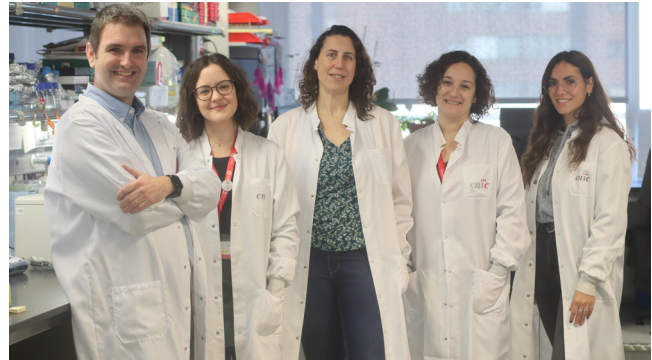


3 SCIENTIFIC HIGHLIGHTS BY PUBLICATION DATE

NATURE CARDIOVASCULAR RESEARCH THE 'GUARDIAN OF THE GENOME' PROTECTS AGAINST CARDIOVASCULAR DISEASE

A team at the CNIC led by Dr. Jose J. Fuster, working in collaboration with institutes in the USA, has demonstrated that acquired mutations in the gene encoding the protein p53 contribute to the development of atherosclerotic cardiovascular disease. Known as the 'guardian of the genome', p53 helps to maintain the integrity of the hereditary material inside cells by regulating multiple cell functions in response to cellular stresses.



Zekavat SM, Viana-Huete V, Matesanz N, Jorshery SD, Zuriaga MA, Uddin MM, Trinder M, Paruchuri K, Zorita V, Ferrer-Pérez A, Amorós-Pérez M, Kunderfranco P, Carriero R, Greco CM, Aroca-Crevillen A, Hidalgo A, Damrauer SM, Ballantyne CM, Niroula A, Gibson CJ, Pirruccello J, Griffin G, Ebert BL, Libby P, Fuster V, Zhao H, Ghassemi M, Natarajan P, Bick AG, Fuster JJ, Klarin D. TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease. *Nat Cardiovasc Res.* 2023 Jan 16;2:144-158. <https://doi.org/10.1038/s44161-022-00206-6>

IMMUNITY

CNIC SCIENTISTS IDENTIFY A NEW THERAPEUTIC TARGET IN MACROPHAGES FOR THE TREATMENT OF OBESITY-RELATED DISEASES

A team at the CNIC has discovered that the metabolic requirements of macrophages differ depending on the organ in which they reside. In other words, these cells adapt to the needs of the organ in which they are located. The discovery "gives us a better understanding of how macrophages regulate their metabolism according to the organ in which they reside. Our results reveal a vulnerability of macrophages that contributes to chronic inflammatory diseases and could be exploited for the treatment of conditions associated with obesity and metabolic syndrome, such as cardiovascular disease", said study leader Dr. David Sancho, who heads the CNIC Immunobiology group.



Wculek SK, Heras-Murillo I, Mastrangelo A, Mañanes D, Galán M, Miguel V, Curtabbi A, Barbas C, Chandel NS, Enríquez JA, Lamas S, Sancho D. Oxidative phosphorylation selectively orchestrates tissue macrophage homeostasis. *Immunity.* 2023 Mar 14;56(3):516-530.e9. <https://doi.org/10.1016/j.immuni.2023.01.011>

ECLINICALMEDICINE

IMAGING THE ADOLESCENT HEART

Magnetic resonance imaging (MRI) has allowed scientists at the CNIC, led by Dr. Rodrigo Fernández-Jiménez, to produce an accurate picture of the healthy heart in adolescence. Using this advanced technology, the research team was able to determine reference values for anatomical and functional parameters in the heart during adolescence. This information has direct implications for clinical practice. "Magnetic resonance imaging has become a very important method for studying the heart because it avoids exposing patients to radiation and provides more information, and with greater precision, than ultrasound, currently the most frequently used cardiac imaging technique", said CNIC General Director Dr. Valentín Fuster, a co-author on the study.



Real C, Párraga R, Pizarro G, García-Lunar I, González-Calvo E, Martínez-Gómez J, Sánchez-González J, Sampedro P, Sanmamed I, De Miguel M, De Cos-Gandoy A, Bodega P, Ibanez B, Santos-Beneit G, Fuster V, Fernández-Jiménez R. Magnetic resonance imaging reference values for cardiac morphology, function and tissue composition in adolescents. *EclinicalMedicine.* 2023 Mar 3;57:101885. <https://doi.org/10.1016/j.eclinm.2023.101885>

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

HIGH-DOSE ANTICOAGULATION CAN REDUCE THE NEED FOR INTUBATION AND IMPROVE SURVIVAL OF HOSPITALIZED COVID-19 PATIENTS



Compared with standard low-dose anticoagulation, high-dose anticoagulation can reduce deaths by 30 percent and intubations by 25 percent among hospitalized Covid-19 patients who are not critically ill. These are the significant findings from the large-scale international “FREEDOM” trial, led by Valentín Fuster, CNIC General Director, President of Mount Sinai Fuster Heart Hospital, and Physician-in-Chief at Mount Sinai Hospital. The study results were announced at the American College of Cardiology Scientific Sessions, held in partnership with the World Congress of Cardiology in New Orleans (USA), and simultaneously published in the *Journal of the American College of Cardiology (JACC)*.

Stone GW, Farkouh ME, Lala A, Tinuoye E, Dressler O, Moreno PR, Palacios IF, Goodman SG, Esper RB, Abizaid A, Varade D, Betancur JF, Ricalde A, Payro G, Castellano JM, Hung IFN, Nadkarni GN, Giustino G, Godoy LC, Feinman J, Camaj A, Bienstock SW, Furtado RHM, Granada C, Bustamante J, Peyra C, Contreras J, Owen R, Bhatt DL, Pocock SJ, Fuster V; FREEDOM COVID Anticoagulation Strategy Randomized Trial Investigators. Randomized Trial of Anticoagulation Strategies for Noncritically Ill Patients Hospitalized With COVID-19. *J Am Coll Cardiol.* 2023 May 9;81(18):1747-1762. <https://doi.org/10.1016/j.jacc.2023.02.041>

NEW ENGLAND JOURNAL OF MEDICINE

A SPANISH TEAM PRESENTS THE FIRST PHARMACOLOGICAL TREATMENT ABLE TO IMPROVE CARDIAC FUNCTION IN STIFF-HEART SYNDROME

The results of this study promise to radically alter the prospects of patients with stiff-heart syndrome. The study was led by Dr. Pablo García-Pavía, who heads the Inherited Cardiomyopathies group at the CNIC and the Inherited Cardiac Diseases Section at Hospital Universitario Puerta de Hierro. Coinciding with the publication of the study, Dr. Pablo García-Pavía presented the results of the first clinical trial of an amyloid-removing drug for the treatment of cardiac amyloidosis. The initial results of the trial, which was coordinated by Dr. García-Pavía and included 40 patients in France, the Netherlands,



Germany, and Spain, show that the new drug is safe and appears to reduce the amount of amyloid protein deposited in the heart. Developed by the Swiss company Neurimmune, the new medication is an antibody that binds to transthyretin amyloid protein. The antibody was first isolated from memory B cells obtained from healthy elderly individuals.

Garcia-Pavia P, Aus dem Siepen F, Donal E, Lairez O, van der Meer P, Kristen AV, Mercuri MF, Michalon A, Frost RJA, Grimm J, Nitsch RM, Hock C, Kahr PC, Damy T. Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid. *N Engl J Med.* 2023 Jul 20;389(3):239-250. <https://doi.org/10.1056/NEJMoa2303765>

NATURE

GLA, THE FATTY ACID THAT MAKES THE HEART FUNCTION PROPERLY AFTER BIRTH

A study conducted in mice and led by Dr. Mercedes Ricote at the CNIC has revealed that maternal milk provides an essential signal that triggers the maturation of heart metabolism after birth, allowing the neonatal heart to function correctly and ensuring postnatal survival. The study shows that the fatty acid gamma-linolenic acid (GLA), present in breast milk, binds to the retinoid X receptor (RXR) protein found in heart cells. RXR acts as a nutritional sensor of lipids and vitamin A derivatives, altering gene expression and influencing biological functions such as immunity, cell differentiation, and metabolism. Once activated by maternal GLA, RXR initiates genetic programs that equip mitochondria—the energy centers of the cell—with the enzymes and other proteins they need to start consuming lipids, the primary source of energy in the mature heart.



Paredes A, Justo-Méndez R, Jiménez-Blasco D, Núñez V, Calero I, Villalba-Orero M, Alegre-Martí A, Fischer T, Gradillas A, Sant'Anna VAR, Were F, Huang Z, Hernansanz-Agustín P, Contreras C, Martínez F, Camafeita E, Vázquez J, Ruiz-Cabello J, Area-Gómez E, Sánchez-Cabo F, Treuter E, Bolaños JP, Estébanez-Perpiñá E, Rupérez FJ, Barbas C, Enríquez JA, Ricote M. γ -Linolenic acid in maternal milk drives cardiac metabolic maturation. *Nature.* 2023 Jun;618(7964):365-373. <https://doi.org/10.1038/s41586-023-06068-7>

NATURE CARDIOVASCULAR RESEARCH

SCIENTISTS IDENTIFY HOW SOME ANGIOGENIC DRUGS USED TO TREAT HEART DISEASE AND CANCER CAUSE VASCULAR DISEASE

Research led by Dr. Rui Benedito at the CNIC has demonstrated that most of the transcriptional changes and angiogenic cell states elicited by targeting Dll4 correlate with, but do not cause, vascular pathophysiology. Therefore, vascular neoplasms are not the cause of the previously reported anti-Dll4 antibody toxicity.

Fernández-Chacón M, Mühleder S, Regano A, García-Ortega L, Rocha SF, Torroja C, Sanchez-Muñoz MS, Lytvyn M, Casquero-García V, De Andrés-Laguillo M, Muhl L, Orlich MM, Gaengel K, Camafeita E, Vázquez J, Benguría A, Iruela-Arispe ML, Dopazo A, Sánchez-Cabo F, Carter H, Benedito R.



Incongruence between transcriptional and vascular pathophysiological cell states. Nat Cardiovasc Res. 2023 May 29;2:2023530-549. <https://doi.org/10.1038/s44161-023-00272-4>

EUROPEAN HEART JOURNAL

ATHEROSCLEROSIS ACCELERATES AGING

Atherosclerosis—the much-feared ‘hardening’ of our arteries—impacts our health long before the appearance of symptomatic cardiovascular disease. A new study by a team at the CNIC shows that atherosclerosis at subclinical stages accelerates the aging process. Lead author and CNIC General Director Dr. Valentín Fuster emphasized that the results underline the benefits of

reducing inflammation by adopting a healthy lifestyle (healthy diet, regular physical activity, etc.) or taking specific medication, such as cholesterol-lowering statins, that can block, or at least slow, the transition from the subclinical phase of atherosclerosis to the appearance of severe cerebrovascular events, like myocardial infarction or stroke.



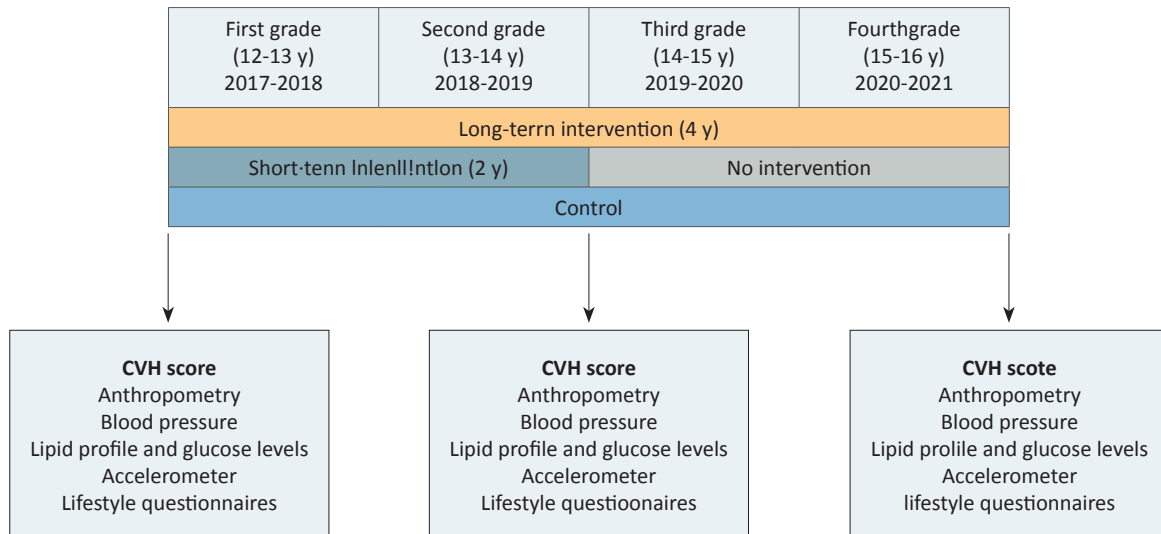
Sánchez-Cabo F, Fuster V, Silla-Castro JC, González G, Lorenzo-Vivas E, Alvarez R, Callejas S, Benguría A, Gil E, Núñez E, Oliva B, Mendiguren JM, Cortes-Canteli M, Bueno H, Andrés V, Ordovás JM, Fernández-Friera L, Quesada AJ, García JM, Rossello X, Vázquez J, Dopazo A, Fernández-Ortiz A, Ibáñez B, Fuster JJ, Lara-Pezzi E. Subclinical atherosclerosis and accelerated epigenetic age mediated by inflammation: a multi-omics study. Eur Heart J. 2023 Aug 1;44(29):2698-2709. <https://doi.org/10.1093/eurheartj/ehad361>

JAMA CARDIOLOGY

PROMOTING CARDIOVASCULAR HEALTH IN ADOLESCENTS AT SCHOOL: A CLUSTER RANDOMIZED CLINICAL TRIAL.

The journal JAMA Cardiology published the results of a project carried out by the SHE Foundation, the CNIC, and the University of Barcelona and which involved the participation of 1326 adolescents from 24 public secondary schools in Madrid and Barcelona. The study showed a beneficial impact of a health-promotion educational intervention on health parameters in adolescents,

with the impact depending largely on the duration and intensity of the intervention. Unfortunately, this impact was not sustained over time. Although health promotion initiatives in the school setting have become increasingly common in recent years, very few have addressed cardiovascular health in a comprehensive manner, and it is therefore important to continue optimizing school-based interventions in order to define the most effective strategies.



Santos-Beneit G, Fernández-Alvira JM, Tresserra-Rimbau A, Bodega P, de Cos-Gandoy A, de Miguel M, Ramírez-Garza SL, Laveriano-Santos EP, Arancibia-Riveros C, Carral V, Orrit X, Rodríguez C, Carvajal I, Haro D, Peyra C, Martínez-Gómez J, Álvarez-Benavides A, Estruch R, Lamuela-Raventós RM, Fernández-Jiménez R, Fuster V. School-Based Cardiovascular Health Promotion in Adolescents: A Cluster Randomized Clinical Trial. JAMA Cardiol. 2023 Sep 1;8(9):816-824. <https://doi.org/10.1001/jamacardio.2023.2231>

NATURE COMMUNICATIONS

A NEW TECHNIQUE IMPROVES DIAGNOSTIC ACCURACY AND PERSONALIZED THERAPY FOR A COMMON ARRHYTHMIA

A multidisciplinary and multicenter study led by Dr. David Filgueiras, head of the Advanced Development in Arrhythmia Mechanisms and Therapy group at the CNIC and a cardiologist at Hospital Clínico San Carlos, has led to the development of a new approach to assessing the structural and electrophysiological changes that occur in the hearts of patients with atrial fibrillation, one of the most frequent types of arrhythmia. This new diagnostic approach is based on the simultaneous evaluation of the electrical and mechanical (contractile) activity of the atria during atrial fibrillation.



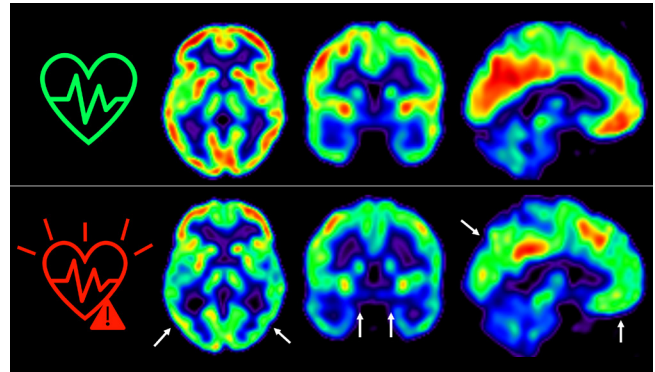
Enríquez-Vázquez D, Quintanilla JG, García-Escolano A, Couselo-Seijas M, Simón-Chica A, Lee P, Alfonso-Almazán JM, Mahía P, Redondo-Rodríguez A, Modrego J, Ortega-Hernández A, Marcos-Alberca P, Magni R, Calvo E, Gómez-Gordo R, Yan P, La Rosa G, Bustamante-Madrón J, Pérez-García CN, Martín-Sánchez FJ, Calvo D, de la Hera JM, García-Torrent MJ, García-Osuna Á, Ordóñez-Llanos J, Vázquez J, Pérez-Villacastín J, Pérez-Castellano N, Loew LM, Sánchez-González J, Gómez-Garre D, Filgueiras-Rama D. Non-invasive electromechanical assessment during atrial fibrillation identifies underlying atrial myopathy alterations with early prognostic value. Nat Commun. 2023 Aug 4;14(1):4613. <https://doi.org/10.1038/s41467-023-40196-y>

LANCET HEALTHY LONGEVITY

THE SOONER WE START CONTROLLING CARDIOVASCULAR RISK FACTORS, THE BETTER FOR OUR BRAINS

Cardiovascular disease and dementia often occur together, but there has been a lack of longitudinal studies in middle-aged people evaluating the impact of atherosclerosis and its risk factors on brain health. Now, research led by Dr. Marta Cortés Canteli at the CNIC provides new data on this relationship and confirms the importance of controlling traditional cardiovascular risk factors, such as hypertension, cholesterol, diabetes, smoking, and sedentary

Tristão-Pereira C, Fuster V, Oliva B, Moreno-Arciniegas A, Garcia-Lunar I, Perez-Herreras C, Schöll M, Suárez-Calvet M, Moro MA, García-Alvarez A, Fernandez-Ortiz A, Sanchez-Gonzalez J, Zetterberg H, Blennow K, Ibanez B, Gispert JD, Cortes-Canteli M. Longitudinal interplay between subclinical atherosclerosis, cardiovascular risk factors, and cerebral glucose metabolism in midlife: results from the PESA prospective cohort study. Lancet Healthy Longev. 2023 Sep;4(9):e487-e498. [https://doi.org/10.1016/S2666-7568\(23\)00134-4](https://doi.org/10.1016/S2666-7568(23)00134-4)



lifestyle not only to protect cardiovascular health, but also to prevent diseases such as Alzheimer's.

NATURE COMMUNICATIONS

A NEW THERAPY DISCOVERED FOR A HEART CONDITION THAT CAUSES AN ESTIMATED 20% OF SUDDEN DEATHS AMONG ATHLETES

A CNIC team led by Dr. Juan Bernal has discovered a possible treatment for a disease that causes the death of elite athletes without warning. Arrhythmogenic cardiomyopathy is an incurable disease of the heart muscle that is responsible for an estimated 20% of sudden deaths recorded in professional athletes. While there is still a long way to go to fully define the molecular basis of this disease, the current study identifies a group of mutations in the placophilin-2 protein that are associated with severe



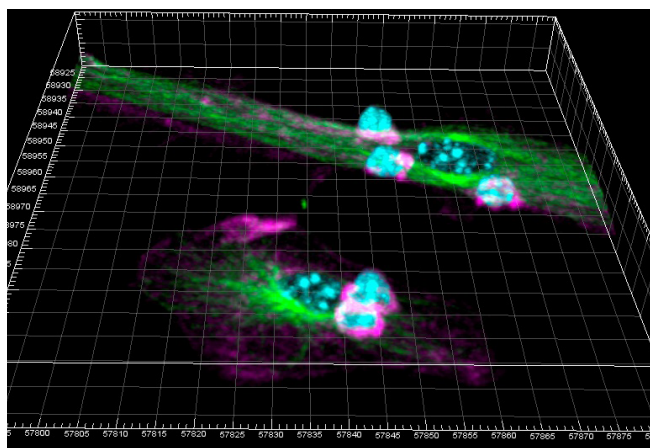
contractile problems that respond to treatment with the myosin activator 4-hydroxyacetophenone.

García-Quintáns N, Sacristán S, Márquez-López C, Sánchez-Ramos C, Martínez-de-Benito F, Siniscalco D, González-Guerra A, Camafeita E, Roche-Molina M, Lytvyn M, Morera D, Guillen MI, Sanguino MA, Sanz-Rosa D, Martín-Pérez D, García R, Bernal JA. MYH10 activation rescues contractile defects in arrhythmogenic cardiomyopathy (ACM). Nat Commun. 2023 Oct 13;14(1):6461. <https://doi.org/10.1038/s41467-023-41981-5>

NATURE COMMUNICATIONS

SPANISH SCIENTISTS IDENTIFY A KEY ACTION OF DENDRITIC CELLS IN THE IMMUNE RESPONSE, WITH POTENTIAL APPLICATIONS IN VACCINE DESIGN

This study, led by Dr. Francisco Sánchez-Madrid, provides invaluable information on the mechanisms involved in the body's immune response to pathogens and opens a new avenue for the design of innovative vaccines against future pandemics. The study reveals that the formation of an immune synapse not only activates the participating lymphocyte, as was already known, but also triggers profound changes in postsynaptic dendritic cells.



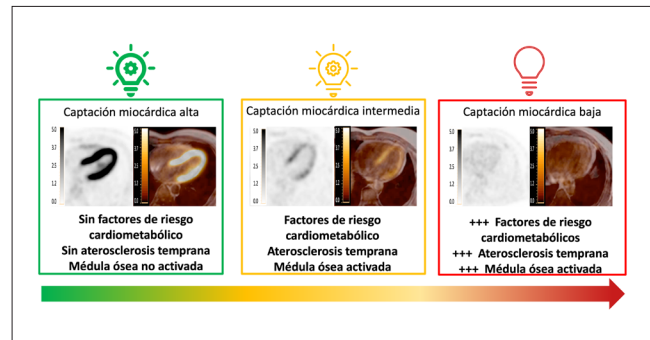
Calzada-Fraile D, Iborra S, Ramírez-Huesca M, Jorge I, Dotta E, Hernández-García E, Martín-Cófreces N, Nistal-Villán E, Veiga E, Vázquez J, Pasqual G, Sánchez-Madrid F. Immune synapse formation promotes lipid peroxidation and MHC-I upregulation in licensed dendritic cells for efficient priming of CD8+T cells. Nat Commun. 2023 Oct 25;14(1):6772. <https://doi.org/10.1038/s41467-023-42480-3>

DIABETES CARE

OBESITY, HYPERTENSION, AND DYSLIPIDEMIA INDUCE A PROGRESSIVE LOSS OF ENERGY IN THE HEART

According to this new study, altered consumption of energy substrates in the heart due to metabolic risk factors such as obesity, hypertension and dyslipidemia can promote the appearance years later of diseases such as heart failure.

This study was carried out as part of the CNIC-SANTANDER PESA project, run jointly by the CNIC and Banco Santander and begun more than 10 years ago. "PESA is the flagship project of the CNIC, since many of the center's leading research groups,



each with expertise in a specific area of cardiovascular disease, work around the study. Combining the participation of basic and clinical researchers around a large cohort such as PESA is unique in the world", explained Dr. Valentín Fuster.

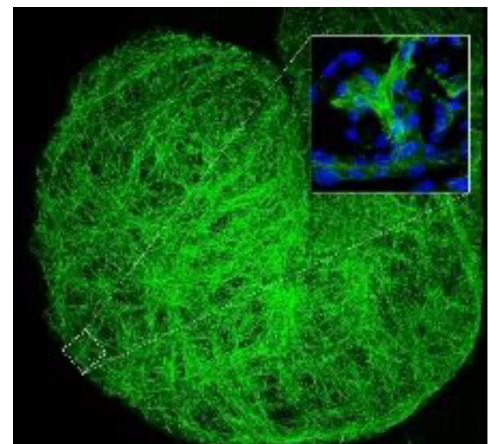
Devesa A, Fuster V, Vazirani R, García-Lunar I, Oliva B, España S, Moreno-Arciniegas A, Sanz J, Perez-Herreras C, Bueno H, Lara-Pezzi E, García-Alvarez A, de Vega VM, Fernández-Friera L, Trivieri MG, Fernández-Ortiz A, Rossello X, Sanchez-Gonzalez J, Ibanez B. Cardiac Insulin Resistance in Subjects With Metabolic Syndrome Traits and Early Subclinical Atherosclerosis. *Diabetes Care*. 2023 Nov 1;46(11):2050-2057. <https://doi.org/10.2337/dc23-0871>

CIRCULATION RESEARCH

KEY ROLE OF THE PROTEIN NRG1 IN PROPER HEART FORMATION

A team of CNIC researchers led by Dr. José Luis de la Pompa has identified the signaling protein Nrg1 as a key player in the process of heart formation. Nrg1 guides the formation of the trabeculae carneae, muscular columns in the ventricles that are some of the first cardiac structures to develop. Nevertheless, the intricate mechanisms by which Nrg1 operates and its role in heart wall maturation remain an enigma.

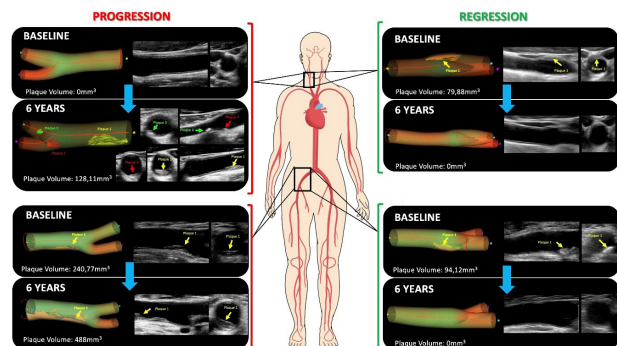
Grego-Bessa J, Gómez-Apiñaniz P, Prados B, Gómez MJ, MacGrogan D, de la Pompa JL. Nrg1 Regulates Cardiomyocyte Migration and Cell Cycle in Ventricular Development. *Circ Res*. 2023 Nov 10;133(11):927-943. <https://doi.org/10.1161/CIRCRESAHA.123.323321>



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

YOUNG PEOPLE ARE MORE VULNERABLE TO THE DAMAGING EFFECT OF HIGH CHOLESTEROL AND HIGH BLOOD PRESSURE

According to this CNIC research, young people are more vulnerable to the detrimental effects of two major cardiovascular risk factors: high cholesterol and high blood pressure. Subclinical atherosclerosis often progresses in middle-aged people, especially when LDL-cholesterol levels and blood pressure are elevated, even slightly or moderately. Both the medical community and the general public should be aware that the progression of atherosclerosis can be halted if risk factors are aggressively managed from an early age.

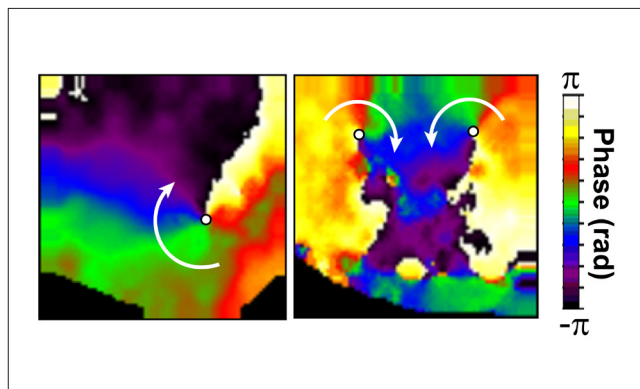


Dr. Valentín Fuster concluded that "screening for subclinical atherosclerosis from an early age, together with aggressive control of risk factors, could help to alleviate the overall burden of cardiovascular disease".

Mendieta G, Pocock S, Mass V, Moreno A, Owen R, García-Lunar I, López-Melgar B, Fuster JJ, Andres V, Pérez-Herreras C, Bueno H, Fernández-Ortiz A, Sanchez-Gonzalez J, García-Alvarez A, Ibáñez B, Fuster V. Determinants of Progression and Regression of Subclinical Atherosclerosis Over 6 Years. *J Am Coll Cardiol*. 2023 Nov 28;82(22):2069-2083. <https://doi.org/10.1016/j.jacc.2023.09.814>

NATURE CARDIOVASCULAR RESEARCH A PROMISING THERAPEUTIC TARGET FOR CARDIAC ARRHYTHMIAS

A study carried out by the teams of Guadalupe Sabio and José Jalife at the CNIC has discovered a link between the p38 γ and p38 δ stress kinase signaling pathway and the onset of ventricular fibrillation, a type of cardiac arrhythmia. During an arrhythmic event, the heart rhythm is disturbed, quickens, and becomes irregular, with potentially fatal consequences. This study offers new hope for tackling the disease.

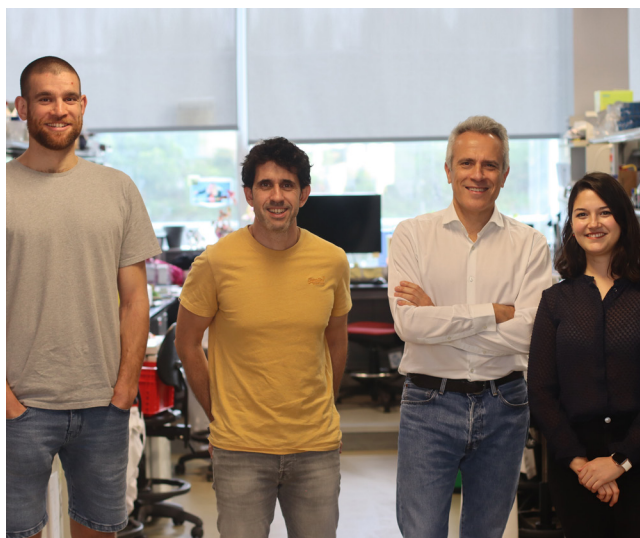


Romero-Becerra R, Cruz FM, Mora A, Lopez JA, Ponce-Balbuena D, Allan A, Ramos-Mondragón R, González-Terán B, León M, Rodríguez ME, Leiva-Vega L, Guerrero-Serna G, Jimenez-Vázquez EN, Filgueiras-Rama D, Vázquez J, Jalife J, Sabio G. p38 γ / δ activation alters cardiac electrical activity and predisposes to ventricular arrhythmia. *Nature Cardiovascular Research*. 2023 Nov 27, (2): 1204–1220. <https://doi.org/10.1038/s44161-023-00368-x>

CIRCULATION RESEARCH MOLECULAR MECHANISMS DISCOVERED THAT GOVERN CRITICAL GENES FOR CARDIAC VALVE FORMATION

A CNIC research team led by Dr. José Luis de la Pompa has identified the molecular mechanisms that control the activity of genes involved in both the proper formation of cardiac valves and the prevention of their subsequent calcification. The study demonstrated that cooperation between the NOTCH and the HIPPO signaling pathways is essential for the correct participation of the endocardium in valve formation

Luna-Zurita L, Flores-Garza BG, Grivas D, Siguero-Álvarez M, de la Pompa JL. Cooperative Response to Endocardial Notch Reveals Interaction With Hippo Pathway. *Circ Res*. 2023 Dec 8;133(12):1022-1039. <https://doi.org/10.1161/CIRCRESAHA.123.323474>



JAMA CARDIOLOGY CNIC RESEARCH IDENTIFIES MUTATIONS THAT UNDERLIE ONE OF THE MOST FREQUENT CONGENITAL HEART DEFECTS

Bicuspid aortic valve is the most frequent congenital heart defect in humans, affecting between 1% and 2% of adults. This defect often causes valve stenosis and endocarditis and is associated with early calcification of the aortic valve. The only treatment currently available is surgical valve replacement, but the results of this new study led by Dr. José Luis de la Pompa at the CNIC could change this situation. By identifying the mutations underlying this defect, the new study points the way to the future design of pharmacological and alternative therapies.



Grego-Bessa J, Gómez-Apiñaniz P, Prados B, Gómez MJ, MacGrogan D, de la Pompa JL. Nrg1 Regulates Cardiomyocyte Migration and Cell Cycle in Ventricular Development. *Circ Res*. 2023 Nov 10;133(11):927-943. <https://doi.org/10.1161/CIRCRESAHA.123.323321>