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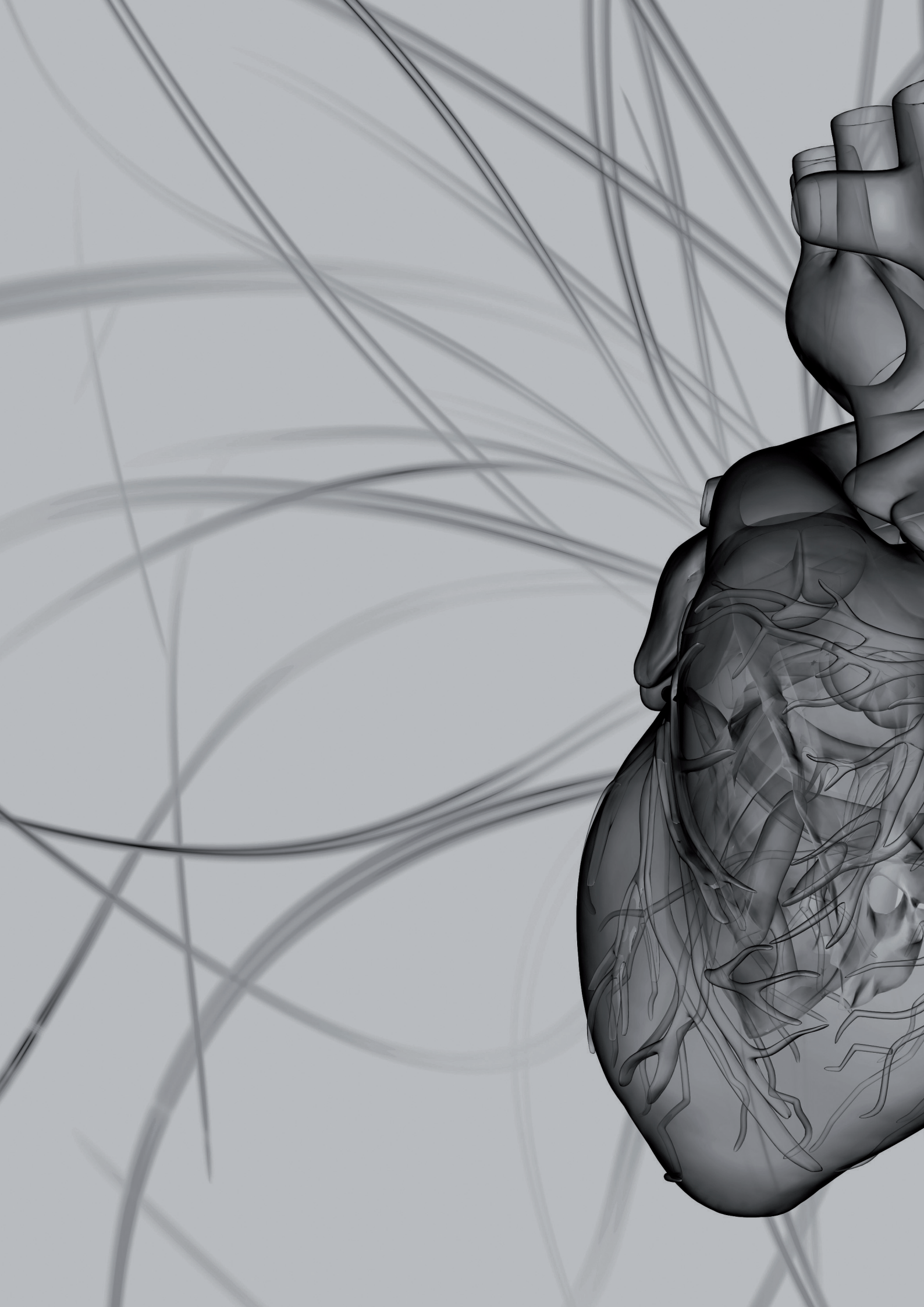
Scientific Report 2017



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Scientific Report 2017

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

Instituto de Salud Carlos III

cnic

EXCELENCIA SEVERO OCHOA

HR EXCELLENCE IN RESEARCH

Infraestructuras Científicas y Técnicas Singulares

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Fundación REPSOL
gasNatural fenosa
INDITEX
"la Caixa"
Santander
PRISA
Telefónica

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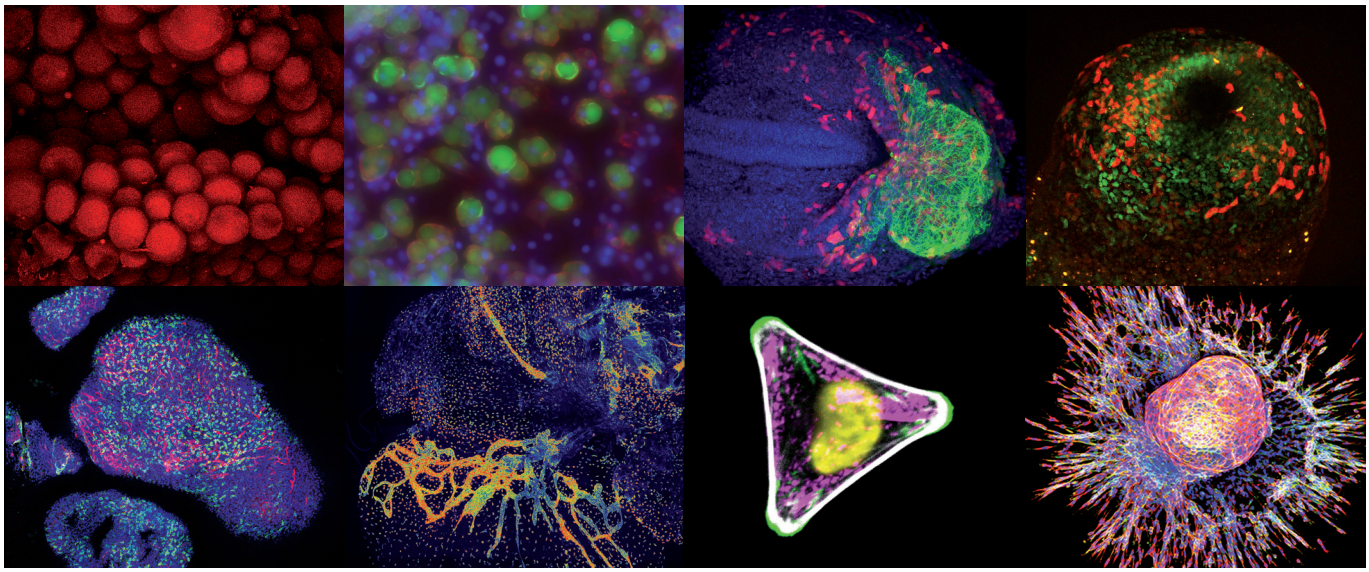


1. Foreword and CNIC mission

The CNIC's mission is to discover the causes of cardiovascular disease (CVD), translate basic research discoveries into clinical practice, promote health in society, and foster training and mentoring of up-and-coming scientists and physicians. Over its relatively short existence, the CNIC has built an unrivalled infrastructure and a powerful, cross-disciplinary research base that embraces multiple disciplines and includes population and patient studies.

One of the keys to this achievement is the commitment of the Spanish government to building a flagship research institute to tackle the CVD epidemic. However, the public purse is only part of the story. The CNIC also boasts an agile management structure that promotes training and the exchange of ideas and expertise, as well as an unrivalled modern infrastructure of technical units and support services. Most importantly, the CNIC is funded through an innovative enterprise between the public sector and a private partner, the Pro-CNIC Foundation, which injects not only added financial security but also the wide-ranging business and management expertise of some of the most prominent Spanish businesses. The CNIC also benefits from the external support and advice of its Scientific Advisory Board, composed of leading international experts who provide guidance on strategy and recruitment and regularly evaluate the CNIC's performance.

At the heart of the CNIC's mission is a shift from the traditional emphasis on treating clinical events to a strategy focused on identifying CVD in its preclinical stages and promoting health. This vision fosters a cohesive and flexible strategy that embraces research infrastructure, professional training, and a clear focus on cross-disciplinary collaborations between basic and clinical researchers to ensure that acquired knowledge is translated into real health benefits.

This report offers an overview of how the young, energetic team of dedicated scientists, clinicians, and technicians is bringing this vision to reality. Reading these pages, what gives us the greatest pleasure is to see how the breadth of the CNIC's research activity integrates the Center into society at so many levels. As you would expect, there are breakthroughs at the frontiers of basic and clinical research. This year, these discoveries span the range from new methods to define gene function in cell populations through to the use of 3D ultrasound to improve CVD risk prediction in human populations, including along the way the arrest and reversal of aortic aneurysm in preclinical models, to cite just three examples.

The impressive collection of high-impact publications in 2017 also documents the CNIC's wider social engagement. The Center's translational studies bear testimony to the enthusiastic participation of healthy volunteers, patients, and emergency service personnel in efforts to define the causes and risk factors of CVD. This commitment of citizens and professionals outside the research community last year made essential contributions to advancing the use of noninvasive imaging technology for diagnosis and research, defining the advantages of early drug intervention after a heart attack, and confirming the importance of lifestyle factors such as eating a healthy breakfast.

The CNIC's commitment to public health promotion is also evident in educational programs that start with children from early age, teaching core health knowledge and instilling a positive emotional attitude.

The Center's public outreach links seamlessly with our strong commitment to training at all levels, from programs to encourage a scientific vocation among high school students to continuing professional training programs for scientists and physicians. 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 after all 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 sanitary and socioeconomic burden associated with CVD.

VALENTÍN FUSTER
General Director

VICENTE ANDRÉS
Basic Research Director

BORJA IBÁÑEZ
Clinical Research Director

2. Research at the Center

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

VASCULAR PATHOPHYSIOLOGY

Coordinator: Almudena Ramiro

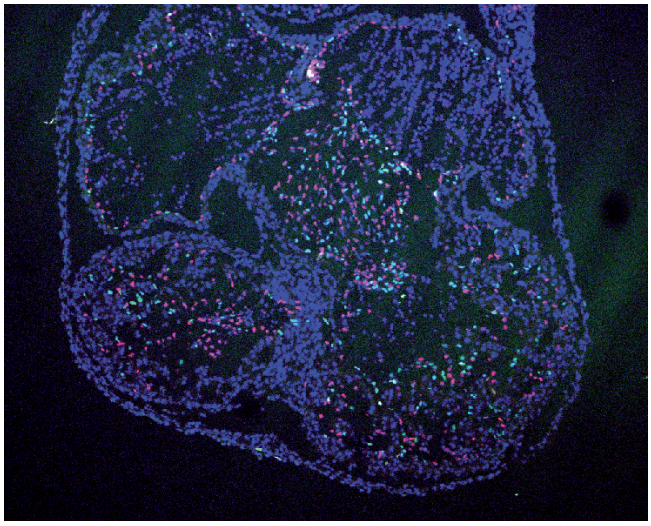
The Vascular Pathophysiology Area (VPA) explores the biology of the vascular system in health and disease through multidisciplinary approaches that include molecular and cell biology, animal models of disease, and translational and clinical approaches. Our research covers the molecular mechanisms that regulate cardiovascular development and disease as well as the cellular and molecular events driving muscle regeneration and growth in health, disease, and aging. We are also interested in understanding the processes through which the organism generates new vasculature and the regulatory pathways involved in vascular wall remodeling. The VPA groups maintain an interest in atherosclerosis, the major cause of myocardial infarction and stroke. We are interested in understanding how atherosclerosis develops and the contribution of aging to these events. A central strand of this work is the exploration of early diagnosis methods and new therapeutic avenues in innovative animal models. New diagnostic and prognostic avenues are being developed through the application of state-of-the-art imaging technologies and deep proteomic analysis in population studies of subclinical atherosclerosis. A further area of interest is the immune and inflammatory component of cardiovascular disease; work in this area focuses on the role of the antibody immune response in atherosclerosis, the mechanisms of intercellular communication between immune cells, and the role of T cell and inflammatory responses in myocarditis. The Vascular Pathophysiology Area hosts three technical units: Genomics, Proteomics/ Metabolomics, and Bioinformatics, which provide state-of-the-art technology to CNIC scientists and actively contribute to the VPA research projects.

RESEARCH GROUPS

- Vicente Andrés
- Jacob Fog Bentzon
- José María Castellano
- José Luis de la Pompa
- Antonio Fernández-Ortiz
- Valentín Fuster
- Alicia García Arroyo
- Pilar Martín
- Pura Muñoz
- Almudena Ramiro
- Juan Miguel Redondo
- Francisco Sánchez-Madrid
- Jesús Vázquez

TECHNICAL UNITS

- Genomics
- Proteomics / Metabolomics
- Bioinformatics



CELL AND DEVELOPMENTAL BIOLOGY

Coordinator: Miguel Ángel del Pozo

The Cell and Developmental Biology (CDB) Area comprises eight research groups and three technical units devoted to basic studies and their translational projection in the areas of vascular development, homeostasis, and disease. One research strand seeks to understand how the temporal and spatial regulation of genome architecture, transcriptional networks, and downstream functional programs determines cell fate decisions in the early embryo and different stages of heart development. These studies have potential application in the advance of regenerative medicine. Other groups investigate cell and tissue mechanisms determining cardiovascular homeostasis and disease, such as angiogenesis, inflammation, and repair. Several research lines aim to elucidate molecular principles and signaling pathways that control the cardiovascular system's mechanical function and adaptability. This research strand deploys multidisciplinary programs integrating cell and systems biology, biophysics, and single-molecule techniques. Efforts are specifically devoted to building bridges between basic research and cardiovascular medicine, with a focus on cardiomyopathies, atherosclerosis, and cerebrovascular disease.

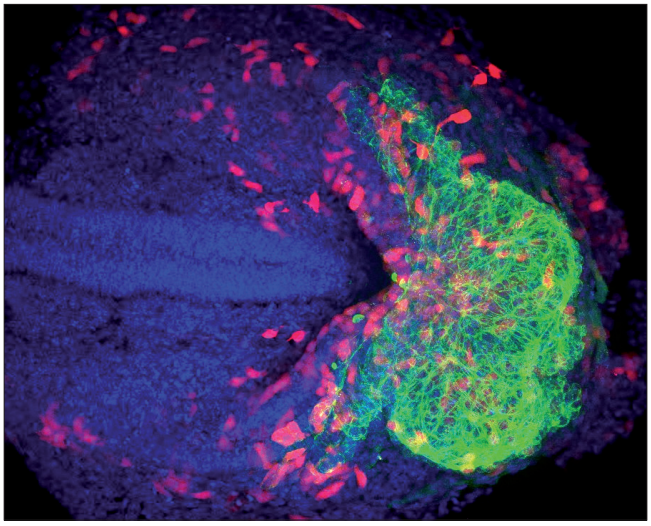
The three core technical units in the CDB Area work with state-of-the-art visualization techniques, providing support and developing novel technologies covering different scales and biological processes. The Microscopy Unit offers advanced confocal, multiphoton, and superresolution imaging technology and expertise, together with specific biophysical approaches for the quantification of processes in living cells and tissues. The Cellomics Unit provides cytometry analysis and separation services (including state-of-the-art spectral cytometry), as well as a full high-content functional genomics screening platform. The Microscopy and Cellomics Units together develop tailored image analysis and data processing solutions for the resolution of subcellular and tissue architecture. The Advanced Imaging Unit is a multidisciplinary group that develops new noninvasive imaging procedures to expand knowledge of the molecular and cellular events underlying cardiovascular disease. Specific programs address cardiovascular imaging, nanomedicine and radiochemistry, and metabolomics.

RESEARCH GROUPS

- Jorge Alegre-Cebollada
- Rui Benedito
- Héctor Bueno
- Miguel Ángel del Pozo
- Andrés Hidalgo
- Miguel Manzanares
- Nadia Mercader
- Miguel Torres

TECHNICAL UNITS

- Microscopy
- Advanced Imaging
- Cellomics



MYOCARDIAL PATHOPHYSIOLOGY

Coordinator: David Sancho

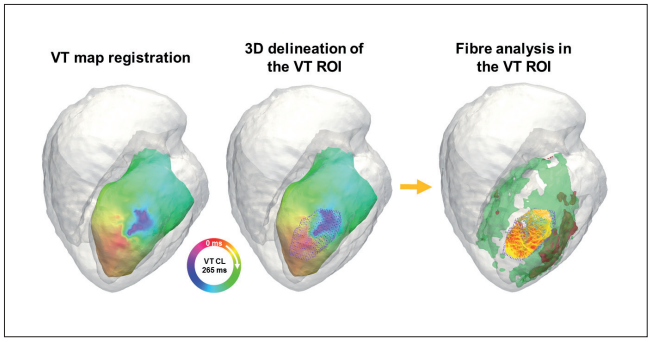
The Myocardial Pathophysiology Area (MPA) brings together scientists from multiple disciplines. Our experimental strategy comprises in vitro and in vivo studies in animal models and humans, an approach that not only provides basic understanding of health and disease, but also improves the translational potential for diagnosis and treatment. MPA groups work on several topics: the oxidative phosphorylation system, role of nuclear receptors in lipid metabolism and inflammatory responses, metabolic syndrome and stress kinases, immunobiology, inherited cardiomyopathies, cardiac arrhythmias, cardiomyocyte electrophysiology, molecular regulation of heart failure, and translational cardiovascular imaging and therapy. Our research in these fields produced several important advances in 2017: definition of a new target for the treatment of heart failure; development of new noninvasive imaging methods in mice for heart failure diagnosis; identification of the beneficial role of the serine and one-carbon metabolic pathway in the heart; description of Lafora disease as a metabolic cardiomyopathy; use of advanced magnetic resonance imaging (MRI) technology to define the postinfarction healing pattern in human hearts and identify how scar-related postinfarction cardiac fiber disorganization affects arrhythmia risk and ventricular tachycardia; investigation of the effect of protective therapies on postinfarction healing; identification of atrial necrosis as a complication of myocardial infarction contributing to chronic heart failure; description of the role of neutrophil beta 1 adrenergic receptor signaling in reperfusion injury; analysis of cardiac channels and their assembly in the cardiomyocyte; development of a proarrhythmia high content screening platform; generation of a whole transcriptome dataset for macrophages at different post-heart-injury stages; work on new strategies to manipulate immune cells for improved immunotherapy; and characterization of thermogenesis modulation in white adipose tissue during obesity and its regulation by stress kinases. Together with these research lines, MPA groups are developing noninvasive technologies through the identification of imaging, genetic, and molecular markers for the diagnosis and specific treatment of diseases that result in cardiovascular injury.

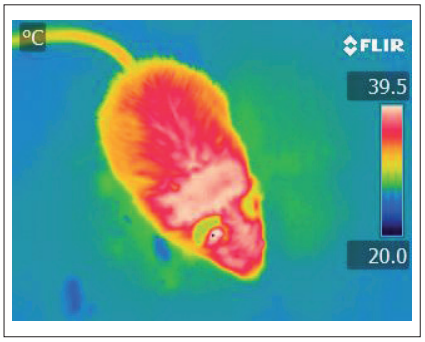
RESEARCH GROUPS

- Juan Antonio Bernal
- José Antonio Enríquez
- David Filgueiras
- Borja Ibáñez
- José Jalife
- Enrique Lara-Pezzi
- Silvia Priori
- Mercedes Ricote
- Guadalupe Sabio
- David Sancho

TECHNICAL UNITS

- Transgenesis
- Pluripotent Cell Technology
- Comparative Medicine
- Viral Vectors





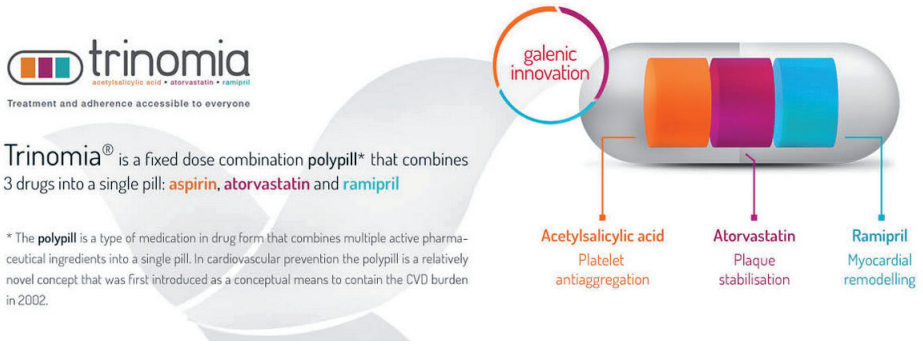
SELECTED CLINICAL STUDIES

ESSOS: a novel methodology to accelerate cardiac magnetic resonance imaging acquisition

Cardiac magnetic resonance (CMR) imaging is the gold standard for anatomical, functional, and tissue composition analysis. Wider implementation of CMR is held back by the time required to perform a complete cardiac scan, which is currently around 45 minutes. CNIC researchers and partners at Philips are working on the joint development of a revolutionary CMR sequence able to shorten the scan time to just 40 seconds. This technology has been tested in large-animal experimental models and in a pilot clinical trial. The sequence will next be tested in an MR scanner outside the CNIC, through a formal collaboration with the *Instituto de Investigación Sanitaria Fundación Jiménez Díaz.* The new technology will then be rolled out to scanners with varying magnetic field strengths at other collaborating hospitals.

SECURE trial

Adherence to treatment after an acute myocardial infarction (MI) is essential for efficient secondary prevention; however, a significant proportion of post-MI patients abandon prescribed therapies. CNIC researchers have developed, in partnership with Ferrer laboratories, a "polypill" that includes the three key pharmacological agents prescribed to post-MI patients (aspirin, an ACE inhibitor, and a statin). Administration of the *Fuster Polypill* significantly increases patient treatment adherence (*J Am Coll Cardiol. 2014;64:2071-82*), and CNIC researchers are now leading SECURE, a multinational randomized clinical trial supported by the EU H2020 Programme. This ongoing trial (trial identifier NCT02596126) will enroll >3000 patients soon after an MI and randomize them to standard treatment vs a *Fuster Polypill*-based strategy. Patients will be followed for a minimum of 2 years and the incidence of major cardiovascular events will be evaluated.



SPHERE-HF trial

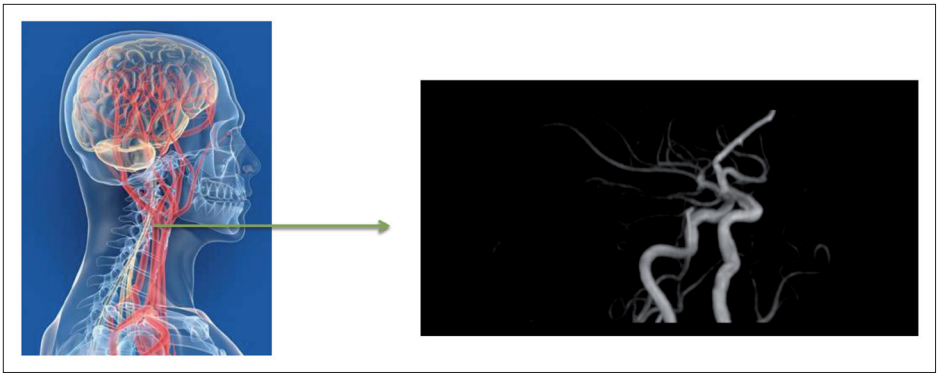
Pulmonary hypertension (PH) secondary to left heart disease (group 2 PH) is the most common form of PH and currently lacks effective therapy. CNIC researchers have identified a novel therapeutic target for this disease in a large animal model of PH: the β3 adrenergic receptor (*Basic Res Cardiol.* 2016;111:49). 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). A total of 80 patients are being recruited in four Spanish hospitals and will be followed under treatment for 4 months. The study endpoints are pulmonary artery hemodynamics and the CMR profile.

PESA-CNIC-Santander study

PESA-CNIC-Santander is a long-term collaboration between the CNIC and Banco Santander. This study aims to identify the presence of atherosclerosis long before symptoms appear and to understand the cues that lead to its development and progression. The study, led by CNIC General Director Valentín Fuster, was initiated in 2010 and enrolled 4200 asymptomatic participants between the ages of 40 and 55 years. Participants undergo a battery of imaging and analytical tests, including 3D vascular ultrasound detection of atherosclerotic plaques in the carotid, aorta, and iliofemoral territories, together with coronary artery calcium quantification. Participants undergo these studies every 3 years, and those showing signs of preclinical atherosclerosis are further examined with other noninvasive imaging technologies. This flagship study involves contributions from several of the CNIC's clinical and basic research groups and has already produced several seminal publications.

H2H study

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



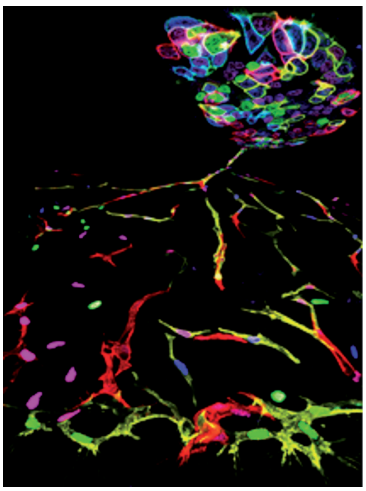
3. Scientific highlights

1. New methods for analyzing gene function

A study published by CNIC scientists in *Cell* will allow any researcher to induce and analyze multispectral genetic mosaics in vertebrate models such as mice and zebrafish. The new technology will allow a high spatio-temporal resolution definition of the function and interaction of genes during development and disease. Genes encode the information needed to synthesize proteins, the functional building blocks of our cells.

According to study leader Rui Benedito, the improved methods for studying gene function will allow researchers to "increase knowledge about how the genome operates in the multiple cell types that make up our bodies and understand gene interaction networks and their regulatory hierarchies." This knowledge, moreover, is crucial for the design of efficient therapeutic strategies to modify or correct genetic activity in disease.

Pontes-Quero, S., Heredia, L., Casquero-García, V., Fernández-Chacón, M., Luo, W., Hermoso, A., Bansal, M., García-González, I., Sánchez-Muñoz, M. S., Perea, J. R., Galiana-Simal, A., Rodríguez-Arabaolaza, I., Del Olmo-Cabrera, S., Rocha, S. F., Criado-Rodríguez, L. M., Giovinazzo, G., Benedito, R. (2017). Dual ifgMosaic: A Versatile Method for Multispectral and Combinatorial Mosaic Gene-Function Analysis. Cell, 170(4), 800-814 e818. [IF: 30.410]



2. Inhibition of a specific protein prevents and reverses aortic aneurysm in models of Marfan syndrome and similar diseases

The inhibition of a protein—inducible nitric oxide synthase, or Nos2—in the arterial wall is able to reverse aortic disease in a mouse model of Marfan syndrome and other types of aneurysm. The findings, published in *Nature Medicine,* suggest a major potential for Nos2 inhibitors in the treatment of thoracic aortic aneurysm. The study was codirected by Miguel Campanero of the CSIC *Instituto de Investigaciones Biomédicas Alberto Sols* and CNIC scientist Juan Miguel Redondo.

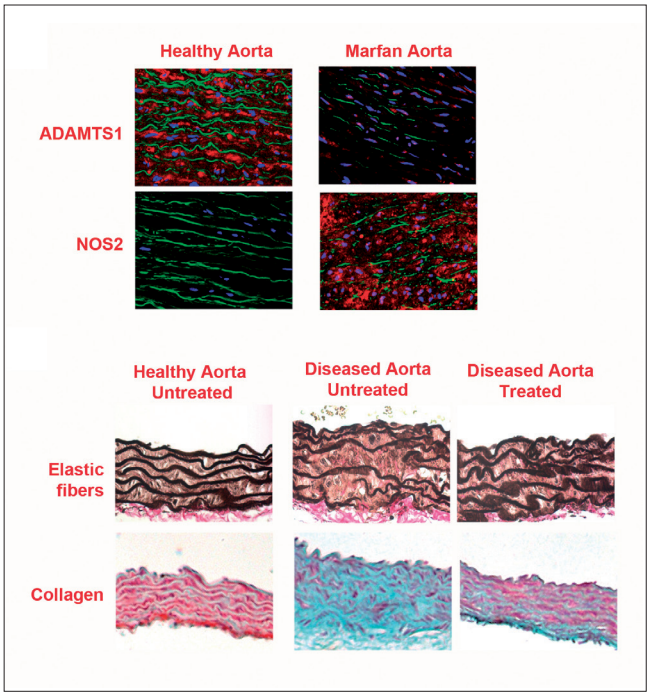
An aneurysm is a swelling or abnormal enlargement of a portion of an artery, resulting from a pathological weakness in the blood vessel wall. For long periods, an aneurysm is an indolent condition that provokes minimal or no symptoms; however, it is an extremely dangerous condition prone to sudden, catastrophic, and often fatal complications. Effective treatment therefore requires early and accurate diagnosis, close patient management, and surgical repair when conditions allow. The vessel dilatation increases the risk of arterial rupture, and current pharmacological treatments are therefore aimed at reducing pressure on the vessel wall. However, these treatments are of limited use because they do not arrest the deterioration of the aortic wall in aortic diseases, including Marfan syndrome, a disease caused by defects in the fibrilin-1 gene. The only truly effective therapy available is surgery, but this dangerous intervention is indicated only when the risk of surgery is lower than the risk of rupture. Moreover, surgery does not cure or stem the underlying condition, which is progressive and not confined to a specific artery wall segment. There is therefore a need to identify the mechanisms underlying aortic wall degeneration and to discover new pharmacological targets for slowing the natural progression of these diseases.

The research team on this study identified two potential therapeutic targets for the treatment and

prevention of aneurysm: the metalloproteinase Adamts1 and the nitric oxide synthase Nos2. The study demonstrates that mice lacking Adamts1 develop a disease similar to Marfan syndrome and that the genetic inactivation of Nos2 expression prevents aortic disease in these mice and in a mouse model of Marfan syndrome. But the study goes further, also demonstrating that pharmacological inhibition of nitric oxide production rapidly and effectively reverses aortic dilatation and aortic medial layer deterioration, both in mice lacking Adamts1 and in the mouse Marfan syndrome model.

Describing the study, Redondo affirmed that it "shows that pharmacological inhibition of Nos2 not only prevents thoracic aortic disease, but also is also curative." The researchers also confirmed that the Nos2 inhibitor 1400W is equally effective in young and old Marfan mice, suggesting that Nos2 is essential for both disease initiation and progression. The authors recognize the need for caution in extrapolating results from mouse models to the human disease; however, Campanero was keen to underline that "the strong and extremely fast action of Nos2 inhibition in reversing aortic disease in the mouse models fully justifies the initiation of preclinical and clinical trials with Nos2 inhibitors, both for Marfan syndrome and for other aortic diseases." The safety of Nos2 inhibitors has been demonstrated in clinical trials targeting other diseases, including rheumatoid arthritis, migraine, and endotoxemia, and therefore specific Nos2 inhibitors could be brought into use to treat aortic disease within a very short time frame.

Oller, J., Méndez-Barbero, N., Ruiz, E. J., Villahoz, S., Renard, M., Canelas, L. I., Briones, A. M., Alberca, R., Lozano-Vidal, N., Hurle, M. A., Milewicz, D., Evangelista, A., Salaices, M., Nistal, J. F., Jiménez-Borreguero, L. J., De Backer, J., Campanero, M. R., Redondo, J. M. (2017). Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome. Nature Medicine, 23(2), 200-212. [IF: 29.886]



3. A new anti-cancer drug linked to cardiovascular problems

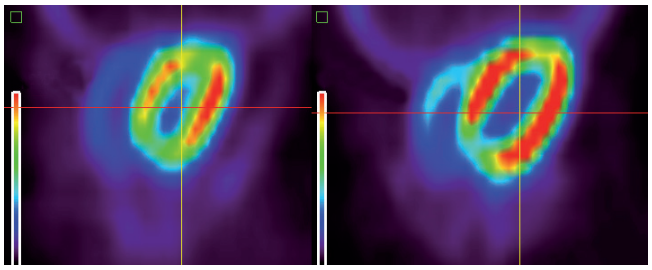
Inhibitors of the enzyme Plk1 were recently authorized as an "innovative therapy for leukemia" by the US Food and Drug Administration (FDA). However, a study published in *Nature Medicine* by researchers from the Spanish National Cancer Research Center (CNIO) in collaboration with researchers at the CNIC suggests that prolonged use of these inhibitors can lead not only to hypertension but also to blood vessel rupture and severe cardiovascular problems.

Progress toward personalized medicine depends on knowing the function of each of our genes and proteins and selecting the appropriate drugs targeting these proteins according to the specific alterations in each patient. In recent years, regulators of the cell cycle, the process that controls the proliferation of all cells, including tumor cells, have demonstrated their usefulness against various cancers, including breast cancer. Among the new drugs used in this strategy is the Plk1 inhibitor volasertib, which has shown very promising results in acute myeloid leukemia and was recently recognized as an "innovative therapy" by the FDA due to its effectiveness against this type of tumor in clinical trials.

In the new study, the CNIC research group led by Juan Miguel Redondo participated in the characterization of cardiovascular defects in mice with decreased Plk1 activity, resulting from genetic deficiency or treatment with volasertib. Together with scientists at the *Centro de Investigación del Cáncer* in Salamanca, the Universidad de Salamanca, and the London Research Institute, the CNIO and CNIC team found that while volasertib treatment of a mouse strain with low Plk1 levels did not cause growth defects, it did cause artery rupture and secondary cardiovascular effects. These results indicated that the arteries are more sensitive to Plk1 inhibition than other adult tissues. The team went on to show that Plk1 is essential for the contraction of cells lining the artery wall, an essential process for maintaining an appropriate blood pressure.

Cardiovascular disease and cancer are the main causes of morbidity and mortality in modern societies. The involvement of Plk1 in the control of both processes will have a major impact on future biomedical developments.

De Carcer, G., Wachowicz, P., Martínez-Martínez, S., Oller, J., Méndez-Barbero, N., Escobar, B., González-Loyola, A., Takaki, T., El Bakkali, A., Cámara, J. A., Jiménez-Borreguero, L. J., Bustelo, X. R., Cañamero, M., Mulero, F., De los Ángeles Sevilla, M., Montero, M. J., Redondo, J. M., Malumbres, M. (2017). Plk1 regulates contraction of postmitotic smooth muscle cells and is required for vascular homeostasis. Nature Medicine, 23(8), 964-974. [IF: 29.886]

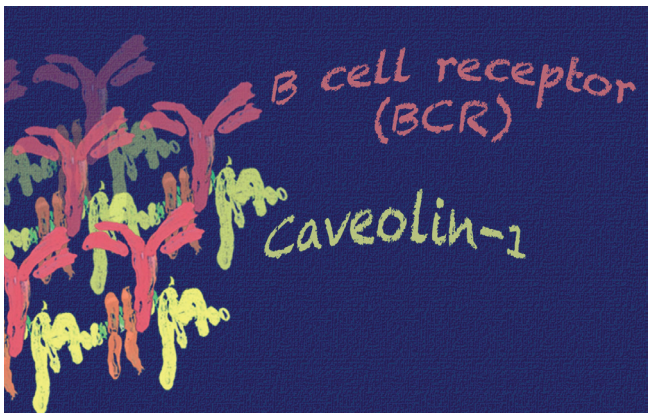


4. Clustering for health

Our immune system protects us from multiple threats such as disease-causing microbes and cancer. However, when our immune system is activated inappropriately, it attacks the body and causes autoimmune diseases. Historically, autoimmunity has been considered the result of immune-system hyperactivity. Recently it has become clear that autoimmunity can also occur as the result of weakened immune responses. In this situation, a strategy based on pharmacological inhibitors would be counterproductive, and an appropriate strategy would be activation or substitution. Working with this new concept, researchers at the University of Freiburg (Germany) and the CNIC have identified the protein caveolin-1 as a key regulator in a unique model of autoimmunity caused by insufficient immune function.

The team identified caveolin-1 as a crucial regulator of the clustering of receptors in the plasma membrane of B lymphocytes. Using experimental models, the authors showed that, in the absence of caveolin-1, B cell receptors are disorganized and, crucially, do not efficiently detect threats. As a result, B cells are not activated appropriately and generate deficient immune responses. These results demonstrate for the first time that the organization of receptors in the B cell membrane ensures the correct activation of these cells.

Minguet, S., Klasener, K., Schaffer, A. M., Fiala, G. J., Osteso-Ibáñez, T., Raute, K., Navarro-Lérida, I., Hartl, F. A., Seidl, M., Reth, M., Del Pozo, M. A. (2017). Caveolin-1-dependent nanoscale organization of the BCR regulates B cell tolerance. Nature Immunology, 18(10), 1150-1159. [IF: 21.506]



5. Spanish research confirms the importance of breakfast in the prevention of cardiovascular disease

Skipping breakfast or eating very little at the start of the day doubles the risk of atherosclerosis. This is the latest finding from the Progression and Early Detection of Atherosclerosis study (PESA), led by the CNIC in partnership with Banco Santander, and published in the *Journal of the American College of Cardiology.* The report shows that people whose breakfast contains less than 5% of the recommended daily calorie intake (100 calories of a daily intake of 2000) have on average twice the number of atherosclerotic lesions as those who eat a high-energy breakfast. This increased risk, moreover, is independent of classical risk factors such as smoking, high cholesterol, and physical inactivity. The report not only confirms the importance of eating breakfast for cardiovascular health, but also suggests that skipping breakfast could indicate more generally unhealthy eating and lifestyle habits.

Uzhova, I., Fuster, V., Fernández-Ortiz, A., Ordovás, J. M., Sanz, J., Fernández-Friera, L., López-Melgar, B., Mendiguren, J. M., Ibáñez, B., Bueno, H., Peñalvo, J. L. (2017). The Importance of Breakfast in Atherosclerosis Disease: Insights From the PESA Study. Journal of the American College of Cardiology, 70(15), 1833-1842. [IF: 19.896]

6. 3D visualization of cholesterol plaques improves cardiovascular risk prediction

Three-dimensional ultrasound could become a central tool for identifying individuals at risk of developing cardiovascular disease. This is the conclusion of a report, published in the *Journal of the American College of Cardiology,* from the CNIC-Santander PESA study (Progression of Early Subclinical Atherosclerosis), a collaborative project between the CNIC and Banco Santander that studies more than 4000 middle-aged participants. The report demonstrates that total atherosclerosis burden is a very useful parameter in the stratification of individual cardiovascular risk, when considered together with classical risk factors (blood cholesterol, blood pressure, diabetes, smoking status, exercise, and obesity).

The results of the study, directed by CNIC Director General Valentín Fuster, show that among the study participants (mean age 45 years) the total atherosclerosis burden is twice as high in men as in women (63.4 versus 25.7 cubic millimeters), is higher in the femoral arteries than in other vascular territories, and increases with age.

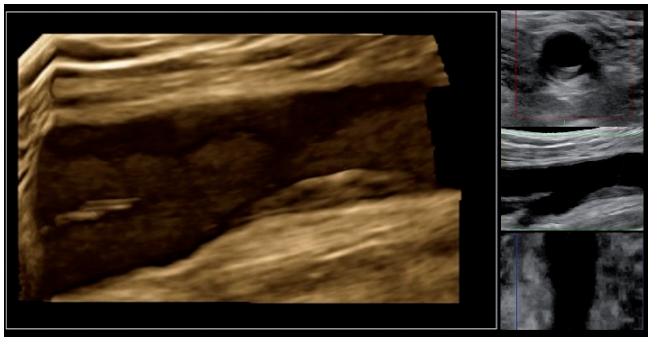
The CNIC scientists explored the most atherosclerosis-prone regions of the carotid and femoral arteries. In each territory, the researchers performed 3D ultrasound examinations of 6 cm arterial segments in both branches, centered on the carotid sinus and the femoral bifurcation. The study population included 3860 middle-aged participants with no disease symptoms and no history of MI or stroke. All participants were Banco Santander employees based in Madrid. PESA is a prospective cohort study that monitors patients over several years. The patients were examined with a new ultrasound system made by CNIC technology partner Philips. The system uses a linear volumetric transducer that acquires 3D images of the arteries and atherosclerotic plaques.

Although 3D ultrasound is still in the development phase, it has already shown clinical promise in several areas, including quantification of atherosclerotic plaque volume. Direct quantification of plaque volume by 3D ultrasound is more accurate than

2D techniques for estimating an individual's total plaque burden.

Borja Ibáñez, CNIC Research Director and a cardiologist at *Fundación Jiménez Díaz* university hospital, commented that "conventional risk factors (blood cholesterol, hypertension, smoking, etc.) allow a broad prediction of the population risk of severe cardiovascular events (infarction or stroke); however, individualized predictions based on these risk factors are not very accurate. Now, with the ability to directly visualize atherosclerotic plaques and quantify their number and size in the body, we will be able to predict individual risk more accurately. The presence and extent of atherosclerosis gives direct information about how risk factors affect the arteries in each individual."

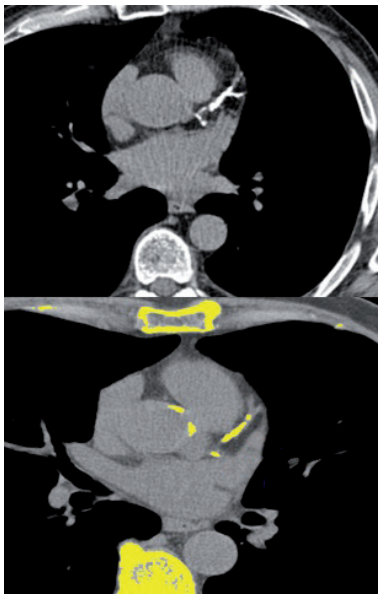
López-Melgar, B., Fernández-Friera, L., Oliva, B., García-Ruiz, J. M., Peñalvo, J. L., Gómez-Talavera, S., Sánchez-González, J., Mendiguren, J. M., Ibáñez, B., Fernández-Ortiz, A., Sanz, J., Fuster, V. (2017). Subclinical Atherosclerosis Burden by 3D Ultrasound in Mid-Life: The PESA Study. Journal of the American College of Cardiology, 70(3), 301-313. [IF: 19.896]



7. LDL cholesterol is the main modifiable predictor of atherosclerosis in individuals with no risk factors

LDL cholesterol (LDL-C), known as 'bad' cholesterol, is the underlying reason why many apparently healthy individuals have a heart attack or stroke during middle age despite having no cardiovascular risk factors such as hypertension, smoking, obesity, dyslipidemia, or diabetes. Even at levels considered normal, LDL-C, after age and being male, is the main predictor of the presence of atherosclerotic plaques in the arteries. This is the finding of research conducted at the CNIC and published in the *Journal of the American College of Cardiology*. The results of the study, led by CNIC Director Valentín Fuster, support the use of more aggressive strategies to reduce LDL-C, including for individuals considered at minimum risk. Fortunately, LDL-C is relatively easy to modify and thus avoid the appearance of atherosclerotic plaques. The new findings have important societal and clinical implications because they demonstrate the importance of aggressively reducing LDL-C, both on an individual level and in the general population. The new findings come from a subanalysis of the PESA study (Progression of Early Subclinical Atherosclerosis). PESA is a joint project between the CNIC and Banco Santander that uses the latest noninvasive vascular imaging technology (magnetic resonance, PET, CT, and 2D and 3D ultrasound) to answer important unresolved questions about cardiovascular disease, such as when and how it begins and what has to happen for it to manifest clinically.

Fernández-Friera, L., Fuster, V., López-Melgar, B., Oliva, B., García-Ruiz, J. M., Mendiguren, J., Bueno, H., Pocock, S., Ibáñez, B., Fernández-Ortiz, A. Sanz, J. (2017). Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors. Journal of the American College of Cardiology, 70(24), 2979-2991. [IF: 19.896]



8. Five health indicators are enough to predict cardiovascular risk in healthy people

Just five indicators of cardiovascular health—blood pressure, physical activity, body-mass index, fruit and vegetable intake, and smoking status—accurately predict cardiovascular risk in healthy individuals. This is the conclusion of a study carried out at the CNIC and published in *The Journal of American College of Cardiology*. The study demonstrates that the Fuster-BEWAT score, which is based on these five cardiovascular health indicators, effectively predicts the presence and extent of subclinical (asymptomatic) atherosclerosis in healthy middle-aged individuals with no known history of cardiovascular disease. Moreover, Fuster-BEWAT predictions are as accurate as those obtained with the widely used Ideal Cardiovascular Health Index (ICHS), the score currently recommended by the American Heart Association, which additionally includes blood analysis of cholesterol and glucose. The new study forms part of the Progression and Early Detection of Atherosclerosis project (PESA), a CNIC initiative conducted in partnership with Banco Santander. The results demonstrate the usefulness of the Fuster-BEWAT score for evaluating cardiovascular risk in situations where it is not possible to obtain blood samples.

Fernández-Alvira, J. M., Fuster, V., Pocock, S., Sanz, J., Fernández-Friera, L., Laclaustra, M., Fernández-Jiménez, R., Mendiguren, J., Fernández-Ortiz, A., Ibáñez, B., Bueno, H. (2017). Predicting Subclinical Atherosclerosis in Low-Risk Individuals: Ideal Cardiovascular Health Score and Fuster-BEWAT Score. Journal of the American College of Cardiology, 70(20), 2463-2473. [IF: 19.896]

9. Dogma overturned: new studies into inflammation in the infarcted heart could lead to changes in therapy

Scientists at the CNIC and the *Fundación Jiménez Díaz* (FJD) and Salamanca University Hospitals have demonstrated that the human heart responds very differently to an infarction than was previously thought. The study, published in two independent articles in the leading journals *Circulation* and *Circulation Research,* overturns the established view that an infarction is followed by progressive repair of the myocardium.

The project arose from research begun more than 10 years ago at Mount Sinai Hospital in New York, directed by Valentín Fuster, who is an author on both of the new CNIC-led studies. Two years ago, the CNIC and the FJD University Hospital signed a collaboration agreement to coordinate their studies of cardiac muscle after an acute MI. The study is the first in the world to study heart attack patients by MRI so soon after the re-establishment of blood flow. In addition to studies in patients, the team have also extended their investigation of infarction in pigs, the experimental model most similar to humans. The unique translational research infrastructure at the CNIC includes equipment for directly comparable imaging in human and animal studies, allowing the team to demonstrate that treatments during an infarction can change the composition of the cardiac muscle during the first hours after reperfusion and result in a much more rapid recovery of the heart. In the words of study author Rodrigo Fernández-Jiménez, "MRI provides an extraordinary ability to noninvasively visualize events occurring after an infarction in real time, including inflammation, tissue volume expansion, hemorrhage, and obstruction of the microcirculation."

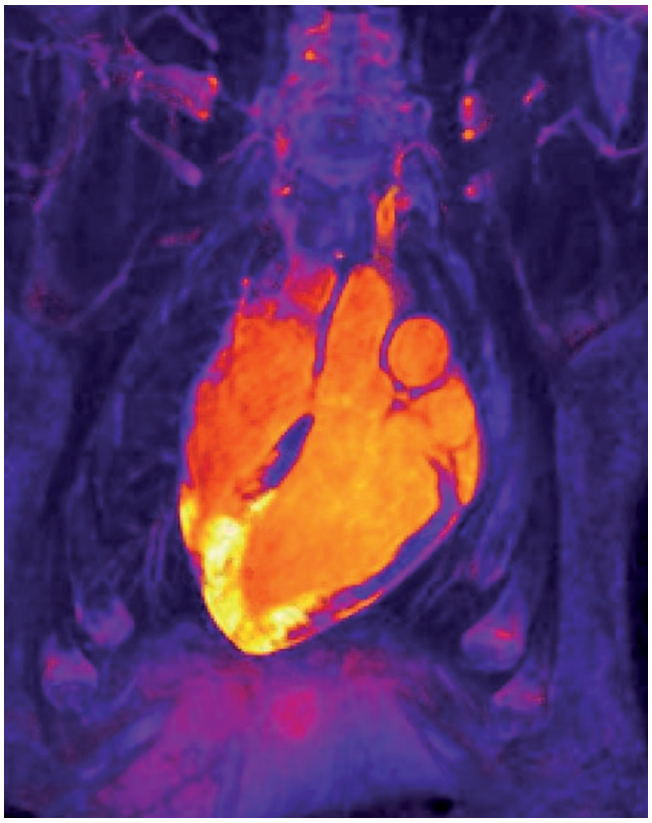
The study was coordinated by Ibáñez, Director of Clinical Research at the CNIC and a cardiologist at FJD University Hospital. In his view, the discovery of the bimodal inflammatory response in the human heart "forces us to think about the best timing for MRI scans used in clinical trials to quantify irreversible injury and to monitor the effectiveness of interventions to reduce this injury. Until now, this question was considered unimportant, and cardiac imaging studies have been conducted on any day in the postinfarction period. The new findings show that the optimal time for these scans is between postinfarction days 4 and 7, when the second wave of inflammation/edema is prominent and affects the entire region that was shut off from the blood supply during the infarction."

This research project was possible thanks to the scientific collaboration between the CNIC and technology partner Philips Iberia. Physicist Javier Sánchez-González, a Philips researcher seconded

to the CNIC, leads the technological development of these cardiac imaging projects, and his input is essential for transferring the initial findings from the CNIC to collaborating hospitals, so that the new algorithms can be tested in a clinical environment.

Fernández-Jiménez, R., Barreiro-Pérez, M., Martín-García, A., Sánchez-González, J., Agüero, J., Galán-Arriola, C., García-Prieto, J., Díaz-Peláez, E., Vara, P., Martínez, I., Zamarro, I., Garde, B., Sanz, J., Fuster, V., Sánchez, P. L., Ibáñez, B. (2017). Dynamic Edematous Response of the Human Heart to Myocardial Infarction: Implications for Assessing Myocardial Area at Risk and Salvage. Circulation, 136(14), 1288-1300. [IF: 19.309]

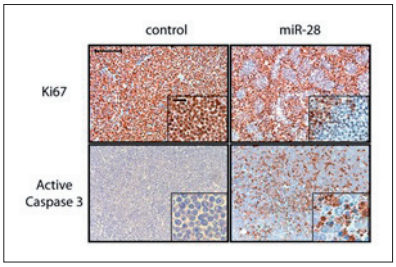
Fernández-Jiménez, R., Galán-Arriola, C., Sánchez-González, J., Agüero, J., López-Martín, G. J., Gómez-Talavera, S., García-Prieto, J., Benn, A., Molina-Iracheta, A., Barreiro-Pérez, M., Martín-García, A., García-Lunar, I., Pizarro, G., Sanz, J., Sánchez, P. L., Fuster, V., Ibáñez, B. (2017). Effect of Ischemia Duration and Protective Interventions on the Temporal Dynamics of Tissue Composition After Myocardial Infarction. Circulation Research, 121(4), 439-450. [IF: 13.965]



10. A new treatment target for aggressive lymphomas

An estimated 400 000 people worldwide are diagnosed with lymphoma every year, and B cell lymphomas kill more than 200 000 people every year. CNIC scientists have identified a possible therapeutic target for two types of very aggressive lymphoma. The CNIC team discovered that the microRNA miR-28 regulates the terminal differentiation of B lymphocytes, blocking the growth of B cell lymphomas. The study, published in *Blood,* establishes the therapeutic potential of synthetic miR-28 analogs for inhibiting the growth of Birkitt lymphoma and diffuse large cell lymphoma. These findings could lead to the development of the first miRNA analog therapy for the treatment of B cell lymphoma and provide the basis for human trials.

Bartolomé-Izquierdo, N., De Yébenes, V. G., Álvarez-Prado, A. F., Mur, S. M., López, J. A., Roa, S., Vázquez, J., Ramiro, A. R. (2017). miR-28 regulates the germinal center reaction and blocks tumor growth in preclinical models of non-Hodgkin lymphoma. Blood, 129(17), 2408-2419. [IF: 13.164]

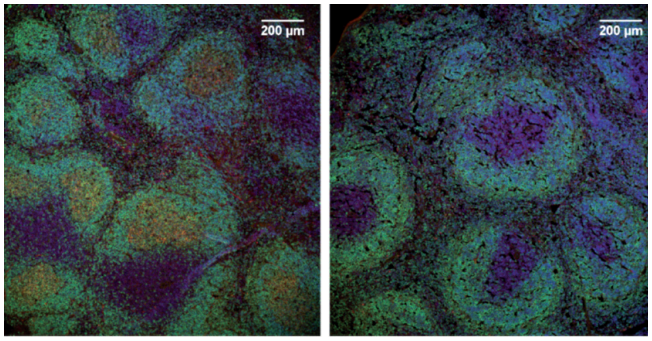


11. CNIC scientists discover an essential mechanism in the immune response

A study led by Almudena Ramiro and published in *Nature Communications* demonstrates an essential role for the transcriptional regulator CTCF in antibody production. The research shows that CTCF is required for the ability of B lymphocytes to correctly protect the body against infection. In the absence of CTCF, the immune system does not function correctly, a finding with implications for vaccine research. The study reveals an essential function for CTCF in the orchestration of transcriptional changes during the terminal differentiation of B lymphocytes and advances our

understanding of the mechanisms that regulate the immune response.

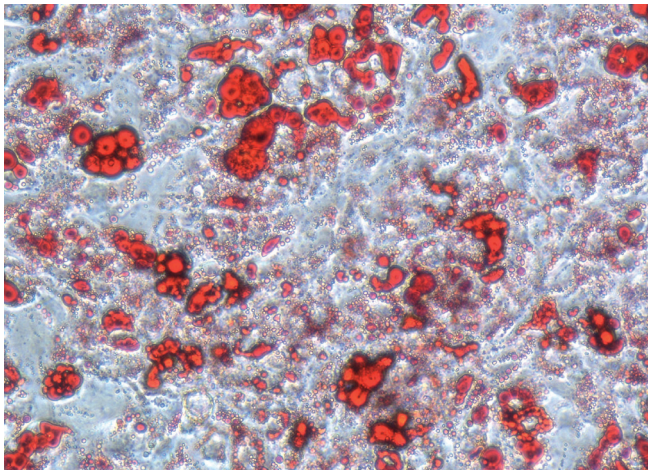
Pérez-García, A., Marina-Zárate, E., Álvarez-Prado, A. F., Ligos, J. M., Galjart, N., Ramiro, A. R. (2017). CTCF orchestrates the germinal center transcriptional program and prevents premature plasma cell differentiation. Nature Communications, 8, 16067. [IF: 12.124]



12. A specific protein regulates the burning of body fat to generate heat

CNIC scientists have identified a protein that holds promise as a target for therapies to reduce obesity. Drs. Guadalupe Sabio and Nuria Matesanz have demonstrated that MKK6 controls the conversion of fat stores, known as white fat, into brown fat, in which lipids are burned to maintain body temperature and reduce obesity. Obesity is a global epidemic, with overweight or obesity affecting an estimated 2200 million people worldwide. In the study, published in *Nature Communications,* the research team showed that the elimination of MKK6 stopped the progression of obesity in mice and led to body mass reductions. These results confirm MKK6 as a potential therapeutic target in the fight against obesity.

Matesanz, N., Bernardo, E., Acín-Pérez, R., Manieri, E., Pérez-Sieira, S., Hernández-Cosido, L., Montalvo-Romeral, V., Mora, A., Rodríguez, E., Leiva-Vega, L., Lechuga-Vieco, A. V., Ruiz-Cabello, J., Torres, J. L., Crespo-Ruiz, M., Centeno, F., Álvarez, C. V., Marcos, M., Enríquez, J. A., Nogueiras, R., Sabio, G. (2017). MKK6 controls T3-mediated browning of white adipose tissue. Nature Communications, 8(1), 856. [IF: 12.124]

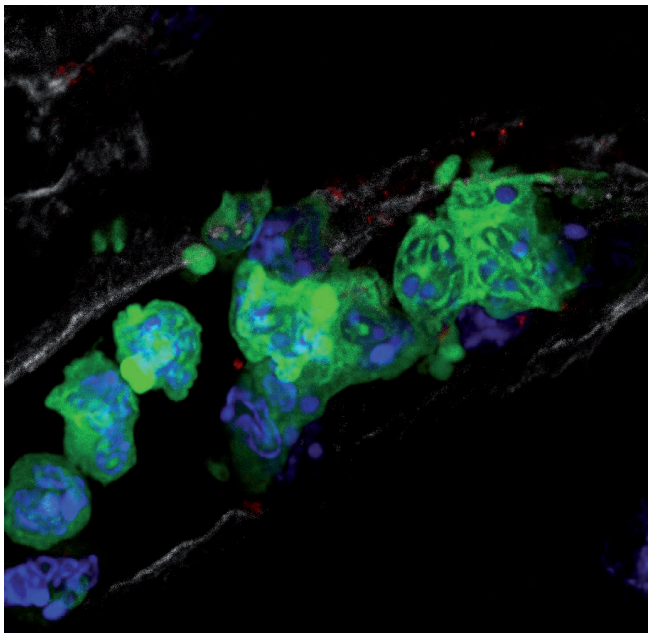


13. A decades-old drug stops the spread of injury after a heart attack

Acute myocardial infarction is a serious disease that affects more than 50 000 people a year in Spain. Treatment has advanced a great deal in recent years, especially in the extensive use of coronary angioplasty, in which a catheter is used to re-establish blood flow through the blocked coronary artery. Nevertheless, many heart attack survivors have seriously impaired heart function that limits their long-term health and generates major health system costs. The search for treatments to limit the irreversible damage caused by a heart attack is an extremely important research area in relation to both patient care and health policy. In an article published in *Nature Communications,* CNIC scientists report a new mechanism of action of metoprolol, a drug that can limit the damage produced during a heart attack if administered early.

The team led by Borja Ibáñez, CNIC Clinical Research Director and a cardiologist at the *Fundación Jiménez Díaz* University Hospital Health Research Institute (IIS-FJD), has identified the mechanism that explains why this drug is so beneficial: rapid administration of metoprolol during a heart attack directly inhibits the inflammatory action of neutrophils, a type of blood cell. The reduced inflammation translates into a smaller amount of damaged tissue in the post-infarcted heart. The finding opens the route to new applications for this cheap, safe, and simple drug.

García-Prieto, J., Villena-Gutiérrez, R., Gómez, M., Bernardo, E., Pun-García, A., García-Lunar, I., Crainiciuc, G., Fernández-Jiménez, R., Sreeramkumar, V., Bourio-Martínez, R., García-Ruiz, J. M., Del Valle, A. S., Sanz-Rosa, D., Pizarro, G., Fernández-Ortiz, A., Hidalgo, A., Fuster, V., Ibáñez, B. (2017). Neutrophil stunning by metoprolol reduces infarct size. Nature Communications, 8, 14780. [IF: 12.124]



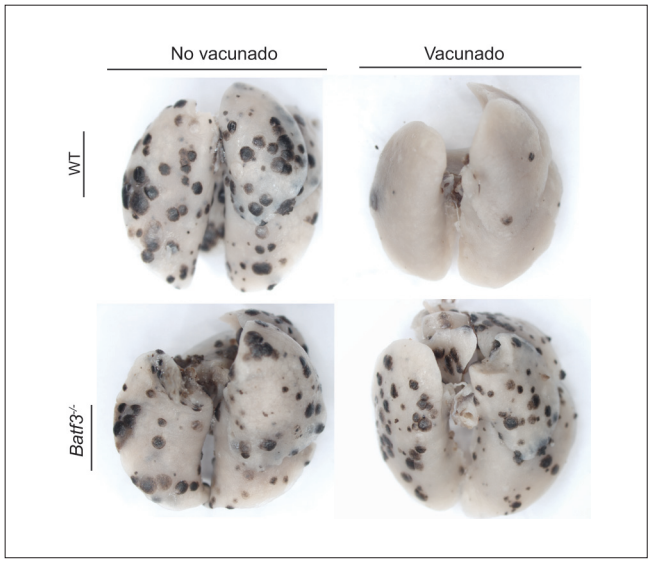
14. The key to improved cancer immunotherapy

CNIC researchers have investigated how different subtypes of essential immune-response cells called CD8+ T lymphocytes cooperate to mount a stronger anti-tumor response. The results show that generation of an optimal immune response to cancer requires cooperation between two types of memory T cell—one circulating in the blood and the other resident in tissues—that can be reactivated with current immunotherapy strategies. These results, published in *Nature Communications,* have the potential to improve current cancer immunotherapy strategies, especially in relation to the prevention of metastasis (dissemination of the tumor to organs distant from the site of origin).

Immunotherapy—the use of the immune system to fight cancer—is revolutionizing treatment, and was selected by the prestigious journal *Science* as the major scientific advance of 2013. According to study leader David Sancho, "Cancer evades the control of the immune system because the cytotoxic T lymphocytes that should recognize and eliminate tumor cells are inhibited. Current immunotherapy is based on reactivating these T lymphocytes; however, little is known about how cytotoxic T cells can be generated more effectively, and in particular how immune memory can be triggered to prevent the development of tumors and metastasis."

The study suggests that an optimal anti-tumor immune response requires the generation of both circulating and tissue-resident T cell memory. Both memory T cells subtypes can be reactivated with current immunotherapy treatments, and reactivation of both requires DC1 dendritic cells. Cancer immunotherapy is not simply a treatment that can effectively promote the rejection of primary tumors; above all, it is a fundamental tool for impeding metastasis after surgery to remove the primary tumor.

Enamorado, M., Iborra, S., Priego, E., Cueto, F. J., Quintana, J. A., Martínez-Cano, S., Mejías-Pérez, E., Esteban, M., Melero, I., Hidalgo, A., Sancho, D. (2017). Enhanced anti-tumour immunity requires the interplay between resident and circulating memory CD8+ T cells. Nature Communications, 8, 16073. [IF: 12.124]



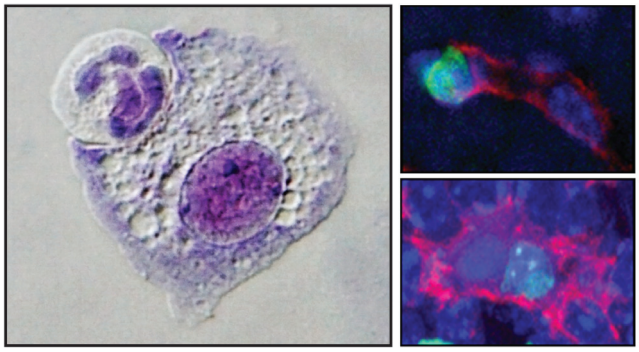
15. Cell "cannibalism" trains our defenses

Phagocytosis is a biological mechanism whereby specialized cells ingest and degrade old, dead, or damaged cells to prevent them accumulating and causing tissue damage. A CNIC-led study has now reported that phagocytosis appears also to have an educational role. *The Journal of Experimental Medicine* report is the fruit of a joint effort by teams from the Spanish National Cancer Research Center (CNIO), the Spanish Superior Scientific Research Council (CSIC), and groups from the USA, and was coordinated by Noelia Alonso-González and Andrés Hidalgo of the CNIC. The study shows that phagocytosis not only eliminates useless cells, but also trains macrophages, the immune cells that carry it out.

It is a paradox of nature that death is a prerequisite for the continuation of life. This is no more evident than in our own bodies, in which billions of cells in the intestine, the blood, the skin, and other tissues die every day so that new ones can take their place. Scientists have long been interested in how organisms eliminate the debris from these expired cells. One of the commonest mechanisms turns out to be that specialized cells eat the old, dead, or damaged cells. This digestive process, called phagocytosis, is carried out by cells called macrophages, a name that means "big eaters".

An important conclusion of the study is that the act of ingesting expired cells trains the immune system in how to maintain tissues in a clean and healthy state, and that macrophages play a very important role in this process. The study identifies in detail the molecules that carry out important tasks in the phagocytic process in each tissue, from the gut to the liver and bone marrow. Surprisingly, the researchers found that each tissue has its own specific molecular toolkit for eliminating unwanted cells. According to Alonso-González, "This discovery suggests that in principle it should be possible to modulate phagocytosis in individual organs, without altering events in neighboring organs. One could, for example, promote the elimination of dangerous cells in the spleen without risking elimination of beneficial cells in the lung." Although any therapeutic application lies in the future, the study, in describing how the body maintains itself clean and healthy, suggests that in time it may be possible to coordinate the work of these cleansing macrophages to our benefit.

A. González, N., Quintana, J. A., García-Silva, S., Mazariegos, M., González de la Aleja, A., Nicolas-Avila, J. A., Walter, W., Adrover, J. M., Crainiciuc, G., Kuchroo, V. K., Rothlin, C. V., Peinado, H., Castrillo, A., Ricote, M., Hidalgo, A. (2017). Phagocytosis imprints heterogeneity in tissue-resident macrophages. Journal of Experimental Medicine, 214(5), 1281-1296. [IF: 11.991]



4. CNIC news & views

AWARDS, SCHOLARSHIPS & HONORS

The Grand Cross of *Alfonso X el Sabio* awarded to Valentín Fuster

The Council of Ministers, at the request of the Ministry of Education, Culture and Sports, has awarded the Grand Cross of the *Orden Civil de Alfonso X el Sabio* to CNIC General Director Dr. Valentín Fuster. This award rewards Spanish and foreign individuals who have distinguished themselves through outstanding contributions in the fields of education, science, culture, teaching, and research in Spain or internationally.

Borja Ibáñez receives the XII *Banco Sabadell* Foundation Award for Biomedical Research

The XII Banco Sabadell Foundation Award for Biomedical Research has been presented to CNIC Clinical Research Director Borja Ibáñez Cabeza for his innovative contribution to the fight against cardiovascular disease through the transfer of basic knowledge and technology to disease prevention and treatment. The prize includes a financial award of €50 000 and acknowledges the career trajectory of young researchers in biomedicine. A total of 58 submissions were received for the 2017 award, including applications from investigators with basic, clinical and epidemiological research profiles.

The *La Caixa* Bank Foundation pays tribute to biomedical researchers

The *La Caixa* Bank Foundation's *Imprescindibles* campaign shines a light on the invaluable contribution made by scientists who dedicate their lives to fighting disease and helping to preserve that most valuable of assets, our health. *La Caixa* Bank Foundation President Isidro Fainé and General Director Jaume Giró, accompanied by Drs. María Blasco, Valentín Fuster, Maite Mendioroz, Eduard Gratacós, Bonaventura Clotet, and Pedro Alonso, joined in the launch of a new advertising campaign that gives a voice to Spanish researchers leading the fight against the diseases with the biggest impact on health in Spain and worldwide. The campaign presents the testimonies of Spanish biomedical research leaders and outlines the essential features

of their research. In his contribution, Fuster notes that "there are two keys to promoting cardiovascular health: science and education."

David Sancho receives the *Constantes y Vitales* Young Talent Award for Biomedical Research

The *Constantes y Vitales* program is an initiative of the TV channel *laSexta* together with the AXA Foundation with the aim of supporting and strengthening Spanish biomedical research and promoting health. In its third year, the Young Talent Award went to CNIC group leader David Sancho, in recognition of his talent and scientific leadership in Spain.

Eduardo Oliver awarded the Spanish Pharmacology Society Young Researcher Award

CNIC researcher Eduardo Oliver has been awarded the Spanish Pharmacology Society's Young Researcher Award, which recognizes the track record of members under 35 years of age. The award comes with a prize of €1200, shared with the other award winner, Miguel Romero of the University of Granada. Oliver's new award joins another he received last year from the Federation of European Pharmacological Societies for his article *The zinc transporter ZIP12 regulates the pulmonary vascular response to chronic hypoxia* (*Nature,* 2015; 524:356-360).

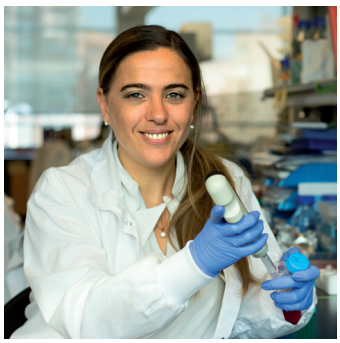
Valentín Fuster, new President of the Health Advisory Board

Valentín Fuster has been appointed President of the Health Advisory Board, replacing Joan Rodés, who was President until his death earlier in 2017. During the official investiture of Fuster, Dolors Montserrat, Spanish Minister of Health, Social Services, and Equality, paid special tribute to Fuster's commitment to spreading the message that "we must be active protagonists of our own health."

Researchers and Cultural Creators

CNIC group leader Guadalupe Sabio received one of 50 *Fundación BBVA* Leonardo Scholarships for Researchers and Cultural Creators in the area of basic research for her project *Inhibition of p38 gamma as a possible therapeutic target for liver cancer*. The 2017 Leonardo Scholarships recognized achievements in nine categories: Basic Sciences (Physics, Chemistry, and Mathematics); Biology, Environmental and Earth Sciences; Biomedicine; Information and Communication Technologies; Engineering and Architecture; Economics and Business Management; Legal and Social Sciences; Humanities; and Literary Creation and Theater.

Guadalupe Sabio was also selected as one of the 100 Top Woman Leaders in Spain in 2017, in an initiative aimed at boosting the presence of women in all areas. With this award, Sabio joins a select group that includes Her Majesty Letizia Ortiz, Almudena Grandes, Amaya Arzuaga, Amaya Valdemoro, Carmen Alborch, Carmen Iglesias, Irene Milleiro, Julia Otero, Margarita Álvarez, María José Alonso, and Marta Martínez Alonso.



Four CNIC students receive the *Certamen Arquímedes* Award

The four students are supervised by CNIC researchers, and each student and supervisor will receive a financial award: the prizewinners get €6000 each and the supervisors €2000. Runners up and their tutors receive €2000 each.

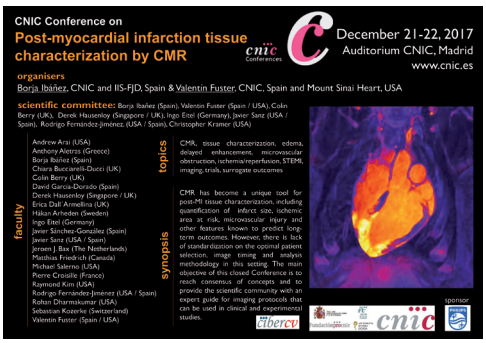
SCIENTIFIC EVENTS

CNIC Conference *Atrial Fibrillation: from Mechanisms to Population Science*

The 2017 CNIC Conference on atrial fibrillation covered the spectrum from the underlying genetics to new advances in therapy. The conference brought together 126 international experts in atrial fibrillation with different areas of expertise.

CNIC Conference *Characterization of postmyocardial infarction tissue by CMR*

The CNIC organized this scientific meeting to sketch out new guidelines for the use of CMR imaging in patients suffering an MI. The main goal of the meeting was to reach a consensus on the appropriate protocols to use to characterize the physiological damage caused by an infarction. The meeting was held on 21-22 December, was attended by internationally renowned cardiologists and MRI specialists and was sponsored by Philips. The meeting once again underlined the central position of the CNIC in cardiovascular research.



PhDAY2017: State of the Art

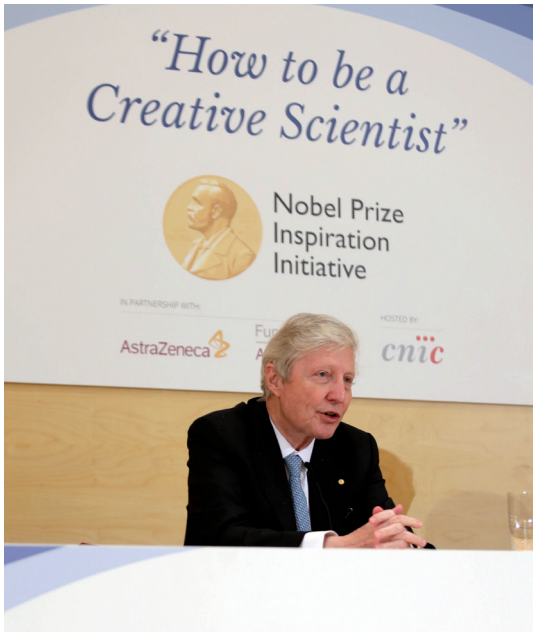
Another year brought another edition of the CNIC PhDay. This one-day event, run by and for early-stage researchers, matches the quality of any internationally renowned conference. PhDay is an open forum for students, graduates, laboratory technicians, and postdoctoral researchers where participants share their research, exchange ideas, and explore career options. In 2017 PhDay celebrated its 4th year.

Fuster participates in the presentation of the 2017 report on *Global Health and the Future Role of the United States*

Valentín Fuster, who doubles his role as CNIC General Director with his position as Director of the Cardiovascular Institute and Physician-in-Chief at Mount Sinai Hospital in New York, was appointed co-director of the committee on Global Health and the Future Role of the United States in September 2016, together with US Assistant Secretary of State for African Affairs Jendayi Frazer. The Committee advises the Presidency on strategies to improve global health through multidisciplinary approaches and provide efficient and responsible use of government resources.

Jules Hoffman: How to be a Creative Scientist

Nobel laureate Profesor Jules Hoffmann visited the CNIC in an event sponsored by the AstraZeneca Foundation as part of the Nobel Prize Inspiration Initiative (NPII). Professor Hoffman presented the audience with his vision of how to be a creative scientist.



The CNIC hosts the 31st annual meeting of the European Macrophage and Dendritic Cell Society (EMDS)

The CNIC hosted the 31st annual meeting of the European Macrophage and Dendritic Cell Society (EMDS), which was organized on this occasion by Amaya Puig of the *Gregorio Marañón* Health Research Institute, Antonio Castrillo of the *Alberto Sols* Biomedical Research Institute, and CNIC group leader David Sancho. The meeting brought more than 220 researchers together in Madrid.

CNIC Invited Seminars: 13 Seminars (www.cnic.es/es/actualidad/agenda)

OUTREACH ACTIVITIES

The CNIC participates in *Science Weekend*

The VII edition of the *Science Weekend,* the science fair with something for everyone, celebrated its fourth consecutive year at the National Museum of Science and Technology in Alcobendas, Madrid on 27-28 May. The event, supported by the *La Caixa* Foundation, enjoyed the participation of more than 40 institutions from all over Spain, with the CNIC proud to be among their number. In all, more than 200 activities, workshops, and games were offered to visitors to promote interest and education in science and technology.

CNIC groups also participated for the sixth year running in the Madrid regional *Science Week* with two new activities: *A family day at the CNIC* for smaller children, and the workshop *Life in 3D: new developments in microscopy* for a general public audience. This last activity was promoted by the grant BFU 2015-70193 REDT

The CNIC affirms its commitment to science and gender equality

Carmen Vela, Secretary of State for Research, Development, and Innovation, chaired this conference held to mark International Women and Girls in Science Day at the CNIC.

The Health Minister supports the *Women for the Heart* campaign

The MAPFRE Foundation, Pro-CNIC Foundation, and Spanish Heart Foundation joined with the Madrid Regional Government to promote this campaign, now in its second year. The campaign was awarded the *Premio iMujer* (iWoman Prize) in the Health Initiative category. This ground-breaking campaign aims to raise awareness among women and girls about the need to adopt healthy lifestyle habits in order to prevent cardiovascular disease.

March for Science: Move for the CNIC

There is no better way to promote cardiovascular health than teaching by example. Promega Biotech Ibérica joined the CNIC in organizing the *Move for the CNIC* event in March. This sports day brought staff from the CNIC and Promega together with family members to join in a range of physical activities in *El Pardo,* near Madrid. For each person enrolled in the event, Promega made a donation to the CNIC training programs.

GRANTS

Launch of the *Severo Ochoa* Centers and *María de Maeztu* Units of Excellence Alliance (SOMMA)

The Spanish *Severo Ochoa* Centers and *María de Maeztu* Units of Excellence Alliance promotes excellence in scientific research. The goal is to promote Spanish science through the recognition of researchers working at the forefront of their fields, helping them increase their impact, international scientific leadership, and competitiveness.

A CNIC project researching new treatments for progeria, funded within the E-Rare 2017 call for proposals

The project is called *Identifying new treatments for Hutchinson-Gilford progeria syndrome (HGPS),* or *TREAT-HGPS* for short, and is coordinated by Vicente Andrés, Basic Research Director at the CNIC and a participant in the cardiovascular disease *Centro de Investigación Biomédica en Red* (CIBER-CV). The project was selected in the E-Rare joint transnational call for 2017: *Transnational Research Projects for Innovative Therapeutic Approaches for Rare Diseases.* Funding of €797 744 will be provided over the next three years (2018-2020).

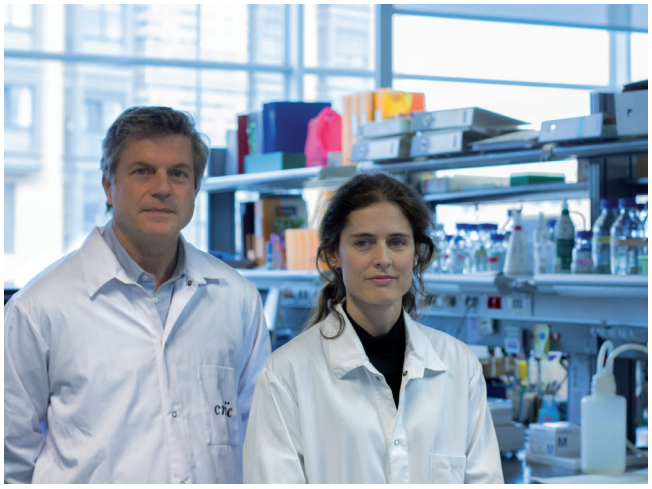
The CNIC is the first Spanish center to coordinate a Leducq Foundation project

For the first time, the Ledduq Foundation has selected a project co-coordinated by a Spanish center, the CNIC. The *Redox Regulation of Cardiomyocyte Renewal* project, coordinated by CNIC researcher Miguel Torres and Hesham A. Sadek of the University of Texas Southwestern-Dallas Medical Center, is one of five projects selected by the Transatlantic Network of Excellence Program of this prestigious foundation, and will receive $6 000 000 over five years. Of this total, $800 000 is destined to the CNIC. The project start date is January 1, 2018, with the launch meeting scheduled for January 28 and 29.

Launch of the 4DHeart Project

The 4DHeart project (4D Analysis of Heart Development and Regeneration Using Advanced Light Microscopy) was launched on January 1, 2017. This European Commission financed European Industrial Doctorate (EID) project is coordinated by Miguel Torres at the CNIC and has a total funding of €1.5 million spread over 4 years. The goal of the project, part of the European Union H2020 Programme, is to foster research partnerships between academia and industry. The 4DHeart

training project includes the participation of 12 European institutions as training centers young scientists.



NEW PARTNERSHIPS

Two of the of the largest research cohort studies in Spain join forces to prevent atherosclerosis and Alzheimer's

The CNIC and the *Pasqual Maragall* Foundation's Barcelonabeta Brain Research Center have come together to investigate the relationship between atherosclerosis and Alzheimer's disease. The agreement covers vascular imaging, cognitive imaging, and neuroimaging in cohort participants at both centers, a total of more than 6000 healthy individuals, making this the largest initiative of its kind in the world.

The CNIC and the SEC encourage young cardiologists to engage in cardiovascular research

The Spanish Society of Cardiology (SEC) and the CNIC have created an ambitious joint plan of postgraduate training for cardiologists in order to promote good quality research in the cardiovascular field.

CNIC & SOCIETY

The King and Queen visit the CNIC

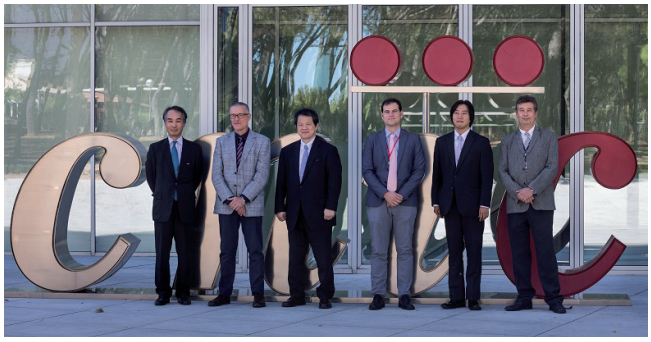
Their Majesties the King and Queen of Spain visited the CNIC in February. The royal visitors were accompanied by Dolors Montserrat, Minister of Health, Social Services, and Equality; Carmen Vela, President of the Board of Trustees of the CNIC and Secretary of State for Research, Development, and Innovation; and Jesús Fernández Crespo, Vice-president of the CNIC Board of Trustees and Director of the *Carlos III* Institute of Health. During their visits, their Majesties learned about the ongoing research projects at the center from CNIC General Director Valentín Fuster and Pro-CNIC Foundation Board of Trustees President Luis de Carlos.

The Madri+d Foundation visits the CNIC

The director of the Madri+d Knowledge Foundation, Jesús Sánchez Martos, visited the CNIC to learn first-hand about its main lines of research and explore new ways to collaborate.

The Japanese Agency for Research and Medical Development at the CNIC

The CNIC hosted this visit from the President of the Japanese Agency for Research and Medical Development (AMED), Mr. Makoto Suematsu, the Managing Director of the Foreign Affairs Department, Mr. Masahiko Noda, and the First Secretary - Aggregate of Science and Technology – of the Japanese Embassy in Spain, Mr. Masahiro Aoki. AMED is the government agency responsible for improving medicine through research and development in Japan.



Visit of the European Commission Health and Food Safety Commissioner

The European Commission Health and Food Safety Commissioner, Vytenis Andriukaitis, visited the CNIC, accompanied by Spanish Health Minister Dolors Montserrat, Secretary of State for Research Carmen Vela, Food Safety Agency Director Teresa Robledo, *Carlos III* Institute of Health Director Jesús Fernández Crespo, CNIC Manager Alberto Sanz, and CNIC Clinical and Basic Research Directors Borja Ibáñez and Vicente Andrés.

A benefactor names the CNIC his sole heir

An anonymous citizen has named the CNIC as his sole beneficiary, donating all his assets to the CNIC in his will. Altruistic acts of this kind are less common in Spain than in English-speaking countries, where there is a more established tradition of charitable donation. The unnamed benefactor in this case is a person with a deep respect for the work of Spanish scientists as well as close personal experience of the world of health care, having witnessed the day-to-day operation of hospitals and seen the need to continually equip medicine with new advances through research. For this generous benefactor, the CNIC is a clear example of this commitment to translating research into improvements in health, and for this reason deserved special consideration.

REACHING THE PATIENT

Fuster Polypill

The first polypill approved in Europe for secondary cardiovascular prevention was developed by CNIC researchers in collaboration with the pharmaceutical company Ferrer. Marketed under the name Trinomia, this polypill has been commercialized in 55 markets in Europe and Latin America after gaining the approval of the European Medicines Agency and national agencies. Trinomia includes three active ingredients: the antiplatelet drug aspirin to prevent the formation of thrombi, the statin atorvastatin to control cholesterol levels and stabilize atherosclerotic plaques, and the ACE inhibitor ramipril, which regulates blood pressure and prevents remodeling of the heart after a heart attack. Since September 2017, Trinomia is available in with a 40 milligram dose of atorvastatin, double the previous 20 milligram dose available since January 2015. Trinomia is given to patients who have had a cardiovascular event and require treatment to reduce the risk of recurrence. This product of public-private collaboration between the CNIC and Ferrer is an example of how Spain can be a world leader in innovation.

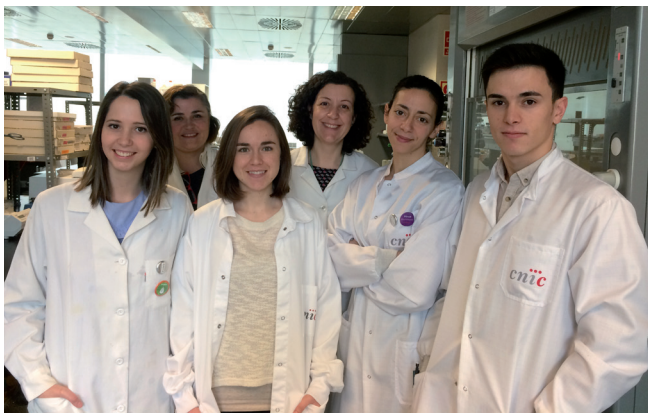
Ultrafast magnetic resonance

The collaboration agreement between the CNIC and its technological partner Philips gives the Center access to the most advanced cardiovascular imaging technology across the spectrum from ultrasound, through hybrid equipment and CAT scans, to MRI. Through this agreement, the aim is to achieve advances in the prevention, diagnosis, and treatment of cardiovascular disease, using technology that Philips continuously updates as

technological advances are made. This partnership has produced the Philips-CNIC VF-3DESSOS joint patent for cardiac MRI. MRI is the best technique for observing heart function and anatomy, but it is a technically complicated procedure with examination times of over 30 minutes. The new Philips-CNIC VF-3DESSOS process shortens scan times to under 1 minute, a milestone in cardiac imaging.

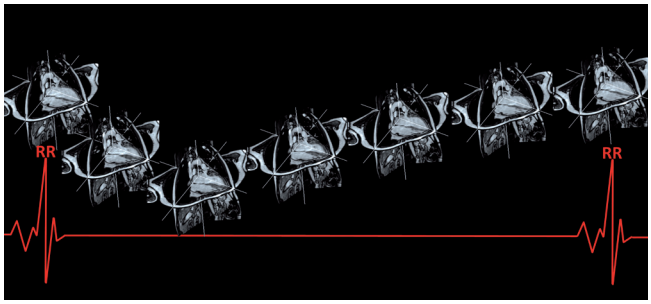
Myocarditis biomarker

Over more than 10 years of work, Pilar Martín Fernández's group has discovered, validated, and now patented a biomarker for the diagnosis of acute myocarditis. Negotiations are underway for the joint development and licensing of the CNIC patent to a venture capital company for the development of a biosensor able to detect the biomarker in patient blood samples in only 30 minutes. This technology promises to be an essential clinical tool for the differential diagnosis of acute myocarditis and MI; these conditions often have a similar presentation and it can be very difficult to distinguish between them. Initial results with the biosensor are positive.



Treatment and diagnosis of thoracic aortic aneurysm (TAA)

Juan Miguel Redondo's group has discovered a method for the prevention or treatment of thoracic aortic aneurysm (TAA). The treatment involves blockade of a newly identified target of the nitric oxide (NO)-methalloproteinase pathway. The discovery also provides an *in vitro* method in which specific biomarkers are used to identify patients at risk of developing TAA. This method involves measuring the expression pattern or level of specific NO-metalloproteinase-pathway components and substrates. The patent also refers to screening methods for identifying compounds useful for TAA treatment, prevention, or inhibition. These new methods are applicable to many diseases: (i) bicuspid aortic valve disease; (ii) syndromic TAAs, such as Marfan syndrome (MFS), vascular Ehlers Danlos, Loeys Dietz Syndrome (Types 1 and 2), and Familial TAA and dissection (familial TAAD); (iii) nonsyndromic TAA; or (iv) any other disease associated with an aortopathy triggered by the metalloproteinase deficiency described in the invention. These findings represent a substantial advance in the understanding of the pathogenesis and molecular mediators underlying aortic diseases.



CNIC study findings inform clinical practice guidelines

The European Society of Cardiology (ESC) publishes concise documents on specific cardiovascular conditions that summarize treatment recommendations based on the latest robust clinical research evidence. These clinical practice guidelines have a massive international impact, since they are used to guide therapy implementation. Two studies undertaken at the CNIC have been included in recent ESC clinical practice guidelines. The *FOCUS trial,* testing the *Fuster Polypill* for treatment adherence in secondary prevention, is featured in the *2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice, while the METOCARD-CNIC trial,* testing the infarct-limiting effect of early i.v. metoprolol in patients having a heart attack, is included in the *2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation.* The 2016 prevention guidelines also cite the PESA study, and the 2017 ESC MI guidelines cite a total of eight CNIC studies.

CNIC investigators participate in 2017 ESC clinical practice guidelines

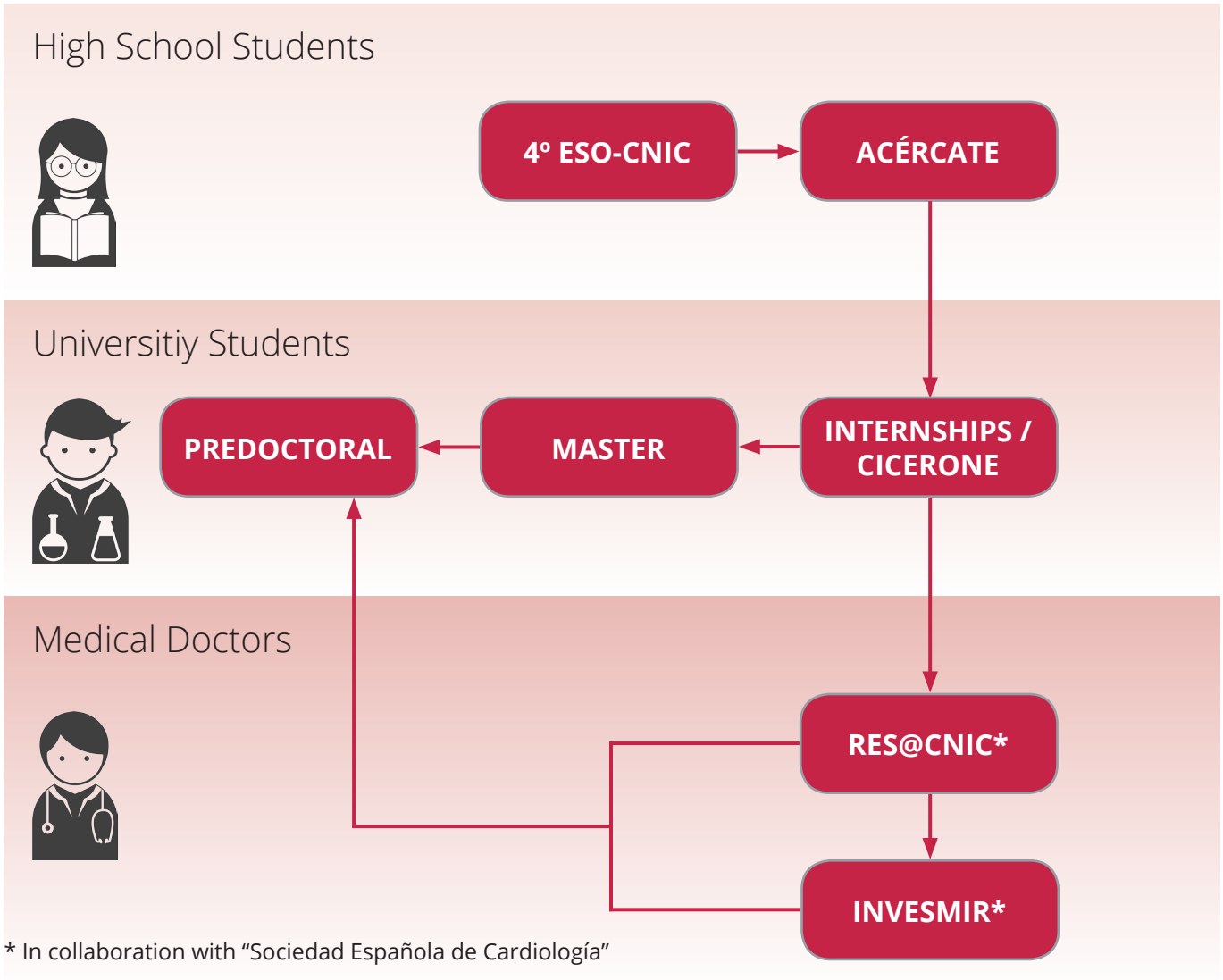
CNIC researchers made important contributions to two ESC clinical practice guidelines released in 2017. CNIC Clinical Research Director Borja Ibáñez served as Chairman on the ESC task force for the 2017 ESC MI guidelines, while Hector Bueno served as a member on the same task force as well as the task force for the *2017 Focused update on Dual Antiplatelet Therapy (DAPT).*

Members of the ESC Task Force for the 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation at the CNIC entrance during the task-force kick-off meeting.

5. Training programs and continuing education

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 excellent researchers in the field of cardiovascular research."

In 2017, 645 participants were enrolled on CNIC training programs and continuing education courses.



* In collaboration with "Sociedad Española de Cardiología"

Programs for high school students

'ACÉRCATE': Grade A+ science students train at the CNIC

The ACÉRCATE Program offers the highest-achieving senior high school students in the natural and health sciences the chance to experience life as a biomedical researcher, with the aim of awakening and strengthening interest in a biomedical research career.

Participants spend two weeks at the CNIC, learning modern techniques used in biomedical research, conducting supervised experiments, operating sophisticated scientific equipment and presenting the results of their work, all under the supervision of CNIC researchers.

Fellowships in 2017: 8

The CNIC collaborates with Community of Madrid high schools in the following training programs:

- **4ºESO-CNIC**
  Five life-science students spent from 3 to 5 days exploring possible scientific careers.
- **Practical experience for Technical School students**
  This program brought ten technical school students studying "Anatomy Pathology and cytological diagnosis" and "Image for Diagnosis and Nuclear medicine" to gain practical experience in the CNIC's laboratories.

Programs for undergraduate students

Internships are offered to university students in the following programs:

Cicerone Program

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

Fellowships in 2017: 30

Curricular and Extracurricular University Practical Program

The CNIC offers practical training in cardiovascular research to visiting undergraduate and postgraduate students, including those on Erasmus internships, completing their Trabajo Fin de Grado (TFG, degree dissertation), Trabajo Fin de Máster (TFM, master's dissertation).

Internships in 2017: 82

Programs for graduate students

- **CNIC Master's Fellowship Program**
- **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 conduct their experimental project in a CNIC laboratory.

Fellowships in 2017: 15

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 2017: 19

Graduate students studying for a PhD degree at the CNIC in 2017: 89 (14% foreigners)

Insights into Research in Cardiovascular Disease Masters 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 at this course are enrolled UAM Master's students, CNIC predoctoral researchers, and participants on the Res@CNIC SEC Program (see below).

Students in 2017: 15

Programs for MDs in collaboration with the Spanish Society of Cardiology (SEC)

RES@CNIC Program
The Res@CNIC SEC Program 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 National Health System centers in partnership with CNIC scientists.

Participants in 2017: 20

INVESMIR SEC Program
The INVESMIR 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.

Fellowships in 2017: 2

SEC-CNIC CARDIOJOVEN Program
The aim of this Program is to foster high-quality translational research in the cardiovascular area in Spanish National Health System centers through training programs providing theory or practical training for cardiologists with a research vocation.

Specific aims:

a) To create the figure of the cardiologist-researcher 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).

Candidates receiving awards 2017: 1

CNIC Continuing Education Program

Cardiovascular Pathophysiology Course: From Symptoms to Genes

The two-day Carciovascular Pathophysiology Course is organized in partnership with the *Sociedad Española de Cardiología.* This course offers resident cardiology interns a translational vision of cardiology by introducing them to the study of pathophysiology and basic research. The 90 participants received an overview of the molecular and genetic factors that underlie cardiac diseases and gain an up-to-date vision of cardiac physiology.

Venue: CNIC Auditorium

Vascular Biology Course

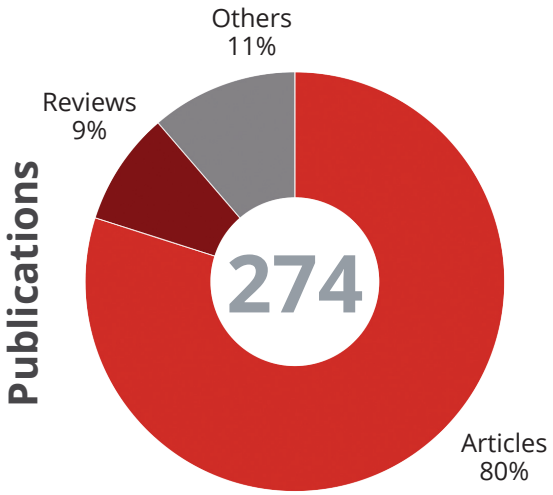
Valentín Fuster delivers this lecture series on *Molecular, Clinical and Population Bases of Cardiovascular Disease and Health* as part of the Universidad Internacional Menéndez Pelayo (UIMP) summer program, sponsored by Ferrer International.

Valentín Fuster tries to "motivate and teach for the future" more than 280 attendees. Most of the attendees are cardiologists, although others are experts in internal medicine or other specialties. In 2017, delegates came from more than 15 countries, most of them in Latin America and Europe.

Venue: V. Fuster Auditorium, Cardona (Barcelona, Spain)

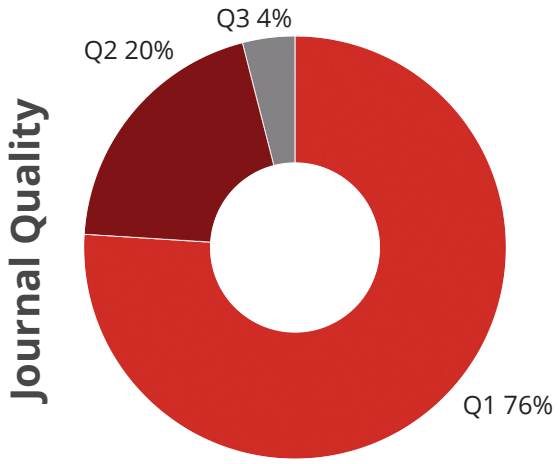
6. Facts and figures

SCIENTIFIC PUBLICATIONS*



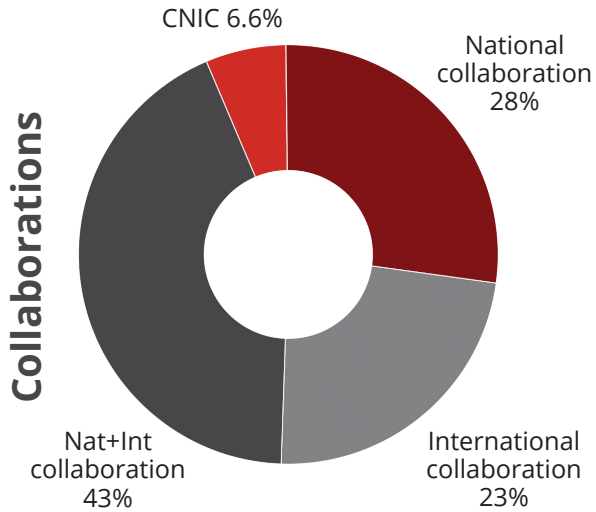
54% CNIC-LED PUBLICATIONS

37% GOLDEN OPEN ACCESS PUBLICATIONS



76 PUBLICATIONS IN TOP JOURNALS (IF>10)

87 PUBLICATIONS IN JOURNALS IN JCR TOP 5
(The five journals with highest IF of their category)



53% COLLABORATION WITH HOSPITALS

85% COLLABORATION WITH UNIVERSITIES

* Complete publication list at 31/12/2017
(https://www.cnic.es/en/investigacion/publicaciones/resultados?y=2017)

COMPETITIVE FUNDING AND PATENTS*

New grants

NATIONAL

55 GRANTS

€ 4 728 100

INTERNATIONAL

12 GRANTS

€ 4 749 008

Patents

7 PATENT APPLICATIONS

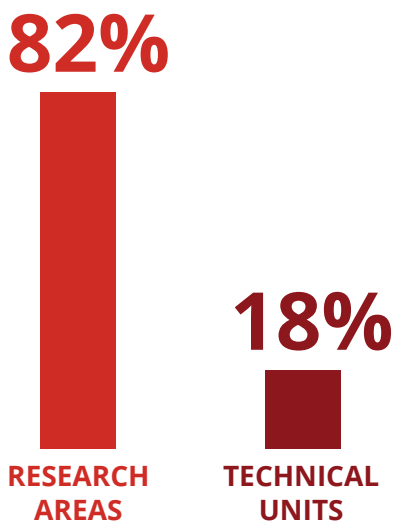
2 NEW PRIVATE-PUBLIC COLLABORATION AGREEMENTS WITH INDUSTRY

HUMAN RESOURCES*

Scientific Staff **383**

60.5% WOMEN

39.5% MEN



GROUP LEADERS **31**

25.8% CARDIOLOGISTS

14.5% OF THE SCIENTIFIC STAFF ARE FROM OUTSIDE SPAIN
(22 countries, with the highest numbers of staff coming from Italy, Greece, and Portugal)

8.6% OF VISITING SCIENTISTS COME FROM OUTSIDE SPAIN
(7 countries, including Switzerland, Italy, USA and the Netherlands)

* All data from 31/12/2017

7. Acknowledgments

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* All data refers to 31/12/2017

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Sociedad Española de Cardiología
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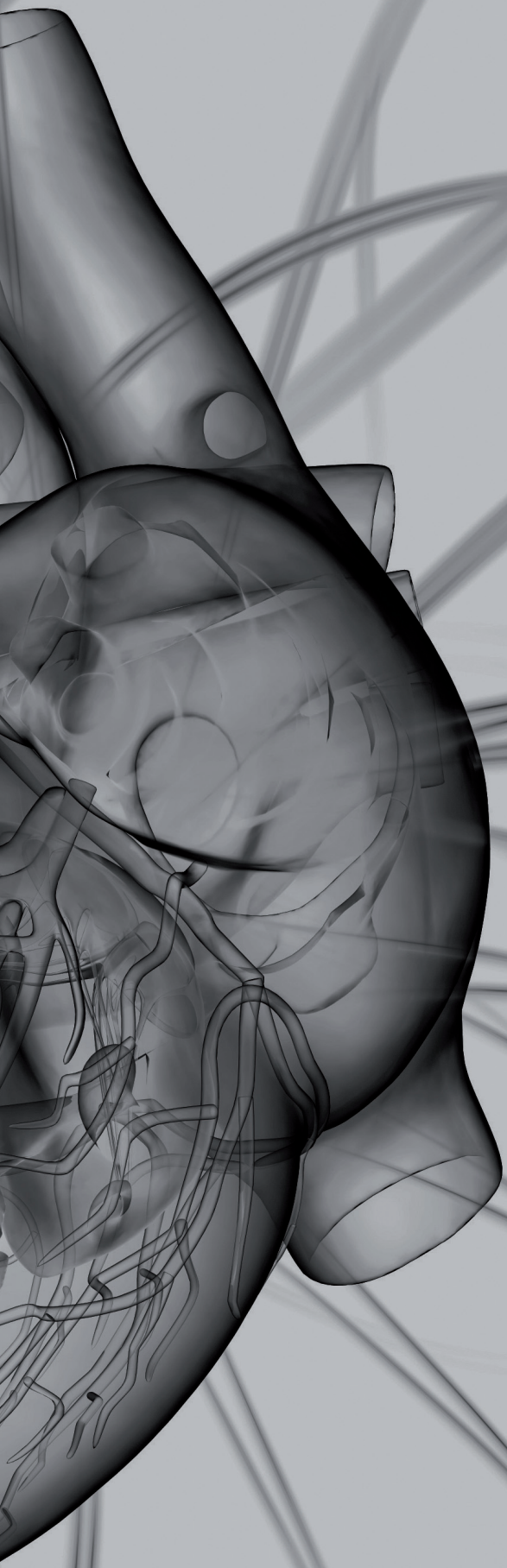
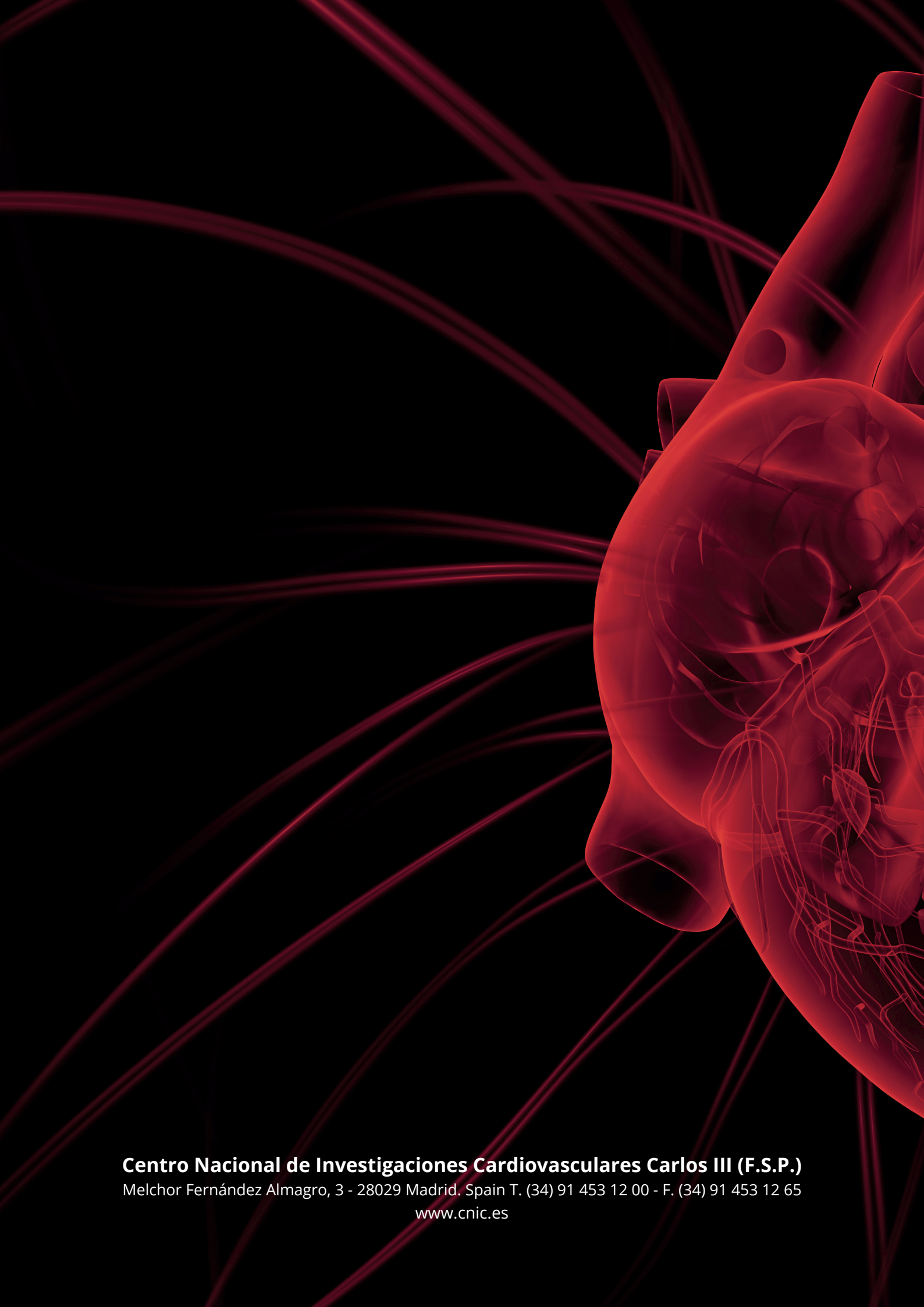
The Marfan Foundation





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