménez-Alejandro R, Rodríguez-Arabaolaza I, Curtabbi A, García-Guimaraes MM, Vera A, Rivero F, Cuesta J, Jiménez-Borreguero LJ, Cecconi A, Duran-Cambra A, Taurón M, Alonso J, Bueno H, Villalba-Orero M, Enríquez JA, Robson SC, Alfonso F, Sánchez-Madrid F, Martínez-González J, Martín P. CD69 expression on regulatory T cells protects from immune damage after myocardial infarction. J Clin Invest. 2022 Nov 1;132(21):e152418. <https://doi.org/10.1172/JCI152418>

NATURE CARDIOVASCULAR RESEARCH

CNIC SCIENTISTS IDENTIFY THE CAUSE OF ARRHYTHMIAS AND SUDDEN DEATH IN ANDERSEN-TAWIL SYNDROME TYPE 1

The Centro Nacional de Investigaciones Cardiovasculares (CNIC) has discovered the cause of arrhythmias and sudden death in the rare disease Andersen-Tawil syndrome type 1 (ATS1), which is caused by mutations affecting potassium channels that regulate electrical activity and the intracellular calcium cycle in cardiac and skeletal muscle.



Macías A, González-Guerra A, Moreno-Manuel AI, Cruz FM, Gutiérrez LK, García-Quintás N, Roche-Molina M, Bermúdez-Jiménez F, Andrés V, Linarejos Vera-Pedrosa M, Martínez-Carrascoso I, Bernal JA, Jalife J. Kir2.1 dysfunction at the sarcolemma and the sarcoplasmic reticulum causes arrhythmias in a mouse model of Andersen-Tawil syndrome type 1. Nat Cardiovasc Res. 2022 Oct;1:900-917. <https://doi.org/10.1038/s44161-022-00145-2>

CIRCULATION

SPECIFIC MODIFIER GENES DETERMINE THE EFFECT OF MUTATIONS THAT CAUSE NON-COMPACTION CARDIOMYOPATHY

Non-compaction cardiomyopathy is a heart condition caused by defects that arise during fetal development and can have diverse health impacts in affected individuals, including sudden cardiac death. The Intercellular Signaling in Cardiovascular Development and Disease group at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) previously reported that this disease can be caused by two distinct mutations in the *Mindbomb1* gene (*Mib1*).

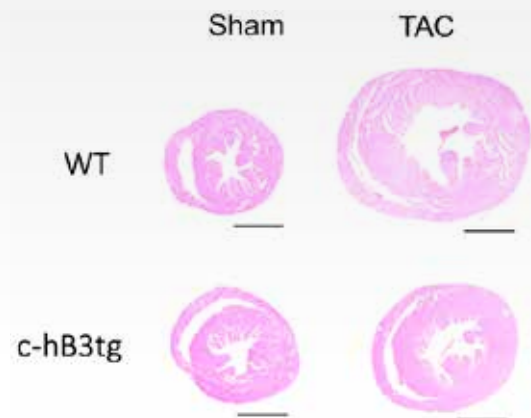


Siguero-Álvarez M, Salguero-Jiménez A, Grego-Bessa J, de la Barrera J, MacGrogan D, Prados B, Sánchez-Sáez F, Piñeiro-Sabarís R, Felipe-Medina N, Torroja C, Gómez MJ, Sabater-Molina M, Escribá R, Richaud-Patin I, Iglesias-García O, Sbroggio M, Callejas S, O'Regan DP, McGurk KA, Dopazo A, Giovinnazzo G, Ibañez B, Monserrat L, Pérez-Pomares JM, Sánchez-Cabo F, Pendas AM, Raya A, Gimeno-Blanes JR, de la Pompa JL. A Human Hereditary Cardiomyopathy Shares a Genetic Substrate with Bicuspid Aortic Valve. *Circulation*. Epub 2022 Nov 3. *Circulation*. 2023 Jan 3;147(1):47-65. <https://doi.org/10.1161/CIRCULATIONAHA.121.058767>

BASIC RESEARCH IN CARDIOLOGY

A NEW THERAPEUTIC TARGET FOR THE PREVENTION OF HEART FAILURE DUE TO AORTIC STENOSIS

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified a new therapeutic target for the prevention of heart failure linked to aortic stenosis. The study was led by Dr. Borja Ibañez, Clinical Research Director at the CNIC, cardiologist at Hospital Universitario Fundación Jiménez Díaz, and member of the Spanish cardiovascular research network (CIBERCV). The study shows that overexpression in cardiac muscle cells of beta-3 adrenergic receptor, a member of the beta adrenergic system, can prevent or even reverse heart failure in a mouse model of aortic stenosis, a condition that currently has few therapeutic options.

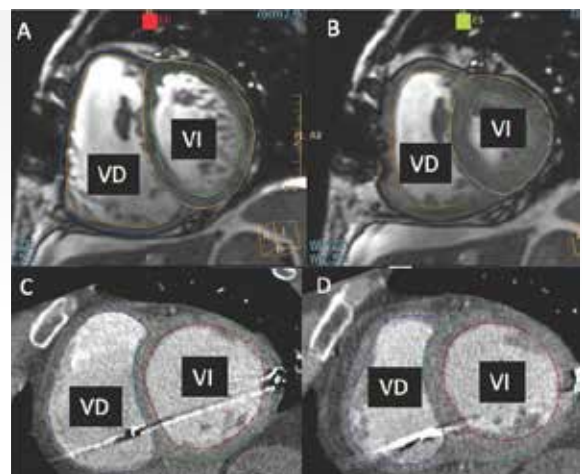


Pun-García A, Clemente-Moragón A, Villena-Gutierrez R, Gómez M, Sanz-Rosa D, Díaz-Guerra A, Prados B, Medina JP, Montó F, Ivorra MD, Márquez-López C, Cannavo A, Bernal JA, Koch WJ, Fuster V, de la Pompa JL, Oliver E, Ibañez B. Beta-3 adrenergic receptor overexpression reverses aortic stenosis-induced heart failure and restores balanced mitochondrial dynamics. *Basic Res Cardiol*. 2022 Nov 29;117(1):62. <https://doi.org/10.1007/s00395-022-00966-z>

EUROPEAN JOURNAL OF HEART FAILURE

A PROMISING DRUG TREATMENT FOR PATIENTS WITH PULMONARY HYPERTENSION ASSOCIATED WITH HEART DISEASE

There is currently no specific treatment for pulmonary hypertension associated with heart disease, a highly prevalent condition with a poor prognosis. Now, a study from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Hospital Clínic de Barcelona/IDIBAPS has shown that mirabegron, a drug that acts on the beta-3 adrenergic receptor, may have a beneficial effect on right ventricular function.



García-Álvarez A, Blanco I, García-Lunar I, Jordà P, Rodríguez-Arias JJ, Fernández-Friera L, Zegri I, Nuche J, Gomez-Bueno M, Prat S, Pujadas S, Sole-Gonzalez E, Garcia-Cossio MD, Rivas M, Torrecilla E, Pereda D, Sanchez J, Garcia-Pavía P, Segovia-Cubero J, Delgado JF, Mirabet S, Fuster V, Barberá JA, Ibañez B; SPHERE-HF Investigators. β_3 adrenergic agonist treatment in chronic pulmonary hypertension associated with heart failure (SPHERE-HF): a double blind, placebo-controlled, randomized clinical trial. *Eur J Heart Fail*. Epub 2022 Dec 4. *Eur J Heart Fail*. 2023 Mar;25(3):373-385. <https://doi.org/10.1002/ehjhf.2745>

ELIFE

CNIC SCIENTISTS IDENTIFY THE ESSENTIAL ROLE OF CELL-SURFACE "NANOFOLDS" AND "GLUE" IN THE MECHANICAL RESPONSE OF CELLS

A study at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has revealed that subcellular structures called caveolae play an essential role in cell mechanics. The results suggest that impaired caveolar function could be involved in a variety of processes, including platelet aggregation, cardiovascular disease, fibrosis, and tumor formation



Lolo FN, Pavón DM, Grande A, Elósegui Artola A, Segatori VI, Sánchez S, Trepát X, Roca-Cusachs P, Del Pozo MA. Caveolae couple mechanical stress to integrin recycling and activation. *Elife*. 2022 Oct 20;11:e82348. <https://doi.org/10.7554/eLife.82348>

BLOOD

RXR, THE CELL PROTEIN THAT KEEPS BLOOD STEM CELLS YOUNG AND FIT

The cell protein retinoid X receptor (RXR) is a key factor in the maintenance of hematopoietic stem cells, the immature stem cells that give rise to all the blood cell lineages. RXR ensures that these cells remain youthful and fit, thereby reducing the risk of developing myeloproliferative syndromes as the body ages.

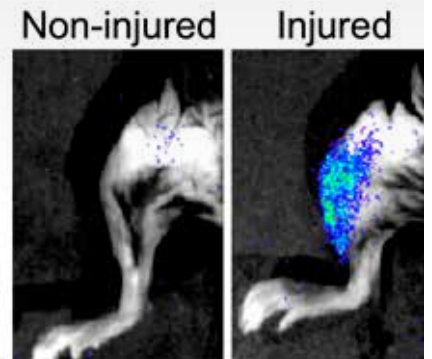


Menéndez-Gutiérrez MP, Porcuna J, Nayak R, Paredes A, Niu H, Núñez V, Paranjpe A, Gómez MJ, Bhattacharjee A, Schnell DJ, Sánchez-Cabo F, Welch JS, Salomonis N, Cancelas JA, Ricote M. Retinoid X receptor promotes hematopoietic stem cell fitness and quiescence and preserves hematopoietic homeostasis. *Blood*. Epub Nov 2022. *Blood*. 2023 Feb 9;141(6):592-608. <https://doi.org/10.1182/blood.2022016832>

NATURE

RESEARCHERS CHARACTERIZE RARE, DAMAGED CELLS THAT BLOCK THE FUNCTIONS OF THEIR NEIGHBOUR HEALTHY CELLS AND IDENTIFY WAYS TO NEUTRALIZE THEM AND IMPROVE TISSUE REGENERATION

Researchers at the Universitat Pompeu Fabra (UPF), ICREA, CIBERNED, CNIC and Altos Labs, among other national and international collaborators, have characterized how damaged cells (senescent cells) that inevitably arise after injury negatively impact tissue regeneration, and how this mechanism operates actively in old age, but surprisingly also in young age. This negative action can be overcome genetically and pharmacologically, hence restoring stem cell regenerative functions.

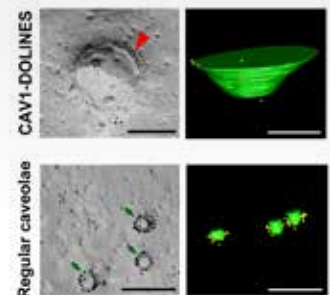


Moiseeva V, Cisneros A, Sica V, Deryagin O, Lai Y, Jung S, Andrés E, An J, Segalés J, Ortet L, Lukesova V, Volpe G, Benguria A, Dopazo A, Benitah SA, Urano Y, Del Sol A, Esteban MA, Ohkawa Y, Serrano AL, Perdiguero E, Muñoz-Cánoves P. Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. *Nature*. Epub 2022 Dec 21. *Nature*. 2023 Jan;613(7942):169-178. <https://doi.org/10.1038/s41586-022-05535-x>

NATURE CELL BIOLOGY

A CNIC STUDY SHOWS THAT CELLS POSSESS 2 MECHANISMS TO ALLOW THEM TO RESPOND TO DIFFERENT FORCE RANGES

A study carried out at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) heralds a paradigm change in the field of mechanobiology. The study reveals that cells respond to forces of differing strength using two distinct mechanisms, one mediated by minute, cup-like invaginations on the cell surface called caveolae and the other by newly discovered large membrane depressions the study authors call dolines.



Lolo FN, Walani N, Seemann E, Zalvidea D, Pavón DM, Cojoc G, Zamai M, Viaris de Lesegno C, Martínez de Benito F, Sánchez-Álvarez M, Uriarte JJ, Echarri A, Jiménez-Carretero D, Escolano JC, Sánchez SA, Caiolfa VR, Navajas D, Trepát X, Guck J, Lamaze C, Roca-Cusachs P, Kessels MM, Qualmann B, Arroyo M, Del Pozo MA. Caveolin-1 dolines form a distinct and rapid caveolae-independent mechanoadaptation system. *Nat Cell Biol*. Epub 2022 Dec 21. *Nat Cell Biol*. 2023 Jan;25(1):120-133. <https://doi.org/10.1038/s41556-022-01034-3>

4

CNIC NEWS AND VIEWS

1. VISITING SCIENTISTS AT THE CNIC



Spain's growing international profile in scientific research makes it an increasingly attractive destination for visiting scientists from all over the world. In 2022, 339 scientists and technicians came to the CNIC for research visits lasting from 2 to 12. Of these visiting researchers, 15% came from foreign institutions, from a total of 11 countries.

JESÚS SERRA FOUNDATION VISITING RESEARCHERS PROGRAM

The Jesús Serra Foundation and the CNIC have worked together since 2013 to bring visiting scientists to the CNIC within the framework of the Jesús Serra Foundation Visiting Researchers program.

The Program supports visits by international scientists to Spanish research centers, with the aim of building strong inter-institutional bonds and promoting new lines of research.

Jesús Serra Foundation President Federico Halpern explained that an important aim of the Program is to “ensure the continuity of research projects that might otherwise be paralyzed due to lack of resources.”

After a hiatus during the Covid-19 pandemic, in 2022 the Jesús Serra Foundation and the CNIC resumed their participation and held a joint event to welcome the latest four visiting researchers joining the CNIC: Hesham Sadek, Guillermo Oliver, Benedetta Izzi, and Raffaele Strippoli. At the event, CNIC Scientific Directors Borja Ibáñez and Vicente Andrés and Managing Director Alberto Sanz were accompanied by Jesús Serra Foundation Vice President Laura Halpern, General Director Ignacio Gallardo-Bravo, and Deputy Director Susana Codina.

This brings the total number of Jesús Serra fellows linked to the CNIC to 7, the preceding beneficiaries being Sandeep V. Pandit, Stuart Pocock and Gabriel Núñez.

CNIC General Director Dr. Valentín Fuster said that “This Visiting Researchers Program is an especially good match with the CNIC’s core aim to attract international talented scientists in order to achieve excellence in cardiovascular research. I am sure that great things will come out of this collaboration”.



**Fundación
Jesús Serra**
Catalana Occidente

WOMEN FOR AFRICA FOUNDATION



In 2022, the CNIC participated as a host Center in the 8th call for fellowships from the Science by Women Foundation. In this call, 22 senior African women scientists were selected for research stays at 21 top Spanish research centers in the following areas: health and biomedicine, agriculture and food security, water, and energy and climatic change.

Mujeres por África 8th Edition- Science by woman- Mujeres por África (mujeresporafrica.es)

Dr. Beatrice Olatundun Oluwatayo, NVRI, Vom, Nigeria was selected to visit the CNIC in the fall of 2023 to collaborate on studies related to cardiovascular health promotion. This collaboration was financed with CNIC Severo Ochoa Grant CEX2020-001041-S

EU CONTEST FOR YOUNG SCIENTISTS (EUCYS)

The CNIC participated in the EUCYS through special award consisting of a three-day stay to the CNIC for a scientist with an individual biomedicine project who, according to the jury, will benefit most from this stay. The award covered travel, meals, and accommodation.

The winner, Lucia Cengelova, will visit the CNIC in June 2023 to learn about the Center's projects directly from our researchers. She will also learn about the infrastructure and technology available at the Center and how these are used to address and solve the challenges of cardiovascular health research.

This award was financed with CNIC Severo Ochoa Grant CEX2020-001041-S.



2-AWARDS AND HONORS

MAHIDOL AWARD FOR MEDICINE PRESENTED TO DR. FUSTER

Her Royal Highness Princess Maha Chakri Sirindhorn of Thailand presented the 2020 Prince Mahidol Award for Medicine to CNIC Director Dr. Valentin Fuster. Due to the COVID-19 Pandemic, Dr. Fuster was unable to collect the award in person until 2022.

This prestigious award acknowledges Dr. Fuster's international leadership over the last forty years, achieved through his innovative contributions to cardiovascular medicine, both in research and clinic care, and more recently as an advocate for global cardiovascular health promotion throughout the world.



DR. GUADALUPE SABIO BUZO AWARDED THE MEDAL OF EXTREMADURA



Guadalupe Sabio Buzo, who leads the group 'The role of the stress-activated kinases in the development of cardiovascular diseases, diabetes and cancer', received the Medal of Extremadura. The President of the Regional Government of Extremadura, Guillermo Fernández Vara, highlighted her work for "bringing science to society, to both adults and children". The winners of the Medal of Extremadura are proposed by citizens, businesses, and municipalities.

Dr. Sabio's work examines features of obesity, such as the altered fat metabolism, dysregulation of internal clocks, and cellular stress, which could be the cause of this disease. Her research also shows that men's higher chance of developing cancer than women might be due to differences in the production of hormones by fatty tissue.



Ganadores Premio CEU Ángel Herrera:
ÉTICA Y VALORES



Valentín Fuster

Por su compromiso social como divulgador, atendiendo a la necesidad de la promoción de hábitos saludables con el objetivo de conseguir mejorar la salud integral de la población.

DR. VALENTÍN FUSTER, GARLANDED WITH THE CEU ÁNGEL HERRERA AWARD

Dr. Valentín Fuster received the CEU Ángel Herrera award in the Ethics and Values category from the San Pablo CEU University Foundation. The award acknowledges Dr. Fuster's social commitment as a disseminator and a promoter of healthy habits. The jury also highlighted Dr. Fuster's important contributions to cardiovascular medicine throughout his extensive scientific career, which have made him the most cited Spanish researcher in history.

THE FRANCISCO COBOS FOUNDATION GRANTS THE 16TH SCIENTIFIC CAREER AWARD TO DR. JOSÉ ANTONIO ENRÍQUEZ

The Francisco Cobos Foundation granted its 16th Scientific Career Award to the CNIC scientist José Antonio Enriquez Dominguez. The €50,000 prize was awarded in recognition of his contributions to the study of mitochondrial biogenesis, respiratory chain function, and mitochondrial pathophysiology and aging.



THE AMERICAN COLLEGE OF CARDIOLOGY CREATES THE VALENTÍN FUSTER AWARD FOR INNOVATION IN SCIENCE

The American College of Cardiology (ACC) has instituted a new award in honor of Dr. Valentín Fuster, to be called the Valentín Fuster Award for Innovation in Science. The award has been established in recognition of Dr. Fuster's significant past and present contributions to cardiovascular medicine, which have made him a world leader in scientific research in this field. Additionally, the award underlines his innovative vision in the promotion of science through transforming mechanisms. The ACC further emphasized that this award recognizes Dr. Fuster's international leadership in promoting scientific research applied to health, with the aim of improving patient care and heart health. The annual award will be given each year to a selected doctor over the next 15 years.



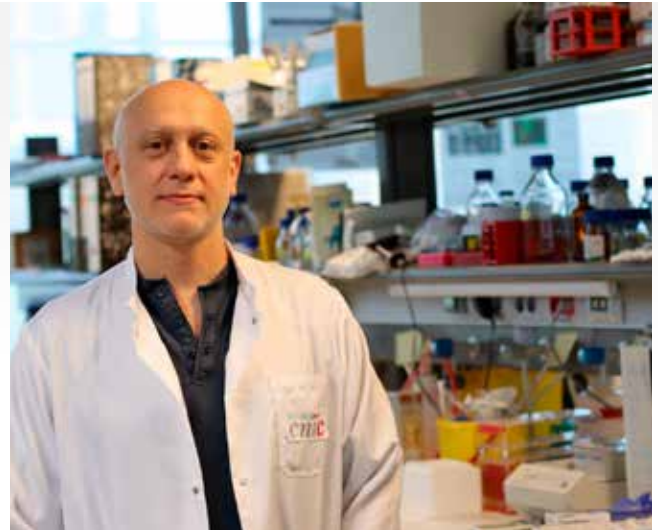
DR. ANDRÉS HIDALGO OBTAINS THE 18TH ANNUAL HEALTH SCIENCES AWARD FROM THE FUNDACIÓN CAJA RURAL GRANADA

The article "Mapping the immune behaviors of inflammation", by the CNIC research group led by Andrés Hidalgo, has received the 18th annual Health Sciences Award from Fundación Caja Rural Granada. The study, published in *Nature* (Jan;601(7893):415-421, 2022), presents "a new way of describing immune cells during the process of inflammation in living organisms". This is an important advance because, as Andrés Hidalgo explained, "inflammation, as a protective organismal response to injury or stress has both advantages and disadvantages." The Caja Rural Granada Foundation co-organizes this award with the Health Technology Park Foundation, with the support of the Regional Government of Andalusia, the University of Granada and the Colleges of Physicians and Pharmacists of Granada.



DR. ANDRÉS HIDALGO, NEW MEMBER OF EMBO

CNIC researcher Andrés Hidalgo has been named a member of EMBO, the European Molecular Biology Organization. Dr. Hidalgo's incorporation brings the number of CNIC scientists in EMBO to six: José Antonio Enríquez, Miguel Ángel del Pozo, Miguel Torres, Pura Muñoz, and Francisco Sánchez Madrid. EMBO members participate actively in the organization. The various committees participate in the EMBO Council and the advisory editorial boards of the EMBO press reviews. The committees also evaluate applications for EMBO funding and act as mentors to scientists at the start of their careers. The new member was welcomed formally at the EMBO annual members meeting, held from 26-28 October, 2022.



DR. VALENTÍN FUSTER RECEIVES A PRESTIGIOUS AWARD FROM THE CARDIOVASCULAR RESEARCH FOUNDATION



Dr. Fuster, Director of the CNIC and Physician-in-Chief of Mount Sinai Hospital, was awarded the 2022 Transcatheter Cardiovascular Therapeutics (TCT) Career Achievement Award by the Cardiovascular Research Foundation (CRF). The award recognizes Dr. Fuster's extraordinary contributions to the field of interventional cardiology and the transformation of patient care through his professional leadership, research projects, and mentorship of many healthcare professionals and researchers.



THE 2022 COMMUNITY OF MADRID MARGARITA SALAS RESEARCH AWARD GOES TO DR. JOSÉ ANTONIO ENRÍQUEZ

The Community of Madrid awarded the Margarita Salas Research Career Award for 2022 to Dr. José Antonio Enríquez, head of the Functional Genetics of the Oxidative Phosphorylation System group at the CNIC, for his important contributions to the understanding of mitochondrial biogenesis and bioenergetics. The award, which includes a financial endowment of €42,000, recognizes Dr. Enríquez's achievements, mentorship, and national and international impact throughout his career.

THE CNIC POLYPILL RECEIVES THE 2022 ABC HEALTH AWARD FOR BEST MEDICINE



Cardiovascular disease is often referred to as "the silent pandemic" and is currently the leading cause of death globally. Experts point out that the control of risk factors, together with the promotion of healthy lifestyle habits, have a clear impact on cardiovascular mortality.

Recently, the SECURE study, led by CNIC General Director Dr. Valentín Fuster, has shown that the cardiovascular polypill reduces

cardiovascular mortality after a first myocardial infarction by 33% (N Engl J Med. 2022 Sep 15;387(11):967-977).

This finding has enabled the polypill, developed by the CNIC and Laboratorio Ferrer, to win the Health Award for Medicine of the Year from the Spanish newspaper ABC. The award was presented by Cristobal Belda-Iniesta, Director of the Instituto de Salud Carlos III, to Oscar Pérez Albet of Ferrer.

Dr. Fuster had the idea of combining the three drugs prescribed after a heart attack into a single pill. This simplifies patients' medication regime and helps to counter forgetfulness. The polypill developed by the CNIC with Ferrer is not only more convenient, it is also more effective, reducing mortality after a heart attack by 33%.

Expressing his gratitude for the award, Dr. Valentín Fuster remarked that this drug is the result of a 15-year project and that it is a "very important example of public-private collaboration between the CNIC and Ferrer Laboratories".

DR. PABLO GARCÍA PAVÍA RECEIVES THE COMCÓRDOBA-CAIXABANK RESEARCH AWARD

The Illustrious Official College of Physicians of Córdoba, through its partnership with CaixaBank, awarded the XX COMCÓRDOBA-CAIXABANK Research Prize to Dr. Pablo García Pavía. The prize, awarded on November 25, 2022, recognized Dr. García Pavía's study "Association of genetic variants with outcomes in patients with nonischemic dilated cardiomyopathy", published in the Journal of the American College of Cardiology (JACC 78, 1682-99, 2021).

Dr. García Pavía leads the Inherited Cardiomyopathies group at the CNIC and heads the Heart Failure and Familial Cardiopathies Section of the Cardiology Unit at Puerta de Hierro University Hospital. He is also an investigator in the Spanish research network on cardiovascular diseases (CIBERCV).



3 - GRANTS

THE BRIGHTFOCUS FOUNDATION AWARDS AN ALZHEIMER'S DISEASE RESEARCH STANDARD AWARD TO A CNIC PROJECT.

The BrightFocus Foundation has awarded an Alzheimer's Disease Research Standard Award to the project "Understanding the impact of midlife cardiovascular risk factors & subclinical atherosclerosis on brain health: a role in Alzheimer's disease". The project is coordinated by CNIC researcher Dr. Marta Cortés Canteli together with CNIC General Director Dr. Valentín Fuster and Dr. Juan Domingo Gispert, a researcher at the CNIC and the Barcelonaβeta Brain Research Center.

The award provides project funding of \$100,000 a year for 3 years. Participants in the project include CNIC colleagues Dr. Borja Ibáñez and Dr. Fátima Sanchez Cabo, together with external partners Dr. Kaj Blennow and Dr. Henrik, Zetterberg at the University of Gothenburg (Sweden), who are world experts in plasma biomarker determination.

The project focuses on the longitudinal determination of specific plasma biomarkers of neuronal damage, neuroinflammation, and Alzheimer's disease in PESA-CNIC-SANTANDER study participants. The BrightFocus Foundation is a nonprofit organization that supports



research and provides public education on brain and eye diseases, including Alzheimer's disease, macular degeneration, and glaucoma.

DR. DAVID FILGUEIRAS RECEIVES THE YOUNG INVESTIGATOR AWARD FROM THE ASTRAZENECA FOUNDATION



The AstraZeneca Foundation Young Investigator Award in the category of Cardiovascular, Renal and Metabolic Diseases has been awarded to a CNIC project. The project, "Use of remote monitoring technology and cardiac electrical signal in patient-specific risk stratification

for deterioration of heart failure and potentially lethal ventricular arrhythmias", is coordinated by Dr. David Filgueiras, who heads the Advanced Development on Arrhythmia Mechanisms and Therapies group at the CNIC and is a cardiologist at Hospital Clínico San Carlos.

CNIC PROJECTS SELECTED IN THE "LA CAIXA" FOUNDATION HEALTH RESEARCH PROJECTS 2022 CALL FOR PROPOSALS

Funding has been awarded to four CNIC projects:

“Identifying new immune targets to treat cardiovascular diseases”- principal investigator Dr. Almudena R. Ramiro

“New approaches to regenerate cardiac tissue after infarction” – principal investigator Dr. Rui Benedito

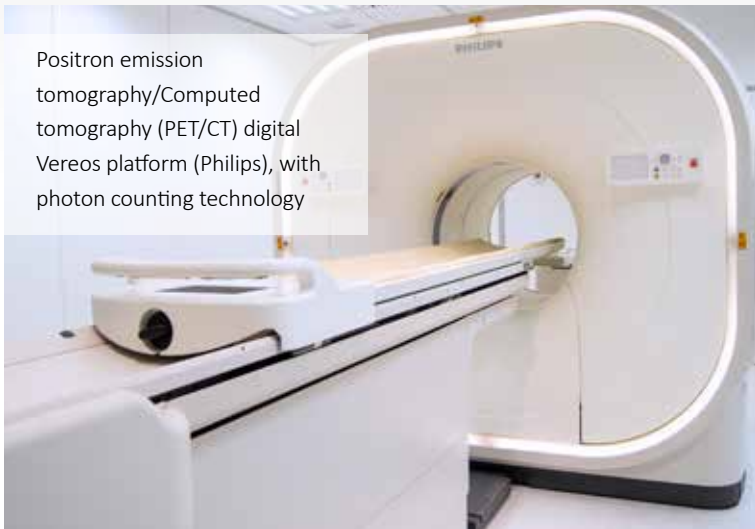
“Identifying new biomarkers for the progression of heart failure” - principal investigator Dr. José Javier Fuster

The CNIC is also involved in a fourth project in the call. CNIC investigator Dr. Borja Ibáñez Cabeza is a participant in the project “Rapid diagnosis of coronary heart disease to prevent early mortality”, a consortium project whose principal investigator is Teresa Correia of the Centro de Ciências do Mar do Algarve (CCMAR) (Portugal).

The CaixaResearch Foundation Health Research Projects 2022 call awarded funding to 33 biomedical and health projects at research centers and universities in Spain and Portugal.



NEW EQUIPMENT FOR THE TRIMA@CNIC NODE OF THE DISTRIBUTED BIOMEDICAL IMAGING NETWORK (REDIB)



Positron emission tomography/Computed tomography (PET/CT) digital Vereos platform (Philips), with photon counting technology



ReDIB is a distributed Unique Scientific and Technical Infrastructure (ICTS) that provides services in molecular and functional imaging and advanced and high-performance imaging. ReDIB is integrated in the current ICTS Map, approved by the Council for Scientific, Technological and Innovation on November 6, 2018, and currently consists of the Advanced Infrastructure for Translational Imaging (TRIMA) node at the CNIC, the CIC-biomaGUNE Molecular and Functional Imaging Platform, the Imaging Platform of La Fe University Hospital Research Foundation, and the Bio-imaging Unit at Madrid Complutense University. ReDIB is coordinated by Dr. Gonzalo Pizarro, Head of the Cardiology Department at Hospital Ruber Juan Bravo Quironsalud and a clinical researcher at the CNIC.

Each ICTS provides unparalleled facilities in its specialist area. ICTS carry out cutting-edge research of the highest quality and act as centers for the transmission, exchange, and preservation of knowledge, technology transfer, and the promotion of innovation. ICTS are publicly owned infrastructure facilities that provide unique

services through competitive access.

In the 2022 national ICTS call, the following new equipment and facilities were approved for incorporation in the in TRIMA@CNIC node:

-A SPECT, PET, CT imaging laboratory that includes both the imaging tools (SPECT-CT equipment) and the setting up of a radiochemical laboratory necessary for the synthesis and characterization of new SPECT radiotracers.

The acquired system has three imaging modalities (PET, SPECT, and CT) that can be used to study 3-4 animals at the same time, increasing the capacity of the unit. It also allows studies of cardiac and/or respiratory synchronism for improved image quality.

In 2022, 17 projects accessed TRIMA@CNIC infrastructure through the Competitive Open Access mechanism, and 12 projects accessed through the Access on Demand mechanism.

Detailed information at: <https://www.redib.net/en-redib>

4 - SCIENTIFIC EVENTS

CNIC CONFERENCE ON CARDIAC REGENERATION: FROM MECHANISMS TO THERAPY



Regeneration of the heart is one of the greatest challenges in scientific research. Unlike other animals, such as the salamander or zebrafish, humans are unable to regenerate their tissues and organs, but the reason for this remains a mystery.

This was the topic of the 2022 CNIC Conference, held November 10-12. The meeting addressed the latest advances in understanding the mechanisms of cardiac repair in naturally regenerating organisms and how these mechanisms can be stimulated in mammals, which lack this regenerative capacity. The CNIC Conference was organized by Miguel Torres, Nadia Mercader, Ely Tanaka, Hesham Sadek, and Mauro Giacca. The meeting brought together more than a hundred international experts for three days to discuss the scientific challenge of achieving regeneration of the human heart to prevent heart failure.

Topics addressed at the meeting encompassed metabolism and the cardiomyocyte microenvironment during cardiac regeneration, cell-cell crosstalk, and the translational path to cardiac regeneration using genetic and tissue engineering approaches.

The participants at the meeting discussed current controversies in the field of cardiac stem cells, as well as the failure, to date, to translate experimental therapies into clinical benefit.





CNIC Conference 2022
Cardiac Regeneration: from Mechanisms to Therapy
 Madrid
 November 10 - 12, 2022
 Registration: www.cnic-conference.com
 Attendance is limited to 100 participants.
 There is no registration fee.

Venue
Centro Nacional de Investigaciones Cardiovasculares (CNIC)
 Melchor Fernández Almagro, 5
 28029 Madrid, Spain

Organizers

 Miguel Torres Centro Nacional de Investigaciones Cardiovasculares (CNIC)	 Hesham Sadek UT Southwestern Medical Center	 Ely Tanaka IMP Vienna	 Nadia Mercader University of Bern	 Mauro Giacca King's College London
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CONFIRMED SPEAKERS

Jeroen Bakkert Hubrecht Institute	Nadia Mercader University of Bern	Hesham Sadek UT Southwestern Medical Center	Florian Weinberger University Medical Center Hamburg Eppendorf and German Center for Cardiovascular Research
Gabriele D'Uva Università di Bologna	Sasha Mendjan Institute of Molecular Biotechnology	Deepak Srivastava Gladstone Institute of Cardiovascular Disease	Karina Yaniv Weizmann Institute of Science
Mauro Giacca King's College London	Jeffrey Molkentin Cincinnati Children's Hospital Medical Center	Henry M. Sucov Medical University of South Carolina	Serena Zacchigna International Centre for Genetic Engineering and Biotechnology
Andrés Hidalgo CNIC, Spain	Pura Muñoz Pompeu Fabra University and CNIC	Ely Tanaka Vienna Biocenter	Lior Zangi Icahn School of Medicine, Mount Sinai
James Martin Baylor College of Medicine	Guillermo Oliver Northwestern University	Eldad Tzahor Weizmann Institute of Science	



CNIC INVITED SEMINARS

In 2022, the CNIC Invited Seminar program brought 20 speakers, most of them from international institutions, to present their findings at the CNIC in seminars open to the scientific community. Highlights included presentations by Rafael Yuste, The Neuro Technology Center at Columbia University, New York, USA and Manuel Mayr, The James Black Centre, King's College, University of London, UK.



19 Dec 2022
12:00 hr.
CNIC Auditorium

cnic

CNIC Invited Seminar
The neural code: emergent properties of neural circuits



Rafael Yuste
The NeuroTechnology Center at Columbia University, New York, USA

Chair:
Jorge Alegre-Cebollada



24 Oct 2022
12:00 pm
CNIC Auditorium

cnic

CNIC Invited Seminar
Proteomics Strategies to Identify New Diagnostic and Therapeutic Targets



Manuel Mayr
The James Black Centre, King's College, University of London, UK

Chair:
Jesús Vázquez

CNIC PHDAY

The CNIC PhDay is an annual meeting organized by PhD students and postdoctoral researchers at the CNIC. The event provides an open forum for the exchange new ideas and networking.

The theme of the 8th PhDay was "from Lab to life" and focused on the translation of scientific discoveries into more refined treatments and technologies. More than 240 early-stage scientists applied to participate in the event, but sadly space limitations meant that only 200 could attend.

The event began with a welcome address from Cristóbal Belda, General Director of Instituto Carlos III. The first part of the program was introduced with an opening debate between Dr. Fuster and Pau Gasol about common diseases, people who inspired them, and motivations in life. This was followed by a round-table discussion about rare diseases chaired by the physician David Araújo, co-founder of the Alexandra Perault Progeria Association, Esther Martínez, and Vicente Andrés.

There then came three sets of parallel workshops about career options in science, (covering industry, startups, and academia), science diplomacy, stress management, and soft skills.



In the second session of the program, Fernando García López, Chariman of the Ethics Committee of Salud Carlos III, gave a talk on bioethics. The closing lecture was given by Fide Mirón, an expert in rare diseases, as well as a patient diagnosed with Gunther's porphyria, who gave wonderful, touching, and encouraging messages to young researchers.

5 - OUTREACH ACTIVITIES

WORKING WOMEN'S DAY: "WE DO RESEARCH AT THE CNIC"

To mark International Women's Day, the CNIC organized a round-table discussed called 'We do research at the CNIC'. The event was led by Dr. Pilar Martín, head of the Regulatory Molecules of Inflammatory Processes group. The round table aimed to give a comprehensive overview of research at the CNIC from a range of female perspectives. The other participants were Dr. Lorena Esteban, a Juan de la Cierva postdoctoral fellow in the Genetic Control of the Development and Regeneration of Organs group; Irene Fernández, laboratory technician in the Cardiovascular Imaging and Population Studies group; Mercedes Grima, FPU predoctoral researcher in the Tissue Regeneration group; Laura Lalaguna, FPI SO predoctoral researcher in the Molecular Reg-



8 de marzo de 2022
Día Internacional de la Mujer Trabajadora (en Ciencias Biomédicas)

ELLAS INVESTIGAN



PILAR MARTÍN



IRENE FERNÁNDEZ



BEATRIZ LÓPEZ



MERCEDES GRIMA



LAURA LALAGUNA



LORENA ESTEBAN

Conoce la labor de las mujeres que trabajan en biomedicina en el CNIC

8 de marzo de 2022
12:00 h

Haz click [aquí](#) para asistir online.

ulation of Heart Failure group; and Beatriz López, FPI predoctoral researcher in the Hematovascular Pathophysiology group.

Each of the panelists explained their motivation for devoting themselves to science, what attracts them to scientific work, the projects they are involved in, and how they think their work contributes to society.

THE CNIC PARTICIPATES IN THE 2022 OPEN ADMINISTRATION WEEK



Semana Administración Abierta
27 junio - 1 julio 2022

RED DISTRIBUIDA DE IMAGEN BIOMÉDICA (REDIB) EN CNIC

30 de junio

Horario: 10:45-12:00

Lugar: Auditorio CNIC (www.cnic.es)

También disponible online:
<https://www.cnic.es/portal/abierta>





- **GONZALO PIZARRO:** "La Infraestructura científico técnica singular Red Distribuida de Imagen Biomédica, ReDIB"



- **MANUEL DESCO:** "Imagen molecular: Un pilar para la medicina personalizada y el desarrollo de fármacos"



- **VALERIA CAIOLFA:** "Microscopía Óptica Avanzada: La luz de la investigación biomédica"





tion. The CNIC participates in ReDIB through the Advanced Infrastructure for Translational Imaging (TRIMA).

The Open Administration Week is an initiative of the Open Government Partnership (Open Gov Week). Its goal is to bring government closer to citizens, according to the open government principles of transparency, accountability, citizen participation, and public integrity and collaboration. During the seminars, participants learned about the equipment and infrastructure available within ReDIB and its capabilities and applications for medical imaging.

Three CNIC researchers, Gonzalo Pizarro, Manuel Desco, and Valeria Caiolfa, gave informative talks within the framework of the Distributed Biomedical Imaging Network (ReDIB), a distributed Unique Scientific and Technical Infrastructure (ICTS) of the Ministry of Science and Innovation.

The event was held in the CNIC auditorium and could also be accessed online.

CNIC AT THE XXII SCIENCE AND INNOVATION WEEK IN MADRID



17 Nov. 2022 **Semana de la Ciencia y la Innovación**

Andrea Moreno, cardióloga investigadora en el Laboratorio Tradicional para la Imagen y Terapia Cardiovascular del CNIC

"Visita a un laboratorio CNIC para conocer de cerca el uso de la tecnología y los aspectos innovadores de la misma en el proyecto RESILIENCE"

19:30 h.
Recepción CNIC




The CNIC participated in the XXII Science and Innovation Week in Madrid. This year, the CNIC ran three activities open to the public: a lecture on "Avoiding toxicity in cancer treatments", a visit to a CNIC laboratory, and a workshop titled "Dismantling the muscle".



THE CNIC AT THE XIII EUROPEAN RESEARCHERS' NIGHT

The CNIC participated in the XIII European Researchers' Night in Madrid through two activities open to the public, which were attended by more than 100 participants.



6. SOCIAL & CNIC

VISIT BY THE MINISTER OF SCIENCE AND INNOVATION, DIANA MORANT



The Minister of Science and Innovation, Diana Morant, visited the CNIC, where she met with CNIC General Director Dr. Valentín Fuster, Director of the Instituto de Salud Carlos III Cristóbal Belda, CNIC Managing Director Alberto Sanz, Pro-CNIC Foundation President Luis de Carlos and Director Iciar Areilza, CNIC Scientific Director Dr. Borja Ibáñez, and CNIC Basic Research Director Dr. Vicente Andrés.

During her visit, Diana Morant toured the center's laboratories and met with researchers Dr. Almudena Ramiro and Dr. Inés García Lunar. The Minister described the CNIC as a center of international prestige and emphasized that its work allows advances in the early diagnosis, prevention, and treatment of cardiovascular disease, which remains the main cause of death in Spain.

THE ALEXANDRA PERAUT PROGERIA ASSOCIATION MAKES A DONATION TO THE CNIC TO FUND RESEARCH INTO THIS DISEASE

The Alexandra Peraut Progeria Association made a donation of €6,500 to the Molecular and Genetic Cardiovascular Physiopathology Laboratory at the CNIC, directed by Dr. Vicente Andrés. The money will support the group's research into Hutchinson-Gilford progeria syndrome.

The donation comes from the income of the book "A girl in twenty million", which tells the story of Alexandra Peraut. The book is aimed at raising the profile of progeria and normalizing minority diseases.

Dr. Andrés' group at the CNIC, which also forms part of the Spanish cardiovascular disease research network (CIBERCV), has been working on this disease for years and recently created the HGPSrev mouse, the first animal model that can suppress the appearance of progerin in a temporally and spatially controlled manner.

This new preclinical model has demonstrated that it is never too late to treat the disease and that therapies directed exclusively at the cardiovascular system can produce very significant therapeutic benefits.



5

TRAINING PROGRAMS



Training is one of the CNIC's core activities, and the Center has devised a comprehensive training plan, the CNIC-Joven Training Plan. This global plan includes programs for participants at all levels, from high-school students to postdoctoral researchers and MDs. The CNIC-Joven Training Plan aims to fulfill the personal goal of Valentín Fuster "to attract and train the brightest young people from the earliest ages to create a pool of researchers of excellence in the field of cardiovascular research."

PROGRAMS FOR UNDERGRADUATE STUDENTS

INTERNSHIPS ARE OFFERED TO UNIVERSITY STUDENTS IN THE FOLLOWING PROGRAMS:

CICERONE PROGRAM

The Cicerone Program is open to advanced undergraduate students (and also to Master's students) in biomedicine-related disciplines. Participants extend their scientific training through hands-on experience of laboratory-based biomedical research during the summer recess. In addition to carrying out a supervised research project, the students also attend CNIC seminars and workshops. The aim of the program is to give students first-hand knowledge of biomedical research so that they can make informed choices about the possibility of pursuing a scientific career.

Fellowships in 2022: 29

CURRICULAR AND EXTRACURRICULAR UNIVERSITY PRACTICAL PROGRAM

The CNIC offers practical training in cardiovascular research to visiting undergraduate students.

The CNIC has signed educational collaborative agreements with 62

universities, 35 of them are foreign universities.

In 2022 twenty-two students from the following universities completed internships at CNIC on their final degree thesis dissertation (TFG) under the guidance of a CNIC supervisor:

- 12 students from the Autonomous University of Madrid*
- 3 students from the University Carlos III of Madrid*
- 2 students from the Complutense University of Madrid*
- 1 student from the Polytechnic University of Madrid*
- 1 student from the University Rey Juan Carlos of Madrid*
- 1 student from the University of Lleida*
- 1 student from the University of Valencia*

In addition, thirty-two students from Spanish and international universities completed other types of university internships at the Center during 2022 under the guidance of a CNIC supervisor: 16 students from Spanish Universities, 9 Erasmus students from Italy, Germany, France and Poland, 5 students from UK, Argentina and Peru, and 2 students from USA holding a Fulbright fellowship.



PROGRAMS FOR MASTER'S AND GRADUATE STUDENTS

MASTER'S FELLOWSHIP CNIC-ACCIONA PROGRAM AND FUNDACIÓN CAROLINA BBVA-CNIC MASTER'S FELLOWSHIP PROGRAM

These grants provide funding for students studying for a master's degree at a Spanish university to carry out their experimental project (TFM) in a CNIC laboratory.

Fellowships in 2022: 15

Other Master Student Internships

In 2022 other sixteen students from the following universities worked on their final master's thesis dissertation (TFM) under the guidance of a CNIC supervisor:

- 7 students from the Complutense University of Madrid
- 7 students from the Autonomous University of Madrid
- 1 student from the Polytechnic University of Madrid
- 1 student from the University Oberta of Cataluña

PREDOCTORAL (PhD) PROGRAM

The Predoctoral Program provides a unified framework for all CNIC researchers who are working toward a doctoral degree. All predoctoral researchers are signed up to this program, irrespective of their funding source.

The aims of the program are to ensure uniform quality of predoctoral training at the CNIC and further to ensure fair and equal access of predoctoral researchers to training opportunities.

The Program schedules regular meetings between the predoctoral fellow and his or her thesis committee, composed of the thesis director, another CNIC group leader, and an external expert.

During 2022 the PhD Office organized the above the scientific and career motivational seminars.

Graduate students at the CNIC awarded a PhD degree in 2022: 17
Graduate students studying for a PhD degree at the CNIC in 2022: 108

CNIC's PhD Office is the forum for scientific support, guidance and growth of all PhD students enrolled in CNIC's Predoctoral Program, independently of their university affiliation or funding source. The office is coordinated by a Group Leader appointed by CNIC's direction.

This office also includes two permanent members (Head of CNIC's Scientific Management office and a manager of the Research Office), and one senior and one junior PhD students, who are elected by CNIC's PhD students.

Frontiers in Cardiovascular Research Master's Module

This postgraduate course is run by the CNIC as part of the Universidad Autónoma de Madrid (UAM) Molecular Biosciences Master's Program. This optional module provides a broad overview of cardiovascular biology, including perspectives from basic, clinical, and translational research. Attendants to this course are enrolled UAM Master's students, CNIC predoctoral researchers, and participants of the Res@CNIC SEC Program (see below).

UAM Master's students: 7

PROGRAMS FOR RESIDENT MEDICAL INTERNS

RES@CNIC PROGRAM

The Res@CNIC-SEC Program (in collaboration with the Spanish Society of Cardiology, SEC) offers resident medical interns the opportunity during the first years of their specialization period to learn about the latest techniques in cardiovascular research being used in the CNIC's laboratories, under the guidance of a CNIC scientist. Residents participating in RES@CNIC also receive training in theoretical aspects of cardiovascular research through an expert-led taught module. The Program also seeks to create links and collaborations so that on

conclusion of their MIR specialization period, these professionals will have the chance to undertake research projects in their respective Hospitals in partnership with CNIC scientists.

Participants in 2022: 25 from the following hospitals:

- Complejo Asistencial Universitario de León
- Hospital Clínico San Carlos
- Hospital Universitario Central de Asturias
- Hospital Universitario Cruces
- Hospital Universitario de Navarra
- Hospital Universitario Ramón y Cajal
- Hospital Universitario Virgen de las Nieves
- Hospital Universitario Virgen del Rocío
- Hospital Universitario Cabueñes
- Hospital Universitario Fundación Jiménez Díaz

PROGRAMS FOR RESEARCHERS

CARDIO JOVEN PROGRAM

The aim of this Program (also organized in collaboration with the SEC)

is to foster high-quality translational research in the cardiovascular area in Spanish National Health System centers through training programs providing theory and practical training for one cardiologist with a research vocation.

POST MIR ARC CNIC PROGRAM

This program offers 1- or 2-year contract for research into electrophysiology or arrhythmias. This contract is available to a physician completing their resident intern specialization (MIR) in cardiology and to members of the SEC Sección de Electrofisiología y Arritmias.

PRACTICAL TRAINING FOR TECHNICAL SCHOOL STUDENTS

This program attracted in 2022 fourteen technical school students studying “Pathological Anatomy and Cytodiagnosics”, “Clinical and Biomedical Science” and “Diagnostic Imaging and Nuclear Medicine” to gain practical curricular experience in the CNIC’s laboratories over a three-month period.

Moreover, two students of “Diagnostic Imaging and Nuclear Medicine”





and one student “Clinical and Biomedical Science” started in September their 10-month internship at the CNIC as part of the DUAL technical study program in which the second course is 100% devoted to practical training in a laboratory.

The CNIC has collaborative agreements for this kind of internships with 19 technical training educational Centers and with both DUAL Centers in Madrid offering courses in the Biomedicine field: Instituto de Educación Secundaria Moratalaz for and “Clinical and Biomedical Laboratory” and Instituto de Educación Secundaria San Juan de la Cruz for “Diagnostic Imaging and Nuclear Medicine”.

CNIC CONTINUING EDUCATION PROGRAM

CARDIOVASCULAR PATHOPHYSIOLOGY COURSE: FROM SYMPTOMS TO GENES

Organized by the CNIC and the SEC, this course is aimed at R3, R4, and R5 residents in cardiology and other specialties related to cardiovascular disease, as well as translational researchers in the field of cardiology.

Participants receive an overview of the molecular and genetic factors that underlie cardiac diseases and gain an up-to-date vision of cardiac physiology. The XV edition of this course was held in the CNIC Auditorium on December 2, 2022.

6

FACTS AND FIGURES

SCIENTIFIC PUBLICATIONS

CITABLE DOCUMENTS



DOCUMENTS	NUMBER
ARTICLES	321
REVIEWS	50
TOTAL	371

CITABLE DOCUMENTS WITH IMPACT FACTOR TOTAL: 331



JOURNAL QUALITY		
D1	137	41%
Q1	233	70%
Q2	78	24%
Q3	16	5%
Q4	4	1%

OPEN ACCESS

ALL TYPES OF OPEN ACCESS	211	64%
GOLD OPEN ACCESS	105	32%

LEADERSHIP

FIRST, LAST OR CORRESPONDING AUTHOR	177	53%
CORRESPONDING AUTHOR	127	38%

PUBLICATIONS IN TOP JOURNALS (IF>10)

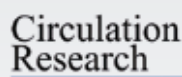
118 (36%)

TOP 3: DOCUMENTS PUBLISHED IN THE TOP THREE JOURNALS WITHIN THEIR CATEGORIES

29 (9%)



The NEW ENGLAND JOURNAL of MEDICINE





AFFILIATION	NUMBER	%
CNIC ONLY	12	4%
CNIC+NATIONAL COLLABORATION	129	39%
CNIC + INTERNATIONAL COLLABORATION	190	57%

OTHER IMPACT INDICATORS	
% DOCS CITED	57,10%
HIGHLY CITED PAPERS	3,32%

Filter Summary:

Dataset: Web of Science

Domestic/International Collaboration: All

Time Period: [2022, 2022]

Include Early Access documents: true

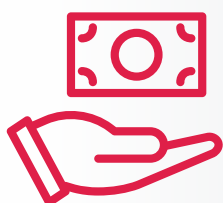
Document Type: [Article, Review]

Organization Name: [Centro Nacional de Investigaciones Cardiovasculares (CNIC)]

Funding Data Source: All Sources

Exported date January 30, 2023

COMPETITIVE **FUNDING***



NEW GRANTS 2022:

PROJECTS, EQUIPMENT AND PERSONNEL

NATIONAL
62 GRANTS
€13,571,564

INTERNATIONAL
13 GRANTS
€ 1,050,745

SEVERO OCHOA AWARD IN 2021 FOR THE
PERIOD 2022-2025 €4,000,000

OTHER ACTIVE GRANTS IN 2022:

NATIONAL
193 GRANTS
€35,083,928

INTERNATIONAL
28 GRANTS
€ 17,019,408

5 ERC-CONSOLIDATOR
1 ERC ADVANCE
4 H2020 HEALTH NETWORKS, 2 OF THEM
COORDINATED BY CNIC
4 LEDUCQ FOUNDATION NETWORKS, 1 OF THEM
COORDINATED BY CNIC



TECHNOLOGY TRANSFER*



- 16** ACTIVE PATENT FAMILIES
- 6** PATENT FAMILIES LICENSED
- 8** NEW PATENT APPLICATIONS
- 50** NEW MATERIAL TRANSFER AGREEMENTS
- 6** NEW CONFIDENTIAL DISCLOSURE AGREEMENTS
- 7** NEW RESEARCH COLLABORATION AGREEMENTS

HUMAN RESOURCES*

SCIENTIFIC STAFF **403**
(90% OF TOTAL CNIC STAFF)



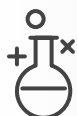
WOMEN

254

149

MEN

TECHNICAL UNITS **82**



GROUP LEADERS **32**

WOMEN

24

8

MEN



CARDIOLOGISTS **15**

43 (11%)

OF THE SCIENTIFIC STAFF ARE FROM OUTSIDE SPAIN

HEADS OF TECHNICAL UNITS **11**



MEN

6

5

WOMEN



VISITING SCIENTISTS **339**

(CARDIOLOGISTS: 24;
FROM INSTITUTIONS OUTSIDE SPAIN: 52 - 11 COUNTRIES)

WOMEN

203

136

MEN

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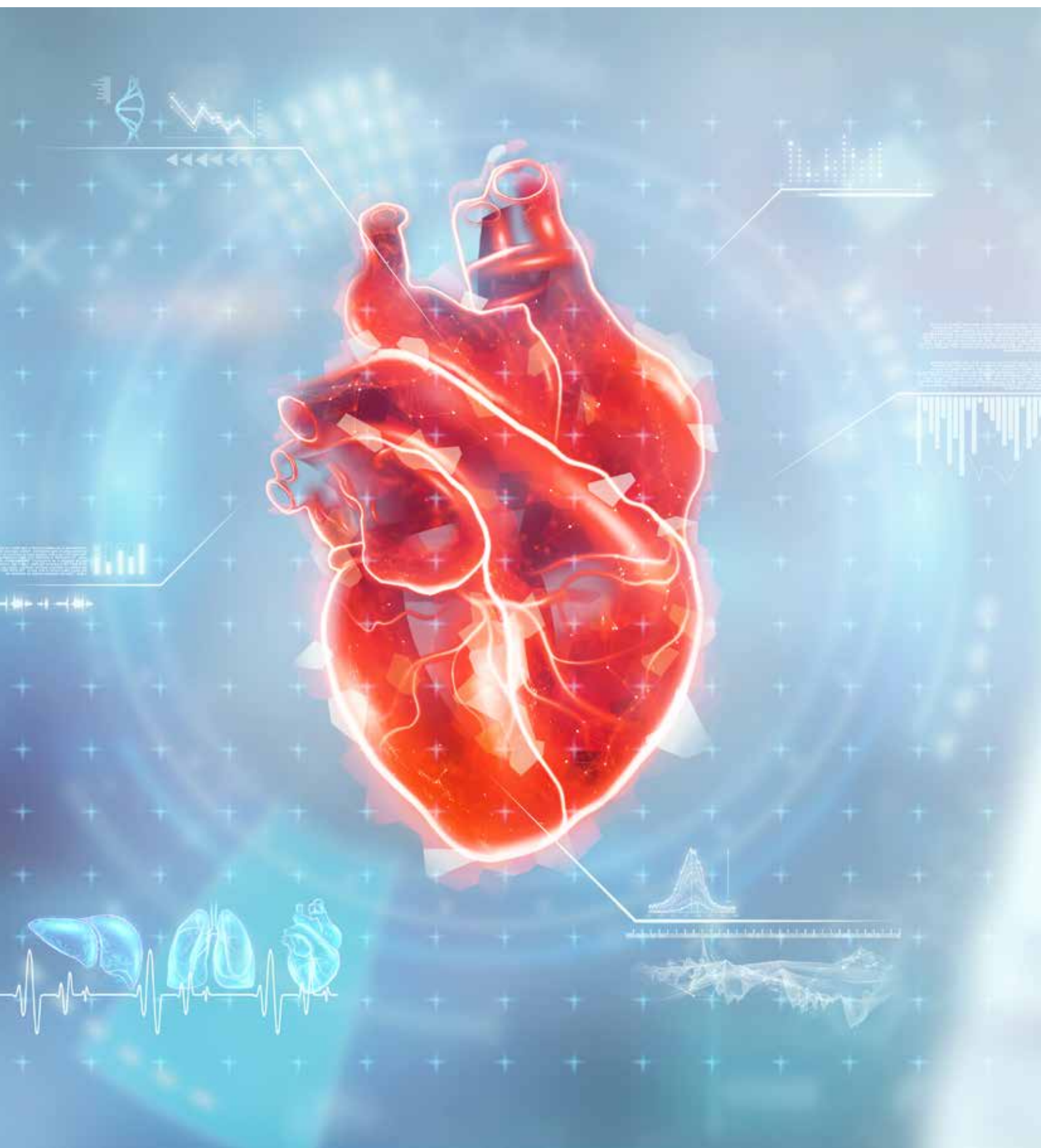
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