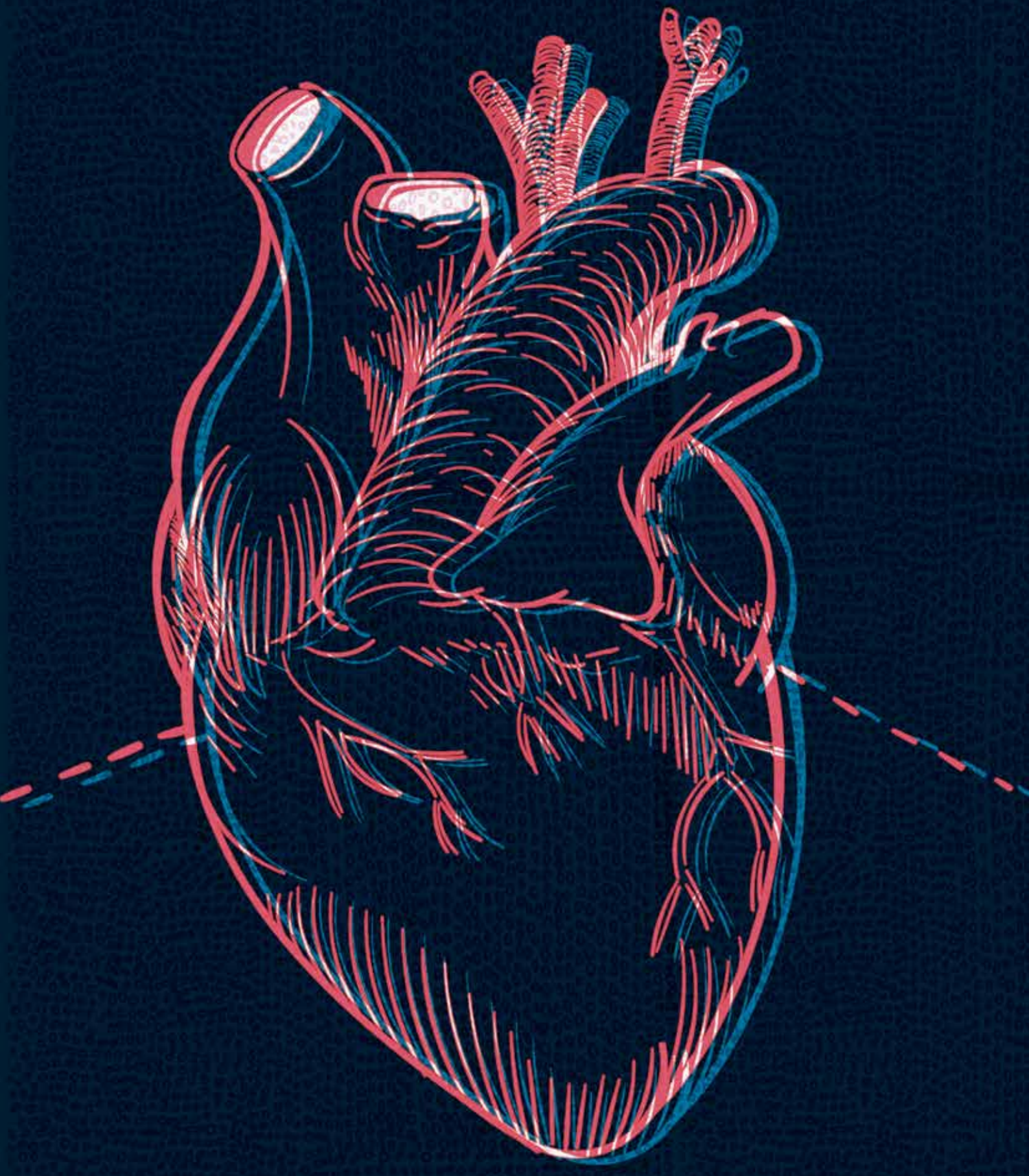
cnic SCIENTIFIC REPORT 2021



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SCIENTIFIC REPORT 2021

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

Fundaciónprocnic

EXCELENCIA SEVERO OCHOA

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The Pro CNIC Foundation brings together 12 of the most important Spanish companies and foundations: Acciona, Santander Bank, BBVA, 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.

DL: M-8203-2022

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Fundación "la Caixa"

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1 FOREWORD AND CNIC MISSION

Valentín Fuster, General Director

Borja Ibáñez, 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 ProCNIC Foundation (composed of twelve Spanish companies unrelated to the biomedical sector). The CNIC 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 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 is moving from a research organization based on three broad research areas to one comprising 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.

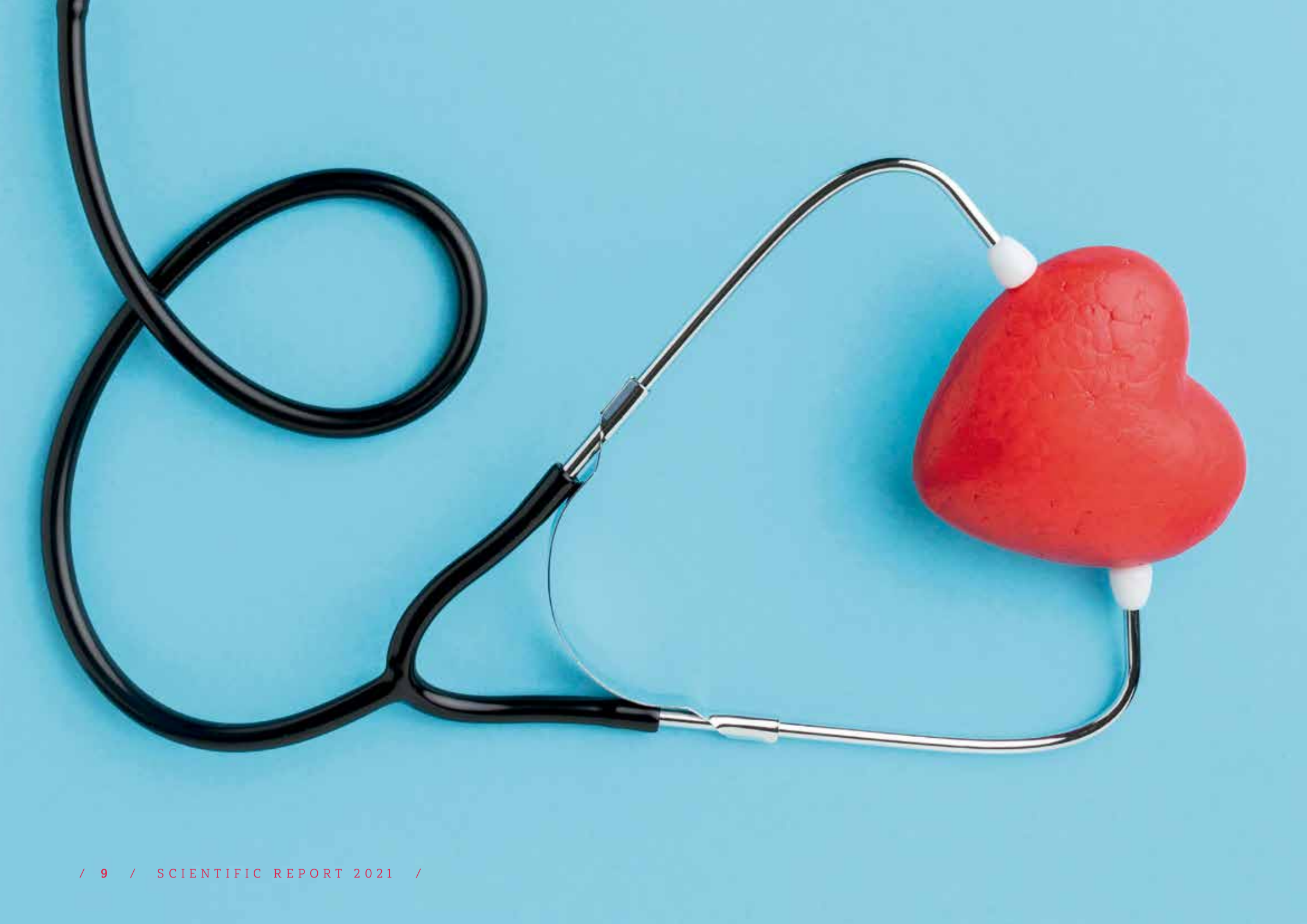
Despite the difficulties that affected all organizations during the COVID-19 pandemic, the CNIC was able to maintain and consolidate its status as world-leading cardiovascular research center and currently has more than 400 researchers and more than 200 visiting scientists.

Major discoveries in 2021 include the identification of ALDH4A1 as a potential diagnostic and therapeutic target for CVD and of the micro RNA miR-721 as the first blood biomarker allowing myocarditis to be distinguished from acute myocardial infarction.

Another landmark event in 2021 was the second renewal of the CNIC's status as a Severo Ochoa Center of Excellence, securing a third round of funding under this program. 2021 was an exceptionally successful year in terms of institution funding, with €6m granted for major infrastructure investments that will ensure the provision of state-of-the-art technologies at the Center. Competitive external project funding totaled €15m, with a substantial share of this coming from international grants.

The Center's eleven large translational studies, including several 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.

Through these endeavors, the CNIC is making a comprehensive, across-the-board investment for societal benefit that integrates biomedical research into the wider society. This is fitting, since we are all stakeholders in our health and in the health of the next generation. 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.



2 RESEARCH AT THE CENTER

The CNIC is organized into two departments, one focused on Basis Research and the other on Clinical Research.Research in these fields is fully interconnected through three multidisciplinary Research Areas.

2.1 VASCULAR PATHOPHYSIOLOGY

Coordinator: **Almudena R. Ramiro**

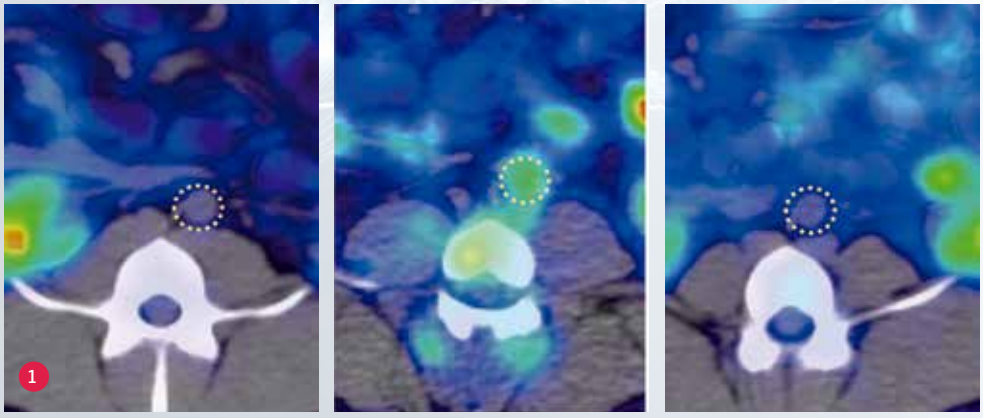
The research groups in the Vascular Pathophysiology (VP) area study the vascular system in health and disease, with a particular focus on the molecular mechanisms governing vascular biology, cardiac and muscle differentiation and regeneration, and atherosclerosis, the main underlying cause of myocardial infarction and stroke. The VP area comprises 12 research groups and 3 core Technical Units (Bioinformatics, Genomics, and Proteomics).

VP-area groups made a number of key advances in 2021. Ongoing research into the mechanisms and mediators of Marfan syndrome (MFS) aortic disease showed that increased NOS2-derived NO activates the guanylate cyclase (sGC)–protein kinase G (PRKG) pathway in MFS patients and causes elevated nitration of certain plasma proteins. This finding has identified potential biomarkers and therapeutic targets for MFS.

Another key research theme is ischemic stroke and cardiovascular risk factor-driven cognitive impairment. Work in this area last year elucidated the role of neutrophil heterogeneity and innate immune pattern recognition receptors in stroke and immunothrombosis.

Mechanisms of atherothrombotic disease are also a focus of research into Hutchinson-Gilford progeria syndrome (HGPS). This rare disorder is characterized by premature aging and death mainly from myocardial infarction, stroke, or heart failure. HGPS is caused by progerin, a mutated variant of lamin A expressed in most differentiated cells of HGPS patients. VP-area scientists have generated a mouse model to assess the reversibility of progerin-induced damage and the relative contribution of specific cell types to the disease. The findings suggest that it is never too late to treat HGPS, although benefit are much greater when progerin is targeted in mice with mild symptoms.

Atheromatous fibrous caps are produced by smooth muscle cells (SMCs) that are recruited to the subendothelial space. By using conditional mouse models, VP-area researchers have found that sequential loss and gain of Notch signaling is needed to build the cap SMC population. The shared



No atherosclerosis **Progressing atherosclerosis** **Regressing atherosclerosis**

RESEARCH GROUPS

- **Vicente Andrés**
  Molecular and Genetic Cardiovascular Pathophysiology
- **Jacob Fog Bentzon**
  Experimental Pathology of Atherosclerosis
- **José Luis de la Pompa**
  Intercellular Signaling in Cardiovascular Development and Disease
- **Valentín Fuster**
  Cardiovascular Imaging and Population Studies
- **José Javier Fuster**
  Hematovascular Pathophysiology
- **Pilar Martín**
  Regulatory Molecules of Inflammatory Processes
- **Mª Angeles Moro**
  Neurovascular Pathophysiology
- **Pura Muñoz**
  Tissue Regeneration
- **Almudena R. Ramiro**
  B Lymphocyte Biology
- **Juan Miguel Redondo**
  Gene regulation in Cardiovascular Remodelling and Inflammation
- **Francisco Sánchez-Madrid**
  Intercellular Communication in the Inflammatory Response
- **Jesús Vázquez**
  Cardiovascular Proteomics

TECHNICAL UNITS

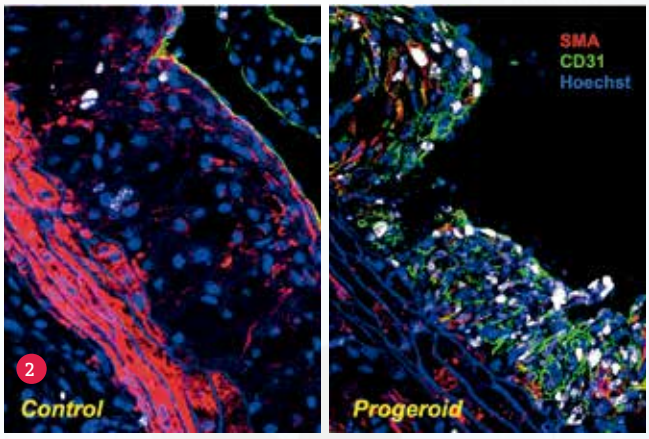
- Bioinformatics **Fátima Sánchez cabo**
- Genomics **Ana Dopazo**
- Proteomics **Juan Antonio López**

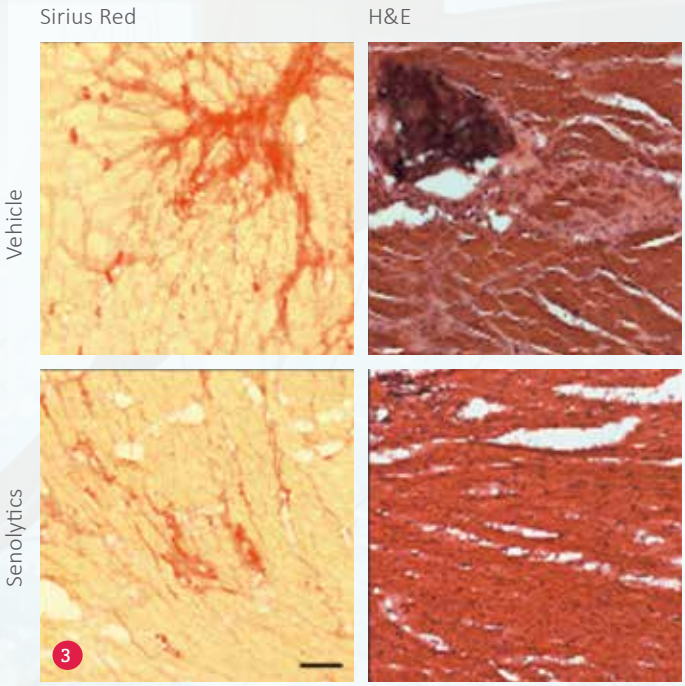
mechanisms with embryonic arterial media assembly suggest that the cap forms as a neo-media that restores the connection between endothelium and subendothelial SMCs, transiently disrupted in early atherogenesis.

Advanced quantitative high-throughput proteomics methods have provided new clues about the implication of oxidative stress in early cardiovascular disease, hypertension-induced endothelial dysfunction, and the immune response in abdominal aortic aneurysm. This analysis has identified a set of three circulating protein biomarkers, promising easy detection of subclinical atherosclerosis in individuals with low cardiovascular risk.

Other studies by VP-area scientists have shown that muscle repair relies on nuclear migration for cellular reconstruction, which provides an alternative, self-repair model for understanding the restoration of muscle architecture in health and disease.

Mutations in the G protein-coupled receptor GPR126/ADGRG6 cause human diseases, and global Gpr126 inactivation in the mouse is embryonically lethal, with mutants having thin-walled ventricles while having no effect on heart patterning and maturation. Through the generation of new genetic mouse and zebrafish models, a VP-area team has found that the placenta–heart axis accounts for



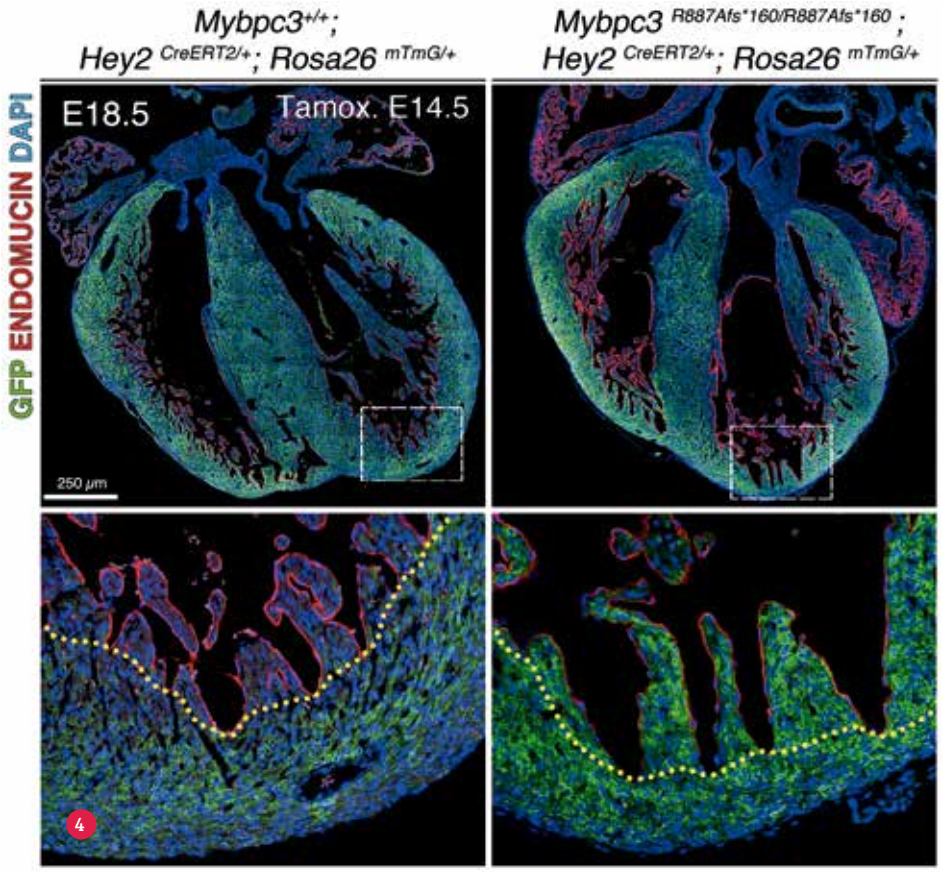


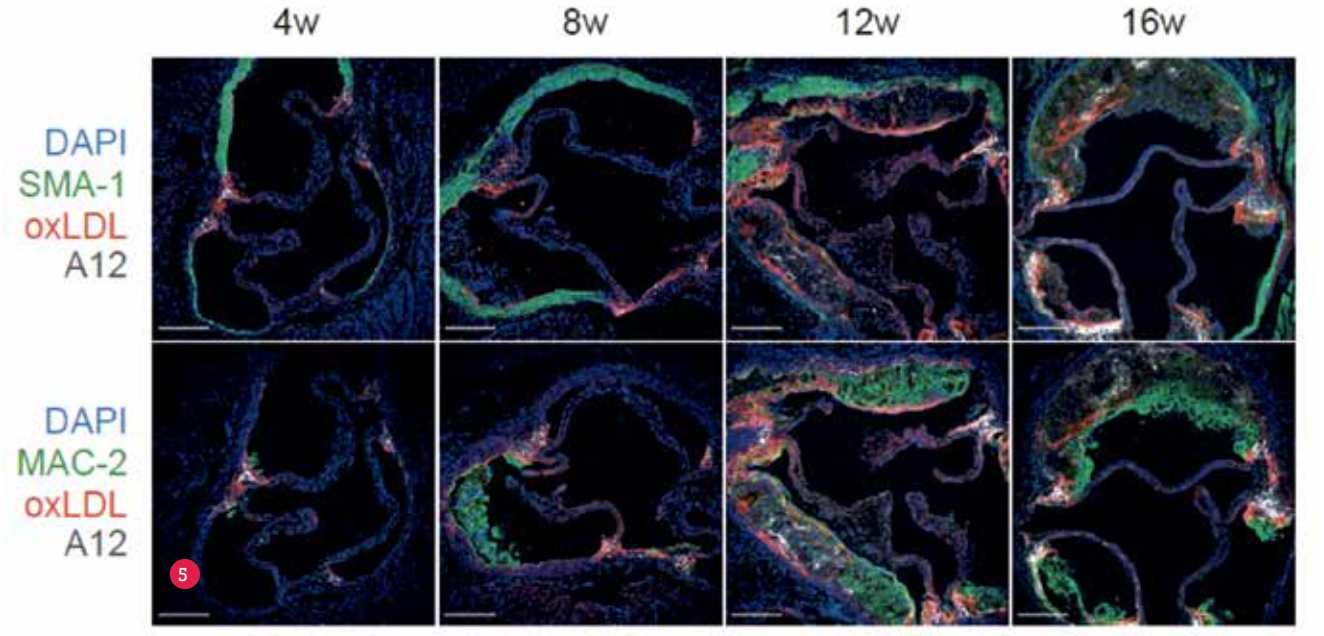
heart abnormalities secondary to placental defects in Gpr126 mutants.

High throughput repertoire analysis in atherosclerotic mice revealed a high predominance of antibodies that recognize the atheroma plaque. A deep proteomics analysis identified the target antigen of one of these autoantibodies (A12) as the mitochondrial enzyme ALDH4A1. Circulating ALDH4A1 is increased in mice and humans with atherosclerosis, and infusion of A12 antibody infusion into atherosclerosis-prone LDLR-/- mice delayed plaque formation, opening new avenues for diagnostic and therapeutic interventions in CVD.

VP-area groups maintain an active research effort on microRNAs (miRNAs). Research in this area showed that the miRNA mmu-miR-721 is synthesized by Th17 cells and is present in the plasma of mice with acute autoimmune or viral myocarditis but not in those with acute myocardial infarction. The human homolog, designated hsa-miR-Chr8:96, was identified in four independent cohorts of myocarditis patients. This miRNA thus serves as a biomarker that distinguishes between patients with myocarditis and those with myocardial infarction.

The miRNA repertoire of human T lymphocytes undergoes dynamic post-transcriptional modification in response to cell activation. These modifications regulate miRNA stability, degradation, and fate. Assessment of the transcriptomic and epigenetic changes triggered in dendritic cells during antigen-cognate synaptic interactions with T lymphocytes revealed the induction of an antipathogenic program that confers resistance and enhanced immune response to further pathogen threats.





2. MYOCARDIAL PATHOPHYSIOLOGY

Coordinator: Guadalupe Sabio

The Myocardial Pathophysiology Area (MPA) includes 10 research groups and 5 core technical units. MPA groups work on a wide range of topics: inherited cardiomyopathies, arrhythmia mechanisms and therapy, molecular regulation of heart failure, metabolism and its effect on cardiovascular disease, functional genetics of the oxidative phosphorylation system, translational cardiovascular imaging and therapy, molecular cardiology, immunobiology, cardiovascular health and imaging, and nuclear receptor signaling. Research in these areas produced several scientific advances during 2021.

José Antonio Enríquez research centers on the mammalian mitochondrial electron transport chain (MtETC) and H+-ATP synthase, which together comprise the oxidative phosphorylation (OxPhos) system. One key research focus is the genetic variability of mtDNA and the repercussions this has on whole-body metabolism, the response to drugs, predisposition to disease, healthy aging, and the borderline pathology and functional variability of mtDNA alterations. The group's work has highlighted the role of mitochondrial reactive oxygen species (ROS) in OxPhos-system adaptation to the metabolic requirements of the cell. The group has also contributed to the identification of mitochondrial Na+ as a second messenger regulating inner mitochondrial membrane fluidity and ROS production by MtETC complex III. Another key research area is the role of OxPhos in metabolic adaptation, and the group has produced a key advance in the understanding of how cells optimize and regulate their metabolic capacity by inducing structural changes in the MtETC. Surprisingly, these adaptations are especially relevant in cardiovascular disease and the immune system.

Rodrigo Fernández leads the EnIGMA (Early ImaGing Markers of unhealthy lifestyles in Adolescents) project, funded by the Fondo de Investigación Sanitaria- Instituto de Salud Carlos III. The project recruited 123 adolescents who underwent multi-territory multi-parametric CMR imaging studies at the CNIC. The first EnIGMA results will be reported soon.

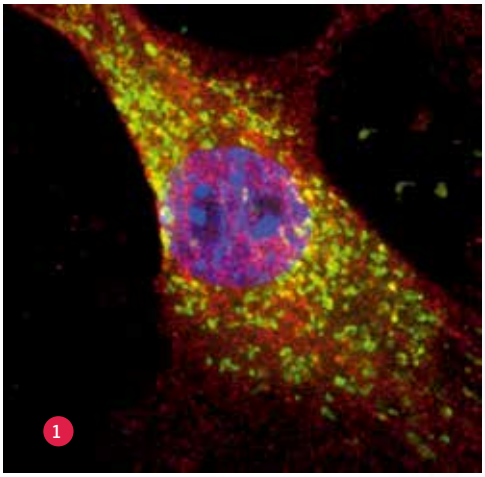
The research group led David Filgueiras has developed a novel noninvasive method to assess the relationship between mechanical and electrical activation rates during atrial fibrillation (AF), enabling the characterization of patient-specific stages of atrial remodeling as the disease progresses. The method has shown early prognostic value in rhythm control management and AF recurrences before other clinical or conventional echocardiography parameters become manifest.

The Translational Laboratory for Cardiovascular Imaging and Therapy (TLCVIT) is led by Borja Ibáñez. Continuing studies with the beta-blocker metoprolol established the use of this drug as a cardioprotective therapy against infarction and showed its utility in the treatment of critical COVID-19 patients. Research into the cardiotoxic effects of chemotherapy explored the use of remote preconditioning (RIPC) and identified microcirculation injury as an early detector of myocardial damage associated with chemotherapy drugs. The team was also central to the development of an ultrafast cardiac resonance protocol to validate a new ultrafast 3D protocol (ESSOS) for complete cardiac resonance analysis. The protocol achieves assessment of anatomy and function, as well as late enhancement to evaluate infarction, all in a single breath hold. The procedure is completed in under a minute.

José Jalife leads the Arrhythmia Research Laboratory, which investigates the role of macromolecular ion channel complexes in the molecular mechanisms of life-threatening rhythm disturbances in patients with Andersen-Tawil syndrome, Short-QT syndrome, and Duchenne muscular dystrophy. The group adopts a multidisciplinary approach, including the use of mouse models of cardiac-specific expression of mutant potassium ion channels, patient-specific iPSC-CMs, in-silico modeling of ion channel structure-function

TECHNICAL UNITS

- Comparative Medicina
- Clinical Trial Coordination **Antonio J. Quesada**
- Pluripotent Cell Technology **Giovanna Giovinazzo**
- Transgenesis **Juan De Dios Hourcade**
- Viral Vectors **Juan A. Bernal**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RESEARCH GROUPS

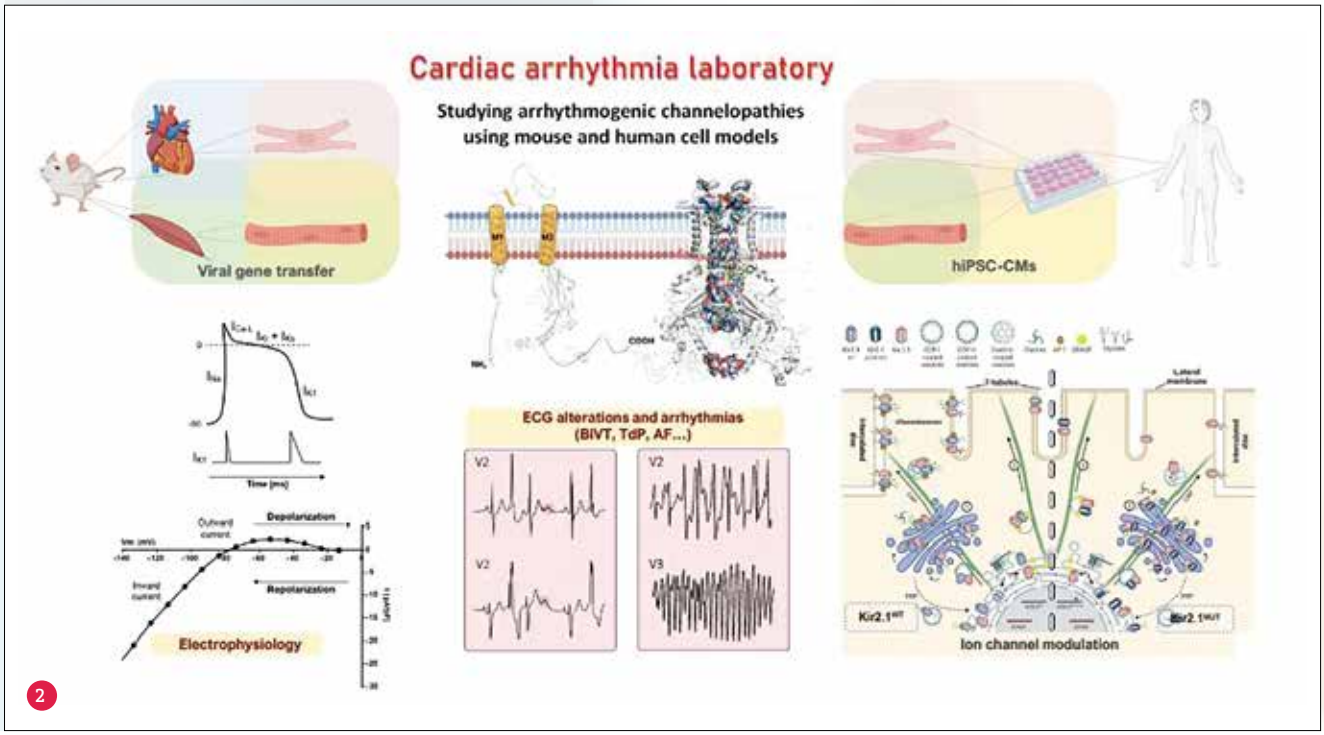
- **José Antonio Enríquez**
  Functional Genetics of the Oxidative Phosphorilation System (GENOPHOS)
- **Rodrigo Fernández**
  Cardiovascular Health and Imaging
- **David Filgueiras**
  Advanced Development in Arrhythmia Mechanisms and Therapy
- **Borja Ibáñez**
  Translational Laboratory for Cardiovascular Imaging and Therapy
- **José Jalife**
  Cardiac Arrhythmia
- **Enrique Lara-Pezzi**
  Molecular Regulation of Heart Failure
- **Silvia Priori**
  Molecular Cardiology
- **Mercedes Ricote**
  Nuclear Receptor Signaling
- **Guadalupe Sabio**
  Stress kinases in Diabetes, Cancer and Cardiovascular Disease
- **David Sancho**
  Immunobiology

relationships, transcriptomics, protein chemistry, patch-clamping, ECG recordings, intracardiac stimulation, and optical mapping. The ultimate goal is that these studies will identify novel targets for the prevention of arrhythmias and sudden cardiac death in patients suffering from these devastating diseases.

Enrique Lara-Pezzi leads a research group investigating the molecular mechanisms underlying the development of pathological cardiac hypertrophy. Their work shows that cardiac hypertrophy in mice is triggered by loss of the expression of SRSF4 (serine- and arginine-rich splicing factor 4), leading to diastolic dysfunction and abnormal repolarization. This response is due to the downregulation of the long noncoding RNA GAS5 (growth-arrest-specific 5) and consequent elevation of glucocorticoid receptor transcriptional activity. These findings may contribute to the development of new treatments for cardiac hypertrophy and myocardial pathology in patients with Cushing syndrome.

The CNIC Molecular Cardiology lab, led by Silvia G. Priori, aims to find new treatments for Timothy syndrome (also known as Long QT syndrome 8) and catecholaminergic polymorphic ventricular tachycardia, two highly lethal inherited diseases caused by mutations in key proteins that generate the heartbeat. Funded by Fundación La Caixa and a Plan Nacional grant, this project studies genetically modified pigs and mice that recapitulate these human diseases.

Mercedes Ricote's lab investigates how nuclear receptors coordinate the transcriptional landscape of cardiomyocytes in homeostasis and disease. Their work has revealed that retinoid X receptors (RXRs) are essential drivers of mitochondrial fitness and nutrient balance in perinatal and adult hearts. By integrating environmental signals, these ligand-activated transcription factors promote an appropriate epigenetic remodeling that allows the expression of key genes encoding key metabolic elements, sarcomere components, and ion channels. The team's work shows that, in addition to sustaining contractile function, RXR-controlled gene signatures are required to prevent the development of heart failure, thus establishing these nuclear receptors as therapeutic targets for treating cardiovascular disease.



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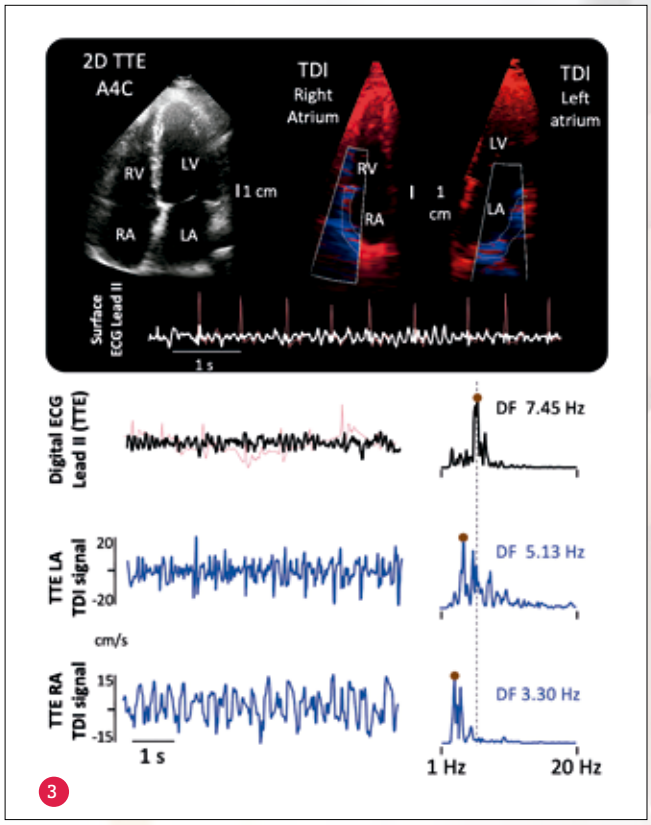
Guadalupe Sabio's lab demonstrated that p38γ/δ kinases control cardiomyocyte metabolic switching during early postnatal development. Activation of these kinases early after birth blocks glycogen production, triggering the oxidation of fatty acid by cardiomyocyte mitochondria. The teams work demonstrates that dysregulation cardiac metabolism can have whole-body metabolic consequences, showing that the heart is a key metabolic organ. These alterations in metabolic organs are due to a cardiac energetic deficit, and the studies highlights the role of heart as endocrine organ.

David Sancho's group investigates how communication between the gut microbiota and the immune system regulates the inflammatory response, and the impact this has on cardiovascular disease. The team has found that mucosal immunotherapy with polybacterial preparations can boost innate responses through a mechanism dependent on epigenetic modifications. This effect can enhance the antiviral response to diverse viruses, including influenza A, vaccinia, and SARS-CoV-2. Trained immunity can also increase vaccine immunogenicity. However, the group is also investigating potential detrimental roles of trained immunity in atherosclerosis.



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The MPA hosts five core technical units that give support to all CNIC scientists.

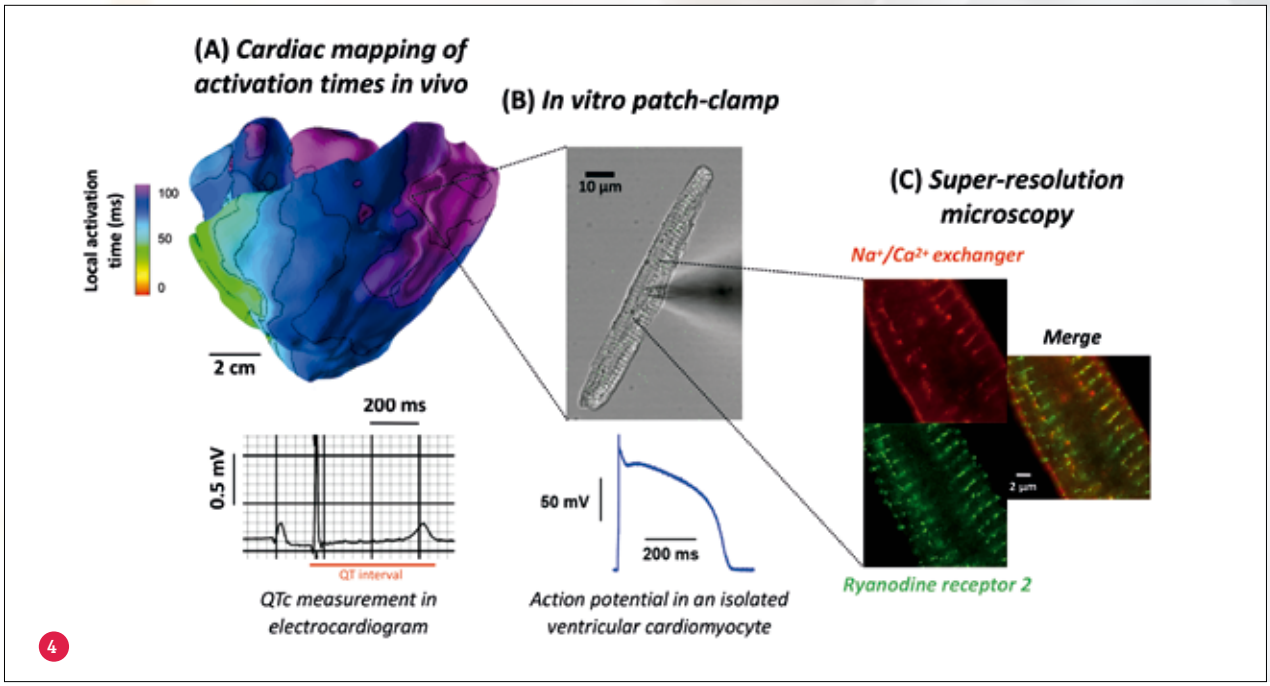
The Transgenesis Unit provides services in mouse strain rederivation, production of genetically modified mice, and cryopreservation of mouse strains. Through collaboration with J.N. Domínguez Macías and M. Torres, the unit is currently developing a microinjection model in post-implantation embryos.

The Pluripotent Cell Technology Unit (PCTUnit) provides state-of-the-art knowledge, training, and technological support in the culture and manipulation of mouse and human pluripotent cells. The PCTUnit has worked with CNIC researchers on the generation of several in vivo and in vitro models, including designing CRISPR/Cas9-based gene-editing strategies and performing the necessary experiments to obtain mouse and pig animal models and in vitro models of cardiovascular disease in hiPSCs.

The Clinical Trials Coordination Unit (CTCU) has continued to provide specialized support for clinical trials and studies carried out at the CNIC. Its ultimate goal is to boost Spanish leadership in clinical trials in the cardiovascular area. In 2021, the CTCU coordinated 11 clinical trials and studies that included more than 10,500 participants in more than 200 European hospitals.

The Viral Vectors Unit provides researchers with access to state-of-the-art viral vector technology for use in preclinical studies and basic research.

The Comparative Medicine Unit supports in vivo work in the animal facility.



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2.3 CELL AND DEVELOPMENTAL BIOLOGY

Coordinator: Jorge Alegre-Cebollada

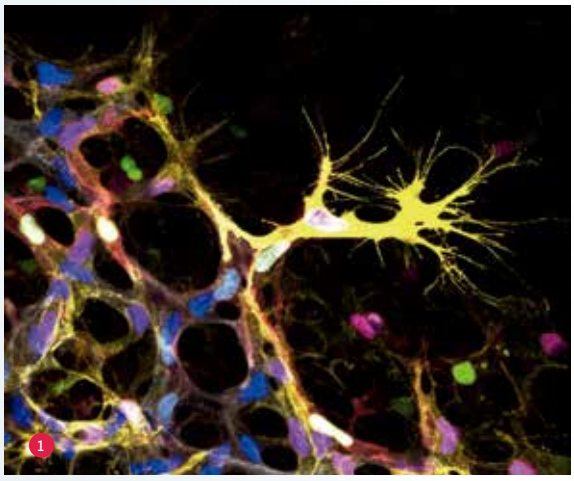
The Cell and Developmental Biology (CDB) area is a multidisciplinary forum of 8 research groups with diverse and complementary approaches to understanding cardiovascular health and disease. The CDB area strategy is to build deep knowledge of the first principles governing the function of biomolecules, cells, tissues, and organisms. Scientific activities are also grounded in the cutting-edge technology provided by the CDB-affiliated Technical Units in Flow Cytometry, Microscopy, and Advanced Imaging, together with the other CNIC Technical Units.

In 2021, CDB-area scientists reported direct targets of key transcription factors during organogenesis and identified pathways playing important roles in congenital heart malformations. This advance was grounded in the strong genetic association between congenital malformations that affect the heart and the limbs. The CDB area also reported new molecular data linking genetic variants to the development of familial cardiomyopathies, providing information useful for the genetic diagnosis of patients and their families. Other recent CDB-area findings suggest that hypertrophic cardiomyopathy can arise as the result of defective nanomechanical properties of sarcomere proteins. CDB-area scientists also reported new insights into the function of immune and vascular cells, obtained through collaborative studies that dissected the transcriptional networks responsible for the activation and programming of neutrophils at inflammatory sites. This is an important finding because neutrophils are the most abundant and potentially damaging type of leukocyte. Other neutrophil studies examined how these cells adjust to circadian patterns and highlighted their role in the pathology of COVID-19. CDB scientists also uncovered angiocrine signatures important for organ homeostasis, growth and regeneration.

Ongoing research in the CDB area includes the generation of novel animal models for in vivo multispectral and single-cell genetic barcoding and the creation of disease models of cardiomyopathy to assess the efficacy of emerging therapies. CDB-area groups are also developing methods that allow unbiased classification of cells in living tissues and are conducting mechanistic studies on how cells sense mechanical properties of the extracellular matrix and how this impacts plaque formation during atherosclerosis. Teams within the CDB area are also deepening understanding of the actions of tissue macrophages, especially in the heart, where they support mitochondrial and metabolic homeostasis.

The impact of the research conducted by the CDB area has resulted in multiple invitations to contribute expert reviews on cell and molecular mechanobiology, biomaterials, and vascular biology, as well as to give presentations at leading research institutions and conferences. In addition, two prestigious ERC-Consolidator grants to CDB scientists began in 2021 and will be active for the next five years. Other honors in 2021 included the election of CDB members to prestigious scientific societies, including the European Molecular Biology Organization, the European Vascular Biology Organization, the Swiss Academy of Medical Sciences, and the Spanish Young Academy, which add to other individual prizes for outstanding achievements awarded to CDB scientists.

CDB-area scientists actively collaborate with other leading international laboratories. For exampe, a collaborative study published in 2021 reported the potential of nicotinamide for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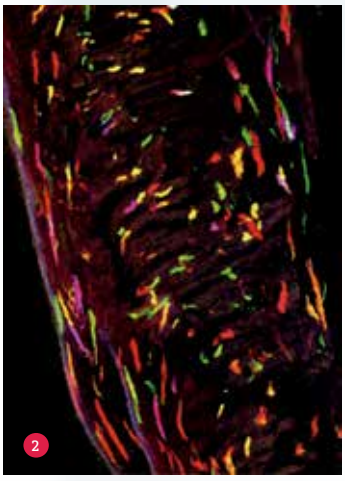
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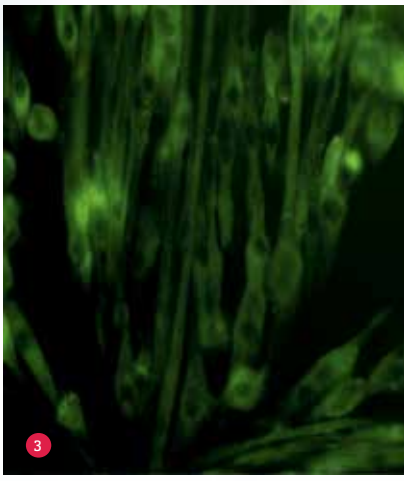
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the treatment of heart failure with preserved ejection fraction. These collaborative efforts are the basis of coordinated grants that synergize the efforts of partners to achieve a shared goal. With the support of Obra Social La Caixa Health Research program, the CDB area has built a multidisciplinary international consortium to determine in unprecedented detail how blood flow forces interplay with other risk factors in atherosclerosis. The knowledge obtained will help to identify novel biomarkers and therapeutic targets to treat and even reverse advanced disease.

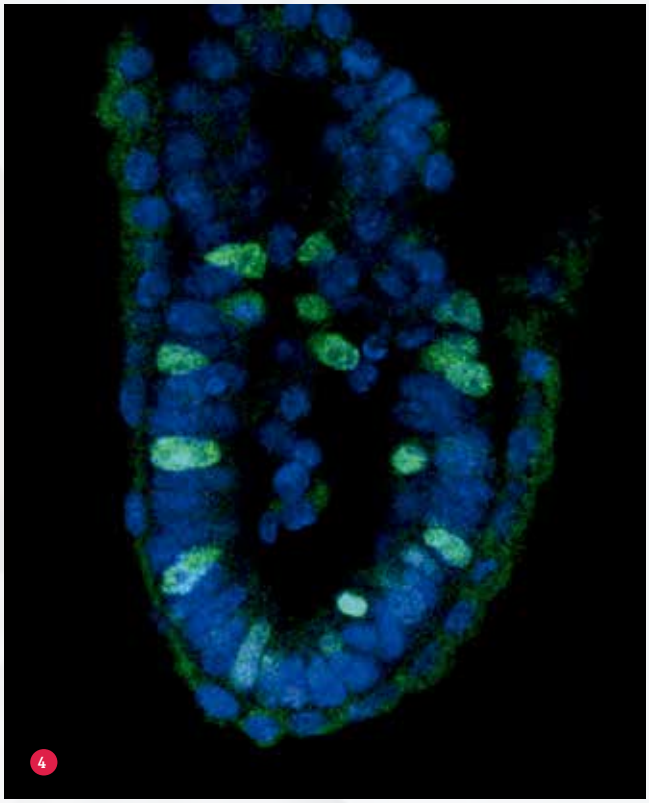
The Technical Units associated with the CDB area have continued to improve their instrumentation and know-how to keep up with ever advancing technologies. The Flow Cytometry Unit received funding for the installation of two new high-end cell-sorter flow cytometers. One of these is a spectral cell sorter that will allow the use of multiple fluorophores, greatly reducing problems derived from cell autofluorescence. This equipment will improve the unit's capacity to offer cell-sorting support to CNIC research groups. The Microscopy Unit, which is part of the National Infrastructure ReDIB network, has secured funding to launch a multiparametric non-linear optical platform, unique in Europe, for metabolic and submicrometer functional imaging in large experimental models. The Advanced Imaging Unit, also part of the National Infrastructure ReDIB network, has secured funding to improve molecular imaging equipment.

TECHNICAL UNITS

- Flow Citometry **Beatriz Álvarez**
- Imaging **Manuel Desco**
- Microscopy **Valeria Caiolfa**

RESEARCH GROUPS

- **Jorge Alegre-Cebollada**
  Molecular Mechanics of the Cardiovascular System
- **Rui Benedito**
  Molecular Genetics of Angiogenesis
- **Héctor Bueno**
  Multidisciplinary Translational Cardiovascular Research (MTCR)
- **Miguel Angel del Pozo**
  Mechanoadaptation and Caveolae Biology
- **Andrés Hidalgo**
  Imaging the Cardiovascular Inflammation and the Immune Response
- **Nadia Mercader**
  Development of the epicardium and its role during regeneration
- **Carlos Pérez-Medina**
  Nanomedicine and Molecular Imaging
- **Miguel Torres**
  Genetic Control of Organ Development and Regeneration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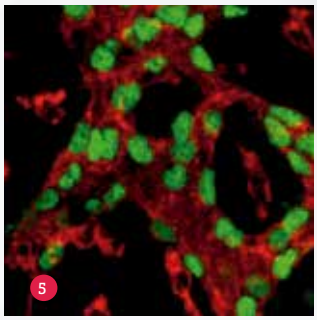
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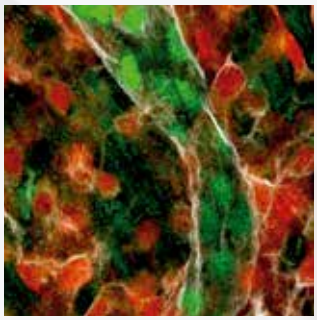


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2.4 CLINICAL STUDIES

EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS, 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 old 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 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-amyloid analysis, and biosampling for omics analysis. In addition, new state-of-the-art substudies have been added, including an investigation of 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 2021, 3481 participants had agreed to continue their participation, and more than 1000 participants had completed their first PESA-Health visit.

SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE IN THE ELDERLY POPULATION

(SECURE)

Principal Investigator: ***Valentín Fuster***
Co-Principal Investigator: ***José Mª Castellano***
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 are now leading a multinational randomized clinical trial supported by the H2020 program. The SECURE trial (trial identifier NCT02596126) has enrolled 2499 patients over 65 years old in 7 European countries (Spain, Italy, Germany, Czech Republic, France, Poland, and Hungary) soon after an MI and randomized them to standard treatment or the CNIC Polypill. Patients have been followed up for a minimum of 2 years, and the incidence of major cardiovascular events is being assessed. The trial completed its follow-up phase by the end of October 2021, and the grant period came to an end in December 2021. The partners are now analyzing the data, and publication of the results is expected in 2022.

The SECURE Trial also has maintained links to other trials funded within the same H2020 call, resulting in a paper on barriers and potential solutions encountered in trials working with the elderly population (Age Ageing. 2021 Nov 10;50(6):1988-1996).

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 used to treat many cancers. From the 4 million new cancer cases diagnosed in Europe every year, >3 million receive anthracyclines (alone or in combination). 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. For the heart, there is plenty of experimental evidence demonstrating that pigs 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, with 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, with examination of the first patients expected in early 2022.

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 5771 had been recruited by the end of 2021. The first follow-up assessment has been completed in 84% of patients, the second follow-up in 58%, and the third follow-up in 3.5%.

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

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 are studying 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) results in changes in behavior, improved control of risk factors, and reduced progression of subclinical atherosclerosis plaque burden (SAPB). TANSNIP is a randomized control trial including middle-aged bank employees from the PESA cohort stratified by SAPB (high SABP n=260; low SABP n= 590). Within each stratum, participants are randomized 1:1 to join a lifestyle program or receive standard care. The program consists 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 is 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 are 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.

The expectation is that individual awareness of CVD risk stratification in the intervention group will lead to a reduction in the prevalence of CV risk factors related to lifestyle and an increase in physical activity compared with the control group. A second rationale is that the level of compliance with the comprehensive 3-year worksite-based lifestyle intervention will be higher among participants with a high imaging defined CV risk.

The analysis is now complete, and the TANSNIP-PESA Study team has submitted an article for publication that is currently under peer-review.

ATHERO-BRAIN. THE HEART TO HEAD (H2H) STUDY

Principal Investigator: ***Héctor Bueno***
Co-Principal Investigator: ***Valentín Fuster***

There is increasing awareness of the association between atherosclerosis and cognitive function, but the mechanisms linking these processes are not fully understood. The Heart-to-Head (H2H) study tested the hypothesis that extensive subclinical atherosclerosis is associated with subtle cognitive decline and beta-amyloid deposition in the brain. This transatlantic collaboration was framed within an agreement between the CNIC and Mount Sinai Hospital in New York and is led by CNIC General Director Valentin Fuster. In Spain, the H2H project was coordinated between the CNIC and Hospital 12 de Octubre. Other university hospitals (Fundación Jiménez Díaz, Clínico San Carlos, and Gregorio Marañón) participate in the project, which received funding from the Carlos III Institute of Health through the Proyecto Integrado de Excelencia program. A total of 300 participants underwent extensive atherosclerosis phenotyping (multi-territory 3D vascular ultrasound and cardiac computed tomography) and thorough brain imaging (anatomical and functional magnetic resonance imaging and positron emission tomography (PET)-amyloid scan), as well as cognitive function testing.

The study is now in the analysis phase.

MULTIMODALITY MYOCARDIAL TISSUE CHARACTERIZATION IN PATIENTS WITH SIGNIFICANT VALVULAR DISEASE (MRVALVE)

Principal Investigators: ***Borja Ibáñez***

The consequences of valvular heart disease (VHD) on left ventricular (LV) dimensions, function, and tissue composition are important determinants in clinical decision-making. Current practice guidelines recommend surgical treatment for patients with significant VHD when symptoms develop or when there is LV remodeling or dysfunction. The most prevalent valvulopathies are aortic valve stenosis (AS) and mitral regurgitation (MR). Transition from asymptomatic to symptomatic disease or from normal LV dimensions and function to LV dilatation/hypertrophy (LVH) and dysfunction is determined by changes in tissue composition (predominantly cardiomyocyte death, extracellular volume expansion, and fibrosis). The current therapies for severe VHD are surgery or percutaneous valve repair or replacement, and the decision to intervene is based on the presence of symptoms and/or gross anatomical and functional LV involvement, evident as significant chamber dilatation or reduced ejection fraction. When these features appear, it is often too late for interventions to fully restore heart function. There is therefore a need for tools for the early detection of myocardial involvement in patients with asymptomatic VHD, to enable appropriate intervention before overt deterioration of heart function. Cardiac magnetic resonance (CMR) is the gold standard for anatomical and functional cardiac assessment, including the detection of focal areas of fibrosis by late gadolinium enhancement (LGE) after contrast-gadolinium administration. Moreover, highly accurate tissue characterization is available with recent CMR advances such as parametric T1/T2 mapping, absolute myocardial perfusion quantification, extracellular volume calculation (a surrogate of diffuse fibrosis), and tagging. The assessment of focal and diffuse fibrosis requires endovenous contrast. We will use the contrast agent gadolinium, which has a superior safety profile and is in routine clinical use. Assessment of diffuse fibrosis also requires a blood sample for determination of the hematocrit. For the study of active deformation of the LV myocardium, the best imaging modality is strain echocardiography, which can detect impaired multidirectional strain (active deformation) even when overall LV function is preserved. We will correlate the imaging data with functional data from the 6-minute walking test, which provides an objective assessment of functional exercise capacity. The amount and extent of calcium deposition in the coronary arteries and heart valves will be assessed by cardiac computed tomography, a noninvasive method that gives the calcium score, a diagnostic and prognostic tool in AS patients. This project will use a multimodality imaging approach (CMR plus strain echocardiography) to better characterize LV status in patients with significant VHD, whether AS (a paradigm of LV pressure overload) or MR (a paradigm of LV volume overload).

So far 62 patients have been recruited, and 34 have completed the one-year follow-up visit.

ß3-AGONIST TREATMENT OF CHRONIC PULMONARY HYPERTENSION SECONDARY TO HEART FAILURE: PHASE-2 PLACEBO-CONTROLLED RANDOMIZED CLINICAL TRIAL (SPHERE- HF)

Principal Investigator: ***Ana García Álverez***
Co-Principal Investigator: ***Valentín Fuster***

Pulmonary hypertension (PH) secondary to left heart disease (group 2 PH) is the most common form of PH and currently lacks effective therapy. CNIC researchers have identified the β3 adrenergic receptor as a novel therapeutic target for this disease in a large animal model of PH (Basic Res Cardiol. 2016;111:49). The CNIC is currently leading a phase 2 clinical trial in which group 2 PH patients are randomized to standard therapy vs standard therapy plus a β3-selective agonist (trial identifier NCT02775539 and Nº EudraCT: 2016-002949-32). A total of 81 patients have been recruited in four Spanish hospitals and have been followed under treatment for 4 months. The study endpoints are pulmonary artery hemodynamics and the CMR profile.

In 2021, we completed the inclusion and follow-up of all study participants (n=81). Images from the participating hospitals were sent to the CNIC (Imaging Core Laboratory), where blinded analysis was performed of echocardiography, cardiac magnetic resonance (CMR), and computed tomography (CT) studies performed at baseline (V0) and at the end of study follow-up (V8). Results are currently being analyzed by Dr. Ana García-Álvarez's group at Hospital Clínic.

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 cardiac toxicity associated with some cancer treatments. MATRIX will be jointly run at 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 2021 we had already hosted 31 participants.

EARLY IMAGING MARKERS OF UNHEALTHY LIFESTYLES IN ADOLESCENTS (ENIGMA)

Principal Investigator: ***Rodrigo Fernández Jiménez***
PI19/01704 ISCIII Grant

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 main objectives of this project are 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 age- and sex-matched participants (n=123) have undergone a multi-territory multi-parameter CMR imaging study. This unique setting allows us to study associations between health factors, behaviors, and early imaging markers of subclinical disease.

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

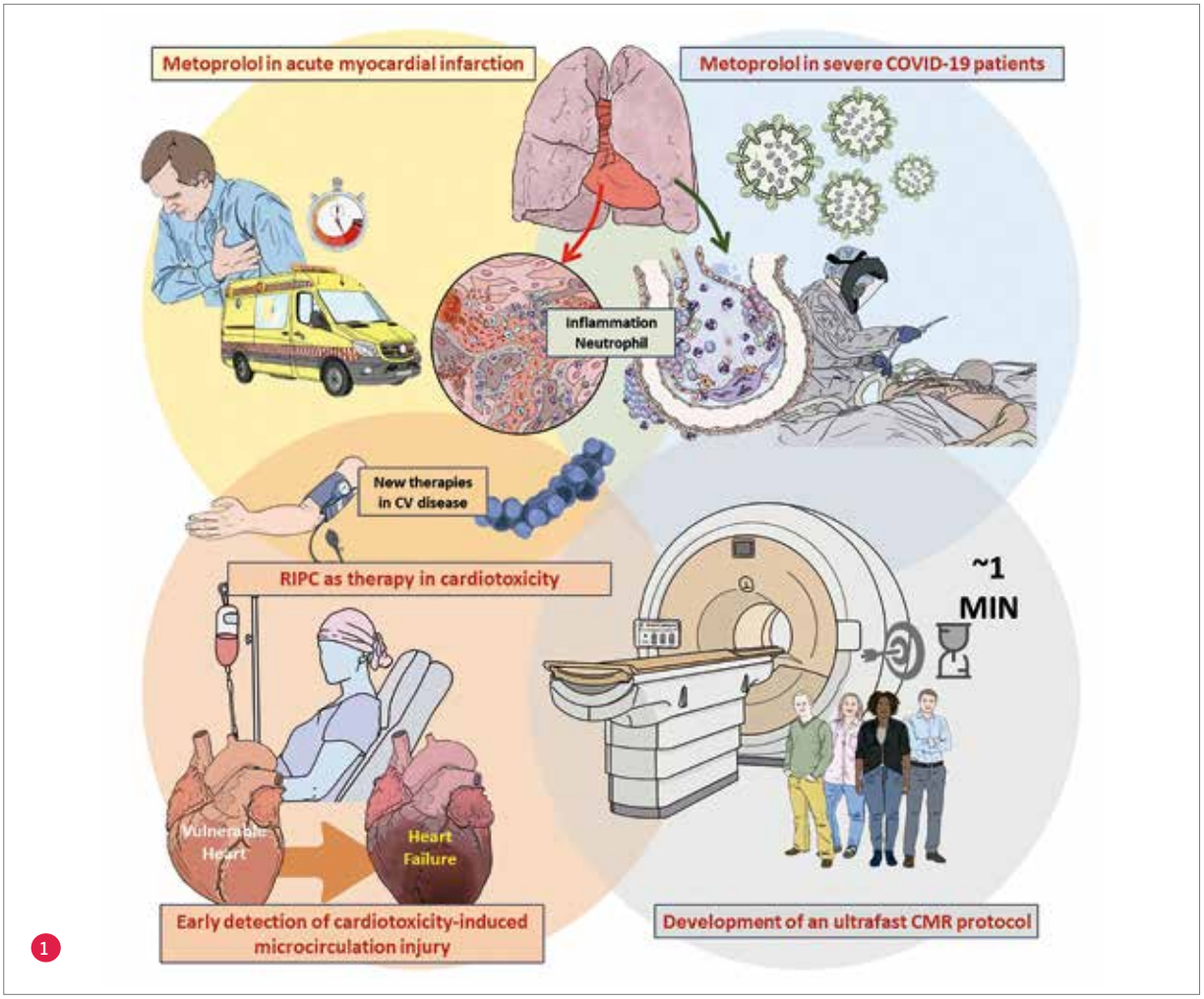
(MYOCARDITIS-CNIC)

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

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

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

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



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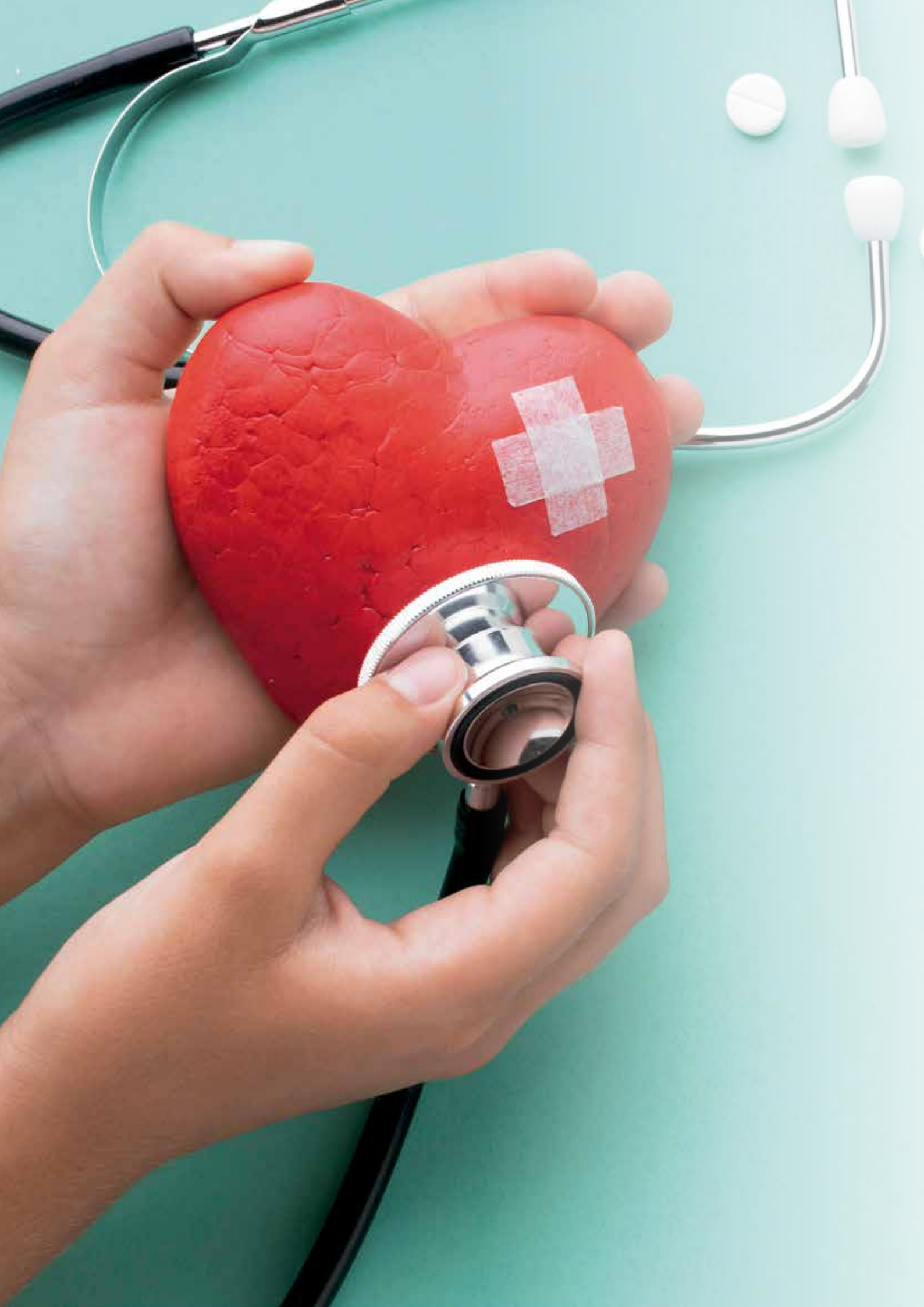


3 SCIENTIFIC HIGHLIGHTS BY PUBLICATION DATE

SCIENCE ADVANCES: CNIC SCIENTISTS IDENTIFY A MECHANISM THROUGH WHICH DENDRITIC CELLS IMPROVE THEIR ANTIVIRAL AND IMMUNE-ACTIVATION ABILITIES

Researchers at the CNIC led by Professor Francisco Sánchez-Madrid have found that dendritic cells, which initiate specific immune responses, can reprogram their genes to improve immune response. The results of the study, published in Science Advances, could have important applications for the development of new vaccination and immunotherapy strategies.

Dendritic cells are professional antigen-presenting cells that initiate adaptive or specific immune responses. As described by the research team, "dendritic cells capture possible pathogenic agents in different tissues and entry sites, process their components, and transport them to lymph nodes. Here, they establish communication with T lymphocytes through the formation of a specialized structure called the immune synapse. The immune synapse allows the dendritic cell to present processed components of the infectious agent to a T cell, so that they can be recognized and initiate a specific T cell immune response."

Until now, activation of T lymphocytes was thought to be dendritic cells' main function. However, Prof. Francisco Sánchez-Madrid's group, working together with the group led by Dr. Almudena R Ramiro, have discovered that the dendritic cell also receives information from the T cell via the immune synapse. "The T cell sends instructions that induce a change in the dendritic cell's gene-expression program, promoting the expression of genes related to motility, antiviral responses, and secretion and thereby increasing the dendritic cell's capacity to generate protective anti-pathogen immune responses," explained Sánchez-Madrid.

"This study describes how gene-expression changes are accompanied by changes in epigenetic marks on DNA. These epigenetic marks in turn produce transient changes in specific genes that promote or hinder their expression," explained first authors Irene Fernández Delgado and Diego Calzada Fraile.

The research team found that, after participating in an immune synapse, dendritic cells migrate more efficiently to lymph nodes, where most processes involved in the activation of specific or adaptive immune responses take place.

The new study, carried out in close partnership with the CNIC Bioinformatics Unit (directed by Fátima Sánchez-Cabo) and Genomics Unit (directed by Ana Dopazo), describes a new mechanism that explains how dendritic cells improve their antiviral and immune-activation abilities.

The researchers conclude that their study shows that dendritic cells, responsible for initiating specific immune responses, reprogram their genes through altered epigenetic DNA marks after interacting with a cognate T cell. "These changes improve their motility, so that they arrive sooner at immune response activation sites, representing a new mechanism for potentiating the immune response."

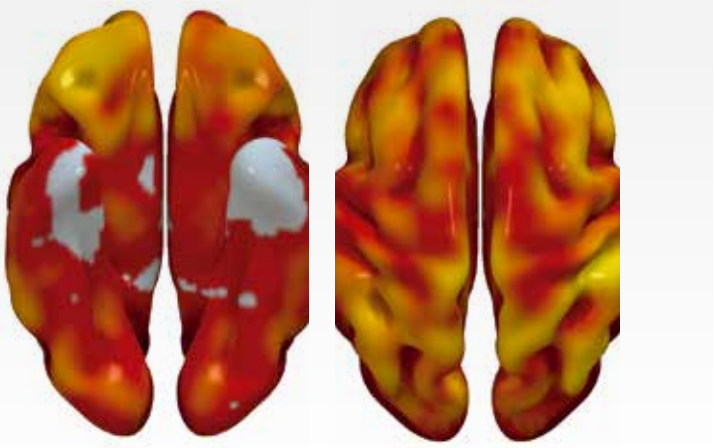
The results also have potential applications in the development of new vaccination and immune therapy strategies. For example, the described mechanism could be used to generate super-migratory post-synaptic dendritic cells able to induce stronger and more effective immune responses.

The study was supported by funding from Fundación 'la Caixa' through Health Research Projects call HR17-00016 and an INPhINIT 'Retaining' doctoral project grant".

Alcaraz-Serna, A., Bustos-Morán, E., Fernández-Delgado, I., Calzada-Fraile, D., Torralba, D., Marina-Zárate, E., Lorenzo-Vivas, E., Vázquez, E., de Alburquerque, J. B., Ruef, N., Gómez, M. J., Sánchez-Cabo, F., Dopazo, A., Stein, J. V., Ramiro, A., & Sánchez-Madrid, F. (2021). Immune synapse instructs epigenomic and transcriptomic functional reprogramming in dendritic cells. Science Advances, 7(6), eabb9965. https://doi.org/10.1126/sciadv.abb9965

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY:

SCIENTISTS UNCOVER EARLY LINKS BETWEEN CARDIOVASCULAR RISK AND BRAIN METABOLISM



The links between cardiovascular disease and cognitive impairment begin years before the appearance of the first clinical symptoms of either condition. In a study carried out at the CNIC in partnership with Santander Bank and neuroimaging experts at the Barcelonaβeta Brain Research Center (BBRC, the research center of the Fundación Pasqual Maragall), the investigators have identified a link between brain metabolism, cardiovascular risk, and atherosclerosis during middle age, years before the first appearance of symptoms.

The report, published in the Journal of the American College of Cardiology (JACC), is important because it suggests that intervention in a modifiable condition (cardiovascular disease) could prevent the development of dementia, a disease for which there is currently no cure.

Dr. Valentín Fuster, CNIC and Mount Sinai Heart General Director, Physician-in-Chief of the Mount Sinai Hospital, and a lead author on the study, explained that "although everybody knows about the importance of caring for ourselves and controlling cardiovascular risk factors in order to avoid a heart attack, the association of these same risk factors with cognitive decline may increase awareness of the need to acquire healthy habits from the earliest stages of life."

Moreover, the results provide yet more support for the importance of implementing primary cardiovascular prevention strategies in middle age as a valuable therapeutic approach to slowing or even halting brain alterations that could contribute to future cognitive decline.

The advanced stages of vascular disease and dementia often occur together, but until now this association has not been documented at earlier stages. The CNIC-coordinated study, led by Dr. Marta Cortés Canteli, shows that in middle age, years before any clinical signs appear, atherosclerosis and cardiovascular risk factors already show an association with low metabolism in the brain regions that are implicated in the future development of dementia, especially Alzheimer disease.

Using advanced imaging by positron emission tomography (PET), the research team quantified brain metabolism in more than 500 participants in the PESA-CNIC-Santander study. The participants had an average age of 50 years and no symptoms, but already had evidence of atherosclerosis in their arteries.

"We found that a higher cardiovascular risk in apparently healthy middle-aged individuals was associated with lower brain metabolism in parietotemporal regions involved in spatial and semantic memory and various types of learning," said Dr. Cortés Canteli. Dr. Juan Domingo Gispert, head of the Neuroimaging group at the BBRC, noted that "the brain areas showing low metabolism in participants with higher cardiovascular risk are the same areas affected in Alzheimer disease, suggesting that these individuals may have higher than normal vulnerability to this disease."

The study is the largest of its type to date in a healthy middle-aged population and could signal a paradigm change in the understanding of the links between vascular and brain disease, say the authors.

Among the modifiable cardiovascular risk factors most closely associated with a reduction in brain metabolism, the investigators saw the biggest effect with hypertension. "We found that the same risk factors that damage the heart and the large arteries, and especially hypertension, are closely linked to the decline in brain metabolism years before the appearance of symptoms," said Dr. Fuster.

The research team also found that a higher number of plaques in the carotid arteries, which carry blood to the brain, was associated with lower brain metabolism in areas of the limbic system and the parietal lobe, both of which are intimately linked to the development of Alzheimer disease.

"The next step will be to determine whether individuals with subclinical atherosclerosis in the carotid arteries and low brain metabolism at the age of 50 go on to experience cognitive decline 10 years later," said Dr. Cortés Canteli.

The PESA study is cofinanced equally by the CNIC and Santander Bank. PESA receives additional funding from the Instituto de Salud Carlos III, Madrid, Spain (ISCIII, PI15/02019, PI17/00590 & PI20/00819), the European Regional Development Fund (ERDF- A Way to Build Europe), and the European Social Fund (ESF - Investing in Your Future). The CNIC is supported by the ISCIII, the MCIN and the Pro-CNIC Foundation. The BBRC is financed mainly by the Fundación "la Caixa", the EU/EFPIA (European Federation of Pharmaceutical Industries and Associations) Innovative Medicines Initiative Joint Undertaking EPAD, and the Innovative Medicines Initiative 2 Joint Undertaking. This joint project was supported by the European Union Horizon 2020 research and innovation programme and the EFPIA.

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY:

CNIC RESEARCHERS EXPLAIN HOW HIGH BLOOD PRESSURE, THE MOST IMPORTANT CAUSE OF DISEASE WORLDWIDE, ACCELERATES ATHEROSCLEROSIS

High blood pressure, the most important cause of disease worldwide, accelerates atherosclerosis, but the mechanism is unknown. Using genetically modified minipigs, researchers from the CNIC and Aarhus University (Denmark), have demonstrated that high blood pressure alters the structure of arteries, leading to more accumulation of LDL cholesterol and faster development of atherosclerosis.

Blood pressure-lowering drugs are routinely used to prevent the development of atherosclerosis and heart disease, but the mechanism of this effect is still unknown. People suffering from high blood pressure (hypertension) often have accompanying changes in the hormones that control blood pressure and it has been unclear whether the pressure itself or the hormonal changes are the driver of accelerated atherosclerosis. To investigate this, the researchers analyzed the development of atherosclerosis in minipigs that were genetically engineered to have high blood cholesterol and develop atherosclerosis.

"Minipigs have arteries that are very similar in structure to human arteries and like humans they develop atherosclerosis in the heart when exposed to high blood cholesterol", said the study coordinator Dr. Jacob Fog Bentzon. As is also the case in humans, the development of the early stages of the disease is asymptomatic, and therefore experiments on atherosclerosis can be conducted in minipigs with high animal welfare.

By manipulating blood pressure in the pigs and by analyzing the effects on arteries in the heart, the researchers found that the direct forces of pressure on arteries leads to structural changes that facilitate the development of atherosclerosis. "Arteries become denser and allow less passage of molecules from the blood. This includes the LDL particles that carry blood cholesterol, which instead accumulate in the innermost layer of arteries, where they drive the development of atherosclerosis", Dr. Jacob Fog Bentzon explained.

This finding uncovers an intimate relationship between the most important risk factors for atherosclerosis, LDL cholesterol and high blood pressure. While it has been known for decades that accumulation of LDL particles in arteries leads to atherosclerosis, the new research shows that high blood pressure accelerates the accumulation of LDL. Therefore, high blood pressure aggravates the effect of having high LDL cholesterol in the blood.

The new insight supports the need to keep both LDL cholesterol and blood pressure low throughout life by healthy diet choices, weight control, exercise, and, when needed, drug therapy. "It could also pave the way to the development of more effective therapies to offset the detrimental effects of hypertension on atherosclerosis", concluded Dr. Jacob Fog Bentzon.

This project was a collaboration among the Experimental Pathology of Atherosclerosis and the Cardiovascular Proteomics groups at CNIC, CIBER Cardiovascular Diseases, and the Atherosclerosis Research Unit at Aarhus University in Denmark.

This work at CNIC was supported by grants from the Ministerio de Economia, Industria y Competividad with cofunding from the Fondo Europeo de Desarrollo Regional (SAF2016-75580-R and PGC2018- 097019-B-I00), the Instituto de Salud Carlos III-Fondo de Investigación Sanitaria (IPT17/0019–ISCIII-SGEFI/ERDF, ProteoRed), the Fundació la Marató de TV3 (grant 122/C/2015) and "la Caixa" Foundation (project code HR17-00247).

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY:

CNIC SCIENTISTS IDENTIFY MUTATIONS ACQUIRED BY BLOOD CELLS THAT ACCELERATE HEART FAILURE PROGRESSION

A team of scientists at the CNIC and the Hospital Universitario Virgen de Arrixaca in Murcia has discovered that clonal hematopoiesis increases the risk of rapidly progressing heart failure, one of the chief causes of death in the world.

The adult human body produces hundreds of billions of blood cells every day. This essential process unavoidably leads to the appearance of mutations in the DNA of the progenitor cells. These are known as somatic mutations because they are acquired, not inherited. While most of these mutations are innocuous, occasionally a mutation gives affected cells a competitive advantage that allows them to expand progressively, generating clonal populations of blood cells. This phenomenon is known as clonal hematopoiesis.

Clonal hematopoiesis is linked to aging, because over time there is an increasing chance that a culprit mutation will be produced, explained Dr. José Javier Fuster, coordinator of the study published today in The Journal of the American College of Cardiology (JACC). The study shows that clonal hematopoiesis is an important pathological process that accelerates and aggravates the clinical progression of heart failure, independently of the presence of atherosclerosis.

In this study, which included input from the CNIC Genomics and Bioinformatics Units and from investigators at Hospital Universitari Germans Trias i Pujol in Badalona (Barcelona), the research team analyzed how the presence of mutations linked to clonal hematopoiesis affects the clinical progression of patients with ischemic or non-ischemic heart failure.

For the researchers, these findings "demonstrate the importance of clonal hematopoiesis as a pathogenic process that accelerates and aggravates heart failure progression, independently of the presence of atherosclerosis."

The authors conclude that their study supports the emerging idea that "clonal hematopoiesis represents a new cardiovascular risk factor and an important link between aging and cardiovascular disease." The results, moreover, "open the way to the development of personalized therapies for patients with these somatic mutations, with the aim of preventing heart failure progression."

This study was funded by a Beca Leonardo para Investigadores y Creadores Culturales (2019) from the Fundación BBVA, the Carlos III Institute of Health, the Spanish Ministry of Science and Innovation, and the Fundación Séneca de Ciencia y Tecnología de la Región de Murcia. José Javier Fuster is a member of the Transatlantic Network on "Clonal hematopoiesis and atherosclerosis", funded by the Leducq Foundation.

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NATURE COMMUNICATIONS:

INHIBITION OF PROTEINS ACTIVATED BY NITRIC OXIDE REVERSES AORTIC ANEURYSM IN MARFAN SYNDROME

Scientists at the CNIC and the Centro de Biología Molecular Severo Ochoa (CBM-CSIC-UAM) have discovered that the nitric oxide (NO) pathway is overactivated in the aortas of mice and patients with Marfan Syndrome and that the activity of this pathway causes the aortic aneurysms that characterize this disease.

The results of the study, published in Nature Communications, reveal the essential role played by NO in Marfan Syndrome aortic disease and identify new therapeutic targets and markers of NO pathway activation that could be used to monitor disease status and progression.

Aortic aneurysm (AA) is a progressive dilatation and weakening of the aortic wall. AA can be harmless, but in some patients can lead to dissection (rupture) of the aorta, resulting in death.

The study identifies new biomarkers associated with this syndrome that have the potential to improve the clinical treatment and prognosis of Marfan Syndrome patient's syndrome.

Current treatments for Marfan Syndrome are aimed at reducing blood pressure on the artery wall, but do not prevent its deterioration. The only effective intervention for the aortic disease in Marfan Syndrome is surgery.

The researchers therefore recognize "the urgent need to identify new targets for the development of pharmacological treatments for thoracic aortic aneurysm and dissection (TAAD) in Marfan Syndrome."

This study reveals the essential role played by NO in Marfan Syndrome aortic disease. "We previously detected high expression of a protein with a high capacity for NO production in the aortas of Marfan Syndrome patients and an mouse model of the disease, and we therefore undertook an in-depth investigation of the role of NO in the associated aortic disease," explained lead investigator Juan Miguel Redondo.

"We observed that treatment of healthy mice with supra-pharmacological doses of an NO donor induced TAAD similar to that seen in Marfan mice. The NO donor treatment also reproduced the degeneration of the aortic wall, an essential step in the development of TAAD," added Dr. Redondo. "Through these experiments, we showed that elevated production of NO is necessary and sufficient for the development of TAAD in Marfan Syndrome."

Given this important role of NO in the development of TAAD, the researchers decided to focus on the enzymes soluble guanylate cyclase (sGC) and type I cGMP-dependent protein kinase (PRKG1), two NO-regulated proteins. "Our analysis detected elevated activities of both sGC and PRKG1 in samples from mice and patients with Marfan Syndrome," said Dr. Redondo.

"We were able to completely reverse the aortic disease in Marfan mice by treating them with inhibitors of these two proteins or by genetically silencing the expression of Prkg1, demonstrating that the NO-sGC-PRKG1 pathway mediates the development of TAAD in Marfan Syndrome," added Dr. Campanero.

Given the need for new pharmacological treatments for Marfan Syndrome aortic disease, "the results of this study open the way to the use of sGC and PRKG1 inhibitors in preclinical and clinical trials for this syndrome and possibly other aortic diseases," said Dr. Redondo.

The research team also explored possible "footprints" left by high blood concentrations of NO.

"This discovery has important implications for patients with this syndrome, because these molecules could be used as biomarkers for disease monitoring, and we are now studying their potential as prognostic indicators," explained Dr. Redondo.

This study was funded by the Fundación "la Caixa" through the CaixaResearch Call for Health Projects, the Ministerio de Ciencia e Innovación and Ministero de Universidades, the Comunidad de Madrid, the CSIC, the Marfan Foundation, the Fundación La Marató and the CIBER Cardiovascular Diseases (CIBER-CV) Instituto de Salud Carlos III.

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JOURNAL FOR IMMUNOTHERAPY OF CANCER:

CNIC SCIENTISTS DISCOVER A NEW STRATEGY TO IMPROVE CANCER IMMUNOTHERAPY

Scientists at the CNIC have designed a new strategy to potentiate immunotherapy. In the study, published in the Journal for Immunotherapy of Cancer, the team led by Dr. David Sancho identifies a mechanism through which dead tumor cells stall the response of the immune system, reducing the antitumor capacity of immune cells that attack cancers.

The scientists improved the efficacy of cancer immunotherapy through an approach that combines blocking antibodies with cytokines or chemotherapy treatments that promote the development of dendritic cells. The team believe that this approach can be transferred to the clinic to optimize cancer immunotherapy.

Unfortunately, not all patients benefit from immunotherapy, because many cancers develop mechanisms to evade the immune system. One of these mechanisms consists of impeding the migration of immune cells to the tumor microenvironment.

The type of immune cells that enter the tumor has a major influence on cancer patient survival. Survival is higher after infiltration by CD8 T cells, which eliminate tumor cells, and by dendritic cell subtypes that attract and activate CD8 T cells. Scientists in the field have therefore focused their efforts on developing methods to increase the numbers of these cells in the tumor microenvironment.

Immune cells have an extensive repertoire of receptors through which they interact with their environment, allowing them to recognize pathogens and also detect tissue damage. Study coordinator Dr. David Sancho's team recently showed that the detection of dead cells by the receptor DNGR-1, expressed on dendritic cells, prevents excessive inflammation. In cancer, this action can cause more harm than good.

"High immune-cell infiltration of the tumor microenvironment will

promote tumor elimination by the immune system," said Dr. Sancho.
In the study, the scientists found that the recognition of dead tumor cells through DNGR-1 expressed on dendritic cells prevents further infiltration of both dendritic cells and the tumor-eliminating CD8 T cells, thus preventing the immune system from attacking the tumor.
The researchers managed to increase the efficiency of antitumor immunotherapy by using blocking antibodies in combination with cytokines or chemotherapy to promote dendritic cell development.
The research shows that the antitumor activity of dendritic cells can be promoted through targeted interventions. The first of these is the administration of the cytokine Flt3L, and the second is antibody blockade of DNGR-1. Flt3L acts as a 'stimulant', increasing the numbers of dendritic cells and promoting their entry into the tumor microenvironment. The team also found that circulating levels of Flt3L can be increased by stimulating the body's own production of the cytokine with specific chemotherapy treatments.

This new study shines a light on some of the mechanisms that promote correct tumor infiltration by antitumor immune cells and proposes a new strategy to potentiate this infiltration and antitumor immunotherapy. The study thus identifies a new tool for combating cancer by strengthening the body's own defense.

The study was funded by the Fundación "la Caixa", the Asociación Española contra el Cáncer, the National Institute for Health Research Manchester Biomedical Research Center, the European Research Council (ERC-2016-Consolidator Grant 725091), the European Commission (635122-PROCROP H2020), the Ministerio de Ciencia, the Agencia Estatal de Investigación, the European Regional Development Fund (ERDF) (SAF2016-79040-R), the IMMUNOTHERCAN de la Comunidad de Madrid, a FIS-Instituto de Salud Carlos III grant, the Fundación Acteria, Atresmedia (Constantes y Vitales), and Fundació La Marató de TV3.

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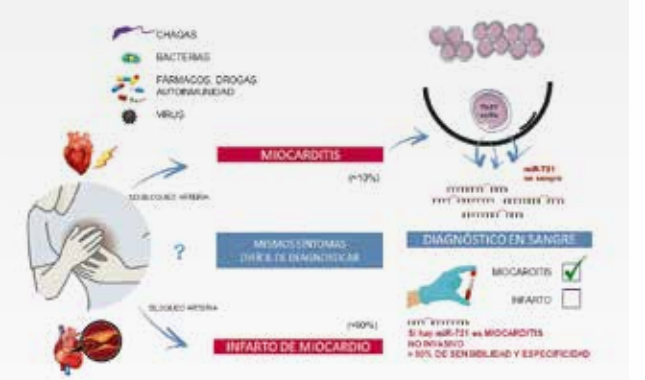
NEW ENGLAND JOURNAL OF MEDICINE:

THE FIRST BLOOD BIOMARKER TO DISTINGUISH BETWEEN MYOCARDITIS AND ACUTE MYOCARDIAL INFARCTION



Scientists at the CNIC have identified the first blood biomarker for myocarditis, a cardiac disease that is often misdiagnosed as myocardial infarction.
The study, led by Dr. Pilar Martín and published in The New England Journal of Medicine, has detected the presence of the human homolog of micro RNA miR-721 in the blood of myocarditis patients.
These results are of paramount importance because they establish the first validated blood marker for myocarditis with high sensitivity and specifity (>90%). This will allow clinicians to distinguish between this disease and other cardiomyopathies like acute myocardial infarction, myocardial infarction with nonobstructive coronary arteries (MINOCA), and other inflammatory diseases with an autoimmune origin.
"Our finding has great potential as a valuable clinical tool for the precise and noninvasive diagnosis of myocarditis from small drops of blood," said Dr. Martín.
The diagnosis of myocarditis is challenging, and the availability of a sensitive and specific marker of acute myocardial inflammation could have a major clinical impact, improving the diagnosis of myocarditis both generally and particularly in its early phases.
Myocarditis is an inflammatory disease of the heart caused by infection, toxins, drugs, or autoimmune disorders. If untreated, myocarditis can progress to potentially fatal dilated cardiomyopathy, requiring heart transplantation.
The prevalence of myocarditis remains uncertain because it is often difficult to achieve a confirmed diagnosis.
Myocarditis is usually diagnosed after coronary angiography or computed tomography scans have discarded coronary artery disease, followed by confirmation of the diagnosis by magnetic resonance imaging (MRI). However, not all centers have access to MRI technology, and the current gold standard for myocarditis diagnosis is endomyocardial biopsy, an invasive procedure normally reserved for severe cases. There is thus a pressing clinical need for the development of reliable and accessible tools for the early diagnosis of acute myocarditis.
Moreover, myocarditis is a side effect of cancer therapy with immunotherapy drugs called "immune checkpoint inhibitors".: Although rare, this effect can have serious consequences for patients. There are currently no specific markers for the diagnosis of patients susceptible to developing myocarditis during cancer immunotherapy.
The researchers are currently designing studies to evaluate the potential of the biomarker as a predictor of short-term and long-term risk; the persistence of myocardial inflammation, and the risk of relapse, clinical progression, and adverse ventricular remodeling.
The CNIC is the sole owner of a patent related to the biomarker and its use for the diagnosis of myocarditis. The CNIC is now exploring licensing agreements with industrial partners to develop and

commercialize this technology in order to make it available for clinical use.

This study received funding from the Ministerio de Ciencia e Innovación(MICINN) through the Instituto de Salud Carlos III (ISCIII)-Fondo de Investigación Sanitaria; the CIBER-CV; the Comunidad de Madrid; a Fundación BBVA Beca Leonardo award; Fundació La Marató TV3; and European Research Council grants ERC-2011-AdG 294340-GENTRIS to F.S-M. and ERC-2018-CoG 819775-MATRIX to B.I.

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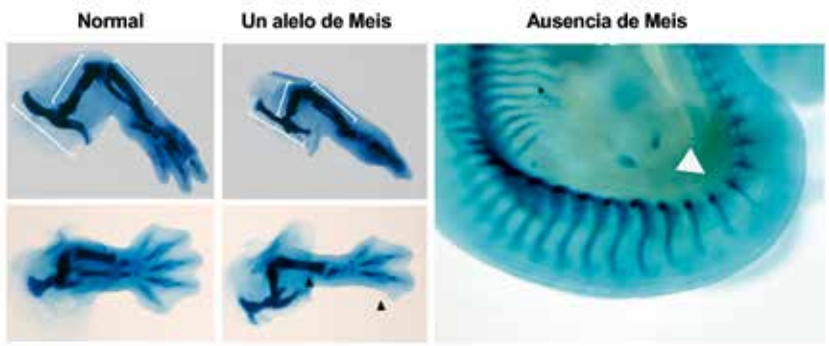
NATURE COMMUNICATIONS:

CNIC SCIENTISTS IDENTIFY ESSENTIAL FACTORS FOR LIMB FORMATION

Scientists at the CNIC, working in partnership with researchers at the Institut de Recherches Cliniques de Montréal (IRCM) in Canada, have identified Meis transcription factors as essential biomolecules for the formation and antero-posterior patterning of the limbs during embryonic development.

In the study, published in Nature Communications, the research team carried out an in-depth characterization of the Meis family of transcription factors. Genetic deletion of all four family members showed that these proteins are essential for the formation of the limbs during embryonic development. "An embryo that develops in the absence of Meis does not grow limbs," said study coordinator Miguel Torres, who leads the Genetic Control of Organ Development and Regeneration group at the CNIC.

Embryonic development is a highly complex process involving interactions among a large array of molecules to ensure the correct formation of a specific organ or tissue from a small initial number of cells. The limbs, explained first author Irene Delgado, "start to form as bulges called limb buds on the flank of the embryo. Growth of the limb bud eventually results in the formation of the skeletal components of the limb."



One of the factors that plays a crucial role in the developing limb is a group of transcription factors called Meis. "In a normal embryo, the Meis genes are expressed very early during the formation of the limb buds," Delgado explained.

In this study, in-depth molecular characterization of developing mouse embryos revealed that Meis factors initiate a signaling cascade that is essential for limb bud development and involves contributions from Fgf10 and Lef1. "Our results identify roles for Meis transcription factors in the developing limb and reveal their participation in essential pathways for limb development. During early limb bud formation, Meis transcription factors are essential for inducing the expression of Fgf10 and Lef1, continued Delgado."

An embryo that lacks Meis genes is unable to grow limbs, but the presence of just one of these four genes (a single allele) "is enough to initiate limb development and also reveals other functions of Meis, such as its importance for the formation of the proximal limb structures (pelvis and femur) and for antero-posterior limb patterning," noted Torres.

Nevertheless, the pelvis and femur of embryos with a single Meis allele are smaller than those of a normal embryo. Moreover, added Delgado, "These embryos have defects in, or simply lack, posterior skeletal elements such as the fibula and posterior digits."

The authors further demonstrated that the molecular basis for these defects is failed initiation of the expression of the Sonic Hedgehog gene, which is essential for antero-posterior limb patterning.

The study was supported by grant PGC2018-096486-B-I00 from the Spanish Ministerio de Ciencia e Innovación.

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY:

A BLOOD SUGAR BIOMARKER IDENTIFIES PATIENTS WITH ATHEROSCLEROSIS AND A RISK OF CARDIOVASCULAR EVENTS

The routine use of the glycosylated hemoglobin test to track blood sugar levels in the general population can identify individuals with more advanced atherosclerotic disease. Currently used in the diagnosis and management of diabetes, glycosylated hemoglobin can provide a useful estimate of atherosclerotic disease, and therefore of cardiovascular risk, in individuals without diabetes may or may not have prediabetes.

The advance heralded by the CNIC study is the use of this blood-sugar measure in apparently healthy middle-aged individuals who do not have diabetes mellitus but with or without possible prediabetes.

When used in combination with traditional risk factors (hypertension, dyslipidemia, and smoking), the glycosylated hemoglobin test more accurately distinguishes between people at high and low risk of atherosclerotic disease.

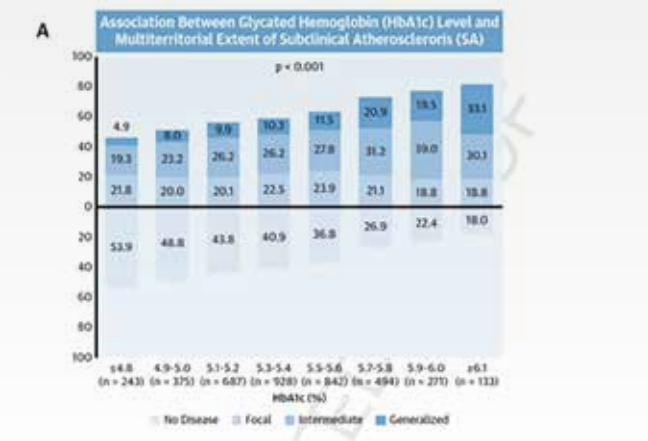
The study, published in The Journal of American College of Cardiology (JACC), proposes that, because glycosylated hemoglobin levels can easily be reduced through lifestyle changes, the test should be at the front line of risk reduction strategies.

The glycosylated hemoglobin diagnostic test is cheap, accessible, and widely used in daily clinical practice, explained Dr. Xavier Rosselló, CNIC scientist and cardiologist at Hospital Universitario Son Espases in Palma de Mallorca. The test can therefore be put to immediate use to calculate the degree of subclinical atherosclerosis in the general population.

The study forms part of the collaborative PESA-CNIC-SANTANDER project.

The new CNIC finding provides a simple way to increase the accuracy of cardiovascular risk ranking in individuals without diabetes and with or without prediabetes.

The authors conclude that "this study establishes glycosylated hemoglobin as a mass-use biomarker because its greatest benefit is in individuals at low cardiovascular risk, who form the immense majority of the general population and account for most cardiovascular deaths in absolute terms."



The study was funded by the Instituto de Salud Carlos III (ISCIII, PI15/ 02019, PI17/00590, PI20/00819) and the European Regional Development Fund (ERDF) "A way to make Europe" and included scientists from the CIBER-CV research network.

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ACS NANO:

CNIC SCIENTISTS DESCRIBE A POSSIBLE DISEASE-CAUSING MECHANISM IN HYPERTROPHIC CARDIOMYOPATHY

Scientists at the CNIC have described a potential disease-causing mechanism in hypertrophic cardiomyopathy (HCM), the most frequent hereditary disease of the heart. The study, published in the journal ACS Nano, provides the first description of an association between this disease and mechanical alterations to a component of the heart's contractile machinery.

The heart muscle is under constant mechanical stress throughout life as it contracts to pump blood to the body. The laboratory led by Dr. Jorge Alegre-Cebollada investigates how the mechanical properties of the cardiac proteins determine the physiological behavior of this muscle and how alterations to these properties lead to the appearance of diseases like HCM. In this disease, the left ventricle becomes enlarged, and severe manifestations include heart failure and sudden death.

Scientists have known for more than 20 years that HCM is caused by mutations in proteins with a mechanical function in the heart. One of the challenges of cardiovascular genetics is to identify which among the genetic variants found in patients and their families cause disease. Knowing if a mutation is disease-causing or not is important because this information will determine the clinical follow-up of family members and, potentially, their treatment.

The study, coordinated by Dr. Alegre-Cebollada, analyzed cardiac myosin-binding protein C (cMyBP-C), the most frequently mutated protein in HCM patients. "A high proportion of mutations in the cMyBP-C gene cause

amino-acid changes in the protein; however, the mechanisms by which these mutations cause HCM are not precisely known."

Dr. Alegre-Cebollada's group, in close partnership with clinical and molecular researchers in Europe and the US, set up a database of cMyBP-C variants with a clear link to HCM in order to define the molecular defects underlying the disease.

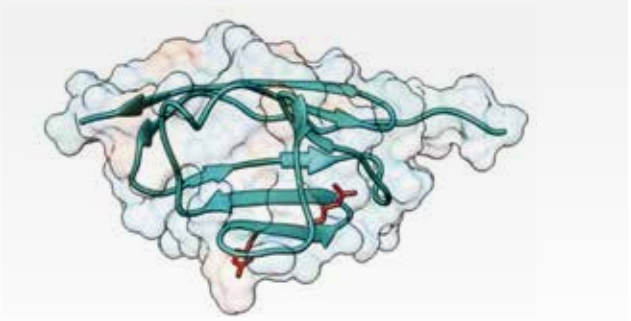
Using bioinformatics and experimental approaches, the research team discovered that around half of these mutations affect the integrity of cMyBP-C messenger RNA (mRNA) or protein. These results have already been accepted for publication in the Journal of Biological Chemistry and have been the subject of a commentary article in the leading medical genetics journal Genetics in Medicine.

While alterations to mRNA or protein integrity could explain the pathogenicity of half the mutations analyzed in the earlier study, Dr. Alegre pointed out that the other half do not cause disease via this route.

Using advanced biophysical techniques based on atomic force microscopy, in the new study the team showed that some of the disease-causing

mutations in cMyBP-C produce defects in the mechanical properties of the protein that can alter the contractile function of cardiomyocytes in HCM patients.

Identifying the molecular mechanisms underlying HCM is essential for determining which cMyBP-C mutations cause the disease. This knowledge is therefore also crucial for the clinical follow-up and possible treatment of patients and their families, said the authors.



The study was funded by the Ministerio de Ciencia e Innovación, the European Research Area Network on Cardiovascular Diseases (MINOTAUR consortium, through the Instituto de Salud Carlos III), the Comunidad de Madrid, the US National Institutes of Health, the government of the Basque region, the Italian Ministry of Education, Universities and Research, and postdoctoral fellowships from the School of Medicine and the Maternal and Child Health Institute at Stanford University. The research team also included scientists from the Cardiovascular Biomedical Research Network (CIBER-CV).

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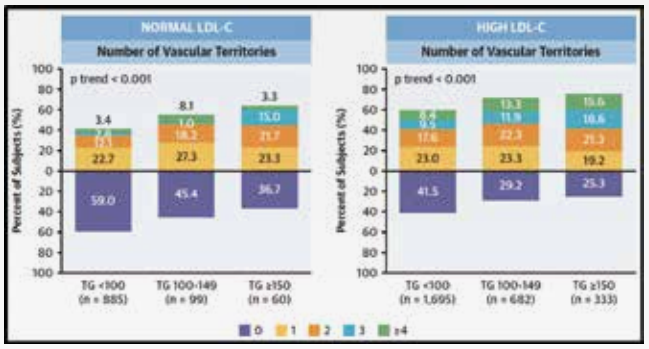
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY: SPANISH SCIENTISTS PROVIDE THE FIRST DEMONSTRATION THAT TRIGLYCERIDES ARE A PRIMARY RISK FACTOR FOR ATHEROSCLEROSIS

Triglycerides can be as important an indicator of cardiovascular risk as high cholesterol. A study conducted by researchers at the CNIC shows for the first time that hypertriglyceridemia is associated with subclinical atherosclerosis and vascular inflammation in individuals with low-to-moderate cardiovascular risk, even if they have normal circulating concentrations of LDL-C, known as 'bad' cholesterol. The results are published in The Journal of American College of Cardiology (JACC).

Until now, triglycerides have been considered a secondary factor in the origin of atherosclerosis, far less important than cholesterol, especially cholesterol bound to low-density lipoproteins (LDL). If, "if LDL-C concentrations are normal, current cardiovascular prevention guidelines do not recommend treatment for high circulating triglyceride concentrations unless the patient has a high cardiovascular risk," said study first author Dr. Sergio Raposeiras-Roubin.

The new study provides the first demonstration that "in individuals with a low-to-moderate cardiovascular risk according to standard scores (the majority of the population), high circulating levels of triglycerides are associated with a greater risk of developing atherosclerosis, even among people with normal LDL-C."

The new study forms part of the PESA CNIC-SANTANDER study (Progression and Early detection of Subclinical Atherosclerosis). The study, led by CNIC General Director Dr. Valentín Fuster, has



demonstrated the high prevalence of subclinical atherosclerosis in the general population, establishing the importance of detecting the disease early in its silent phase.

Moreover, this article shows that triglyceride levels are associated not only with the presence of atherosclerosis, but also with vascular inflammation.

CNIC Clinical Research Director Dr. Borja Ibáñez explained that this result indicates a strong association between elevated circulating triglyceride levels and the early stages of atherosclerosis, a finding "with important implications for the design of prevention strategies."

The results indicate that clinical practice guidelines should be modified to emphasize the need to control not only LDL-cholesterol but also triglyceride levels. "The measurement of blood triglycerides is routine, and fortunately there are abundant effective medicines available to ensure appropriate levels," concluded Dr. Fuster.

The study received funding from the Carlos III Institute of Health and the European Regional Development Fund. Dr. Ibáñez's research is supported by the European Research Council through the MATRIX project (ERC-COG-2018-ID: 819775).

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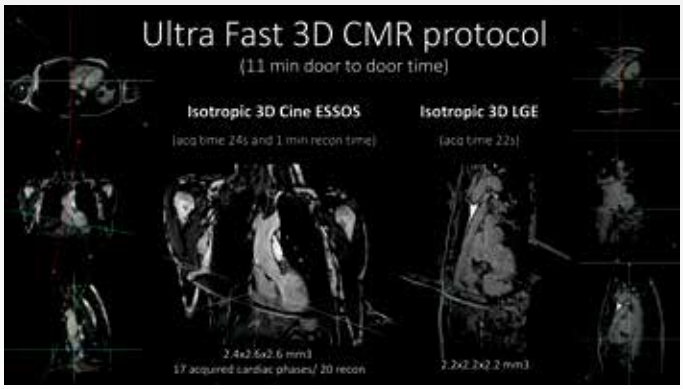
JACC-CARDIOVASCULAR IMAGING: CNIC AND PHILIPS DEVELOP ULTRAFAST CARDIAC MAGNETIC RESONANCE TECHNOLOGY THAT ANALYZES THE HEART IN LESS THAN 1 MINUTE



Scientists at the CNIC and Philips have developed a revolutionary technology that can perform cardiac magnetic resonance (CMR) scans in under a minute. ESSOS (Enhanced SENSE by Static Outer volume Subtraction) allows precise assessment of heart anatomy and function, as well as reducing healthcare costs and increasing patient comfort. The new methodology has been tested on more than 100 patients with a range of heart conditions. The results have been published in JACC: Cardiovascular Imaging, the world-leading journal in the field of cardiac imaging.

CMR provides a noninvasive and radiation-free method for exploring the heart and is the ideal technique for studying heart anatomy, function, and even cell composition. Although most hospitals have magnetic resonance scanners, these are not often used for heart studies because a complete CMR study takes so long. Study first author Dr. Sandra Gómez-Talavera, a CNIC investigator and cardiologist at Fundación Jiménez Díaz University Hospital, explained that "a complete CMR study takes 45-60 minutes, and many patients don't go through with it because remaining in the scanner for this long is too uncomfortable."

In addition, hospital magnetic resonance scanners are needed for other studies, limiting their availability for long-duration cardiac assessments.

To overcome these obstacles to CMR, CNIC scientists working in partnership with Philips have developed a technique for accelerated CMR acquisition. The technique, explained Dr. Gómez-Talavera, "allows the study of the anatomy and function (The motility) of the heart muscle, as well as infarcted and fibrotic tissue. The method can be used to study the whole thoracic cavity in 3D, with algorithms used to focus exclusively on the heart and major vessels (the mobile elements), reducing the scan time."

"We have demonstrated in a large group of patients that CMR with this technology yields the same information as the standard technique, but at less than 10% of the patient scan time," said CNIC Clinical Research Director Dr. Borja Ibáñez, a cardiologist at Fundación Jiménez Díaz University Hospital and a CIBER-CV group leader. Dr. Ibáñez is one of the two lead authors on the study.

ESSOS is protected by a patent held jointly by the CNIC and Philips and is the fruit of almost 10 years' collaboration. The research team believe that this new technology will revolutionize cardiac imaging.

ESSOS allows images to be obtained 34 times faster than with the standard technology in current use. "All the information needed to understand heart form and function can be acquired in a little over 20 seconds," noted Sánchez-González, adding that "a further 20-second acquisition is all that is needed to detect infarction or fibrosis. This brings the scan to an end, in less than 1 minute."

A key advantage of the technology is that it can be used with the magnetic resonance scanners already installed in hospital.

This research was funded by the Instituto de Salud Carlos III through a FIS technology development grant, a Spanish Society of Cardiology Translational Research award, the European Research Council (ERC), and the Comunidad de Madrid (Red Madrileña de Nanomedicina en Imagen Molecular).

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CIRCULATION RESEARCH: CNIC SCIENTISTS DESCRIBE ONE OF THE MECHANISMS UNDERLYING CARDIAC HYPERTROPHY

CNIC Scientists have identified a new mechanism involved in the regulation of cardiac hypertrophy. The mechanisms underlying this disease remain largely unknown, and this situation is impeding the development of effective treatments.

The findings, published in Circulation Research, may spur the development of new tools for the treatment of cardiac hypertrophy, especially in Cushing syndrome patients.

The results, explained principal investigator Dr. Enrique Lara Pezzi, who leads the Molecular Regulation of Heart Failure group at the CNIC, reveal that the "The protein SRSF4 binds to and stabilizes the non-coding RNA GAS5, enabling it to block the action of the glucocorticoid receptor and thus prevent cardiac hypertrophy".

The contractile function of the heart is enacted by cardiomyocytes. Although in the adult heart these cells have almost no ability to divide, Dr. Lara Pezzi explained that they have a remarkable ability to adapt to the changing demands placed on the heart.

One example of this capacity is the response to aortic stenosis. "With stenosis, the aortic valve cannot open fully, and the narrowing of the opening obliges the left ventricle to pump blood with greater force. This requires the heart muscle to contract more strongly," continued Dr. Lara Pezzi.

Although cardiomyocytes cannot divide, Dr. Lara Pezzi explained that "to increase contractile capacity, these cells become enlarged, a process known as hypertrophy."

However, while this response is effective at first, the thickening of the left ventricular wall (cardiac hypertrophy) triggers structural changes in the heart that cause a progressive loss of contractile capacity.

Continuing lack of knowledge about the mechanisms underlying cardiac hypertrophy is impeding the development of effective treatments. Dr. Lara-Pezzi's group, in partnership with researchers at Hospital Puerta de Hierro in Majadahonda, the Spanish Cardiovascular Research Network (CIBER-CV), and the University of Frankfurt, has analyzed possible mechanisms underlying the development of this disease.

The researchers found that mice lacking the RNA-binding protein SRSF4 develop cardiac hypertrophy and have an impaired ability to relax the heart muscle, a condition known as diastolic dysfunction.

Further analysis showed that the absence of SRSF4 severely reduces the expression of the non-coding RNA GAS5. "SRSF4 binds directly to GAS5, preventing GAS5 degradation in the cell. GAS5 is an inhibitor of the glucocorticoid receptor, whose activation contributes to the development of cardiac hypertrophy," explained Dr. Lara Pezzi.

First author, Dr. Javier Larrasa clarified that "the absence of SRSF4 triggers the degradation

of GAS5, and this results in activation of the glucocorticoid receptor. In contrast, overexpression of GAS5 with a viral vector inhibits the glucocorticoid receptor and reduces cardiac hypertrophy."

The research team concludes that the identification of the SRSF4–GAS5–glucocorticoid-receptor cell signaling pathway is a major advance in the characterization of the molecular mechanisms underlying cardiac hypertrophy and could serve as the basis for new treatments.

Dr. Lara Pezzi also commented that, the findings could be "particularly applicable to patients with Cushing syndrome, who develop cardiac hypertrophy in part through glucocorticoid receptor activation."

An analysis of samples from Cushing syndrome patients revealed a degree of dysregulation of SRSF4 and GAS5 expression; however, confirming a role of this pathway in this disease will require further research.

This study received funding from the European Union (CardioNeT-ITN-289600 and CardioNext-ITN-608027), the Ministerio de Economía y Competitividad, and the Community of Madrid (2010-BMD-2321 "Fibroteam"). Funding was also provided by the Plan Estatal de I+D+I 2013-2016 and the European Regional Development Fund "A way to build Europe" program.

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY:

A DRUG COSTING LESS THAN €2 A DAY HELPS IN THE TREATMENT OF SEVERELY ILL COVID-19 PATIENTS

Metoprolol, a drug widely used to treat cardiovascular disease, is beneficial when administered to COVID-19 patients. This is the finding of a study by investigators at the CNIC, published in the Journal of American College of Cardiology (JACC).

The most severe form of COVID-19 is severe respiratory failure, which requires intubation and is associated with a high mortality rate. Pulmonary infection with the SARS-CoV2 virus can progress to acute respiratory distress syndrome (ARDS), in which inflammation and neutrophil hyperactivation play a central role. There is currently a lack of therapies for ARDS associated with COVID-19.

The study was led by Dr. Borja Ibáñez, group leader of the Translational Laboratory for Cardiovascular Imaging and Therapy at the CNIC, cardiologist at the Hospital Universitario Fundación Jiménez Díaz (FJD) in Madrid, and member of the CIBER-CV cardiovascular research network. The research team recently discovered that metoprolol, a well-established beta-blocker, has a highly selective effect on hyperactivated neutrophils during situations of acute stress such as a myocardial infarction. Given the central role played by neutrophils in ARDS, the team postulated that metoprolol might be an effective treatment for patients with severe COVID-19.

MADRID-COVID is a randomized clinical trial conducted in close collaboration between the CNIC and the cardiology, ICU, pulmonology, and biobank services at FJD Hospital. This pilot trial

examined the effect of intravenous metoprolol administration on lung inflammation and respiratory function in severe COVID-19 patients intubated after developing ARDS.

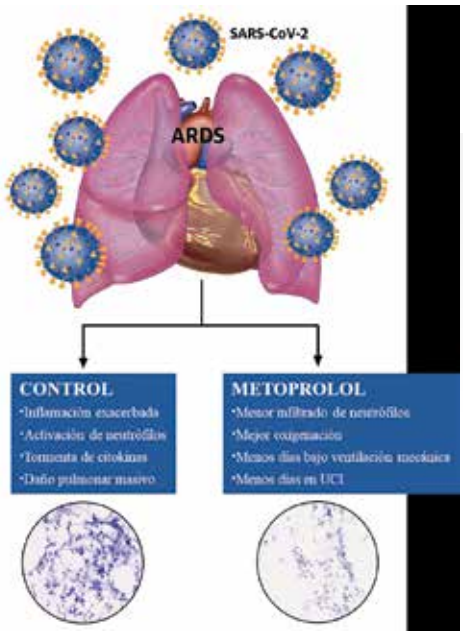
The team "randomized 20 intubated COVID-19 patients to receive intravenous metoprolol (15 mg per day over 3 days) or to a control group that did not receive the drug. We analyzed the inflammatory infiltrate in bronchoalveolar fluid before and after treatment and also monitored clinical progression parameters such as oxygenation and days on mechanical ventilation."

The intravenous metroprolol treatment significantly reduced neutrophil infiltration of the lungs and improved oxygenation.

Dr. Ibáñez added that "while we need to be cautious with these results of a pilot trial, we have observed that metoprolol treatment in this clinical setting is safe, is associated with a very significant reduction in lung infiltration, and appears to lead to very rapid improvements in patient oxygenation."

The researchers therefore propose intravenous metoprolol as a "promising intervention that could improve the prognosis of severely ill COVID-19 patients." They also emphasize that metoprolol is a safe and cheap drug (daily treatment cost below €2) that is readily available.

Joint first author Agustín Clemente-Moragón added that "the effect of metoprolol on the hyperactivation of inflammatory cells implicated in ARDS is exclusive to this beta-blocker." In a previous experimental study, the same group recently demonstrated that other apparently similar beta-blockers have no effect on exacerbated lung inflammation.



The research team led by Dr. Ibáñez was awarded funding from the Instituto de Salud Carlos III (ISCIII) for a clinical trial to definitively demonstrate the clinical benefits of metoprolol in 350 ADRS patients admitted to 14 ICUs across Spain. The MAIDEN clinical trial will be coordinated by the cardiovascular CIBER research network and will include the participation of cardiovascular and respiratory specialists.

The study was partly funded by the European Comission (EERC-CoG grant Nº 819775) and the Ministerio de Ciencia e Innovación (MCN; 'RETOS 2019' grant Nº PID2019-107332RB-I00). The study was also supported by the Programa de Atracción de Talento de la Comunidad de Madrid.

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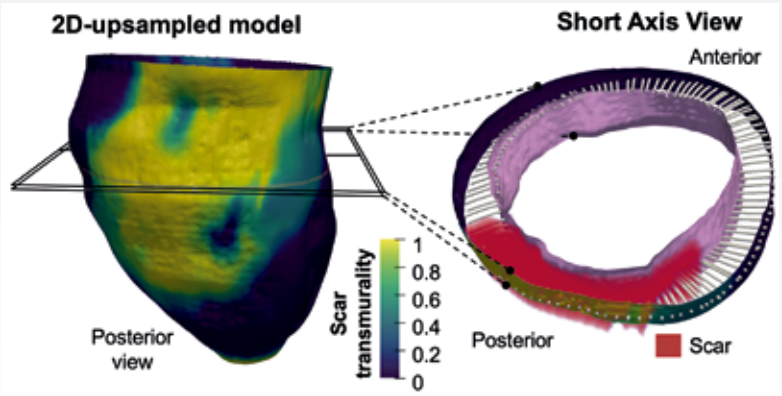
SCIENTIFIC REPORTS:

3D MAPPING OF POST-INFARCTION SCARRING INCREASES THE PROGNOSTIC POTENTIAL OF CARDIAC MAGNETIC RESONANCE IMAGING



A multidisciplinary team of scientists based the CNIC and the Universidad de Valladolid, has developed a highly efficient method for identifying the 3-dimensional features of the scar tissue formed after a myocardial infarction. The study was carried out in partnership with scientists and clinicians at Hospital Clínico San Carlos, Hospital Universitario la Paz, Fundación Jiménez Díaz, Hospital Rúber Juan Bravo Quironsalud, Universidad Politécnica de Madrid, el Centro de Supercomputación de Barcelona, Philips healthcare Iberia, CIBER-CV1 and CIBER-BBN.

The new method allows 3-dimensional transmural (across the ventricular wall) mapping of scar tissue in the infarcted muscle. Transmural mapping of the infarcted tissue enables highly detailed characterization of the morphology of the damaged tissue and provides an accurate measure of infarct size relative to myocardial wall thickness, a parameter known as transmurality.

According to CNIC scientist David Filgueiras, "a major advantage of this new method is its full compatibility with standard cardiac magnetic resonance (CMR) sequences that take just a few minutes to acquire. This approach can thus significantly shorten the time needed for image acquisition, easing access to in-demand nuclear magnetic resonance scanners."

"This novel methodology may provide an efficient approach in clinical practice after manual or automatic segmentation of myocardial borders in a small number of conventional 2D slices and automatic scar detection," write the authors.

The results of the study show that low scar transmurality on CMR (below 10% of ventricular wall thickness for 3D sequences or 20% for 2D sequences) is associated with the clinical presentation of tachycardias involving infarcted ventricular tissue, known as ventricular tachycardias.

Describing the results study first authors Susana Merino, of Valladolid University, and Lilian Karina Gutiérrez, of the CNIC, said that the results reveal a significant correlation between low scar transmurality and the cardiac frequency of spontaneous ventricular tachycardia episodes.

The results also show that patients with low scar transmurality values had a higher probability of ventricular tachycardia recurrences during long-term follow-up.

The new method is especially promising because it uses conventional 2D delayed gadolinium-enhanced CMR sequences and requires only a limited number of slices. This technology is available at all centers that carry out CMR studies, and the method does not require 3D CMR studies.

The method was developed through technical, experimental, and clinical collaboration under the umbrella of a specific partnership between Valladolid University and the CNIC. Joint lead author Carlos Alberola explained that the technical advances of the method are built on procedures developed in the Image Processing Laboratory of the Escuela Técnica Superior de Ingenieros de Telecomunicación at Valladolid University.

"The first of these advances is a method for image interpolation that preserves topology. This allows high-resolution 3D images to be generated with a high level of precision from the images obtained with conventional CMR procedures."

"A second advance is a mathematical method for characterizing fibrous tissue formed in the myocardial wall after an infarction. This tool provides a measure of the full 3D morphology of the scar relative to the thickness of the myocardium, a parameter known as transmurality." The method uses a procedure based on partial differential equations to provide point-wise correspondences between the endocardium and the epicardium. These correspondences allow the definition of multiple indicators of the extent of the infarction.

The experimental arm of the study involved input from the Advanced Development in Arrhythmia Mechanisms and Therapy group at the CNIC, led by Dr. David Filgueiras. This group provided expertise in experimental models of myocardial infarction, essential for validating the methodology. The CNIC laboratory also coordinated the study of the clinical application of the new method, in partnership with a multidisciplinary team of experts in the diagnosis and treatment of complex cardiac arrhythmias.

The study received funding from the Ministerio de Ciencia e Innovación (TEC2017-82408-R y PID2019-109329RB-I00); Fondo Europeo de Desarrollo Regional (CB16/11/00458); Heart Rhythm Association de la Sociedad Española de Cardiología; Fundación Interhospitalaria para la Investigación Cardiovascular (FIC); Fundación Eugenio Rodríguez Pascual; programa H2020 de la Unión Europea; el Ministerio de Asuntos Económicos y Transformación Digital, and the Fundación Carolina-BBVA.

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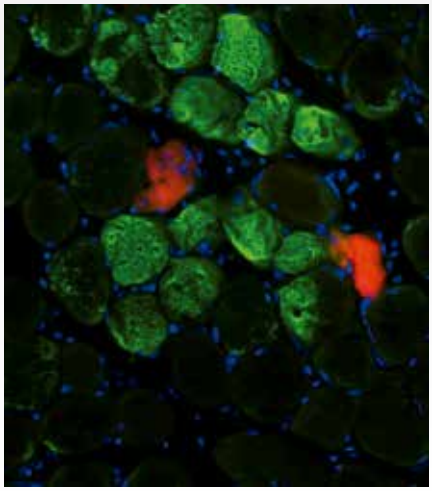
SCIENCE:

A RAPID MECHANISM FOR MUSCLE SELF-REPAIR INDEPENDENT OF STEM CELLS

Muscle is known to regenerate through a complex process that involves several steps and relies on stem cells. Now, a new study led by researchers at Universitat Pompeu Fabra (UPF), the CNIC, CIBER-NED, and the Instituto de Medicina Molecular João Lobo Antunes (iMM, Portugal) describes a new mechanism for muscle repair after physiological damage that relies on the rearrangement of muscle fiber nuclei and is independent of muscle stem cells. This protective mechanism paves the way to a broader understanding of muscle repair in physiology and disease.

Skeletal muscle, the organ responsible for locomotion, is formed of cells (fibers) that have more than one nucleus, an almost unique feature in the body. Despite the plasticity of these fibers, their contraction can be associated with muscle damage. William Roman, first author of the study and researcher at UPF, explained: "Even in physiological conditions, regeneration is vital for muscle to endure the mechanical stress of contraction, which often leads to cellular damage. Although muscle regeneration has been investigated in depth in recent decades, most studies centered on mechanisms involving several cells, including muscle stem cells, which are required when extensive muscle damage occurs."

"In this study, we found an alternative mechanism of muscle tissue repair that is muscle-fiber autonomous," said study leader Pura Muñoz-Cánoves, ICREA professor and principal investigator at UPF and the CNIC.



Using in vitro models of injury and models of exercise in mice and humans, the researchers—Antonio Serrano (UPF) and Mari Carmen Gómez-Cabrera (Universitat de València e INCLIVA)—found that nuclei are attracted to sites of muscle injury, accelerating the repair of the contractile units. The team then went on to dissect the molecular mechanism underlying this phenomenon. "Our laboratory

experiments with muscle cells showed that the movement of nuclei to injury sites resulted in the local delivery of mRNA molecules. These mRNA molecules are translated into proteins at injury site that act as building blocks for muscle repair," explained William Roman. "This muscle fiber self-repair process occurs rapidly in mice and humans after exercise-induced muscle injury, and thus represents a time- and energy-efficient protective mechanism for the repair of minor lesions," noted Pura Muñoz-Cánoves.

In addition to the implications of the study for muscle research, the movement of nuclei to injury sites introduces a concept of more general cell biological interest. "One of the most fascinating things about these cells is the movement during the development of their nuclei, the biggest organelles inside the cell, but the reasons why nuclei move are largely unknown. Now, we have shown the functional importance of this phenomenon in adulthood during cell repair and regeneration," said study co-leader Edgar R. Gomes, group leader at the Instituto de Medicina Molecular and professor at the University of Lisbon Faculty of Medicine.

On the importance of these discoveries, Pura Muñoz-Cánoves, Antonio Serrano and Mari Carmen Gómez-Cabrera agree that "These findings constitute an important advance in the understanding of muscle biology, exercise physiology, and muscle dysfunction."

The study was conducted at the UPF, CNIC, and CIBER-NED and at the iMM in collaboration with the University of Valencia e INCLIVA. This study was funded by the European Research Council, Association Française contre les Myopathies, the European Molecular Biology Organization, the Human Frontiers Science Program, and the Spanish Ministry of Science.

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CIRCULATION:

IT'S NEVER TOO LATE TO TREAT PROGERIA

Scientists led by Dr. Vicente Andrés at the CNIC and the Spanish Cardiovascular Research Network (CIBER-CV) have generated the HGPSrev experimental mouse model. This is the first animal model to develop Hutchinson-Gilford Progeria Syndrome (HGPS) and also allow its suppression through the controlled regulation of the expression of progerin, the aberrant protein that causes the disease. Using the new model, the researchers have demonstrated that it is never too late to treat HGPS.

The study, published in Circulation, also establishes that the cardiovascular alterations and early death associated with HGPS can be prevented with treatments specifically targeting cells of the cardiovascular system.

HGPS is an ultra-rare genetic disease that affects fewer than 400 children worldwide and for which there is no known cure. The disease is caused by a mutation in the LMNA gene and is characterized by accelerated aging and death in the second decade of life, principally due to cardiovascular complications derived from atherosclerosis.

In the absence of mutations, LMNA encodes type A lamin proteins (Lamins A and C). The mutation found in HGPS patients results in the synthesis of progerin, a mutant protein that provokes multiple molecular and cellular alterations in the tissues where it accumulates, causing their life to pass at a highly accelerated rate, where minutes are hours and hours are lost days.

Now, thanks to the HGPSrev mouse generated by the CNIC Molecular and Genetic Cardiovascular Pathophysiology group, the research team has managed to suppress progerin expression and reestablish lamin A expression in mice of different ages, both throughout all body tissues and in specific cell types.

The characterization of the animal model was carried out with the participation of researchers at Queen Mary University of London.

Joint first authors Drs Amanda Sánchez López and Carla Espinós Estévez

explained that while some palliative therapies are effective in animal models and are the subject of clinical trials, their therapeutic benefit is very limited. "A true cure would require the elimination of the culprit mutation," commented Dr Sánchez López. However, this is not yet possible, and progeria is only diagnosed once the first symptoms have already appeared. "We therefore sought to reverse symptoms once they are already present and to determine how long treatment could be delayed and still have a beneficial impact," explained Carla Espinós Estévez.

The extent to which the damage caused by progerin can be reversed is currently not known, and patients often do not start to receive treatment until symptoms are quite advanced. The investigators therefore addressed a key question: Can the progression of HGPS be stopped or slowed if treatment commences when the disease is advanced, or does therapeutic benefit depend on starting treatment early, when symptoms are mild?

Another important question is how treatment should be targeted. Progerin is expressed in many tissues, but it was not known if treatment needs to be directed at all affected cells or if it would be effective if targeted at a specific cell type.

To answer these questions, Dr Andrés's team used CRISPR-Cas9 technology to generate HGPSrev mice.

The results show that HGPSrev mice show the major features of the human disease, including growth retardation, lipodystrophy, cardiovascular alterations, and early death.

The investigators also showed that elimination of progerin and

restoration of lamin A expression increased life expectancy by 84.5% in HGPSrev mice with very mild symptoms; moreover, this approach extended lifespan by 6.7% even in mice with very advanced symptoms. These results establish not only that starting treatment when symptoms are mild has a huge positive impact, but also that treatment can be beneficial no matter how late it is started.

"We managed to prevent vascular alterations and normalize survival in progeric mice by eliminating progerin expression and restoring lamin A expression specifically in vascular smooth cells and cardiomyocytes, even though other cell types remained diseased," explained Dr Andrés.

The investigators conclude that these results "could contribute to the design of future clinical treatments, given that they suggest that strategies exclusively targeting the cardiovascular system could have a very significantly beneficial effect on patients' life quality and expectancy."

This study received funding from the Ministerio de Ciencia e Innovación (MCIN)/Agencia Estatal de Investigación (AEI)/10.13039/501100011033 (grants SAF2016-79490-R, PID2019-108489RB-I00, SVP-2014-068334, FJCI-2017-33299); Instituto de Salud Carlos III (ISCIII; grant AC17/00067-TREAT-HGPS), an E-Rare Joint Transnational call project, European Union Horizon 2020 Framework Programme 2017); the Fondo Europeo de Desarrollo Regional ("a way to build Europe"); the Welcome Trust (grant 098291/Z/12/Z); the Comunidad Autónoma de Madrid (grant 2017-T1/BMD-5247); the Asociación Apadrina la Ciencia-Ford España-Ford Motor Company Fund; and the Fundación "la Caixa".

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PLOS BIOLOGY:

CNIC SCIENTISTS IDENTIFY TWO PROTEINS ESSENTIAL FOR POSTNATAL CARDIAC METABOLISM

A study, published in PLoS Biology, shows for the first time that cardiac metabolism in the postnatal period determines the regulation of metabolism throughout the body.

Scientists at the CNIC have identified essential roles for two proteins is cardiac metabolism after birth. The study, shows that forced premature activation of these proteins in the mouse heart during the first days of life causes irreversible damage and alters whole-body metabolism, leading to diabetes and impaired thermoregulation later in life.

Lead investigator Dr. Guadalupe Sabio explained that, fortunately, the study shows that "these effects could in principle be treated through a change in diet."

During fetal development and the first days after birth, the heart derives most of its energy from the metabolism of glucose, stored in the form of glycogen. But, explained first author Ayelén Santamans, soon after birth, the rapid growth of the heart increases the organ's energy demands, requiring the heart to become "much more efficient at obtaining energy."

The *PLoS Biology* study shows that the **proteins p38γ and p38δ** are activated in the heart shortly after birth and reduce the activity of the enzyme responsible for glycogen synthesis. This precipitates a metabolic change in the heart, which begins to use fatty acids as its main energy source.

Perturbation of cardiac metabolism by forced premature p38γ and p38δ expression during the postnatal period causes irreversible damage that manifests in adulthood as insulin resistance, glucose intolerance, and an impaired ability to maintain body temperature.

But the new study shows that, since the problem is an insufficient supply

of energy to the heart, the damage can be repaired by a change in diet.

To demonstrate this, the researchers fed female mice a high-fat diet during pregnancy and lactation.

Newborn mice in these experiments had no cardiac damage and did not go on to develop diabetes symptoms even when p38γ and p38δ expression was prematurely activated.

The study is the first to show that heart metabolism in the postnatal period determines whole-body metabolism. "Our results show that the gradual increase in p38γ and p38δ activity is tightly regulated and that premature activation produces an energy deficit that is deleterious both for the heart and for the metabolism of the rest of the body," said Dr Sabio.

The scientists think that both p38γ and p38δ might underlie some congenital cardiometabolic diseases that currently have no known cause, suggesting that dietary supplementation could be a valid treatment for these conditions.

The study was supported by the following funding bodies: EFSD, Lilly European Diabetes Research Programme; Ministerio de Ciencia, Innovación y Universidades; Comunidad de Madrid; Fundación Jesús Serra; Instituto de Salud Carlos III, y Fundación "la Caixa".

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SCIENCE ADVANCES:

CNIC SCIENTISTS IDENTIFY THE ESSENTIAL ROLE OF A GENE IN PLACENTAL DEVELOPMENT

Scientists working with an experimental mouse model at the CNIC have identified the essential role of the gene GPR126 in the development of the placenta during pregnancy.

The results, published in Science Advances, show that GPR126 (adhesion G protein-coupled receptor 126) is essential for the development of a specific placental cell type that regulates the remodeling of the uterine vasculature. Cardiac defects in mouse Gpr126 mutants are secondary to placental defects, reflecting the intimate relationship between the placenta and the fetal heart.

There is evidence that GPR126 may play a similar role in placental development in humans. The babies of women who carry mutations in GPR126 die during gestation or soon after birth, and 30% of these women develop preeclampsia. This pregnancy complication, which affects 5%-8% of pregnancies in the general population, is characterized by high blood pressure that damages both mother and fetus and can result in fetal death.

Experiments in animal models have shown that GPR126 is required for the maturation of the peripheral nervous system (PNS), the formation of bone and cartilage, and the development of the inner ear. In humans, mutations in GPR126 are associated with skeletal malformations and muscle cramping in the limbs.

The CNIC Intercellular Signaling in Cardiovascular Development and Disease group, led by Dr. José Luis de la Pompa, initially identified GPR126 as a gene regulated by the NOTCH signaling pathway (a highly conserved intercellular signaling system in animals) during heart development.

This suggested that GPR126 might influence the proliferation and differentiation of cardiomyocytes (heart muscle cells) in the developing heart.

Other groups had already proposed a requirement for GPR126 in heart development in mice and zebrafish, but research had not provided conclusive evidence to confirm this hypothesis.

In the new study, the CNIC team used genetic techniques to demonstrate that GPR126 is not necessary for heart development in the mouse but plays an essential role in the formation of the placenta, a process known as placentation.

Explaining the results, Dr. de la Pompa said that “We observed that whole-body inactivation of GPR126 in mice caused thinning of the walls of the heart and resulted in embryonic death. However, when we inactivated the gene specifically in the heart, embryonic development was unaffected and heart function unaltered.”

The investigators also found that the lethal effect of whole-body GPR126 deletion “was not reversed by specific re-expression of GPR126 in the heart, indicating that embryonic death in the mutants was not due to a defect in cardiac development,” explained first author Rebeca Torregrosa.

Further studies in the zebrafish model confirmed that GPR126 “is not involved in heart development".

During embryonic development, GPR126 is expressed in giant trophoblast cells, a cell type specific to the placenta. “These cells,” noted de la Pompa, “are vitally important for the implantation of the embryo and the maintenance of pregnancy.”

The research team demonstrated that GPR126 inactivation in the embryo is compatible with survival if the placenta retains at least one normal copy of the GPR126 gene. However, inactivation of the gene in both the embryo and the placenta causes embryonic death “One of the crucial steps in placental development is the remodeling of the maternal arteries. Known as the spiral arteries, these vessels increase their diameter to increase blood flow to the embryo. Defects in this process are associated with pregnancy complications such as preeclampsia, restricted fetal growth, and even miscarriage,” said de la Pompa.

The study shows that trophoblast GPR126 is necessary for the expression of specific proteases involved in spiral artery remodeling, which is essential for the viability of the fetus.

Based on these results, the investigators herald mice lacking GPR126 as an experimental model for studying spiral artery remodeling and preeclampsia. This animal model, moreover, has possible clinical applications in preimplantation genetic diagnosis.

The study was funded by the CIBER CV cardiovascular research network CIBER-CV (PID2019-104776RB-I00, CB16 / 11/00399), TERCEL (RD16 / 0011/0021) del Ministerio de Ciencia de España, Innovación y Universidades (MCIU), the BBVA Foundation, “La Caixa” Foundation, an EMBO fellowship, Boehringer Ingelheim Fonds, and the Programa de Atracción de Talento de la Comunidad de Madrid (Ref.2016T1 / BMD1540).

Torregrosa-Carrión R, Piñeiro-Sabarís R, Siguero-Álvarez M, Grego-Bessa J, Luna-Zurita L, Fernandes VS, MacGrogan D, Stainier DYR, de la Pompa JL. (2021). Adhesion G protein-coupled receptor Gpr126/Adgrg6 is essential for placental development; Sci Adv. 7(46):eabj5445. doi: 10.1126/sciadv.abj5445.

4 CNIC NEWS AND VIEWS

1 - GRANTS

CNIC AWARDED SEVERO OCHOA CENTRE OF EXCELLENCE ACCREDITATION

Severo Ochoa Center of Excellence accreditation provides funds of €1 million per year over four years. The CNIC has once again been awarded this prestigious accreditation by the Spanish Ministry of Science and Innovation. The CNIC was first recognized as a Severo Ochoa Center of Excellence in 2011. The aim of the award is to fund and acknowledge public research centers and units that advance their field, show international scientific leadership, and collaborate widely in their social and business environment.

The award is given to organizations that run highly competitive, groundbreaking programs that are among the finest in the world in their fields of endeavor.

EXCELENCIA SEVERO OCHOA

In addition to the core funding, Severo Ochoa Center of Excellence accreditation allows priority access to other research development initiatives.

PROJECTS STARTING IN 2021

In 2021, 62 CNIC projects started with national competitive funding, representing a total amount of €12.9 million. A further 10 international projects began last year, with funding coming mainly through European Union calls (Horizon 2020) and totalling €7.1 million: 2 ERC CoG projects and the CNIC-led H2020-RESILIENCE project / clinical trial ***Remote Ischemic Conditioning in Lymphoma Patients Receiving Anthracyclines.*** RESILIANCE will receive €6 million over 5 years, of which the CNIC will receive €1.7 million.

Selected CNIC international projects

Funding Body	Grant code	Amount Granted	Acronym	Title	Start date of project
EC-European Commission	SC1-BHC-08-2020	53.957,00 €	RITA ME 2	Rituximab in patients with acute myocardial infarction: a phase 2 placebo-controlled randomised clinical trial	01/06/2021
EC-European Commission	SC1-BHC-06-2020	801.000,00 €	MAESTRIA	Machine learning artificial intelligence early detection stroke atrial fibrillation	01/03/2021
EC-European Research Council	H2020-ERC-2020-COG	2.000.000,00 €	ProtMechanics-Live	Uncovering Protein Mechanics in Physiology and Disease	01/06/2021
EC-European Research Council	H2020-ERC-2020-COG	1.998.500,00 €	AngioUnrestUHD	Understanding and modulating vascular arrest with ultra-high definition	01/03/2021
EC-European Commission	SC1-BHC-08-2020	1.725.938,00 €	RESILIENCE	Remote Ischemic Conditioning in Lymphoma Patients Receiving Anthracyclines	01/06/2021

A CNIC PROJECT RECEIVES FUNDING FROM THE LA CAIXA FOUNDATION TO INVESTIGATE A TYPE OF FATAL TACHYCARDIA

The La Caixa Foundation awarded funding to the project 'Relation between triadin loss and cardiac proteostasis in catecholaminergic polymorphic ventricular tachycardia type 5', which is coordinated by Dr Silvia Priori, leader of the CNIC Molecular Cardiology group, cardiologist at the Istituti Clinici Scientifici Maugeri de Pavia, and Professor at the University of Pavia (Italy). This three year project was selected in the fourth CaixaResearch Health Call and will receive funding of €496 100."

YOUNG POSTDOCTORAL WOMEN'S PROJECTS

Gillian Dunphy and **Dieke Van Dinther,** in Dr. David Sancho's group, started two new Marie Sklodowska Curie projects (H2020-MSCAIF). The projects, titled 'STING signaling modulation via the electron transport chain' (Dunphy) and 'Functional relevance of mitochondrial supercomplex assembly in myeloid cells'(Van Dinther) were awarded €160,932 and €172,932, respectively.

Marta Cortés Canteli, in Dr. Valentin Fuster's group, started a new project on the 'Preclinical connection between cardiovascular disease and Alzheimer's disease' (AD) that was awarded a **BBVA Foundation** 2021 **Leonardo Grant** for Researchers and Cultural Creators.



This project, which will receive €40,000, will determine the blood concentrations of plasma biomarkers of AD— particularly the phosphorylated tau-181 protein—in asymptomatic middle-aged individuals with cerebral hypometabolism and subclinical atherosclerosis. This information has the potential to show if these individuals are already in the initial stages of AD.

2-AWARDS AND HONORS

THE ASSOCIATION OF CARDIOVASCULAR IMAGING OF THE SPANISH SOCIETY OF CARDIOLOGY (SEC) AWARDS ITS GOLD MEDAL TO DR VALENTÍN FUSTER.

CNIC General Director Dr. Valentín Fuster was awarded the Gold Medal of the Association of Cardiovascular Imaging of the Spanish Society of Cardiology (SEC) for his original and innovative use of cardiovascular imaging to expand understanding of the health of the heart and brain. Dr Luis Jesús Jiménez Borreguero, President of the SEC Association of Cardiovascular Imaging, "Dr Fuster has promoted major studies in this field, such as the High-Risk Plaque Initiative and the Progression of Early Subclinical Atherosclerosis study, an original, pioneering project in the use of noninvasive imaging techniques to improve the estimation of cardiovascular disease progression before the onset of symptoms."

PURA MUÑOZ-CÁNOVES RECEIVES THE NATIONAL SANTIAGO RAMÓN Y CAJAL AWARD

The Ministry of Science and Innovation awarded the Santiago Ramón y Cajal National Prize in the area of Biology to Dr. Pura Muñoz-Cánoves for her scientific contributions in the field of tissue regeneration. Dr. Muñoz-Cánoves is Professor of Cell Biology in the Department of Experimental and Health Sciences at ***Universitat Pompeu Fabra*** in Barcelona, Research Professor at the ***Institució Catalana de Recerca i Estudis Avançats*** (ICREA), and a group leader at the CNIC and the Spanish Neurodegenerative Diseases Research Network (CIBERNED).

Created in 1982, the Santiago Ramón y Cajal awards are Spain's most important recognition of scientific research. They recognize the achievements of Spanish researchers carrying out outstanding, internationally recognized research in their respective scientific fields, making exceptional contributions to the advancement of science, improved knowledge of human beings and their coexistence, the transfer of technology, and the progress of humankind. The total amount of the awards is €300,000, with €30,000 destined to each award winner.

Dr. Pura Muñoz joins two previous winners of the same award at the CNIC, Dr. Francisco Sánchez Madrid, in 2020, and Dr. Valentín Fuster, in 2019.

BORJA IBÁÑEZ WINS THE FUNDACIÓN JESÚS SERRA RESEARCH AWARD FOR HIS WORK IN THE FIELDS OF NUTRITION AND FOOD SCIENCE

Dr. Borja Ibáñez, Scientific Director at the CNIC the CNIC and an interventional cardiologist at the ***Fundación Jiménez Díaz***, is one of the winners of the third edition of the Fundación Jesús Serra Research Awards. This initiative of the ***Fundación Jesús Serra***, part of the ***Catalana Occidente*** group, is aimed at scientists younger than 45 who specialize in nutrition and diet.

Dr. Borja Ibáñez was awarded the prize for his clinical research on "Nutritional approaches to the prevention of cardiotoxicity associated with cancer treatments", which focuses on the development of new treatments to reduce the prevalence of chronic heart failure in cancer survivors.

Award winners receive €35,000, and the goal of the awards is to incentivize research into nutrition and food science, an area with a fundamental influence on health. Innumerable research studies show that appropriate lifestyle and dietary habits can prevent or mitigate the impact of diseases such as ischemic heart disease, hypercholesterolemia, diabetes, cancer, and obesity.

GUADALUPE SABIO AWARDED THE *BANCO SABADELL* FOUNDATION PRIZE FOR BIOMEDICAL RESEARCH

The ***Banco Sabadell*** Foundation awarded its Biomedical Research Prize to CNIC researcher Dr. Guadalupe Sabio Buzo for her research into how obesity causes cardiometabolic disease.

Dr. Sabio Buzo heads a team researching the roles of stress-activated protein kinases in the development and progression of cardiovascular disease, diabetes, and cancer. The group's work focuses on understanding alterations observed in obese individuals that may trigger the onset of these diseases, such as changes in lipid profiles, dysregulation of internal body clocks, and cellular stress.

In addition to the ***Banco Sabadell*** prize, Dr Sabio's group received the Antoni Esteve Foundation Research Award for an article published in the journal Nature in 2019. The study revealed the involvement of the protein p38gamma in the development of hepatocellular carcinoma, the main type of primary liver cancer, which affects over a million people a year worldwide.

The international jury, which awards the Antoni Esteve Foundation Research Award every two years, considered the study to be the most important pharmacological publication by a Spanish author in 2019 and 2020.

ALMUDENA RAMIRO RECEIVES THE *CAJA RURAL DE GRANADA* FOUNDATION HEALTH SCIENCES AWARD

Dr. Almudena Ramiro received the XVII ***Caja Rural*** de Granada Health Sciences Award for her research into the treatment of atherosclerosis.

Vascular disease is the main cause of death in developed societies. Heart attack and ischemic stroke are both caused by a thrombus that forms and obstructs an artery, resulting in death of tissues starved of oxygen. A thrombus forms through atherosclerosis, a slow process that has a long asymptomatic phase. Scientists have long known that atherosclerosis involves a major contribution from the immune response, but details of this involvement have remained opaque.

Dr. Ramiro and her team approached this problem using highly innovative technology to study the antibody-encoding genes in the B lymphocytes of mice with atherosclerosis. The team catalogued 18 antibodies that identify atherosclerotic plaques. Closer analysis revealed that one of them, called A12, targets a molecule of the organism itself called ALDH4A1.

The award jury valued the quality of the data and the study's originality and clinical significance. Not only does the study identify a target structure for the altered immune response in atherosclerosis, but the A12 antibody has great potential for the development of innovative strategies to treat vascular diseases. This study was published in Nature.

JOSÉ ANTONIO ENRÍQUEZ AND ANDRÉS HIDALGO RECEIVE THE *CONSTANTES Y VITALES* AWARD FOR THE BEST BIOMEDICAL PUBLICATION OF THE YEAR

José Antonio Enríquez and Andrés Hidalgo were received the ***Constantes y Vitales*** award for the best biomedical publication of the year for their article "A Network of Macrophages Supports Mitochondrial Homeostasis in the Heart". The article, published in Cell, is the result of a joint project run by the CNIC groups led by Dr. Andrés Hidalgo and Dr. José Antonio Enríquez and presents the results of more than five years of research and collaborations with several laboratories in Europe, Asia, and the USA. The study shows that macrophages, a type of immune cell, help heart cells to eliminate their waste material, thus allowing the heart to maintain its metabolic and contractile capacity.

This discovery suggests that cardiac dysfunction may, in some cases, arise from defects in these resident immune cells rather than from defects in cardiomyocytes, an idea has important implications for the diagnosis and treatment of heart disease.

BORJA IBAÑEZ, AWARDED THE *ZENDAL-BALMIS* BLUE CROSS FOR HIS CONTRIBUTION TO THE FIGHT AGAINST THE COVID-19 PANDEMIC

Dr. Borja Ibáñez received the ***Zendal-Balmis*** Blue Cross in the "Gold" category, awarded to individuals and institutions that have contributed to the fight against the major health crisis of the beginning of the 21st century, highlighting their commendable work, sacrifice, commitment, and dedication to this challenge.

The award highlights Dr. Ibañez's research work since the beginning of the pandemic and his team's discovery of beneficial effects of metoprolol in patients with severe Covid-19.

In this study carried out by researchers from the CNIC and the ***Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz*** (IIS-FJD), metoprolol, a safe and cheap beta-blocker traditionally used to treat cardiovascular disease, improved the outcomes of critically ill patients with Covid-19. The study was published in the Journal of American College of Cardiology.

The team found that metoprolol, due to its highly selective effect on hyperactivated neutrophils under acute stress conditions such as myocardial infarction, could be repurposed as a treatment for severe Covid-19.

JORGE ALEGRE-CEBOLLADA RECEIVES THE *MICHÈLE AUGER* AWARD FROM IUPAB

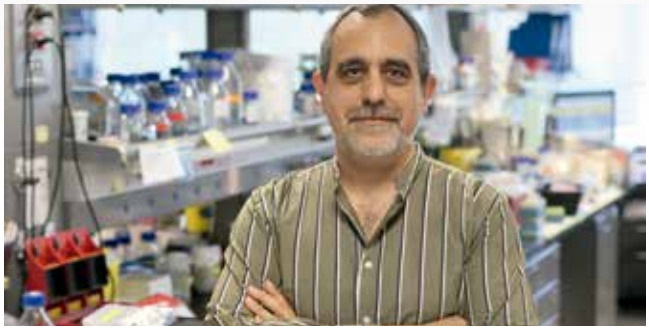
Dr. Jorge Alegre-Cebollada received the ***Michèle Auger*** Prize from the International Union for Pure and Applied Biphysics (IUPAB), through its scientific journal Biophysical Reviews. The award recognizes the research of young scientists working in the field of biophysics who, at the time of application, are younger than 40 years old.

The award was launched in 2019 to honor the memory of Professor Michèle Auger, a much loved and respected member of the Biophysical Reviews Editorial Board, who passed away in 2018.

Dr. Alegre-Cebollada, who heads the Laboratory of Molecular Mechanics of the Cardiovascular System at the CNIC, conducts research aimed at elucidating the nanomechanical principles that govern protein structure, function, and regulation.

Dr. Alegre-Cebollada's studies, which address both the effects of mechanical forces on protein structure and the mechanisms through which these forces are transduced into biological function, represent a significant advance in the field of protein research.

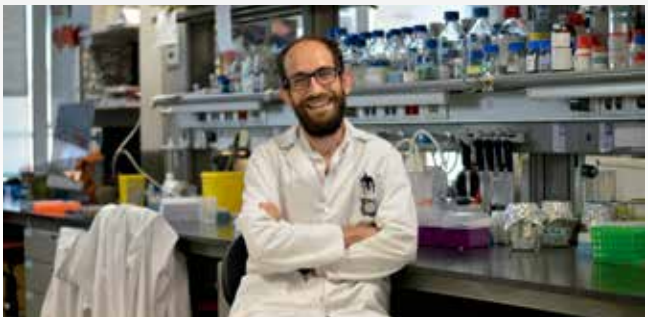
JOSÉ ANTONIO ENRÍQUEZ AND MIGUEL ÁNGEL DEL POZO, NEW MEMBERS OF EMBO



The researchers José Antonio Enríquez and Miguel Ángel del Pozo were named members of the European Molecular Biology Organization (EMBO). Dr Enríquez and Dr del Pozo join their colleagues Miguel Torres, Pura Muñoz, and Francisco Sánchez Madrid, bringing the number of CNIC scientists who are also EMBO members to five.

EMBO members actively participate in the organization, sitting on the EMBO board, the various EMBO committees, and the editorial boards of EMBO Press journals. They also evaluate the applications of EMBO calls for funding and act as mentors for scientists who are just starting out on their professional careers. The new members were formally inducted at the EMBO members annual meeting, held on October 27–29, 2021.

JORGE ALEGRE, MEMBER OF THE *ACADEMIA JOVEN DE ESPAÑA*



Dr. Jorge Alegre Cebollada has been voted one of ten new members of the ***Academia Joven de España***, an organization dedicated to representing young scientists and giving them greater visibility.

Academia Joven de España is linked to the Global Young Academy and the ***Instituto de España*** (the umbrella organization for Spanish Royal Academies and Institutes).

Dr. Alegre leads the CNIC Molecular Mechanics of the Cardiovascular System research group, which investigates how mechanical forces determine muscle function at molecular, cellular, tissue, and organismal levels.

One of the distinguishing characteristics of the ***Academia Joven de España*** is that permits full membership of young Spanish researchers working abroad. This measure was introduced to foster collaboration among young Spanish researchers and to connect those who are working outside the country with academic institutions in Spain.

MIGUEL TORRES APPOINTED ASSOCIATE EDITOR OF SCIENCE ADVANCES

The CNIC researcher Dr. Miguel Torres has been appointed Associate Editor of the prestigious scientific journal Science Advances. The journal is a peer-reviewed, open access, multidisciplinary scientific journal launched in early 2015 and published by the American Association for the Advancement of Science (AAA).

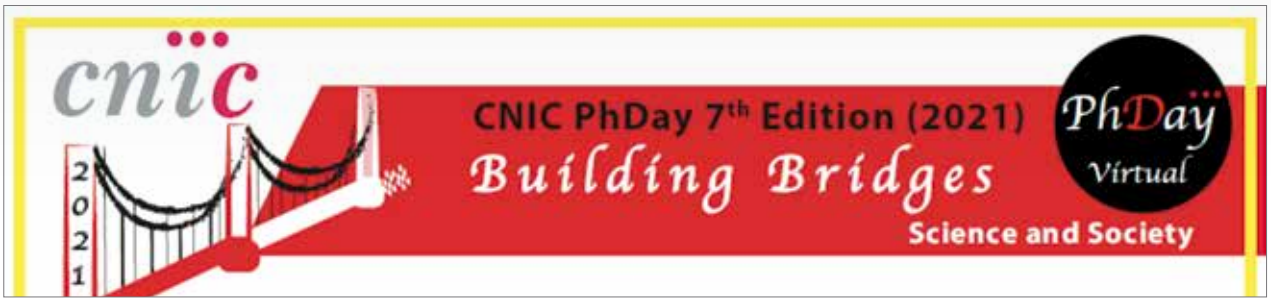
3- SCIENTIFIC EVENTS

CNIC INVITED SEMINARS AND WEBINARS

Ten seminars and webinars open to the scientific community were held in 2021. Highlights included presentations by: Akiko Iwasaki (Howard Hughes Medical Institute, Yale University School of Medicine, USA: Inmmune responses to SARS-CoV 2), Juan Domingo Gispert (Barcelonabeta Brain Research Center, Spain: Can Alzheimer's Disease Be Prevented?), Eldad Tzahor (Weizmann Institute of Science, Israel: Novel Strategies for Heart Regeneration), and Karina Yaniv (Weizmann Institute of Science, Israel: Vascular control of organ growth and regeneration).

CNIC PHDAY

The 7th edition of **CNIC PhDay** was held online. The topic for 2021 was **Building Bridges, Science and Society**. The event was divided into two parts. The first consisted of two parallel sessions: knowledge transfer and science communication. Topics covered included the creation of science-based companies and the best ways to minimize distortion in the communication of scientific results. The second part focused on diversity in science, pseudoscience and pseudotherapies and how to deal with them. More than 140 people participated, about half of them from outside the CNIC and three-quarters of them PhD students.



4 - OUTREACH ACTIVITIES

CONFERENCE: BRAIN AND HEART. DR. VALENTÍN FUSTER , DIRECTOR GENERAL DEL CNIC - SEMANA DE LA CIENCIA 2021

The CNIC participated once again in Science and Innovation Week, which is held annually in the first half of November. In the Community of Madrid, this event is organized by the Madri+d Foundation for Knowledge. The goal is to bring science closer to the public, promote knowledge and interest, and involve members of the pubic in its development. The theme of this year's Science Week was 'Science for the great challenges of humanity'.

As part of the week, CNIC General Director Dr. Valentín Fuster organized the Heart and Brain online conference, which showcased recent research advances in an accessible and entertaining way, with a particular focus on heart and brain health.

CNIC AT THE RESEARCH FAIR OF THE EUROPEAN RESEARCH NIGHT WITH THE "LA CAIXA" FOUNDATION

Participants took part in activities and live demonstrations illustrating the scientific research being carried out at research centers and universities in the area. The CNIC was the center with the highest level of participation.

CNIC PARTICIPATES IN THE "INSPIRING ENCOUNTERS WITH PROFESSIONALS" HIGH-SCHOOL OUTREACH EVENT

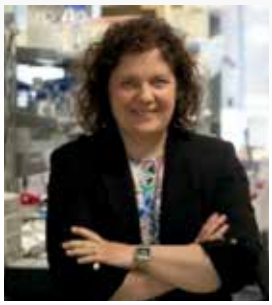
Sixty professionals from various fields talked about their professional experience with 6000 secondary students during an event promoted by the Bertelsmann Foundation and ***Empieza Por Educar.*** The "Inspiring encounters between professionals and students" encounter was aimed at the 100 educational centers participating in the Xcelence-Schools pilot project.

Researcher Marta Cortés Canteli and imaging technician Braulio Pérez represented the CNIC joining in the four day event, in which professionals from very varied academic backgrounds talked about their experience via Zoom and YouTube with 6000 high-school students in their fourth year of compulsory secondary education (15–16 year-olds) at schools in Madrid and Catalonia.

Videos of the event aimed at schools and students and their families can be seen at https://www.empresasqueinspiran.es/. This series of 60 short videos (10-12 minutes) presents a wide range of professions and academic fields, with the aim of inspiring students, arousing curiosity, broadening professional aspirations, and dismantling stereotypes.

5 - PARTNERSHIPS

VISITING RESEARCHERS PROGRAM WITH THE *JESÚS SERRA* FOUNDATION



The ***Jesús Serra*** Foundation, part of ***Grupo Catalana Occidente***, is funding the scientific stay at the CNIC of Dr. Benedetta Izzi, from the IRCCS, Istituto Neurologico Mediterraneo Neuromed, Italy. Dr. Izzi began her visit at the end of the year as a ***Fundacion Serra*** Visiting Scientist in the group led by Dr. José Javier Fuster Ortuño, working on "Hematovascular Pathophysiology". This fellowship is part of the ***Jesús Serra*** Foundation's Visiting Researchers program, which aims to promote interaction among researchers and in this way contribute to scientific advances. Started in 2009, the Visiting Researchers Program finances visits of several months to Spanish research centers by promising and internationally renowned scientists. The goals are to deepen the scientific relationship between the host research group and the visiting researcher's center of origin and to start new lines of research based on shared scientific interests.

6-SOCIAL AND CNIC

CNIC NEW EQUALITY AGREEMENT 2021-2024

The CNIC Equality Agreement 2021-2024 was officially validated and successfully registered with the Community of Madrid. This agreement can be viewed on the CNIC's transparency page: https://www.cnic.es/en/transparencia

NEW LACTATION ROOM

The new CNIC lactation room was inaugurated in 2020, days before the Covid-19 pandemic restrictions came into force, and is now available to all CNIC employees and visiting scientists. The CNIC lactation room is sponsored by Philips, which provided some of the equipment.

CNIC RESEARCHER JESÚS VICTORINO SANTOS, WINNER OF THE FAMELAB SCIENTIFIC MONOLOGUE CONTEST

CNIC researcher Jesús Victorino Santos will represent Spain in the international final of scientific monologues FameLab, after winning the national final, which was presided over by H.M. Queen Letizia.

The event was also attended by the Minister of Science and Innovation, Diana Morant, and the director of the British Council, Mark Howard.

Famelab is a scientific monologue contest that aims to bring scientific knowledge to the general public through a combination of rigor and entertainment. Jesús won thanks to the monologue "En clave de gen" (In the key of gene), a monologue in which he talked about genetics. The "letters" of our DNA code have been known for 20 years, and yet we have not learned how to read it completely. Jesús explained approaches to deciphering our genetic code in the context of cardiovascular disease.

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

CICERONE PROGRAM

The Cicerone Program is open to advanced undergraduate students and 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.
Participants in 2021: 29

CURRICULAR AND EXTRACURRICULAR UNIVERSITY PRACTICAL PROGRAM

The CNIC offers practical training in cardiovascular research to visiting undergraduate students.
The CNIC has signed collaborative educational agreements with 37 Spanish Universities and 30 foreign Universities.

In 2021 thirty-one students from the following universities completed internships at CNIC on their final degree thesis dissertation (TFG) under the guidance of a CNIC supervisor:

16 students from the Autonomous University of Madrid
4 students from the Polytechnic University of Madrid
4 students from the University Carlos III of Madrid
2 students from the Complutense University of Madrid
2 students from the Francisco de Vitoria University
1 student from the University of Alcalá de Henares
1 student from the Ramón Llull University of Barcelona
1 student from the University Rey Juan Carlos of Madrid

In addition, sixteen Spanish students and twelve students from different international universities completed internships at the Center during 2021 under the guidance of a CNIC supervisor. Amongst the latter students, seven were Erasmus fellowship holders from Italy and Germany, and the other five were from France, Germany, the USA, Peru and Japan.

PROGRAMS FOR MASTER'S AND GRADUATE STUDENTS

MASTER'S FELLOWSHIP PROGRAM CNIC-ACCIONA 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 2021: 19

Other Master Student Internships

In 2021 other twenty-two students from the following universities worked on their final master's thesis dissertation (TFM) under the guidance of a CNIC supervisor:

11 students from the Complutense University of Madrid
8 students from the Autonomous University of Madrid
1 student from the University of Alcalá de Henares
1 student from the University Carlos III of Madrid
1 student from the Autonomous University of Barcelona

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.

Graduate students at the CNIC awarded a PhD degree in 2021: 17
Graduate students studying for a PhD degree at the CNIC in 2021: 108

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

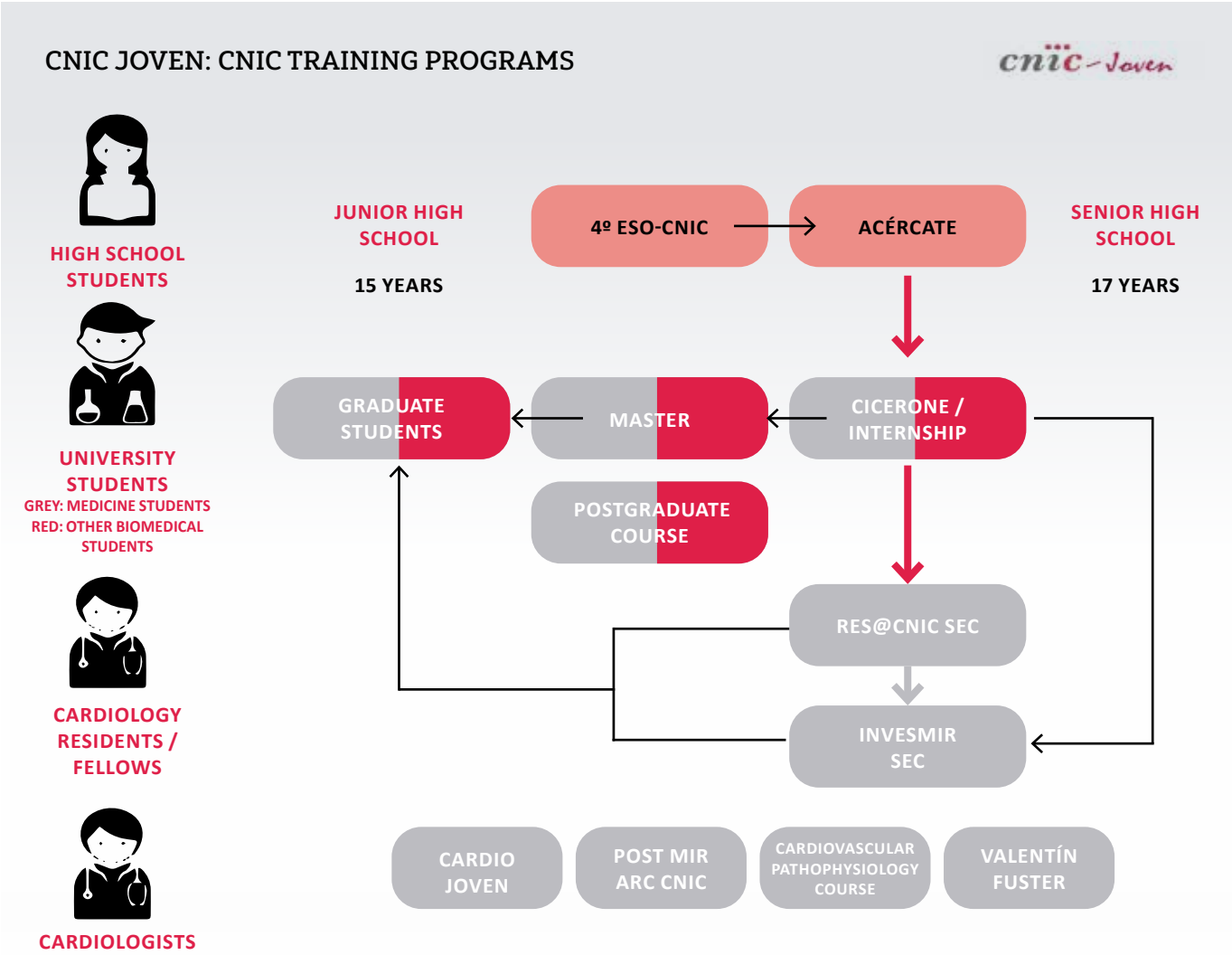
The Res@CNIC-SEC Program (in collaboration with the Spanish Society of Cardiology, SEC) offers resident medical interns the opportunity during the first years of their specialization period to learn about the latest techniques in cardiovascular research being used in the CNIC's laboratories, under the 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 2021: 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 Donostia
Hospital Universitario Nuestra Señora de Candelaria
Hospital Universitario Ramón y Cajal
Hospital Universitario Virgen de las Nieves
Hospital Universitario Virgen del Rocío
Hospital Universitario Virgen Macarena

INVESMIR SEC PROGRAM

The INVESMIR SEC Program offers resident medical interns the opportunity during their specialization period to further their training



through a research project in one of the CNIC's laboratories, under the supervision of a CNIC scientist.
An important aim of the program is for participants to establish contacts and collaborations with CNIC researchers that will support them, after completion of their MIR specialization training, in pursuing their own research projects at their centers within the Spanish National Health System. In 2021 one resident cardiologist intern from Hospital Universitario Joan XXIII (Tarragona) participated in this Program. One participant in 2021

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.

Specific aims:

a) To create the figure of the cardiologistresearcher by providing high-quality training in clinical research methods, including statistical analysis and the latest basic research techniques used in cardiovascular biomedicine, as well as opportunities to explore any clinical area of cardiology in greater depth (sub-specialization).

The program is aimed at cardiologists who aspire to carry out advanced clinical and research work at any center within the Spanish National Health System.

b) International training. The Program offers a period of training toward a Master's Degree in Epidemiology at the London School of Hygiene and Tropical Medicine (90 ECTS)

One participant in 2021

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.
One participant in 2021

PRACTICAL TRAINING FOR TECHNICAL SCHOOL STUDENTS

This program attracted in 2021 nineteen technical school students studying "Pathological Anatomy and Cytodiagnostics", "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, one students of "Diagnostic Imaging and Nuclear Medicine" and two students "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

This course is organized by the CNIC in partnership with the Sociedad Española de Cardiología Participants receive an overview of the molecular and genetic factors that underlie cardiac diseases and gain an up-to-date vision of cardiac physiology.

Venue: online
Dates: April 13- June 13, 2021
Participants: 149

6 FACTS AND FIGURES

SCIENTIFIC PUBLICATIONS

CITABLE DOCUMENTS

DOCUMENTS	NUMBER
ARTICLES	263
REVIEWS	57
TOTAL	320

CITABLE DOCUMENTS WITH IMPACT FACTOR

TOTAL: 300

JOURNAL QUALITY		
D1	110	37%
Q1	209	70%
Q2	78	26%
Q3	10	3%
Q4	3	1%

OPEN ACCESS		
OPEN ACCESS	215	72%
GOLD OPEN ACCESS	114	38%

LEADERSHIP		
FIRST, LAST OR CORRESPONDING AUTHOR	186	62%
CORRESPONDING AUTHOR	109	36%

PUBLICATIONS IN TOP JOURNALS (IF>10)

90 (30%)

AFFILIATION	NUMBER	
CNIC	13	4%
NATIONAL COLLABORATION	110	37%
INTERNATIONAL COLLABORATION	177	59%

OTHER IMPACT INDICATORS	
% DOCS CITED	65,72%
CATEGORY NORMALIZED CITATION IMPACT	2,05
% HIGHLY CITED PAPERS	1,41%
% DOCUMENTS IN TOP 10%	19,79%
% DOCUMENTS IN TOP 1%	2,12%
% INDUSTRY COLLABORATIONS	6,36%

Filter Summary:

Dataset: Web of Science

Schema: Shanghai GRAS

Domestic/International Collaboration: All

Time Period: [2021, 2021]

Include Early Access documents: true

Document Type: [Article, Review]

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

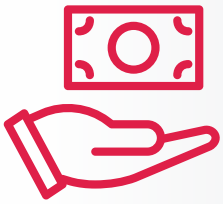
Funding Data Source: All Sources

Exported date Apr 11, 2022.

InCites dataset updated 2022-04-01. Includes Web of Science content indexed through 2022-03-12.

Complete list of CNIC 2021 publications at:
https://www.cnic.es/es/investigacion/publicaciones/resultados?y=2021

COMPETITIVE **FUNDING***



NEW GRANTS 2021:

PROJECTS, EQUIPMENT AND PERSONNEL

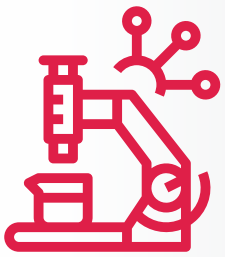
NATIONAL
62 GRANTS
€12,901,403

INTERNATIONAL
10 GRANTS
€ 7,113,705

7 H2020 GRANTS
€ 6,913,259

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

TECHNOLOGY TRANSFER*



18 ACTIVE PATENT FAMILIES

6 PATENT FAMILIES LICENSED

3 NEW PRIORITY PATENT APPLICATIONS

1 NEW OPTION CONTRACTS FOR LICENCE AGREEMENT

48 NEW MATERIAL TRANSFER AGREEMENTS

19 NEW CONFIDENTIAL DISCLOSURE AGREEMENTS

2 NEW RESEARCH COLLABORATION AGREEMENTS

*DATA AS OF 31/12/2021

HUMAN RESOURCES*

SCIENTIFIC STAFF 409
(91% OF TOTAL CNIC STAFF)

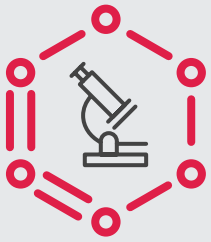
WOMEN 260 | 149 MEN

RESEARCH AREAS 336

GROUP LEADERS 30

WOMEN 8 | 22 MEN

TECHNICAL UNITS 73



CARDIOLOGISTS 16

HEADS OF TECHNICAL UNITS 11

MEN 6 | 5 WOMEN

52 (13%) OF THE SCIENTIFIC STAFF ARE FROM OUTSIDE SPAIN

VISITING SCIENTISTS 250

(FROM INSTITUTIONS OUTSIDE SPAIN: 38 - 16 COUNTRIES)

WOMEN 152 | 98 MEN

*DATA AS OF 31/12/2021

7 ACKNOWLEDGMENTS

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AGENCIA ESTATAL DE INVESTIGACIÓN

ASOCIACIÓN ESPAÑOLA CONTRA EL CANCER

BOEHRINGER INGELHEIM GMBH

CANCER RESEARCH INSTITUTE

COMUNIDAD DE MADRID

EC-EUROPEAN COMMISSION

EC-EUROPEAN RESEARCH COUNCIL

EUROPEAN MOLECULAR BIOLOGY ORGANIZATION

EUROPEAN SOCIETY OF ENDOCRINOLOGY

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SOCIEDAD ESPAÑOLA DE CARDIOLOGIA

SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

8 FIGURES LEGENDS AND CREDITS BY RESEARCH AREA

VASCULAR PATHOPHYSIOLOGY

1 FDG-PET/CT imaging of the abdominal aorta (yellow circle) in gene modified minipigs with progressing and regressing atherosclerosis. (P. Nogales, J. F. Bentzon).

2 Atherosclerotic lesions in progeroid Apoe-null mice exhibit abnormal CD31 expression and exacerbated cellular proliferation. Confocal microscopy images in aortic root from control and progeroid Apoe-null mice fed high-fat diet for 16 weeks. White, Ki67 (proliferation marker); red, smooth muscle α–actin (SMA, smooth muscle cell marker); green, CD31 (endothelial cell marker); blue, Hoechst 33342 (R.M. Nevado, M. Hamczyk, P. Gonzalo and V. Andrés)

3 Elimination of senescent cells reduces fibrosis and necrosis in hearts of mdx dystrophic mice. Mdx mice of 12 months of age were treated with senolytics for 3 months, and hearts were analyzed for fibrosis and necrosis by Sirius Red staining and hematoxylin and eosin (H&E), respectively. (P.Muñoz-Canoves)

4 Increased immature cardiomyocyte lineage contribution to the ventricular wall of mice with Mybpc3 mutations causing HCM. Left, Control mice. Right, mutant mice. Note the increased territory of CM expressing GFP. (J.L. de la Pompa)

5 A12 antibody recognizes the atheroma plaque. (A. R. Ramiro)

MYOCARDIAL PATHOPHYSIOLOGY

1 Murine embrionic fibroblasts under hypoxia (A. Santamans, G. Sabio)

2 The Cardiac Arrhythmia Laboratory investigates the molecular mechanisms of arrhythmias in ion channel diseases and cardiomyopathies. (J. Jalife)

3 Representative atrial electromechanical assessment by noninvasive transthoracic echocardiography in a patient with overt electromechanical dissociation at early stages of persistent atrial fibrillation. The data show faster lead II ECG-derived electrical activation rates (7.45 Hz) than their simultaneously acquired tissue Doppler imaging-derived mechanical counterparts (5.13 Hz and 3.30 Hz for the left and right atria, respectively), which defines the presence of atrial electromechanical dissociation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TDI, tissue Doppler imaging; TTE, transthoracic echocardiography. (D. Filgueiras)

4 The Molecular Cardiology team uses a holistic approach to study inherited arrhythmogenic diseases. This approach encompasses morpho-functional studies in living animals (A) and cells (B), as well as super-resolution microscopy (C) and molecular biology. The figure illustrates some of the techniques employed in experiments in pigs. (S. Priori)

CELL AND DEVEOLPENTAL BIOLOGY

1 iFlpMosaics showing an endothelial tip cell (yellow) branching out from a crowd of endothelial cells in a mouse retina (I. Garcia Gonzalez, R. Benedito).

2 Multispectral analysis of heart cells in the myocardium (I. Garcia Gonzalez, R. Benedito).

3 Differentiation of skeletal muscle cells (R. Silva, J. Alegre-Cebollada)

4 A Notch activity reporter shows mosaic activity in the early mouse embryo (M. Sendra, M. Torres)

5 Developing coronary lymphatics (E. de la Cruz, M. Torres)

6 Multicolor immunophenotyping of human bone marrow (B. Álvarez)

CLINICAL STUDIES

1 Scientific highlights in 2021 of the Translational Laboratory for Cardiovascular Imaging and Therapy: from metoprolol effectiveness in acute myocardial infarction and COVID-19 critical patients to new advances in cardio-oncology targeted-therapies and development of faster cardiac magnetic resonance protocols (C Galán, B Ibáñez)

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