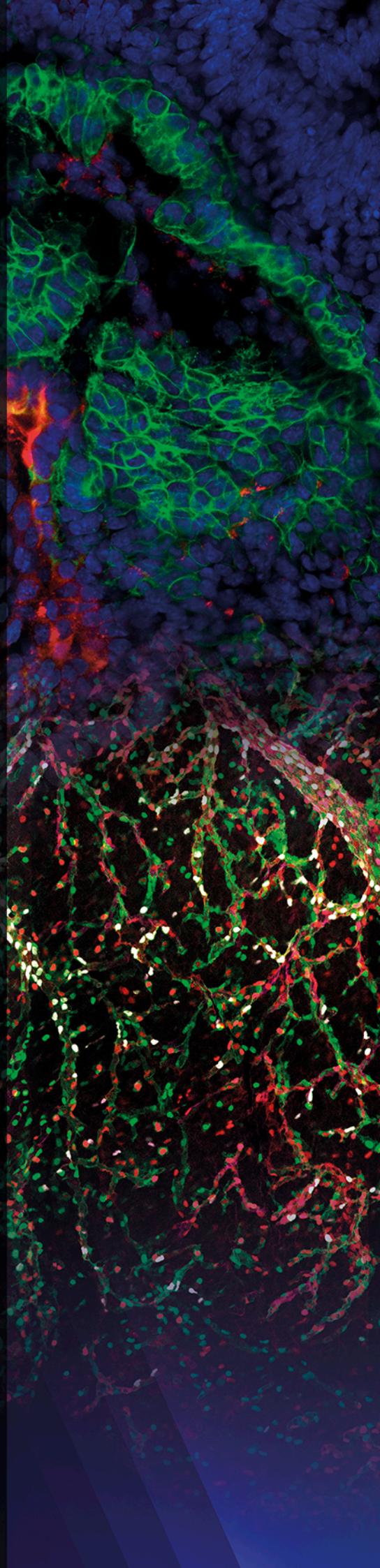




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2018

SCIENTIFIC REPORT



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**SCIENTIFIC REPORT 2018**



Fundación *procnic* EXCELENCIA  
SEVERO OCHOA

# Fundación proCnic



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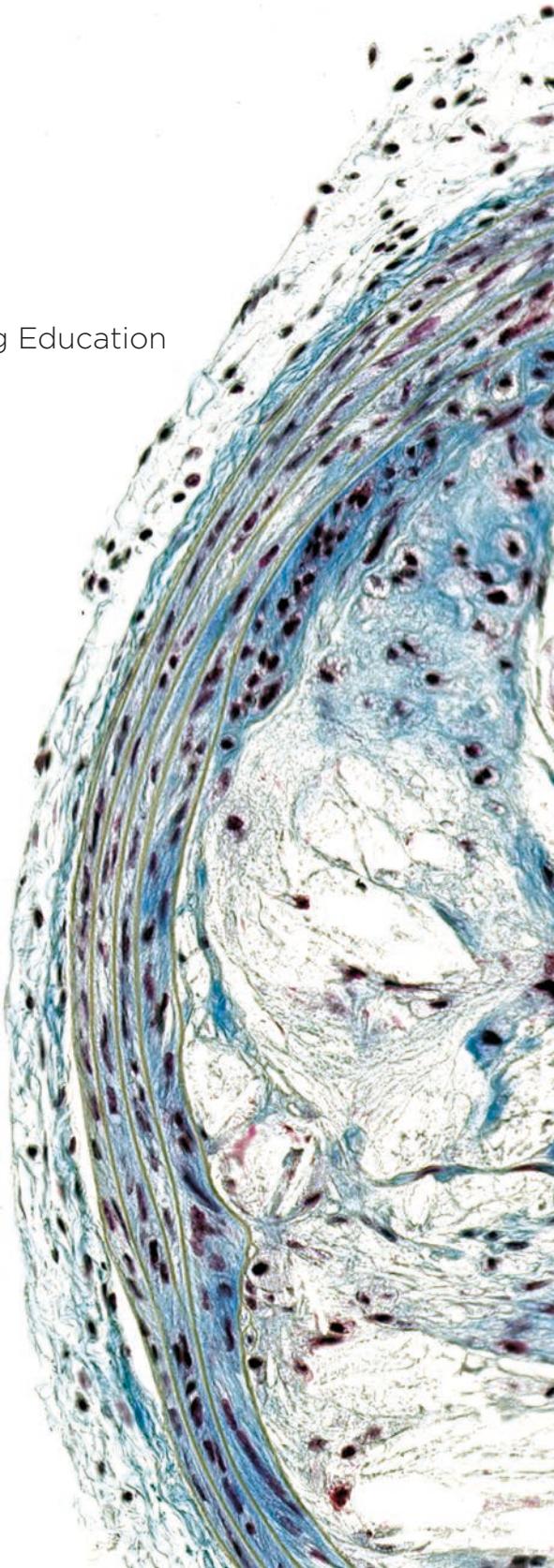
Telefónica

The Pro CNIC Foundation brings together 13 of the most important Spanish companies and foundations: Acciona, Santander Bank, BBVA, Endesa, the Mapfre Foundation, the Mutua Madrileña Foundation, the Ramón Areces Foundation, the Repsol Foundation, Naturgy, Inditex, la Caixa, Prisa, and Telefónica.

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

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# 1 Foreword and CNIC mission



**Vicente Andrés**  
*Basic Research Director*



**Valentín Fuster**  
*General Director*



**Borja Ibáñez**  
*Clinical Research Director*

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 many disciplines and includes population and patient studies.

A key factor in this achievement is the commitment of the Spanish government to building a flagship research institute to tackle the CVD epidemic. But 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 a modern infrastructure of technical units and support services.

Most importantly, the CNIC is supported through an innovative public-private initiative financed by the Instituto de Salud Carlos III and the Pro CNIC Foundation. In 2018, the Pro CNIC Foundation renewed its commitment to the CNIC for a further

10 years. The CNIC has been a Severo Ochoa Center of Excellence program since the inaugural awards in 2012. The most recent award was mainly used to fund seven intramural projects in a competitive call aimed at fostering collaborative projects between basic and clinical research groups. The CNIC is also a member of the alliance of Severo Ochoa Centers and María de Maeztu Units (SOMMA).

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 performance of the Center and its group leaders. In 2018, José Javier Fuster and Carlos Pérez Medina joined the Center as Assistant Professor and Assistant Health Scientist, respectively.



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. To support its clinical research activity, in 2018 the CNIC established the Clinical Trials Coordination Unit (UCEC); in addition to supervising clinical trials, the UCEC also organizes clinical research with medicines and healthcare products.

This report offers an overview of how our 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 from work showing ways to control the damage caused by the immunoinflammatory response to the discovery of the cause of accelerated atherosclerosis and premature death in progeria.

The impressive collection of high-impact publications in 2018 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 is making essential contributions to advancing the use of noninvasive imaging technology for diagnosis and research. The CNIC's commitment to public health promotion is also evident in educational programs that start with children from an 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 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.

## 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. The core technical units hosted by each Area support the work of all CNIC scientists.

### Cell & Developmental Biology

*Coordinator: Miguel Ángel del Pozo*

The Cell and Developmental Biology (CDB) Area comprises nine research groups and three technical units devoted to basic studies and their translational projection in vascular development, homeostasis, and disease. Some groups seek to understand how the spatiotemporal regulation of genome architecture and expression determine cell decisions in the early embryo and heart development, contributing to the advance of cardiovascular (CV) regenerative medicine. Other groups investigate cell and tissue mechanisms that determine CV function, such as angiogenesis, inflammation, and repair, and explore principles controlling the mechanical function and adaptability of the CV system. This research line 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 Area's three core technical units provide support on state-of-the-art visualization techniques and develop solutions covering different scales and biological processes. The Microscopy Unit offers advanced confocal, multiphoton, and super-resolution imaging technologies, together with approaches for quantitative biology. The Cellomics Unit provides cytometry and separation services (including state-of-the-art spectral cytometry), as well as a high-content functional genomics screening platform. Both units provide support for tailored image analysis and data processing. The Advanced Imaging Unit offers a portfolio of cutting-edge preclinical imaging services for small animals (ultrasound, magnetic resonance, PET/CT, optical imaging, and radiochemistry). The unit provides support to the center's research groups in the assessment of various animal models and performs its own technical

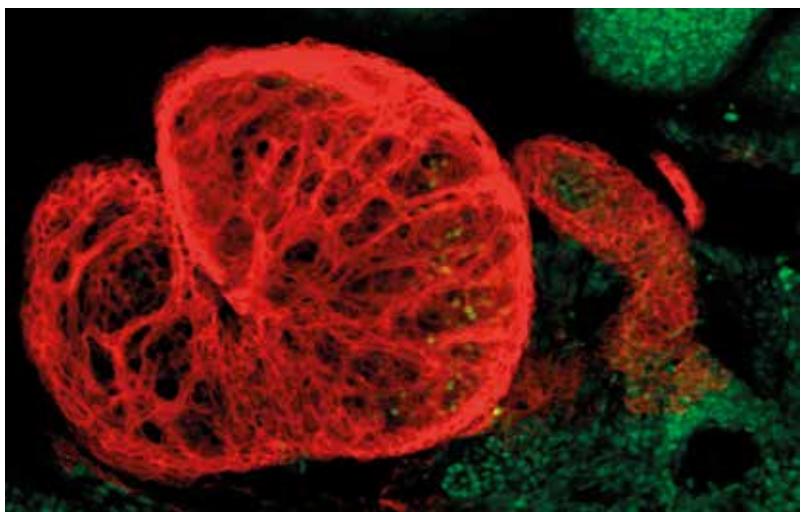
research on advanced molecular imaging techniques. Since June 2018, the Advanced Imaging Unit holds the ISO 9001:2015 quality certificate.

#### RESEARCH GROUPS

Jorge Alegre-Cebollada  
Rui Benedito  
Héctor Bueno  
Miguel Ángel del Pozo  
Andrés Hidalgo  
Miguel Manzanares  
Nadia Mercader  
Carlos Pérez Medina  
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, the 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 areas produced several significant advances in 2018. 1) We identified how p38 $\alpha$  deficiency in adipose tissue protects against high-fat diet (HFD)-induced obesity by increasing thermogenesis in brown adipose tissue. 2) New findings show that dendritic cells regulate neutrophil infiltration during inflammation, which is associated with heart failure. 3) Analysis of animal models with genome-wide techniques such as RNA-seq, ChIP-seq, and ATAC-seq revealed how nuclear receptors integrate transcription and epigenetics to regulate the function of macrophages and cardiomyocytes. 4) Work continued on the definition of new targets for the treatment of heart failure. 5) *In vivo* approaches were developed to optically map complex arrhythmias in the beating heart, promising to bring about a new era of high-performance mapping in clinical and translational cardiac electrophysiology. 6) A role

was demonstrated for mitochondria in triggering pulmonary hypertension with heart right ventricle failure. 7) Kinase modulators and next generation gene-therapy vectors were used to develop therapies for complex cardiomyopathies for which no treatment currently exists. 8) Intra-cardiomyocyte edema was identified by *in vivo* magnetic resonance imaging as the earliest marker of cardiac toxicity caused by anthracyclin treatment. 9) Another study showed that cardiotoxicity can be prevented or treated by therapeutic strategies targeting mitochondria.

The Area's core technical units support the work of all CNIC scientists in transgenesis, pluripotent cell technology, viral vectors, and comparative medicine, which supports *in vivo* work in the animal facility. The Transgenesis Unit is using and refining the CRISPR/Cas9 gene-editing system and microinjection of a single blastomere into a two-cell mouse embryo. The new Clinical Trials Coordination Unit began its activity in 2018, coordinating the CNIC's mission to boost Spanish leadership in clinical trials in the cardiovascular area.

### RESEARCH GROUPS

Juan A. 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  
Clinical Trials Coordination

## Vascular Pathophysiology

**Coordinator:** Almudena R. Ramiro

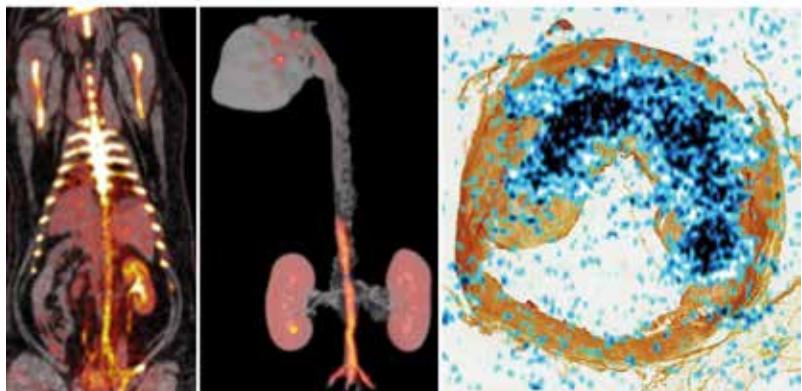
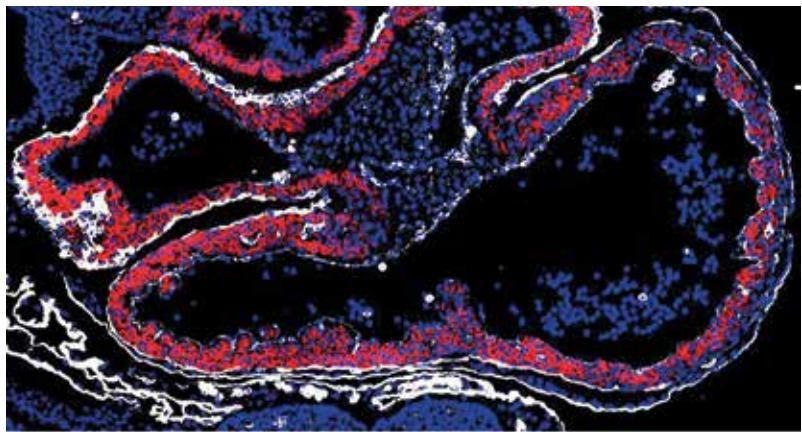
In the Vascular Pathophysiology Area, we focus on the biology of the vascular system in health and disease, making use of multidisciplinary approaches that include molecular and cellular biology, animal systems to model disease, and translational and clinical approaches. Our research covers the signaling pathways that regulate cardiovascular development and disease and age-associated alterations of muscle cells that could account for the decline in tissue regeneration with age. The Area also conducts translational research into atherosclerosis, the main underlying cause of heart attack and stroke. We are interested in dissecting the regulatory pathways involved in vessel wall and cardiac remodeling and the contribution of aging to these events. We also investigate the role of smooth muscle cells and the interplay between the hematopoietic and cardiovascular systems during atherosclerosis development, with a focus on using new animal models to achieve early diagnosis and develop new therapeutic avenues. We have developed state-of-the-art imaging technologies to perform population studies on preclinical atherosclerosis. In combination with deep proteomic analysis, this research line will open up new diagnostic and prognostic avenues. Finally, we investigate the immune and inflammatory component of cardiovascular disease, including the role of the antibody immune response in atherosclerosis, the mechanisms of intercellular communication between immune cells, and the role of T cell and immunomodulatory molecules in the development of myocarditis. The Vascular Pathophysiology Area hosts three technical units: Genomics, Proteomics/Metabolomics, and Bioinformatics. These units provide state-of-the-art technology to CNIC scientists while actively participating in the Area's research projects.

### RESEARCH GROUPS

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

### TECHNICAL UNITS

Genomics  
Proteomics / Metabolomics  
Bioinformatics



## Selected Clinical Studies

### PESA-CNIC-Santander study

The PESA-CNIC-Santander study is a long-term endeavor carried out by the CNIC in collaboration with Santander Bank. This study aims to identify the presence of atherosclerosis long before symptoms appear and to understand the cues leading to its development and progression. The study, led by CNIC General Director Valentin Fuster, launched in 2010 and enrolled 4200 asymptomatic individuals between the ages of 40 and 55. Participants undergo serial (every 3 years) imaging and analytical tests, including 3D vascular ultrasound of the carotid arteries, aorta, and iliofemoral arteries to detect atherosclerotic plaques, coronary artery calcium quantification by computed tomography, and biosampling for omics analysis. A subset of 800 participants showing signs of disease are undergoing vascular <sup>18</sup>FDG PET/MR and cardiac MR. In 2019, the third (6-year) visit will be completed for the full cohort. Several CNIC clinical and basic research groups participate in PESA, which is the Center's flagship study. The PESA-CNIC-Santander study is already making seminal contributions to our understanding of the origin and progression of atherosclerosis.

### SECURE trial

Adherence to treatment after an acute myocardial infarction (MI) is essential for efficient secondary prevention. Despite this, many post-MI patients abandon prescribed medication. To address this issue, CNIC researchers and FERRER laboratories developed a "polypill" including three key drugs prescribed to post-MI patients (aspirin, an ACE-inhibitor, and a statin). Having demonstrated that prescription of the CNIC Polypill significantly increases treatment adherence among post-MI patients (J Am Coll Cardiol. 2014;64:2071-82), CNIC researchers are now leading a multinational randomized clinical trial supported by the H2020 program. The ongoing SECURE trial (trial identifier NCT02596126) will enroll >3000 patients soon after an MI and randomize them to standard treatment or a CNIC Polypill-based strategy. Patients will be followed-up for a minimum of 2 years, and the incidence of major cardiovascular events will be assessed. Trial enrolment will be completed in the third quarter of 2019.

### REBOOT trial

The prescription of beta-blockers to patients after an MI is based on evidence from trials performed in the pre-reperfusion era. While there is solid evidence for their benefit in post-MI patients with reduced ejection fraction, such evidence is lacking for patients with preserved ejection fraction. Despite this, more than 80% of post-MI patients in this category are prescribed beta-blockers for the rest of their lives. REBOOT (tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion) is a multinational trial that will enroll 8600 post-MI patients with a left ventricular ejection fraction above 40%. Patients will be randomized to beta-blocker therapy (type and dose decided by the attending physician) or to no treatment. The primary endpoint is the composite of all-cause death, reinfarction, or heart failure admission during 3-year follow-up. This trial is coordinated by the CNIC Clinical Trials Coordination Unit and is run in close collaboration with the Mario Negri Institute of Research in Milan. More than 50 hospitals in Spain and more than 20 in Italy participate in this large-scale project that will have a major impact on clinical practice. The first patients were enrolled in October 2018.

### H2H study

There is increasing awareness of the association between atherosclerosis and cognitive function, but the mechanisms linking these processes are not fully understood. The Heart-to-Head (H2H) study 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 and is led by CNIC General Director Valentin Fuster. In Spain, the H2H project is coordinated between the CNIC and 12 de Octubre Hospital. Other university hospitals (Fundación Jiménez Díaz, Clínico San Carlos, and Gregorio Marañón) participate in the project, which receives funding from the Carlos III Institute of Health through the Proyecto Integrado de Excelencia program. A total of 300 participants are undergoing extensive atherosclerosis phenotyping (multi-territory 3D vascular ultrasound and cardiac computed

tomography) and thorough brain imaging (anatomical and functional magnetic resonance imaging and positron emission tomography (PET)-amyloid scan), as well as cognitive function testing. Enrollment will be completed in the second quarter of 2019.

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

Cardiac magnetic resonance (CMR) imaging is the gold standard for the analysis of heart anatomy, function, and tissue composition. Universal implementation of this technique is impeded by the time required to perform a complete cardiac scan (around 45 minutes). Researchers from the CNIC and 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 experimental animal models and in a pilot clinical experiment. The sequence will next be tested in a scanner outside the CNIC through a scientific agreement between the CNIC and the Instituto de Investigación Sanitaria Fundación Jiménez Díaz. After this, the trial will be expanded to include clinical scanners with differing field strengths at other participating hospitals.

### **SPHERE-HF trial**

Pulmonary hypertension (PH) secondary to left heart disease (group 2) is the most common form of PH. In research addressing the lack of therapies for this disease, CNIC researchers identified the  $\beta_3$  adrenergic receptor as a novel target in a large animal model (Basic Res Cardiol. 2016;111:49). The CNIC is leading a phase 2 clinical trial in which patients with group 2 PH are randomized to standard therapy vs. standard therapy plus a  $\beta_3$ -selective agonist (trial identifier NCT02775539). A total of 80 patients are being recruited at four Spanish hospitals and will be studied under treatment for four months. The main study endpoints are pulmonary artery hemodynamics and CMR parameters. More than 50% of the study population was recruited by the end of 2018.

### **Translation of CNIC studies into clinical practice guidelines.**

The European Society of Cardiology (ESC) produces concise guideline documents for specific cardiovascular conditions that present up-to-date treatment recommendations based on robust clinical research evidence. The international impact of these clinical practice guidelines is huge, with therapies being implemented on the basis of these documents. Recent ESC clinical practice guidelines have included recommendations based on two CNIC studies. The FOCUS trial, testing the effect of the CNIC polypill on treatment adherence in secondary prevention, features in the 2016 Cardiovascular Disease Prevention in Clinical Practice guidelines, and the METOCARD-CNIC trial, testing the infarct-limiting effect of early i.v. metoprolol in patients having an acute myocardial infarction, features in the 2017 Guidelines for the Treatment of Acute Myocardial Infarction. The 2016 cardiovascular prevention guidelines also reference the PESA study, and the recent ESC myocardial infarction guidelines cite a total of eight CNIC studies.

The large ongoing CNIC-led clinical trials SECURE and REBOOT will have an impact on clinical practice guidelines in the coming years.



## 3 Scientific Highlights: by publication date

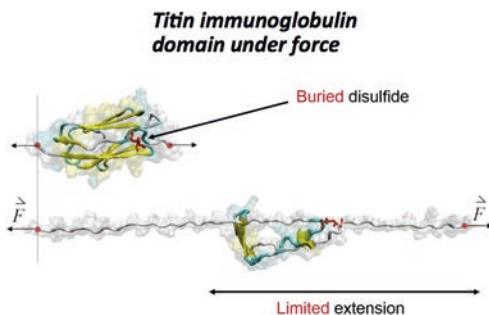
### 1. Nature Communications

**Scientists identify a key mechanism regulating a protein required for muscle and heart function**



Scientists at the CNIC and Columbia University in New York have discovered an important mechanism in the regulation of a protein that plays an essential role in the function of skeletal muscle and the heart. The study, published in *Nature Communications* and coordinated by CNIC researcher Jorge Alegre-Cebollada, describes a new mechanism in the regulation of the elasticity of the giant protein titin. Titin, explained Alegre-Cebollada, is a key protein in the functioning of striated muscles throughout the body, particularly in the heart: “the proof of this is that mutations in the titin gene are a common cause of diseases affecting the muscles of the body and the heart.”

*Giganti D, Yan K, Badilla CL, Fernandez JM, Alegre-Cebollada J. Disulfide isomerization reactions in titin immunoglobulin domains enable a mode of protein elasticity. Nat Commun. 2018;9(1):185. doi: 10.1038/s41467-017-02528-7*

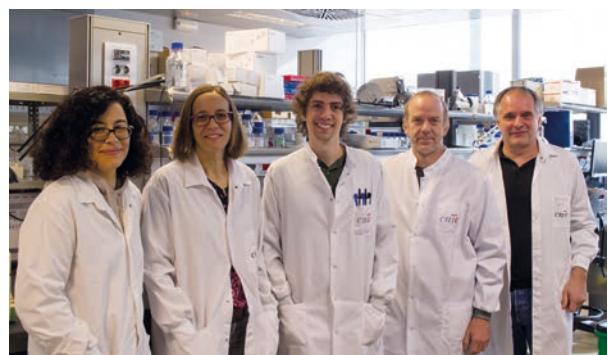


### 2. Journal of Experimental Medicine

**CNIC scientists produce an atlas of genes mutated by an immune-system protein and linked to lymphoma**

Researchers at the CNIC have identified the largest collection to date of genes mutated by AID, a key protein in the immune response. The study reveals a new link between the mutagenic activity of AID and the generation of lymphomas. The information obtained, published in the *Journal of Experimental Medicine*, will increase understanding of the molecular mechanisms that control the activity of this enzyme and its possible contribution to the development of cancer. The research team led by Almudena Ramiro has compiled an atlas of the mutations that accumulate in the DNA of B lymphocytes during the immune response.

*Álvarez-Prado ÁF, Pérez-Durán P, Pérez-García A, Benguria A, Torroja C, de Yébenes VG, Ramiro AR. A broad atlas of somatic hypermutation allows prediction of activation-induced deaminase targets. J Exp Med. 2018;215(3):761-71. doi: 10.1084/jem.20171738*



### 3. Journal of the American College of Cardiology An enzyme variant reduces cardiac hypertrophy and improves heart function



Scientists at the CNIC have identified a variant of the enzyme calcineurin, called CnA $\beta$ 1, whose action reduces cardiac hypertrophy and improves heart function. The results of the study, published in the Journal of the American College of Cardiology (JACC), are the first to identify the beneficial effects of a CnA $\beta$ 1-induced metabolic pathway in the hypertrophic heart, and may open the path to new treatment strategies. The findings also show how alternative forms of the same protein, produced from the same gene, can have opposite effects on a biological or pathological process.

The study was led by CNIC scientist Enrique Lara, with group members Laura Padrón, María Villalba, and Jesús Gómez Salinero as joint first authors. The research was carried out through collaboration with Jose Antonio Enríquez and Jesús Vázquez at the CNIC and Pablo García-Pavía of Puerta de Hierro University Hospital in Majadahonda, Madrid.

*Padrón-Barthe L, Villalba-Orero M, Gómez-Salinero JM, Acín-Pérez R, Cogliati S, López-Olañeta M, Ortiz-Sánchez P, Bonzón-Kulichenko E, Vázquez J, García-Pavía P, Rosenthal N, Enríquez JA, Lara-Pezzi E. Activation of Serine One-Carbon Metabolism by Calcineurin Abeta1 Reduces Myocardial Hypertrophy and Improves Ventricular Function. J Am Coll Cardiol. 2018;71(6):654-67. doi: 10.1016/j.jacc.2017.11.067*

### 4. Nature Communications CNIC scientists describe a mechanism of heart regeneration in the zebrafish

Some animals, including the zebrafish, have a high capacity to regenerate tissues, allowing them to recover fully after cardiac injury. During this process, the heart muscle cells divide to replace the damaged tissue. However, there has been uncertainty about whether all cells contribute equally to the reconstruction of the heart wall. Now, a team of scientists led by Nadia Mercader at the CNIC and the University of Bern (Switzerland), working with collaborators at the University of Zurich (Switzerland), have discovered a high level of plasticity among the cells of the zebrafish heart muscle. The study is published in *Nature Communications*.



After a heart attack, the human heart loses millions of cardiomyocytes, the cells that form the muscle wall. In contrast, other animal species have a high regenerative capacity, enabling them to replace the injured myocardium with new cardiomyocytes. One such species is the zebrafish (*Danio rerio*). According to first author Héctor Sánchez-Iranzo, the zebrafish "is a widely used model system in cardiovascular research into the mechanisms controlling regeneration, and an inspiration for attempts to develop future regenerative therapies."

Sánchez-Iranzo H, Galardi-Castilla M, Minguillón C, Sanz-Morejón A, González-Rosa JM, Felker A, Ernst A, Guzmán-Martínez G, Mosimann C, Mercader N. *Tbx5a lineage tracing shows cardiomyocyte plasticity during zebrafish heart regeneration.* Nat Commun. 2018;9(1):428. doi: 10.1038/s41467-017-02650-6

## 5. Nature Communications

### Blocking a protein could improve the effectiveness of intravascular cellular ‘policing’



Researchers at the CNIC, led by Alicia G. Arroyo, have identified a function of a protease that could be targeted for the treatment of some infections and even tumor metastasis. The study shows that blockade of the protease MT4-MMP increases the surveillance activity of a type of white blood cell in the circulation, the blood-patrolling monocytes. These cells act like ‘police patrols’ to detect foreign or undesired material in the blood. The findings, indicated Alicia G Arroyo, “have possible clinical implications and could contribute to strategies to eliminate foreign or undesired materials from the blood, such as infectious agents or tumor cells.” The study thus “suggests new strategies to combat infection or prevent metastasis, which are currently being evaluated for patent protection.”

Clemente C, Rius C, Alonso-Herranz L, Martín-Alonso M, Pollán Á, Camafeita E, Martínez F, Mota RA, Núñez V, Rodríguez C, Seiki M, Martínez-González J, Andrés V, Ricote M, Arroyo AG. *MT4-MMP deficiency increases patrolling monocyte recruitment to early lesions and accelerates atherosclerosis.* Nat Commun. 2018;9(1):910. doi: 10.1038/s41467-018-03351-4

## 6. Circulation Scientists discover the cause of accelerated atherosclerosis and premature death in progeria

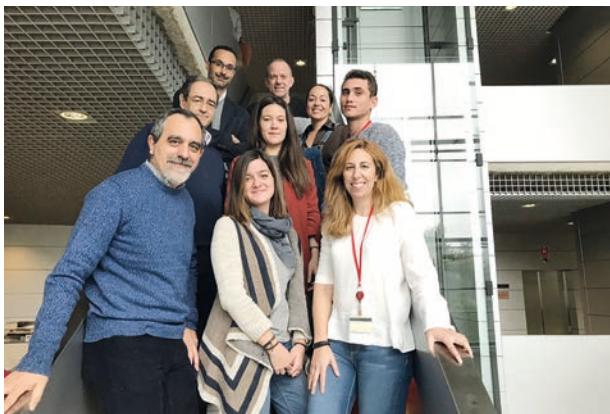
Scientists at the CNIC and the CIBER de Enfermedades Cardiovasculares (CIBERCV), led by Vicente Andrés, have generated the first genetically modified mice with accelerated atherosclerosis induced by the protein progerin, which causes the development of HGPS. The research team found that the main cause of accelerated atherosclerosis and premature death in these mice was alterations in the smooth muscle cells lining the blood vessels. The results of the study, published in Circulation, identify vascular smooth muscle cells as a possible therapeutic target for combatting the premature atherosclerosis in progeria. The study was conducted in collaboration with Carlos López-Otín of the University of Oviedo and Jacob Bentzon at the CNIC.

Hamczyk MR, Villa-Bellosta R, Gonzalo P, Andrés-Manzano MJ, Nogales P, Bentzon JF, López-Otín C, Andrés V. *Vascular Smooth Muscle-Specific Progerin Expression Accelerates Atherosclerosis and Death in a Mouse Model of Hutchinson-Gilford Progeria Syndrome.* Circulation. 2018;138(3):166-82. doi: 10.1161/CIRCULATIONAHA.117.030856



## 7. Science Translational Medicine

### CNIC scientists identify a promising target for the treatment of heart failure



Researchers at the CNIC led by José Antonio Enríquez have described a new therapeutic target for the prevention of heart failure, one of the leading causes of death and disability in the world. The new target, a mitochondrial protease called OMA1, is activated when the heart is under stress. Inhibition of OMA1 protects cardiomyocytes (the muscle cells of the heart), preventing their death and stemming the deterioration in heart function. The study is published in *Science Translational Medicine*.

*Acín-Pérez R, Lechuga-Vieco AV, Del Mar Muñoz M, Nieto-Arellano R, Torroja C, Sánchez-Cabo F, Jiménez C, González-Guerra A, Carrascoso I, Benincá C, Quiros PM, López-Otín C, Castellano JM, Ruiz-Cabello J, Jiménez-Borreguero LJ, Enríquez JA. Ablation of the stress protease OMA1 protects against heart failure in mice. Sci Transl Med. 2018;10(434):eaan4935. doi: 10.1126/scitranslmed.aan4935*

## 8. Nature Communications

### Mitochondrial DNA in exosomes is the alarm that initiates the antiviral response

Researchers at the CNIC have provided valuable information about the defense mechanisms of the immune system during the early stages of the response to pathogens such as viruses and bacteria. The research findings, published in *Nature*

Communications, contribute to the understanding of the cellular processes initiated at early stages and explain how the distinct cell populations of the immune system communicate to mount an effective response against pathogens.

The CNIC researchers have shown that mitochondrial DNA contained in nanovesicles triggers a state of alertness in recipient cells that activates an antiviral genetic program. These nanovesicles, known as exosomes, are produced by T lymphocytes and taken up by dendritic cells via intercellular contacts.

*Torralba D, Baixauli F, Villarroya-Beltri C, Fernández-Delgado I, Latorre-Pellicer A, Acín-Pérez R, Martín-Cófreces NB, Jaso-Tamame ÁL, Iborra S, Jorge I, González-Aseguinolaza G, Garaude J, Vicente-Manzanares M, Enríquez JA, Mittelbrunn M, Sánchez-Madrid F. Priming of dendritic cells by DNA-containing extracellular vesicles from activated T cells through antigen-driven contacts. Nat Commun. 2018;9(1):2658. doi: 10.1038/s41467-018-05077-9*



## 9. PLoS Biology P38 alpha: the switch controlling obesity and diabetes

One of the research lines targeting the worldwide obesity epidemic is the manipulation of brown fat, a 'good' type of fat tissue that burns lipids to maintain an appropriate body temperature. Researchers at the CNIC have now uncovered the mechanism by which brown fat cells are activated to generate heat and eliminate excess fat. The results, published in *PLoS Biology*, have potential clinical implications for the treatment of obesity and related diseases like diabetes.



Matesanz N, Nikolic I, Leiva M, Pulgarín-Alfaro M, Santamans AM, Bernardo E, Mora A, Herrera-Melle L, Rodríguez E, Beiroa D, Caballero A, Martín-García E, Acín-Pérez R, Hernández-Cosido L, Leiva-Vega L, Torres JL, Centeno F, Nebreda AR, Enríquez JA, Nogueiras R, Marcos M, Sabio G. p38 $\alpha$  blocks brown adipose tissue thermogenesis through p38 $\delta$  inhibition. *PLoS Biol.* 2018 Jul 6;16(7):e2004455. doi: 10.1371/journal.pbio.2004455.

## 10. Journal of Experimental Medicine The dual and unknown function of the immune system



The cells of the immune system sustain life by infiltrating infected and damaged tissue and eliminating pathogenic microorganisms and cell debris. However, immune action produces a collateral damage of its own that can lead to autoimmune disease or contribute to the injury associated with myocardial infarction or stroke. Now, a new study led by CNIC researcher Andrés Hidalgo and published in the Journal of Experimental Medicine shows that in addition to its defense function and the associated damage to affected tissues, the immune system also

plays an important role in the day-to-day function of healthy organs. The research results show that the immune cells called neutrophils help to maintain the normal function of healthy tissues.

Casanova-Acebes M, Nicolás-Ávila JA, Li JL, García-Silva S, Balachander A, Rubio-Ponce A, Weiss LA, Adrover JM, Burrows K, A-González N, Ballesteros I, Devi S, Quintana JA, Crainiciuc G, Leiva M, Gunzer M, Weber C, Nagasawa T, Soehnlein O, Merad M, Mortha A, Ng LG, Peinado H, Hidalgo A. Neutrophils instruct homeostatic and pathological states in naïve tissues. *J Exp Med.* 2018;215(11):2778-95. doi: 10.1084/jem.20181468 10.1084/jem.20171738

## 11. Science A new mechanism in the control of inflammation

In response to infection or tissue injury, our bodies react by activating the inflammatory immune response, which attacks the infection and repairs the damaged tissue. However, excess inflammation can sometimes have the opposite effect, increasing injury in a process known as immunopathology. Now, researchers at the CNIC have discovered a new inflammation control mechanism that shows how the damage caused by the immune response can be controlled. The study is published in Science.

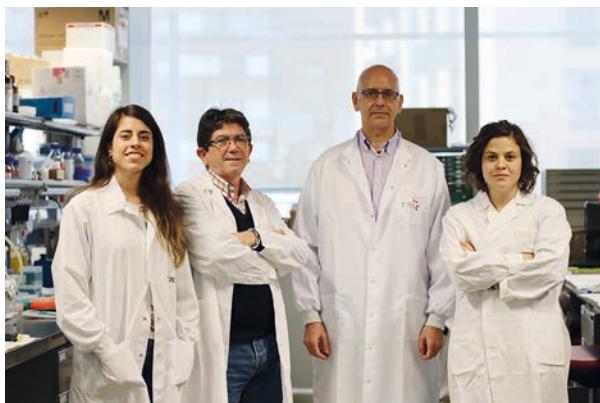
Del Fresno C, Saz-Leal P, Enamorado M, Wculek SK, Martínez-Cano S, Blanco-Menéndez N, Schulz O, Gallizzioli M, Miró-Mur F, Cano E, Planas A, Sancho D. DNGR-1 in dendritic cells limits tissue damage by dampening neutrophil recruitment. *Science.* 2018;362(6412):351-6. doi: 10.1126/science.aan8423



## 12. Nature Communications

### Blocking hypertension with antihypertensive drugs prevents the development of a lethal disease

Researchers at the CNIC and the Consejo Superior de Investigaciones Científicas (CSIC) have discovered that effective control of high blood pressure with antihypertensive drugs prevents the development of aortic intramural hematoma (IMH), a serious and potentially lethal disease. The research has also identified specific proteins implicated in the disease, and the authors have generated a preclinical model for the study of intramural hematoma that will be useful for evaluating possible pharmacological treatments. The study, published in *Nature Communications*, was co-directed by Miguel Campanero of the Instituto de Investigaciones Biomédicas Alberto Sols (CSIC), and CNIC group leader Juan Miguel Redondo.

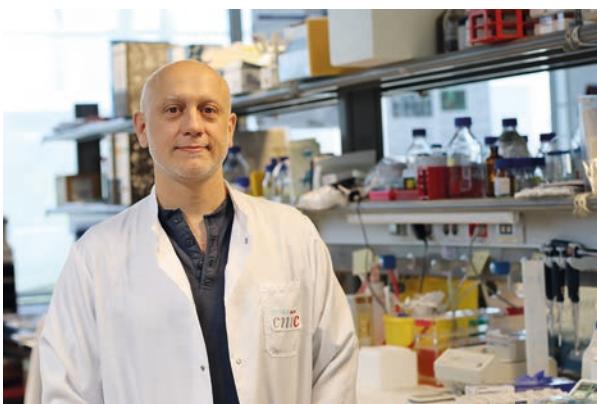


Villahoz S, Yunes-Leites PS, Méndez-Barbero N, Urso K, Bonzon-Kulichenko E, Ortega S, Nistal JF, Vazquez J, Offermanns S, Redondo JM, Campanero MR. Conditional deletion of Rcan1 predisposes to hypertension-mediated intramural hematoma and subsequent aneurysm and aortic rupture. *Nat Commun.* 2018;9 (1):4795. doi: 10.1038/s41467-018-07071-7

## 4 CNIC News and Views

### Grants

#### CNIC coordinates a project from the Leducq Foundation



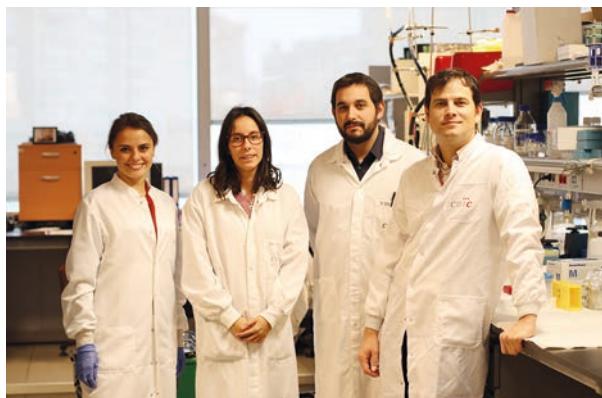
A project coordinated by the CNIC has been selected by the Leducq Foundation to receive funding of \$6,000,000 over five years. The project 'Clonal hematopoiesis and atherosclerosis,' coordinated by Andrés Hidalgo of the CNIC and Alan Tall of the Columbia University Medical Center, New York, is one of the five projects chosen by the 2018 Transatlantic Networks of Excellence Program of this prestigious foundation.

The Leducq Transatlantic Networks of Excellence Program funds teams of scientists who collaborate in the research of cardiovascular and neurovascular diseases. Since 2004, the Foundation has supported 57 networks, which include more than 400 researchers from 130 institutes in 21 countries.

This is the second Leducq Transatlantic Networks of Excellence to be coordinated by the CNIC. Miguel Torres is the European coordinator of the Redox Regulation of Cardiomyocyte Renewal project, which started on 01/01/2018 and will last until 31/12/2022.

#### European Union ERC Consolidator grant awarded to a project led by Borja Ibáñez of the CNIC and the FJD

The MATRIX Project led by Borja Ibáñez, Director of Clinical Research at the CNIC, has been awarded an ERC Consolidator grant by the European Commission. The award provides funding of €2 million over the next five years to develop new and innovative treatments for the cardiac toxicity associated with some cancer treatments. MATRIX (Novel mitochondria-targeted therapies for cancer treatment-induced cardiotoxicity) will be undertaken jointly by the CNIC and the University Hospital Jiménez Díaz Foundation (FJD) within a collaborative framework begun in 2015 to study myocardial diseases.



The CNIC obtained a second project in the same ERC-2018-COG call, entitled "Transgenerational epigenetic inheritance of cardiac regenerative capacity in the zebrafish". This project is coordinated by the University of Bern, and the CNIC participates as a partner with a shared PI: Nadia Mercader.

The CNIC currently holds seven active ERC Grants.

## A CNIC-coordinated international project is set to receive €1 million in funding over the next 3 years

An international research effort led by the CNIC will receive \$1,350,000 (€1,100,062) over the next 3 years through an award from the International Human Frontiers Science Program Organization (HFSPO). HFSPO funds pioneering research projects in the life sciences, fostering collaboration between scientists from different countries across the globe and working in different specialties.

This HFSPO international program targets support to risk-taking and pioneering projects and is the only program that finances scientific teams across the globe, without regard to borders. Support is provided for the explicit purpose of encouraging innovation and creativity. The project coordinated by CNIC research scientist José Antonio Enríquez is titled ‘Handling OXPHOS structural heterogeneity and metabolic plasticity’. The project tackles a fundamental biological question: have diploid organisms evolved mechanisms to ensure monoallelic expression of defined groups of genes and thus avert functional conflict between alternative protein variants?



## Two projects funded in the ERA-NET Cardiovascular Diseases Joint Translational Call, 2018

Transnational Cardiovascular Research Projects driven by Early Career Scientists:

- 1 “Fibrosis Treatment by Enhancer Targeting” CNIC as partner; PI, Luis Luna. Coordinated by Thomas Moore-Morris (INSERM UMR1251, Marseille Medical Genetics, France)
2. “Dissecting Mesenchymal-Endothelial Cross-Talk, Heterogeneity and Function to Mend Vascular Ageing and Atherosclerosis” CNIC as partner; PI, Rui Benedito. Coordinated by Universitätsklinikum AACHEN for the Medical Faculty of RWTH, Aachen, Germany

## Four CNIC projects receive €2.5 million in the La Caixa Proyectos de Investigación en Salud 2017 program

Four CNIC projects have been selected by the Fundación Bancaria La Caixa within the La Caixa Proyectos de Investigación en Salud – 2017. Three of the CNIC projects are centered on cardiovascular disease: ‘Somatic mutation-driven clonal hematopoiesis in atherosclerosis - International Consortium’, led by CNIC Director Valentín Fuster; ‘The antibody immune response during vascular remodeling’, led by Almudena R. Ramiro; and ‘Therapeutic targeting of the neutrophil clock in cardiovascular disease’, led by Andrés Hidalgo. The fourth project is related to infectious diseases: ‘Readyng immune cells prior to disease-inducing encounters’, coordinated by Francisco Sánchez Madrid.



## Awards & Honors

### The cardiovascular polypill, named the best Multidisciplinary Adherence project

The cardiovascular polypill, developed by the CNIC and Ferrer, has been named the best Multidisciplinary Adherence project in the 1st edition of the OAT prizes for Improvements in Treatment Adherence. These prizes acknowledge contributions by organizations and individuals to improving treatment adherence. The polypill, marketed under the name Trinomia®, is a major advance in cardiology because each capsule contains three drugs indicated for the prevention of a second myocardial infarction in individuals who have already had one (atorvastatin, aspirin, and ramipril). The advantage of this treatment is its simplicity; patients need to take only one pill instead of three. This makes adherence to treatment much easier for high-risk patients requiring long-term treatment, who tend to be elderly.



### Valentín Fuster awarded honorary degree by the Universidad Alfonso X el Sabio



The Universidad Alfonso X el Sabio has awarded an honorary degree to Valentín Fuster de Carulla for his extensive scientific contributions to cardiology and his tireless work in health promotion, aimed at advancing the treatment and prevention of myocardial infarction.

### Fuster receives the Health Care Personality Award

Fuster has been awarded the Health Care Personality Award in recognition of his contributions to research and his promotion of a healthy life style to combat obesity and cardiovascular disease through improved diet and physical activity.



## Guadalupe Sabio awarded the Fundación Jesús Serra research prize



The CNIC investigator received the award in a ceremony attended by Carmen Vela, Secretary of State for Research, Development, and Innovation and Fundación Jesús Serra president Federico Halpern. Sabio was joined by the other prize winner in the first edition of these awards, Pablo Pérez Martínez of the Hospital Universitario Reina Sofía, Córdoba

## Oriol Bonnín prize awarded to CNIC investigator Xavier Rosselló



CNIC investigator Xavier Rosselló has been awarded the Oriol Bonnín prize for research on cardiocirculatory disease. The Oriol Bonnín award program is run by the Instituto de Investigación Sanitaria Illes Balears, el Servicio de Salud, and the Hospital Universitario Son Espases and is funded by

the La Caixa Foundation. Xavier Rosselló received €3000 for his project “Targeting myocardial infarction consequences in the acute and chronic setting using experimental and statistical approaches”.

## CNIC researcher Guadalupe Sabio receives the IV AstraZeneca Foundation Jóvenes Investigadores prize



Dr Guadalupe Sabio has been awarded the Jóvenes Investigadores prize in the Type 2 Diabetes and Obesity category for her research on “The role of p38MAPK in the development of obesity and associated diseases”. Her research focuses on the control of the p38MAPK signaling pathway. This pathway induces the transformation of white adipose tissue into brown adipose tissue (BAT), and this research is revealing the divergent potential of the distinct p38MAPK isoforms for the treatment of obesity. The prize supports Sabio’s research with an award of €20000 from the Fundación AstraZeneca. Guadalupe Sabio will also have the opportunity to visit AstraZeneca research facilities and meet with executive team in charge of selecting the talented scientists receiving these awards.

## Jorge Alegre-Cebollada to represent arsenic in the IUPAC 'Young Chemists' Periodic Table



CNIC investigator Jorge Alegre-Cebollada was selected to represent the element arsenic (As) in the 'Young Chemists' Periodic Table being organized to celebrate the centenary of the International Union of Pure and Applied Chemistry, the world authority on chemical nomenclature and terminology.

To mark the centenary and the International Year of the Periodic Table, the IUPAC and the International Young Chemists Network (IYCN) are creating a periodic table of young chemists whose achievements will be honored in July 2019 at the World Chemistry Congress and the IUPAC General Assembly in Paris. The selected investigators form a group of 118 young chemists from all over the world who personify the mission and values of the IUPAC. The resulting periodic table will showcase the career diversity, creativity, and dedication of the young chemists of the 21st century.

## Scientific Events

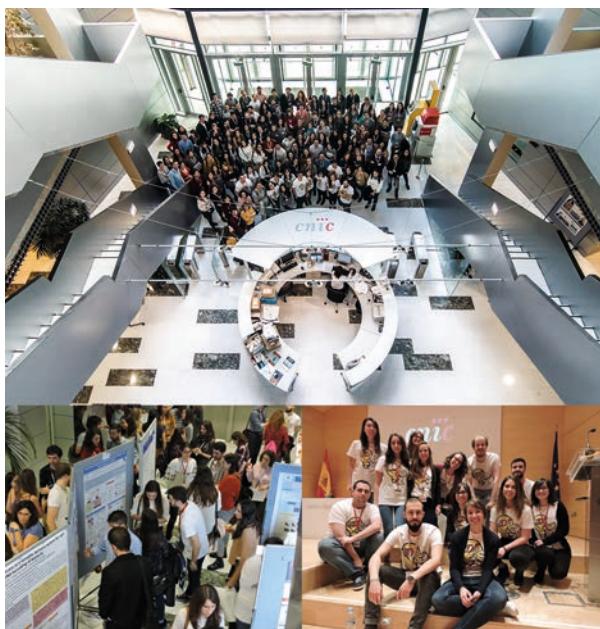
### CNIC Conference addresses the emerging concepts in cardiovascular biology



A new CNIC Conference under the title Emerging Concepts in Cardiovascular Biology was held at the CNIC on November 16 and 17. The meeting brought together more than 100 scientists from 15 European countries, China, the USA, Japan, and Russia. The meeting was coordinated by Rui Benedito and José Luis de la Pompa of the CNIC, José María Pérez Pomares of the University of Málaga, and Didier Stainier of the Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany. The attendees included experts on blood vessel biology, the role of the cardiac endothelium in the heart development and its impact on congenital heart diseases, and the interaction between coronary angiogenesis and cardiomyocytes during tissue development and regeneration.

The poster features the CNIC logo and the conference title 'Emerging Concepts in Cardiovascular Biology'. It includes a photograph of a heart and several smaller images of cellular and tissue structures. The text provides details about the organizers (Rui Benedito, José Luis de la Pompa, José María Pérez Pomares, Didier Stainier), speakers, and the venue (Centro Nacional de Investigaciones Cardíacas, Madrid). Logos for Fundación Príncipe Felipe and Fundación Caja de Pensiones para la Vejez y de Ahorros are also present.

## CNIC PhDay 2018: Scientific Growth



Under the slogan “Scientific Growth”, a new edition of the CNIC PhDay was held in November 2018. This annual event is on a par with any international congress. The PhDay provides an open forum for students and graduates, laboratory technicians, and postdoctoral researchers wishing to develop their careers as scientists and is based on the exchange of new ideas.

This year, the theme centered on scientific growth and covered stages in the life of a scientist from childhood through to the establishment of a scientific career in adulthood.

**The CNIC hosts the third Hackathon de Salud, the biggest health programming marathon in Spanish**



The CNIC hosted the third Hackathon de Salud, the biggest health programming marathon in Spanish. The event is organized by the Asociación de Investigadores en eSalud (AIES) and the COM Salud communications agency, and its commercial sponsors include Boehringer Ingelheim. The Hackathon invites patients, healthcare professionals, and managers to join with software developers in co-creating programs and applications to assist in disease management. The aim is to empower patients and ensure the adaptability and responsiveness of the healthcare system. In previous years, more than 30 multidisciplinary teams presented projects, and last year more than 120 ‘health hackers’ participated in the program.

## Outreach Activities

### CNIC participates in Madrid Science Week



For the seventh consecutive year, the CNIC participated in a new edition of the Madrid Science Week. This year, the CNIC ran three activities: a conference open to the general public entitled "Cardiovascular research for good heart health: Learn how we work at the CNIC"; the traditional "Un día en familia en CNIC" event, open to youngsters; and an event called "Find your scientific vocation in the CNIC", aimed at junior and senior high-school students.

### Several CNIC female researchers give talks at schools on the International Day of Women and Girls in Science (February 11)



### The CNIC gets closer to schools

Students from the final year of junior school and years 1 through 3 of high school spent a day with CNIC researchers who are at different stages in their research career talking about students' doubts and answering questions about research work. The best projects were awarded with diplomas handed out by Valentín Fuster.



## New Partnerships

### Agreement signed between the CNIC and Xerencia De Xestión Integrada de A Coruña-Fundación Profesor Novoa Santos (FPNS)



The CNIC and *Xerencia De Xestión Integrada de A Coruña (XXIAC)-Fundación Profesor Novoa Santos (FPNS)* have signed an agreement to launch the project 'Development of large experimental animal models for cardiac surgery with extracorporeal circulation and cardiac arrest.' The agreement was signed at a ceremony attended by CNIC General Director Valentín Fuster, CNIC Managing Director Alberto Sanz Belmar, XXIAC Managing director and FPNS President Luis Verde Remeseiro, CNIC Clinical Research Director Borja Ibáñez, and project leader Víctor Bautista Hernández of the XXIAC and the FPNS.



The agreement covers a 4-year period until December, 2021. The lead investigator on the project is Víctor Bautista Hernández, Head of Pediatric and Congenital Surgery and Coordinator of Structural and Congenital Heart Disease Research at the XXIAC and the FPNS.

## CNIC and FIBAO team up to advance knowledge on cardiovascular diseases



The CNIC and la Fundación Pública Andaluza para la Investigación Biosanitaria de Andalucía Oriental (FIBAO) have signed an agreement to exchange knowledge and professional experience to advance the prevention and treatment of cardiovascular diseases.

Through the agreement, the two institutions will cooperate in biomedical and clinical research projects and share training opportunities.

## The Pro CNIC Foundation and HM Hospitales form an alliance to promote cardiovascular health, with a focus on women



During a meeting at HM Montepríncipe University Hospital, the Pro CNIC Foundation and HM Hospitales agreed to develop joint initiatives aimed at promoting cardiovascular health and a healthy lifestyle.

## CNIC and Quirónprevención sign an agreement to promote cardiovascular health



Quirónprevención has signed an agreement with the CNIC to advance knowledge about cardiovascular health. The agreement will focus on studies into cardiovascular risk prevention and related diseases. Quirónprevención will provide a completely anonymized and untraceable database of more than 5 million medical checkups. The project will analyze cardiovascular risk in Spain and will assess a number of variables, including job type (office and manual workers have very different levels of physical activity), dietary habits, alcohol consumption and smoking, and overall daily physical activity.



## Social & CNIC

### The Pro CNIC Foundation renews its commitment to the CNIC until 2028



Pro CNIC Foundation President Mr. Luis de Carlos and General Secretary of Scientific Coordination Mr. Rafael Rodrigo formalized an agreement to renew the commitment of this body of 13 private companies to continue its support for the CNIC until 2028. The Pro CNIC Foundation is an innovative example of public-private collaboration that has allowed the CNIC to establish itself as a world leader in biomedical research, contributing to the CNIC gaining Severo Ochoa accreditation in recognition of its international excellence in research. Through the Pro CNIC Foundation, 13 leading Spanish companies channel their business knowhow and financial support to the CNIC, representing a benchmark in successful scientific patronage. The companies participating in the Pro CNIC Foundation are Acciona, Santander Bank, BBVA Bank, Endesa, the Mapfre Foundation, the Mutua Madrileña Foundation, the Ramón Areces Foundation, the Repsol Foundation, Naturgy, Inditex, "la Caixa", Prisa, and Telefónica. The Pro CNIC Foundation enables the CNIC's research to have a direct impact on patient care and health improvements in the general population. The Pro CNIC Foundation also helps in the conversion of innovations into patents that generate an economic return and support research and development in Spain.

### The Minister for Science, Innovation, and Universities, Pedro Duque, attended the Pro CNIC Foundation Board of Trustees meeting



The Minister for Science, Innovation, and Universities, Pedro Duque, accompanied by Secretary of State for Science Pablo Martín, attended the meeting of the Pro CNIC Foundation Board of Trustees. The meeting was chaired by Pro CNIC Foundation President Luis de Carlos and provided an overview of the foundation's activities. Pedro Duque and CNIC General Director Valentín Fuster released a joint statement in which they emphasized the need for governments to encourage private investment in scientific projects by creating the conditions to ensure the profitability of this type of enterprise and providing public funds where necessary. In his summary the Minister highlighted the importance of these measures: "There is much at stake, and the longer we delay taking the necessary measures, the harder the task will be in the future."

### Raquel Yotti, new Instituto de Salud Carlos III (ISCIII) Director, visits the CNIC

The new Director of the Instituto de Salud Carlos III (ISCIII), Raquel Yotti Álvarez, was shown round the CNIC by Managing Director Alberto Sanz and Research Directors Vicente Andrés and Borja Ibáñez. Yotti, accompanied by Margarita Blázquez Herranz, Subdirector of the ISCIII Redes y Centros de Investigación Cooperativa, learned about the CNIC's

major projects and visited some of the Center's laboratories.



### **“The Tribe of the Heart” Campaign**

The Social Project of Mediaset Spain, together with the Pro CNIC Foundation and Valentín Fuster, have launched The Tribe of the Heart, a community project that aims to create awareness about cardiovascular disease. The project's motto is 'Having a healthy heart is in your hands' and its goal is to instill in children the need to care for this organ that moves the world and gives us life. Activities based on music, art, and humor are used to create awareness about the need for healthy lifestyle habits to prevent cardiovascular diseases. Our heart has many things to tell us; listen to it!



### **Meeting with Repsol: The Future of Health, with Valentín Fuster**

CNIC General Director Valentín Fuster held a meeting with REPSOL shareholders at the CNIC in an act dedicated to health promotion. The shareholders also learned about the Center's main scientific and medical findings during an informal breakfast with Fuster and four CNIC researchers: José María Castellano, Antonio Fernández Ortiz, Pilar Martín, and Gonzalo Pizarro.



## 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 2018, 609 participants were enrolled on CNIC training programs.



## HIGH SCHOOL AND UNDERGRADUATE STUDENTS INTERNSHIPS

### Acérdate Program

The Acérdate 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 2018: 8*

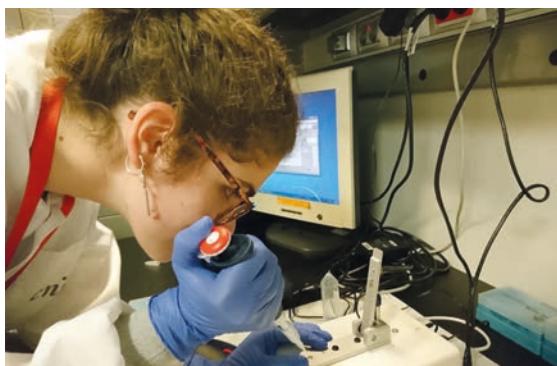
The CNIC collaborates with high schools of the Madrid Community in the following training programs:

**4ºESO-CNIC:** Sixteen life-science students from eight schools spent from 4 to 5 days at the CNIC laboratories exploring possible scientific careers.

**Practical experience for Technical School students:** This program brought sixteen technical school students studying "Pathological and Cytodiagnostic Anatomy" and "Clinical and Biomedical Laboratory Science" to gain practical curricular experience in the CNIC's laboratories over a three-month period.

Moreover, three students of "Diagnostic Imaging and Nuclear Medicine" and "Clinical and Biomedical Laboratory Science" spent 10 months at the CNIC as part of the DUAL technical study program.

The CNIC has signed collaborative agreements for this kind of internships with both DUAL Centers in Madrid offering courses in the Biomedicine field.



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

*Fellowships in 2018: 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), or master's dissertation.

Internships in 2018: 69 internships from 16 Universities, 4 of them outside Spain.

## MASTERS AND GRADUATE STUDENTS

### Master's Fellowship Program (CNIC-ACCIONA) and Fundacion 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 (TFM) in a CNIC laboratory.

*Fellowships in 2018: 16*

### 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 2018: 21*

*Graduate students studying for a PhD degree at the CNIC in 2018: 89*



### 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).

## MEDICAL INTERN RESIDENTS

### RES@CNIC Program

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

*Participants in 2018: 20*

### INVESMIR SEC Program

The INVESMIR SEC Program offers resident medical interns the opportunity during their specialization period to further their training through a research project in one of the CNIC's laboratories, under the supervision of a CNIC scientist.

An important aim of the program is for participants to establish contacts and collaborations with CNIC researchers that will support them, after completion of their MIR specialization training, in pursuing their

own research projects at their centers within the Spanish National Health System. In 2018 one resident cardiologist intern participated in this Program.



## Post MIR SEA CNIC Program

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

## RESEARCHERS

### Cardio Joven Program

The aim of this Program (also organized in collaboration with the SEC) is to foster high-quality translational research in the cardiovascular area in Spanish National Health System centers through training programs providing theory and practical training for one cardiologist with a research vocation.

Specific aims:

- a) To create the figure of the 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)



## CONTINUING TRAINING

### **Cardiovascular Pathophysiology Course: From Symptoms to Genes**

The two-day Cardiovascular Pathophysiology Course is organized by the CNIC (Borja Ibáñez) in partnership with the SEC (Ángel Cequier). This course offers cardiologists a translational vision of cardiology by introducing them to the study of pathophysiology and basic research. Participants receive an overview of the molecular and genetic factors that underlie cardiac diseases and gain an up-to-date vision of cardiac physiology.

*Venue:* CNIC Auditorium

*Dates:* November 30-December 1, 2018

*Attendees:* 99

### **Vascular Biology Course**

Valentín Fuster delivers this lecture series on Vascular Biology: Basic and Clinical Research as part of the Universidad Internacional Menéndez Pelayo (cUIMPB) summer program, sponsored by Ferrer International.

In this course, Valentín Fuster tries to “motivate and teach for the future”. Most of the attendees are cardiologists, although others are experts in internal medicine or other specialties. In 2018, delegates came from more than 15 countries, most of them in Latin America and Europe.

*Venue:* Cardona Auditorium

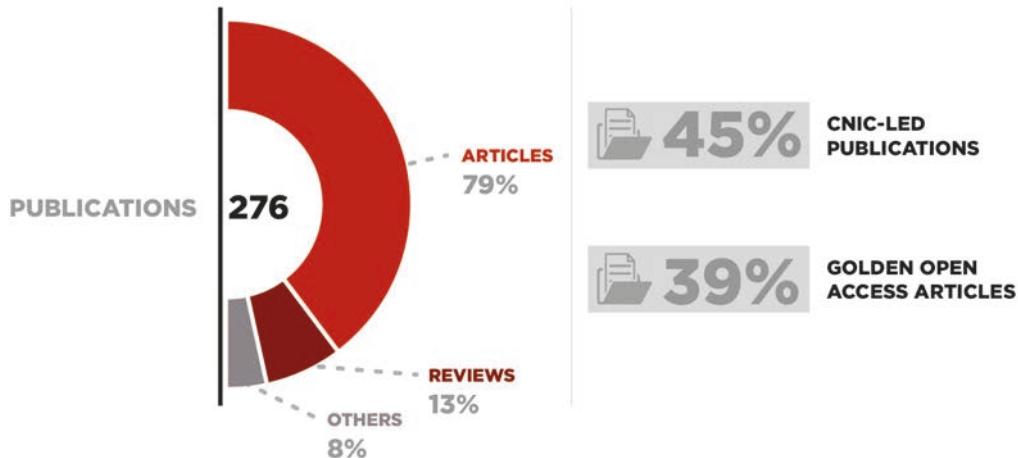
*Dates:* July 17-18, 2018

*Attendees:* 226



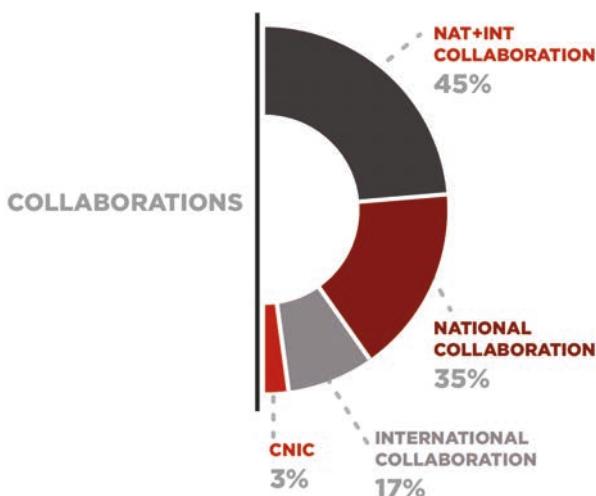
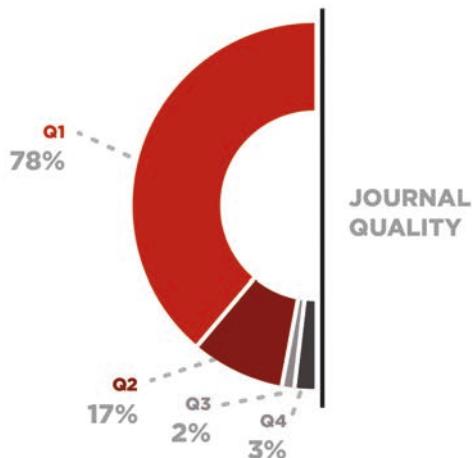
## 6 Facts and Figures

### Scientific Publications



**72** PUBLICATIONS IN TOP JOURNALS (IF>10)

**80** PUBLICATIONS IN JOURNALS IN JCR TOPS



**52%** COLLABORATION WITH HOSPITALS

**90%** COLLABORATION WITH UNIVERSITIES

<https://www.cnic.es/en/investigacion/publicaciones/resultados?y=2018>



## Competitive Funding and Patents\*

### New Grants



### Transfer of Technology

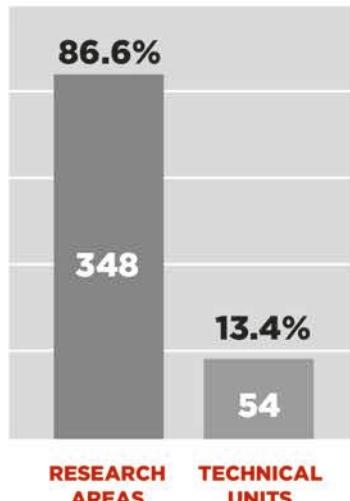
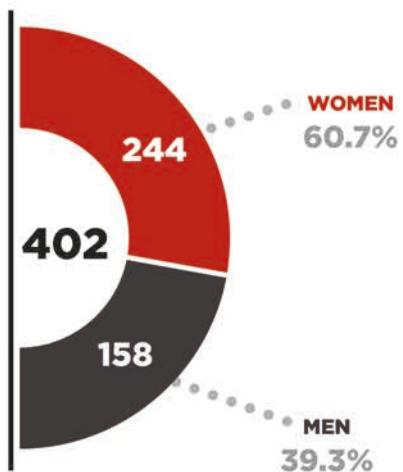


\*All data from 31/12/2018



## Human Resources\*

### Scientific Staff



### Group Leaders

**33**      24.2% **women**  
              75.8% **men**  
              24.2% **Cardiologists**

### Heads of Technical Units

**11**      45.5% **women**  
              54.5% **men**

**43**      10.7% **of the Scientific Staff are from outside Spain**  
(21 countries, with the highest numbers coming from Italy, Portugal and USA)

**161**      12.4% **of Visiting Scientists come from outside Spain**  
(12 countries, including Switzerland, Denmark, Italy, UK, and USA)

\*All data from 31/12/2018



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