

# 2 Research at the CNIC



## Scientific Programs

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### Novel Mechanisms of Atherosclerosis

**Coordinator:** José Javier Fuster

**Clinical Leaders:** Valentín Fuster & Inés García-Lunar

The Novel Mechanisms of Atherosclerosis Program aims to advance our mechanistic understanding of atherosclerosis, the leading cause of cardiovascular and cerebrovascular disease. Despite major progress in controlling traditional risk factors, a substantial residual risk of atherosclerotic cardiovascular disease persists, even in individuals with low estimated cardiovascular risk. A central goal of the Program is therefore the identification of new risk factors and mechanisms of atherosclerosis in order to develop novel strategies for the prediction, prevention and treatment of atherosclerosis.

To achieve this, the Program brings together multidisciplinary teams, integrating experimental studies in animal models with translational research in humans, leveraging large cohorts such as the Progression of Early Subclinical Atherosclerosis (PESA) study. Research efforts focus on inflammatory mechanisms, vascular cell biology, and novel imaging and molecular biomarkers of atherosclerosis.

#### Key Achievements in 2025

**A microbiota metabolite-receptor axis as a new therapeutic opportunity.** A major advance was the identification of imidazole propionate (ImP) as a microbial metabolite linked to the development of atherosclerosis in mice and humans. The study, published in *Nature* (1), also identified the imidazoline 1 receptor in myeloid cells as the sensing receptor mediating ImP-induced proinflammatory reprogramming and accelerated atherosclerosis development. The translational relevance of these findings was reinforced by associations with active atherosclerosis in human cohorts, including PESA. Pharmacological blockade of the ImP-sensing pathway prevented atherosclerosis in mice.

**Targeting dendritic cell-driven adaptive immunity to slow disease progression.** Program researchers identified conventional type 1 dendritic cells (cDC1s) as key orchestrators of adaptive immune responses promoting atherosclerosis. This work, published in *Circulation Research* (2), showed that cDC1s regulate local Th1 immunity within atherosclerotic plaques and play a causal role in disease progression. Importantly, it also provided a new preventive strategy: dexamethasone-loaded nanoparticles targeted to cDC1s suppressed plaque Th1 immunity and prevented atherosclerosis progression in experimental models.

**Mechanistic understanding of imaging-based stratification and treatment monitoring strategies.** Imaging with the radiolabeled glucose analog fluorodeoxyglucose (FDG) is widely used to monitor atherosclerosis in clinical trials, but the cellular and

molecular processes underlying FDG uptake in the vascular wall remain incompletely defined. Using a large-animal model of atherosclerosis, program researchers showed that atherosclerotic disease activity correlates with glycolytic enzyme expression across multiple plaque cell types, which in turn correlates with vascular FDG uptake. Published in *Science Translational Medicine* (3), these findings provide a mechanistic rationale for FDG uptake as a readout of plaque activity, linking this imaging signal to glycolytic programs in vascular and immune cells within the lesion.

#### Funding and awards

A major milestone in 2025 was the award of an ERC Advanced Grant to Almudena R. Ramiro, reinforcing CNIC's leadership in immune mechanisms of atherosclerosis. In addition, Vicente Andrés' group received the Best Publication Award (1ª Edición Premios Cátedra Enfermedades Poco Frecuentes, Universidad de Almería) for prior work within the Program describing the contribution of endothelial-to-mesenchymal transition to accelerated atherosclerosis in Hutchinson-Gilford progeria syndrome.

#### Outreach and engagement

Program researchers presented findings at major international meetings, including ESC, AHA Vascular Discovery, Gordon Conferences, Keystone Symposia, EMBO workshops, ESC Cardio-Oncology, ESC Heart Failure Congress, and CARDIOTOX, with invited lectures by group leaders and presentations by early-stage investigators. David Sancho co-organized the European Phagocyte Workshop 2025 at the CNIC.

Public engagement activities included participation in the European Researchers' Night, Madrid Science Week, the International Day of Women and Girls in Science, the International Day of Persons with Disabilities, and educational activities in primary and secondary schools across the Comunidad de Madrid.

#### Highlighted Publications

1. *Nature* 2025 Sep;645(8079):254-261. doi: [10.1038/s41586-025-09263-w](https://doi.org/10.1038/s41586-025-09263-w)
2. *Circ Res.* 2025 Jul 18;137(3):400-416. doi: [10.1161/CIRCRESAHA.124.325792](https://doi.org/10.1161/CIRCRESAHA.124.325792)
3. *Sci Transl Med.* 2025 Aug 13;17(811):eado6467. doi: [10.1126/scitranslmed.ado6467](https://doi.org/10.1126/scitranslmed.ado6467)
4. *Arterioscler Thromb Vasc Biol.* 2025 Sep;45(9):1616-1635. doi: [10.1161/ATVBAHA.124.322893](https://doi.org/10.1161/ATVBAHA.124.322893)
5. *Arterioscler Thromb Vasc Biol.* Epub 2025 Dec 23;46(2):e323323. doi: [10.1161/ATVBAHA.125.323323](https://doi.org/10.1161/ATVBAHA.125.323323)
6. *Nat Commun.* 2025 Apr 9;16(1):3369. doi: [10.1038/s41467-025-58289-1](https://doi.org/10.1038/s41467-025-58289-1)
7. *Immunity.* 2025 Feb 11;58(2):381-396.e9. doi: [10.1016/j.immuni.2024.12.012](https://doi.org/10.1016/j.immuni.2024.12.012)



## RESEARCH GROUPS

**Vicente Andrés**

Molecular and Genetic Cardiovascular Pathophysiology

**Jacob Fog Bentzon**

Experimental Pathology of Atherosclerosis

**Miguel Ángel del Pozo**

Mechanoadaptation and Caveolae Biology

**José Javier Fuster**

Hematovascular Pathophysiology

**Valentín Fuster**

Cardiovascular Imaging and Population Studies

**Inés García Lunar**

Cardiovascular Prevention Through Non-Invasive Imaging

**Carlos Pérez-Medina**

Nanomedicine and Molecular Imaging

**Almudena R. Ramiro**

B Lymphocyte Biology

**Fátima Sánchez-Cabo**

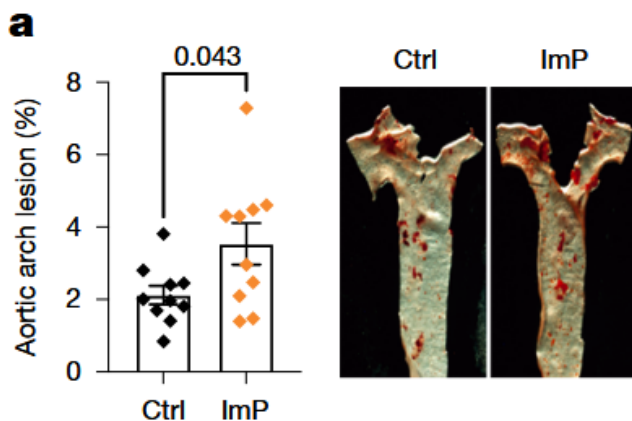
Computational Systems Biomedicine

**David Sancho**

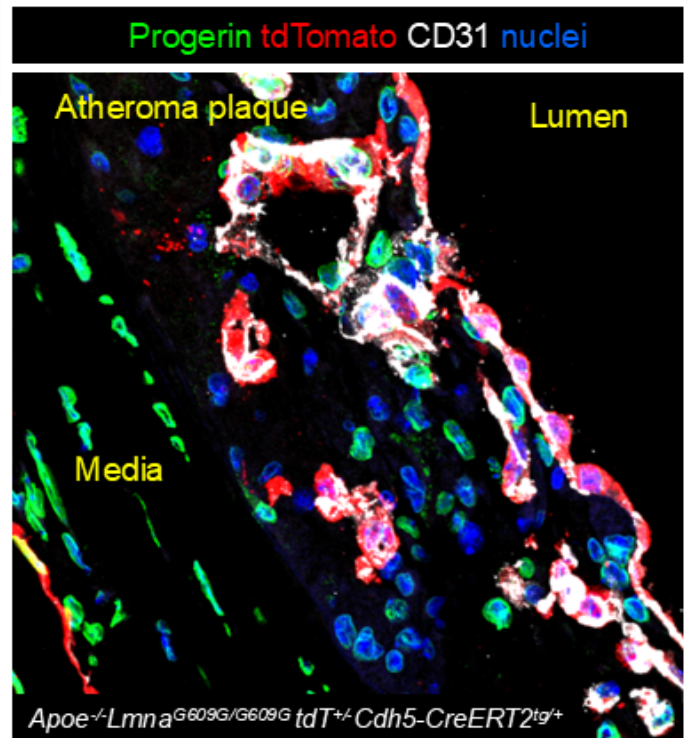
Immunobiology

**Jesús Vázquez**

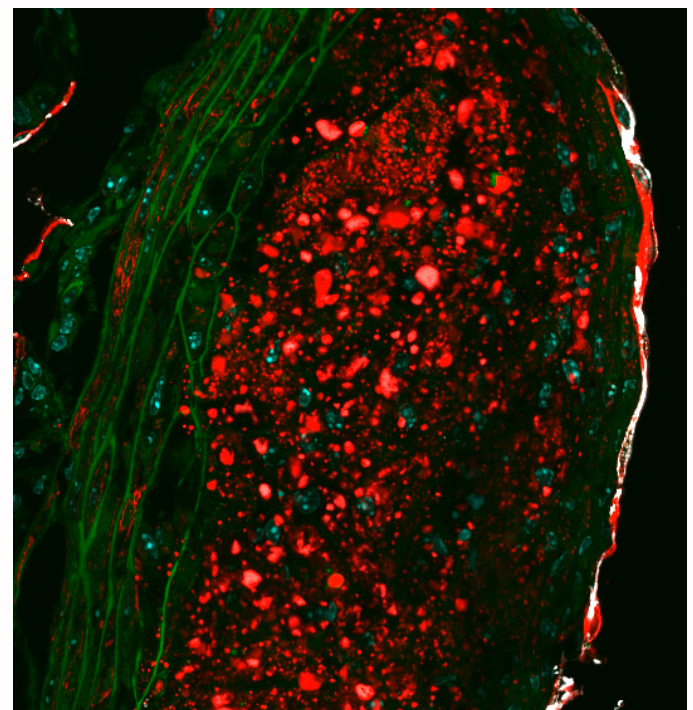
Cardiovascular Proteomics



**Fig 1.** Imidazole propionate promotes aortic atherosclerosis in **ApoE-deficient mice**, an effect prevented by **AGN192403**. Lesion area in the aortic arch was quantified by Oil Red O staining (left), with representative images shown on the right. Mastrangelo A, Robles-Vera I et al, *Nature* 2025.



**Fig 2.** Lineage tracing reveals the abnormal presence of endothelial-derived cells within the atheroma of progeroid, atherosclerosis-prone **tdT<sup>+</sup>/Cdh5-CreERT2<sup>tg</sup>** mice. Representative immunofluorescent image.



**Fig 3.** Endothelial and medial CAV1 expression during atherogenesis. Representative immunofluorescence image of the left coronary sinus showing CD31 (white), CAV1 (red), and nuclei (blue) in hypercholesterolemic mice. Muñoz-Anquela et al, *ATVB Epub* 2025 Dec 23.



## Myocardial Homeostasis and Cardiac Injury (MERCURY)



**Coordinator: Enrique Lara-Pezzi**

**Clinical Leader: Borja Ibáñez**

The MERCURY program investigates the molecular, genetic, and physiological mechanisms that determine how the heart responds to stress, injury, and inherited disease, with the aim of developing more precise and effective therapies.

In 2025, the program continued to explore two complementary research areas:

- (i) cardiotoxicity induced by cancer therapies and systemic stress, and
- (ii) the genetic and molecular basis of inherited cardiomyopathies, with a strong focus on translational and gene-based therapies

### Key Achievements in 2025

#### Cardiotoxicity and cardiac vulnerability

During 2025, we continued to explore cardiotoxicity as a context-dependent process influenced by metabolic state and genetic background. Using integrated approaches combining mouse models, large animal studies, and clinical research, we re-examined long-standing assumptions in cardiovascular therapy and cardioprotection.

Results from the REBOOT randomized clinical trial and a complementary meta-analysis (1, 2) showed that chronic beta-blocker therapy is not required in many post-myocardial infarction patients with preserved cardiac function. In parallel, studies in large-animal models demonstrated that subclinical metabolic alterations can increase susceptibility to chemotherapy-induced cardiac injury, even at doses traditionally considered safe. Together, these findings provide a framework for improved risk stratification and for preventive strategies tailored to individual metabolic profiles.

#### Sarcomere mechanics and structural integrity

We also made progress in understanding how force transmission is maintained in striated muscle. We found that loss of mechanical tension across the giant protein titin – caused either by proteolytic cleavage or post-translational modification – disrupts cardiomyocyte adhesion and promotes myocardial fibrosis.

Using single-molecule approaches applied to native titin, including the study of modifications induced by glycation stress, we identified new links between metabolic stress, sarcomeric mechanics, and pathological remodeling. These results connect mechanisms of cardiac and skeletal muscle disease and suggest new therapeutic strategies aimed at preserving force transmission and tissue integrity.

#### Inherited cardiomyopathies: clinical and molecular studies

The second pillar of the program focused on inherited cardiomyopathies and yielded several major advances in 2025.

At the clinical level, we helped define how genetic subtype influences disease progression, complications, and treatment response in hypertrophic and dilated cardiomyopathies. We completed a left-right ventricular differential expression study using myocardial samples from patients with pathogenic mutations who required heart transplantation, providing direct

evidence of chamber-specific molecular programs in advanced disease.

In addition, results of the MAPLE-HCM study established a new therapeutic paradigm for obstructive hypertrophic cardiomyopathy, showing that genotype-guided strategies can directly improve patient management.

#### Gene-based therapies for cardiomyopathy

We made important progress in the development of gene-based therapies for inherited cardiac disease. In a model of severe arrhythmogenic cardiomyopathy, adeno-associated virus-mediated overexpression of wild-type TMEM43 improved cardiac function, electrical stability, fibrosis, and survival. Both preventive and therapeutic administration were effective, demonstrating that dominant cardiomyopathies can be treated by restoring protein balance rather than silencing mutant alleles.

We also provided the first in vivo demonstration that CRISPR-based transcriptional activation can correct electrical defects caused by haploinsufficient truncating variants that cannot be treated by conventional gene replacement. Activation of endogenous gene expression using compact AAV-delivered CRISPRa systems reversed arrhythmogenic phenotypes in adult animals, opening a new therapeutic approach for a broad class of inherited cardiac diseases.

#### Precision modeling and variant interpretation

To support next-generation gene therapy, we established an integrated computational-experimental framework for the analysis of arrhythmogenic cardiomyopathy variants. Focusing on PKP2, the most frequently affected gene in this disease, we generated and analyzed hundreds of structural models of clinically annotated variants using artificial-intelligence-based methods.

These models allow systematic classification of pathogenic mechanisms and predicted functional behavior, strengthening the link between genetic diagnosis and therapeutic design, and enabling the development of mutation-aware gene therapy vectors.

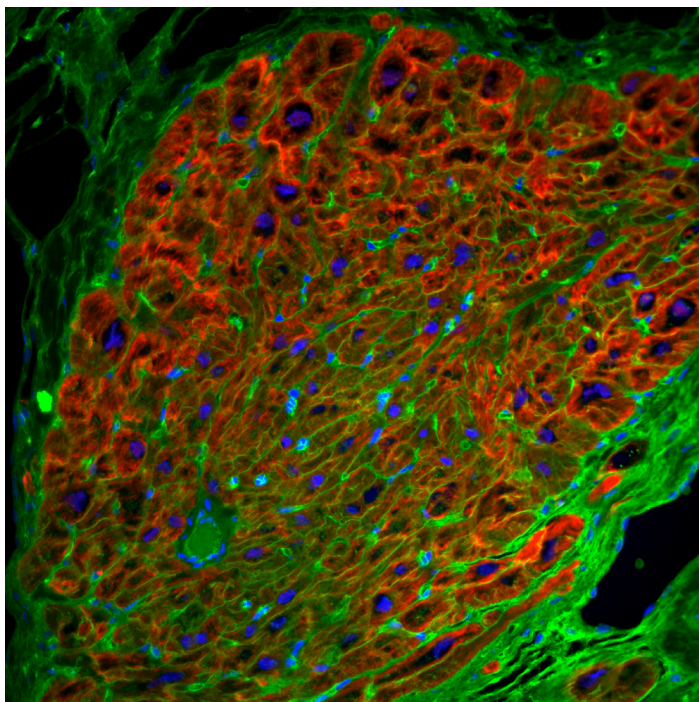
Together, these advances support a unified view of cardiac disease as the result of dynamic interactions between genetic background, molecular regulation, and systemic context, and demonstrate the feasibility of mechanism-based, genetically informed strategies.

#### Awards and Recognition

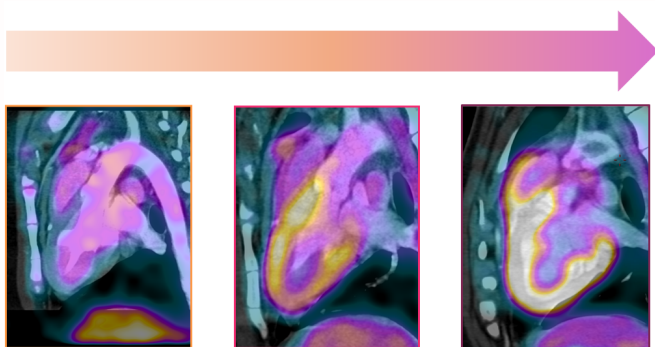
- Agustín Clemente Moragón received the CNIC Award for Outstanding Doctoral Thesis.
- Results from highlighted publications 1-3 were presented in plenary sessions at the European Society of Cardiology Congress 2025 (Madrid) and received broad media coverage.
- Biophysical Society – Michael and Kate Bárány Award (2026)

### Highlighted Publications

1. N Engl J Med. 2025 Nov 13;393(19):1889-1900. doi: [10.1056/NEJMoa2504735](https://doi.org/10.1056/NEJMoa2504735)
2. N Engl J Med. Epub Nov 9, 2025. 394(6):540-55 (2026) doi: [10.1056/NEJMoa2512686](https://doi.org/10.1056/NEJMoa2512686)
3. N Engl J Med. 2025 Sep 11;393(10):949-960. doi: [10.1056/NEJMoa2504654](https://doi.org/10.1056/NEJMoa2504654)
4. Eur Heart J. 2025 Nov 14;46(43):4610-4613. doi: [10.1093/eurheartj/ehaf703](https://doi.org/10.1093/eurheartj/ehaf703)
5. Nat Biomed Eng. 2025 Oct;9(10):1758-1774. doi: [10.1038/s41551-025-01403-x](https://doi.org/10.1038/s41551-025-01403-x)



**Fig 1.**  
Immunofluorescence analysis of a myocardial sample from a hypertrophic cardiomyopathy patient. Blue, DAPI; Green, agglutinin; Red, troponin.



**Fig 2.**  
PET scan during cardiotoxicity development showing abnormal glucose metabolism with a prior hypertensive stimulus.

### RESEARCH GROUPS



**Jorge Alegre-Cebollada**

Molecular Mechanics of the Cardiovascular System



**Ana Devesa**

Cardiometabolic Disease and Advanced Imaging



**Ana García Álvarez**

Heart Failure and Pulmonary Hypertension Translational Research



**Pablo García-Pavía**

Inherited Cardiomyopathies



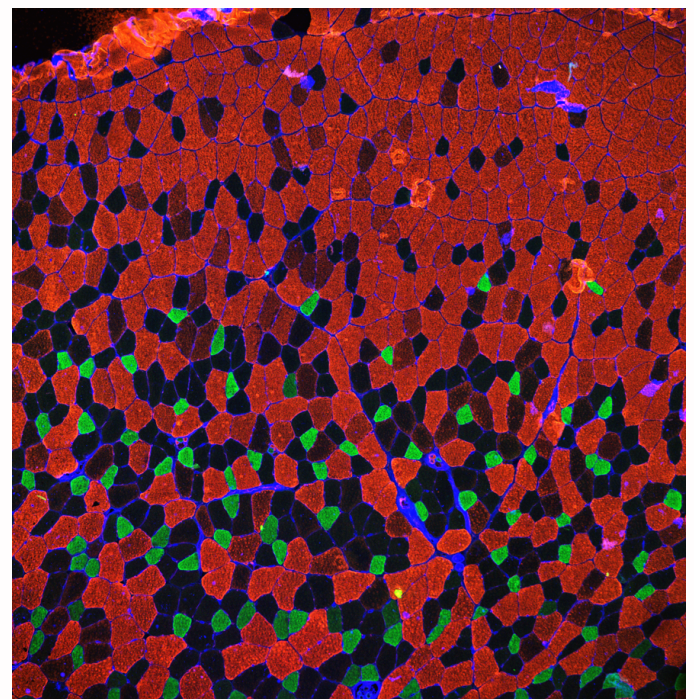
**Borja Ibáñez**

Translational Laboratory for Cardiovascular Imaging and Therapy



**Enrique Lara-Pezzi**

Molecular Regulation of Heart Failure



**Fig 3.**  
A cross section of mouse skeletal muscle stained to distinguish different types of muscle cells.



**Coordinator: Miguel Torres**  
**Clinical Leader: Hesham Sadek**

The Cardiovascular Regeneration Program (**CVRP**) investigates the fundamental mechanisms governing cardiovascular development, injury, and regeneration, with the goal of translating this knowledge into therapeutic strategies for cardiovascular disease.

In 2025, the program advanced understanding of the cardiac response to injury and generated new experimental tools and therapeutic approaches.

### Key Achievements in 2025

#### Metabolic Regulation of Cardiac Function

- **Conscore—A conservation-based framework for the analysis of mitochondrial energy production:** Jose Antonio Enriquez's group developed *ConScore*, a conservation-based tool that predicts the pathogenicity of mutations associated with oxidative phosphorylation (OxPhos). Using this approach, they mapped the coevolution of the 103 OxPhos protein subunits, identifying key constraints that ensure proper function. This unified framework integrates structural biology, population genetics, and evolutionary analysis, improving detection of clinically relevant genetic variants and deepening understanding of the architecture, adaptability, and pathogenic potential of the mitochondrial energy production system (1).

#### Heart Injury and Regeneration

- **Paternal influences on offspring response to cardiac injury:** Following cardiac injury, systemic stress can alter the function of remote organs. Whether such stress affects gametogenesis and transmits heritable changes to subsequent generations remains unclear. Using a mouse model, the Mercader group showed that offspring of males subjected to cardiac cryoinjury during early postnatal life exhibit enhanced transient ventricular plasticity and improved LV compliance (2).
- **Resetting the body clock to improve outcome after myocardial infarction:** The Hidalgo lab identified a mechanism by which circadian oscillations confer time-of-day-dependent cardioprotection through the redistribution of neutrophils away from the healthy tissues. They further identified a pharmacological intervention capable of modulating this immune timing to align with periods of maximal protection (8).
- **Activating cardiomyocytes to boost cardiac regeneration:** The Torres lab demonstrated that induced Myc expression at homeostatic levels induces partial dedifferentiation of adult mouse cardiomyocytes, increasing their proliferative capacity and improving functional recovery after myocardial infarction (4).
- **Forced activation of cardiomyocyte proliferation improves cardiac function:** The Sadek lab showed that temporally regulated overexpression of pro-cytokinetic factors in the adult heart induces cardiomyocyte proliferation and enhances left ventricular systolic function after myocardial infarction (3).

- **A secreted factor that induces heart regeneration:** The Sadek lab also identified the paracrine factor *Igfbp3* as a secreted molecule induced in the neonatal heart after injury that mediates regenerative responses. Forced expression of *Igfbp3* in the adult heart promotes cardiomyocyte proliferation and improves functional recovery after injury (*J Mol Cell Cardiol*, 2025).

#### Mechanistic Studies in Heart Disease and Tissue Repair

- **Cellular mechanisms underlying skin barrier protection:** The Hidalgo lab identified a population of immune cells in the skin that contribute to tissue repair, protection, and fibrotic responses (9).
- **Signals that disturb cardiac electrical conduction:** Jose Luis de la Pompa's group discovered signaling mechanisms that control ventricular wall and conduction system maturation and are linked to cardiomyopathy (*PLoS One* 2025). The group has also advanced the characterization of novel genes involved in ventricular development and heart disease.

#### Cardiovascular Development

- **A revised cellular map of heart development:** Miguel Torres and colleagues used single-cell live tracking and prospective lineage labelling to redefine the origins of the cell populations that form the heart and to map their interactions during mammalian embryogenesis (5).
- **Lymphatic vessels find their niche in the epicardium:** The Torres lab identified epicardial signals required for coronary lymphangiogenesis, establishing the sub-epicardium as a critical niche for cardiac lymphatic vessel development (6).

#### Experimental therapies in model organisms

- **Retuning cardiac rhythm:** José Jalife and colleagues showed that treatment with the polyamines spermine or spermidine restores normal cardiac electrical activity and reduces arrhythmia susceptibility in a mouse model of Short QT Syndrome type 3 (SQT3). Polyamines corrected potassium channel dysfunction and improved sodium channel function, supporting their potential as a therapeutic strategy for SQT3-related arrhythmias (*bioRxiv*, 2025).
- **Repurposing risedronate for genetic cardiomyopathy:** Hesham Sadek's group used virtual docking to identify risedronate, an FDA-approved drug, as a candidate therapy able to structurally and functionally correct the sarcomeric troponin T K210del mutation in mice and human iPSC-derived cardiomyocytes (7).

#### Awards and Recognition

- Miguel Torres was awarded **The National Prize in Genetics** from the Spanish Society of Genetics in July 2025.

#### Highlighted Grants in 2025

- **Advanced ERC Grant.** José Antonio Enriquez was awarded 2.5€ million for the project MINTRAF: Cell-Cell Communication by Mitochondrial Intercellular Traffic (2025-2030).



- **Horizon Europe EIC Pathfinder Grant.** Florian Weinberger was awarded €690,000 for the project HEARTVISION: ILLUMINATING NEW PATHS IN HEART FAILURE THERAPY (2026-2030).
- **ERA4Health.** Hesham Sadek was awarded €175,000 as part of the multi-investigator FONTANA project to develop novel therapeutics for myocardial regeneration (2025-2028).

### Highlighted Publications

1. Cell Genom. 2025 Sep 10;5(9):100945. doi: [10.1016/j.xgen.2025.100945](https://doi.org/10.1016/j.xgen.2025.100945)
2. Circulation. 2025 Apr;151(13):968-971. doi: [10.1161/CIRCULATIONAHA.124.070323](https://doi.org/10.1161/CIRCULATIONAHA.124.070323)
3. Circulation. 2025 Apr 8;151(14):1009-1023. doi: [10.1161/CIRCULATIONAHA.124.065763](https://doi.org/10.1161/CIRCULATIONAHA.124.065763)
4. J Mol Cell Cardiol. 2025 Oct;207:93-106. doi: [10.1016/j.yjmcc.2025.08.004](https://doi.org/10.1016/j.yjmcc.2025.08.004)
5. Commun Biol. 2025 Jul 18;8(1):1069. doi: [10.1038/s42003-025-08360-w](https://doi.org/10.1038/s42003-025-08360-w)
6. Dev. Cell. 2025 Sep 22;60(18):2434-2444.e5. doi: [10.1016/j.devcel.2025.05.002](https://doi.org/10.1016/j.devcel.2025.05.002)
7. EMBO Reports 2025 Jun;26(11):2803-2818. doi: [10.1038/s44319-025-00431-7](https://doi.org/10.1038/s44319-025-00431-7)
8. J Clin Invest. 2025 Feb 17;135(4):e174081. doi: [10.1172/JCI174081](https://doi.org/10.1172/JCI174081)
9. J Exp Med. 2026 Feb 2;223(2):e20250240. doi: [10.1084/jem.20250240](https://doi.org/10.1084/jem.20250240)
10. Nature. 2025 May;641(8063):740-748. doi: [10.1038/s41586-025-08741-5](https://doi.org/10.1038/s41586-025-08741-5)

### RESEARCH GROUPS



#### Rui Benedito

Molecular Genetics of Angiogenesis



#### José Luis de la Pompa

Intercellular Signaling in Cardiovascular Development and Disease



#### José Antonio Enríquez

Functional Genetics of the Oxidative Phosphorylation System (GENOPHOS)



#### Andrés Hidalgo

Imaging the Cardiovascular Inflammation and the Immune Response



#### José Jalife

Cardiac Arrhythmia



#### Nadia Mercader

Development of the Epicardium and its Role during Regeneration



#### Hesham Sadek

Myocardial Regeneration via Cardiomyocyte Cell Cycle Regulation



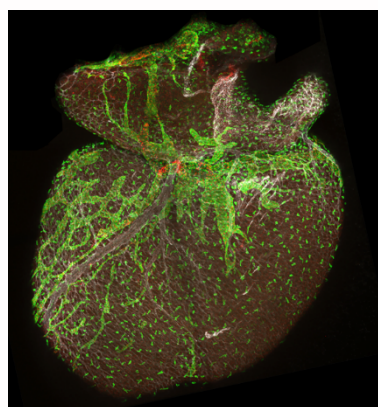
#### Miguel Torres

Genetic Control of Organ Development and Regeneration



#### Florian Weinberger

Cardiac Tissue Engineering and Regenerative Therapies



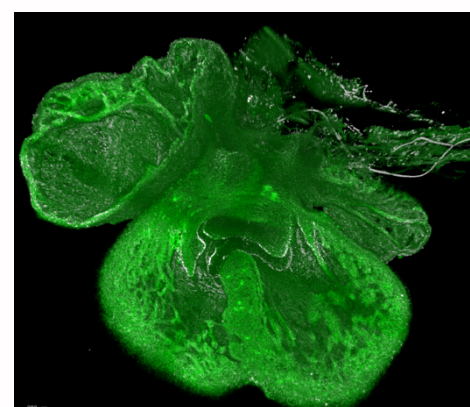
**Fig1.**

A late fetal mouse heart, showing the coronary lymphatic vasculature in green+red, macrophages in green, and coronary veins in gray.



**Fig2.**

The developing heart of an E8 mouse embryo, showing myocardium in red and endothelial cells in green.



**Fig3.**

3D reconstruction of an E13.5 wild-type heart, transverse view. The myocardium (green) is labeled with Tnnt2 and the endocardium (white) with Isolectin-B4. Note the trabeculae extending toward the ventricular lumen.



## 4

**Novel Arrhythmogenic Mechanisms****Coordinator: Silvia Priori****Clinical Leader: David Filgueiras**

The Novel Arrhythmogenic Mechanisms program investigates the cellular, molecular, and electrophysiological processes that lead to cardiac arrhythmias, with the aim of identifying new therapeutic targets and improving the prevention and treatment of life-threatening rhythm disorders. The program combines experimental models, computational approaches, and translational studies to understand both rare inherited channelopathies and common arrhythmias associated with structural heart disease.

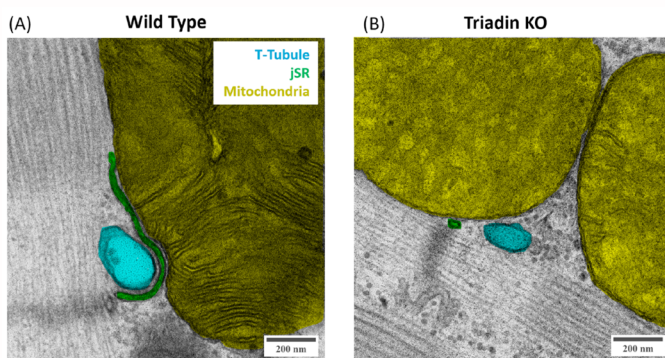
In 2025, the program made advances in three main areas: calcium-handling disorders, gene-based therapies for inherited channelopathies, and the identification of electrophysiological substrates responsible for ventricular arrhythmias.

**Disruption of intracellular calcium regulation**

Research during the past year focused on the consequences of defective calcium handling using a mouse model of Triadin-knockout syndrome, a recessive inherited disorder characterized by severe arrhythmias caused by the absence of Triadin, a protein essential for the organization of cardiac  $\text{Ca}^{2+}$  release complexes.

We found that  $\text{Ca}^{2+}$  handling proteins in Triadin-deficient hearts fail to localize correctly to  $\text{Ca}^{2+}$  release units and are instead degraded through autophagy and lysosomal pathways. These findings explain the reduced expression of  $\text{Ca}^{2+}$  handling proteins previously reported in this disease.

Structural studies confirmed that  $\text{Ca}^{2+}$  release complexes are severely disorganized in Triadin-knockout hearts. Introduction of either Triadin itself or the structural protein Juncophilin 2 in affected animals restored normal ultrastructure and significantly improved the arrhythmic phenotype, demonstrating that correction of structural defects can reverse the functional consequences of the disease (Figure 1).



**Fig 1.** Transmission electron microscopy micrographs of cardiac  $\text{Ca}^{2+}$  release units and associated mitochondria. (A) Wild-type hearts show normal association between T-tubules, junctional sarcoplasmic reticulum (jSR), and mitochondria, whereas Triadin-knockout hearts display marked structural disorganization—with T-tubule and jSR shrinkage and separation—associated with abnormal  $\text{Ca}^{2+}$  handling.

**New targets and gene therapies for inherited channelopathies**

A second line of work focused on the development of new therapies for inherited channelopathies, with particular attention to Timothy Syndrome type 1, a severe arrhythmogenic disorder with very poor survival in affected patients.

In collaboration with the Molecular Cardiology laboratory at IRCCS Maugeri and the University of Pavia, we developed a gene-therapy approach for Timothy syndrome and tested it in knock-in swine carrying the disease mutation. Treatment improved the electrical phenotype *in vivo*, providing proof of principle that gene therapy can correct this disorder.

Computational studies performed in collaboration with the University of Pavia generated *in-silico* models of cardiomyocytes derived from induced pluripotent stem cells, allowing detailed analysis of the electrophysiological alterations associated with Timothy syndrome (in press). Ongoing work is evaluating the gene therapy strategy in human iPSC-derived cardiomyocytes to assess its translational potential.

**Electrophysiological substrates of ventricular arrhythmias**

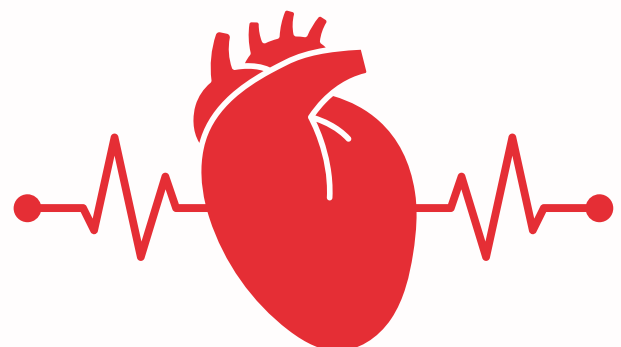
The program also continued long-standing work aimed at identifying the myocardial substrate responsible for ventricular arrhythmias in ischemic cardiomyopathy.

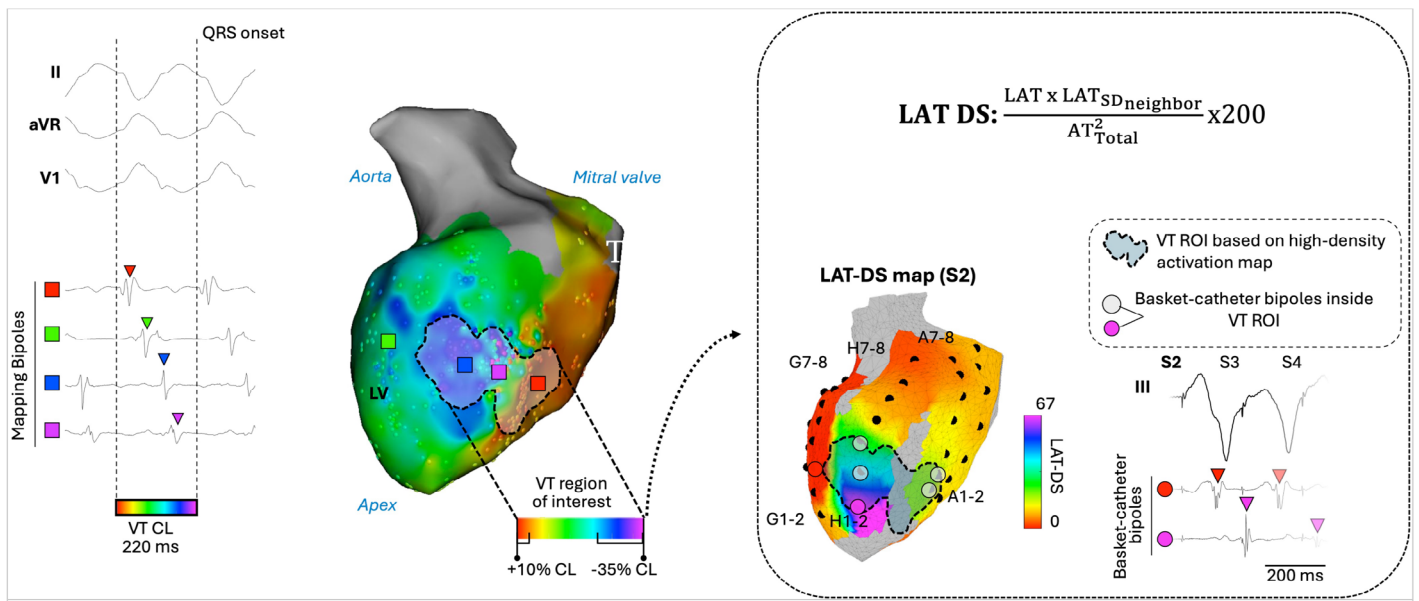
Using single-beat multipolar recordings obtained during programmed ventricular stimulation, we showed that regions with large activation-time dispersion reliably identify protected isthmus sites responsible for infarct-related monomorphic ventricular tachycardia (Figure 2). Increasing degrees of activation-time dispersion were associated with progressively more severe post-stimulation outcomes, ranging from non-inducible arrhythmia to ventricular fibrillation. Although obtained in experimental models, these findings can be translated to clinical practice using already available mapping tools.

Additional studies examined the electrophysiological and structural mechanisms that determine ventricular fibrillation dynamics. We identified interventricular differences in endocardial and epicardial activation rates during both short and prolonged episodes of fibrillation, reflecting unequal tolerance to global ischemia. Similar activation-rate patterns were observed in surface ECG recordings from patients, where higher activation rates were associated with poor neurological outcomes. The results indicate that ventricular activation rate during fibrillation may serve as a dynamic marker of ischemia damage in both the heart and other vital organs.

**Training, Meetings, and Recognition**

Program researchers participated in major international meetings, including the ESC, EHRA, and EWGCE conferences. Ana Simón-Chica received the Outstanding Thesis Dissertation Award from the Universidad Carlos III (Madrid).





**Fig 2.** Electrophysiological mapping of ventricular tachycardia (VT) circuits in a heart with infarct-related scarring. Left, Three surface ECG leads during VT and sample electrograms at different mapping locations on the color-coded high-density activation map. On the map, the VT region of interest (ROI), containing the critical site for VT maintenance (isthmus site) is demarcated with a black dashed line.

Right, The VT isthmus site is identified on the local activation time dispersion score (LAT-DS) map of the first coupled extra-stimulus (S2) of the programmed ventricular stimulation prior to VT induction. Basket-catheter bipoles inside the VT ROI are highlighted with gray and purple circles. Sample electrograms are also shown from basket catheter bipoles inside (purple) and outside (red) the VT ROI.

#### Highlighted Publications and Conference Presentations

1. Eur Heart J. 2025 Nov; 46(Supplement 1). [doi: 10.1093/eurheartj/ehaf784.4747](https://doi.org/10.1093/eurheartj/ehaf784.4747)
2. Sci Rep. 2026 Feb 16;16(1):9260. [doi: 10.1038/s41598-026-37707-4](https://doi.org/10.1038/s41598-026-37707-4)
3. European Society of Cardiology, 2025 Congress. Late-Breaking Basic & Translational Science Session. [Treating Timothy Syndrome.](#)

#### RESEARCH GROUPS



**David Filgueiras**

Advanced Development in Arrhythmia Mechanisms and Therapy



**Silvia Priori**

Molecular Cardiology



## Cardiovascular Risk Factors and Brain Health

**Coordinator: María Ángeles Moro**  
**Clinical Leader: Valentin Fuster**

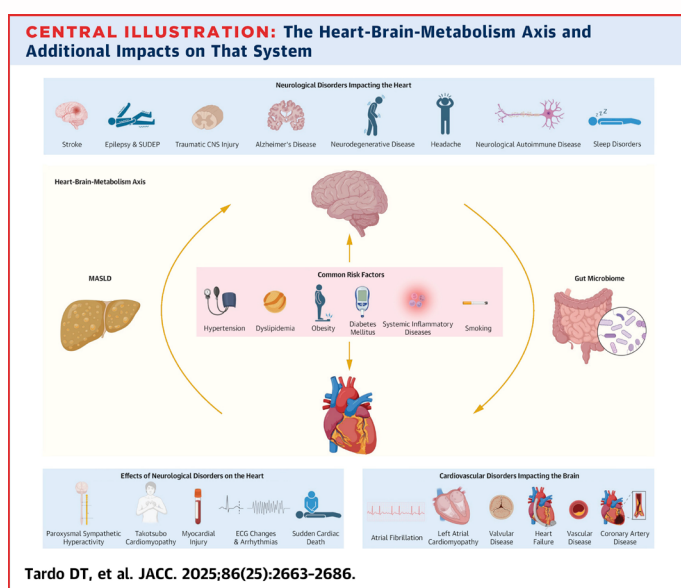
The Cardiovascular Risk Factors and Brain Health program investigates the bidirectional relationship between cardiovascular disease and neurological disorders, with particular emphasis on stroke, Alzheimer's disease, vascular cognitive impairment, immune-metabolic interactions, and mental health. The program integrates vascular biology, immunology, neuroinflammation, translational stroke research, cardiovascular prevention, and clinical consensus development to advance mechanistic understanding and therapeutic innovation.

In 2025, the program made major advances in the study of the heart-brain axis, combining conceptual work, translational studies, imaging innovation, and international clinical initiatives that were reflected in publications in leading journals. The program's collective contributions reinforced the view of cardiovascular disease as a systemic condition with critical neurological consequences and identified immune and thrombo-inflammatory pathways as actionable therapeutic targets.

### Key Achievements in 2025

#### The heart-brain-metabolism axis

A major conceptual milestone was the publication of a review in the *Journal of the American College of Cardiology* (Tardo et al., 2025)—with key contributions from program members Valentin Fuster and Marta Cortes-Canteli—defining the heart-brain-metabolism axis as a unifying framework linking cardiometabolic dysfunction with neurodegeneration and cognitive decline (**Fig. 1**). This review brought together evidence showing that cardiovascular and neurological diseases share inflammatory, thrombo-inflammatory, and metabolic pathways, providing a roadmap for integrated therapeutic strategies.

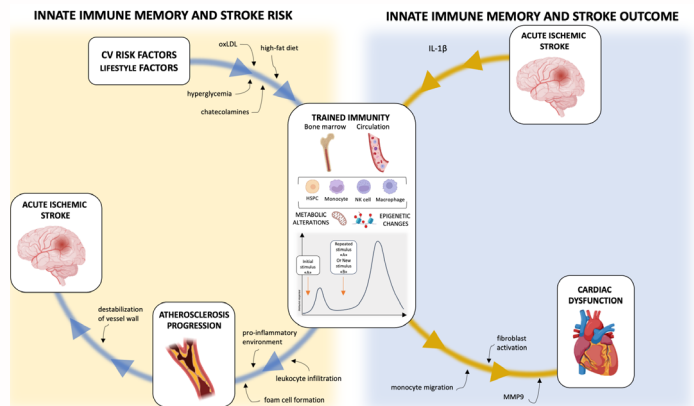


**Fig 1.**

The heart-brain-metabolism axis and additional impacts on that system.

#### Stroke, inflammation, and trained immunity

Stroke research remained a central pillar of the program. A perspective article in *Stroke*(5) highlighted innate immune memory as a modifiable determinant of stroke susceptibility and outcome, positioning trained immunity as a target for prevention (**Fig. 2**).



**Fig 2.**

The role of innate immune memory in stroke risk and outcome.

Translational work from María Ángeles Moro's group (*Stroke*, 2025) further showed that daytime DNase-I administration protects mice from ischemic stroke without increasing haemorrhagic risk, even in the presence of aspirin, supporting the safety of therapeutic strategies targeting neutrophil extracellular traps (NETs).

Complementary studies from Hector Bueno's group characterized NETs in acute myocardial infarction, strengthening the mechanistic link between thrombosis, inflammation, and ischemic injury (*J Cardiovasc Transl Res*, 2025). In addition, María Ángeles Moro's participation in a Leducq-funded multicenter collaboration bore fruit in methodological recommendations to standardize post-stroke cognitive assessment in preclinical models, improving reproducibility and translational alignment (*J Cereb Blood Flow Metab*, 2025).

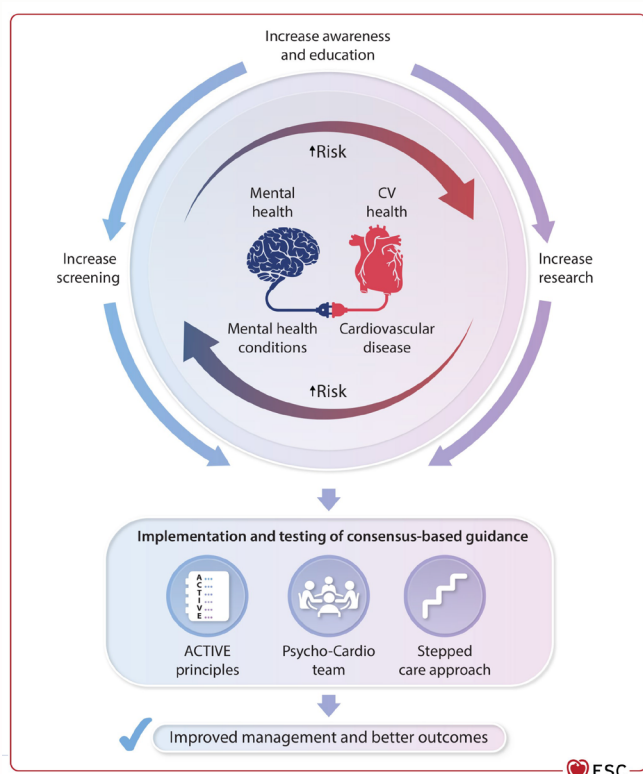
#### Vascular mechanisms in Alzheimer's disease

Program scientists also advanced the vascular dimension of Alzheimer's disease. A review from Marta Cortes-Canteli (*Curr Opin Cell Biol*, 2025) consolidated evidence that Alzheimer's disease involves a procoagulant and vascular dysfunction component, reinforcing the concept of the disease as a thrombo-inflammatory disorder.

In parallel, new brain-penetrant peptide and antibody radioligands were developed to enable PET imaging of fibrin, providing a translational tool to visualize vascular pathology in vivo (*EJNMMI Radiopharm Chem*, 2025).

#### Mental health and cardiovascular disease

Mental health and cardiovascular disease constituted another strategic area of activity. The 2025 ESC Clinical Consensus Statement on mental health and cardiovascular disease (*Eur Heart J*, 2025) represented a major international effort integrating psychiatric and cardiovascular care (**Fig. 3**). Additional work explored the relationship between depression, seasonal patterns, and cardiovascular risk, highlighting the importance of psychosocial determinants of cardiovascular outcomes (*Eur J Prev Cardiol*, 2025).

**Fig 3.**

Mental/cardiovascular health, disease interaction, and future directions. (CV: cardiovascular. ACTIVE: **A**cknowledge, **C**heck, (use validated) **T**ools, **I**mplement, **V**enture, **E**valuate).

### Immune-vascular interactions in cardiovascular disease

The program also contributed to broader immunocardiovascular research. A comprehensive review in the *Journal of Clinical Investigation*, authored by Pilar Martín with Francisco Sánchez-Madrid (*J Clin Invest*, 2025), examined the role of T cells in cardiac health and disease, advancing understanding of adaptive immunity in cardiovascular pathology. An additional study explored systemic immune-vascular interactions in cardio-oncology showing how peripheral ischemia induces myeloid-skewed hematopoiesis and systemic immune remodeling, underscoring the impact of vascular stress on innate immune regulation and inflammatory responses (*JACC CardioOncol*, 2025).

### Awards and Recognition

In 2025, several program members received national and international awards and fellowships, including the *Alumna Illustris* distinction from the Universidad de Alcalá School of Pharmacy to María Ángeles Moro, MSCA postdoctoral fellowships, regional predoctoral contracts, and young investigator awards from the Spanish Society of Biochemistry and Molecular Biology and the European Society of Cardiology.

### Highlighted Publications

#### Original Articles

1. Rev Esp Cardiol (Engl Ed). Epub Sep 19, 2025. 79(3):247-256 (2026). doi: [10.1016/j.rec.2025.08.005](https://doi.org/10.1016/j.rec.2025.08.005)
2. N Engl J Med. 2025 Nov 13;393(19):1889-1900. doi: [10.1056/NEJMoa2504735](https://doi.org/10.1056/NEJMoa2504735)
3. Eur Heart J. 2025 Nov 3;46(41):4156-4225. doi: [10.1093/eurheartj/ehaf191](https://doi.org/10.1093/eurheartj/ehaf191)

#### Commentaries, Editorials, Guidelines, Reviews

4. Eur J Prev Cardiol. 2025 18:zwaf736. doi: [10.1093/eurjpc/zwaf736](https://doi.org/10.1093/eurjpc/zwaf736)
5. Stroke. 2025 Oct;56(10):3095-3098. doi: [10.1161/STROKEAHA.125.049900](https://doi.org/10.1161/STROKEAHA.125.049900)
6. JACC CardioOncol. 2025 Aug;7(5):578-579. doi: [10.1016/j.jaccao.2025.07.002](https://doi.org/10.1016/j.jaccao.2025.07.002)
7. J Clin Invest. 2025 Jan 16;135(2):e185218. doi: [10.1172/JCI185218](https://doi.org/10.1172/JCI185218)
8. Rev Esp Cardiol (Engl Ed). 2025 Mar;78(3):286-287. doi: [10.1016/j.rec.2024.11.013](https://doi.org/10.1016/j.rec.2024.11.013)
9. Kardiol Pol. 2025;83(5):543-545. doi: [10.33963/v.phj.105682](https://doi.org/10.33963/v.phj.105682)
10. Rev Esp Cardiol (Engl Ed). 2025 Jul;78(7):628-636. doi: [10.1016/j.rec.2024.11.009](https://doi.org/10.1016/j.rec.2024.11.009)

### RESEARCH GROUPS



#### Héctor Bueno

Multidisciplinary Translational Cardiovascular Research



#### Valentín Fuster

Cardiovascular Imaging and Population Studies



#### Pilar Martín

Regulatory Molecules of Inflammatory Processes



#### María Ángeles Moro

Neurovascular Pathophysiology



**Coordinator: Rodrigo Fernández Jiménez**  
**Clinical Leader: Valentín Fuster**

Cardiovascular disease (CVD) remains one of the leading causes of death and disability worldwide, and its high prevalence and impact are largely driven by modifiable risk factors, such as smoking, unhealthy diet, and physical inactivity. Alarming, the burden is expected to increase due to rising rates of unhealthy lifestyles and obesity, particularly among children.

The Cardiovascular Health Promotion Program (CHPP) addresses this challenge through multidisciplinary studies and clinical trials conducted in collaboration with schools and communities. These initiatives target both children and adults, with the aim of implementing early prevention strategies and developing non-invasive technologies to support translational research and population studies on preclinical atherosclerosis.

The ultimate goal of the program is to reduce the personal and societal burden of CVD through health promotion and prevention strategies, with the potential to increase life expectancy and reduce the risk of other diseases, including dementia and cancer. The program focuses on three key objectives:

- Refining primordial prevention strategies in children and adolescents.
- Improving primary prevention by addressing the early, subclinical development and progression of atherosclerosis in young adults.
- Translating health-promotion initiatives to the general population.

The program comprises two research groups: Cardiovascular Imaging and Population Studies (PI, Valentín Fuster) and Cardiovascular Health and Imaging (PI, Rodrigo Fernández-Jiménez). In 2025, the program achieved significant scientific advances, summarized below.

### Key Achievements in 2025

#### Gender-related differences in adolescents' cardiovascular health

Analysis from the SI! Program for Secondary Schools trial showed that overall cardiovascular health, measured using the American Heart Association's Life's Essential 8 score, declined during adolescence, with a greater decrease in boys than in girls (Figure 1) (1). Sex-related differences were observed in most individual cardiovascular health metrics, highlighting the need for sex-specific strategies to improve the effectiveness of adolescent health-promotion programs.

#### Impact of sleep on cardiac remodeling in adolescents

As part of the EnIGMA (Early Imaging Markers of unhealthy lifestyles in Adolescents) project, sleep patterns were objectively assessed in 109 adolescents by accelerometry, combined with magnetic resonance imaging of the heart and liver. Shorter sleep duration was independently associated with adverse markers of cardiac remodeling and increased liver fat accumulation (2), emphasizing the importance of sleep health early in life and supporting its inclusion as a target for public health policy.

#### A community-based educational intervention for cardiovascular health and well-being

An interim two-year analysis of the Cardona Healthy Community 2030 program showed that participation in health-education workshops produced dose-dependent improvements in physical activity, adherence to the Mediterranean diet, and lipid and blood-pressure metrics (*JACC Advances*, in press).

#### Beta-blocker therapy after myocardial infarction with preserved ejection fraction

Program researchers participated in the REBOOT trial, which showed that patients discharged after invasive care for myocardial infarction with left ventricular ejection fraction above 40% derived no benefit from long-term beta-blocker therapy, as measured as the incidence of death from any cause, reinfarction, or hospitalization for heart failure (5).

#### Cost-effectiveness of the cardiovascular polypill

An international multidisciplinary analysis of data from the SECURE trial demonstrated that the cardiovascular polypill is an effective and cost-effective strategy for secondary prevention, reducing cardiovascular events and healthcare costs in Spain (Figure 2) (3).

#### Inclusion of the cardiovascular polypill in the WHO List of Essential Medicines

A state-of-the-art review described the epidemiological need for, and barriers to, wider implementation of the cardiovascular polypill, a simple and scalable strategy for secondary prevention. The polypill is now included in several European guidelines for CVD management, and the World Health Organization has added it to the List of Essential Medicines, an important step toward expanding access to care worldwide, particularly in low- and middle-income countries (Figure 3) (4).

#### Funding, Outreach, and Recognition

Funding supporting studies involving program researchers included grants from the "la Caixa" Foundation (LCF/PR/CE16/10700001 and LCF/PR/MS19/12220001), Fundació la Marató de TV3 (369/C/2016), the ISCIII with European Union co-funding (PI19/01704 and PI22/01560), and the MSCA-COFUND Cure Heart & Brain program (GA 101126521).

The program also maintains strong outreach activity to promote cardiovascular health awareness. In 2025, members participated in public events, including the XXV Science and Innovation Week in Madrid.

Clinical leader Valentín Fuster received several distinctions, including the title of Doctor Honoris Causa from the European University of Cyprus, the Presidential Honorary Award from the President of Cyprus, and the Order of Merit of Duarte, Sánchez, and Mella from the Dominican Republic. He also delivered the inaugural World Heart Federation lecture at the European Society of Cardiology Congress 2025 in Madrid, where he received the WHF Lifetime Achievement Award.

#### Highlighted Publications

1. Eur J Prev Cardiol. 2025;zwaf210. doi: [10.1093/eurjpc/zwaf210](https://doi.org/10.1093/eurjpc/zwaf210)
2. JACC Cardiovasc Imaging. 2025;18(9):1062-1064. doi: [10.1016/j.jcmg.2025.05.006](https://doi.org/10.1016/j.jcmg.2025.05.006)
3. Lancet Reg Health Eur. 2025 Jun 27;55:101348. doi: [10.1016/j.lanepe.2025.101348](https://doi.org/10.1016/j.lanepe.2025.101348)
4. Nat Cardiovasc Res. 2025;4(3):259-265. doi: [10.1038/s44161-025-00619-z](https://doi.org/10.1038/s44161-025-00619-z)
5. N Engl J Med. 2025 Nov 13;393(19):1889-1900. doi: [10.1056/NEJMoa2504735](https://doi.org/10.1056/NEJMoa2504735)



## RESEARCH GROUPS



Rodrigo Fernández Jiménez

Cardiovascular Health and Imaging



Valentín Fuster

Cardiovascular Imaging and Population Studies

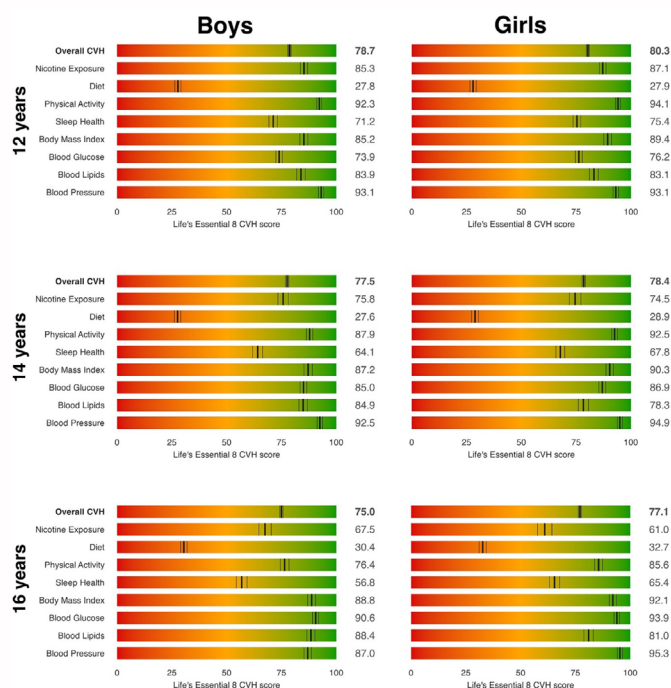


Fig1.

Scores for overall Life's Essential 8 (LE8) cardiovascular health (CVH) and each of the LE8 CVH metrics in boys and girls at 12, 14, and 16 years of age. Study population size was 1324 (641 girls, 48.4%), 1211 (580 girls, 47.9%), and 1095 (528 girls, 48.2%) adolescents at 12, 14, and 16 years of age, respectively. The charts show mean scores (thick vertical black lines) and 95% confidence intervals (thin vertical lines). Reproduced from *Eur J Prev Cardiol*, 2025.

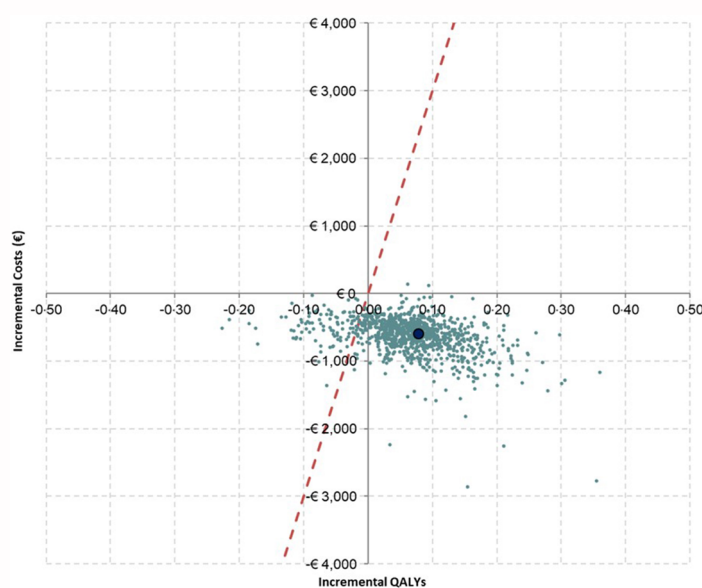


Fig2.

Cost-effectiveness analysis of the cardiovascular polypill for Spanish healthcare. Cost-effectiveness plane from probabilistic sensitivity analysis. Most simulations fall in the southeast quadrant, below the €30,000 threshold per additional Quality-Adjusted Life Year (QALY) gained, indicating that the CV-Polypill is both less costly and more effective than standard care. Reproduced from *Lancet Reg Health Eur*, 2025



Fig3.

Road to the development and clinical impact of the cardiovascular polypill.

It has taken more than 20 years to move from conceptual debate to solid evidence supporting the cardiovascular polypill as a proven strategy for improving adherence and outcomes while serving as a cost-effective, affordable, and accessible intervention worldwide. 2023 marked a turning point, following inclusion of the polypill in several European CVD management guidelines. Its subsequent inclusion in the WHO's List of Essential Medicines represents a key step in global efforts to expand access to care and combat CVD. ESC, European Society of Cardiology; ESH, European Society of Hypertension. Reproduced from *Nat Cardiovasc Res*, 2025.

**Coordinator: Beatriz Álvarez**

The eleven Technical Units (TUs) of the CNIC Technology Development Program (TDP) play a pivotal role in positioning the Center at the cutting edge of cardiovascular research. The TUs ensure that the CNIC remains a benchmark of scientific excellence through the development and implementation of advanced biomedical technologies, the provision of high quality internal and external services, and active engagement in training initiatives and collaborative funded projects.

Our work is fully aligned with the CNIC's strategic vision, integrating state-of-the-art technological innovations, strengthening communication and protocol harmonization, and ensuring the highest quality standards. This commitment is underpinned by robust infrastructure support and ISO-certified quality management systems, with all Technical Units holding UNE-EN ISO 9001:2015 certification.

**Key achievements in 2025**

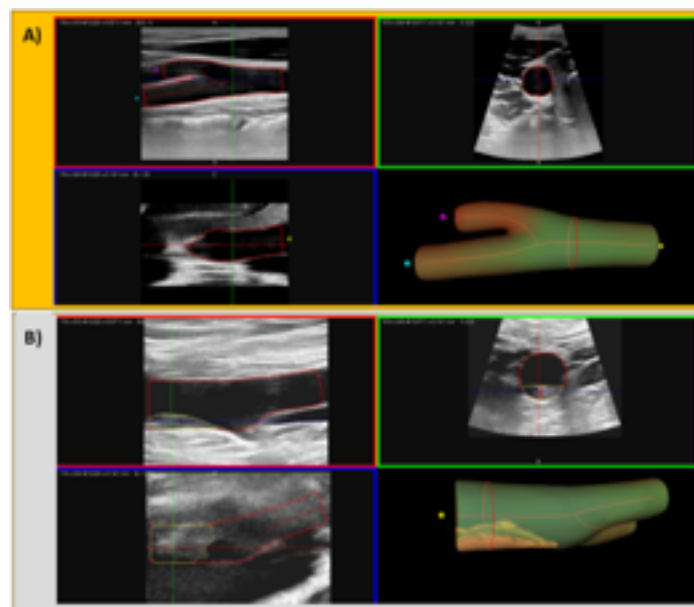
Deployment and optimization of the equipment acquired under the previous EQC2024 call, funded by the Ministry of Science, Innovation, and Universities, ensuring its readiness and maximal scientific impact:

1. Through EQC2024-007986-P, the Clinical Trials Coordination Unit (CTCU) acquired a spectral CT scanner at the end of 2024, and this equipment is now available to researchers.
2. Thanks to EQC2024-008058-P, the Metabolomics platform finalized the tender to acquire a high-sensitivity mass spectrometer for targeted lipidomics and metabolomics.
3. Through EQC2024-008109-P, the Advanced Imaging Unit purchased two ultrasound systems, now available to researchers for work with small animal models.
4. The Microscopy Unit incorporated a multimodal spinning-disk, high-resolution epifluorescence microscope with real-time image restoration and on-the-fly deconvolution. Thanks to the EQC2024-008059-P the system, the first of its kind in Spain, produces images with confocal-level quality.
5. Through EQC2024-008195-P, the Bioinformatics unit acquired and deployed equipment to build a computational platform for storing and analyzing biomedical images. The platform includes 16 new NVIDIA H100 cards to support the use of AI algorithms in CNIC projects. This project also includes renewal of the CNIC CPD cooling system.

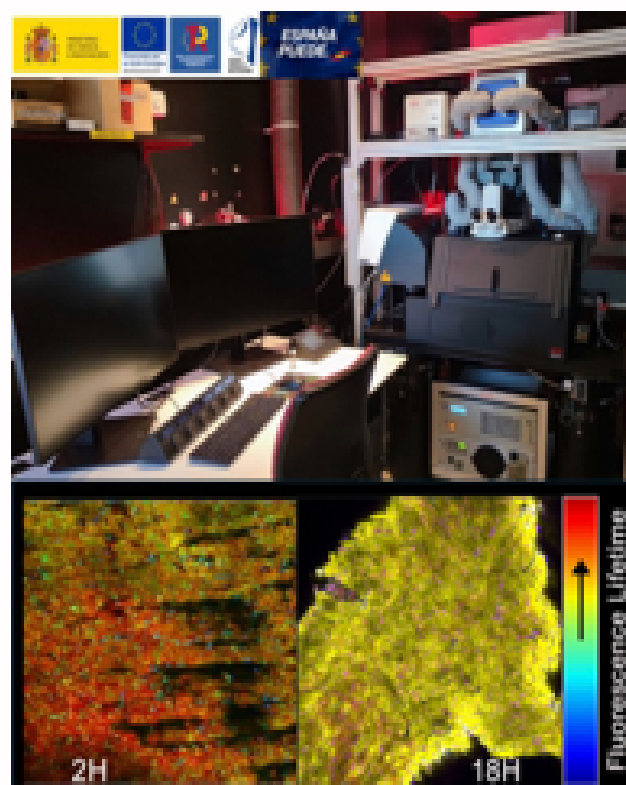
The TUs play a key role in the CNIC's scientific activity by providing specialized expertise, methodological support, and technological implementation, enabling high-quality data generation and strengthening research competitiveness. Their close collaboration with researchers also promotes service innovation and enhances scientific capacity.

In 2025, this joint effort resulted in 88 publications, 78% of them research articles. Of these, 85% (75 documents) were published in Q1 journals and 58% (51 documents) in D1 journals, and 65% (57 documents) involved international collaboration. The TUs also contributed to four Highly Cited Papers (HCPs), ranking in the top 1% most cited publications in their subject category over the past decade.

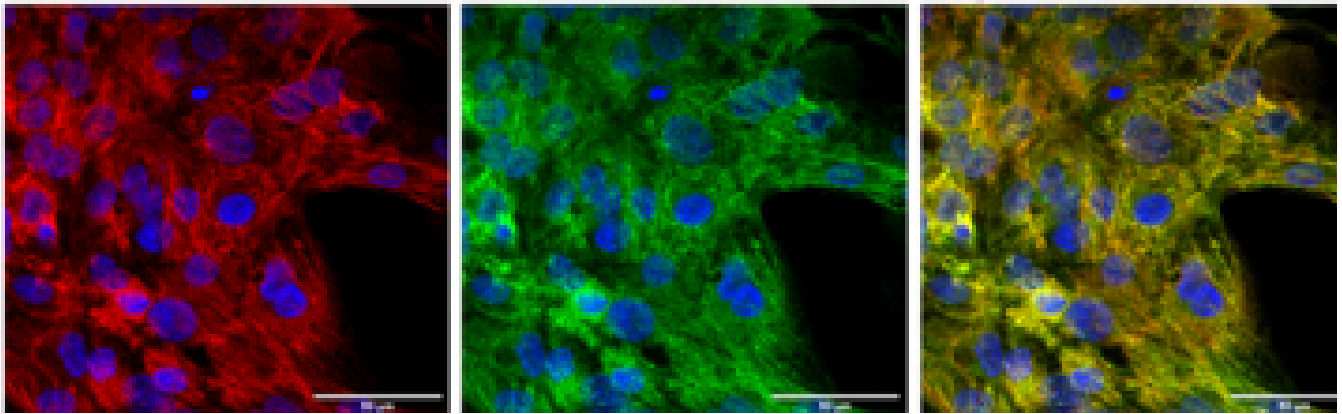
Training is a core pillar of the CNIC, and the TDP supports this mission through participation in the UAM Master's Program in Molecular Biomedicine and in initiatives such as Acércate, Res@cnic, the CNIC Seminar Series, Science Week, and Researchers' Day.



**Fig1.**  
3D imaging and reconstruction of atherosclerotic plaque in the carotid artery. Images in (A) show a carotid artery free of plaque, while images in (B) show a carotid artery with atherosclerotic plaque.



**Fig2.**  
FLIM imaging of doxorubicin in heart. The FLIM platform (top) can monitor the intracardiac clearance of doxorubicin and its cardiotoxic metabolite in freshly excised mouse heart tissue (bottom). Using intrinsic fluorescence-lifetime contrast, the drug distribution was assessed at 2, 12 and 24 hours after in-vivo administration. The longer fluorescence lifetimes (red areas) detected at 2 hours indicate substantial drug accumulation within cardiac tissue, which persists predominantly as metabolic derivatives localized mainly in cardiomyocyte nuclei at 12 hours [FLIM images were generated in collaboration with Laura Cádiz and Borja Ibáñez from the Translational Laboratory for Cardiovascular Imaging and Therapy].

**Fig3.**

CRISPR-Cas9 strategy for generating compound heterozygous human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). The hiPSC-CM line contains eGFP and HaloTag reporters knocked into the same genomic position on each titin (TTN) allele. [hiPSC-CMs were generated by the Pluripotent Cell Technology Unit.]

## TECHNICAL UNITS

**Fátima Sánchez Cabo**

Bioinformatics

**Antonio J. Quesada**

Clinical Trial Coordination

Advanced Imaging (Acting Head)

**Beatriz Álvarez**

Flow Cytometry



Comparative Medicine

**Ana Dopazo**

Genomics

**Valeria Caiolfa**

Microscopy

**Giovanna Giovinazzo**

Pluripotent Cell Technology

**Juan Antonio López**

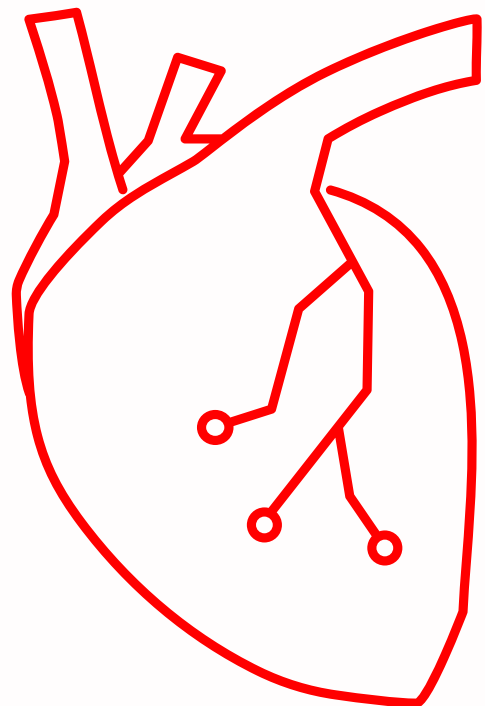
Proteomics

**Juan De Dios Hourcade**

Transgenesis

**Juan A. Bernal**

Viral Vectors





# Clinical Studies at the CNIC



Translational research plays a vital role in turning laboratory discoveries into real-world medical solutions. By bridging the gap between science and practice, this research helps develop new treatments, diagnostic tools, and prevention strategies that directly benefit patients. This approach combines insights from basic science with clinical expertise to accelerate medical progress and improve healthcare outcomes.

This patient-oriented approach is a cornerstone of our work at the CNIC. We are committed to advancing these studies and ensuring their impact on patient care through the clinical guides. Below, we highlight the clinical projects that were active in 2025.

## PESA-Health-CNIC-Santander: Early Detection of Subclinical Atherosclerosis, Disease Progression, and Cardiovascular Health

Principal Investigator: **Valentín Fuster**



The PESA-Health-CNIC-Santander Study builds on the original PESA Study, launched in 2010 by the CNIC in collaboration with Santander Bank. That study enrolled 4,184 asymptomatic individuals aged 40–55 to detect subclinical atherosclerosis (SA) long before symptoms arise and to investigate the factors driving its development and progression.

PESA-Health extends this work by following the same participants for an additional 10 years. The expanded program incorporates new research areas, including the links between SA and Alzheimer's disease or cognitive decline, the role of age-related somatic mutations, and how these mutations may influence cardiovascular events and SA progression.

As in the original PESA Study, PESA-Health employs advanced imaging technologies, including 3D vascular ultrasound of the carotid arteries and aorta, coronary artery calcium quantification by computed tomography, cardiac magnetic resonance imaging, coronary CT angiography (CTA), PET, and PET-amyloid analysis. The protocol also includes extensive biosampling for multi-omics analysis, alongside new substudies examining the association between SA and sleep apnea.

As the CNIC's flagship study, PESA-Health brings together numerous clinical and basic research groups across the center. Findings from the original PESA Study have already contributed substantially to our understanding of the origins and progression of atherosclerosis.

PESA-Health began in February 2020, with 3,496 original PESA participants continuing in the new phase. By the end of 2025, 319 participants had completed the second round of follow-up visits, corresponding to the fifth visit since the PESA Study's inception in 2010.



## REACT: Reversal of Early Atherosclerosis through Personalized Curative Treatment

Principal Investigator: **Borja Ibáñez**



Atherosclerosis—the progressive accumulation of plaque within arterial walls—is the leading cause of cardiovascular disease worldwide. As cholesterol, lipids, inflammatory cells, and other components build up over time, arteries narrow and blood flow to vital organs is reduced. The process often begins early in life, progresses silently, and can affect multiple vascular territories, contributing substantially to global morbidity and mortality.

To address this major health challenge, the CNIC and Rigshospitalet in Copenhagen have launched Phase 1 of the REACT project (Reversal of Early Atherosclerosis through Personalized Curative Treatment), funded by the Novo Nordisk Foundation. The primary goal of this phase is to determine the prevalence of asymptomatic (silent) atherosclerosis in a European-ancestry cohort across a broad age range (18–70 years). This will be achieved through advanced imaging techniques and circulating biomarkers, integrated with conventional cardiovascular risk factors.

Phase 1 is a large-scale prevalence study involving 16,000 participants (8,000 in Spain and 8,000 in Denmark). The study combines vascular ultrasound (3DVUS), coronary artery calcium scoring, CT angiography (CTA), and biomarker analysis to generate a detailed age-stratified profile of subclinical atherosclerosis. The findings will support the development of a more precise risk stratification algorithm than those currently in use.

The Phase 1 results will inform the design of Phase 2, a randomized clinical trial evaluating whether early, imaging-guided intervention—including lifestyle modification, non-pharmacological strategies, and lipid-lowering therapy—can reduce atherosclerotic plaque burden or even promote regression.

By the end of 2025, 5,714 participants aged 18–70 years (2,825 women and 2,889 men) had been enrolled. Recruitment is expected to reach the target of 8,000 participants by June 2026.

## RESILIENCE: Remote Ischemic Conditioning in Lymphoma Patients Receiving Anthracyclines

Principal Investigator: **Borja Ibáñez**

H2020 Grant No. 945118



Anthracyclines are a widely used class of anticancer drugs, administered to more than 3 million of the approximately 4 million patients diagnosed with cancer each year in Europe. Although highly effective, these drugs carry a substantial risk of cardiotoxicity: recent data indicate that more than 35% of treated patients develop some degree of cardiomyopathy. This trade-off between cancer control and long-term heart failure (HF) represents a growing clinical and healthcare challenge, with significant consequences for cancer survivors.

Remote ischemic preconditioning (RIPC) offers a potential strategy to mitigate this risk. RIPC is a non-invasive, safe, and cost-effective procedure involving brief, reversible episodes of ischemia—typically induced in a limb—followed by reperfusion. These cycles activate systemic protective mechanisms that can reduce tissue injury during subsequent ischemic events. Experimental studies in large-animal models have shown that 3–5 cycles of 5-minute limb ischemia followed by 5-minute reperfusion reduce infarct size after induced myocardial ischemia. Importantly, evidence suggests that RIPC must be applied before the damaging event to confer protection. Because chemotherapy is a planned intervention, anthracycline-induced cardiomyopathy provides a well-defined setting in which to test this approach.

RESILIENCE is a multinational, phase II, double-blind, sham-controlled, randomized clinical trial evaluating the efficacy and safety of RIPC in patients with lymphoma or breast cancer who are receiving treatment with anthracyclines. Eligible patients scheduled to receive  $\geq 240$  mg/m<sup>2</sup> of anthracyclines undergo baseline cardiac magnetic resonance (CMR) imaging and blood testing for high-sensitivity troponin (hsTn) and NT-proBNP. Patients with a CMR-confirmed left ventricular ejection fraction  $>40\%$  are randomized 1:1 to receive either RIPC or a sham procedure.



Nine weeks after completing chemotherapy, participants undergo repeat CMR imaging and biomarker assessment. Clinical follow-up visits are scheduled at 12, 18, 30, and 42 months, continuing until the final CMR evaluation is completed.

The trial aims to enroll 608 patients across 22 sites in six European countries (Spain, Portugal, France, Germany, the Netherlands, and Denmark). Funded by the European Commission (Grant Agreement No. 945118-RESILIENCE), RESILIENCE began its grant period in June 2021, with patient recruitment starting in 2022. Recruitment is expected to conclude in December 2026. By the end of 2025, all 22 sites remained active, and 445 participants had been enrolled.

## REBOOT: Treatment with Beta-blockers after Myocardial Infarction Without Reduced Ejection Fraction

Principal Investigator: **Borja Ibáñez**

### REBOOT

The routine use of beta-blockers for patients after myocardial infarction (MI) is largely supported by clinical trials conducted before the widespread adoption of reperfusion strategies. Although these agents provide clear benefit in patients with reduced left ventricular ejection fraction, their value in patients with preserved ejection fraction has remained unclear. Despite this limited evidence, more than 80% of post-MI patients in this category are prescribed lifelong beta-blocker therapy.

The REBOOT trial was designed to address this gap by evaluating whether beta-blocker therapy improves outcomes in post-MI patients with a left ventricular ejection fraction greater than 40%. This multinational, randomized study enrolled 8,506 patients, who were assigned either to receive beta-blockers (with the specific agent and dose determined by the treating physician) or to receive no beta-blocker therapy. The primary endpoint was a composite of all-cause mortality, reinfarction, or hospitalization for heart failure over a median follow-up of 3 years.

Coordinated by the CNIC Clinical Trials Coordination Unit and conducted in collaboration with the Mario Negri Institute of Pharmacological Research in Milan, the trial involved 77 hospitals in Spain and 29 in Italy.

In total, 4,243 patients were assigned to beta-blocker therapy and 4,262 to no beta-blocker therapy; after exclusions, 8,438 patients were included in the main analysis. Among patients discharged after invasive management of myocardial infarction with preserved ejection fraction (>40%), beta-blocker therapy did not reduce the incidence of death from any cause, reinfarction, or hospitalization for heart failure.

In 2025, the results were published in three papers, two in *The New England Journal of Medicine* ([doi: 10.1056/NEJMoa2504735](https://doi.org/10.1056/NEJMoa2504735)); ([doi: 10.1056/NEJMoa2512686](https://doi.org/10.1056/NEJMoa2512686)) and one in *The Lancet*. ([doi: 10.1016/S0140-6736\(25\)01592-2](https://doi.org/10.1016/S0140-6736(25)01592-2)). Full details are presented in the Scientific Highlights section.

## MRVALVE: Multimodality Myocardial Tissue Characterization in Patients with Significant Valvular Disease

Principal Investigator: **Borja Ibáñez**



The MRVALVE study uses a multimodality imaging strategy—combining cardiac magnetic resonance (CMR) and strain echocardiography—to characterize left ventricular (LV) structure, function, and tissue composition in patients with significant valvular heart disease (VHD). The study focuses on the two most common forms of VHD: aortic stenosis (AS) as a model of chronic LV pressure overload, and mitral regurgitation (MR) as a model of LV volume overload.

Valvular heart disease profoundly affects LV dimensions, function, and myocardial tissue properties, all of which are central to clinical decision-making. Current guidelines recommend surgical or percutaneous intervention once symptoms develop or when there is clear evidence of LV remodeling or dysfunction. However, disease progression—from asymptomatic stages to overt symptoms, and from preserved function to dilatation, hypertrophy, and failure—is driven by underlying myocardial changes, including cardiomyocyte loss, extracellular matrix expansion, and fibrosis.



Although valve repair or replacement is effective in severe VHD, intervention is typically triggered by symptoms or measurable LV dysfunction. By that stage, myocardial damage may already be partially reversible. MRVALVE addresses the need for earlier detection of myocardial involvement in asymptomatic patients, enabling better timing of intervention before permanent structural damage occurs.

CMR serves as the reference standard for anatomical and functional cardiac assessment. The procedure detects focal fibrosis using late gadolinium enhancement and enables advanced tissue characterization through parametric T1/T2 mapping, calculation of extracellular volume (ECV, a marker of diffuse fibrosis), and absolute myocardial perfusion assessment. These techniques require gadolinium-based contrast agents, which have an established safety profile. Hematocrit measurement is incorporated to refine ECV calculation.

Strain echocardiography provides sensitive assessment of myocardial deformation and can detect multidirectional strain abnormalities even when global LV function appears preserved. In MRVALVE, imaging findings are correlated with functional capacity measured by the six-minute walk test. Cardiac computed tomography is also performed to quantify coronary and valvular calcium deposition, generating a calcium score with diagnostic and prognostic relevance, particularly in AS.

To date, 71 patients have been enrolled, and all have completed their 1-year follow-up visit.

## MATRIX: Novel Mitochondria-targeted Therapies for Cancer Treatment-induced Cardiotoxicity

Principal Investigator: **Borja Ibáñez**

ERC Consolidator Grant No. 819775



The MATRIX Project aims to develop innovative therapies for cancer treatment-induced cardiotoxicity (CTiCT), a major limitation of modern oncology. This initiative is a joint effort between the CNIC and Fundación Jiménez Díaz University Hospital, building on a collaborative program established in 2015 to study myocardial diseases.

Although advances in cancer therapy have improved survival among the approximately 4 million patients diagnosed annually in Europe, many treatments carry significant cardiovascular risk. CTiCT affects up to 25% of patients receiving anthracyclines or trastuzumab and can lead to progressive cardiomyopathy, chronic heart failure, or death. This adverse effect represents a serious long-term burden for cancer survivors.

Current strategies for managing CTiCT remain suboptimal. Early detection tools lack sensitivity, and available heart failure therapies are largely nonspecific. Recent findings from our group suggest that CTiCT is closely associated with altered mitochondrial dynamics and subsequent metabolic reprogramming in cardiomyocytes.

MATRIX addresses this challenge through a comprehensive, mitochondria-centered approach. We hypothesize that early-stage CTiCT may be reversible through targeted metabolic reprogramming aimed at restoring mitochondrial substrate utilization. To enable timely intervention, the project incorporates a novel imaging-based algorithm developed by our team to detect subclinical myocardial injury in patients receiving commonly used anticancer drugs before conventional clinical parameters become abnormal.

In advanced stages of CTiCT, where mitochondrial dysfunction may be irreversible, MATRIX explores a more radical strategy: in vivo mitochondrial transplantation to replenish damaged myocardium with functional mitochondria.

The project has strong translational potential, spanning early diagnostic technologies, novel therapeutic strategies, and mechanistic insights into the pathophysiology of CTiCT.

Patient recruitment began in 2020. By the end of the study, 56 participants were enrolled, and the first results have been submitted for publication.



## PRECOGNITIVE: Effect of Remote Ischemic Preconditioning on Cognitive Function and Cerebral Vasculature

Principal Investigator: **Gonzalo Pizarro Sánchez**



Arterial hypertension can damage the cerebral vasculature even when blood pressure is adequately controlled. Current therapies primarily focus on managing blood pressure and preventing target-organ injury, including damage to the brain. Remote ischemic preconditioning (RIPC), first shown more than 30 years ago to protect organs such as the heart and brain in experimental models, has since been translated into clinical research. The technique consists of repeated cycles of cuff inflation and deflation on the arm—typically 4 cycles of 5 minutes each. The brief, controlled ischemia induced in the limb activates systemic protective mechanisms that may shield distant organs, including the brain, from subsequent ischemic injury.

Our research has contributed substantially to this field, with recent studies demonstrating that RIPC can improve cognitive performance and cerebral vascular function in patients with vascular dementia. PRECOGNITIVE is a proof-of-concept randomized clinical trial involving 45 women with hypertension and evidence of target-organ damage, such as left ventricular hypertrophy. Participants are allocated to one of three groups:

- 1.- **RIPC group:** undergoes the RIPC procedure, with the cuff inflated to 20 mmHg above systolic blood pressure.
- 2.- **RIPC-sham group:** follows the same protocol, but the cuff is inflated only to 50 mmHg, insufficient to induce ischemia.
- 3.- **Control group:** receives no cuff intervention.

The study evaluates whether RIPC exerts a protective effect on the cerebral vasculature in hypertensive patients without significant cognitive impairment. Outcomes are assessed using comprehensive neurocognitive testing and non-invasive imaging, including echocardiography, non-contrast brain magnetic resonance imaging, and transcranial Doppler ultrasound.

As of the end of 2025, 15 patients had been recruited.

## MACADAMIA: Characterization of Cardiac Metabolism Using Multimodal Imaging in Idiopathic Cardiomyopathy

Principal Investigator: **Borja Ibáñez**



Heart failure (HF) remains one of the most significant health challenges in modern societies, placing a heavy burden on healthcare systems. Developing effective therapies requires a deeper understanding of the mechanisms that drive the onset and progression of HF.

The heart is the most energy-demanding organ relative to its size. Under physiological conditions, it derives most of its ATP from fatty acid  $\beta$ -oxidation (approximately 60%), with carbohydrate metabolism via the Krebs cycle providing most of the remaining energy. Other substrates, such as amino acids, contribute minimally to overall energy production.

In HF, however, the myocardium undergoes a metabolic reprogramming often referred to as the “metabolic switch,” characterized by a shift from fatty acid oxidation toward a greater reliance on glucose metabolism. Although initially considered an adaptive response, accumulating evidence from experimental and clinical studies suggests that this shift may be energetically inefficient and contribute to progressive contractile dysfunction.

Our group has shown that the metabolic switch plays a central role in heart failure secondary to idiopathic dilated cardiomyopathy (IDCM). In mouse models, a diet rich in fatty acids reversed metabolic remodeling and improved cardiac phenotype. Similar findings were observed in pigs, whose metabolism more closely resembles that of humans.



Before initiating an interventional clinical trial in IDCM, it is essential to determine how prevalent the metabolic switch is in patients. The MACADAMIA study addresses this question through an observational analysis of a cohort of patients with IDCM. Using multimodal imaging—including transthoracic echocardiography with strain analysis, cardiac magnetic resonance (CMR), and positron emission tomography/computed tomography (PET/CT) with the radiotracer 18F-FDG—the study characterizes myocardial metabolic profiles without therapeutic intervention.

As of February 2026, 43 patients had been enrolled.

In the medium to long term, a randomized clinical trial is planned in IDCM patients demonstrating evidence of the metabolic switch. Participants will be assigned either to a fatty acid-enriched dietary intervention or to a standard diet, with outcomes assessed by CMR (cardiac function) and PET/CT (metabolic activity).

## ATTRACKING CNIC: The ATTRACKING Registry

Principal Investigator: **Pablo García-Pavía**



Tafamidis, acoramidis and vutrisiran are approved therapies for transthyretin amyloid cardiomyopathy (ATTR-CM), a rare and life-threatening disease caused by the buildup of transthyretin amyloid fibrils in the heart. The pivotal clinical trials demonstrated that these medications reduce mortality and cardiovascular hospitalizations. However, as with many pivotal trials, the study population may not fully reflect contemporary clinical practice.

Recent advances in diagnostic imaging and disease awareness have enabled earlier detection of ATTR-CM, resulting in changes in patient profiles and overall prognosis compared with those enrolled in the original trial. These shifts raise important questions about the effectiveness and safety of tafamidis in routine care. The ATTRACKING CNIC registry was established to evaluate ATTR-CM medications in a real-world, unselected cohort of patients with ATTR-CM across Spain.

### Objectives

1. To characterize the contemporary Spanish population of patients with ATTR-CM treated with ATTR-CM medications.
2. To assess the safety profile of ATTR-CM medications in routine clinical practice.
3. To compare real-world outcomes with those reported in the pivotal trials.

### Study Design

ATTRACKING CNIC is a prospective, multicenter, non-randomized observational registry enrolling patients diagnosed with ATTR-CM who initiate treatment with ATTR-CM medications.

As of February 2026, agreements have been signed with 51 hospitals, and 521 participants have been enrolled.

## TAILOR-AF: Patient-specific Ablation of Persistent Atrial Fibrillation Drivers Guided by Frequency and Amplitude Modulation Criteria

Principal Investigator: **David Filgueiras**

Co-Promoters: CNIC and Hospital Universitario Clínico San Carlos



Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation for persistent atrial fibrillation (AF). However, despite more than two decades of clinical use, long-term success rates remain modest. Approximately 40% of patients remain free of AF at 12 months following ablation without antiarrhythmic drug therapy, underscoring the need for more individualized treatment strategies.



To address this limitation, our group has developed a computational mapping tool that enables interventional electrophysiologists to identify atrial “driver regions” responsible for maintaining persistent AF. Using conventional electroanatomic mapping systems and multielectrode catheters, these regions are localized through novel signal-processing algorithms that analyze frequency and amplitude modulation of atrial electrograms during fibrillation. The algorithms—publicly available (Quintanilla JG et al. *Circ Res.* 2019;125:609-627)—quantify individual frequency modulation (iFM) and amplitude modulation (iAM), allowing precise identification of rotational activity and leading AF drivers.

The primary goal of the TAILOR-AF study is to apply iAM/iFM-guided mapping to identify and ablate the dominant drivers in patients with symptomatic persistent AF despite having undergone two or more prior PVI procedures. Secondary objectives include the evaluation of circulating biomarkers, advanced atrial imaging parameters, and surface electrocardiographic phenotypes associated with atrial remodeling. In selected patients undergoing minimally invasive thoracoscopic ablation, left atrial appendage tissue samples are collected to investigate the molecular mechanisms underlying AF maintenance.

As of the end of 2025, recruitment had been completed, and 80% of participants had finished the 1-year follow-up to assess arrhythmia recurrence. The results are expected to be communicated to the scientific community and the broader public during the third quarter of 2026.

## SIR-CVT: Spanish Immunotherapy Registry – Cardiovascular Toxicity

Co-Promotors: Sociedad Española de Cardiología, Sociedad Española de Oncología Médica



SIR-CVT is a prospective, non-interventional registry with two primary objectives:

1. To evaluate risk factors and current clinical management practices related to cardiovascular (CV) toxicity in patients with solid tumors receiving immune checkpoint inhibitors (ICIs) for approved indications.
2. To validate the human homolog of miR-721 as a biomarker for the early diagnosis of immunotherapy-induced myocarditis.

In addition, the study addresses several secondary objectives:

- To identify clinical, electrocardiographic, imaging, laboratory, and genetic markers associated with early diagnosis of ICI-related myocarditis.
- To detect markers of other ICI-related CV toxicities beyond myocarditis.
- To evaluate the association between prior chemotherapy exposure and subsequent ICI-related CV risk.
- To investigate the pathogenic mechanisms underlying myocarditis induced by immune checkpoint blockade (anti-PD-L1/PD1 and anti-CTLA4 therapies).
- To assess the impact of structured CV monitoring on patients' quality of life and perceived quality of care.

After a baseline visit, participants are managed according to standard clinical practice, including routine follow-up schedules determined by their treating physicians. Patients are followed for 12 months after enrollment, or until death or loss to follow-up. All data collected are used exclusively for research purposes.

As of February 2026, 10 patients had been enrolled and had undergone cardiac magnetic resonance imaging and echocardiographic evaluation at the CNIC.



## HF4HF: Cardiac Metabolic Reprogramming by Nutritional Intervention — High-Fat Diet for Heart Failure

Principal Investigator: **Borja Ibáñez**

Co-PI: **Pablo García-Pavía**



The heart is a highly energy-dependent organ that requires a continuous supply of ATP to sustain contractile function. Cardiac mitochondria generate this energy using multiple substrates, including fatty acids, glucose, and, to a lesser extent, amino acids. Under physiological conditions, fatty acid  $\beta$ -oxidation provides the majority of myocardial ATP, as it is the most energy-dense substrate.

In heart failure (HF), however, the myocardium undergoes metabolic reprogramming characterized by a shift from fatty acid oxidation toward increased reliance on glucose metabolism. Although initially considered adaptive, growing evidence suggests that this “metabolic switch” may contribute to impaired energetic efficiency and progressive contractile dysfunction.

HF4HF is funded by the ERA4Health Partnership and is coordinated by the CNIC. Participating institutions include the Fundación para la Investigación Biomédica Hospital Universitario Puerta de Hierro (IIS Majadahonda, Spain), INSERM (France), the University of Medicine and Pharmacy “Carol Davila” (Bucharest, Romania), and the University of Florence (Italy).

This project brings together a multidisciplinary consortium including cardiologists, nutrition specialists, imaging experts, and industry partners focused on heart failure.

Our consortium has demonstrated in experimental models that a high-fat dietary intervention can reverse this metabolic shift, restoring fatty acid utilization in cardiac mitochondria and improving cardiac function. These findings provide the mechanistic basis for translating this concept into a clinical setting.

HF4HF is a pilot clinical study designed to evaluate whether a structured high-fat dietary program can favorably modulate cardiac metabolism in patients with HF. The intervention will be assessed using state-of-the-art non-invasive imaging techniques to quantify changes in cardiac function and metabolic substrate utilization. Complementary translational analyses will be performed in explanted human hearts and in blood samples from experimental models and enrolled patients. Additional preclinical studies will examine whether different fat-based dietary compositions exert metabolic effects on the failing myocardium.

At the end of 2025, a substantial protocol amendment aimed at facilitating recruitment through revised eligibility criteria was approved by the Hospital Puerta de Hierro ethics committee (December 19, 2025). The amendment is currently being prepared for submission in Italy, France, and Romania. To strengthen recruitment, Fundación Jiménez Díaz University Hospital has joined the study as an additional center, with local ethics approval already obtained. As of February 2026, two participants had been enrolled. Recruitment is expected to accelerate once the remaining regulatory approvals are secured.

## DIREQT2Heart: Direct quantitative assessment of myocardial perfusion using cardiovascular magnetic resonance imaging

Principal Investigators: **Borja Ibáñez (CNIC)**, **Javier Escaned (Hospital Universitario Clínico San Carlos)**



Coronary artery disease—whether involving epicardial vessels or the microvasculature—is the leading cause of myocardial ischemia due to impaired coronary perfusion. The current reference standard for assessing coronary flow is invasive cardiac catheterization with physiological measurements, such as coronary thermodilution. Although highly accurate, these procedures carry procedural risks.



Several non-invasive imaging techniques have been developed to estimate myocardial perfusion, including SPECT-MIBI and computed tomography. However, most available methods provide qualitative or semi-quantitative information, limiting their diagnostic accuracy in complex scenarios such as three-vessel disease or microvascular dysfunction.

Cardiovascular magnetic resonance (CMR) is the reference modality for evaluating cardiac structure and function. In recent years, quantitative perfusion sequences have been introduced, enabling measurement of absolute myocardial blood flow. Nonetheless, these sequences remain constrained by limited spatial resolution and incomplete cardiac coverage.

To overcome these limitations, our group has developed a novel CMR sequence—DIREQT—that enables highly accelerated image acquisition, improving temporal resolution and myocardial coverage while generating fully quantitative perfusion maps. This approach has the potential to provide a more precise and comprehensive assessment of myocardial blood flow.

The objective of DIREQT2Heart is to validate the DIREQT sequence against the invasive reference standard of coronary thermodilution. The study aims to enroll 30 patients representative of the clinical populations in which this technique would be applied. Participants are divided into three groups:

1. Patients with significant epicardial disease of the proximal-to-mid left anterior descending artery.
2. Patients with microvascular disease (structural endotype).
3. Control patients without significant epicardial disease and with preserved coronary flow reserve.

Patients undergoing clinically indicated coronary angiography and physiological assessment at Hospital Clínico San Carlos are invited to participate. Those who provide informed consent are referred to the CNIC for CMR evaluation using the DIREQT sequence.

As of February 2026, 10 patients had been enrolled and had completed the CMR examination.

## PATAGONIA: Prevalence of Vascular Toxicity Among long-term Cancer Survivors Treated with Anthracyclines

Principal Investigator: **Inés García-Lunar**

Promotor: Centro Nacional de Investigaciones Cardiovasculares (CNIC)

Participating centers: CNIC; Unidad de Oncohematología Pediátrica, Hospital La Paz; Servicio de Hematología, Fundación Jiménez Díaz; Servicio de Cardiología, Hospital Universitario Puerta de Hierro.



Cardiovascular disease (CVD) and cancer are the two leading causes of mortality worldwide and are increasingly interconnected. Anthracyclines (ACs) are widely used chemotherapeutic agents for both hematologic malignancies and solid tumors. Although highly effective, ACs are associated with cardiotoxicity, which may manifest years after treatment and often progresses to heart failure. As cancer survival has improved substantially over recent decades, the burden of CVD among long-term survivors has also risen, representing a growing public health challenge.

The mechanisms underlying AC-related cardiotoxicity remain incompletely understood, and no targeted preventive therapies have yet demonstrated clear efficacy. Most research has focused on direct myocardial injury. However, accumulating experimental and early clinical evidence suggests that AC-induced vascular damage may precede overt cardiac dysfunction. We hypothesize that AC-related vascular injury may remain subclinical for years and contribute to the later development of heart failure.

PATAGONIA addresses this hypothesis through a comprehensive evaluation of vascular function in long-term cancer survivors previously exposed to ACs. Using state-of-the-art, non-invasive, radiation-free imaging techniques at the CNIC, the study assesses both coronary and peripheral vascular function. Findings are compared with those from non-exposed control participants.

The distinctive feature of PATAGONIA, compared with other contemporary survivor cohorts, is its primary focus on vascular dysfunction as a potential mechanistic driver of subsequent cardiac disease. By identifying early vascular abnormalities, the project aims to develop new strategies for risk stratification and early detection of AC-related cardiovascular damage.

As of February 2026, 50 patients had been enrolled and had undergone cardiac magnetic resonance imaging and vascular ultrasound assessment at the CNIC.