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.

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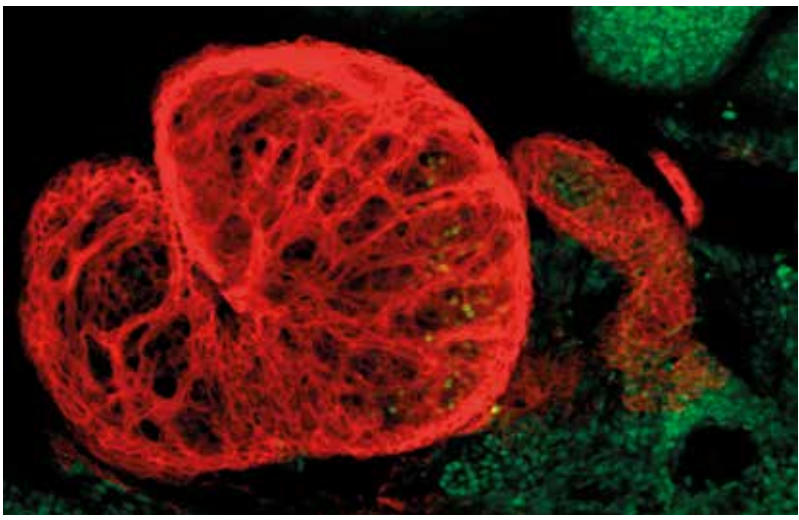
TECHNICAL UNITS

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 p38α 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 curently 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.

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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

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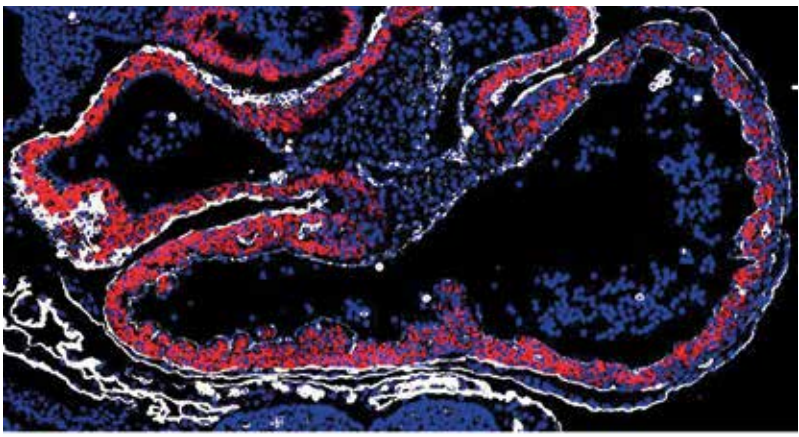
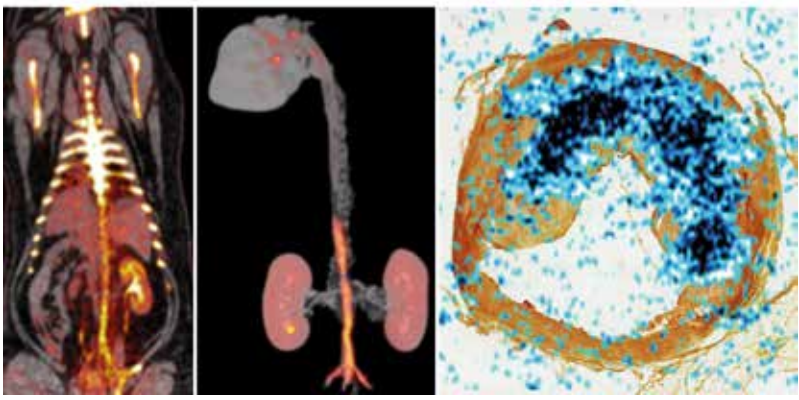
TECHNICAL UNITS

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 ^{18}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 β3 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 β3-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.