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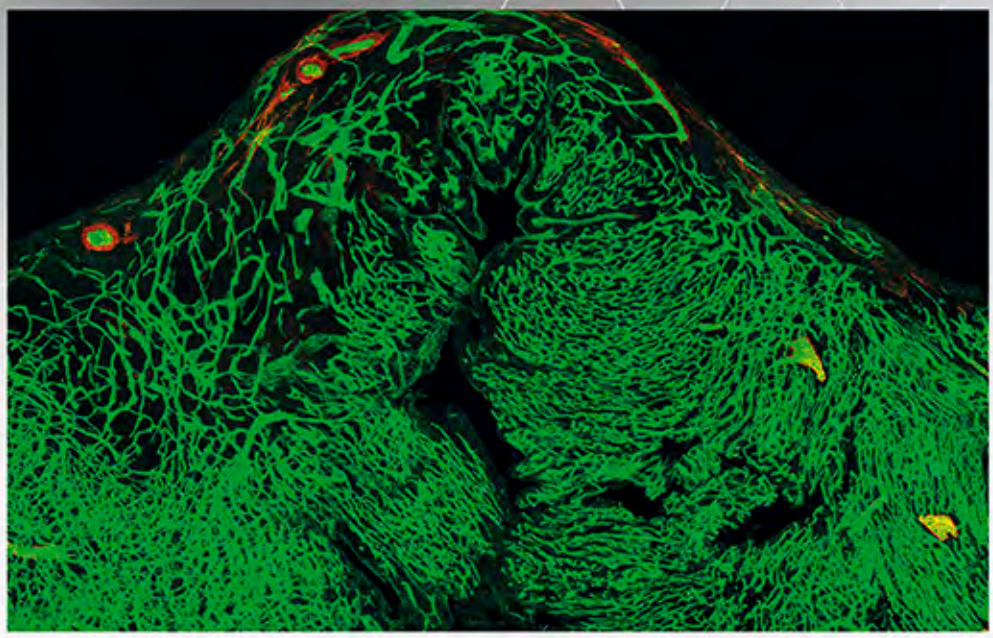
Centro Nacional de Investigaciones **Cardiovasculares** Carlos III

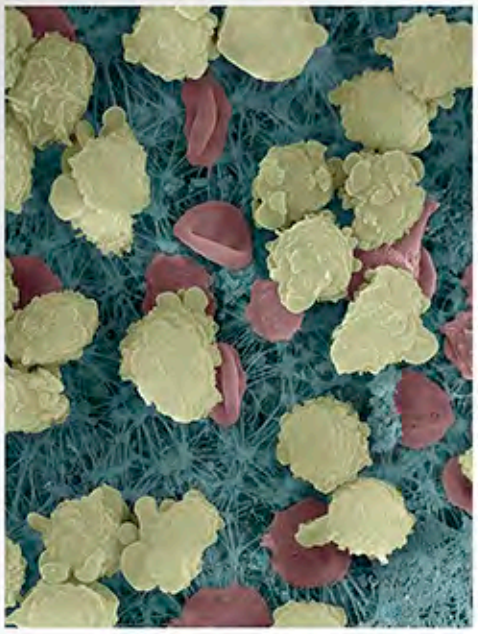
EXCELENCIA SEVERO OCHOA 2012 - 2019

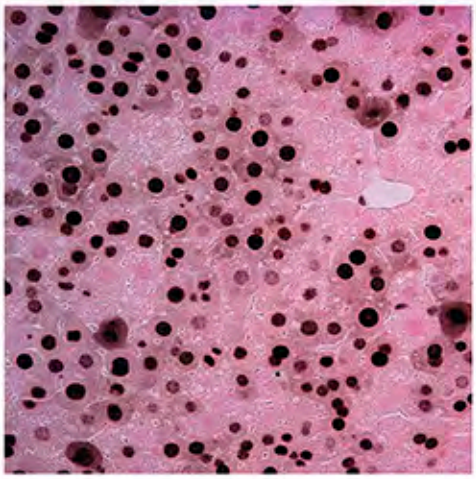
HR EXCELLENCE IN RESEARCH

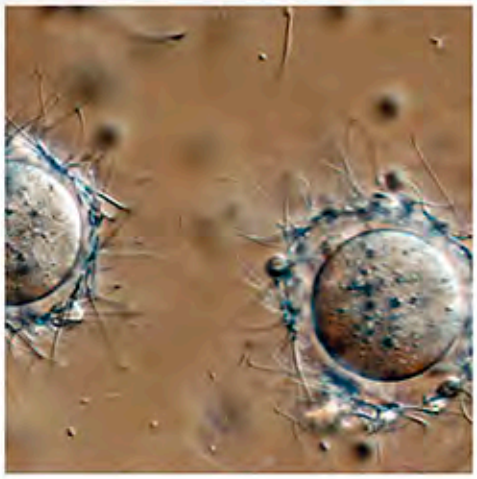
Infraestructuras Científicas y Técnicas Singulares

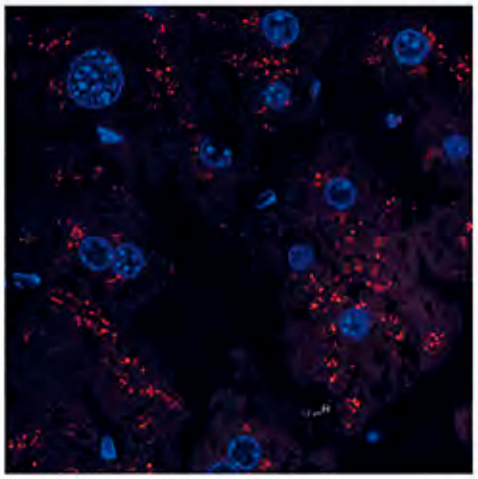
SCIENTIFIC REPORT 2016

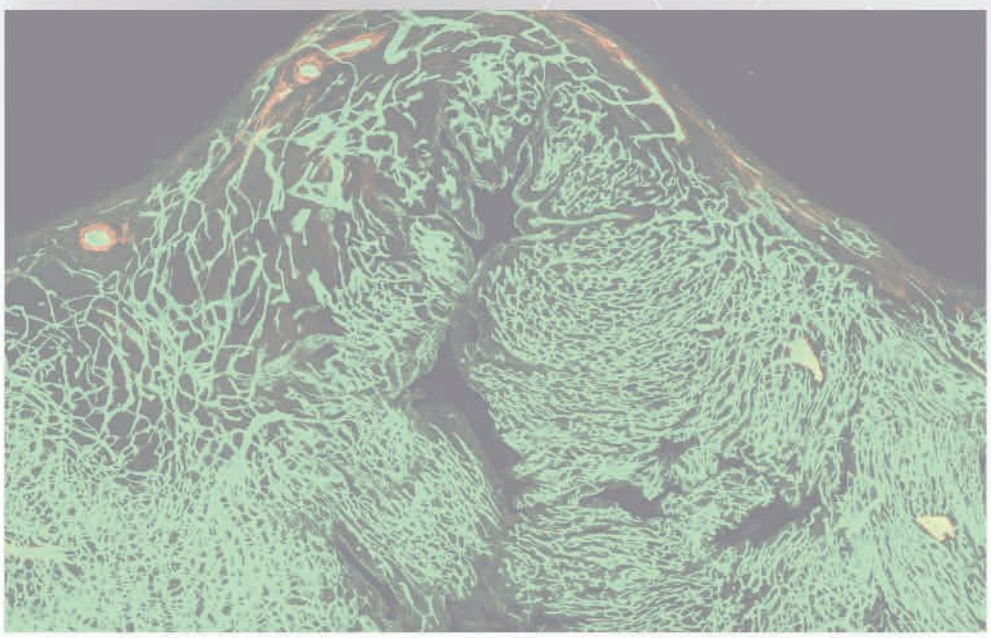


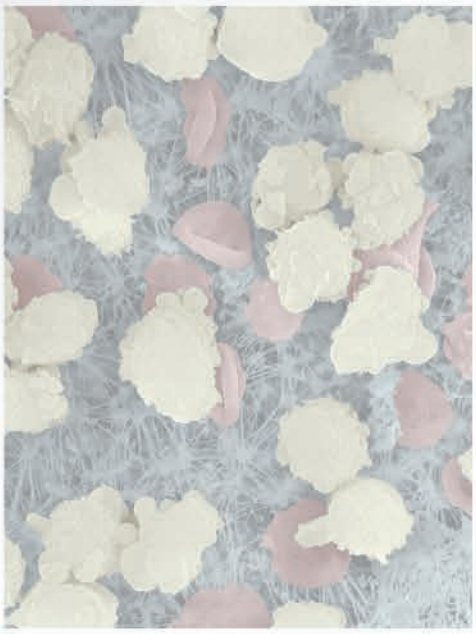


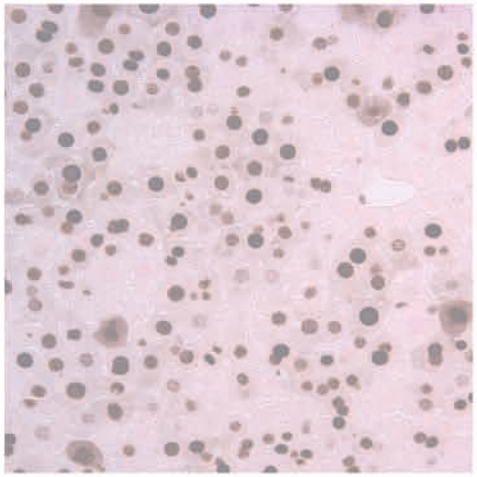


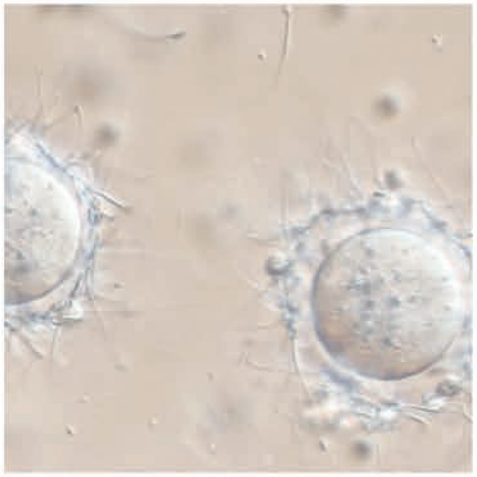


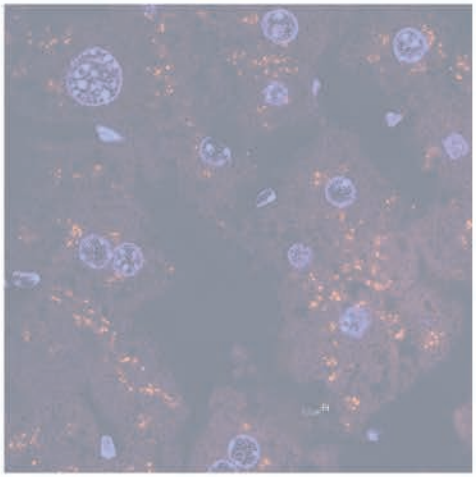












Valentín Fuster
General Director

Critical evaluation is at the heart of science and medicine, and at the CNIC we pay keen attention to all available indicators that track our quality. One of the key measures is the periodic quality audit by the Scientific Advisory Board. This external body provides detailed appraisal and guidance to help us maintain our focus on excellence in research that delivers real benefits to society. In last year's evaluation, the SAB members congratulated the CNIC on an impressive research program that again brought success in teaching, securing external funding, and publishing in high-ranking journals, with knock-on effects on science and medicine at large. The SAB feels that the CNIC puts Spain in the front row of cardiovascular research and stands as a model of the successful melding of basic and translational research.

Another objective measure of the CNIC's performance last year was the renewal for 2016-2019 of our status as a Center of Excellence within the *Severo Ochoa* program, a Spanish government initiative promoting and supporting outstanding research centers in Spain. This accreditation formalizes the CNIC's commitment to strengthening the integration of basic and clinical research toward a common translational goal. We are using the *Severo Ochoa* funds to set up the Intramural Grants Program-Severo Ochoa (IGP-SO), which will provide €2.1 million (~55% of the awarded direct costs) for internal translational research projects involving at least two CNIC group leaders. The IGP-SO will provide our research groups with opportunities to collaborate on new projects at the forefront of biomedical research, with priority given to proposals with a cardiovascular focus and a well-defined translational strategy.

The CNIC has also continued to strengthen its scientific competitiveness internationally, highlighted by the Center's high representation in projects funded by the European Research Council (ERC), with 5 ERC projects awarded to CNIC groups under FP7 and 4 awarded under H2020. Moreover, the Center is the top-ranking Spanish institution for funding awarded under the EC Societal Challenge Health, Demographic Change and Wellbeing (H2020-2014 call) and participates prominently in the Marie Curie-Skłodowska programme, with 21 projects in FP7 and 5 in H2020, including 1 Coordinated Industrial Doctorate ITN.

The surest sign of research quality is the publication record in peer-reviewed journals, and last year CNIC scientists published more articles than in any previous year. Compared with 2015, the percentage of first quartile publications increased by 5% and the percentage of first decile publications by 7%. In 2016, CNIC scientists published 33 leading articles and reviews in journals with an impact factor of 10 or higher, including Nature, Nature Medicine, Cell Metabolism, the Journal of the American College of Cardiology, Circulation, the European Heart Journal, and many others. This represents an increase of 51% compared to 2015, and several of these papers were classified as highly cited by the Web of Science. Some of the standout contributions made by CNIC research groups in 2016 are summarized in the Research Highlights section of this report.

Our confidence that this strong performance will continue in future years was given a major boost by the recruitment of Dr. Silvia Priori and Dr. Pura Muñoz. Dr. Priori has dedicated her clinical and research career to understanding the molecular mechanisms underlying inherited arrhythmias, and her current focus is the development of molecular therapies for these conditions. Dr. Muñoz leads research into the role of stem cells and myeloid cells in muscle repair and maintenance, and how these processes are altered with aging. It is a delight to warmly welcome these renowned scientists to our team.

Vicente Andrés
Basic Research Director

Borja Ibáñez
Clinical Research Director

Our links with the clinical sector were consolidated through an agreement with the *Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz de Madrid* (IIS-FJD). This partnership will facilitate the development of clinical assays and training exchanges for medical professionals and scientists. The agreement is specifically focused on clinical applications of research results in patients with acute myocardial infarction. We also strengthened our profile in the coordination of multicenter randomized clinical trials through a new partnership with the *Empresa Pública de Emergencias Sanitarias* (EPES 061), forming a central contact point for the improved management and treatment of cardiac arrest in Spain.

Training tomorrow's researchers continues to be one of the CNIC's core activities. In 2016, the different programs and courses of the CNIC-JOVEN Training Plan hosted more than 500 people at all career stages, from senior high school students to predoctoral and postdoctoral researchers and other professionals. Moreover, through our status as a *Severo Ochoa* Center of Excellence we are now a host institution within the INPhINIT "la Caixa" Fellowship Program, a new doctoral fellowship program devoted to attracting international early-stage researchers to top Spanish research centers. Through INPhINIT, the "la Caixa" Foundation aims to revolutionize European doctoral training in terms of quality, researcher excellence, the scope of the benefits offered, and impact. As an INPhINIT host, the CNIC is seeking highly talented and motivated young scientists to carry out research in the cardiovascular area.

Scientific research can only be conducted through the critical exchange of research findings and ideas. The Center's active engagement in scientific congresses is an essential part of this process, and the CNIC hosted more than 30 scientific events in 2016. The highlight was the VI CNIC Conference, held on November 4 and 5. The annual CNIC Conference has become a key international event in the scientific calendar for researchers in the cardiovascular field. Last year's meeting, on "Mechanical forces in physiology and disease", was organized by four CNIC researchers—Jorge Alegre-Cebollada, Nadia Mercader, María Montoya, and Miguel Á. del Pozo—together with Martin Schwartz from Yale University. The meeting brought together international research leaders with expertise in diverse areas of mechanobiology, including research technology, cell biology, animal models, human disease, and development.

We also remain as committed as ever to communicating our mission and the outcomes of our research program findings to the public, our ultimate paymasters and beneficiaries. This year's scientific report includes a new section on Translation to Society, containing summaries of our public Communications activity and a Research Highlights section giving brief summaries of the standout contributions made by CNIC research groups in 2016. We hope that in this way this report will be informative to interested specialists and non-specialists alike.

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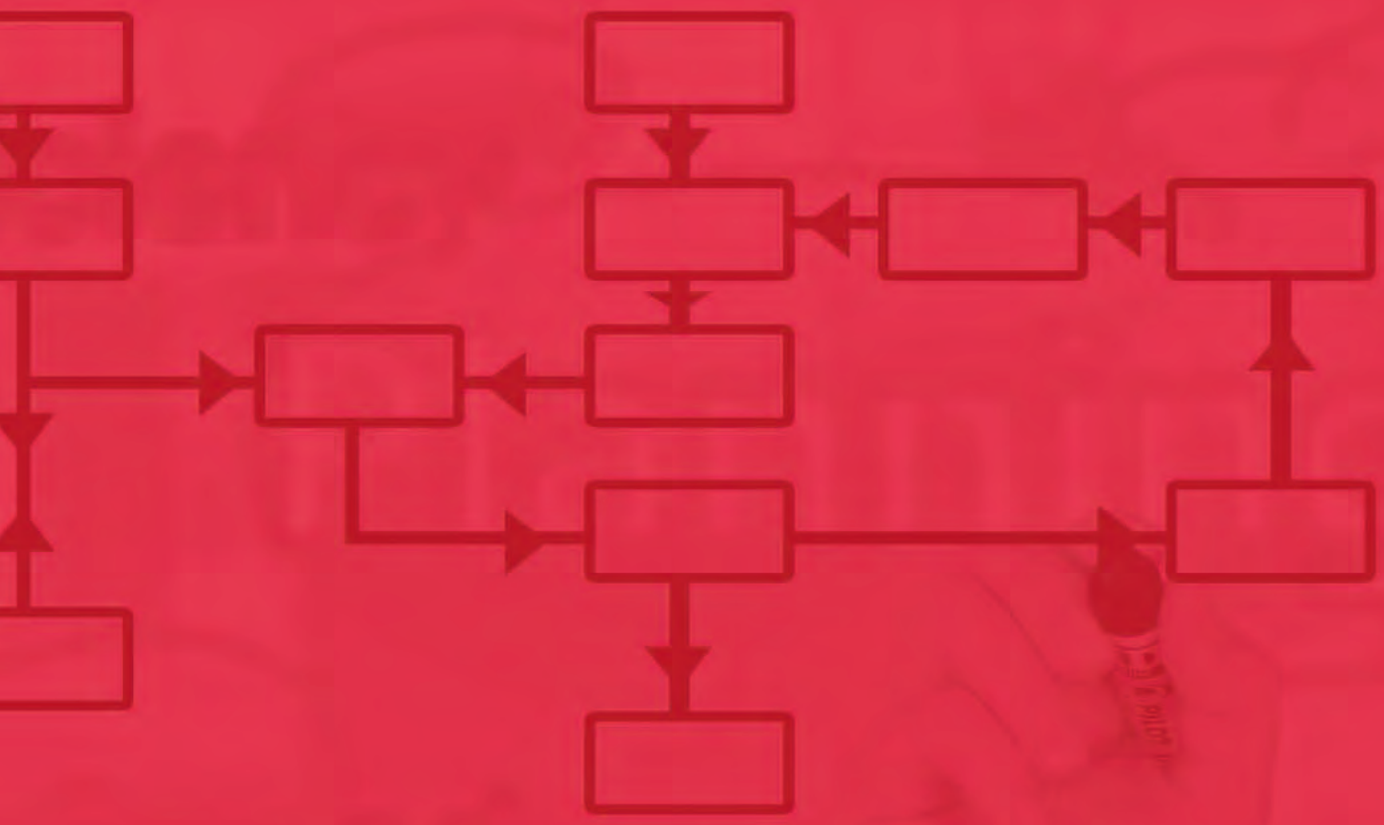

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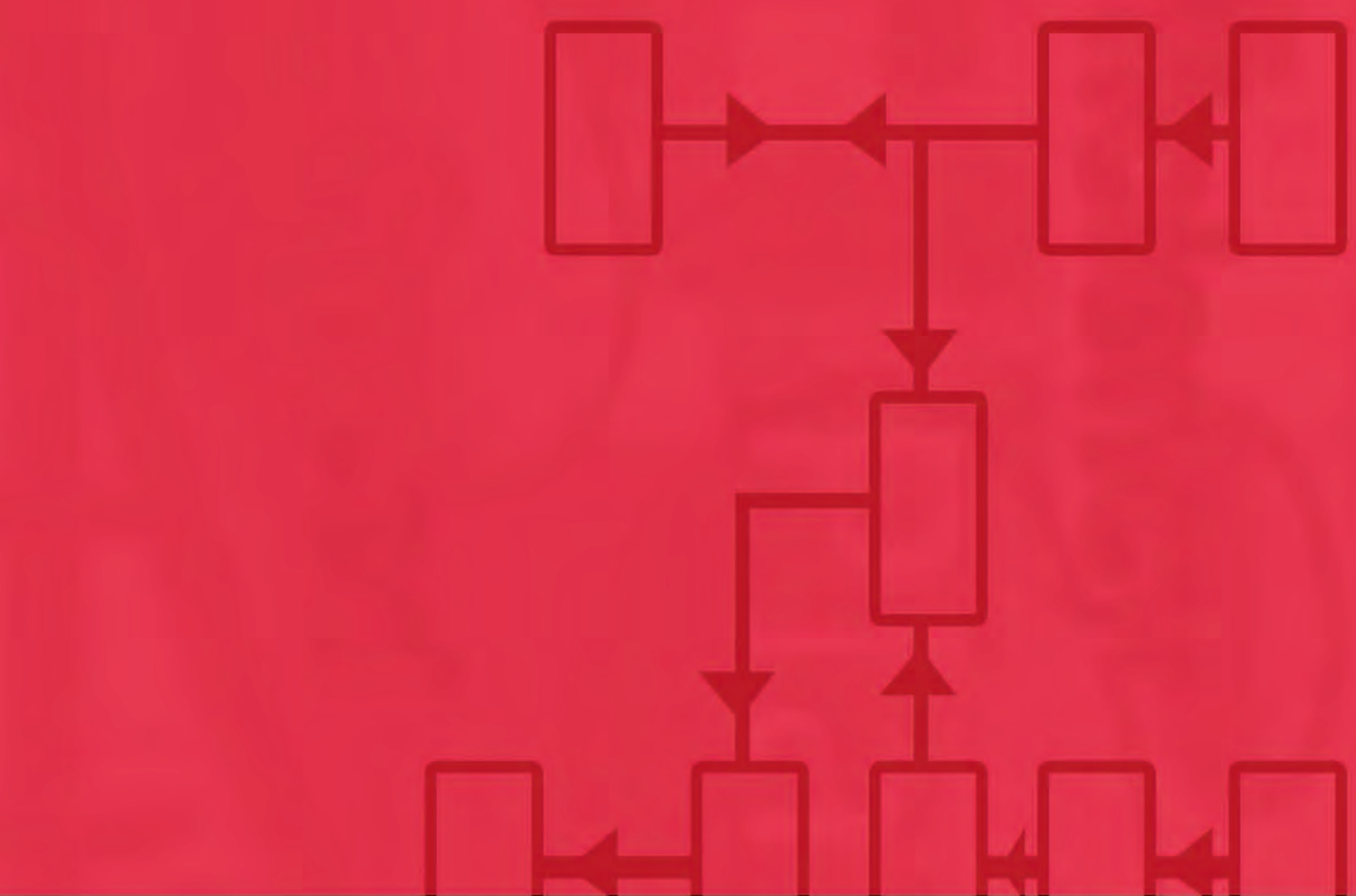

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RESEARCH AREAS

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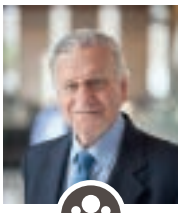
1. Myocardial Pathophysiology
2. Vascular Pathophysiology
3. Cell and Developmental Biology



Cardiovascular imaging and population studies

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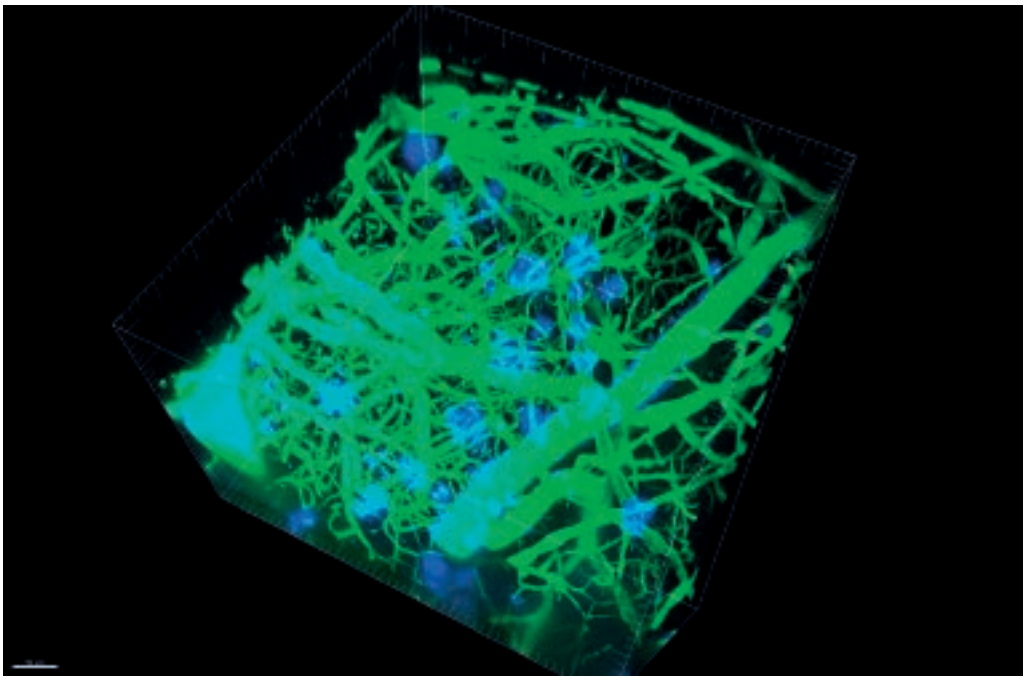
RESEARCH INTEREST

Our multidisciplinary research group brings together investigators from basic to clinical research, promoting collaboration between experts from different disciplines. This unique mix of professionals from different fields creates a fertile environment that maximizes the translational potential of our research, which centers on clinical studies for cardiovascular prevention by using the latest advanced imaging methodologies. We believe that early prevention is the key to winning the battle against cardiovascular diseases (CVD), and this conviction underpins our leadership of several educational programs promoting healthy habits in children (Program SI!) and adults (50/50 Project, in collaboration with the *Observatorio de la Nutrición y de Estudio de la Obesidad*).

Our research covers major CVD risk factors including diet, exercise, genetics and epigenetics, metabolic factors, the environment, and psychosocial factors. These themes are combined in the development and research application of advanced noninvasive imaging technologies for the early diagnostic and prognostic assessment of atherosclerosis. We are central participants in the CNIC's major population studies: PESA (Progression of Early Subclinical Atherosclerosis), TANSNIP (Trans-Atlantic Network to Study Stepwise Noninvasive Imaging as a Tool for Cardiovascular Prognosis and Prevention), SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population, an EU Horizon2020-funded continuation of research into the successful Fuster-CNIC-Ferrer polypill concept), and SPHERE (testing the efficacy of a novel therapy discovered at the CNIC for the treatment of pulmonary hypertension).

In our newest research line, we are using advanced imaging techniques to analyze the damaged cerebral vasculature in the Alzheimer's disease (AD). The delivery of oxygenated blood, glucose, and nutrients to the brain is essential for correct cerebral function, and therefore any disruption to the cerebral vasculature plays a fundamental role in the progression of neurological disorders. We are using PET and MRI to develop new imaging tools to noninvasively identify the composition and origin of vessel obstructions in the AD brain, which are partly responsible for the brain hypoperfusion found in this disease. We perform these studies in different animal models of AD, including transgenic mouse models and also large animals, providing the study with important translational applicability.

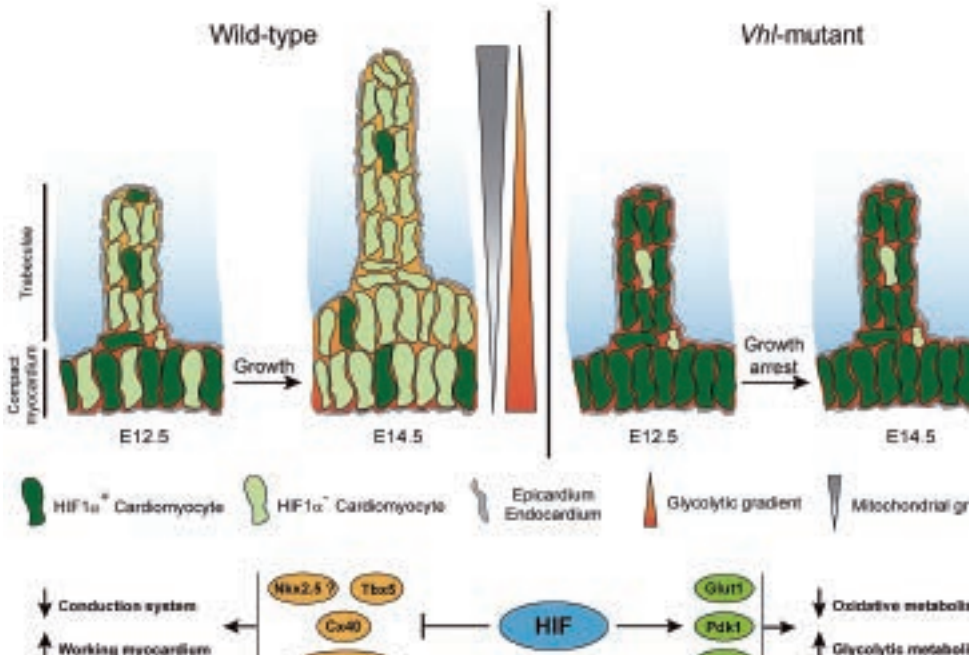
Recruitment map for the SECURE trial.



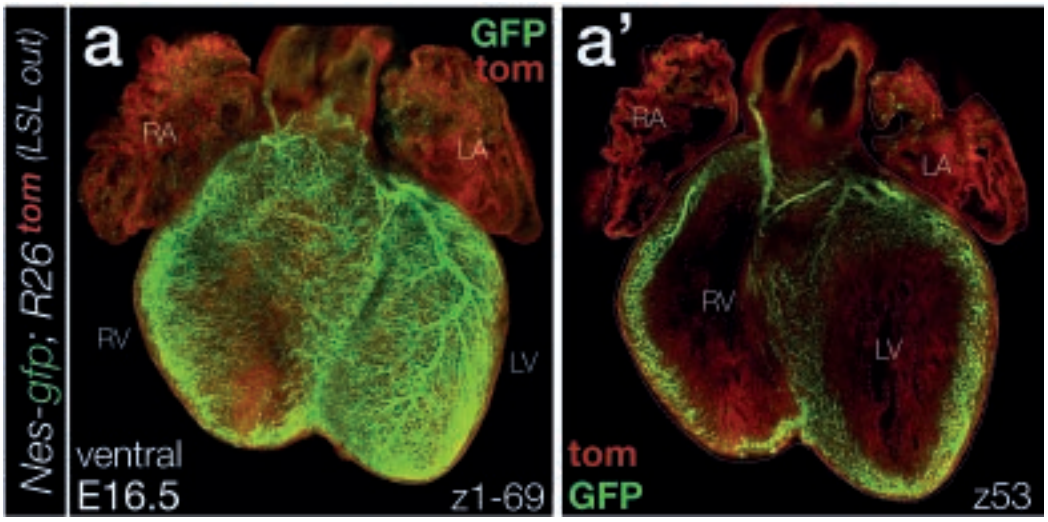
Brain vasculature in Alzheimer's disease (AD). Cranial windows were opened over the cortex of AD mice. Blood flow (green) and amyloid deposits (blue) were visualized *in vivo* with a two-photon microscope. 3D reconstruction of a Z-stack acquisition shows the first 400 µm of the mouse cerebral cortex. Blood vessels in the brain of AD mice are surrounded by cerebral amyloid angiopathy and by amyloid plaques in the brain parenchyma.

Another independent research line in the group, led by Dr. Silvia Martín Puig, examines the role of oxygen homeostasis in the cardiovascular system. Our goal is to understand the function of hypoxia inducible transcription factors (HIFs) in heart development and disease. Using novel genetic tools, we have determined the critical roles played by HIF1 and VHL in delineating discrete metabolic territories during cardiac development; these metabolic territories are essential for proper ventricular chamber formation and maturation and the correct establishment of cardiac conduction system. Our results link the hypoxia pathway to cardiac function and metabolism, and may have therapeutic implications in the setting of ischemic heart disease and cardiomyopathies when HIF1 is reactivated upon oxygen deprivation. We are currently characterizing the phenotype of additional mouse models to evaluate the role of VHL/HIFs in the formation and stability of the coronary vascular network, and are examining possible connections between the observed defects and human congenital heart disease.

Another independent research line in the group, led by Dr. Joan Isern, is mainly interested in tissue organogenesis, focusing on the mammalian cardio- & hemato-vascular systems. Our team is currently investigating how the coronary vasculature is assembled during cardiac development, using both in vitro and in vivo genetic murine models and high-resolution imaging approaches.



Myocardial VHL-HIF signaling controls an embryonic metabolic switch essential for cardiac maturation. Model illustrating how spatiotemporal activation of VHL/HIF signaling within the developing myocardium delineates metabolic compartments with an enhanced glycolytic signature in the compact myocardium, compared with increased mitochondrial activity in midgestation trabeculae. Sustained HIF1 activation results in ventricular chamber defects, cardiac dysfunction, and altered expression of conduction system genes (Menendez-Montes et al. Dev Cell 2016).



High-resolution imaging of intact tissue-clarified hearts. (a) Whole-mount view of E16.5 mouse heart. The image (ventral side) is resulting from a max-intensity projection over a 0.5-mm-thick volume dataset (composed by 69 individual optical sections); GFP marks the developing coronary vessels. (a') Selected single optical plane from the z-stack at the indicated depth. Inner cardiac cavities and intramyocardial coronary endothelium can be appreciated.

MAJOR GRANTS

- H2020-PHC-2014-two-stage (GA633765). PI: V. Fuster
- NHLBI - 5U01HL114200-02. PI: V. Fuster
- AHA – HS 14-01054. PI: V. Fuster
- NIH/NIHLBI RO1. Collaborator: V. Fuster
- PESA CNIC-Santander. PI: Fuster V.
- Ayudas proyectos investigación La Marató. (Subproject 20151731) PI: V. Fuster
- FP7-PEOPLE-2013-IIF (GA 624811). PI: M. Cortés
- Instituto de Salud Carlos III (PI13/02339). PI: A. García
- Instituto de Salud Carlos III (PI15/02019). PI: L. Fernández-Friera
- Ministerio de Ciencia e Innovación. FIS (CP09/00100). PI: S. Martín Puig
- Ayudas proyectos investigación La Marató. (Subproject 20150731). PI: S. Martín Puig
- Ministerio de Economía y Competividad (BFU2012-35892). PI: J. Isern
- Ministerio de Economía y Competividad (RYC-2011-09209). PI: J. Isern

SELECTED PUBLICATIONS

Fuster V, Ibanez B, Andres V. The CNIC: a successful vision in cardiovascular research. *Circ Res* (2016) 119: 785-9

Arbab-Zadeh A, Fuster V. **The risk continuum of atherosclerosis and its implications for defining CHD by coronary angiography**. *J Am Coll Cardiol* (2016) 68: 2467-78

Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, Garcia-Alonso F, Lizano I, Arnold RJ, Rajda J, Steinberg G, Fuster V. **Assessing the impact of medication adherence on long-term cardiovascular outcomes**. *J Am Coll Cardiol* (2016) 68: 789-801

Peñalvo JL, Fernández-Friera L, López-Melgar B, Uzhova I, Oliva B, Fernández-Alvira JM, Laclaustra M, Pocock S, Mocoroa A, Mendiguren JM, Sanz G, Guallar E, Bansilal S, Vedanthan R, Jiménez-Borreguero LJ, Ibañez B, Ordovás JM, Fernández-Ortiz A, Bueno H, Fuster V. **Association between a social-business eating pattern and early asymptomatic atherosclerosis**. *J Am Coll Cardiol* (2016) 68 :805-14

Menendez-Montes I, Escobar B, Palacios B, Gómez MJ, Izquierdo-Garcia JL, Flores L, Jiménez-Borreguero LJ, Aragones J, Ruiz-Cabello J, Torres M, Martin-Puig S. **Myocardial VHL-HIF signaling controls an embryonic metabolic switch essential for cardiac maturation**. *Dev Cell* (2016) 39: 724-39

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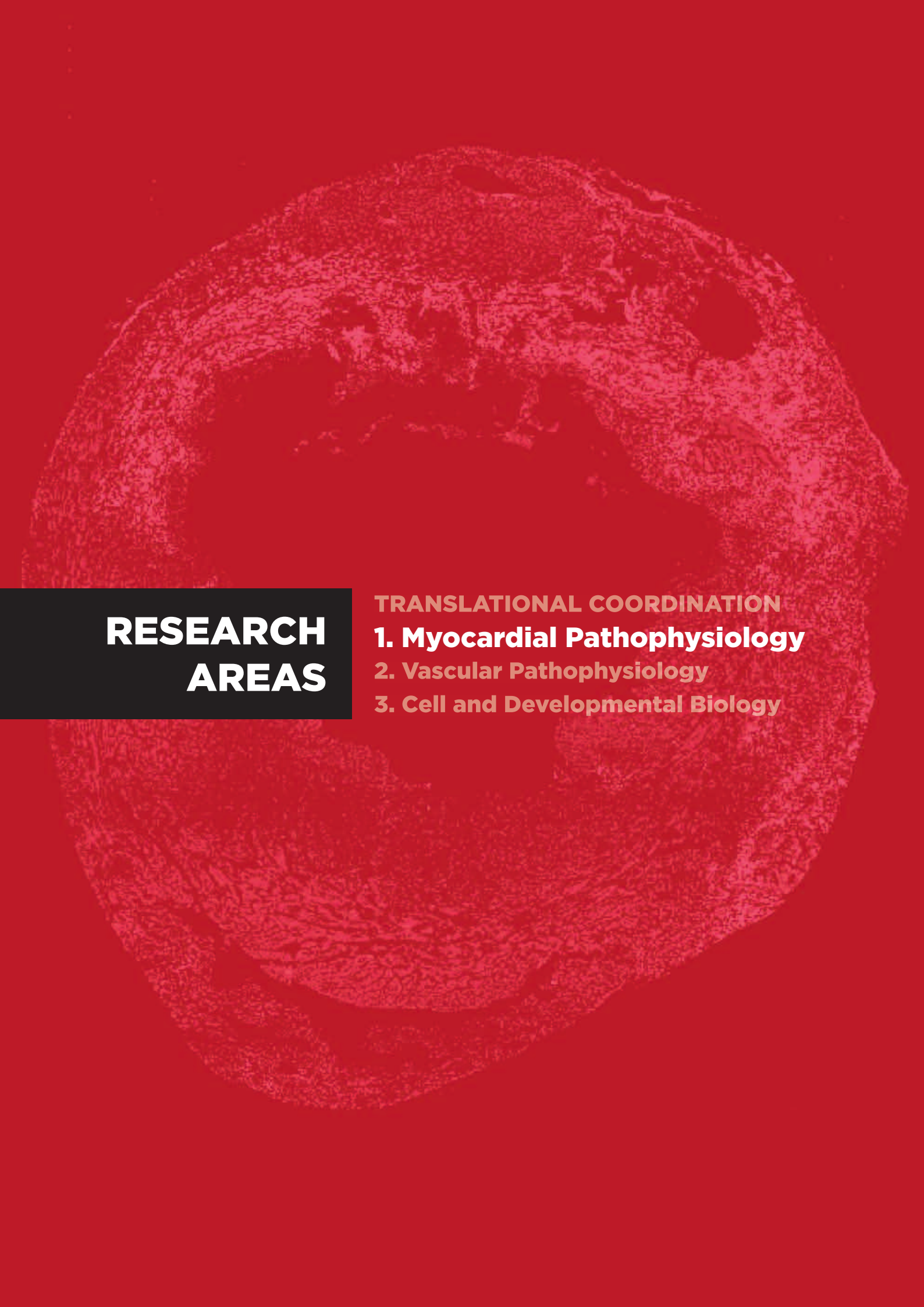


RESEARCH AREAS

TRANSLATIONAL COORDINATION

1. Myocardial Pathophysiology

2. Vascular Pathophysiology

3. Cell and Developmental Biology

cnic | RESEARCH AREAS

1. Myocardial Pathophysiology

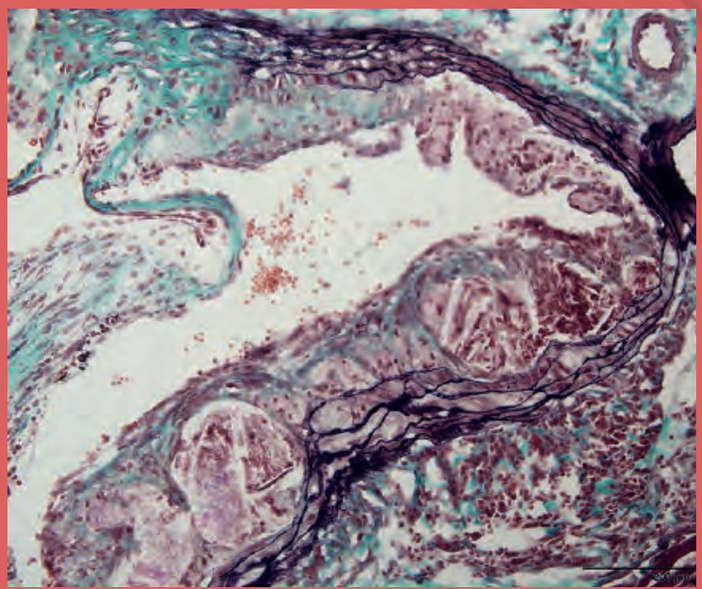
AREA COORDINATORS:

JOSE ANTONIO ENRIQUEZ

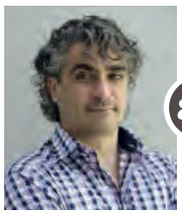
ENRIQUE LARA-PEZZI

RESEARCH INTEREST

The myocardial pathophysiology area integrates scientists from multidisciplinary fields. Basic scientists, cardiologists, and engineers work in a coordinated way to provide invaluable information on the molecular mechanisms that manage the cardiovascular system in homeostasis and disease. 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 of diagnosis and treatment. Our research focuses on several topics: the oxidative phosphorylation system, role of nuclear receptors in lipid metabolism and inflammatory responses, metabolic syndrome and stress kinases, immunobiology of inflammation, inherited cardiomyopathies, cardiac arrhythmias, electrophysiological characterization of healthy and diseased cardiomyocytes, epigenetic regulation, alternative splicing in cardiac development and heart disease, and cardioprotection during myocardial infarction.



Inherited cardiomyopathies



RESEARCH INTEREST

Our research into cardiovascular disease is based on a simple principle: create to understand, create to treat.

Animal models are essential investigative tools for expanding our understanding of disease; however, the generation and maintenance of genetically modified mouse colonies for research is costly. We have developed an alternative method that uses adeno-associated virus (AAV) vectors, widely used for gene-therapy approaches, to express disease-causing dominant-negative mutants to generate disease models in wild-type mice. Single systemic injection of AAV virus is more versatile, cost-effective, simpler, and time-efficient than transgenic approaches for generating mutant animals.

Our major area of interest is arrhythmogenic right ventricular cardiomyopathy (ARVC). This heart muscle disease is characterized by right ventricular anatomical abnormalities and ventricular arrhythmias that can lead to sudden cardiac death, especially in young athletes. To be able to study the effect of exercise on hearts of mice carrying the most prevalent ARVC-associated mutation in *plakophilin-2 (PKP2)*, we used AAV to express the *R735X* mutant in wild-type mice. Our work shows that injected AAV-*R735X* animals develop an overt ARVC phenotype when subjected to endurance training, supporting the recommendation for exercise cessation in carriers of this mutation.

At the histological level, the right ventricles of endurance-trained R735X-infected mice display connexin 43 delocalization (Cx43) at intercardiomyocyte gap junctions, a change not observed in sedentary mice. To better understand the molecular mechanism underlying the effect of mutant PKP2 expression on Cx43 mislocalization we have developed new molecular reporters and live cell imaging approaches to monitor this important process.

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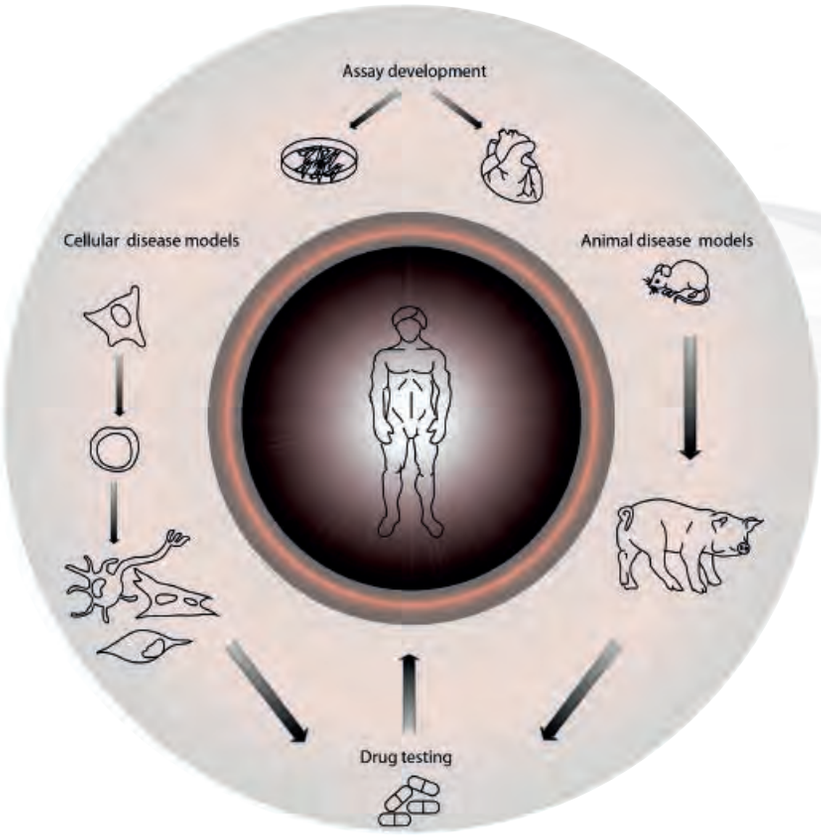
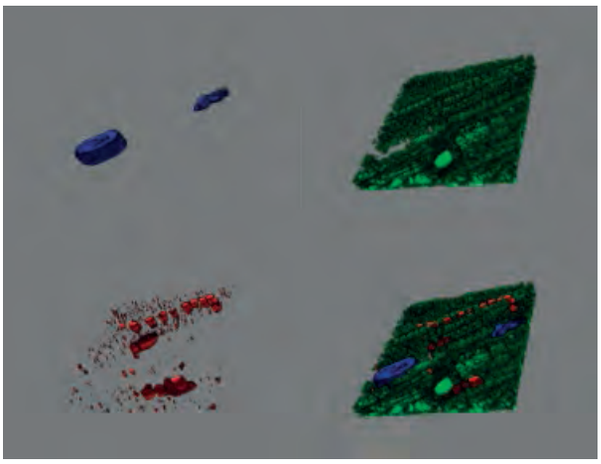
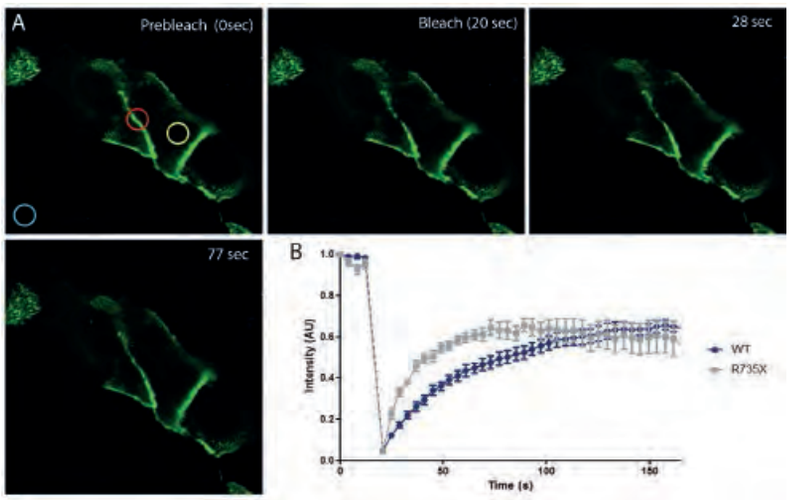


General working-model used in the laboratory to investigate and test compounds in a specific disease. For example, for ARVC we have already developed a cellular model in human induced pluripotent stem cells (iPS) and a mouse model. In the near future we plan to develop a pig model of ARVC, to take advantage of the closer similarity to human physiology.



Super-resolution studies to analyze the effect of the PKP2 mutant protein R735X on its interacting partner connexin 43 (Cx43). Mouse cardiomyocytes from right ventricle expressing human R735X were immunolabeled for gap junctions (Cx43, red) and mitochondria (Tom20, green). Nuclei are visualized by DAPI staining. Z-stacks were acquired at 0.15 µm intervals, and maximum projections of different channels are shown.



Fluorescence recovery after photobleaching (FRAP) measurements to elucidate human PKP2 assembly stability in desmosomes. (A) Typical FRAP experiment using GFP-PKP2 and confocal optical sectioning. The image brightness was adjusted to more clearly depict desmosomes. A reference region in a nonphotobleached area (ROI, blue) was used to correct for unintentional bleaching. A negative control region (ROI, yellow), also outside the photobleached area, was selected to confirm successful correction for unintentional photobleaching, following the correction steps using the reference region. (B) Fluorescence recovery dynamics of GFP-PKP2 (blue) and the mutant GFP-R735X (grey).

MAJOR GRANTS

- Ministerio de Economía y Competitividad (BFU2016-75144-R)

SELECTED PUBLICATIONS

Bárbara González-Terán, Juan Antonio López, Elena Rodríguez, Luis Leiva, Sara Martínez-Martínez, Bernal JA, Luis Jesús Jiménez-Borreguero, Juan Miguel Redondo, Jesus Vazquez, and Guadalupe Sabio. **p38γ and δ promote heart hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation**. *Nat Commun* (2016) 7:10477

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* Co-corresponding Authors

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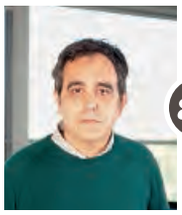
Nakagawa Y, Sedukhina AS, Okamoto N, Nagasawa S, Suzuki N, Ohta T, Hattori H, Roche-Molina M, Narváez AJ, Jeyasekharan AD, Bernal JA, Sato K. **NF-κB signaling mediates acquired resistance after PARP inhibition**. *Oncotarget* (2015) 6: 3825-39

Roche-Molina M, Sanz-Rosa D, Cruz FM, García-Prieto J, López S, Abia R, Muriana FJ, Fuster V, Ibáñez B, Bernal JA. **Induction of sustained hypercholesterolemia by single adeno-associated virus-mediated gene transfer of mutant hPCSK9**. *Arterioscler Thromb Vasc Biol* (2015) 35: 50-9

Functional genetics of the oxidative phosphorylation system



RESEARCH INTEREST

The group researches the mammalian mitochondrial electron transport chain (MtETC) and H+-ATP synthase, which together constitute the oxidative phosphorylation (OXPHOS) system. We view this system as a functional entity, and use a range of approaches aimed at determining its role in health and disease. We are particularly interested in role the OXPHOS system in the development of the cardiovascular system, its relevance to ischemia-reperfusion, and its influence on microvascular blood flow. To better understand the role of mitochondria and their response to metabolic challenges during aging, angiogenesis, and lung performance we use mice with the same nuclear background but carrying different nonpathological variants of mitochondrial DNA throughout the organism (conplastic mice) or a mix of mtDNA variants in the same cell (heteroplasmic mice).

We also study the organization of the respiratory complexes and interacting partners using methods to visualize and quantitatively estimate the supercomplexes (I/III/IV, I/III, and III/IV) in intact cells without the use of detergents that disrupt the mitochondrial inner membrane. This research line includes the use of stimulated emission depletion microscopy to observe different combinations of respiratory complex subunits in mitochondria.

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María Sánchez
Mª Belén Crespo
Oscar Yang Li
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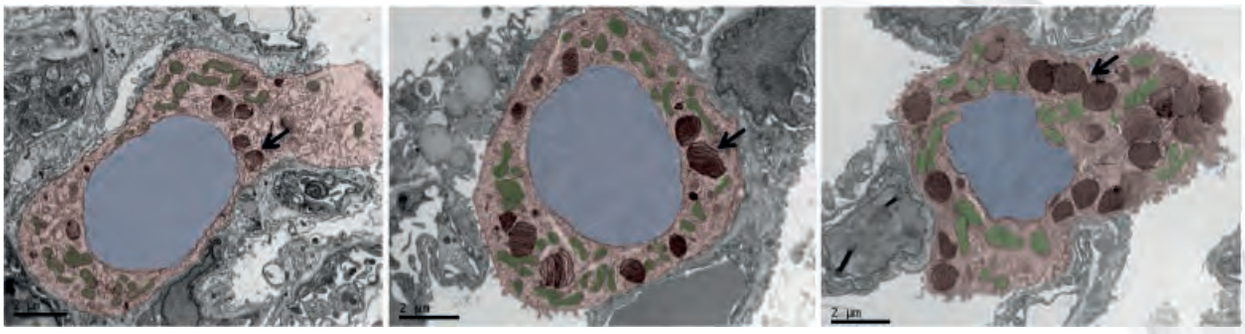
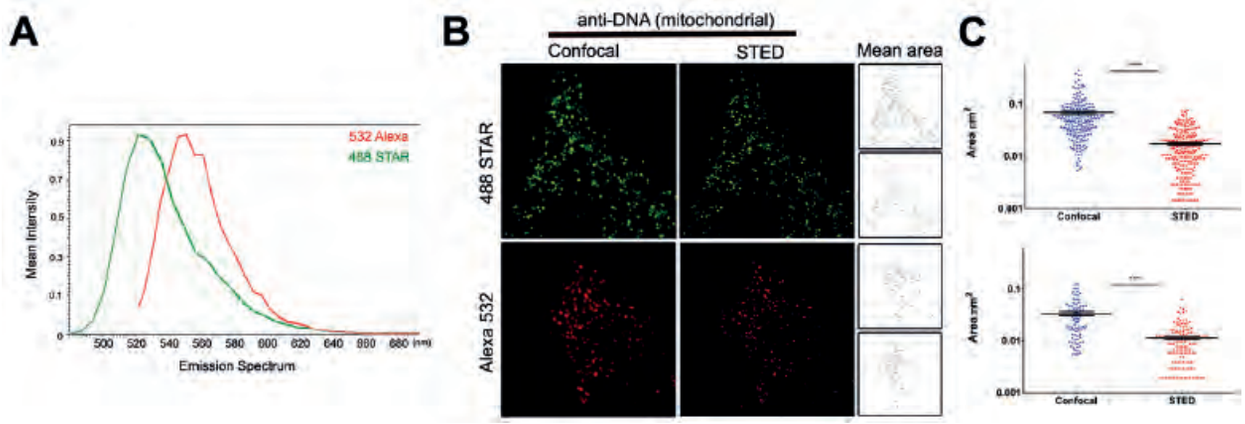


Ultrastructural analysis of type II alveolar epithelial cell (AEC) alterations in heteroplasmic mice. A) Control BL/6^{C57} mice. B) Conplastic BL/6^{NZB} mice. C) Heteroplasmic BL/6$^{C57\text{-}NZB}$ mice. Cytoplasm is shown in red, nuclei in blue, and mitochondria in green. Arrows indicate lamellar bodies (LB), lysosome-related secretory organelles of epithelial cells.



A) Scan of emission wavelengths for Alexa 532 and 488 STAR secondary antibodies bound to the specific IgGs used in this study. (**B**) *Left*. ρ^{0Ctrl} cells were labeled with anti-DNA and 488 STAR (green) or Alexa Fluor 532 (red) secondary antibodies. *Right*. Confocal and STED images were acquired, quantified, and represented as bare particle outlines from ImageJ. (**C**) Data show mean particle area (µm2) ± s.e.m. ***p <0.0001 by Mann Whitney test.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2015-71521-REDC)
- Ministerio de Economía y Competitividad (BFU2013-50448)
- Ministerio de Economía y Competitividad (SAF2012-32776). PI: JA Enríquez
- Marie Curie Initial Training Networks (ITN). Mitochondrial European Educational Training (GA Nº 317433).
- Ministerio de Economía y Competitividad (RyC 2011-07826). PI: Rebeca Acín
- European Commission. Marie Curie Career Integration Grant. PI: Rebeca Acín

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*Equal contribution
^Co-corresponding authors

Ana Latorre-Pellicer, Raquel Moreno-Loshuertos, Ana Victoria Lechuga-Vieco, Fátima Sánchez-Cabo, Carlos Torroja, Rebeca Acín-Pérez, Enrique Calvo, Esther Aix, Andrés González-Guerra, Angela Logan, María Luisa Bernad-Miana, Eduardo Romanos, Raquel Cruz, Sara Cogliati, Beatriz Sobrino, Ángel Carracedo, Acisclo Pérez-Martos, Patricio Fernández-Silva, Jesús Ruíz-Cabello, Michael P. Murphy, Ignacio Flores, Jesús Vázquez, José Antonio Enríquez. **mtDNA and nuclear DNA matching shapes metabolism and healthy ageing**. *Nature* (2016) 535: 561-5

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Enriquez, J. A. **Supramolecular Organization of Respiratory Complexes**. *Ann Rev Physiol* (2016) 241: 78:533-61

Advanced development in arrhythmia mechanisms and therapy

RESEARCH INTEREST

The laboratory focuses on the mechanisms underlying complex cardiac arrhythmias found in highly prevalent cardiovascular diseases, as well as in specific population subsets at particular risk of sudden cardiac death. Atrial fibrillation (AF), ventricular fibrillation (VF), and infarct scar-related ventricular tachycardia (VT) are three of the most prevalent cardiac rhythm disorders, and the capacity of current therapeutic strategies to accurately eliminate or prevent the arrhythmogenic substrate in these diseases is limited. Our goal is to achieve in-depth insight into the mechanisms of these complex arrhythmias through the use of appropriate experimental and numerical models, and for this insight to be used to improve patient care and develop new and more specific therapies. We use a translational approach to study infarct scar-related VT in pigs and clinical infarct-related reentrant VT. High-resolution MRI images, both in humans (in vivo) and animals (ex vivo) provide detailed structural information for creating anatomically precise patient and animal-specific 3D reconstructions of the ventricles. Electrophysiologically realistic numerical simulations can be incorporated into the 3D model to induce and characterize reentrant VTs. Computational simulations are validated and compared with electropysiological data and outcomes obtained during the electrophysiological study and ablation procedure, either in animals or in patients.

Sensing and detecting VF with current implantable cardioverter defibrillators (ICDs) is highly reliable in the vast majority of cases. However, an adequate R-wave/electrogram amplitude during VF is crucial to avoid undersensing during spontaneous episodes, which otherwise might lead to a delay or even cessation of ICD therapy. We recently reported that baseline rhythm R-wave amplitudes ≤2.5 mV (interquartile range: 2.3–2.8) can increase the rate of VF R-wave undersensing to the point where detection drops below the minimum nominal sensitivity during spontaneous VF, potentially causing delays in or cessation of VF therapy.

For AF, we aim to develop new computational tools for accurate mapping of the propagation dynamics during fibrillation that will enable clinical electrophysiologists to effectively target the main drivers of the arrhythmia. We use a porcine translational model of different AF stages (paroxysmal, persistent, and long-standing persistent AF) that resembles the human disease. The combination of detailed structural characterization of the atria with *in vivo* and *ex vivo* propagation dynamics will provide the most precise data to date about the propagation dynamics underlying AF maintenance.

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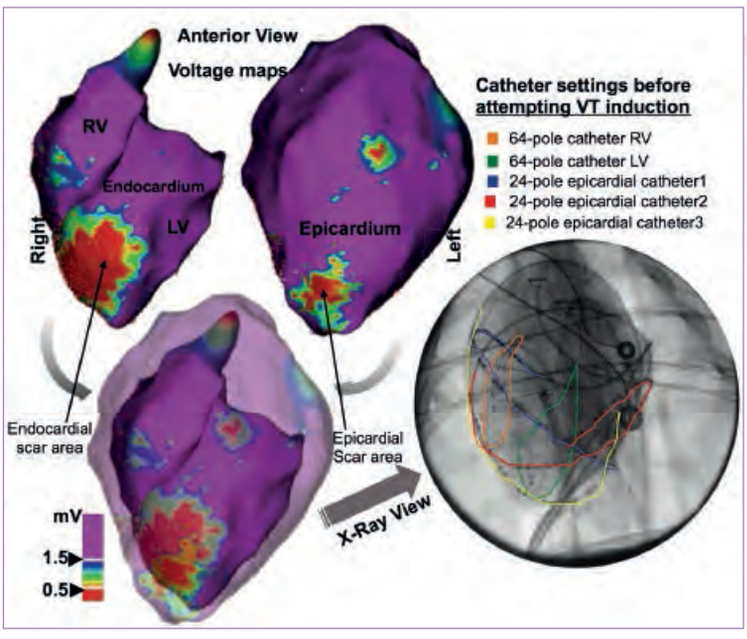
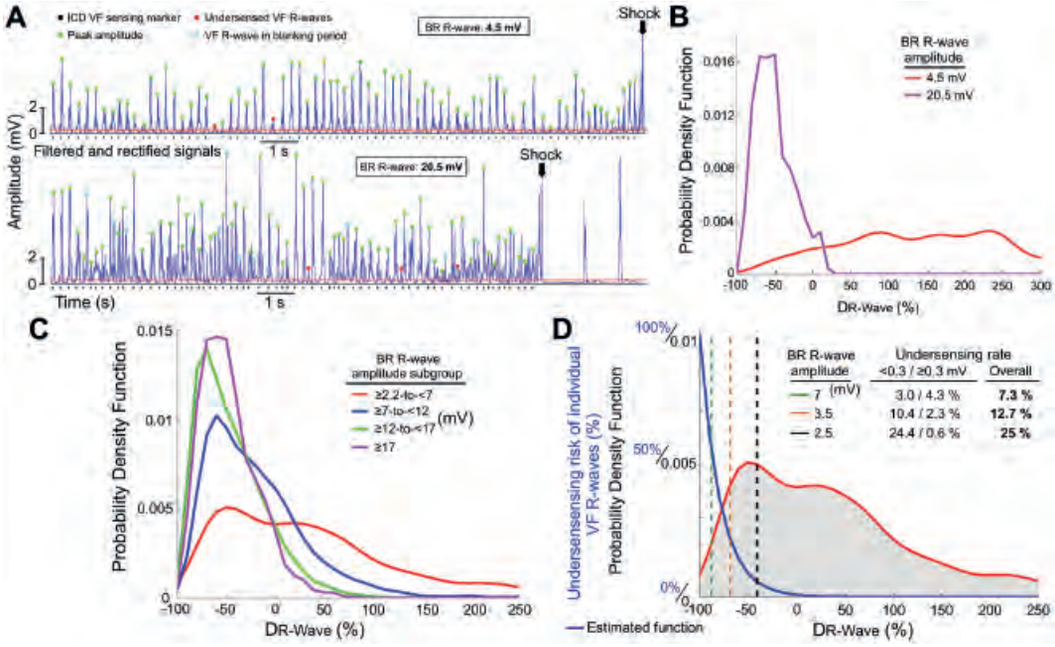


Endocardial and epicardial reconstruction of infarct-related susbtrate.
Voltage maps of the endocardium and epicardium of both ventricles. The structures are superimposed in the lower left panel, and separate in the top panels. The right panel shows an X-ray view of the cardiac silhouette and the multipolar catheters (color coded as indicated) used to charactherize VT activation upon programmed ventricular stimulation and induction.



R-wave amplitude distribution in the four subgroups of BR R-wave amplitude and calculation of the safety threshold.
(A) R-wave amplitude variability during ventricular fibrillation (VF) in two sample episodes of low (upper trace) and high (lower trace) BR R-wave amplitude. (B) Probability density function (PDF) of amplitude differences occurring in the episodes shown in A. (C) PDF of amplitude differences in the four BR R-wave amplitude subgroups. (D) Calculation of the safety threshold for BR R-wave amplitude values using the PDF and the estimated undersensing risk function from the ≥2 to <7 mV subgroup. Three BR R-wave amplitude values are depicted to show a progressive increase in undersensing rates of VF R-waves as the BR R-wave amplitude decreases, mostly due to R-waves <0.3 mV.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2016-80324-R)
- Salud 2000 Foundation.
- Jesús Serra Foundation.
- Pro-CNIC Foundation.

SELECTED PUBLICATIONS

Quintanilla JG, Perez-Villacastin J, Perez-Castellano N, Pandit SV, Berenfeld O, Jalife J, Filgueiras-Rama D **Mechanistic approaches to detect, target, and ablate the drivers of atrial fibrillation**. *Circ Arrhythm Electrophysiol* (2016) 9 e002481

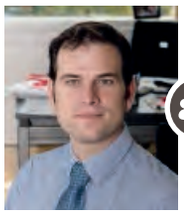
David Filgueiras-Rama, José Jalife. **Structural and functional bases of cardiac fibrillation: differences and similarities between atria and ventricles**. *JACC Clin Electrophysiol* (2016) 2: 1-3

Lillo-Castellano JM, Marina-Breysse M, Gomez-Gallanti A, Martinez-Ferrer JB, Alzueta J, Perez-Alvarez L, Alberola A, Fernandez-Lozano I, Rodriguez A, Porro R, Anguera I, Fontenla A, Gonzalez-Ferrer JJ, Canadas-Godoy V, Perez-Castellano N, Garofalo D, Salvador-Montanes O, Calvo CJ, Quintanilla JG, Peinado R, Mora-Jimenez I, Perez-Villacastin J, Rojo-Alvarez JL, Filgueiras-Rama D **Safety threshold of R-wave amplitudes in patients with implantable cardioverter defibrillator** *Heart (*2016) 102: 1662-70

González-Cambeiro MC, Rodríguez-Mañero M, Abellas-Sequeiros A, Moreno-Arribas J, Filgueira-Rama D, González-Juanatey JR. **Prognostic effect of body mass index in patients with an implantable cardioverter-defibrillator for primary prevention of sudden death**. *Rev Esp Cardiol (*2016) 69: 990-2

Rivera-Torres J, Calvo CJ, Llach A, Guzman-Martinez G, Caballero R, Gonzalez-Gomez C, Jimenez-Borreguero LJ, Guadix JA, Osorio FG, Lopez-Otin C, Herraiz-Martinez A, Cabello N, Vallmitjana A, Benitez R, Gordon LB, Jalife J, Perez-Pomares JM, Tamargo J, Delpon E, Hove-Madsen L, Filgueiras-Rama D, Andres V **Cardiac electrical defects in progeroid mice and Hutchinson-Gilford progeria syndrome patients with nuclear lamina alterations** *Proc Natl Acad Sci U S A* (2016) 113: E7250-E7259.

Translational laboratory for cardiovascular imaging and therapy



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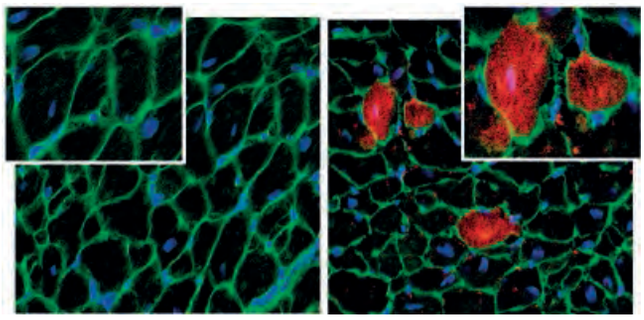
RESEARCH INTEREST

The primary focus of our laboratory is the study of myocardial diseases, from ischemia/reperfusion to heart failure, combining basic and clinical research and including experts in molecular biology, clinical cardiology and neurology, and cardiovascular imaging. We specialize in advanced imaging techniques in animal models that can also be applied to humans, which potentiates the translational nature of our research. Our clinical research is carried out in close collaboration with the Biomedical Research Institute of the Fundación Jiménez Díaz University Hospital.

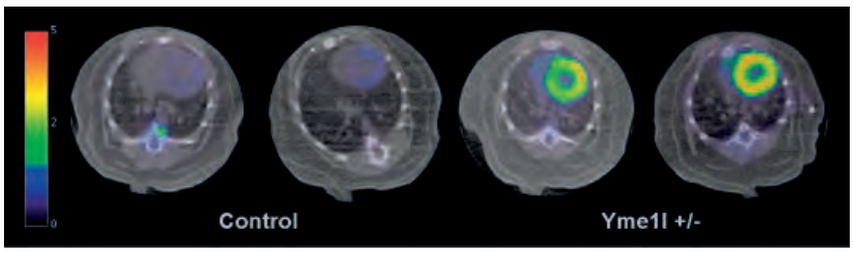
One of our main interests is cardioprotection during myocardial infarction (MI). We study the mechanisms underlying the beneficial effects of several cardioprotective strategies in rodent and large animal models of MI, mainly related to modulation of the beta-adrenergic system. The group is pioneering the use state-of-the-art magnetic resonance imaging (MRI) to better characterize post-infarcted myocardial healing by combining studies in large animal models and human study participants, having also conducted several clinical trials. We have already published the results of the successful randomized METOCARD-CNIC clinical trial, which used MRI to evaluate the effectiveness of early intravenous metoprolol in patients suffering a myocardial infarction, and the study has been continued with the EARLY-BAMI trial, conducted in the Netherlands and Spain. Our most recent trial is the VF-3D-ESSOS study, designed to revolutionize the use of cardiac MRI in the clinical setting. The goal of this study is to clinically validate the use of two ultra-fast sequences that could shorten the duration of cardiac magnetic resonance studies from the current 45 minutes to less than 60 seconds. After validating the sequences in large animals and healthy volunteers, the VF-3D-ESSOS study is now being performed in patients with different types of cardiac injuries.

In parallel with these clinical trials, we study the cellular and molecular mechanisms underlying the observed cardioprotective effect of beta-blockers in in vitro assays and genetically modified small animal models. In addition, following a recent discovery by our group, we are also opening new fields of research focused on the metabolism of heart failure and the study of revolutionary nutritional approaches to treat this condition.



Deletion of Yme1l induces cardiomyocyte necrosis in mice. Immunofluorescence images of 20-week-old Yme1l knockout mice (right) and control mice (left), showing increased cellular necrosis (Evans Blue staining in red) in mutant hearts. Hearts were stained with Evans Blue (red), wheat germ agglutinin (green), and DAPI (blue).

The group is also interested in the myocardial response to pulmonary hypertension. We have developed small and large animal models of pulmonary hypertension and use imaging technology to evaluate the response to different therapies. We have identified beta-3-adrenergic receptor stimulation as a novel therapeutic approach for the treatment of pulmonary hypertension in preclinical studies and have received funding to bring this therapy to a pilot clinical trial (SPHERE-HF) that will start during the coming year.



Ablation of Yme1l induces dilated cardiomyopathy in mice. Positron emission tomography–computed tomography (PET-CT) images of 40-week-old Yme1l knockout and control mice after [^{18}F]FDG injections, showing increased glucose consumption in failing hearts.

MAJOR GRANTS

- Ministerio de Economía y Competitividad - EXPLORA CIENCIA (SAF2013-49663-EXP)
- Ministerio de Economía y Competitividad - Acciones de Dinamización Europa investigación (EUIN2013-50881)
- Ministerio de Economía y Competitividad. ISCIII-FIS (PI13/01979)
- Ministerio de Economía y Competitividad. ISCIII-RETICS (RiC, RD12/0042/0054)
- Marató, Fundación TV3 (REF: 70/C/2012)
- European Commision FP7-PEOPLE-2013-ITN (CARDIONEXT).
- Fundación BBVA. Ayudas a Equipos de Investigación Científica (Proyectos-BBVA-2016)

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Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* (2015) 65: 1454-71

Wai T, Garcia-Prieto J, Baker MJ, Merkwirth C, Benit P, Rustin P, Ruperez FJ, Barbas C, Ibanez B*, Langer T*. **Imbalanced OPA1 processing and mitochondrial fragmentation cause heart failure in mice**. *Science* (2015) 350:aad0116.

Garcia-Alvarez A, Garcia-Lunar I, Pereda D, Fernandez-Jimenez R, Sanchez-Gonzalez J, Mirelis JG, Nuno-Ayala M, Sanchez-Quintana D, Fernandez-Friera L, Garcia-Ruiz JM, Pizarro G, Aguero J, Campelos P, Castella M, Sabate M, Fuster V, Sanz J, Ibanez B. **Association of myocardial T1-mapping CMR with hemodynamics and RV performance in pulmonary hypertension**. *JACC Cardiovasc Imaging* (2015) 8: 76-82

Garcia-Alvarez A, Pereda D, Garcia-Lunar I, Sanz-Rosa D, Fernandez-Jimenez R, Garcia-Prieto J, Nuno-Ayala M, Sierra F, Santiago E, Sandoval E, Campelos P, Aguero J, Pizarro G, Peinado VI, Fernandez-Friera L, Garcia-Ruiz JM, Barbera JA, Castella M, Sabate M, Fuster V, Ibanez B. **Beta-3 adrenergic agonists reduce pulmonary vascular resistance and improve right ventricular performance in a porcine model of chronic pulmonary hypertension**. *Basic Res Cardiol* (2016) 111: 49

Garcia-Ruiz JM, Fernandez-Jimenez R, Garcia-Alvarez A, Pizarro G, Galan-Arriola C, Fernandez-Friera L, Mateos A, Nuno-Ayala M, Aguero J, Sanchez-Gonzalez J, Garcia-Prieto J, Lopez-Melgar B, Martinez-Tenorio P, Lopez-Martin GJ, Macias A, Perez-Asenjo B, Cabrera JA, Fernandez-Ortiz A, Fuster V, Ibanez B. **Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function**. *J Am Coll Cardiol* (2016) 67: 2093-104

Cardiac arrhythmia

Head of Laboratory:
José Jalife

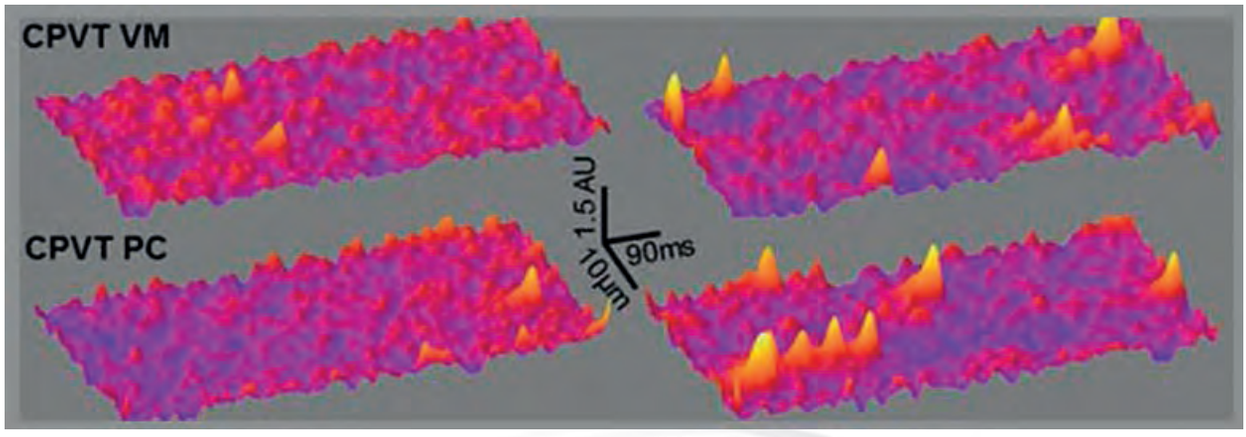
Visiting Student:
Sandeep V. Pandit

RESEARCH INTEREST

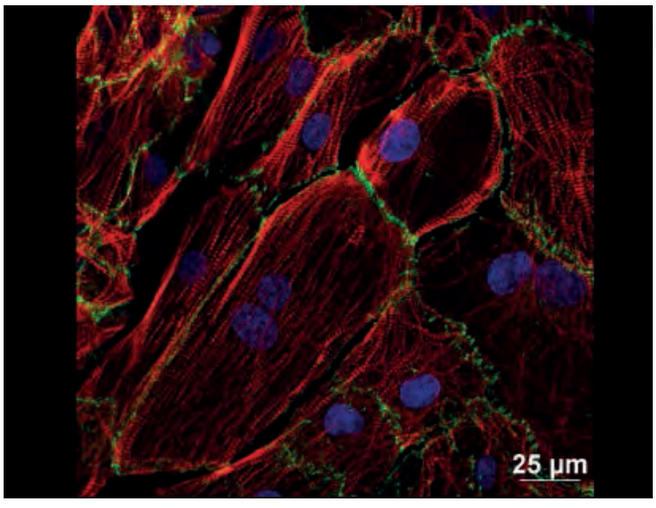
The laboratory investigates the causes of cardiovascular disease and arrhythmias at the molecular, cellular, and electrophysiological levels. Our specific research interests center on 1) the mechanisms of atrial and ventricular fibrillation at the structural and functional level, 2) the molecular genetics of cardiac fibrillation, and 3) the cellular basis of cardiac arrhythmia in genetic and rare diseases that can lead to sudden death, and 4) the use of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to investigate molecular mechanisms of arrhythmogenesis.

The laboratory has well-established collaborations with expert engineers, biologists, and clinicians around the world, as well as with other CNIC groups. These partnerships provide a unique research environment in which to generate new and clinically relevant breakthroughs on arrhythmia mechanisms to the benefit of the medical and basic science communities, and ultimately the patient.

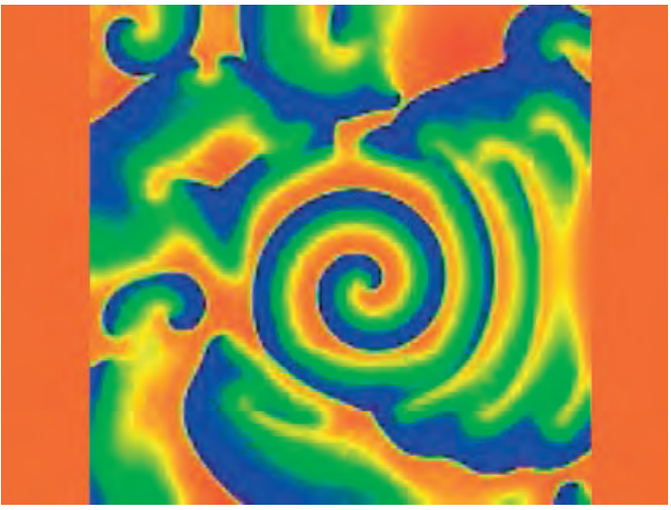
An ongoing multidisciplinary project is the whole genome characterization of large animal models of atrial fibrillation with a clear translational impact. The project aims to define transcriptomic changes in a sheep model of induced atrial fibrillation. Bioinformatic analysis of changes in gene expression and correlation with proteomic data generated by the group will enable mapping of the networks and pathways altered in paroxysmal and persistent states of atrial fibrillation. These results are also being validated in a pig atrial fibrillation model that has recently been established at the CNIC. The use of these models will allow us to better understand the molecular determinants and consequences of atrial fibrillation and to offer new insights into therapeutic targets for this disease.



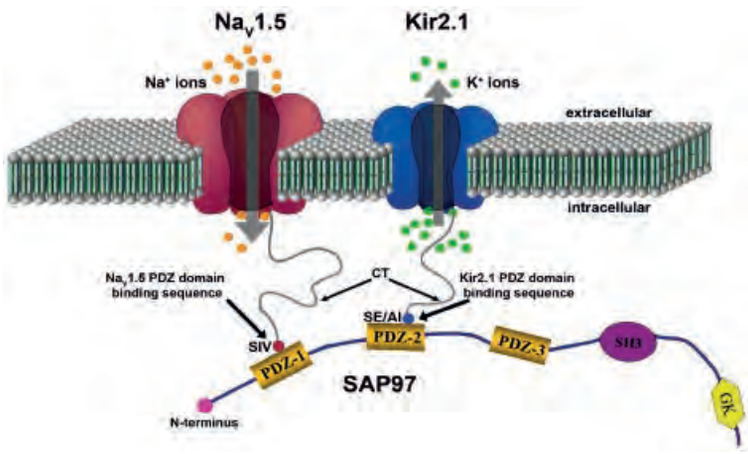
Ca2+ spark frequency (CaSpF) is higher in control and catecholaminergic polymorphic ventricular tachycardia (CPVT) Purkinje cells (PCs) than in ventricular myocytes (VMs). The figure shows 3-dimensional surface plots of representative line scan images for a CPVT VM and CPVT PC for baseline (left) and after treatment with 10 nM/L isoproterenol (right). Willis BC. et al *Circulation* 2016.



Structurally mature human iPSC-derived cardiomyocyte (CM) monolayer cultured on a soft surface. The figure shows CMs with well organized sarcomeres and localization of troponin T (red), N-cadherin (green), and nuclear dapi (blue). Jalife et al, unpublished.



In cardiac fibrillation, the rotor is the driver of reentry located at the center of a spiral wave. The rotational speed determines the degree of turbulence (wave fragmentation) around the rotor; the higher the spin speed the greater the degree of fragmentation. Rotors are not easy to find in the heart. In this computer simulation, the mother rotor occupies less than 0.1% of the total area; the rest is fibrillatory conduction. Samie F, et al. *Circulation Research* 2001.



"Cardiac Channelosome". In the heart, the strong inward rectifier potassium channel (Kir2.1) and the main cardiac sodium channel (Nav1.5) form part of a macromolecular complex ("channelosome") mediated by SAP97 through their respective carboxyl terminus PDZ binding domains.

MAJOR GRANTS

- Leducq Foundation Transatlantic Networks of Excellence Program (not CNIC). Peincipal Investigator
- NIH / NHLBI - R01 (HL122352) (not CNIC). Principal Investigator
- NIH / NHLBI - T32 (HL125242) (not CNIC). Principal Investigator
- The University of Michigan Health Sciences-Peking University Health Science Center Joint Institute. (not CNIC). Principal Investigator.
- Medtronic, Inc. Collaborative Grant to investigate detection of AF sources rom the body surface (non CNIC) Principal Investigator
- Abbott EP. Rotors and AF Reserch Grant (non CNIC) Principal Investigator

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Herron TJ, Rocha AM, Campbell KF, Ponce-Balbuena D, Willis BC, Guerrero-Serna G, Liu Q, Klos M, Musa H, Zarzoso M, Bizy A, Furness J, Anumonwo J, Mironov S, Jalife J. **Extracellular matrix-mediated maturation of human pluripotent stem cell-derived cardiac monolayer structure and electrophysiological function**. *Circulation Arrhythmia & Electrophysiol.* (2016) 9: e003638

Willis C, Pandit SV, Ponce-Balbuena D, Zarzoso M, Guerrero-Serna G, Limbu B, Deo M, Camors E, Ramirez RJ, Mironov S, Herron TJ, Valdivia HH, Jalife J. **Purkinje intracellular sodium surplus drives calcium-linked ventricular arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia**. *Circulation* (2016) 133: 2348-59

Monteiro da Rocha A, Guerrero-Serna G, Helms A, Luzod C, Mironov S, Russell M, Jalife J, Day SM, Smith GD, Herron TJ. **Deficient cMyBP-C protein expression during cardiomyocyte differentiation underlies human hypertrophic cardiomyopathy cellular phenotypes in disease specific human ES cell derived cardiomyocytes**. *J Mol Cell Cardiol.* (2016) 99: 197-206

Rivera-Torres J, Calvo CJ, Llach A, Guzmán-Martínez G, Caballero R, González-Gómez C, Jiménez-Borreguero LJ, Guadix JA, Osorio FG, López-Otín C, Herraiz Martínez A, Cabello N, Vallmitjana A, Benítez R, Gordon LB, Jalife J, Pérez-Pomares JM, Tamargo J, Delpón E, Hove-Madsen L, Filgueiras-Rama D, Andrés V. **Cardiac electrical defects in progeroid mice and Hutchinson-Gilford progeria syndrome patients with nuclear lamina alterations**. *Proc Natl Acad Sci USA* (2016) 15: 113: E7250-9

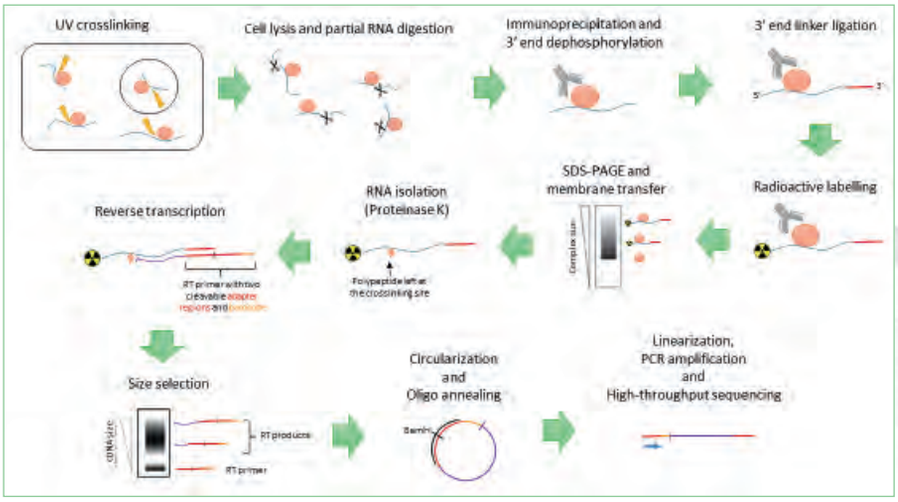
Takemoto Y, Ramirez RJ, Yokokawa M, Kaur K, Ponce-Balbuena D, Sinno MC, Willis BC, Ghanbari H, Ennis SR, Guerrero-Serna G, Henzi BC, Latchamsetty R, Ramos-Mondragon R, Musa H, Martins RP, Pandit SV, Noujaim SF, Crawford T, Jongnarangsin K, Pelosi F, Bogun F, Chugh A, Berenfeld O, Morady F, Oral H and Jalife J. **Inhibition of Galectin-3 Mitigates Atrial Fibrosis and Vulnerability to AF and Increases Rate of Spontaneous Cardioversion to Sinus Rhythm in a model of Persistent Atrial Fibrillation**. *JACC: Basic to Translational Science* (2016) 1: 143–54

Molecular regulation of heart failure

RESEARCH INTEREST

Our laboratory investigates the molecular pathways driving heart remodeling and the development of heart failure, which are still poorly understood. In particular, we focus on the role of RNA binding proteins (RBPs) and alternative splicing in these processes. For this purpose, we developed ATtRACT, an integrated database of RPBs and their associated RNA motifs (Giudice et al., 2016), which is the largest RBP database to date. Using ATtRACT and other bioinformatic tools, we have identified a potential role of some SR-rich splicing factors (SRSF) in post-infarction remodeling. In addition, we have reported that the alternative splicing variant of calcineurin, CnAβ1, has a mechanism of action completely different from other calcineurin isoforms (Gómez-Salinero et al., 2016). Instead of targeting the transcription factor NFAT, CnAβ1 activates the Akt/mTOR signaling pathway to regulate mesodermal differentiation in embryonic stem cells.

Our research also focuses on the study of the pathological mechanisms undelying different cardiomyopathies. In recent years, we have focused on the study of Lafora disease. This disease is characterized by seizures and epilepsy caused by the accumulation of abnormal glycogen deposits in neurons. It was unknown, however, whether these deposits could affect cardiac function. Using two mouse models of Lafora disease, we found that cardiomyocytes accumulate glycogen deposits that result in cardiac hypertrophy and defective contraction. These results suggest that Lafora disease should be considered an inherited metabolic cardiomyopathy like Fabri's or Danon's disease and that Lafora disease patients should be assessed for cardiac abnormalities.



Summary of the cross-linking immunoprecipitation and massive parallel sequencing (CLIP-Seq) protocol. To identify the targets of an RNA-binding protein (RBP), RPBs are cross-linked to their bound RNA, immunoprecipitated, separated on a polyacrylamide gel, and labeled with radioactive ATP. Following reverse transcription, cDNAs of the appropriate size are selected and circularized. The circular DNA molecules are then linearized, amplified by PCR and sequenced by next generation sequencing.

Head of Laboratory:
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Río Hortega Fellow:
Esther González

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Alberto Gatto
Enda Clinton
Girolamo Giudice
Paula Ortiz Sánchez
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Technician:
Marina López Olañeta

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Juan M. Monteagudo Ruiz

Visiting Scientists:
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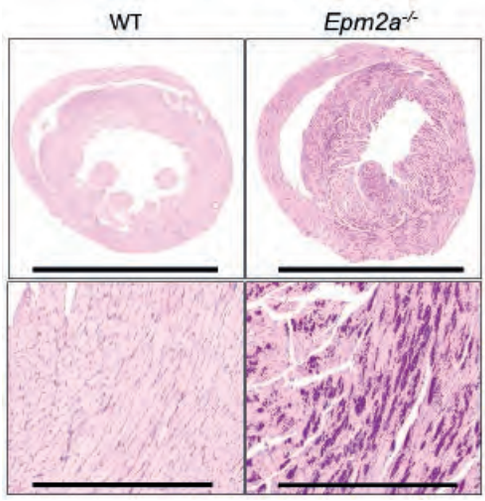
Elísabet Bello Arroyo
Fernando Domínguez Rodríguez
Marta Román Carmena



Glycogen deposits in cardiomyocytes of a Lafora disease mouse model. Heart sections from wild type (WT) mice or mice lacking laforin (Epm2a$^{-/-}$) were analyzed by Periodic acid-Schiff (PAS) staining, which labels glycogen deposits. Lafora knockout mice develop Lafora disease and show abnormal accumulation of glycogen deposits in cardiomyocytes, which is associated with a decline in systolic function. Wild type mice (left) are included as a negative control. Bar, 5 mm (top) or 500 µm (bottom).

MAJOR GRANTS

- European Commission. Marie Curie Action Initial Training Network (ITN) (FP7-PEOPLE-2013-ITN, "CardioNext" 608027)
- European Commission. Marie Curie Action Initial Training Network (ITN) (FP7-PEOPLE-2011-ITN, "CardioNeT" 289600)
- Comunidad de Madrid (GRUPOSCAM10, "Fibroteam" S2010/BMD-2321)
- Instituto de Salud Carlos III (MSII14/00027)
- Ministerio de Economía y Competitividad (SAF2015-65722-R)

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Lara-Pezzi E, Desco M, Gatto A, Gómez-Gaviro MV. **Neurogenesis: regulation by alternative splicing and related posttranscriptional processes**. *Neuroscientist* pii: 1073858416678604. [Epub ahead of print Nov 10 2016]

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González-Santamaría J, Villalba M, Busnadiego O, López-Olañeta MM, Sandoval P, Snabel J, López-Cabrera M, Erler JT, Hanemaaijer R, Lara-Pezzi E*, Rodríguez-Pascual F*. **Matrix cross-linking lysyl oxidases are induced in response to myocardial infarction and promote cardiac dysfunction**. *Cardiovasc Res* (2016) 109: 67-78
*Co-corresponding authors.

Molecular cardiology

RESEARCH INTEREST

The molecular cardiology laboratory was launched in April 2016, and the period since has been occupied with installing equipment, recruiting expert staff, and establishing knock-in mouse colonies from Professor Priori's laboratory in the CNIC facilities. The patch clamp unit has been set up, and work is progressing on finalizing equipment to simultaneously record intracellular calcium and other ion currents in isolated cardiac cells. Methods are also being established to derive cardiomyocytes from induced pluripotent stem cells (iPSC), with the goal of studying cardiomyocytes differentiated from iPSCs of patients with inherited arrhythmias.

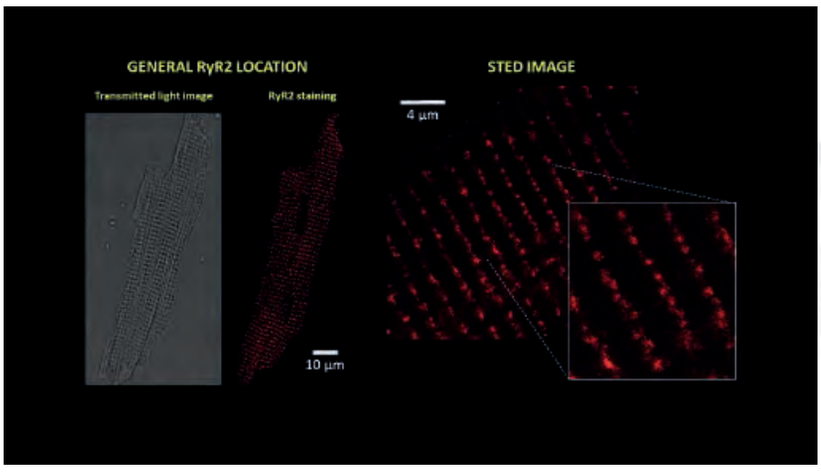
Dr. Priori has dedicated her clinical and research career to understanding the molecular mechanisms underlying inherited arrhythmias, and since 2013 she has focused her attention on the development of molecular therapies for these conditions. A major obstacle in the field is the lack of models for the arrhythmogenic syndromes of interest. The team therefore dedicates part of its effort to developing disease models, ranging from the patient-iPSC-derived cardiomyocytes described above to knock-in and knock-out models in mice and pigs.

The team's current research focuses on 2 severe inherited arrhythmogenic diseases: dominant catecholaminergic polymorphic ventricular tachycardia (CPVT) and Long QT syndrome type 8 (LQT8). The group is currently working with mouse models of the dominant and the recessive forms of CPVT to determine the effects of gene-therapy strategies on intracellular calcium handling and cell electrophysiology. These strategies have been developed by the Molecular Cardiology Laboratory at the ICS Maugeri Institute in Pavia, Italy. The group is also working on an ambitious project to develop a knock-in pig model of LQT8.

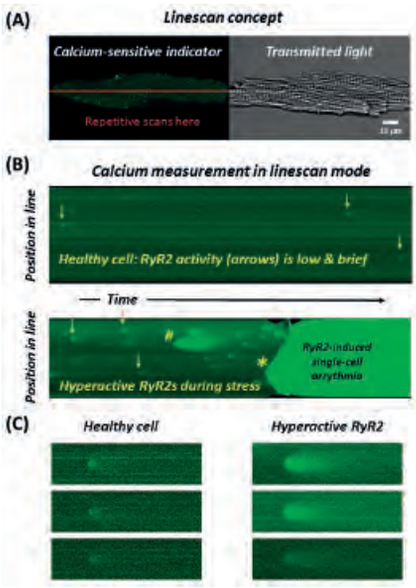
Head of Laboratory:
Silvia Giuliana Priori

Postdoctoral Researchers:
Demetrio Julián Santiago Castillo
Jaroslaw Karol Sochacki

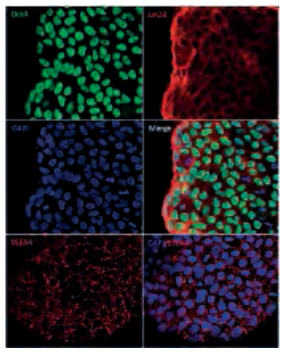
Graduate Technician:
Francesca Romana Antonucci



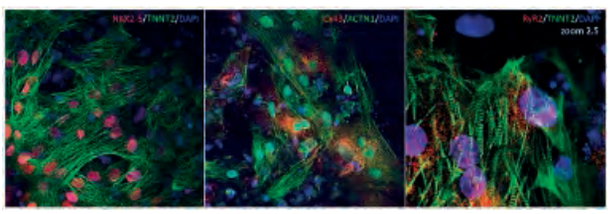
Left: Mouse ventricular myocyte immunostained for the cardiac ryanodine receptor (RyR2), a protein that mobilizes calcium (necessary for cell contraction) during the heartbeat. *Right*: Expanded view of the RyR2 arrangement (super-resolution microscopy). We are investigating whether arrythmogenic cardiovascular disease modifies the diversity of RyR2 cluster shapes, inter-cluster distances, and cluster grouping into "super-clusters".



(A) During a *linescan*, a single line within a cell is repetitively scanned. **(B)** Study of RyR2 activity in *linescan* mode, through calcium movements. In a healthy quiescent cell, RyR2 activition is low, and each calcium release event lasts a few milliseconds (arrows). In unhealthy, stressed, or diseased cells (eg, CPVT), RyR2 activity becomes high (arrows), extremely high and grouped (#), or extremely high, long-lived, and propagated among RyR2 clusters (*). This may interphere with membrane potential, causing arrythmias. **(C)** Details of short-lived calcium release events (*sparks*). Each spark lasts for 20-50 ms (depending on cell status) and extends for about 2 microns.



Correct expression of the pluripotency markers Oct4, Lin28, and SSEA4 in a CPVT-patient-derived iPS cell line. Nuclei are counterstained with DAPI. 40x objective.



Human iPSC-derived cardiomyocytes expressing typical lineage markers: cardiac transcription factor (NKX2-5), cardiac muscle troponin T (TNNT2), gap junction protein connexin 43 (Cx43), cytoskeletal alpha actinin (ACTN1), and cardiac ryanodine receptor (RyR2). 40x objective.

MAJOR GRANTS

- ERC Advanced Grant 2014. Molecular Strategies to Treat Inherited Arrhythmias
- International Postdoctoral Programme, 5th call, CNIC, 2016-19. Shaking the current view: Catecholaminergic polymorphic ventricular tachycardia is a nano-cardiomyopahy

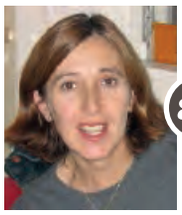
SELECTED PUBLICATIONS

Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, Novelli V, Baiardi P, Bagnardi V, Etheridge SP, Napolitano C, Priori SG. **Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3.** *J Am Coll Cardiol* (2016) 67: 1053-8

Bezzina CR, Lahrouchi N, Priori SG. **Genetics of sudden cardiac death.** *Circ Res* (2015) 116: 1919-36

Park DS, Cerrone M, Morley G, Vasquez C, Fowler S, Liu N, Bernstein SA, Liu FY, Zhang J, Rogers CS, Priori SG, Chinitz LA, Fishman GI. **Genetically engineered SCN5A mutant pig hearts exhibit conduction defects and arrhythmias.** *J Clin Invest* (2015) 125: 403-12

Nuclear receptor signaling



RESEARCH INTEREST

Macrophages are hematopoietic cells of the myeloid lineage with important functions in development, homeostasis, tissue repair, and immunity. Macrophages can be found in practically all tissues, making important contributions to their homeostasis and protection against injury. Projects in our group focus on elucidating the transcriptional control of macrophages in different tissues, especially in the heart and bone marrow, with special emphasis on their possible medical utility in the treatment of metabolic and cardiovascular diseases.

A special interest of our group is the molecular mechanisms regulating macrophage development and function. Our laboratory has shown that the nuclear receptor retinoid X receptor (RXR) plays a major regulatory role in macrophages, with implications for homeostasis, inflammation, and immunity. Our studies have demonstrated that RXR regulates macrophage transcriptional programs necessary for cell migration, debris clearance, macrophage polarization, cell proliferation and osteoclastogenesis, antiviral response, and lipid metabolism. Our more recent studies suggest that RXR may play important roles in the control of hematopoietic stem cell maintenance and the development and function of different tissue resident macrophages, which might have implications for tissue repair and regeneration. Other studies in our laboratory are aimed at deciphering the role of RXR during heart development, as part of a wider effort to understand the regulatory molecular mechanisms involved in cardiogenesis. To pursue these goals, we are currently conducting complementary loss-of-function and drug-mediated gain-of-function mouse studies and genome-wide transcriptomic (RNA-seq and GRO-seq) and cistromic (ChIP-seq) studies. Using these approaches, we will examine mice lacking RXR in hematopoietic stem cells, macrophages, endothelial cells, and cardiomyoctes, allowing us to examine the specific role of these receptors in tissue homeostasis and injury.

Head of Laboratory:
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Verdiana Trappetti

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Guadalupe González
Jesús Porcuna

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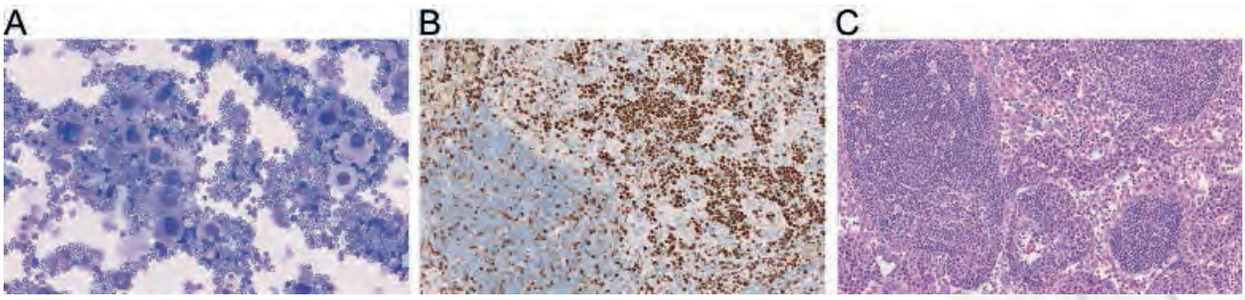
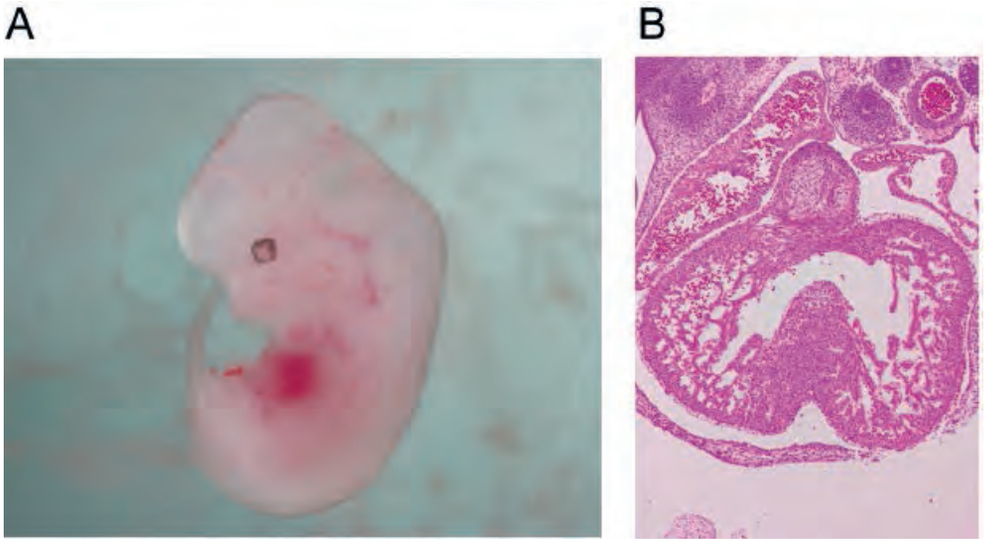
Vanessa Núñez González



Role of RXR in hematopoiesis. **(A)** May-Grünwald-Giemsa staining of cytospinned bone marrow cells from RXR-deficient mouse. **(B)** Proliferating cells revealed by Ki67 staining on sections of paraffin-embedded spleen from an RXR-deficient mouse. **(C)** H&E staining of sections of paraffin-embedded lymph node from an RXR-deficient mouse.



Role of RXR during heart development. **(A)** Gross morphological appearance of an RXR-deficient embryo (E12.5). **(B)** H&E staining of the heart of an RXR-deficient embryo (E12.5).

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2015-64287-R)
- Ministerio de Economía y Competitividad (SAF2015-71878-REDT)
- European Commission, 7th Frame Program (FP7-PEOPLE-2013-ITN) (PITN-GA-2013-608027)
- Ministerio de Economía y Competitividad (SAF2012-31483)
- Fundación TV3 Marató 2012 (ref 165/C/12)

SELECTED PUBLICATIONS

Vivas Y, Díez-Hochleitner M, Izquierdo-Lahuerta A, Corrales P, Horrillo D, Velasco I, Martínez-García C, Campbell M, Sevillano J, Ricote M, Ros M, Ramos MP, Medina-Gomez G. **Peroxisome proliferator activated receptor gamma 2 modulates late pregnancy homeostatic metabolic adaptations**. *Mol Med* (2016) 22: 724-36

Natrajan MS, de la Fuente AG, Crawford AH, Linehan E, Nuñez V, Johnson KR, Wu T, Fitzgerald DC, Ricote M, Bielekova B, Franklin RJ. **Retinoid X receptor activation reverses age-related deficiencies in myelin debris phagocytosis and remyelination**. *Brain* (2015) 138: 3581-97

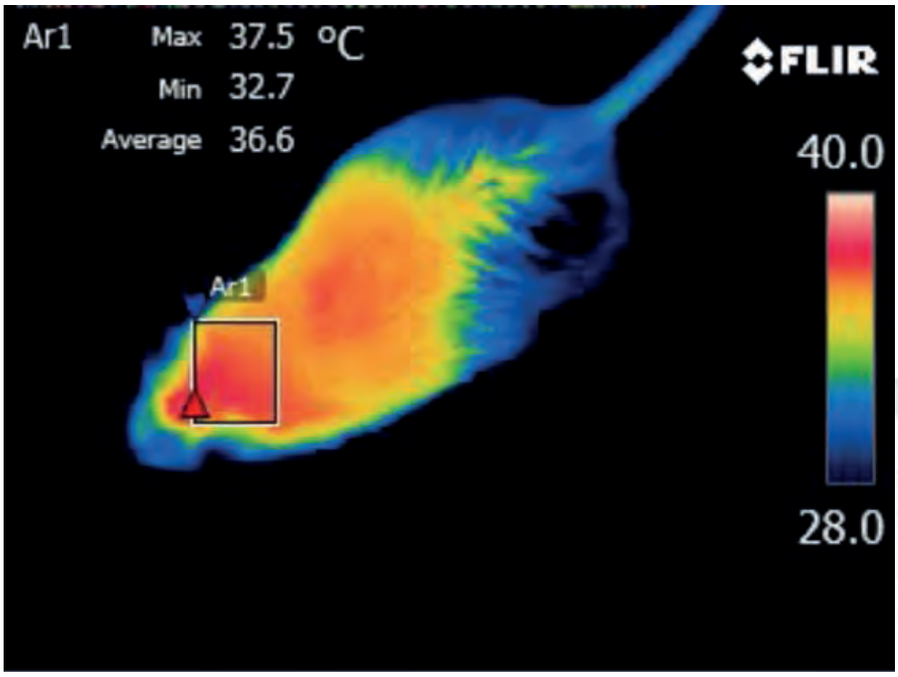
Walter W, Sánchez-Cabo F, Ricote M. **GOplot: an R package for visually combining expression data with functional analysis.** *Bioinformatics* (2015) 31: 2912-4

Menéndez-Gutiérrez MP, Rőszer T, Fuentes L, Núñez V, Escolano A, Redondo JM, De Clerck N, Metzger D, Valledor AF, Ricote M. **Retinoid X receptors orchestrate osteoclast differentiation and postnatal bone remodeling.** *J Clin Invest* (2015) 125: 809-23

Stress kinases in diabetes, cancer, and cardiovascular disease

RESEARCH INTEREST

We are working on the role of stress kinases in the development of metabolic diseases such as diabetes, fatty liver disease, and cardiovascular diseases. We have shown that these kinases control TNF production through the phosphorylation of eEF2K and activation of the elongation factor EF2 (*J Clin Invest*, 2013). Our recent work (*EMBO J*, 2016) shows that the lack of p38γ and p38δ in myeloid cells impairs neutrophil migration to the liver and thus protects against diet-induced steatosis and further liver damage. We have also demonstrated that these kinases control postnatal cardiac growth (*Nature Commun*, 2016). Current projects in the lab are continuing our efforts to uncover the role of these kinases in health and disease.



Infrared thermal image of a mouse showing regions surrounded by interscapular brown adipose tissue.

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Leticia Herrera
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Victor Emilio Bondia
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Technician:
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Visiting Scientist:
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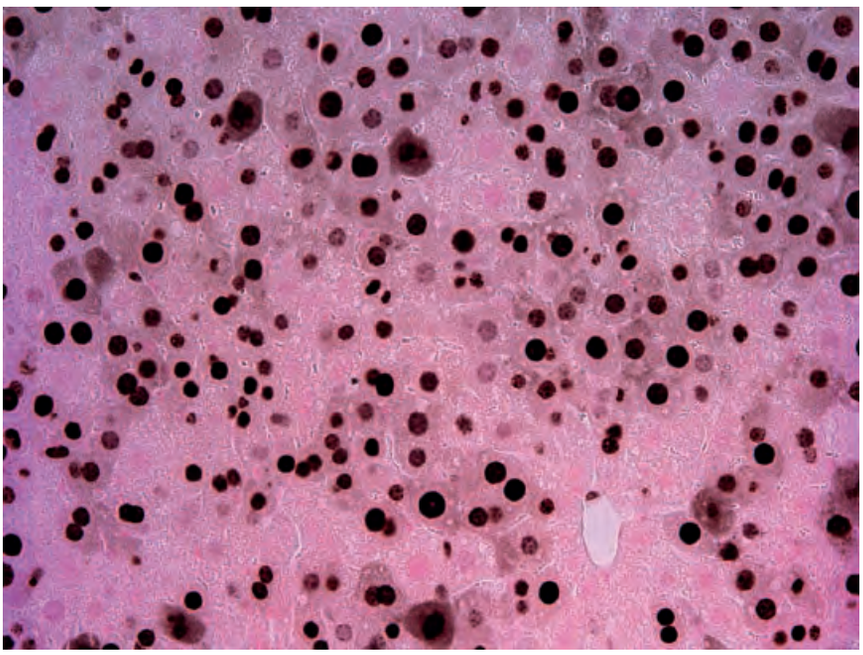
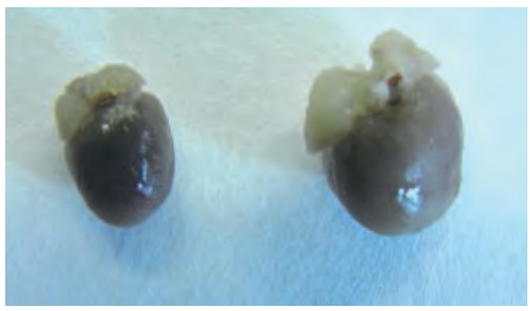


Liver stained with Ki67, showing cell cycle initiation after partial hepatectomy.



Mice lacking p38γ and p38δ have smaller than normal hearts size. Representative images of hearts from a KO mouse (left) and a WT mouse (right).

MAJOR GRANTS

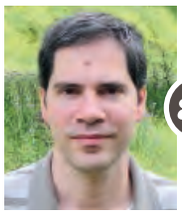
- Ministerio de Economía y Competitividad (SAF2016-79126-R)
- Ministerio de Economía y Competitividad (SAF2013-43506-R)
- European Commission. European Research Council Starting Independent Researcher Grant (ERC-StG-260464)
- Comunidad de Madrid. INMUNOTHERCAN (S2011/BMD-2326)

SELECTED PUBLICATIONS

González-Terán B, Matesanz N, Nikolic I, Verdugo MA, Sreeramkumar V, Hernández-Cosido L, Mora A, Crainiciuc G, Sáiz ML, Bernardo E, Leiva-Vega L, Rodríguez E, Bondía V, Torres JL, Perez-Sieira S, Ortega L, Cuenda A, Sanchez-Madrid F, Nogueiras R, Hidalgo A, Marcos M, Sabio G. **p38γ and p38δ reprogram liver metabolism by modulating neutrophil infiltration.** *EMBO J* (2016) 35: 536-52

González-Terán B, López JA, Rodríguez E, Leiva L, Martínez Martínez S. Jiménez Borreguero LJ, Redondo JM, Vázquez J, Sabio G. p38 and δ promote heart hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation. *Nat Commun* (2016) 7:10477

Manieri E, Sabio G. **Stress kinases in the modulation of metabolism and energy balance**. *J Mol Endocrinol* (2015) 55: R11-22



Immunobiology

RESEARCH INTEREST

We are interested in the manipulation of dendritic cells (DCs) and macrophages for immunotherapy. The analysis of different DC subsets indicates that they have specific functions and can be selectively targeted to induce specific immune responses. We have investigated the role of DC1s in the generation of $CD8^+$ T cell memory and have found that these cells provide unique signals for the generation of resident memory precursors (Figure 1), which are crucial for surveying and mounting an effective and rapid immune response upon reinfection of skin and mucosae (Iborra et al. 2016a. Immunity).

C-type lectin receptors sense a diversity of endogenous and exogenous ligands that can trigger differential responses. We recently found that Mincle detects a ligand in *Leishmania* (Figure 2) that triggers an inhibitory axis characterized by SHP1 coupling to the FcRγ chain. We conclude that *Leishmania* shifts Mincle to an inhibitory ITAM (ITAMi) configuration that impairs DC activation. Thus, ITAMi can be exploited for immune evasion by a pathogen and may represent a paradigm for self and non-self sensing by ITAM-coupled receptors.

We also explored the mitocondrial adaptations following sensing of bacteria by macrophages (Figure 3) and found that recognition of viable bacteria through TLR- and NLRP3-dependent pathways induces a transient switch in the relative contribution of complexes CI and CII to mitocondrial respiration in macrophages. Notably, pharmacological inhibition of CII during *E. coli* infection decreased IL-1β and increased IL-10 serum-concentrations, resulting in impaired control of bacteria. Our research thus has potential for the development of new vaccines and immunotherapy strategies.

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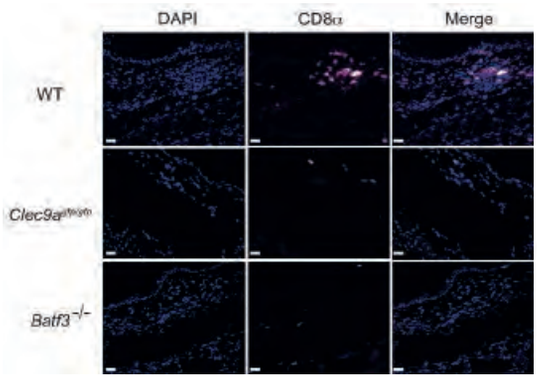
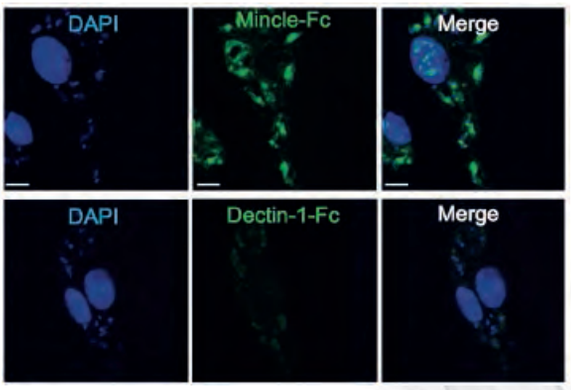
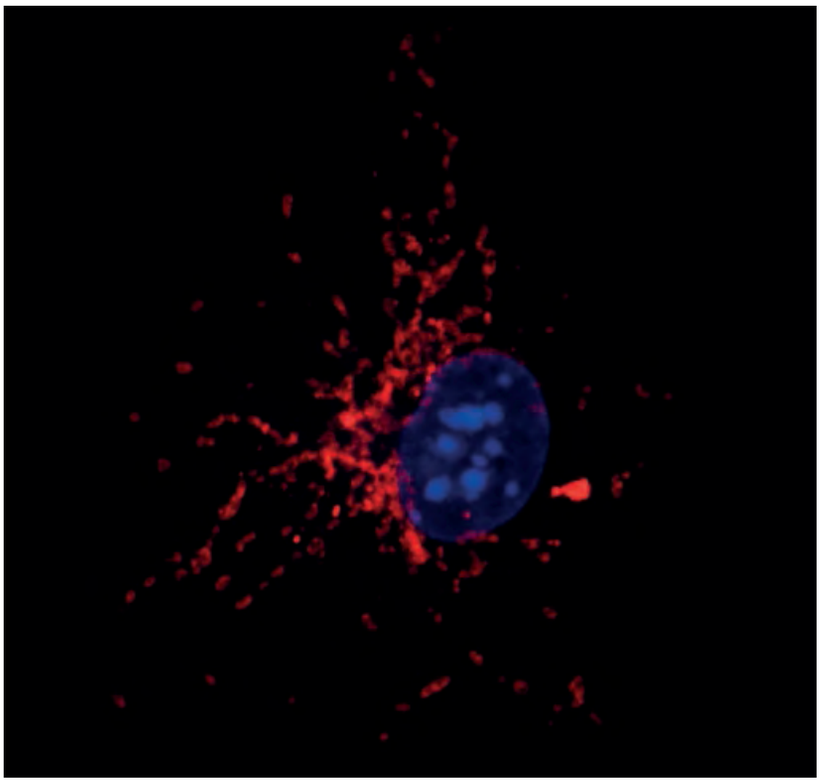


Wild-type mice (WT) or mice deficient in DNGR-1 ($Clec9a^{gfp/gfp}$) or Batf3 ($Batf3^{-/-}$) were infected with vaccinia virus and generation of resident memory CD8+ T cells was tracked for 30 days post-infection in the infected skin by immunofluorescence staining as indicated. Scale bar: 10 µm.



Bone marrow-derived macrophages were preincubated with *Leishmania* promastigotes, fixed, permeabilized and stained with Mincle-Fc or Dectin-1-Fc. Confocal images are shown. Nuclei were counterstained with DAPI. Scale bar: 5 µm.



Bone marrow-derived macrophages were stained for mitochondria using mitotracker (red) and nucleus was counterstained with DAPI.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2016-79040-R)
- Ministerio de Economía y Competitividad (EUIN2015-62652)
- Ministerio de Economía y Competitividad. Programa Redes de Excelencia 2014. (SAF2014-53563- REDT).
- EU Framework Programme for Research and Innovation H2020. Call: H2020-PERSONALISING HEALTH AND CARE (GA635122-PROCROP).
- Ministerio de Economía y Competitividad (SAF2013-42920-R)
- European Commission. European Research Council Starting Independent Researcher Grant (ERC-StG-260414)
- Research cooperation agreement with MedImmune (Cambridge, UK)
- ERS/EU Marie Curie Post-doctoral Research Fellowships (RESPIRE 2 - 3708-2013).

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Iborra S, Martínez-López M, Khouili SC, Enamorado M, Cueto FJ, Conde-Garrosa R, del Fresno C, Sancho D. **Optimal generation of tissue-resident but not circulating memory T cells during viral infection requires crosspriming by DNGR-1+ dendritic cells**. *Immunity (*2016a) 45:847-60

Iborra S, Martínez-López M, Cueto FJ, Conde-Garrosa R, Del Fresno C, Izquierdo HM, Abram CL, Mori D, Campos Martín Y, Reguera RM, Kemp B, Yamasaki S, Robinson MJ, Soto M, Lowell CA Sancho D. **Leishmania uses Mincle to target an inhibitory ITAM pathway in dendritic cells that dampens adaptive immunity to infection**. *Immunity (*2016b) 45:788-801

Garaude J, Acín-Pérez R, Martínez-Cano S, Enamorado M, Ugolini M, Nistal-Villán E, Hervás-Stubbs S, Pelegrín P, Sander LE, Enríquez JA, Sancho D. **Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense**. *Nat Immunol* (2016) 17:1037-45

Sanchez-Paulete AR, Cueto FJ, Martinez-Lopez M, Labiano S, Morales-Kastresana A, Rodriguez-Ruiz ME, Jure-Kunkel M, Azpilikueta A, Aznar MA, Quetglas JI, **Sancho D***, Melero I*. **Cancer immunotherapy with immunomodulatory anti-CD137 and anti-PD-1 monoclonal Abs requires Batf3-dependent DCs**. *Cancer Discov* (2016) 6: 71-9 *Co-corresponding authors

Blanco-Menéndez N, Del Fresno C, Fernandes S, Calvo E, Conde-Garrosa R, Kerr WG, Sancho D. **SHIP-1 couples to the dectin-1 hemITAM and selectively modulates reactive oxygen species production in dendritic cells in response to candida albicans**. *J Immunol* (2015) 195: 4466-78

RESEARCH AREAS

TRANSLATIONAL COORDINATION

1. Myocardial Pathophysiology
2. Vascular Pathophysiology
3. Cell and Developmental Biology

2. Vascular Pathophysiology

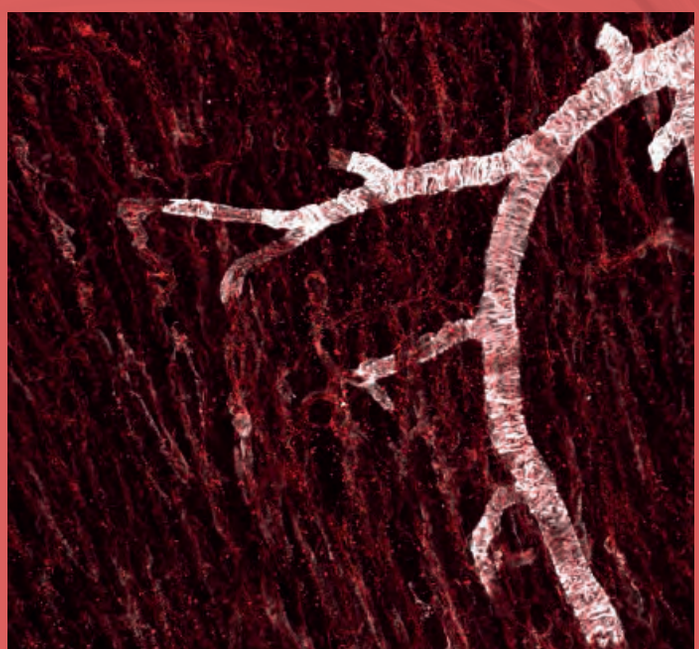
AREA COORDINATORS:

ALMUDENA RAMIRO

ANTONIO FERNÁNDEZ-ORTIZ

RESEARCH INTEREST

Research in the Vascular Pathophysiology Area (VPA) focuses on the biology of the vascular system in health and disease, using a multidisciplinary and transverse approach, embracing molecular and cellular biology as well as translational and clinical research. Our research groups use a wide variety of techniques, including animal, tissue, cell and molecular models, to investigate normal vascular function and the key steps in the vascular alterations that underlie cardiovascular diseases. We are also interested in the cellular and molecular mechanisms regulating striated muscle regeneration and growth in physiology and pathology, as well as in aging. VPA groups also work on translational and clinical research through several research projects, including Secure and PESA. We also have a major interest in cardiovascular proteomics. The VPA hosts three technical units: Genomics, Proteomics/Metabolomics, and Bioinformatics.

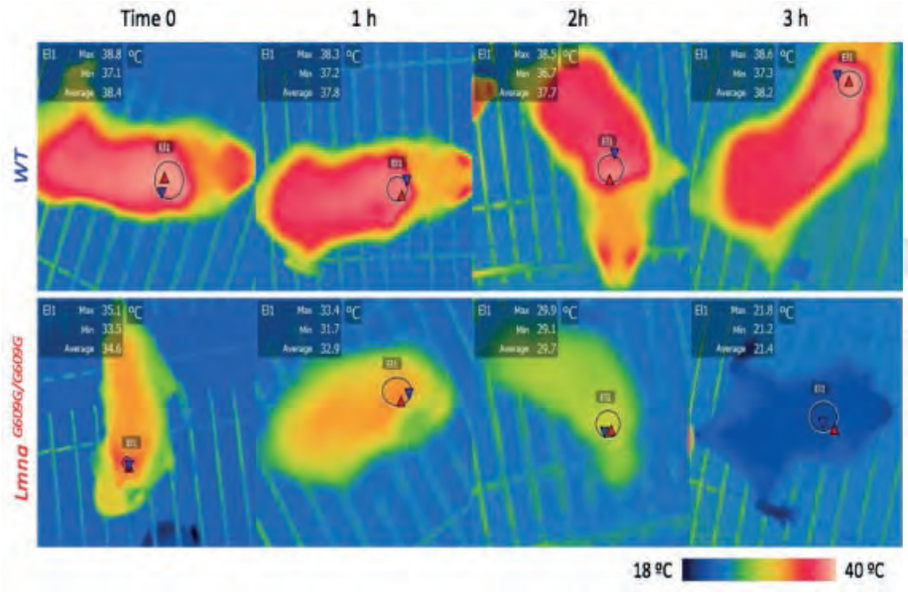


Molecular and genetic cardiovascular pathophysiology

RESEARCH INTEREST

The World Health Organization has estimated that cardiovascular disease (CVD) will by 2020 be the main health and socioeconomic problem worldwide, in part due to the progressive aging of the world population. Atherosclerosis and heart failure contribute significantly to CVD-related morbimortality in the elderly. These anomalies and the aging process are greatly accelerated in Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder caused by the expression of progerin, a mutant form of lamin A. The most serious aspect of HGPS is extensive atherosclerosis and cardiac electrophysiological alterations that are associated with early death (average lifespan, 14.6 years; range, 8-21 years), predominantly from myocardial infarction or stroke. Progerin is also expressed at low level in aged tissues of non-HGPS individuals, suggesting a role in normal aging. Understanding how this mutant form of lamin A causes CVD and premature aging may therefore shed light on normal aging.

Our current research focuses on the following areas: 1) The role of nuclear A-type lamins in atherosclerosis and aging; 2) Cellular and molecular mechanisms underlying progerin-induced cardiovascular damage; 3) Generation of a new HGPS mouse model to assess the reversibility and tissue-specificity of progerin-induced damage; 4) Generation of a porcine model of HGPS using CRISPR/Cas9 technology to accelerate translational research in HGPS; and 5) The molecular mechanisms common to premature and physiological aging and specific to each process.



Representative thermographs showing basal hypothermia and impaired heat production in the dorsal brown adipose tissue of 4-month-old progeroid *Lmna*$^{G609G/G609G}$ mice exposed to 4ºC for 3 h, resulting in accelerated loss of body temperature compared with age-matched WT controls.

Head of Laboratory:
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Cristina Rius Leiva

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Magda Rita Hamczyk
Amanda Sánchez López
Raquel Toribio Fernández

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Esther Ramírez Zapata
Andrea Martín García

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Elba Expósito
Cristina González Gómez

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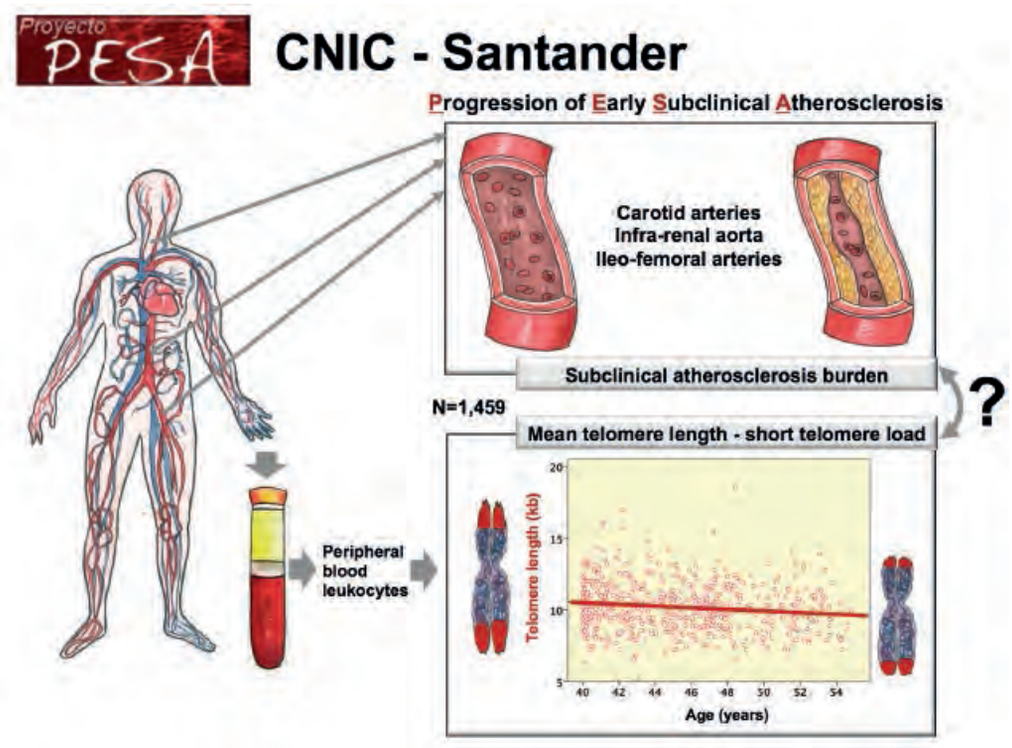
Ricardo Villa Bellosta
Maria Simona Caleprico



In a cross-sectional study, different vascular territories were analyzed by 2-dimensional and 3-dimensional ultrasound to quantify subclinical atherosclerosis burden and examine possible associations with mean telomere length and short telomere load in peripheral blood leukocytes examined by high-throughput quantitative fluorescence in situ hybridization (Fernández-Alvira et al. *J Am Coll Cardiol* 67: 2467-76, 2016).

MAJOR GRANTS

- Progeria Research Foundation (Established Investigator Award PRF 2014)
- Ministerio de Economía y Competitividad. Modalidad Retos Investigación (SAF2013-46663-R)
- Ministerio de Economía y Competitividad. Modalidad Retos Investigación (SAF2016-79490-R)
- Marató TV3 (20153731).
- Ministerio de Economía y Competitividad. FIS RETICS (RiC, RD12/0042/0028)
- Ministerio de Economía y Competitividad. FIS (CP11/00145) PI: J.M. González Granado
- Fundación Ramón Areces (XVII Concurso Nacional para la Adjudicación de Ayudas a la Investigación en Ciencias de la Vidas y de la Materia). PI: J.M. González Granado

SELECTED PUBLICATIONS

Rivera-Torres J, Calvo CJ, Llach A, Guzmán-Martínez G, Caballero R, González-Gómez C, Jiménez-Borreguero LJ, Guadix JA, Osorio FG, López-Otín C, Herraiz-Martínez A, Cabello N, Vallmitjana A, Benítez R, Gordon LB, Jalife J, Pérez-Pomares JM, Tamargo J, Delpón E, Hove-Madsen L, Filgueiras-Rama D, Andrés V. **Cardiac electrical defects in progeroid mice and Hutchinson-Gilford progeria syndrome patients with nuclear lamina alterations**. *Proc Natl Acad Sci U S A* (2016) 113: E7250-E7259

Fernández-Alvira JM, Fuster V*, Dorado B, Soberón N, Flores I, Gallardo M, Pocock S, Blasco MA, Andrés V*. **Short telomere load, telomere length, and subclinical atherosclerosis: the PESA study**. *J Am Coll Cardiol* (2016) 67: 2467-76 (* corresponding authors)

Villa-Bellosta R, Hamczyk MR, Andrés V. **Alternatively activated macrophages exhibit an anti-calcifying activity dependent on extracellular ATP/pyrophosphate metabolism.** *Am J Physiol Cell Physiol* (2016) 310: C788-99

Fuster V, Ibáñez B, Andrés V. **The CNIC: a successful vision in cardiovascular research.** *Circ Res* (2016) 119: 785-9

Molina-Sánchez P, Chèvre R, Rius C, Fuster JJ, Andrés V. **Loss of p27 phosphorylation at Ser10 accelerates early atherogenesis by promoting leukocyte recruitment via RhoA/ROCK**. *J Mol Cell Cardiol* (2015) 84:84-94

Experimental pathology of atherosclerosis

RESEARCH INTEREST

Living a long life is the main risk factor for suffering atherosclerotic heart attack or stroke; the longer you survive other threats, the more likely you are to face the consequences of atherosclerosis developing insidiously within your arteries. Consequently, as lifespan increases around the world due to improvements in socioeconomic conditions and health care, so does the need to find efficient ways of retarding atherosclerosis.

The goals of our laboratory are to improve understanding of the mechanisms underlying initiation and progression of atherosclerosis and to develop tools that can eventually monitor atherosclerosis in humans. Our work relies heavily on genetic tools to induce atherosclerosis in mice and minipigs by increasing the principal causal factor for atherosclerosis, apoB-containing lipoproteins (apoB-LP).

Current work in the lab focuses on the interaction of apoB-LP with the vascular wall and how local arterial wall cells transform their phenotype and engage in atherosclerotic lesion development. Recently we have described how blood flow forces modulate the artery wall to sequester more apoB-LP from the bloodstream. Furthermore, we have characterized the clonal architecture of smooth muscle cells in atherosclerotic lesions, showing that these cells are derived from a surprisingly low number of pre-existing cells undergoing substantial clonal expansion during disease development.

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Paula Nogales Gómez-Imaz *(from September 2016)*

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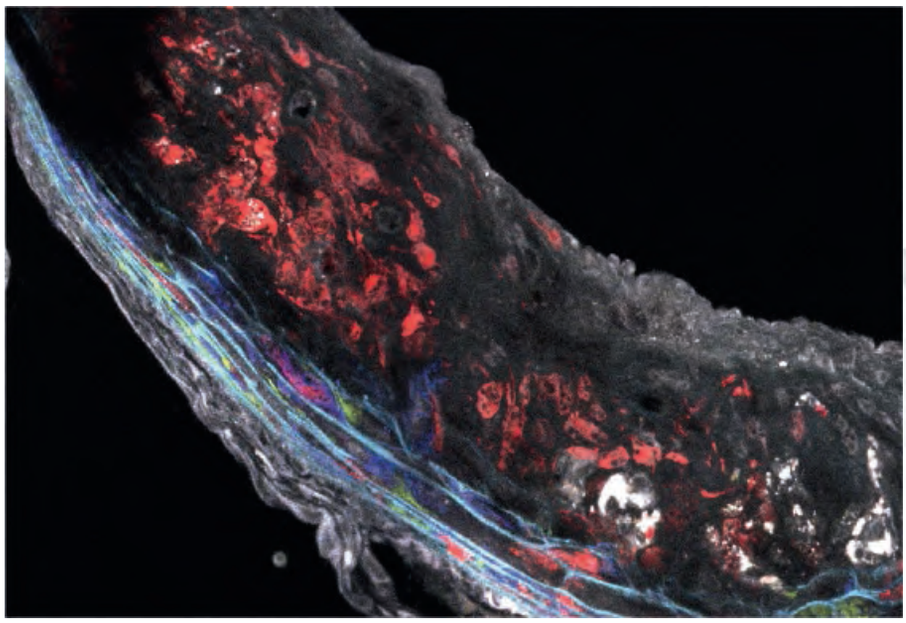


Clone in atherosclerosis. Atherosclerosis induced in mice with mosaic expression of fluorescent proteins in smooth muscle cells (SMC). The large population of red fluorescent SMCs is descended with high probability from a single cell that underwent massive clonal expansion during atherosclerotic plaque development.

ApoB-LP retention. ApoB-LP retention (black) across the vascular tree of a normal mouse. Locations of ApoB-LP binding in the vascular tree under physiological conditions are the same as those that develop atherosclerosis when ApoB-LP levels are high.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2016-75580-R)
- Det Frie Forskningsråd, Sapere Aude Level II grant (DFF – 4004-00459). Funds held at Aarhus University.
- Novo Nordisk Fonden, Interdisciplinary Synergy grant (PI: Søren Moestrup). Funds held at University of Southern Denmark

SELECTED PUBLICATIONS

Bentzon JF. **Targeting inflammation in atherosclerosis**. *J Am Coll Cardiol* (2016) 68: 2794-6

Mortensen MB, Nilsson L, Larsen TG, Espeseth E, Bek M, Bjørklund MM, Hagensen MK, Wolff A, Gunnersen S, Füchtbauer EM, Boedtkjer E, Bentzon JF. **Prior renovascular hypertension does not predispose to atherosclerosis in mice**. *Atherosclerosis* (2016) 249: 157-63

Poulsen CB, Mortensen MB, Koechling W, Sørensen CB, Bentzon JF. **Differences in hypercholesterolemia and atherogenesis induced by common androgen deprivation therapies in male mice**. *J Am Heart Assoc* (2016) 5: e002800

Al-Mashhadi RH, Bjørklund MM, Mortensen MB, Christoffersen Christina, Larsen T, Falk E, Bentzon JF. **Diabetes with poor glycemic control does not promote atherosclerosis in genetically modified hypercholesterolemic minipigs**. *Diabetologia* (2015) 58: 1926-36

Steffensen LB, Mortensen MB, Kjolby M, Hagensen MK, Oxvig C, Bentzon JF. **Disturbed laminar blood flow vastly augments lipoprotein retention in the artery wall: A key mechanism distinguishing susceptible from resistant sites**. *Arterioscler Thromb Vasc Biol* (2015) 35: 1928-35

Intercellular signaling in cardiovascular development & disease

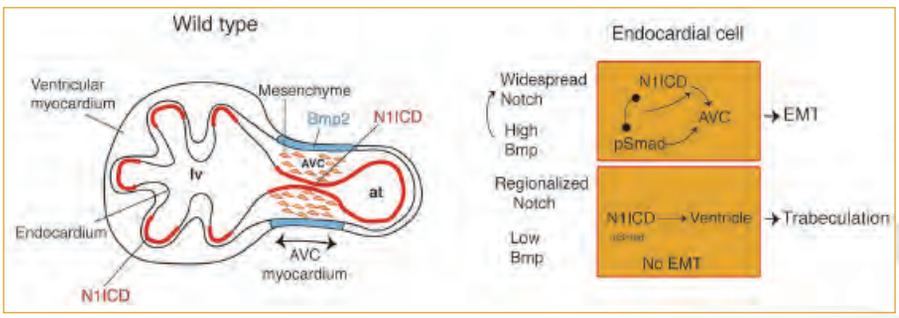
RESEARCH INTEREST

We investigate the signaling pathways regulating cardiovascular development and how their alteration can cause congenital heart disease. We use the mouse as our main experimental model, and also study heart regeneration in the zebrafish. Our experimental approach couples genetics with live imaging, global gene expression analysis, cardiac explant assays, cell biology/biochemistry experiments, and ultimately validation studies in human samples.

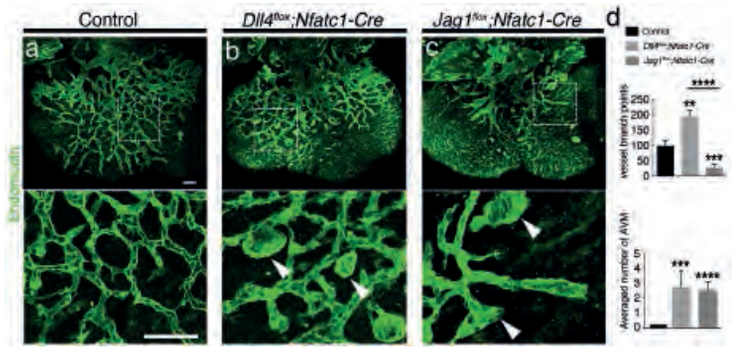
During heart valve development, the myocardial signal Bmp2 activates and functions together with the endocardial signal Notch to pattern the embryonic endocardium as cardiac valve tissue (Figure 1). NOTCH signaling alterations in humans lead to aortic valve dysmorphogenesis; we are currently investigating the potential interplay between NOTCH and WNT signaling in a cohort of aortic valve disease patients.

The coronary vasculature develops to satisfy the increasing oxygen demand of the expanding ventricular walls. We have found that dynamic Notch ligand-receptor signaling regulates capillary sprouting, coronary artery specification, and vascular tree remodeling. The absence of a functional primary coronary plexus in mutant mice leads to an adaptive hypoxia response and reduced cardiomyocyte proliferation, resulting in a thinner myocardial wall and ultimately heart failure and embryonic death (Figure 2).

In adult life, the combination of genetic predisposition and poor dietary habits leads to atherosclerosis, which can ultimately result in obstruction of the main coronary arteries and myocardial infarction. Notch regulates the inflammatory response associated with atherosclerosis and, in the coronaries of atherosclerotic patients, expression of the NOTCH ligand JAG1 is increased, suggesting that this (together with NOTCH-dependent metabolites) may be diagnostic markers of disease progression (Figure 3; Nus et al., 2016).



Model of Bmp2 and Notch1 interplay. E9.5 wild-type heart. Bmp2 expression (blue) restricted to the AVC myocardium induces Notch1 activity and EMT in the AVC endocardium. Uniform N1ICD expression in AVC endocardium and in the atrium (red); in ventricular endocardium N1ICD is restricted to the base of the forming trabeculae. In the ventricles, low Bmp and N1ICD signaling prevent physical interaction of the effectors.



Dorsal view of E12.5 whole-mount hearts stained for the endothelial marker endomucin. (**a**) Control, (**b**) *Dll4^{flox};Nfatc1-Cre*, and (**c**) Jag1^{flox}; Nfatc1-Cre mutant embryos. Mutant embryos show defective vessel branching (**d**) and arterio-venous malformations (AVM, **d**).

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Alejandro Salguero Jiménez
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Rebeca Torregrosa Carrión
Stanislao Igor Travisano

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Patricia Martínez Martín

Technicians:
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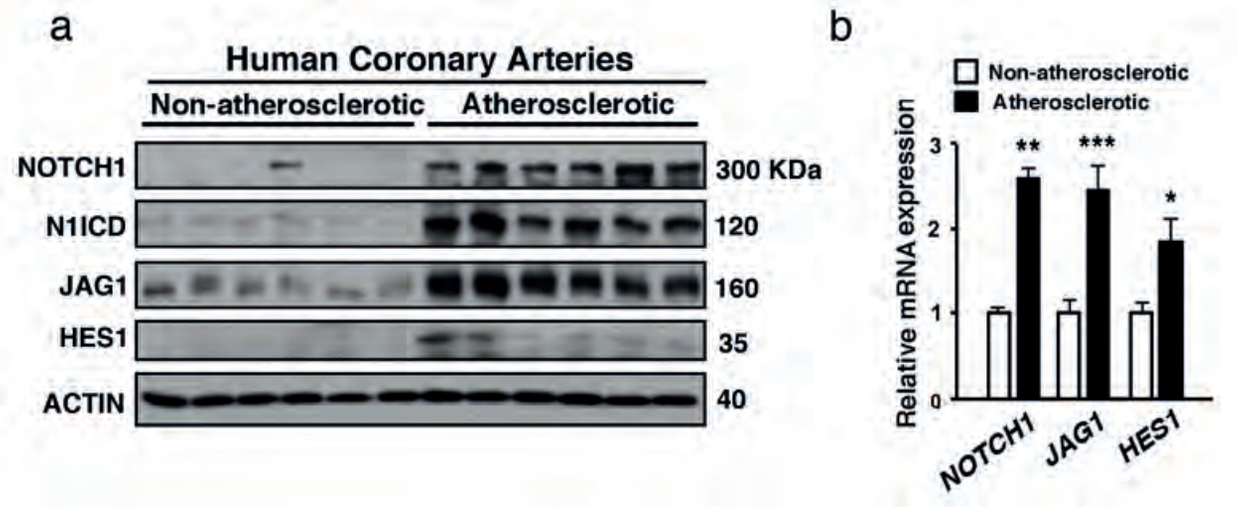
Sara Perruca Magro
Beatriz Ríos

Visiting Scientist:
José María Pérez-Pomares



NOTCH signaling upregulation in human atherosclerosis. (**a**) Western blot showing NOTCH1 and N1ICD, JAG1, and HES1 in atherosclerotic and nonatherosclerotic human coronary arteries. (**b**) qPCR analysis of NOTCH signaling genes in atherosclerotic and nonatherosclerotic human coronary arteries.

MAJOR GRANTS

- Ministerio de Economía, Industria y Competitividad (SAF2016-78370-R)
- Ministerio de Economía y Competitividad. Red de excelencia Temática (SAF2015-71863-REDT)
- Ministerio de Economía y Competitividad. FIS RETICS (TERCEL: RD12/0019/0003 and RIC: RD12/0042/0005)
- Ministerio de Economía y Competitividad (SAF2013-45543-R)
- Fundación BBVA (Ref. : BIO14_298)
- Fundació La Marató (Ref.: 20153431)
- European Commission. International IPP (Ref.: UE0COF1214) . PI: L. Luna Zurita
- Ministerio de Economía y Competitividad. (BES-2014-068818) PI: P. Gómez Apiñaniz
- Ministerio de Economía y Competitividad. (SVP-2014-068723) PI: M. Siguero Álvarez
- Fundación La Caixa. (CX_E-2015-04). PI: R. Torregrosa Carrión
- Ministerio de Educación, Cultura y Deporte. (FPU15/01011). PI: A. Salguero Jiménez
- Comunidad de Madrid. (PEJ15/BIO/TL-0428). PI: B Ríos Lara

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MacGrogan D, D'Amato G, Travisano S, Martinez-Poveda B, Luxán G, Del Monte-Nieto G, Papoutsi T, Sbroggio M, Bou V, Gomez-Del Arco P, Gómez MJ, Zhou B, Redondo JM, Jiménez-Borreguero LJ, de la Pompa JL. **Sequential ligand-dependent Notch signaling activation regulates valve primordium formation and morphogenesis**. *Circ Res* (2016) 118:1480-97

D'Amato G, Luxán G, Del Monte-Nieto G, Martínez-Poveda B, Torroja C, Walter W, Bochter MS, Benedito R, Cole S, Martinez F, Hadjantonakis AK, Uemura A, Jiménez-Borreguero LJ, de la Pompa JL **Sequential Notch activation regulates ventricular chamber development**. *Nat Cell Biol* (2016) 18: 7-20

de Luxán G, D'Amato G, MacGrogan D, de la Pompa JL. **Endocardial Notch signaling in cardiac development and disease**. *Circ Res* 118: e1-e1

D'Amato G, Luxán G, de la Pompa JL. **Notch signalling in ventricular chamber development and cardiomyopathy**. *FEBS J* (2016) 283: 4223-4237

Gómez-Del Arco P, Perdiguero E, Yunes-Leites PS, Acín-Pérez R, Zeini M, Garcia-Gomez A, Sreenivasan K, Jiménez-Alcázar M, Segalés J, López-Maderuelo D, Ornés B, Jiménez-Borreguero LJ, D'Amato G, Enshell-Seijffers D, Morgan B, Georgopoulos K, Islam AB, Braun T, de la Pompa JL, Kim J, Enriquez JA, Ballestar E, Muñoz-Cánoves P, Redondo JM. **The chromatin remodeling complex Chd4/NuRD controls striated muscle identity and metabolic homeostasis**. *Cell Metab*. (2016) 23: 881-92

Matrix metalloproteinases in angiogenesis and inflammation

RESEARCH INTEREST

The vasculature ensures optimal delivery of nutrients and oxygen throughout the body, and to achieve this function must continually adapt to varying tissue demands, particularly after tissue damage. Our group studies the cellular and molecular mechanisms that govern vascular responses during inflammation and how these mechanisms contribute to tissue repair. We focus mainly on the actions in these responses of membrane-type matrix metalloproteinases in endothelial and vascular smooth muscle cells and macrophages.

We previously showed that the protease MT1-MMP is required for endothelial cell sprouting by processing extracellular matrix components and for macrophage migration by regulating intracellular signals. Our recent studies have expanded our knowledge of MT1-MMP actions in these cell types, showing its role in capillary remodeling and also in macrophage-vessel crosstalk in the mouse heart.

Our understanding of the pathophysiology of the vascular system is also benefiting from our current research into MT4-MMP, a GPI-anchored protease whose substrates and functions have previously received scant attention. Our recent analysis of MT4-MMP-deficient mice complemented with proteomics approaches has identified an essential requirement for MT4-MMP in aorta vessel wall development and function and in aneurysm formation. We are following up these findings by extending the analysis to atherosclerosis, an inflammatory arterial disease, and to arteriogenesis, the de novo formation of collateral arteries, after cardiac ischemia.

For these projects, we are using 2D and 3D angiogenic models, high-resolution microscopy, 3D image analysis, proteomics, bioinformatics, protein modeling, lentiviral strategies, and genetically modified mouse lines and disease models. We ultimately intend to apply this knowledge to develop novel angiotherapies aimed at improving tissue perfusion and/or modulating inflammatory responses in various pathophysiological contexts.

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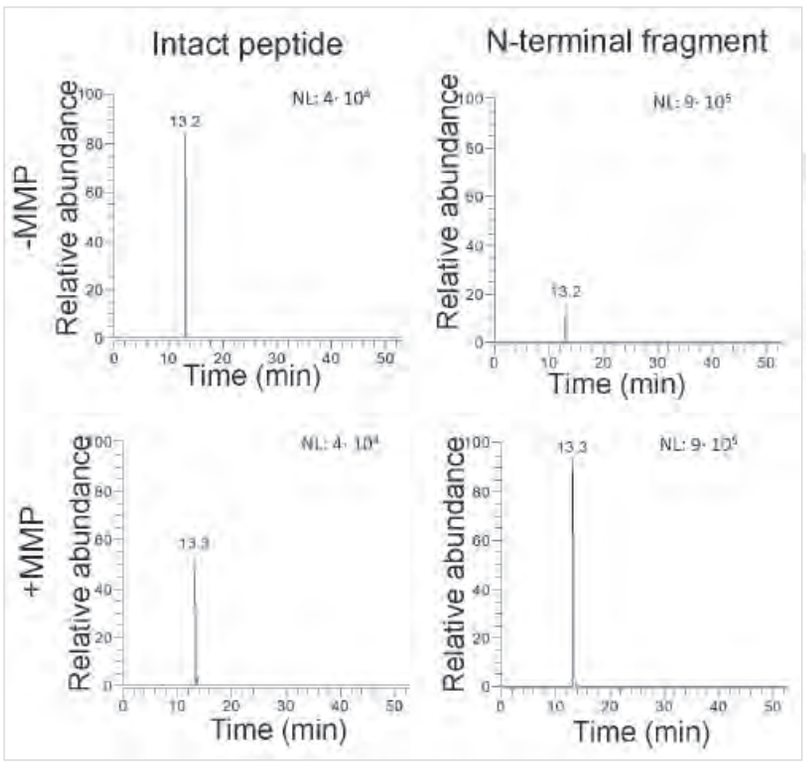
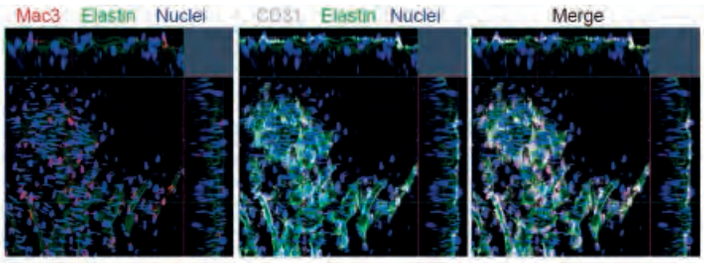
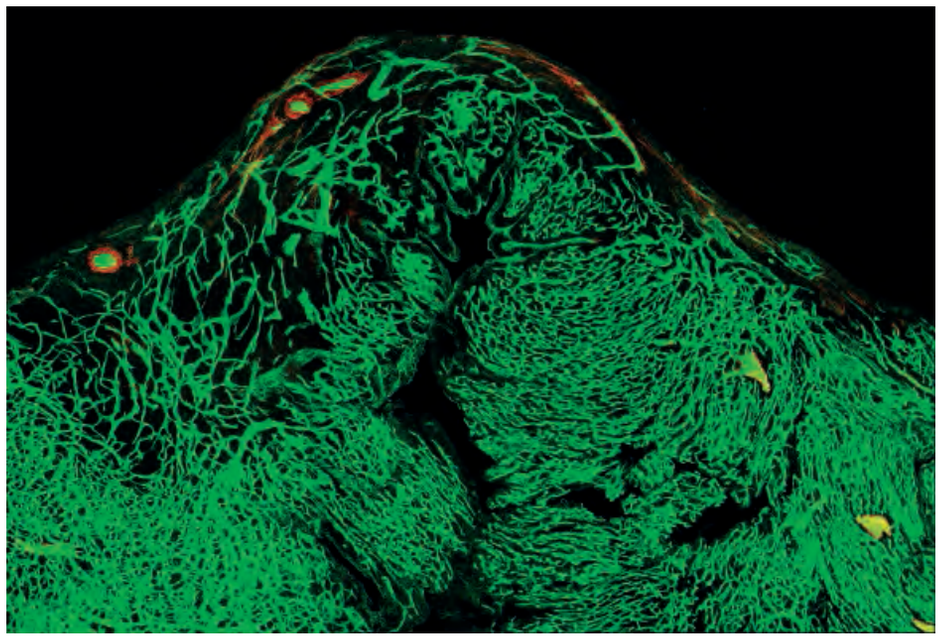


Analysis of protease-mediated substrate cleavage by mass spectrometry. In collaboration with the Proteomics Unit, we are analysing a synthetic peptide containing a putative MMP cleavage site by mass spectrometry in the absence or presence of the recombinant catalytic domain of a given protease. The charts show the profiles obtained for the intact peptide and the N-terminal fragment generated after proteolytic cleavage. This approach is particularly useful for transmembrane protein substrates.



Exploring macrophage-vascular communication in vivo. Whole-mount staining of the aortic arch from Ldlr$^{-/-}$ mice fed a high-fat diet for 3 days allows visualization of macrophage entrapment in the inflamed aortic vessel wall, particularly in the athero-prone lesser curvature of the aorta. The panel shows a representative orthogonal view compiled from confocal images of macrophages (Mac3, red), endothelial cells (CD31, white), vascular elastin (autofluorescence, green), and nuclei (blue).

3D confocal microscopy image analysis of the cardiac microvasculature. 3D-volumetric composition of confocal microscopy images from thick heart sections allows the visualization and analysis of the cardiac microvasculature at unprecedented resolution. The image shows the maximal projection of multiple images acquired from thick heart sections (60 µm) and stained for the endothelial cell marker ICAM-2 (green) and the perivascular cell marker smooth muscle actin (SMA; red). The heart shown in the image is from a newborn mouse 5 days after cryoinjury; note the reduced vascular density and the presence of arterioles in the affected area.



MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2014-52050R)
- Ministerio de Economía y Competitividad FIS RETICS (Red de Investigación Cardiovascular: RD12/0042/0023)
- Fundació La Marató TV3 (165/C/2012)
- European Union (PITN-GA-2013-608027) (CardioNext) (Coordinator)

SELECTED PUBLICATIONS

Barreiro O, Cibrian D, Clemente C, Alvarez D, Moreno V, Valiente Í, Bernad A, Vestweber D, Arroyo AG, Martín P, von Andrian UH, Sánchez Madrid F. **Pivotal role for skin transendothelial radio-resistant anti-inflammatory macrophages in tissue repair**. *Elife* (2016) 5: e15251

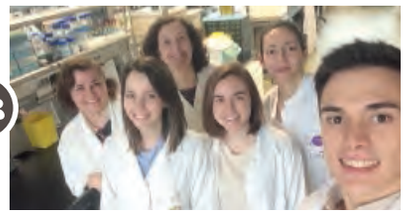
Gkontra P, Żak MM, Norton K-A, Santos A, Popel AS, Arroyo AG. **A 3D fractal-based approach towards understanding changes in the infarcted heart microvasculature**. Medical Image Computing and Computer-Assisted Intervention-MICCAI 2015. *Lecture Notes in Computer Science* (2015) 9351: 173-80

Oller J, Alfranca A, Méndez-Barbero N, Villahoz S, Lozano-Vidal N, Martín-Alonso M, Arroyo AG, Escolano A, Armesilla AL, Campanero MR, Redondo JM. **C/EBPβ and nuclear factor of activated T cells differentially regulate Adamts-1 induction by stimuli associated with vascular remodeling**. *Mol Cell Biol* (2015) 35: 3409-22

Martín-Alonso M, García-Redondo AB, Guo D, Camafeita E, Martínez F, Alfranca A, Méndez-Barbero N, Pollán Á, Sánchez-Camacho C, Denhardt DT, Seiki M, Vázquez J, Salaices M, Redondo JM, Milewicz D, Arroyo AG. **Deficiency of MMP17/MT4-MMP proteolytic activity predisposes to aortic aneurysm in mice**. *Circ Res* (2015) 117: e13-26

Arroyo AG, Andrés V. **ADAMTS7 in cardiovascular disease: from bedside to bench and back again?** *Circulation* (2015) 131: 1156-9

Regulatory molecules of inflammatory processes



RESEARCH INTEREST

Cardiovascular diseases (CVD) are a leading cause of death worldwide and are increasing due to unhealthy modern lifestyles. While a number of treatments are available to address the many risk factors associated with CVD, surgical intervention remains the primary treatment option to prevent or treat an episode of acute myocardial injury. Heart failure can progress to end-stage dilated cardiomyopathy requiring heart transplantation. This process is characterized by inflammation and loss of cardiomyocytes combined with impaired function of the remaining cells, leading to decreased blood flow and increased risk of morbidity and mortality. Inflammation and autoimmune abnormalities play an important role in the progression of heart and vascular failure.

Our group is interested in the peripheral mechanisms operating in autoimmune and chronic inflammation and their exploitation for the design and development of novel therapies. Our work has shown that exacerbated Th17 responses or suboptimal behaviour of regulatory T (Treg) cells increase inflammation and fibrosis of the heart, arteries, peritoneum, and kidneys, resulting in exacerbated myocarditis, atherosclerosis, or hypertension-driven renal dysfunction and associated comorbidities. Our recent work shows that Tregs are a first line defense against CVD. Tregs can directly mediate neutrophil apoptosis, thereby protecting the tissue from damage, or can inhibit Th17 responses, controlling the recruitment of inflammatory cells to the target tissues. Detailed knowledge of Th17 and Treg biology will pave the way to the development of new therapeutic and prevention strategies to control inflammation and fibrosis related to cardiovascular diseases.

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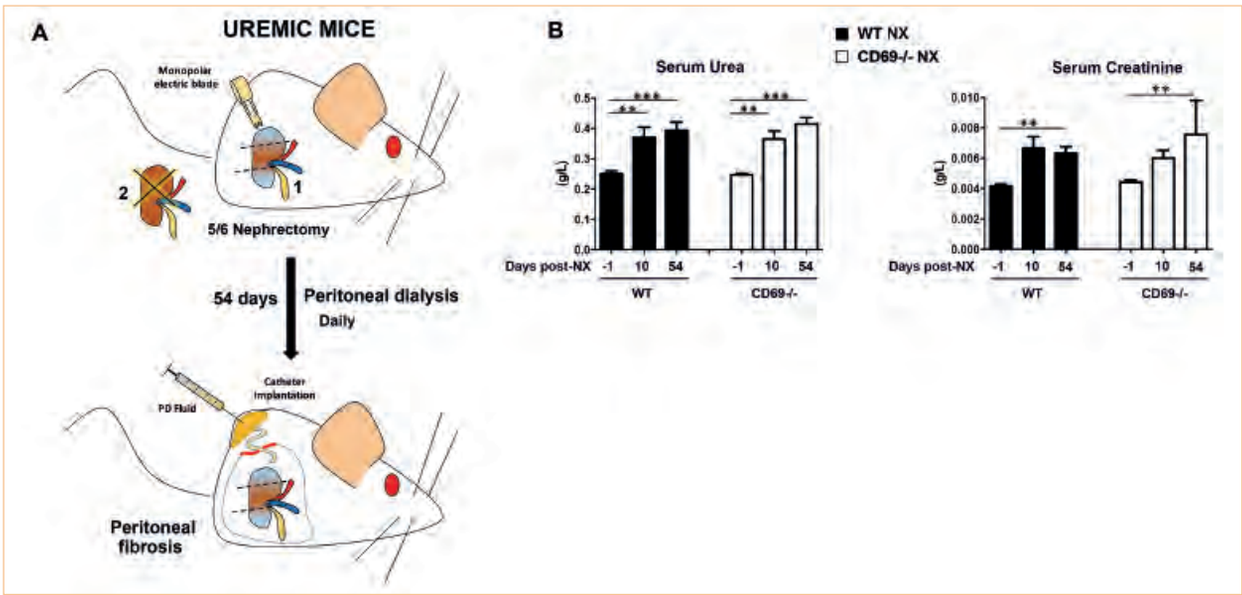
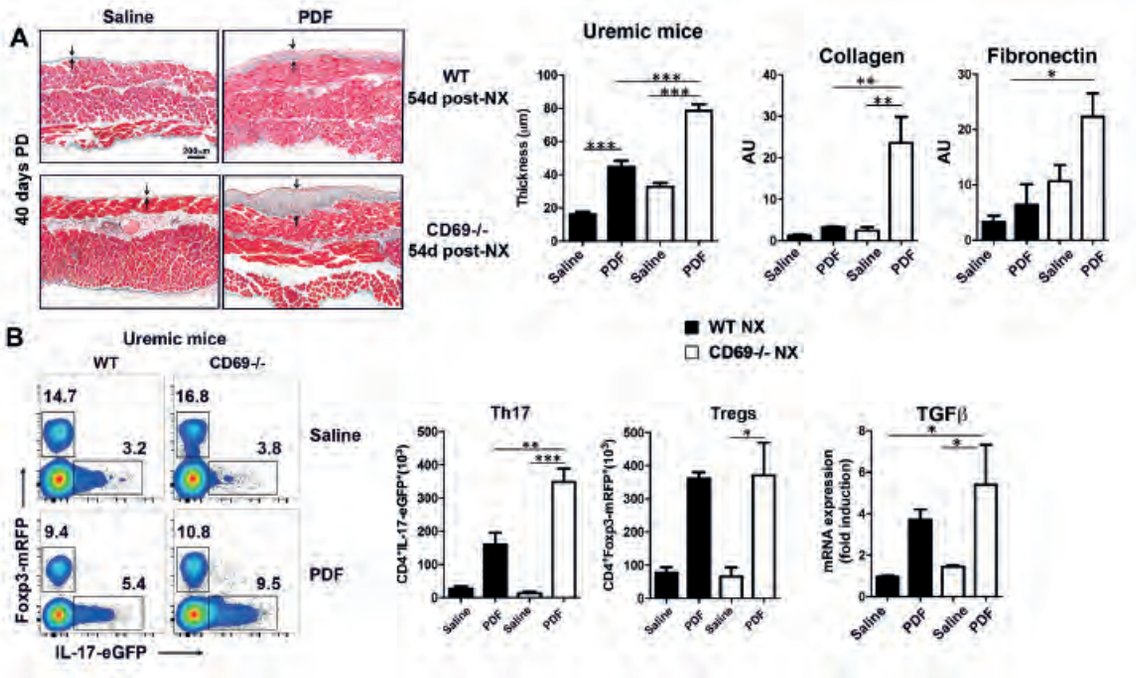
Lucía Wang
María José Lafuente Monasterio
Tania Sonia Luque Díaz



Generation of uremic mice. (A) 5/6 nephrectomy (NX) was performed by laparotomy of the right kidney, and the anterior and posterior 1/3 parts of the left kidney were injured using a monopolar electric blade. The remaining functional 1/3 of the left kidney was replaced in its original position in the abdominal cavity before treatment with saline or standard peritoneal dialysis fluid (PDF) for an additional period of 40 days, starting 14 days after NX. (B) Serum levels of urea and creatinine were measured before and 10 and 54 days after 5/6 nephrectomy throughout the treatment period.



CD69 regulates fibrosis in mice with abnormal renal function. (A) Peritoneal membrane fibrosis assessed by Masson's Trichrome staining 54 days post-nephrectomy. Arrows indicate peritoneal membrane thickness. Right, quantification of peritoneal fibrosis in uremic mice (n≥10). Fibrosis in peritoneal tissue from uremic WT and CD69$^{-/-}$ mice was assessed by qPCR analysis of collagen I and fibronectin. Bars represent means ± SD (n≥6). (B) Density plots of flow-cytometry analysis in peritoneal effluents from uremic CD69$^{-/-}$ double reporter mice (Foxp3-mRFP in the foxp3 locus and IL-17A-eGFP in the Il17a locus) or wt littermates. Panels show analysis of CD4+FoxP3-RFP and IL-17eGFP in the indicated groups. TGF levels were assessed by qPCR.

MAJOR GRANTS

- Comunidad de Madrid. Redes de Excelencia (S2010/BMD-2332)
- Ministerio de Economía y Competitividad. FIS RETICS (RIC: RD12/0042/0056)
- Fundación BBVA (IN[16]_BBM_TRA_0365)
- Ministerio de Economía y Competitividad. Proyectos de investigacion en salud (AES 2016). Modalidad proyectos en salud (PI16/01956)
- CIBER de Enferemedades Cardiovasculares, ISCIII.

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Borroto A, Reyes-Garau D, Jimenez MA, Carrasco E, Moreno B, Martinez-Pasamar S, Cortes JR, Perona A, Abia D, Blanco S, Fuentes M, Arellano I, Lobo J, Heidarieh H, Rueda J, Esteve P, Cibrian D, Martinez-Riano A, Mendoza P, Prieto C, Calleja E, Oeste CL, Orfao A, Fresno M, Sanchez-Madrid F, Alcami A, Bovolenta P, Martin P, Villoslada P, Morreale A, Messeguer A, Alarcon B. **First-in-class inhibitor of the T cell receptor for the treatment of autoimmune diseases**. *Sci Transl Med* (2016) 8: ra184

Barreiro O, Cibrian D, Clemente C, Alvarez D, Moreno V, Valiente Í, Bernad A, Vestweber D, Arroyo AG, Martín P, von Andrian UH, Sánchez Madrid F. **Pivotal role for skin transendothelial radio-resistant anti-inflammatory macrophages in tissue repair**. *Elife* (2016) 5: e15251

Liappas G^, González-Mateo GT^, Sánchez-Díaz R^, Lazcano JJ, Lasarte S, Matesanz-Marín A, Zur R, Ferrantelli E, Ramírez LG, Aguilera A, Fernández-Ruiz E, Beelen RH, Selgas R, Sánchez-Madrid F, Martín P*, López-Cabrera M*. **Immune-regulatory molecule CD69 controls peritoneal fibrosis**. *J Am Soc Nephrol.* (2016) 27(12):3561-3576. ^Co-first authors. *Co-corresponding authors.

Fabbiano S, Menacho-Márquez M, Robles-Valero J, Pericacho M, Matesanz-Marín A, García-Macías C, Sevilla MA, Montero MJ, Alarcón B, López-Novoa JM, Martín P, Bustelo XR. **Immunosuppression-independent role of regulatory T cells against hypertension-driven renal dysfunctions**. *Mol Cell Biol* (2015) 35: 3528-46

Tissue regeneration

Head of Laboratory:
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Predoctoral Researcher:
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Masters Student:
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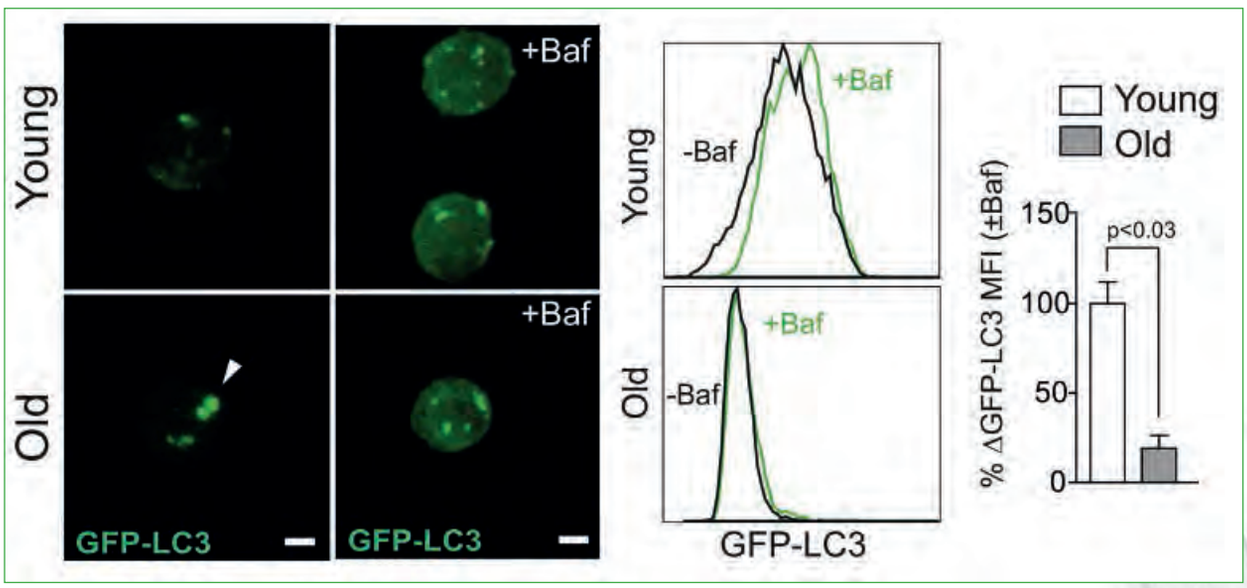
RESEARCH INTEREST

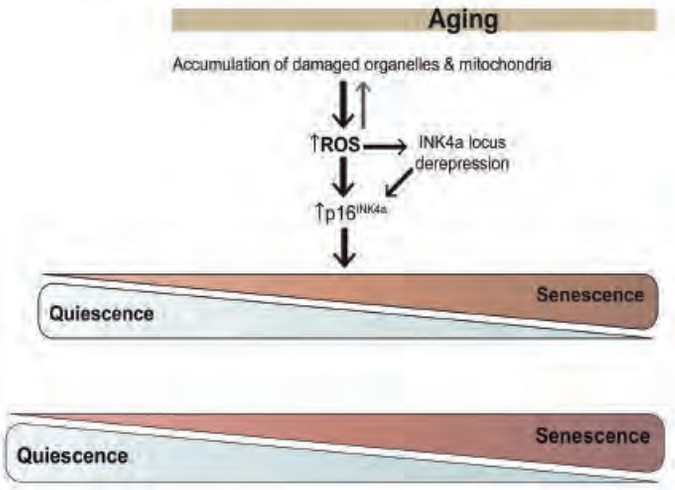
Autophagy is required for the maintenance of muscle stem cell function

During aging, there is a decline in the regenerative function of muscle stem cells (satellite cells). This decline intensifies with advanced old age as cellstransition from quiescence to irreversible senescence. How satellite cells maintain quiescence and avoid senescence during their long life remains largely unknown. We have shown that basal autophagy is indispensable for maintaining the quiescent stem-cell state. Autophagy failure in physiologically aged satellite cells causes senescence entry due to loss of proteostasis and increased mitochondrial dysfunction, resulting in a decline in the number of functional satellite cells. Reestablishment of autophagy reverses senescence and restores regenerative functions in geriatric satellite cells. Since autophagy also declines in human geriatric satellite cells, these findings uncover autophagy as a decisive stem-cell-fate regulator and have implications in sarcopenia.

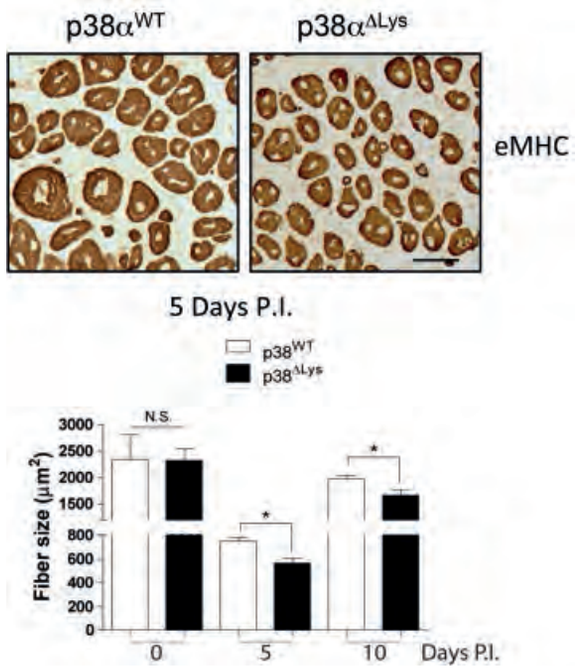
Myeloid cells are essential in the advanced stage of muscle regeneration

In response to tissue damage, innate immune cells phagocytose cellular debris and secrete factors that promote repair. In the initial response to muscle injury, M1 macrophages infiltrate the damaged tissue concomitantly with the expansion of the resident muscle stem cells and mesenchymal progenitors. Subsequently, M1 cells are substituted by M2-like macrophages, coinciding with growth of the newly formed myofibers and new vascularization. How this late repair process is coordinated is poorly understood. We have found an essential role for myeloid-produced p38alpha in the late resolving phase of muscle injury. Deletion of p38alpha MAPK in M2-like macrophages seriously compromised muscle tissue regeneration by causing defective angiogenesis and aberrant fat accumulation.





Model of how autophagy decline leads to muscle stem cell senescence and tissue regenerative decline with aging



Delayed muscle regeneration in mice with deletion of p38alpha MAPK in the myeloid lineage. Analysis of muscle regeneration (indicated by the size of new myofibers expressing embryonic myosin heavy chain (eMHC)) after an acute injury in wild type (WT) and p38alpha deficient mice. Absence of p38alpha in the myeloid compartment causes a delay in muscle regeneration that persists until at least 10 days post-injury (P.I.). eMHC staining is shown at 5 days P.I.

MAJOR GRANTS

- Association française pour les myopaties (AFM)-France (MDA418174). Funds held at UPF and CNIC.
- Ministerio de Economía y Competitividad e Instituto de Salud Carlos III (PIE14/00061). Funds held at UPF.
- European Commission. European Research Projects on Rare Diseases. Funds held at UPF
- Ministerio de Economía y Competitividad e Instituto de Salud Carlos III (CIBERNED 2015-2). Funds held at UPF
- Ministerio de Economía y Competitividad (SAF2015-67369-R). Funds held at UPF.
- Muscular Dystrophy Association (MDA)-USA. Funds held at UPF.

SELECTED PUBLICATIONS

García-Prat L, Martínez-Vicente M, Perdiguero E , Ortet L, Garcia-Ubreva J, Rebollo E, Ruiz-Bonilla V, Gutarra S, Ballestar E, Serrano AL, Sandri M, Muñoz-Cánoves P. **Autophagy maintains stemness by preventing senescence.** *Nature* (2016) 529: 37-42

Segalés J, Islam AB, Kumar R, Liu QC, Sousa-Victor P, Dilworth FJ, Ballestar E, Perdiguero E, Muñoz-Cánoves P. **Chromatin-wide and transcriptome profiling integration uncovers p38α MAPK as a global regulator of skeletal muscle differentiation.** *Skelet Muscle* (2016) 6:9 doi: 10.1186/s13395-016-0074-x.

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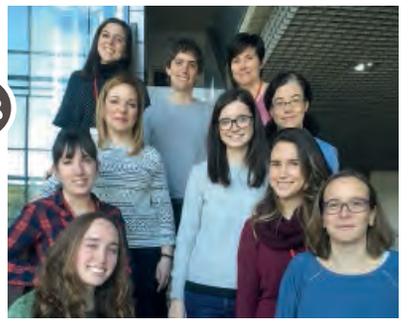
Pessina P, Kharraz Y, Jardí M, Fukada SI. Serrano AL, Perdiguero E, Muñoz-Cánoves P. **Fibrogenic cell plasticity blunts tissue regeneration and aggravates muscular dystrophy.** *Stem Cell Reports* (2015) 4:1046-60

Sousa-Victor P, García-Prat L, Serrano AL, Perdiguero E, Muñoz-Cánoves P. **Muscle stem cell aging: regulation and rejuvenation.** *Trends Endocrinol Metab*. (2015) 26287-96

B lymphocyte biology



RESEARCH INTEREST

B cells execute the humoral immune response, an essential defence mechanism that relies on the generation of a huge repertoire of antibodies that will selectively and specifically bind and mark pathogens for destruction. A critical step in antibody diversification occurs during the germinal center reaction, whereby B cells that have been activated by an infectious agent generate high affinity memory B cells and antibody-secreting plasma cells. Antibody diversification, while enabling the humoral immune response, is also linked to various health problems, including autoimmunity and cancer.

In our lab we are particularly interested in the molecular characterization of the humoral immune response and the germinal center reaction. In recent years our work has covered the molecular biology of secondary antibody diversification by activation induced deaminase (AID) and the regulation of B cell function by microRNAs, and the links between these events and human disease through the generation and characterization of genetically modified animal models.

Current research projects of the lab include 1) analysis of the specificity of AID activity during antibody remodeling in germinal centers and its impact on B cell lymphomagenesis; 2) the role of the chromatin organizer CTCF during the germinal center reaction and terminal B cell differentiation; and 3) characterization of the antibody repertoire associated with atherogenesis.

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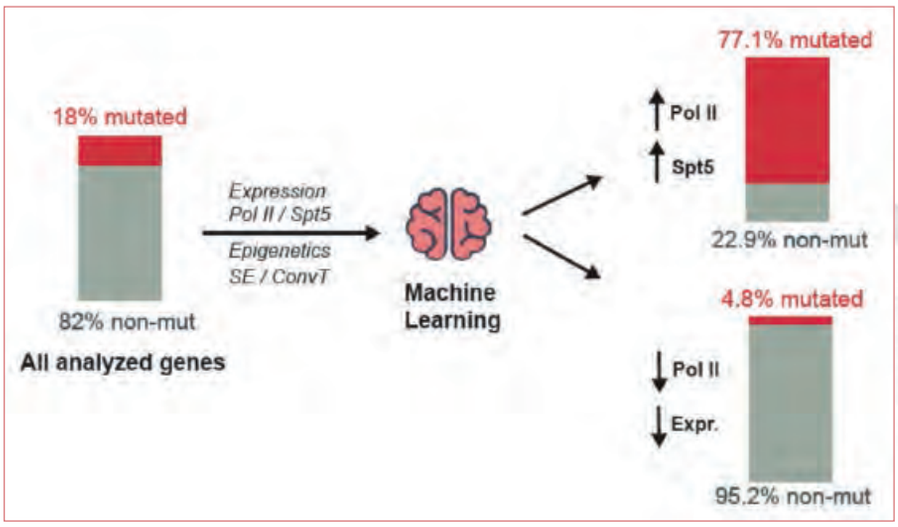
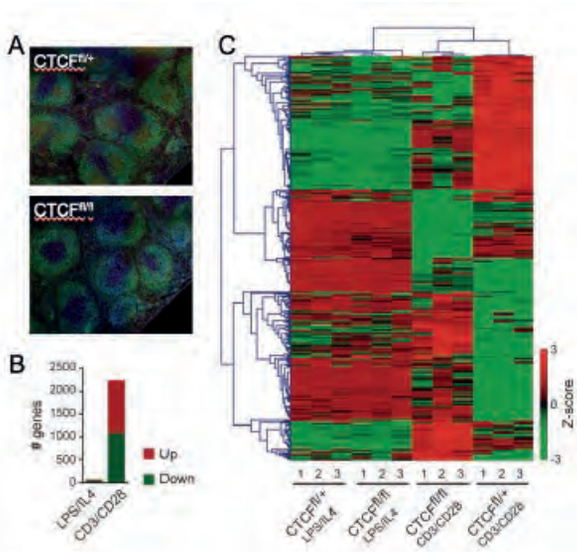
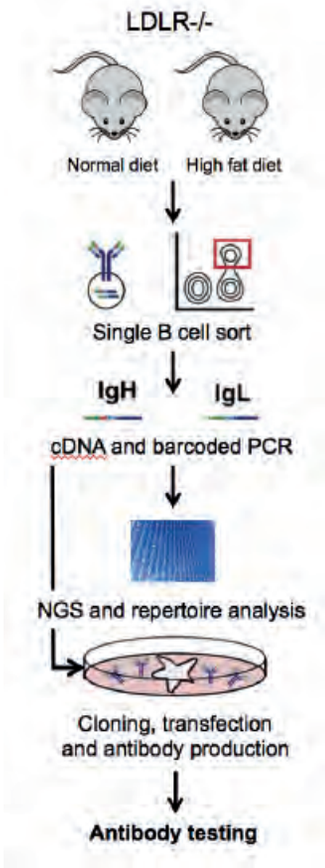


A gene selection representing ≈10% of the mouse genome was enriched with an RNA probe library and sequenced by next generation sequencing. Mutation frequency was determined to identify genes undergoing AID-mediated mutagenesis and a machine learning algorithm was used to integrate mutation data with expression and PolII and Spt5 binding, among other features, to predict gene mutability.



B cell sensitivity to CTCF loss is determined by the B cell activation pathway. A. CTCF is absolutely required for germinal center formation in vivo. CTCF control ($CTCF^{fl/+}$) and deficient ($CTCF^{fl/fl}$) mice were immunized and spleens were analyzed by immunofluorescence (Blue, DAPI; Green, B220; Red, PNA). B-C. LPS/IL4 stimulated B cells are refractory to CTCF loss. B. Number of transcriptionally altered genes in CTCF-deficient B cells activated in the presence of LPS and IL4 or of CD3/CD28 activated T cells. C. Representative heatmap of genes in B.



Experimental pipeline for analysis of atherosclerosis-associated antibody repertoires. Individual spleen B cells isolated from $LDLR^{-/-}$ mice fed a normal or high-fat diet are isolated by single-cell FACS. Heavy and light antibody cDNAs are amplified, barcoded and sequenced by next generation sequencing. For functional analysis, amplified heavy and light cDNAs are cloned in expression vectors and transfected into cells, and secreted antibodies are collected and assayed.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2016-75511-R)
- European Commission. ERC PROOF OF CONCEPT GRANT 2015 (ERC-2015-PoC- 713728)
- Ministerio de Economía y Competitividad (SAF2013-42767-R)

SELECTED PUBLICATIONS

Azagra A, Román-González L, Collazo O, Rodríguez-Ubreva J, de Yébenes VG, Barneda-Zahonero B, Rodríguez J, Castro de Moura M, Grego-Bessa J, Fernández-Duran I, Islam AB, Esteller M, Ramiro AR, Ballestar E, Parra M. **In vivo conditional deletion of HDAC7 reveals its requirement to establish proper B lymphocyte identity and development**. *J Exp Med* (2016) 213: 2591-601

Marin AV, Jiménez-Reinoso A, Briones AC, Muñoz-Ruiz M, Aydogmus C, Pasick LJ, Couso J, Mazariegos MS, Alvarez-Prado AF, Blázquez-Moreno A, Cipe FE, Haskologlu S, Dogu F, Morín M, Moreno-Pelayo MA, García-Sánchez F, Gil-Herrera J, Fernández-Malavé E, Reyburn HT, Ramiro AR, Ikinciogullari A, Recio MJ, Regueiro JR, Garcillán B. **Primary T-cell immunodeficiency with functional revertant somatic mosaicism in CD247**. *J Allergy Clin Immunol* doi: 10.1016/j.jaci.2016.06.020. [Epub ahead of print]

Thornton TM, Delgado P, Chen L, Salas B, Krementsov D, Fernandez M, Vernia S, Davis RJ, Heimann R, Teuscher C, Krangel MS, Ramiro AR, Rincón M. **Inactivation of nuclear GSK3β by Ser(389) phosphorylation promotes lymphocyte fitness during DNA double-strand break response**. *Nat Commun* (2016) 7:10553

Pérez-García A, Pérez-Durán P, Wossning T, Sernandez IV, Mur SM, Cañamero M, Real FX, Ramiro AR. **AID-expressing epithelium is protected from oncogenic transformation by an NKG2D surveillance pathway**. *EMBO Mol Med* (2015) 7:1327-36

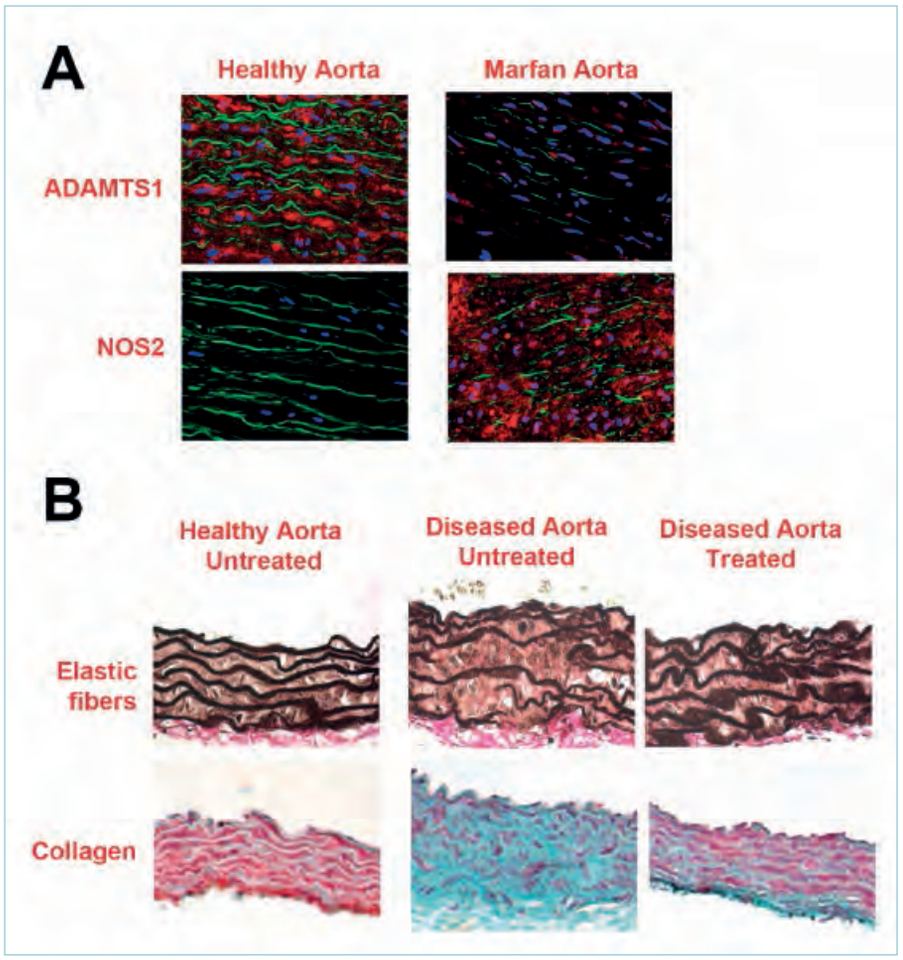
Ramiro AR, Barreto VM. **Activation-induced cytidine deaminase and active cytidine demethylation**. *Trends Biochem Sci* (2015) 40:172-81

Gene regulation in cardiovascular remodeling and inflammation

RESEARCH INTEREST

Much of our recent effort has centered on the mechanisms mediating aortic diseases such as familial forms of thoracic aortic aneurysm and dissection (TAAD), including Marfan syndrome.We have identified new pathophysiological mechanisms and targets in aortic diseases, showing that Adamts1 is a major mediator of vascular homeostasis and that inhibition of inducible nitric oxide synthase (Nos2) is able to prevent and reverse aortic dilation and medial degeneration in a mouse model of Marfan syndrome and other types of aneurysm. These findings suggest a major potential for NOS2 inhibitors in the treatment of thoracic aortic aneurysm.

Our group has an established history in the study of the regulation of calcineurin (CN) signaling in angiogenesis and inflammation. We have characterized the mechanisms and sequences involved in the interactions of CN with a range of substrates, including immunosuppressive drugs, and have shown how specific CN targeting modulates inflammatory responses. In addition, we have studied mediators of vascular and cardiac remodeling related to the angiotensin II and CN pathways. We are currently using conditional mice deficient for CN and Rcan1 isoforms in the endothelial, vascular smooth muscle, and cardiomyocyte compartments to elucidate the mechanisms that mediate this remodeling. We have already identified CN-regulated genes in different mouse models of cardiac hypertrophy (CH) and are characterizing their roles in CH using mice conditionally lacking CN and Rcan1 in cardiac tissue. We are also elucidating the role of Chd4/NuRD in cardiac homeostasis and have found that the NuRD complex determines skeletal muscle identity by silencing the skeletal muscle program in cardiomyocytes and the cardiac program in skeletal muscle.



Inhibition of NOS2 protein has therapeutic potential in Marfan syndrome. (**A**) Comparison of the expression of ADAMTS1 and NOS2 proteins (both in red) and elastic fibers (green) in the aortic wall of a healthy donor and a Marfan syndrome patient. (**B**) Staining showing elastic fiber organization (dark brown) and collagen deposits (blue) in the aortic wall of a healthy mouse (Healthy Aorta Untreated), a mouse with untreated syndromic aortic disease (Diseased Aorta Untreated), and a diseased mouse treated with a NOS2 inhibitor (Diseased Aorta Treated). The images show how this treatment restores the blood vessel wall structure to the pre-disease state.

Head of Laboratory:
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Research Scientists:
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Pablo Gómez del Arco

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Jorge Oller Pedrosa
Silvia Villahoz
Paula Sofía Yunes Leites

Technicians:
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Rut Alberca Rodríguez
Beatriz Carolina Ornés Poleo
Alicia Peral Rodríguez
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Visiting Scientists:
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Miguel Ramón Campanero García

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2015-63633-R)
- Ministerio de Economía y Competitividad. FIS RETICS (Red de Investigación Cardiovascular: RD12/0042/0022)
- Fundació La Marató TV3 (20151331)
- Fundació La Marató TV3 (264/C/2012) (PI: Sara Martínez)

SELECTED PUBLICATIONS

Oller J, Méndez-Barbero N, Josue Ruiz E, Villahoz S, Renard M, Canelas LI, Briones AM, Alberca R, Lozano-Vidal N, Hurlé MA, Milewicz D, Evangelista A, Salaices M, Nistal JF, Jiménez-Borreguero LJ, De Backer J, Campanero MR*, Redondo JM*. **Nitric oxide mediates the pathogenesis of Marfan syndrome and a related aortic disease triggered by Adamts1 deficiency**. *Nat Med* (accepted)

Gómez-Del Arco P, Perdiguero E, Yunes-Leites PS, Acín-Pérez R, Zeini M, Garcia-Gomez A, Sreenivasan K, Jiménez-Alcázar M, Segalés J, López-Maderuelo D, Ornés B, Jiménez-Borreguero LJ, D'Amato G, Enshell-Seijffers D, Morgan B, Georgopoulos K, Islam AB, Braun T, de la Pompa JL, Kim J, Enriquez JA, Ballestar E, Muñoz-Cánoves P, Redondo JM. **The chromatin remodeling complex Chd4/NuRD controls striated muscle identity and metabolic homeostasis**. *Cell Metab* (2016) 23:881-92

González-Terán B, López JA, Rodríguez E, Leiva L, Martínez-Martínez S, Bernal JA, Jiménez-Borreguero LJ, Redondo JM, Vazquez J, Sabio G. **p38γ and δ promote heart hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation**. *Nat Commun* (2016) 7:10477

Oller J, Alfranca A, Méndez-Barbero N, Villahoz S, Lozano-Vidal N, Martín-Alonso M, Arroyo AG, Escolano A, Armesilla AL, Campanero MR, Redondo JM. **C/EBPβ and nuclear factor of activated T cells differentially regulate Adamts-1 induction by stimuli associated with vascular remodeling**. *Mol Cell Biol* (2015) 35:3409-22

Martín-Alonso M, García-Redondo AB, Guo D, Camafeita E, Martínez F, Alfranca A, Méndez-Barbero N, Pollán Á, Sánchez-Camacho C, Denhardt DT, Seiki M, Vázquez J, Salaices M, Redondo JM, Milewicz D, Arroyo AG. **Deficiency of MMP17/MT4-MMP proteolytic activity predisposes to aortic aneurysm in mice**. *Circ Res* (2015) 117:e13-26

CNIC-UAM COLLABORATIVE PROGRAM

Intercellular communication in the inflammatory response

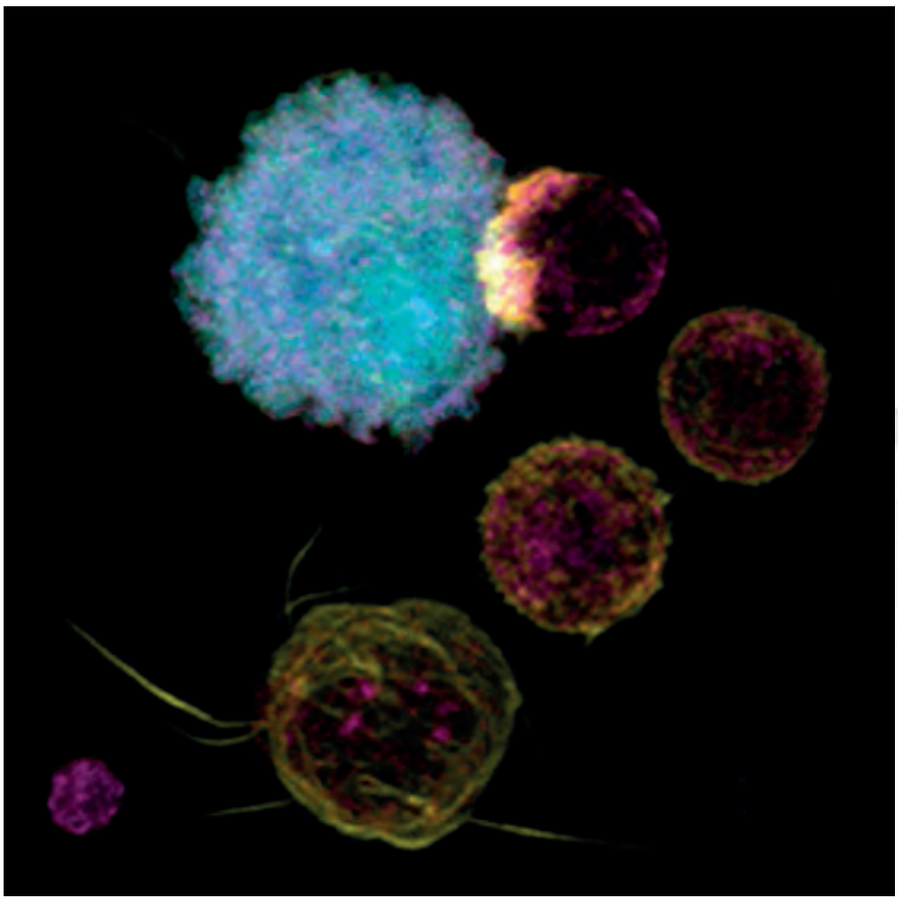
RESEARCH INTEREST

The group pursues three main lines of research.

1) **Regulation of immune synapse formation and function**. We are exploring precise roles of centrosomal proteins in IS formation, especifically the role of posttranslational modifiers such as Ser/Thr kinases. In addition, we are analyzing the role of mitochondrial components in the biogenesis and secretion of exosomes and their impact on macrophage and dendritic cell function.

2) **Fine tuning of T cell biology by controlling exosome biogenesis**. Exosome production and their specific constituents are being examined with the aim of identifying and characterizing specific proteins that are sorted into exosomes through ISG-ylation, a posttranslational modification.

3) **Immunoregulatory molecules and cells in steady state and inflammatory diseases**. We are analyzing the role of the immunoregulatory molecule CD69 and newly described partners such as aminoacid transporters in animal models of atherosclerosis and psoriasis and in patients. These studies are aimed at identifying the molecular basis of these inflammatory diseases. This includes the study of the role of specific subsets of macrophages in the immunesurveillance of blood vessels at steady-state.



Aurora A regulates T cell activation. Aurora A accumulates at the immune synapse and regulates the activity of Lck and the centrosome as a microtubule-organizing center in T cells

Head of Laboratory:
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Noa Martín
Danay Cibrián
Vera Rocha
Lola María Fernández

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Carolina Villarroya
Francesc Baixauli
María Laura Saiz
Olga Moreno
Daniel Torralba
Noelia Blas
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Ana Rodríguez
Irene Fernández

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Marta Ramírez

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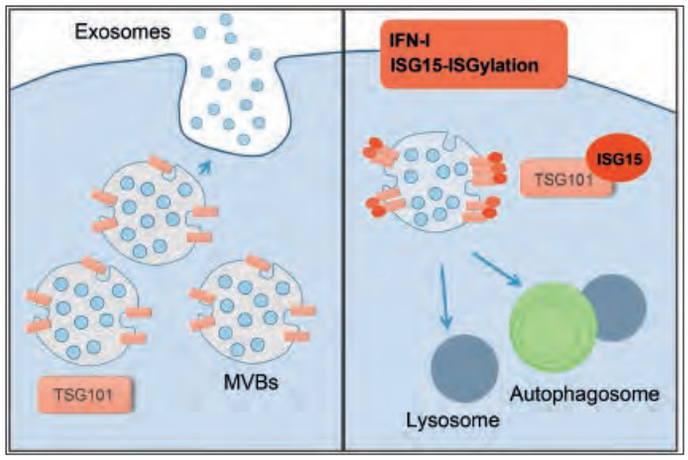
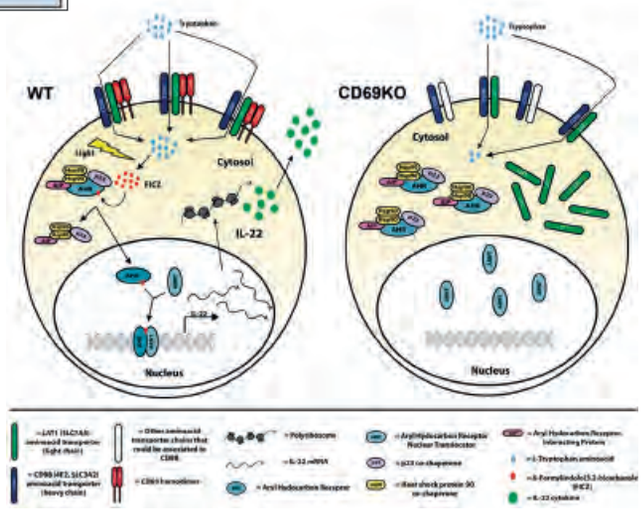
Rafael González
Alba Juanes
Laura Martínez
María de la Nieves Navarro
Javier Silván

Student Internship:
Diego Calzada



ISG-ylation: a posttranslational modification regulating proteostasis. ISG-ylation controls the activity of multivesicular bodies for protein degradation. From *Nat Commun* (2016) 7: 13588.



CD69 and LAT1 act as immuno-shuttles in psoriasis. CD69 interaction with the aminoacid transporter LAT1 regulates the production of IL-22 and psoriasis severity. From Nat Immunol. 2016. 17:985-96

MAJOR GRANTS

- European Commission. ERC Advanced Investigators Grant (ERC-2011-AdG 20110310) (GENTRIS)
- Ministerio de Economía y Competitividad (SAF2014-55579-R)
- Ministerio de Economía y Competitividad. FIS RETICS (RIC: RD12/0042/0056)
- Redes de Excelencia de la Comunidad de Madrid (P2010/BMD-2332)
- Fundación La Marató-2015 (281/C/2015).
- European Union. COST-Action BM1202.

SELECTED PUBLICATIONS

Barreiro O, Cibrian D, Clemente C, Alvarez D, Moreno V, Valiente Í, Bernad A, Vestweber D, Arroyo AG, Martín P, von Andrian UH, Sánchez Madrid F. **Pivotal role for skin transendothelial radio-resistant anti-inflammatory macrophages in tissue repair**. *Elife* (2016) 5. pii: e15251

Blas-Rus N, Bustos-Morán E, Pérez de Castro I, de Cárcer G, Borroto A, Camafeita E, Jorge I, Vázquez J, Alarcón B, Malumbres M, Martín-Cófreces NB, Sánchez-Madrid F. **Aurora A drives early signalling and vesicle dynamics during T-cell activation**. *Nat Commun* (2016) 7: 11389

Cibrian D, Saiz ML, de la Fuente H, Sánchez-Díaz R, Moreno-Gonzalo O, Jorge I, Ferrarini A, Vázquez J, Punzón C, Fresno M, Vicente-Manzanares M, Daudén E, Fernández-Salguero PM, Martín P, Sánchez-Madrid F. **CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis**. *Nat Immunol* (2016) 17: 985-96

Villarroya-Beltri C, Baixauli F, Mittelbrunn M, Fernández-Delgado I, Torralba D, Moreno-Gonzalo O, Baldanta S, Enrich C, Guerra S, Sánchez-Madrid F. **ISGylation controls exosome secretion by promoting lysosomal degradation of MVB proteins**. *Nat Commun* (2016) 7: 13588

Torralba D, Baixauli F, Sánchez-Madrid F. **Mitochondria Know No Boundaries: Mechanisms and Functions of Intercellular Mitochondrial Transfer**. *Front Cell Dev Biol* (2016) 4: 107.

Cardiovascular proteomics

RESEARCH INTEREST

We are working on novel high-throughput quantitative approaches for the dynamic analysis of the deep proteome, including novel bioinformatics algorithms for protein identification, quantification, and systems biology interpretation in very large numbers of samples and for the study of posttranslational modifications using novel hypothesis-free approaches.

Using a pig model of ischemia reperfusion, we are applying these proteomics technologies to study the molecular events taking place in the heart after infarction and the molecular effects of protective treatments, including the impact on postranslational modifications.

We have also developed a translational proteomics platform, with which we are studying the molecular mechanisms implicated in early atherosclerosis. This platform is being applied to the search for protein, metabolic and lipid factors correlating with subclinical atherosclerosis markers such as calcium deposition and plaque formation and activity in the PESA project. We are also studying atherosclerosis models in other clinical stages, including molecular changes taking place in the aorta at early stages of plaque formation, including the plaque itself and its secretome.

Finally, we are studying the molecular mechanisms that regulate assembly and superassembly of the electron transport chain complexes in mitochondria, using Blue-DiS, an advanced technology that allows analysis of the interactome and the implication of protein factors, isoforms, and postranslational modifications with unprecedented molecular detail.

Head of Laboratory:
Jesús María Vázquez Cobos

Postdoctoral Researchers:
Estefanía Núñez Sánchez
Elena Bonzón Kulichenko
Inmaculada Jorge Cerrudo
Alessia Ferranini
Spyridon Michalakopoulos

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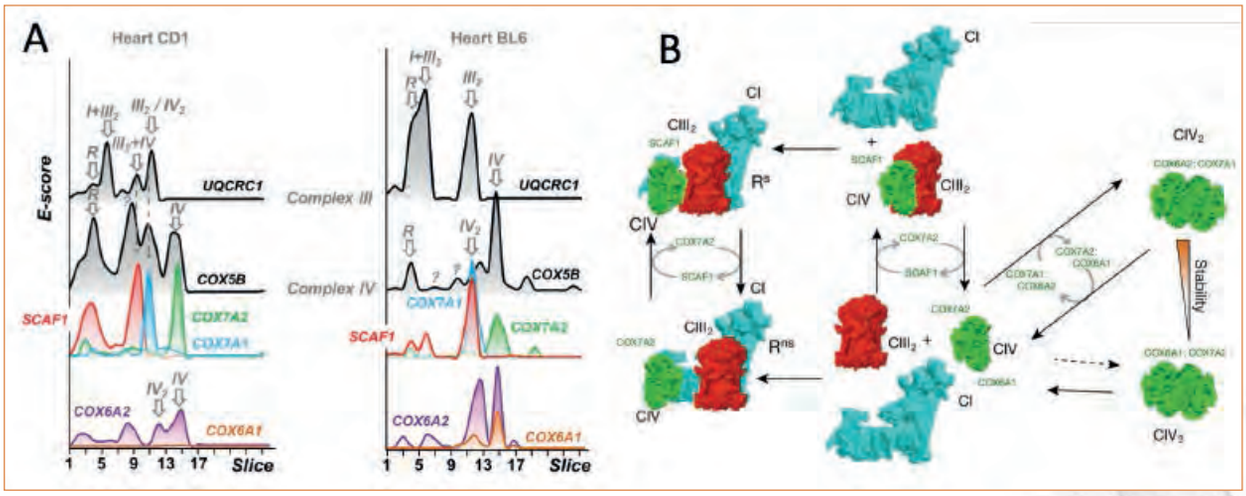
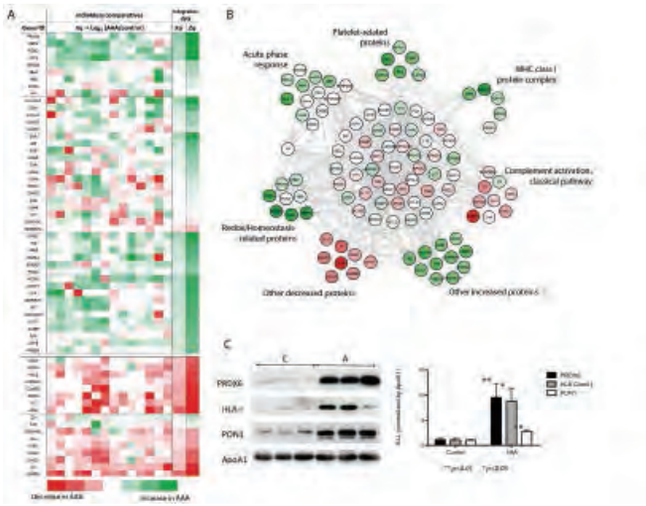
Fernando García Marqués
Marco Trevisan Herraz
Marta Loureiro
Navratan Bagwan
Aleksandra Ronja

Masters Students:
Celia Castañs García
Jesús Lavado García

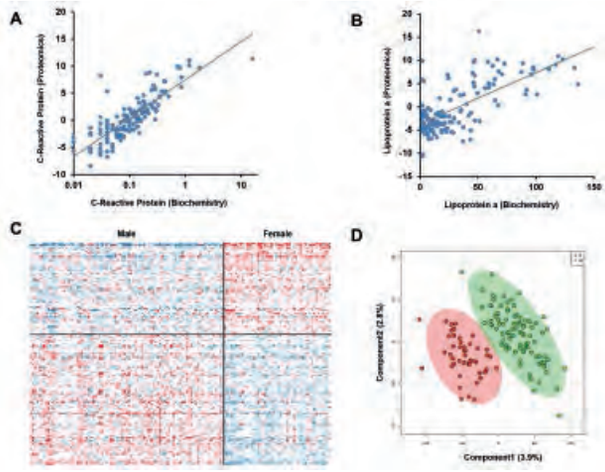
Visiting Scientists:
Elena Burillo
Diego Martínez López
Montserrat Baldán



Super-assembly of CIII and CIV into different structures depends on the subunit composition of CIV. (A) Quantitative protein profiles of mitochondrial supercomplexes separated by blue native gel electrophoresis and analyzed by DiS, a novel data-independent mass spectrometry technology developed in our laboratory. (B) Model of CIV dimerization and superassembly driven by the exchange of CIV subunit isoforms.



Quantitative proteomics reveals high-density-lipoprotein (HDL) alterations in human abdominal aortic aneurysm (AAA) highlighted by increased peroxiredoxin-6 (PRDX6) levels and consistent with systemic redox imbalance. A. Altered HDL-associated proteins in AAA patients. B. Network interaction analysis of dynamic changes. C. Western-blot validation of the proteins most altered in AAA.



Performance of the Translational Proteomics Platform. Agreement between biochemistry and proteomics for levels of C-reactive protein (A) and lipoprotein a (B). (C) The platform allows gender determination from quantitative data (red: increase; blue: decrease). (D) PLS-DA analysis showing good discrimination between male (green) and female participants (red).

MAJOR GRANTS

- Ministerio de Economía y Competitividad (BIO2012-37926)
- Ministerio de Economía y Competitividad. FIS Proteored (PT13/0001/0017)
- Ministerio de Economía y Competitividad. FIS RETICS (RIC: RD12/0042/0056)
- European Commission: 7th Framework Programme for Research (FP7-PEOPLE-ITN-2013-PITN-GA-2013-608027) (CardioNext)
- Progeria Research Fund Specialty Award (USA)
- Fundació La Marató de TV3

SELECTED PUBLICATIONS

Burillo E, Jorge I, Martínez-López D, Camafeita E, Blanco-Colio LM, Trevisan-Herraz M, Ezkurdia I, Egido J, Michel JB, Meilhac O, Vázquez J *, Martin-Ventura JL* (*co-corresponding authors). **Quantitative HDL proteomics identifies peroxiredoxin-6 as a biomarker of human abdominal aortic aneurysm**. *Sci Rep* (2016) 6: 38477

Cogliati S*, Calvo E*, Loureiro M, Guaras AM, Garcia-Poyatos C, Nieto-Arellano R, Ezkurdia I, Mercader N, Vázquez J#, Enriquez JA#. (#:co-corresponding authors). **Mechanism of superassembly between respiratory complexes III and IV**. *Nature* (2016) 539: 579-82

Cibrián D, Saiz ML, de la Fuente H, Sánchez-Díaz R, Moreno-Gonzalo O, Jorge I, Ferrarini A, Vázquez J, Punzón C, Fresno M, Vicente-Manzanares M, Daudén E, Fernández-Salguero PM, Martin P, Sánchez-Madrid F.**CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis**. *Nat Immunol* (2016) 17: 985-96

García-Marqués F, Trevisan-Herraz M, Martínez-Martínez S, Camafeita E, Jorge I, Lopez JA, Méndez-Barbero N, Méndez-Ferrer S, del Pozo MA, Ibáñez B, Andrés V, Sánchez-Madrid F, Redondo JM, Bonzon-Kulichenko E*, Vázquez J* (*: co-corresponding authors). **A novel systems-biology algorithm for the analysis of coordinated protein responses using quantitative proteomics**. *Mol Cell Proteomics* (2016) 15: 1740-60

Bonzon-Kulichenko E, Garcia-Marques F, Trevisan-Herraz M, Vázquez J. **Revisiting peptide identification by high-accuracy mass spectrometry: problems associated to the use of narrow mass precursor windows**. *J Proteome Res* (2015) 14: 700-10

RESEARCH AREAS

TRANSLATIONAL COORDINATION

1. Myocardial Pathophysiology
2. Vascular Pathophysiology
3. Cell and Developmental Biology

3. Cell and Developmental Biology

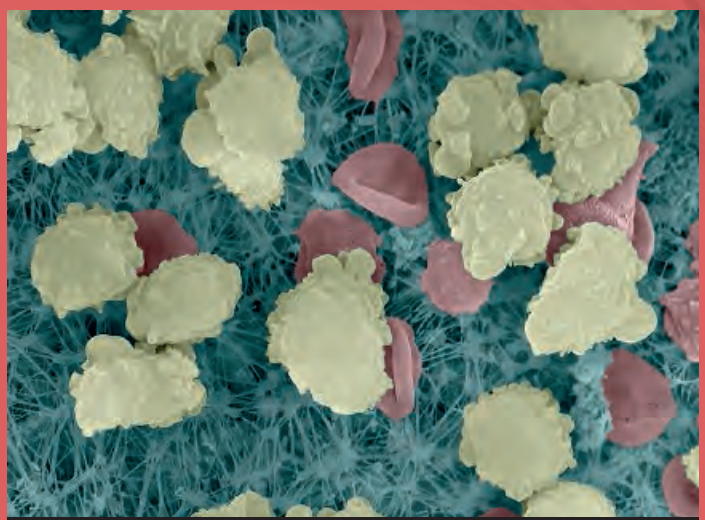
AREA COORDINATORS:

MIGUEL MANZANARES

MIGUEL ÁNGEL DEL POZO

RESEARCH INTEREST

The Cell and Developmental Biology Area comprises 10 laboratories that conduct basic and translational research, ranging from mechanistic aspects of cell signaling and behavior to the principles of cardiovascular development. Research topics include the molecular and cellular embryology of the heart, mechanisms of tissue repair, the underpinnings of heart and vascular homeostasis, and how these aspects relate to disease. Specific research lines are aimed at understanding how temporally and spatially regulated transcriptional networks determine the very first cell fate decisions in the early embryo, as well as the different stages of heart development. Laboratories in the CDB Area also investigate processes important for cardiovascular homeostasis such as angiogenesis, inflammation, and regeneration. Finally, a number of research lines are aimed at elucidating key cell signaling pathways and molecular principles underlying the mechanical properties, function and adaptability of the cardiovascular system, using state-of-the-art cell biophysics and single-molecule techniques.



Scanning electron micrograph of aged neutrophils (yellow) and erythrocytes (red) on a synthetic substrate (green).

Molecular mechanics of the cardiovascular system

RESEARCH INTEREST

Our group investigates how the mechanical activity of the heart emerges from the nanomechanical properties of cardiac proteins. We hypothesize that several cardiac diseases result from impaired function of proteins with key mechanical roles or are aggravated by maladaptive modifications that affect protein mechanics. Our group aims define how the mechanical properties of cardiac proteins, as determined by single-molecule atomic force microscopy (AFM), translate into the macroscopic function of the heart. In 2016, we found that several mutant forms of cardiac myosin-binding protein C (cMyBP-C) that cause hypertrophic cardiomyopathy have altered mechanical properties but show no other major structural or functional changes. These mechanical alterations might be the trigger that leads to cardiac hypertrophy, an idea we aim to explore in the future using animal models. Also in 2016, we optimized methods based on mass spectrometry and fluorescent polyacrylamide gels that allow us to monitor redox posttranslational modifications that target titin and other cardiac proteins. We are now investigating if the levels of these modifications change during different forms of heart disease. As an alternative approach to bringing protein nanomechanics to the macroscopic level, we have produced new biomaterials from proteins whose mechanical properties we determine in the laboratory. For this project, we have set up a customized gel stretcher machine to systematically determine the behavior of our engineered protein hydrogels under a pulling force.

Head of Laboratory:
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Postdoctoral Researcher:
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Predoctoral Researcher:
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Masters Students:
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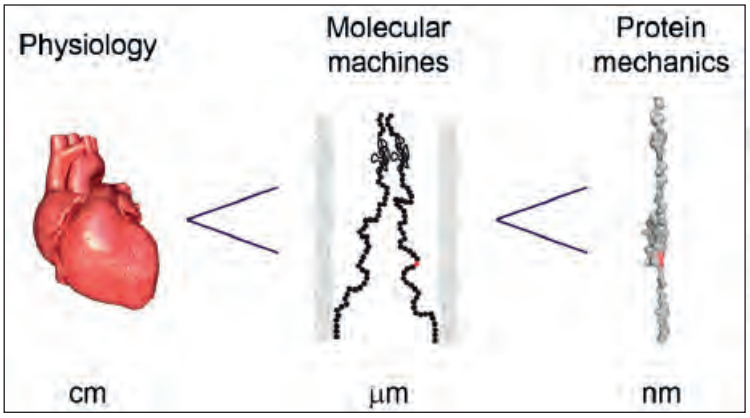
Carmen Suay-Corredera

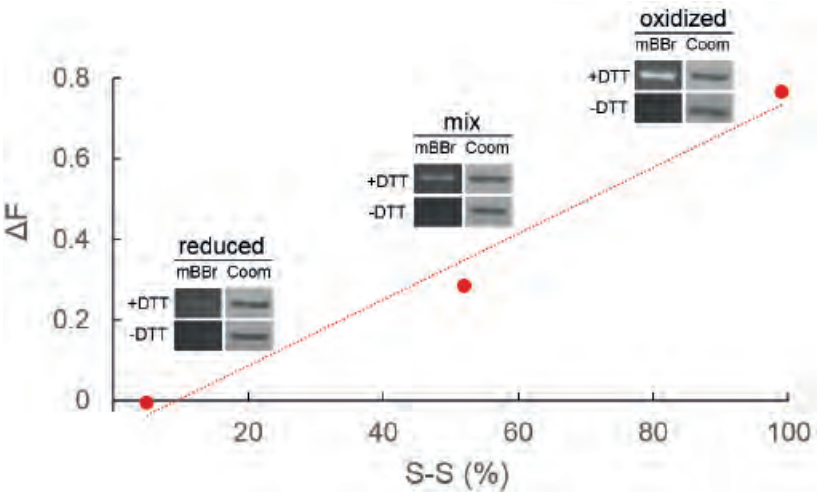
Visiting Scientists:
María Plaza
Maria Rosaria Pricolo

Visiting Students:
Iñigo Urrutia
Ricardo Esteban

Technician:
Diana Velázquez-Carreras



The goal of our lab is to understand how the mechanics of proteins at the nanometer scale determine the mechanical properties of the heart at the macroscopic level.



In-gel fluorescent assay to determine the redox state of cysteines in proteins. The method is based on the reduction of oxidized cysteines by incubation with DTT and subsequent labeling with monobromobimane (mBBr). mBBr reacts with free thiols, generating a flourescent adduct only in samples pretreated with DTT. We use Coomassie staining to normalize the fluorescent signal to the total amount of protein (insets). To test the method, we have used purified proteins of controlled redox state (oxidized or reduced, or mixtures of both).

MAJOR GRANTS

- Comisión Europea and ISCIII (AC16/00045)
- Comunidad de Madrid (PEJ 16/MED/TL-1593)
- Ministerio de Economía y Competitividad (BIO2014-54768-P)
- Ministerio de Economía y Competitividad (RYC-2014-16604)

SELECTED PUBLICATIONS

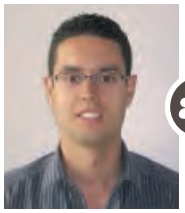
Rivera-de-Torre E, Garcia-Linares S, Alegre-Cebollada J, Lacadena J, Gavilanes JG, Martinez-Del-Pozo A. **Synergistic Action of Actinoporin Isoforms from the Same Sea Anemone Species Assembled Into Functionally Active Heteropores**. *J Biol Chem* (2016) 291: 14109-19

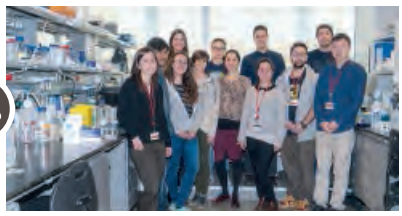
Echelman DJ, Alegre-Cebollada J, Badilla CL, Chang C, Ton-That H, Fernandez JM. **CnaA domains in bacterial pili are efficient dissipaters of large mechanical shocks**. *Proc Natl Acad Sci USA* (2016) 113: 2490-5

Saqlain F, Popa I, Fernandez JM, Alegre-Cebollada J. **A novel strategy for utilizing voice coil servoactuators in tensile tests of low volume protein hydrogels**. *Macromol Mater Eng* (2015) 300: 369-76

Rivas-Pardo JA, Alegre-Cebollada J, Ramirez-Sarmiento CA, Fernandez JM, Guixe V. **Identifying sequential substrate binding at the single-molecule level by enzyme mechanical stabilization**. *Acs Nano* (2015) 9: 3996-4005

Molecular genetics of angiogenesis





RESEARCH INTEREST

Our group investigates the cellular and molecular mechanisms involved in the formation and homeostasis of blood vessels in different organs and pathological contexts. Therapeutic modulation of vascular structure and function in disease remains a major challenge, in part due to our inability to induce the exact mechanisms that vessels use to grow under normal physiological conditions.

This past year we revisited and challenged some settled concepts in vascular biology by using new genetic tools that enable us to study the function of vascular genes at higher cellular resolution. We developed new transgenic and gene-targeting strategies to perform conditional mosaic gene function analysis. We also identified a molecular mechanism that prevents excessive and unsustained angiogenesis in the presence of a high mitogenic stimulus. This mechanism is important in the setting of active angiogenesis and high VEGF signaling, as occurs in tumors or after cardiac injury. With this knowledge, we are now working to develop more efficient ways to promote sustained and functional vascular growth.

In addition, we continued to investigate some of the most basic mechanisms involved in the differentiation of endothelial cells into hematopoietic stem and progenitor cells and also how some genes control the development, differentiation, and homeostasis of coronary vessels.

Head of Laboratory:
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Sarita Saraswati

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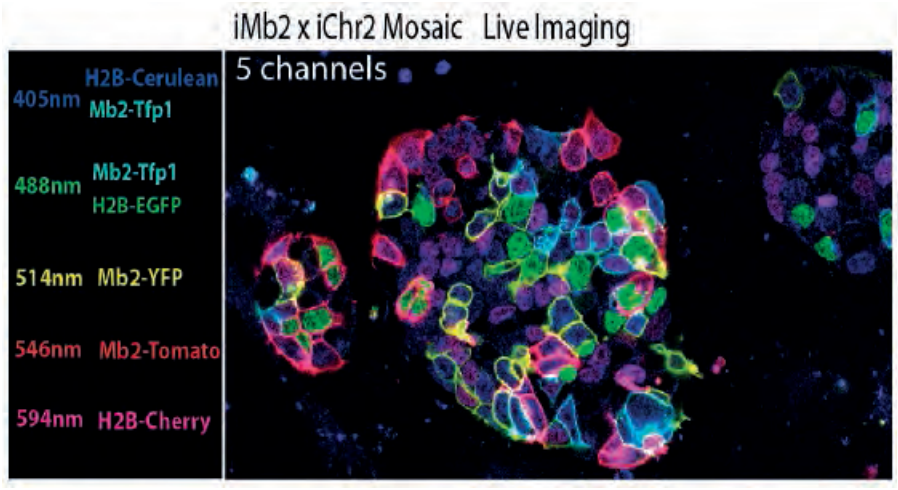
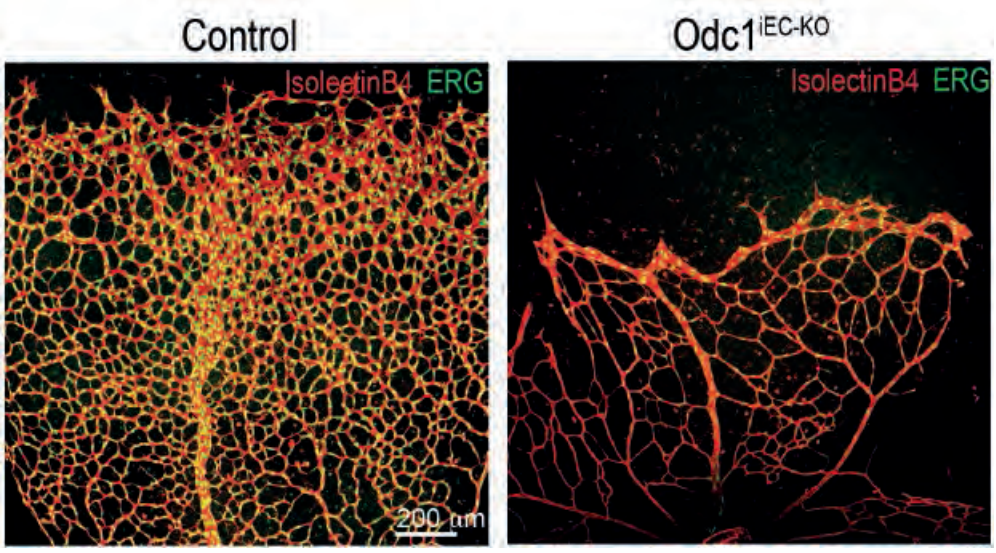
Macarena Fernández Chacón
Irene García González
Briane D. Laruy
Carlos López Fernández de Castillejo
Samuel Pontes Querol

Graduate Technicians:
Verónica Casquero García
Ana Hermoso Castro

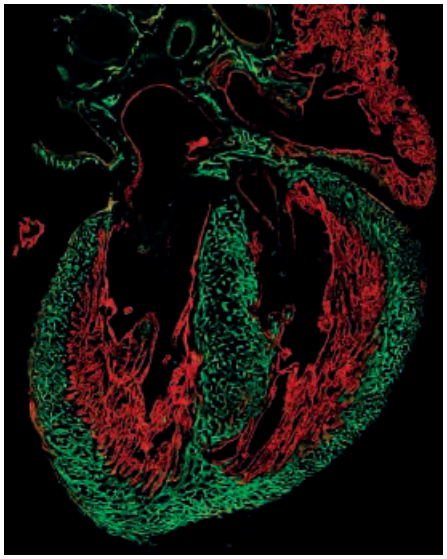
Technician:
M. Sofía Sánchez Muñoz



Multi-channel high-speed confocal imaging of cells expressing different combinations of fluorescent proteins and genes involved in the control of endothelial differentiation and proliferation.



We found Odc1 to be a very important gene for angiogenesis. The formation of new blood vessels is completely blocked in mutant mice specifically lacking Odc1 function in endothelial cells for 4 days.



We used new inducible CreERT2 and reporter mouse lines to genetically target and specifically label the coronary vessels (green) and distinguish them from the endocardium (red). This new methodology will allow us to characterize the role of different genes in coronary vessel development at high molecular and cellular resolution.

MAJOR GRANTS

- European Research Council Starting Grant 2014. (ERC-2014-StG 638028_AngioGenesHD)
- Ministerio de Economía y Competitividad (SAF2013-44329-P)
- Ministerio de Economía y Competitividad. Contrato Ramón y Cajal (RYC-2013-13209)
- Ministerio de Economía y Competitividad. Posdoctoral contract. PI: Tania Sánchez (FPDI-2013-18049)
- European Commission. International IPP contract. PI: Wen Luo
- European Commission. International IPP contract. PI: Sarita Saraswati
- Fundación La Caixa CNIC Severo Ochoa. Predoctoral Fellowship. PI: Samuel Pontes
- Fundación La Caixa. Predoctoral Fellowship. PI: Macarena Fernández
- Ministerio de Economía y Competitividad. Predoctoral contract (BES-2014-069205) PI: Briane Laruy
- Fundación La Caixa CNIC Severo Ochoa. Predoctoral Fellowship. PI: Irene García
- Boheringer Ingelheim Fons. Predoctoral Fellowship. PI: Carlos López Fernández de Castillejo

SELECTED PUBLICATIONS

D'Amato G, Luxán G, Del Monte-Nieto G, Martínez-Poveda B, Torroja C, Walter W, Bochter MS, Benedito R, Cole S, Martinez F, Hadjantonakis AK, Uemura A, Jiménez-Borreguero LJ, de la Pompa JL. **Sequential Notch activation regulates ventricular chamber development**. *Nat Cell Biol* (2016) 18: 7-20

Bernier-Latmani J, Cisarovsky C, Demir CS, Bruand M, Jaquet M, Davanture S, Ragusa S, Siegert S, Dormond O, Benedito R, Radtke F, Luther SA, Petrova TV **DLL4 promotes continuous adult intestinal lacteal regeneration and dietary fat transport** *J Clin Invest* (2015) 125: 4572-86

Multidisciplinary translational cardiovascular research

Head of Laboratory:
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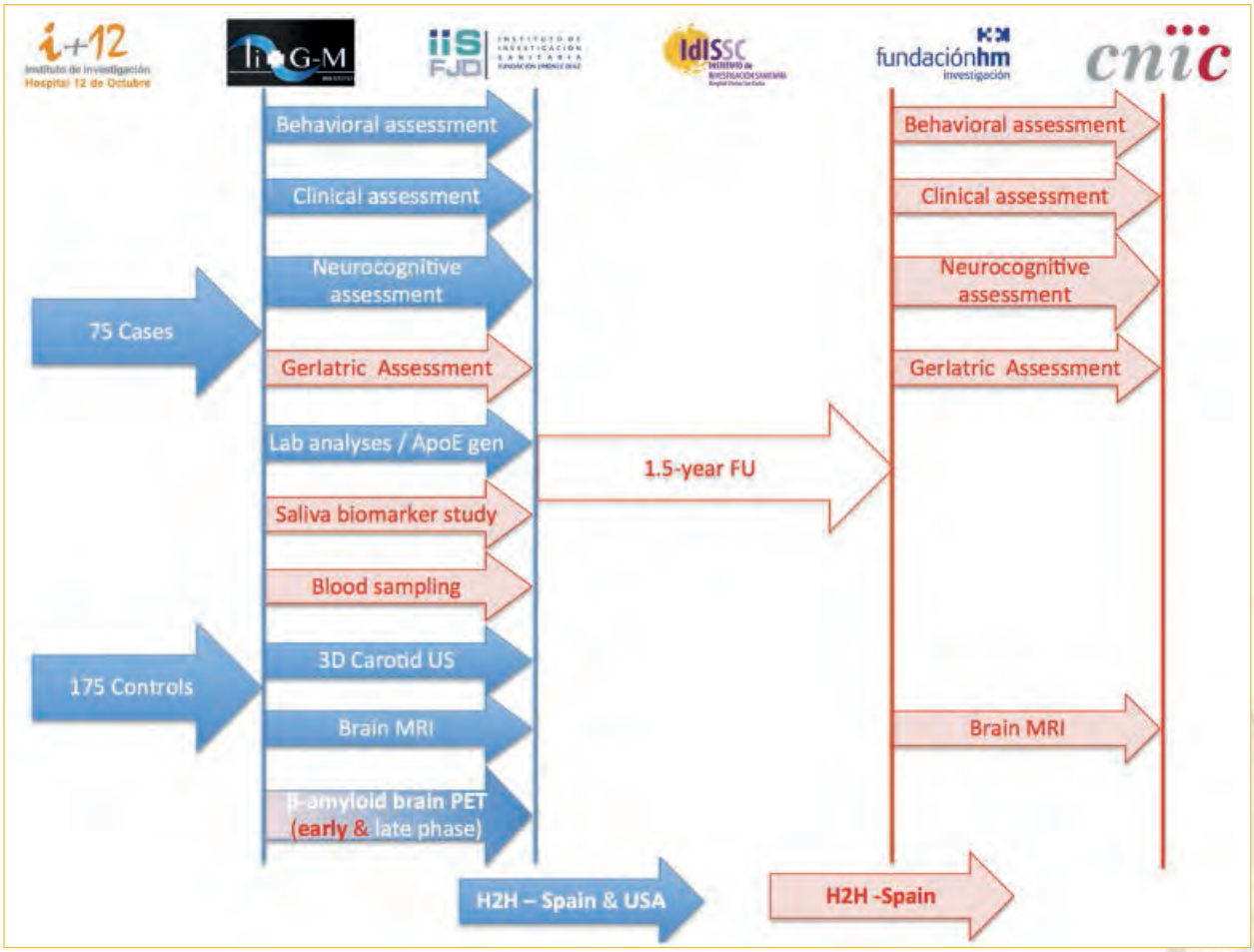
Cardiologist
Juan Górriz,
Cardiology resident
Ana Ramos,
Neuroradilogist
Adolfo Gómez,
Specialist in Nuclear Medicine

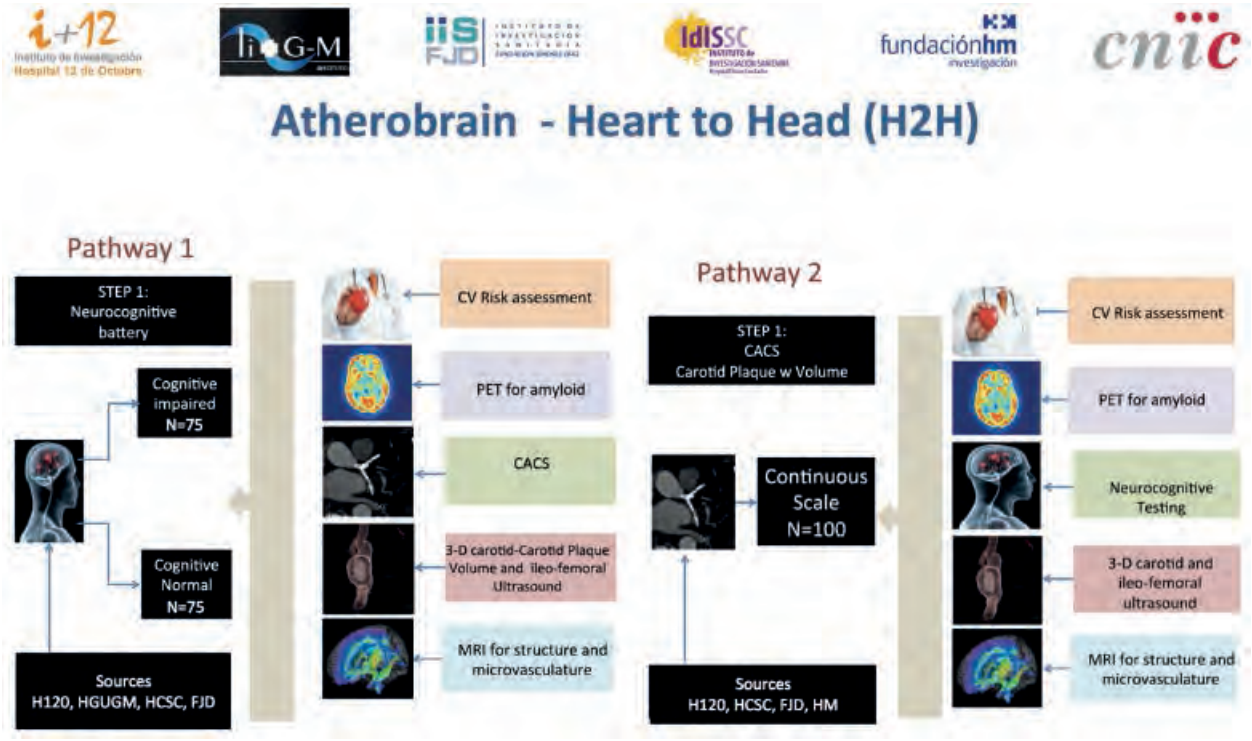
RESEARCH INTEREST

The MTCR group has a strong connection with clinical research in different fields, including atherosclerosis, acute coronary syndromes, acute and chronic heart failure, pulmonary hypertension, cardiovascular ageing and frailty, heart-valve disease, advanced cardiovascular imaging, and genetic and familial cardiovascular diseases. The MTCR group participates actively in the main CNIC translational projects, including the PESA study and the SECURE trial comparing the polypill with standard care for secondary CV prevention.

A major interest of the group is non-standard pathophysiological connections between the cardiovascular system and brain function. A key project in this area is the Atherobrain - Heart to Head (H2H) study. This ISCIII-funded project is run through partnership between the CNIC imaging area, the i+12 institute and *Hospital 12 de Octubre*, and and several hospitals (*12 de Octubre, Gregorio Marañón, Clínico San Carlos, Fundación Jiménez Díaz,* and *Hospitales de Madrid*). H2H examines the relationship between subclinical atherosclerosis, cognitive decline, and Alzheimer´s disease. Related interests include the pathophysiology of stress cardiomyopathy (Tako-Tsubo syndrome) and the role of a positive mental attitude in CV disease patients.

We work in partnership with other CNIC research groups in several research fields, including the basic mechanisms of the early atherosclerosis development (MA Del Pozo and Jacob Benzon), the role of specific microRNAs in cardiovascular disease (Almudena Ramiro and Pilar Martín), the role of progerin and lamin A in aging and atherosclerotic disease (Vicente Andrés), mechanical properties of myocardium and derived translational models (Jorge Alegre), basic mechanisms of the pathophysiology of pulmonary hypertension (Jesus Cabello), and new therapies for pulmonary hypertension (Borja Ibañez).





MAJOR GRANTS

- Ministerio de Economía y Competitividad (PIE16/00021)

SELECTED PUBLICATIONS

Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H. **Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure.** *Eur J Heart Fail* (2016) 18(7):869-75.

Hall M, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, Brieger D, Timmis A, Batin PD, Deanfield JE, Hemingway H, Fox KA, Gale CP. **Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non-ST-Elevation Myocardial Infarction, 2003-2013.** *JAMA* (2016) 316(10):1073-82.

Peñalvo J, Fernandez-Friera L, Lopez-Melgar B, Uzhova I, Oliva B, Fernández-Alvira JM, Laclaustra M, Pocock S, Mocoroa A, Mendiguren JM, Sanz G, Guallar E, Bansilal S, Vedanthan R, Jiménez-Borreguero J, Ordovas jm, Fernandez-Ortiz A, Bueno H, Fuster V. **Association between a social-business eating pattern and early asymptomatic aterosclerosis**. *J Am Coll Cardiol* (2016) 68(8):805-14.

Ponikowski P, Voors AA, Anker SK, Bueno H, Cleland J, Coats A, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska E, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley J, Rosano G, Ruilope L, Ruschitzka F, Rutten FH, van der Meer, Filippatos G, McMurray JJV. 2016 **ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.** *Eur Heart J* (2016) 37(27):2129-2200.

Mechanoadaptation and Caveolae Biology

RESEARCH INTEREST

Our long-term aim is to understand reciprocal communication between cells and their environment, with a focus on the biological roles of integrin signaling and caveolae and their components. Caveolae are actin-linked plasma membrane nano-invaginations, abundant in mechanically stressed tissues (heart, vessels, muscle, and fat). Among their many functions, caveolae transduce mechanical cues and communicate tensile stress between cells and the extracellular matrix (ECM), thus driving ECM remodeling; however, understanding is limited about how this happens and how it is coordinated with other cell functions. Ongoing projects address these questions at three levels:

(1) Molecular mechanisms mediating cell-ECM communication and mechanotransduction

We use state-of-the-art cell biology and biophysics methodologies to characterize the contribution of essential caveolar components (such as Cav1 and PTRF) to mechanosensing and the reciprocal interaction between the cell and the ECM. We combine these approaches with high-throughput techniques (HCScreens, quantitative transcriptomics and proteomics, and MS-based interactomics). We recently implemented microfluidics approaches to elucidate whether and how these mechanisms are engaged in the vasculature to counter mechanical challenges derived from blood flow. Reflecting these interests, we co-organized the CNIC conference on Mechanical Forces in Physiology and Disease, which brought together international leaders in the field.

(2) Crosstalk between integrin-associated and caveolar-associated functions and other cell functions

We are studying novel relationships between caveolar components and functions such as organelle trafficking and homeostasis, metabolism, and cell differentation. Our studies support a role for Cav1 in the communication between endoplasmic reticulum and mitochondria, which might specifically enable different steps of fatty acid and cholesterol metabolism. We are also exploring the role of Cav1 in the orchestration of key pleiotropic signaling pathways, such as TGFbeta and Wnt.

(3) Contribution of caveolin-dependent mechanotransduction and signaling regulation to physiology and disease

Our work with different Cav1 KO models reveals a pervasive impact of Cav1 on the regulation of lipid metabolism (fig. 2), ECM remodeling, and mechanotransduction. We are studying the impact of these different contributions to organismal homeostasis and disease.

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(October 2015-July 2016)

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Visiting Scientist:
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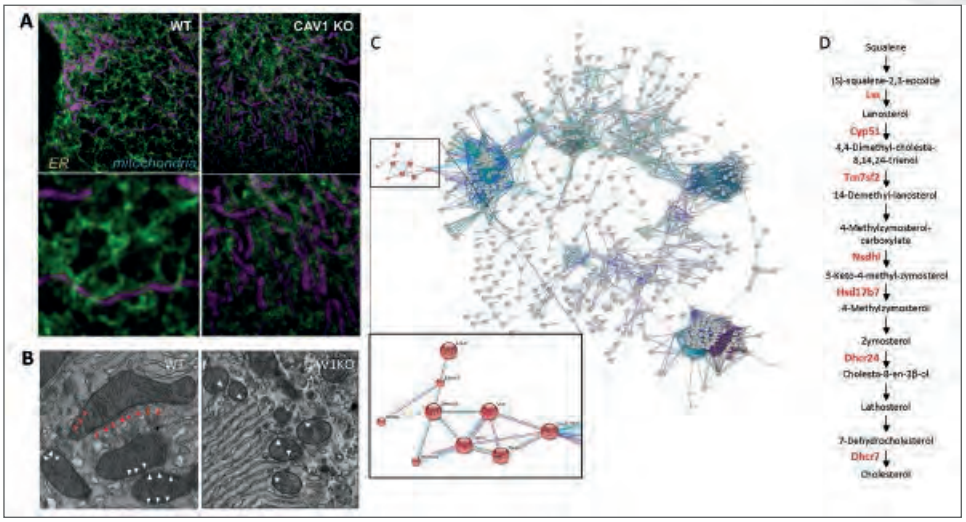
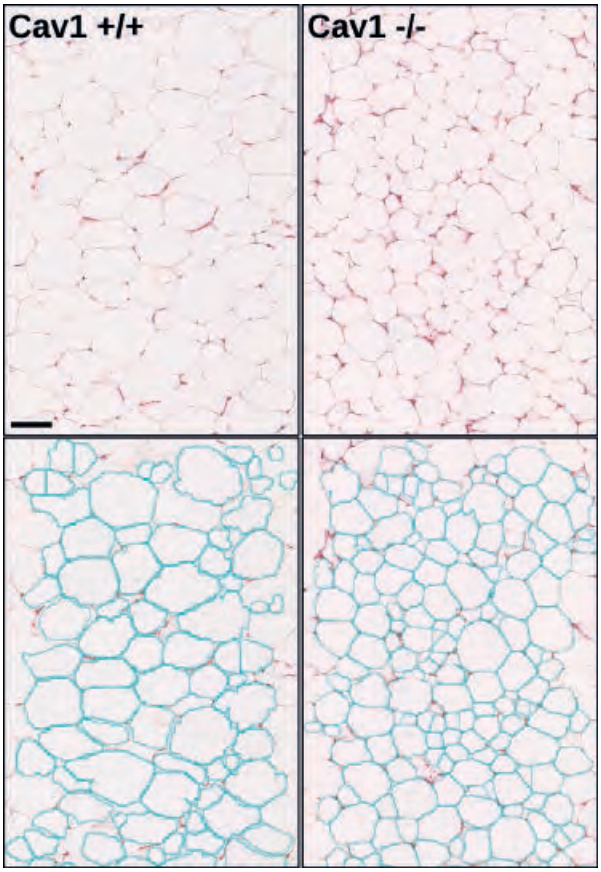


Visualization of the spatial relationship of endoplasmic reticulum (ER) and mitochondrial networks by (A) optical superresolution microscopy and (B) electron microscopy. Cav1 KO cells exhibit disorganized networks of tubular ER, partial fragmentation of mitochondria, and reduced extension of ER-mitochondria contacts. (C and D) Genetic networks established by enriched components of ER-mitochondria contacts include conserved modules for endogenous cholesterol anabolism in hepatocytes, which are profoundly affected upon Cav1 downregulation.



Top. Masson's trichrome staining of visceral Cav1$^{+/+}$ and Cav1$^{-/-}$ adipose tissue sections. Lipodystrophic syndrome is a hallmark of caveolinopathies, and one of its features is the lower volume and altered functioning of adipocytes.

Bottom. Computer vision segmentation allows unbiased quantitation of single-cell level properties (collaboration with Daniel Jiménez, Cellomics Unit, CNIC). Scale bar, 100µm.

MAJOR GRANTS

- European Commission. Marie Curie Actions Initial Training Network (ITN) (Horizon 2020, "BIOPOL")
- WorldWide Cancer Research (UK) (formerly known as AICR) (AICR 15 – 0404)
- Ministerio de Economía y Competitividad (SAF2014-51876-R)
- Ministerio de Economía y Competitividad. Consolider COAT (CSD2009-00016)
- Ministerio de Economía y Competitividad. Red de Excelencia en Mecanobiología (BFU2014-52586-REDT)
- Fundació La Marató TV3 (674/C/2013)

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Bravo-Cordero JJ, Cordani M, Díez-Cabezas B, Muñoz-Agudo C, Casanova M, Boullosa C, Guadamillas MC, Ezkurdia I, Soriano SF, González-Pisano D, del Pozo MA and Montoya MC*. **A novel high content analysis tool reveals Rab8-driven actin and FA reorganization through Rho GTPases and calpain/MT1**. *J Cell Sci* (2016) 129: 1734-49

Navarro-Lérida I, Pellinen T, Sánchez SA, Guadamillas MC, Wang Y, Mirtti T, Calvo E, Del Pozo M.A. **Rac1 nucleocytoplasmic shuttling drives nuclear shape changes and tumor invasion**. *Dev Cell* (2015) 32: 318-34

Strippoli R, Loureiro J, Benedicto I, Pérez-Lozano ML, Moreno V, Barreiro O, Pellinen T, Minguet S, Foronda M, Osteso MT, Calvo E, Vázquez J, López-Cabrera M, Del Pozo MA. **Caveolin-1 deficiency induces MEK-ERK1/2-Snail1-dependent epithelial-mesenchymal transition and fibrosis during peritoneal dialysis**. *EMBO Mol Med* (2015) 7: 102-23

Regeneration and aging

RESEARCH INTEREST

Our group studies the molecular mechanisms involved in heart regeneration. A key element of our strategy is the comparison of animal models that differ greatly in their regeneration capacity, from the zebrafish, which can restore up to 20% of its heart after injury, through the newborn mouse, whose heart possesses transient regenerative potential, to the adult mouse, in which heart regeneration capacity is very limited.

In 2015-2016, we found a correlation between the activity of the anti-aging enzyme telomerase and the degree of heart regeneration: relatively high telomerase activity in adult zebrafish and newborn mice, contrasting with low activity in juvenile and adult mice. This prompted us to study in more detail the role of telomerase and telomere length in the process of heart regeneration. In the zebrafish, we found that telomerase is essential for heart regeneration. The inability of zebrafish hearts lacking telomerase to regenerate is mainly due to strong inhibition of the proliferation response, associated with accumulation of cardiac cells with DNA damage and senescence characteristics (Bednarek *et al*. 2015). In the mouse, we found that telomerase is rapidly inactivated during postnatal cardiac maturation and that cardiomyocytes undergo telomere shortening. We also found that telomere shortening activates a DNA damage response, triggers the formation of anaphase bridges, and upregulates the cell-cycle inhibitor p21, leading to the cell-cycle arrest of postnatal cardiomyocytes (Aix *et al*. 2016). We also discovered that telomere length defines the cardiomyocyte differentiation potential of mouse induced pluripotent stem cells (iPSCs). This finding highlights the importance of selecting iPSCs with ample telomere reserves in order to generate high numbers of cardiomyocytes in a fast, reliable, and efficient way (Aguado *et al*. 2016)

Through these efforts, we hope to achieve a more complete knowledge of the role of telomerase and telomere length in cardiomyocyte proliferation and heart regeneration, which could lead to new therapies for heart failure.

Head of Laboratory:
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Posdoctoral Researchers:
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Tania Aguado

Predoctoral Researcher:
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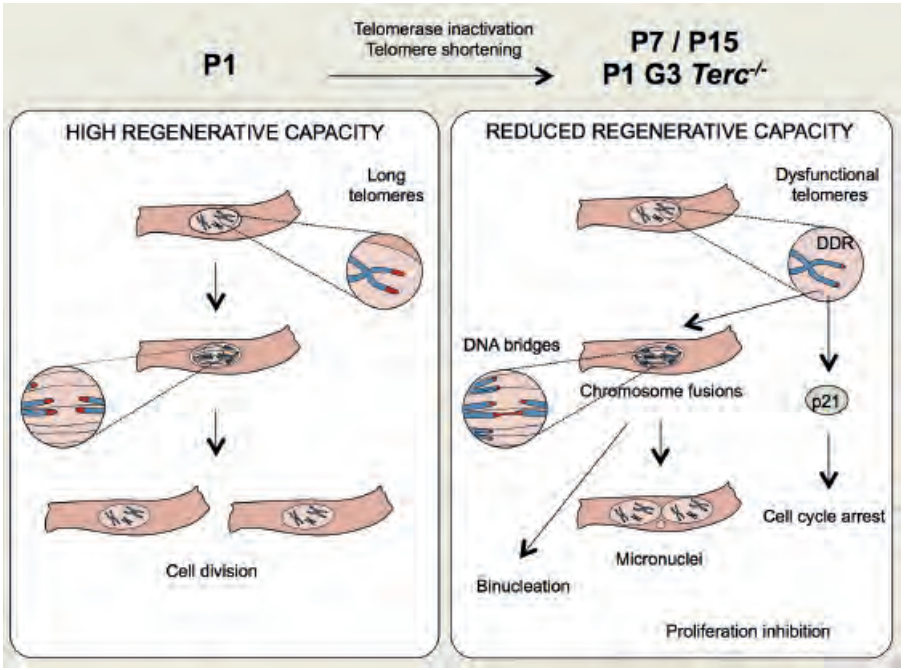
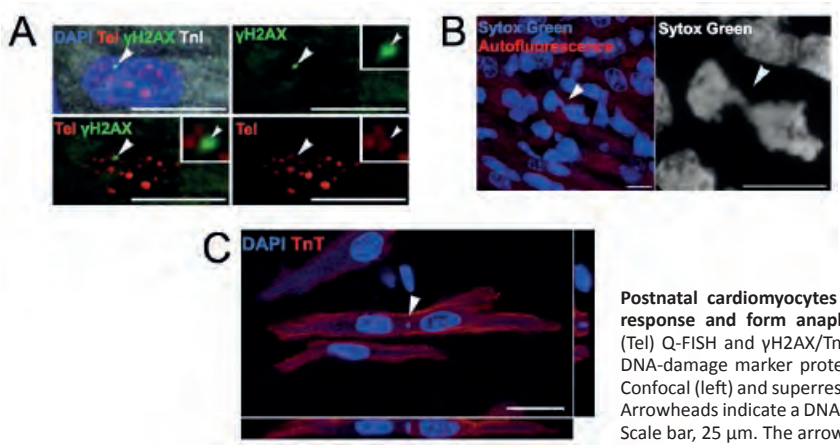
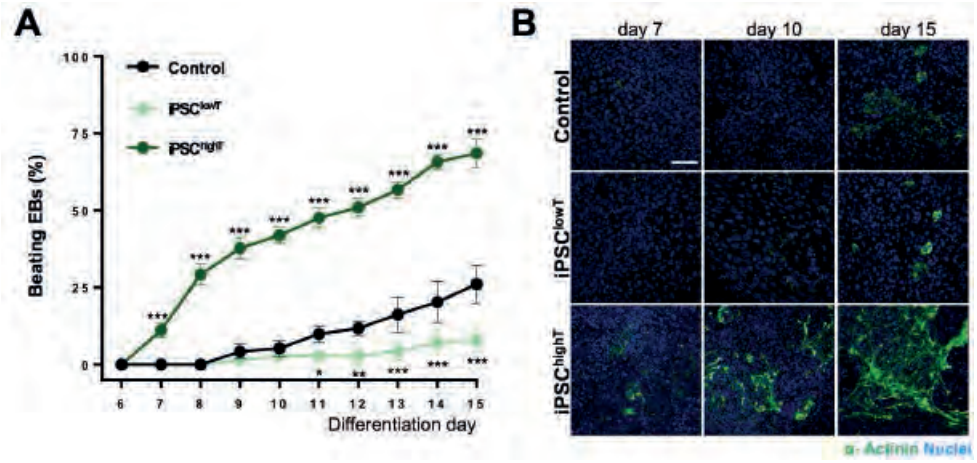
Technician:
Irene de Diego



Postnatal telomere dysfunction induces cardiomyocyte cell-cycle arrest through p21 activation: proposed model. At postnatal day P1, a proportion of cardiomyocytes (CM) presents long telomeres, giving them potential to proliferate during postnatal development and in response to cardiac injury. However, during the first two postnatal weeks, most CMs inactivate telomerase and shorten their telomeres. Telomere shortening leads to the appearance of dysfunctional damaged telomeres, chromosome fusions, micronuclei, and binucleation, and at the same time activates p21, ultimately leading to CM cell-cycle arrest. CMs with premature telomere shortening (P1 G3 *Terc*$^{-/-}$ CMs) precociously activate the DNA damage response at telomeres, form anaphase bridges, upregulate p21, and binucleate. These outcomes reinforce the role of telomere shortening in CM cell-cycle withdrawal.



Postnatal cardiomyocytes with telomere shortening activate the DNA damage response and form anaphase bridges and micronuclei. (**A**) Detail of telomere (Tel) Q-FISH and γH2AX/TnI immunofluorescence. Arrowheads indicate foci of the DNA-damage marker protein γH2AX at telomeres in a CM. Scale bars, 10 µm. (**B**) Confocal (left) and superresolution (right) images of DNA bridges in a dividing P8 CM. Arrowheads indicate a DNA bridge. Scale bars, 10 µm. (**C**) P8 CM with a micronucleus. Scale bar, 25 µm. The arrowhead indicates the micronucleus.



Selection of iPSCs with relatively long telomeres improves spontaneous cardiomyocyte differentiation efficiency. (**A**) Percentages of beating EBs during iPSC differentiation. Control, G1 iPSCs; iPSC^{lowT}, G1 iPSCs with relatively short telomeres; iPSC^{highT}, G1 iPSCs with relatively long telomeres. (**B**) Representative images showing α-actinin expression during iPSC differentiation to CMs. Scale bar, 80 µm. Nuclei are counterstained with DAPI.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2012-38449)
- Ministerio de Economía y Competitividad. FIS. RETICS (Red de Investigación Cardiovascular RD12/0042/0045)
- Asociación Española contra el Cáncer PI: Tania Aguado

SELECTED PUBLICATIONS

Bednarek D, Gonzalez-Rosa JM, Guzman-Martinez G, Gutierrez-Gutierrez O, Aguado T, Sanchez-Ferrer C, Marques IJ, Galardi-Castilla M, de Diego I, Gomez MJ, Cortes A, Zapata A, Jimenez-Borreguero LJ, Mercader N*, Flores I*. **Telomerase is essential for zebrafish heart regeneration**. Cell Rep (2015) 12: 1691-703
*Co-corresponding authors

Aix E, Gutiérrez-Gutiérrez Ó, Sánchez-Ferrer C, Aguado T, Flores I. **Postnatal telomere dysfunction induces cardiomyocyte cell-cycle arrest through p21 activation**. *J Cell Biol* (2016) 213: 571-83

Aguado T, Gutiérrez FJ, Aix E, Schneider RP, Giovinnazo G, Blasco MA, Flores I. **Telomere length defines the cardiomyocyte differentiation potency of mouse induced pluripotent stem cells**. *Stem Cells* doi: 10.1002/stem.2497, Sept 26, 2016

Fernández-Alvira JM, Fuster V, Dorado B, Soberón N, Flores I, Gallardo M, Pocock S, Blasco MA, Andrés V. **Short telomere load, telomere length, and subclinical atherosclerosis: the PESA study**. *J Am Coll Cardiol* (2016) 67: 2467-76

Latorre-Pellicer A, Moreno-Loshuertos R, Lechuga-Vieco AV, Sánchez-Cabo F, Torroja C, Acín-Pérez R, Calvo E, Aix E, González-Guerra A, Logan A, Bernad-Miana ML, Romanos E, Cruz R, Cogliati S, Sobrino B, Carracedo Á, Pérez-Martos A, Fernández-Silva P, Ruíz-Cabello J, Murphy MP, Flores I, Vázquez J, Enríquez JA. **Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing**. *Nature* (2016) 525: 561-65

Imaging cardiovascular inflammation and the immune response

RESEARCH INTEREST

Our lab studies immunity, in particular the innate arm of the immune system, which provides continuous support to tissues without undergoing somatic mutations. One of the main cellular components of innate immunity are macrophages, which perform specialized functions in all tissues. We study the mechanisms by which tissue-resident macropahges phagocytose other cells and also investigate the consequences of this activity. We pay special attention to macrophages in the heart, as both the signals that help program their properties and their function in healthy cardiac tissue are unknown. We are working to define both processes by using a model that specifically depletes these cells in adult mice. We also study neutrophils, the most abundant component of the innate immune system. Neutrophils are highly migratory leukocytes that eliminate microbes efficiently but can also inflict severe injury to tissues when they become abnormally activated in vessels. We focus our attention on intrinsic programs within neutrophils that boost immune protection but prevent vascular injury. Neutrophils also participate in homeostatic processes, and we study this activity in the bone marrow, the home of blood stem cells. A population of neutrophils enters the bone marrow each day (with circadian frequency) to regulate hematopoietic niches. We study this regulation and how it influences stem cell maintenance and tissue regeneration.

Head of Laboratory:
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Sandra Martín Salamanca

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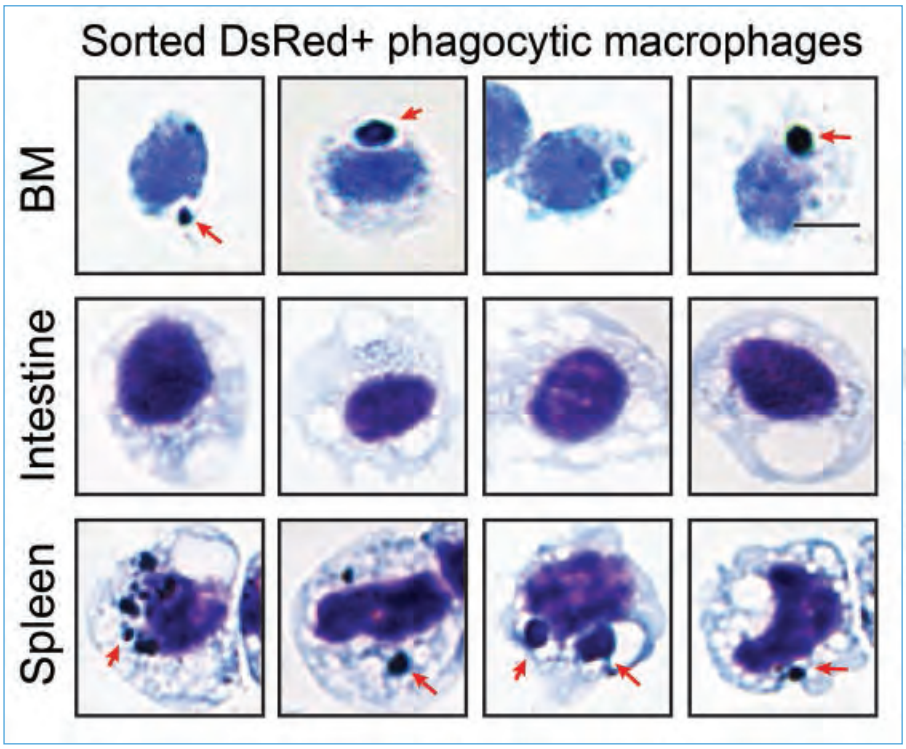
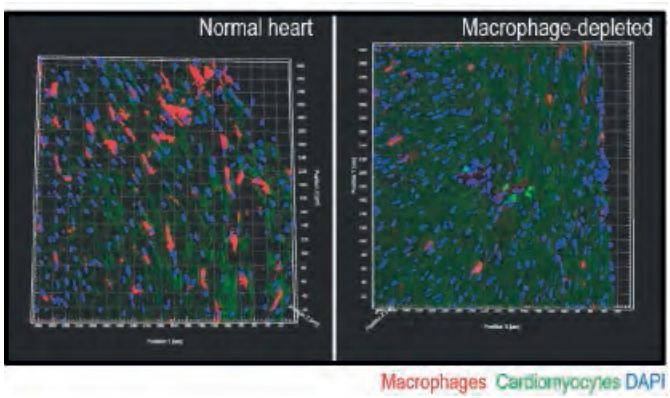
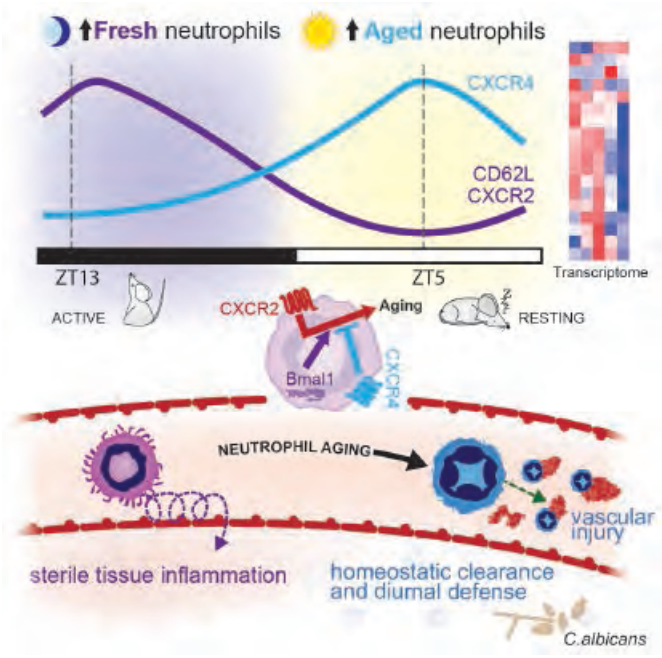
María Casanova Acebes



Phagocytic macrophages in tissues
Images of sorted phagocytic macrophages from the bone marrow (BM), intestine, and spleen, showing evidence of phagocytotic cell uptake and vacuolization (arrowheads).



Tissue-resident macrophages in the heart
3D images of heart sections, showing abundant macrophages (MHCII+, red) interacalated between cardiomyocytes (green) in a normal heart. In a new mouse model, treatment with a drug achieves dramatic depletion of these cells without decreasing other cardiac populations. Blue shows nuclei stained with DAPI.



Dynamics of neutrophils in homeostasis
Neutrophil numbers change with circadian frequency and undergo transcriptomic and phenotypic changes. These circadian changes are regulated by a neutrophil-intrinsic program regulated by the molecular clock and chemokine receptors. This program might be important for neutrophil clearance from tissues, diurnal defense, and prevention of vascular injury.

MAJOR GRANTS

- Ministerio de Economía y Competitividad (SAF2013-49662-EXP)
- Ministerio de Economía y Competitividad (ERA-NET Infect-ERA 2014 PCIN-2014-103 / 143 BActInfectERA)
- Ministerio de Economía y Competitividad (SAF2015-65607-R)
- Fundación La Marató-TV3 (120/C/2015)
- Comunidad de Madrid (P2010-BMD-2314)

SELECTED PUBLICATIONS

Leiva M, Quintana JA, Ligos JM and Hidalgo A. **Hematopoietic ESL-1 enables stem cell proliferation in the bone marrow by limiting TGFβ availability**. *Nat Commun* (2016) 7: 10222

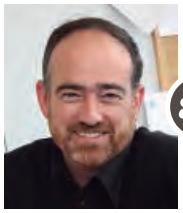
Silvestre-Roig C, Hidalgo A and Soehnlein O. **Neutrophil heterogeneity: implications for homeostasis and pathogenesis**. *Blood* (2016) 127: 2173-81

Adrover JM, Nicolas-Avila JA and Hidalgo A. **Aging, a temporal dimension of neutrophils**. *Trends Immunol* (2016) 37: 334-45

Rossaint J, Kuhne K, Skupski J, Van Aken H, Looney MR, Hidalgo A and Zarbock A. **Directed transport of neutrophil-derived extracellular vesicles enables platelet-mediated innate immune response**. *Nat Commun* (2016) 7: 13464

Di Scala M and Hidalgo A. **Angiogenin defines heterogeneity at the core of the hematopoietic niche**. *Cell Stem Cell* (2016) 19: 284-6

Functional genomics



RESEARCH INTEREST

In our lab we are interested in the gene regulatory networks that control the early stages of mammalian development and underlie cardiovascular disease. Our research focuses on understanding how cis-regulatory elements located in the non-coding portion of the genome influence the spatial and temporal expression of nearby genes, as well as how their activity is modulated by chromatin structure. We are also exploring how these elements are the target of variation that results in increased risk of human disease.

With these goals in mind, we have explored how 3-dimensional genome structure relates to gene expression in the cardiovascular system. Using high-resolution deep-sequencing-based chromatin conformation techniques in combination with CRISP/R genome editing tools, we have described how a gene-specific regulatory loop is established and is essential for proper expression of the ventricle-specific regulatory gene *Irx4*. We further showed that this loop is dependent on the architectural chromatin factor CTCF during embryonic development. At present we are applying similar approaches to investigate the regulatory basis of atrial fibrillation, the most common type of cardiac arrhythmia and a serious health burden worldwide.

We are also exploring the role of pluritopiency factors in the transition from the undetermined state to lineage commitment through the use of inducible genetic systems for Oct4 and Nanog. These studies are revealing how these factors control both initial repression and later activation of a critical subset of specification factors during development.

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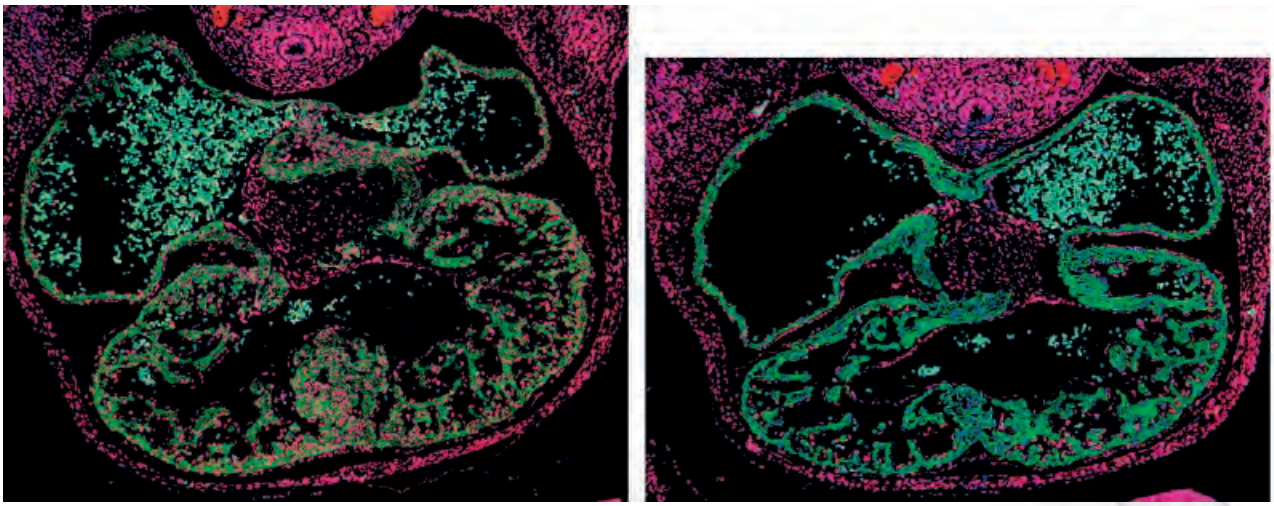
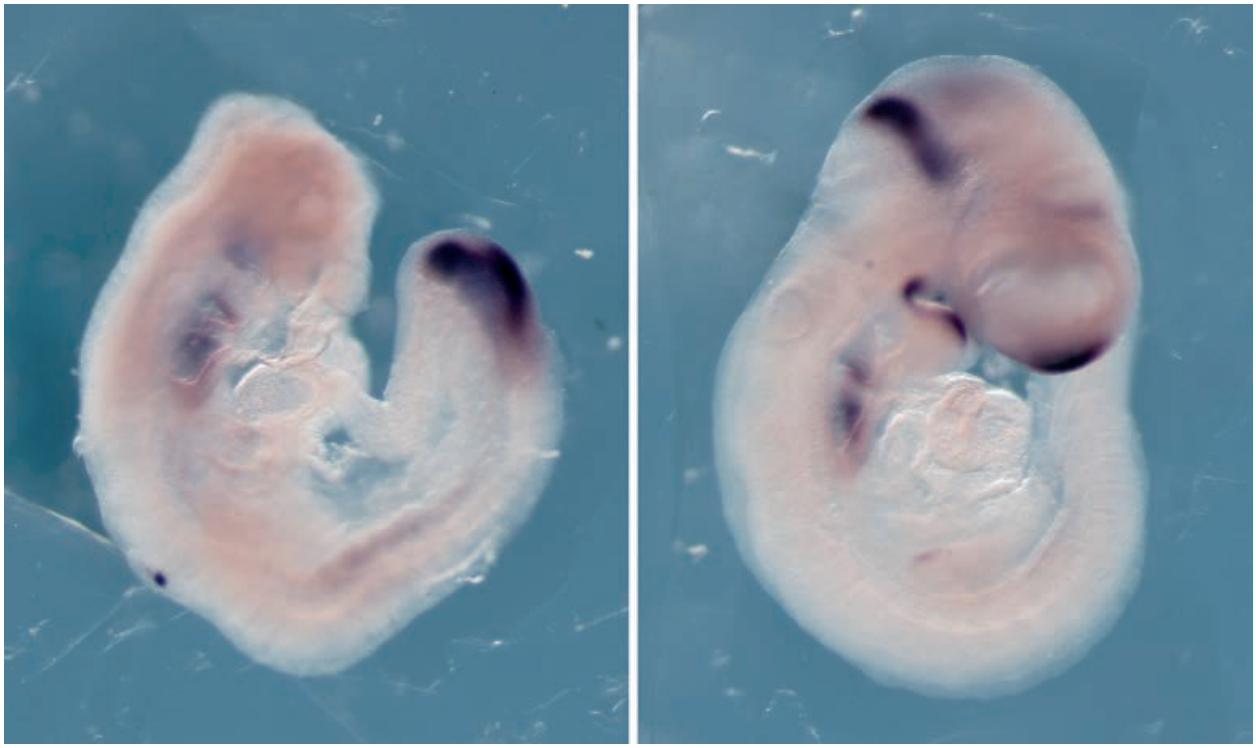


Loss of CTCF in the developing mouse heart leads to cardiac developmental arrest. Comparison of E11.5 control hearts (left) with mutant hearts (right) with conditional homozygous deletion of a Ctcf allele using an Nkx2.5-Cre line. Mutant hearts show a grossly disorganized interventricular septum, as well as thinning of the ventricular myocardial wall. Immunohistochemistry shows CTCF in red and cardiac troponin (CT3) in green. Nuclei are stained with DAPI (blue).



Expression of the developmental marker Fgf8 in control E9.5 embryos (left) and in embryos where expresson of the pluripotency factor Oct4 has been induced from E6.5 to E9.5 (right). While some Fgf8 expression domains are unchanged (such as the tail bud), others are clearly affected (anterior expression in the fronto-nasal mass and expression at the isthmus).

MAJOR GRANTS

- Ministerio de Economía y Competitividad BFU2014-57703-REDC
- Ministerio de Economía y Competitividad BFU2014-54608-P
- Ministerio de Economía y Competitividad BFU2015-72319-EXP

SELECTED PUBLICATIONS

Menchero S, Rayon T, Andreu MJ, Manzanares M. Signaling pathways in mammalian preimplantation development: Linking cellular phenotypes to lineage decisions. *Dev Dyn* doi:10.1002/dvdy.24471 (Epub Nov 18, 2016)

Rayon T, Menchero S, Rollan I, Ors I, Helness A, Crespo M, Nieto A, Azuara V, Rossant J, Manzanares M. **Distinct mechanisms regulate Cdx2 expression in the blastocyst and in trophoblast stem cells**. *Sci Rep* (2016) 6: 27139

Bogdanovic O, Smits AH, de la Calle Mustienes E, Tena JJ, Ford E, Williams R, Senanayake U, Schultz MD, Hontelez S, van Kruijsbergen I, Rayon T, Gnerlich F, Carell T, Veenstra GJ, Manzanares M, Sauka-Spengler T, Ecker JR, Vermeulen M, Gomez-Skarmeta JL, Lister R. **Active DNA demethylation at enhancers during the vertebrate phylotypic period**. *Nat Genet* (2016) 48: 417-26

Aguirre LA, Alonso ME, Badia-Careaga C, Rollan I, Arias C, Fernandez-Minan A, Lopez-Jimenez E, Aranega A, Gomez-Skarmeta JL, Franco D, Manzanares M. **Long-range regulatory interactions at the 4q25 Atrial Fibrillation risk locus involve PITX2c and ENPEP**. *BMC Biol* (2015) 13: 26

CNIC-UNIVERSITY OF BERN COLLABORATIVE PROGRAM

Development of the epicardium and its role during regeneration

RESEARCH INTEREST

In our group we aim to understand the cellular and molecular basis of heart regeneration. Unlike mammals, adult zebrafish have the capacity to regenerate their hearts upon injury to as much as a quarter of the cardiac ventricle with a liquid nitrogen cooled cryoprobe. As an early response, inflammatory cells are recruited to the damaged heart, followed by the expansion of the other layer of the heart, the epicardium, and the endocardium lining the cardiac lumen. This is followed by the formation of a transient scar. This fibrotic tissue is finally replaced by new cardiac muscle, the myocardium. Thus, regeneration occurs in the presence of a scar. We are studying how fibrosis influences heart regeneration. The epicardium is one source of the fibroblasts which contribute to cardiac fibrosis in response to cryoinjury. The epicardium also plays an important trophic role during heart regeneration. We are therefore also interested in understanding the formation of the epicardium during embryogenesis. Due to the small size and transparency of its embryos, the zebrafish offers a unique system for studying heart development. Using live imaging in zebrafish embryos, we are studying the mechanisms through which the proepicardial cells emerge from the pericardial wall and attach to the myocardium.

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Carolina García-Poyatos
Marcos Sande Melón
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Visiting Student:
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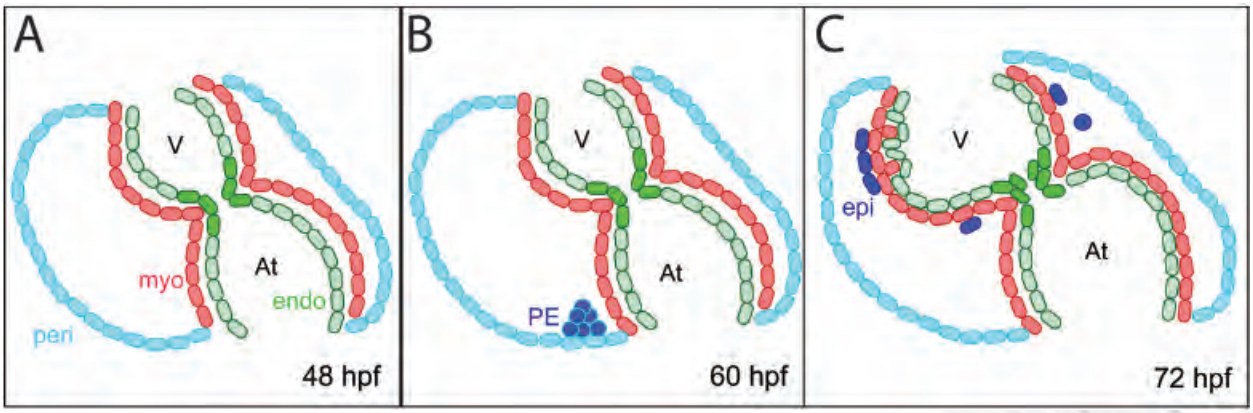

Epicardium development in the zebrafish. The developing heart tube in the zebrafish. Proepicardial (PE) cells delaminate from the pericardial mesothelium lining the pericardial cavity. PE cells are released into the cavity and attach to the surface of the ventricular myocardium. At, atrium; endo, endocardium, hpf, hours postfertilization; PE, proepicardium; peri, pericardium, v, ventricle.

MAJOR GRANTS

- European Commission. European Research Council Starting Independent Researcher Grant (ERC-337703 2013)
- Ministerio de Educación, Cultura y Deporte. FPU contract (FPU12/3007) PI: H. Sánchez Iranzo
- Ministerio de Economía y Competitividad. Posdoctoral contract (FPDI-2013-16319). PI: L. Andrés Delgado

SELECTED PUBLICATIONS

Cogliati S, Calvo E, Loureiro M, Guaras AM, Nieto-Arellano R, Garcia-Poyatos C, Ezkurdia I, Mercader, N, Vázquez J, Enriquez JA. **Mechanism of super-assembly of respiratory complexes III and IV**. *Nature* (2016) 539: 579-82

Andres-Delgado, L., Mercader, N., **Interplay between cardiac function and heart development**. *Biochim Biophys Acta* (2016)1863: 1707-16

Rodius S, Androsova G, Götz L, Liechti R, Crespo I, Merz S, Nazarov PV, de Klein N, Jeanty C, González-Rosa JM, Muller A, Bernardin F, Niclou SP, Vallar L, Mercader N, Ibberson M, Xenarios I, Azuaje F. **Analysis of the dynamic co-expression network of heart regeneration in the zebrafish**. *Sci Rep* (2016) 6: 26822

Di Donato V, De Santis F, Auer TO, Testa N, Sánchez-Iranzo H, Mercader N, Concordet JP, Del Bene F. **2C-Cas9: a versatile tool for clonal analysis of gene function**. *Genome Res* (2016) 26: 681-92

Bednarek D, González-Rosa JM, Guzmán-Martínez G, Gutiérrez-Gutiérrez Ó, Aguado T, Sánchez-Ferrer C, Marques IJ, Galardi-Castilla M, de Diego I, Gómez MJ, Cortés A, Zapata A, Jiménez-Borreguero LJ, Mercader N*, Flores I*. **Telomerase is essential for zebrafish heart regeneration**. *Cell Rep*. (2015) 12: 1691-703
*Co-corresponding authors

Genetic control of organ development and regeneration

RESEARCH INTEREST

We are interested in understanding the cellular basis of developmental processes and how this is controlled by transcription factor networks (TFN). We have developed genetic methods in the mouse that allow us to trace cell lineages using clonal analysis or functional mosaics. We have also established culture methods for the live analysis of developmental processes in embryonic stem cells and in the early mouse embryo. Using these new approaches, we have demonstrated the importance of cell competition in the early mouse embryo and in the cardiomyocyte lineage of the developing and adult heart. We are currently exploring the molecular and cellular mechanisms underlying cell-cell comparison and loser-cell elimination.

In recent years we have identified the role of *Meis* transcription factors in organogenesis, including limb, eye, cardiovascular, and hematopoietic system development. We have formulated new molecular models of Meis TFN activity underlying pattern formation and organ regeneration. Furthermore, we have identified Myc-driven cell competition as a strategy for stimulating the proliferation and replacement of adult cardiomyocyte populations, without compromising cardiac function. A current focus of the lab is the transcriptional control of cardiomyocyte proliferation in the adult heart and its impact on cardiac function and repair. Based on evidence from animal models, we are exploring the cardiac regenerative potential of Myc and the role of Meis in maintaining heart function in the adult mouse.

Head of Laboratory:
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Ghislaine Lioux
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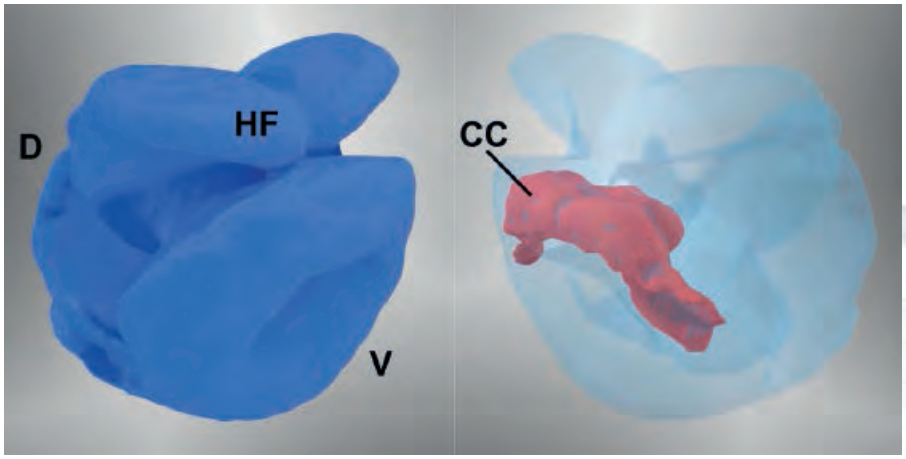
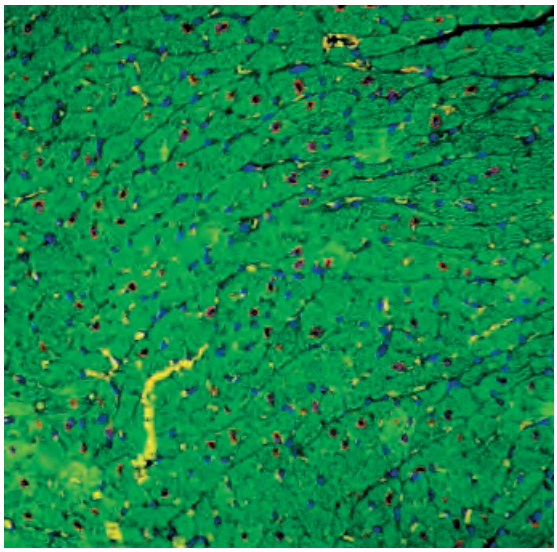
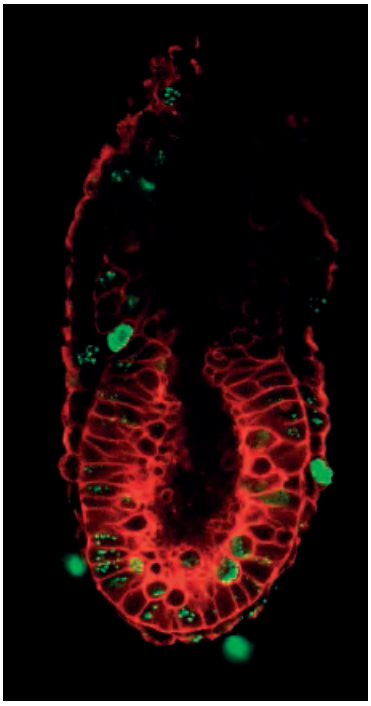
Rocío Sierra Muñoz
Susana Temiño Valbuena



Analyzing heart development by 3D imaging. Surface renderings of complete 3D reconstructions of the mouse embryo (blue) imaged using light-sheet microscopy. On the right, the embryo has been made transparent to show the geometry of the cardiac crescent (red, CC). HF, head fold; V, ventral; D, dorsal. Image: Isaac Esteban-Varela



Characterizing transcription factor function in the adult myocardium. Immunofluorescence analysis of the adult myocardium in a mouse in which *Myc* has been specifically deleted in cardiomyocytes. Troponin-T is shown in green and cell nuclei in blue, and cardiomyocyte nuclei are surrounded by PCM1 signal (red). Image: Noelia Muñoz



Pluripotent cells in the early mouse embryo. Very active cell division is detected in the epiblast of the early mouse embryo, which contains the pluripotent cells able to generate the new organism. At this stage, the pluripotent stem cell pool "cleans" the epiblast of suboptimal cells by cell competition. Cell membranes are shown in red, and chromatin in dividing cells is visualized by Ph3 immunofluorescence (green). Image: Covadonga Díaz-Díaz

MAJOR GRANTS

- Ministerio de Economía y Competividad. FIS RETICS (TERCEL: RD12/0019/0005)
- Ministerio de Economía y Competividad (BFU2015-71519-P)
- Ministerio de Economía y Competividad. Red de Excelencia Temática. (BFU2015-70193-REDT). PI and Network Coordinator: M Torres
- European Commission and Ministerio de Economía y Competividad. (PCIN-2015-020)
- Ministerio de Economía y Competividad. (EUIN2015-62897)
- Marie Sklodowska-Curie Innovative Training Networks (H2020-MSCA-ITN-2016) (GA nº 722427). PI and ITN Coordinator: M Torres
- Ministerio de Economía y Competividad. Juan de la Cierva Incorporación. (IJCI-2014-19108). PI: I. Delgado.
- Human Frontier Science Program. Long-term fellowship 2015. PI: K. Ivanovitch
- Ministerio de Educación, Cultura y Deporte. Predoctoral contract (FPU12/02114). PI: C. Díaz Díaz
- Ministerio de Economía y Competitividad. Predoctoral contract (BES-2013-064374) PI: A.C López
- Fundación La Caixa CNIC Severo Ochoa. Predoctoral Fellowship 2014. PI: N. Muñoz
- Fundación La Caixa CNIC Severo Ochoa. Predoctoral Fellowship 2015. PI: J A. Valvelde
- Ministerio de Educación, Cultura y Deporte. Predoctoral contract (FPU15/02955). PI: M.E. de la Cruz Crespillo

SELECTED PUBLICATIONS

Villa Del Campo C, Lioux G, Carmona R, Sierra R, Muñoz-Chápuli R, Clavería C, Torres M. **Myc overexpression enhances of epicardial contribution to the developing heart and promotes extensive expansion of the cardiomyocyte population**. *Sci Rep* (2016) 6: 35366

Clavería C, Torres M. **Cell Competition: Mechanisms and Physiological Roles**. *Annu Rev Cell Dev Biol* (2016) 32: 411-39

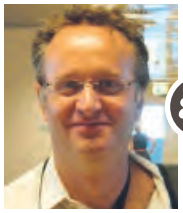
Delgado I, Torres M. **Gradients, waves and timers, an overview of limb patterning models**. *Semin Cell Dev Biol* (2016) 49: 109-15

Fernández LC, Torres M*, Real FX*. **Somatic mosaicism: on the road to cancer**. *Nat Rev Cancer* (2016) 16: 43-55
*Co-corresponding authors

Torres M. **Regeneration: Limb regrowth takes two**. *Nature* (2016) 533: 328-30

TECHNICAL UNITS

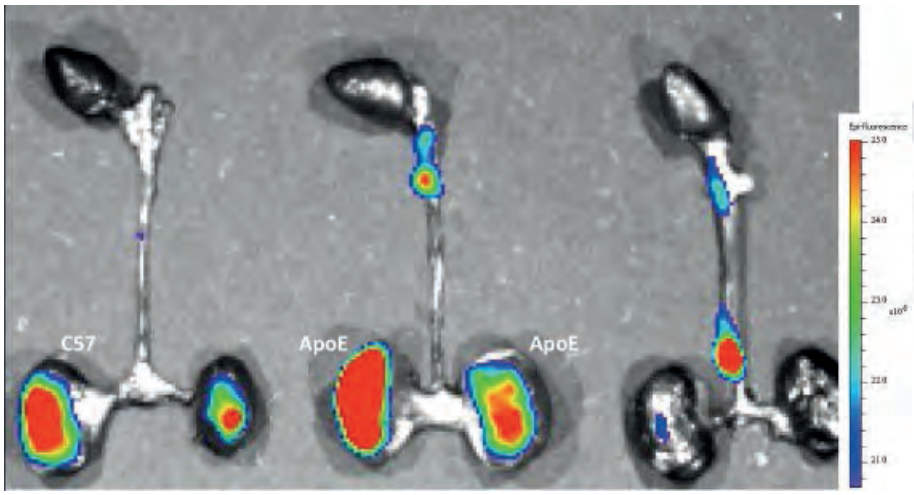
Advanced imaging
Bioinformatics
Cellomics
Comparative medicine
Genomics
Microscopy and dynamic imaging
Pluripotent cell technology
Proteomics/Metabolomics
Transgenesis
Viral vectors



Advanced imaging

RESEARCH INTEREST

The Advanced Imaging Unit (AIU) is a multidisciplinary group offering a range of services to CNIC scientists and carrying out its own research in imaging-related technologies. The three core areas of the AIU's research and service are 1) cardiovascular imaging, 2) nanomedicine and radiochemistry, and 3) metabolomics (research only). The AIU offers the CNIC support and expertise in cardiovascular imaging using five state-of-the-art modalities: MRI, X-ray CT, nuclear imaging (PET), ultrasound (echocardiography) and optical (2- and 3-dimensional luminescence and fluorescence). For its nanomedicine and radiochemistry program, the AIU has a dedicated nanotechnology and bioorganic chemistry laboratory focused on developing new nanotracers, molecular probes, and techniques for site-directed biofunctionalization of biomolecules (peptides, proteins, and antibodies). Currently the unit produces multifunctional nanoparticles for all imaging techniques available at the CNIC, and our research program enables the development of new cardiovascular probes for targeted imaging. The range of nanoparticles includes iron oxide, liposomes, carbon dots, and gold nanoparticles, and all of them are functionalized with specifc cardiovascular biomarkers. The Unit's radiochemistry laboratory is experienced in radiolabeling with ^{68}Ga and ^{89}Zr, providing the Center with in-house developed PET radiotracers for cardiovascular nuclear imaging. The CNIC is one of the few centers in Spain with this technology, situating the center at the forefront of radiochemistry research. On a daily basis, the imaging unit works with conventional (cyclotron obtained) radiotracers (^{18}F-FDG, ^{18}F-FMISO, ^{18}F-NaF, etc.) for the noninvasive assessment of different cardiovascular diseases. The Unit also has long experience in metabolic data analysis using ^{18}F-FDG PET, magnetic resonance spectroscopy (^{13}C, ^{31}P, ^{1}H) and mass spectrometry, as well as statistical and image and spectroscopic processing tools developed in-house. The Unit is also engaged in developing new techniques for cardiovascular imaging (PET, CT and MRI), which are tested and validated on small and large animal models and finally transferred to human applications. Our research in these areas ranges from technical developments and chemistry advances to in vitro studies and tracking of biological processes *in vivo*.



Nano-radiotracers for plaque detection. Plaque detection with a neutrophil-specific fluorescent nano-radiotracer in C57 and ApoE$^{-/-}$ mice.

Head of Unit:
Jesús Ruiz-Cabello Osuna

Postdoctoral Researchers:
Fernando Herranz
Jesús Mateo de Castro
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Jose Luis Izquierdo
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Carlos Velasco

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Lidia Miguel
Irene Godino
Cristina Moratilla

Visiting Scientists:
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Palmira Villa
Sandra Pérez Rial
Clara Uriel
Claudia Martínez
Ana Fernández
Lara García
Germán Peces-Barba
Sergio Garnica
Juan Miguel Parra

MAJOR GRANTS

- Instituto de Salud Carlos III. Desarrollo tecnológico en Salud (DTS16/00059) PI: Fernando Herranz
- Ministerio de Economía y Competitividad. Plan Nacional de Excelencia (SAF2016-79593-P) PI: Fernando Herranz
- Instituto de la Salud Carlos III. FIS-FEDER (PI14/01427) PI: Jesús Mateo
- Ministerio de Economía y Competitividad. SAF2014-58920-R PI: Samuel España
- Ministerio de Economía y Competitividad. SAF2014-59118-JIN. PI: Marco Filice
- Madrid-MIT M+Visión (MIT14 - X7118248R) PI: Arnoldo Santos
- Madrid-MIT M+Visión (PRMIT2013) PI: Samuel España
- European Commission FP7-PEOPLE-2013-ITN (CardioNext PITN-GA-2013-608027)
- European Commission FP7-PEOPLE-2010-ITN (Π-NET 264864) (NO CNIC).
- Ministerio de Sanidad y Consumo (CIBERES CB06/06/1090)

SELECTED PUBLICATIONS

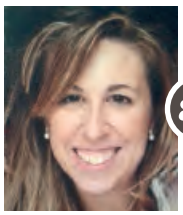
Viswanath P, Najac V, Izquierdo JL, Pankov A, Hong C, Eriksson P, Costello JF, Pieper RO, Ronen SM. **Mutant IDH1 gliomas down-regulate expression of monocarboxylate transporters**. *Oncotarget* (2016) 7: 34942

Marciello M, Pellico J, Fernandez-barahona I, Herranz F, Ruiz-Cabello J, Filice M **Recent advances in the preparation and application of multifunctional iron oxide and liposome-based nanosystems for multimodal diagnosis and therapy** *Interface Focus* (2016) 6: 20160055

Pellico J, Ruiz-Cabello J, Saiz-Alía M, del Rosario G, Caja S, Montoya M, Fernández de Manuel L, Morales M.P., Gutiérrez L., Galiana B., Enríquez J.A., and Herranz F. **Fast synthesis and bioconjugation of 68Ga core-doped extremely small iron oxide nanoparticles for PET/MR imaging** *Contrast Media Mol Imaging* (2016) 11: 203–10

Bujak R, Mateo J, Blanco I, Izquierdo-García JL, Dudzik D, Markuszewski MJ, Peinado VI, Laclaustra M, Barberá JA, Barbas C, Ruiz-Cabello J. **New Biochemical Insights into the Mechanisms of Pulmonary Arterial Hypertension in Humans.** *PLoS One*. (2016) 11: e0160505

Zahraei M, Marciello M, Lazaro-Carrillo A, Villanueva A, Herranz F, Talelli M, Costo R, Monshi A, Shahbazi-Gahrouei D, Amirnasr M, Behdadfar B, and Morales M.P. **Versatile theranostics agents designed by coating ferrite nanoparticles with biocompatible polymers** *Nanotechnology* (2016) 27: 255702



Bioinformatics

RESEARCH INTEREST

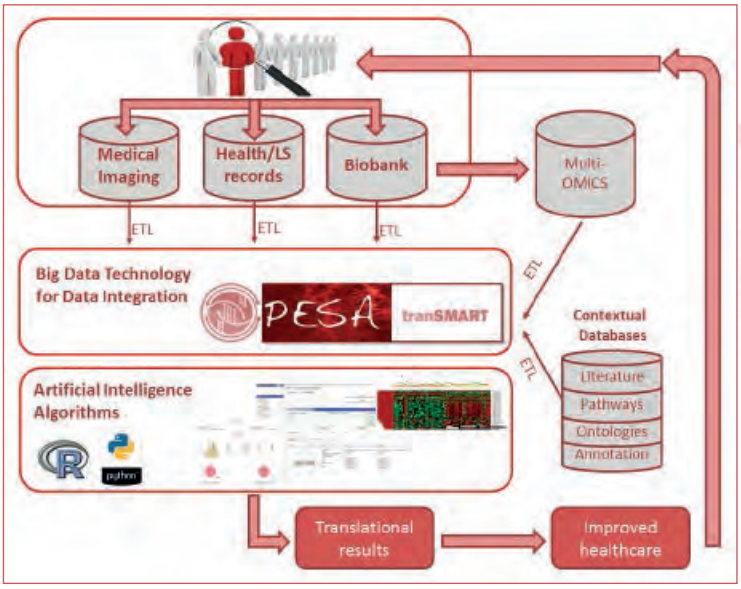
During 2016, the CNIC Bioinformatics Unit implemented new tools and algorithms in three areas of central importance to achieving excellence in biomedical research:

(i) **Big data infrastructure and artificial intelligence methods** to enable **precision medicine** in large cohort studies. The Unit has implemented a web-based warehousing system called tranSMART that enables the integration and analysis of high dimensional data from different sources. Currently, this application supports 3 large cohort studies at the CNIC: **PESA, IM-Joven, and AWHS**.

(ii) Analysis of DNA samples. A pipeline has been established for variant calling from NGS data and a web-based application has been implemented to ease access to results. We are currently working on *ad-hoc* filtering schemes for the prioritization of variants linked to hereditary cardiomyopathies.

(iii) Analysis of single-cell omics data. An analysis pipeline has been established for single-cell data generated with omics technologies and applied to several CNIC projects.

The Unit currently supports 21 CNIC groups and 3 technical units through these and previously established services: downstream analysis and mathematical models for omics technologies, transcriptomics data analysis, data integration, statistical analysis consultancy, administration of HPC infrastructure, modeling of protein structure, and lab automatization (LIMS). The Unit also provides training in bioinformatics through co-supervision of junior bioinformaticians and dedicated training courses in bioinformatics-related fields, such as the BMM9 Masters program and the CNIC Statistics Course).



Data warehousing system implemented by the CNIC Bioinformatics Unit to enable precision medicine through data integration in large cohorts using big data infrastructure and artificial intelligence methodologies.

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Jorge Aurelio Zamora

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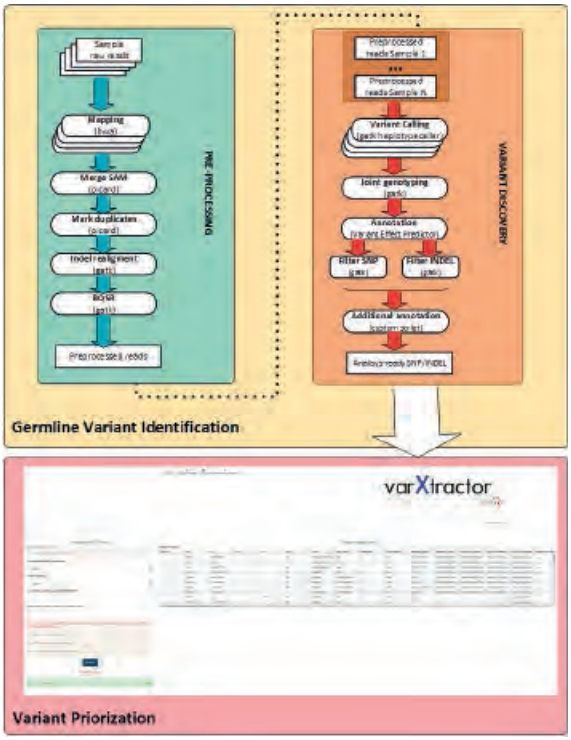
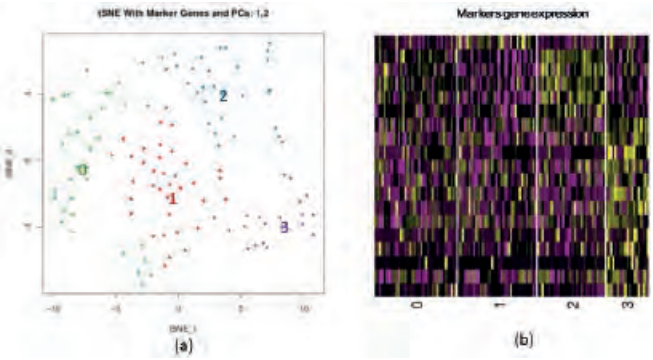
Girolamo Giudice
(from the Molecular Regulation of Heart Development and Disease Laboratory, led by Enrique Lara-Pezzi)
Victor Jiménez
(from the Integrin Signaling Lab, led by Miguel Angel del Pozo)
Carlos Martí
(from the Molecular Regulation of Heart Development and Disease Laboratory, led by Enrique Lara-Pezzi)
Wencke Walter
(from the Nuclear Receptor Signaling Laboratory, led by Mercedes Ricote)



Analysis pipeline for variant calling from NGS Data. Web-based application for ad-hoc filtering and results visualization.



scRNASeq data: (a) tSNE applied to scRNA-Seq data identified 4 cell clusters according to the expression of a combination of automatically selected markers. (b) Data generated by JA Nicolas (A. Hidalgo Lab) at the CNIC Genomics Unit and SIgN

MAJOR GRANTS

- European Commission. H2020-PERSONALISING HEALTH AND CARE (H2020-PHC-2014-two-stage). APERIM-GA633592.

SELECTED PUBLICATIONS

Menendez-Montes I, Escobar B, Palacios B, Gómez MJ, Izquierdo-Garcia JL, Flores L, Jiménez-Borreguero LJ, Aragones J, Ruiz-Cabello J, Torres M, Martin-Puig S. **Myocardial VHL-HIF signaling controls an embryonic metabolic switch essential for cardiac maturation**. *Dev Cell* (2016) 39: 724-39

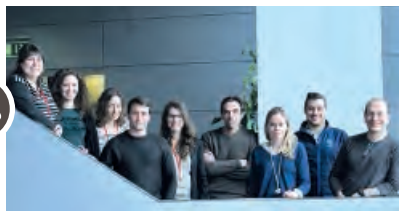
Enríquez JA, Sánchez-Cabo F, Vázquez J. **Hypothesis driven versus hypothesis-free: filling the gaps in CoQ biosynthesis.** *Cell Metab* (2016) 24: 525-26

Latorre-Pellicer A, Moreno-Loshuertos R, Lechuga-Vieco AV, Sánchez-Cabo F, Torroja C, Acín-Pérez R, Calvo E, Aix E, González-Guerra A, Logan A, Bernad-Miana ML, Romanos E, Cruz R, Cogliati S, Sobrino B, Carracedo Á, Pérez-Martos A, Fernández-Silva P, Ruíz-Cabello J, Murphy MP, Flores I, Vázquez J, Enríquez JA. **Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing.** *Nature* (2016) 535: 561-5

Giudice G, Sánchez-Cabo F, Torroja C, Lara-Pezzi E. **ATtRACT-a database of RNA-binding proteins and associated motifs**. *Database* (*Oxford*) (2016) *baw035*

Walter W, Sánchez-Cabo F,* Ricote M*. **GOplot: an R package for visually combining expression data with functional analysis**. *Bioinformatics* (2015) 31: 2912-4
*Co-corresponding authors

D'Amato G, Luxan G, Del Monte-Nieto G, Martinez-Poveda B, Torroja C, Walter W, Bochter MS, Benedito R, Cole S, Martinez F, Hadjantonakis AK, Uemura A, Jimenez-Borreguero LJ, de la Pompa JL. **Sequential Notch activation regulates ventricular chamber development**. *Nat Cell Biol* (2016) 18: 7-20



Cellomics

RESEARCH INTEREST

The Cellomics Unit provides the CNIC with the two principal cell analytical techniques, flow cytometry and high content screening (HCS), and supports quantitative image-based research.

In 2016, we implemented automated analysis of multidimensional cytometry data. We co-organized the **"High-Content Screening Conference"** at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, and also co-organized the CNIC Conference on **"Mechanical forces in phisiology and disease"**. We also established a novel high content analysis (HCA) tool that obtains cytoskeletal rearrangement signatures from the accurate quantification of features, revealing cytoskeletal organization at subcellular resolution (Fig. 2). This tool enabled us to investigate Rab8-induced cytoskeletal reorganizations using siRNA knockdown and drug inhibitors, establishing the role of Rab8 in directional cell migration and delineating the molecular pathways involved in this process. In partnership with the Genetic Control of Organ Development and Regeneration laboratory, we have successfully developed ESC-Track, a computer workflow for 4D segmentation, tracking, lineage tracing, and dynamic context analysis of ESCs. ESC-Track is the only method currently available that enables 4D tracking of cells in the context of both lineage and neighborhood. The Unit has also developed customized image analysis tools for the quantification of macrophages, adipocytes, and collagen or elastin in immunohistological tissue sections and the analysis of lipid droplet subcellular organization and mitochondrial fragmentation in confocal fluorescence images.

Head of Unit:
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Research Scientists:
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Laura Fernandez
Daniel Jimenez

Predoctoral Researcher:
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Technicians:
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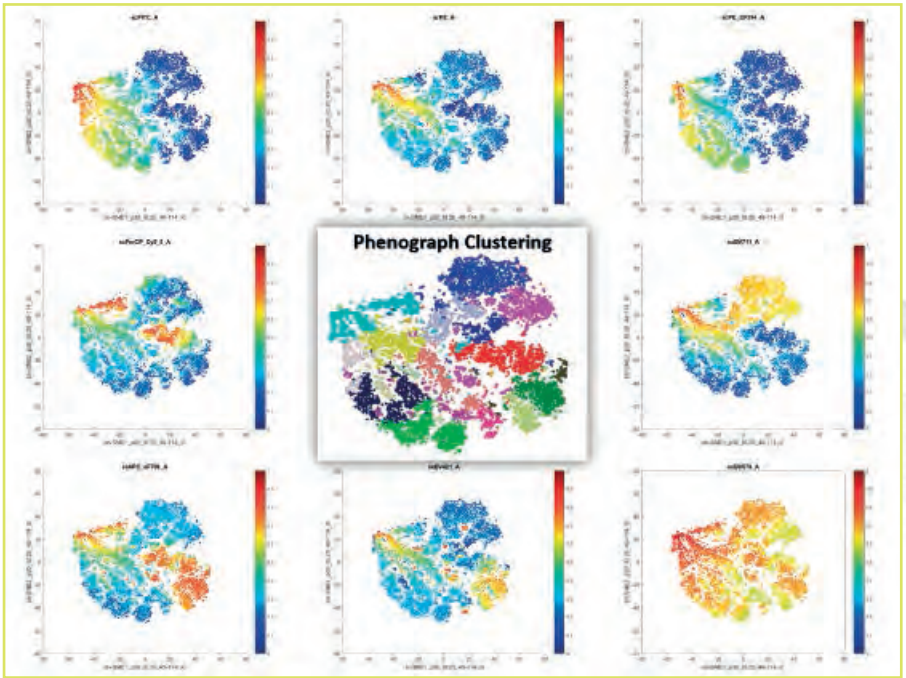
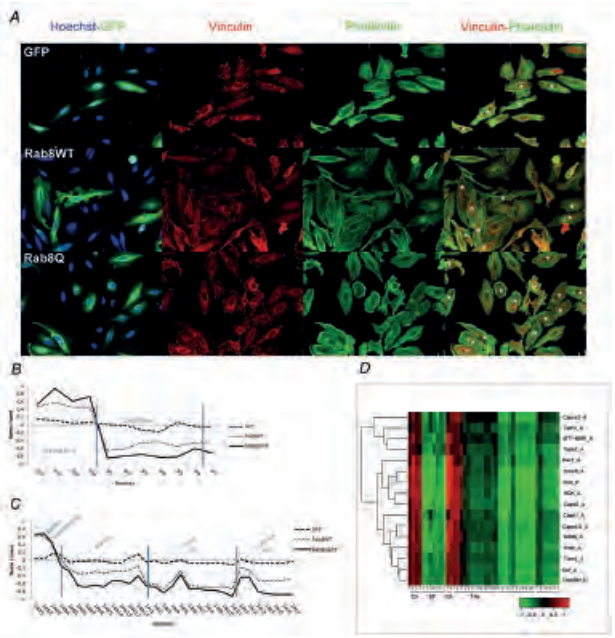
Mariano Vitón
Irene Palacios Doiztua
Elena Prieto

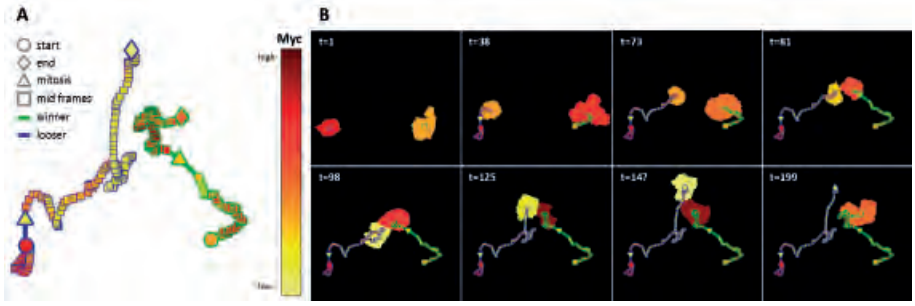
Visiting Scientist:
Marco Cordani



Automated analysis of high dimensional (spectral) cytometry data in mouse lymph node for detection of dendritic cells. Phenograph clustering is used to automatically detect cell populations, represented in a t-SNE map obtained with dimensionality-reduction techniques. Color-coded plots of fluorochrome expression allow identification of populations stained with MHC II (FITC), XCR1 (PE), CD19 (PE-CF59), Ly6C (PerCP_Cy_5.5), CD4 (BV711), CD8 (APC-Fire750), CD103 (BV421), and CD45 (BV570).



HCA analysis of Rab8-promoted cytoskeletal rearrangements: profiling and resulting hierarchical clustering analysis of the effect of siRNAs. HeLa cells expressing GFP (GFP), Rab8Q67L–GFP (Rab8Q), or Rab8WT-GFP (Rab8WT) were stained with phalloidin, anti-vinculin, and Hoechst to reveal actin, focal adhesions (FA), and nuclei. **A)** Representative confocal images. **B,C)** HCA phenotypic profiles were plotted as normalized z values of FA and actin features. **D)** HeLa cells transfected with nontargeting siRNA (Ctrl) or siRNAs targeting the indicated genes (right) were then transfected with Rab8WT-GFP and analyzed by HCA as in B and C. The heatmap shows unsupervised hierarchical clustering of phenotypic profiles.



ESC-T tracking and representation of cell trajectories and contacts and their relationship to GFP expression. mESCs expressing GFP and tdTomato were imaged every 7 minutes by 3D confocal microscopy (Z stacks spaced at 2 µm) and tracked using ESC-T. **a)** Trajectories and color-coded GFP normalized intensity values were obtained at each time-point using ESC-T. Cell coordinates are presented at each time point, with squares color-filled according to the GFP intensity. Mitotic events and starting and final locations are represented by triangles, circles, and diamonds, respectively. Trajectories are highlighted in green and blue. **b)** Video stills obtained at the indicated time points, combining the GFP expression levels and trajectories as in (a).

MAJOR GRANTS

- Ministerio de Economía y Competitividad (BIO2014-62200-EXP)
- European Union (641639) (H2020 ITN-BIOPOL)

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Bravo-Cordero JJ, Cordani M, Soriano SF, Diez B, Munoz-Agudo C, Casanova-Acebes M, Boullosa C, Guadamillas MC, Ezkurdia I, Gonzalez-Pisano D, Del Pozo MA, Montoya MC. **A novel high content analysis tool reveals Rab8-driven actin and FA reorganization through Rho GTPases and calpain/MT1.** *J Cell Sci* (2016) 129: 1734-49

Rallon NI, Mothe B, Lopez Bernaldo DE Quiros JC, Plana M, Ligos JM, Montoya MC, Muñoz MA, Esteban M, Garcia F, Brander C, Benito JM; RISVAC03 Study Group. **Balance between activation and regulation of HIV-specific CD8 T cells response after MVA-B therapeutic vaccination.** *AIDS* (2016) 30: 553-62

Pellico J, Ruiz-Cabello J, Saiz-Alia M, Del Rosario G, Caja S, Montoya MC, Fernandez de Manuel L, Morales MP, Gutierrez L, Galiana B, Enriquez JA, Herranz F. **Fast synthesis and bioconjugation of Ga core-doped extremely small iron oxide nanoparticles for PET/MR imaging.** *Contrast Media Mol Imaging* (2016) 11: 203-10

Leiva M, Quintana JA, Ligos JM, Hidalgo A. **Haematopoietic ESL-1 enables stem cell proliferation in the bone marrow by limiting TGFbeta availability.** *Nat Commun* (2016) 7: 10222

Comparative medicine

RESEARCH INTEREST

The Unit develops and manages laboratory animal models to reproduce the principal human cardiovascular diseases, working closely with the CNIC research teams and apllying the 3 Rs. The Unit tries to refine these animal models by identifying factors that could interfere with research project aims, be a source of non-representative data, or have a major impact on animal welfare.

The Comparative Medicine Unit's support for in vivo work at the CNIC is organized into five core work areas.

- Animal Husbandry. The Unit's technicians, managers and veterinarians are trained to work under the facility's SPF conditions and take charge of the daily husbandry of the animal colonies. The Unit enacts an environmental enrichment program to support species-specific behaviors to maximize animal welfare and wellbeing.

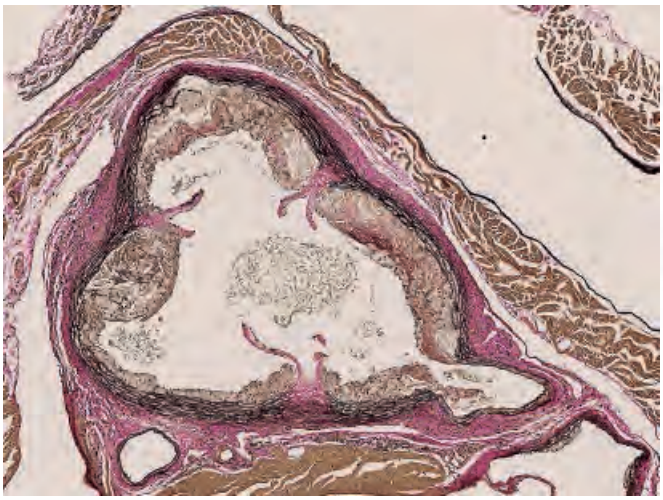
- Pathology Core (PC). The Histopathology Laboratory provides specialized hispathological services including animal necropsy, paraffin and OCT processing and sectioning, histochemical and immunohistochemical staining of tissue sections, digital scanning and image analysis, optical projection tomography with an OPT 3001 scanner, and general support to CNIC researchers with phenotyping and histopathological evaluation of their animal models.

- Phenotyping Core (PhC). In this area, we continue to provide technical support to the CNIC research groups. We perform analysis of hematology, clinical biochemistry, and coagulation and tests of electrocardiography and blood pressure measurements.

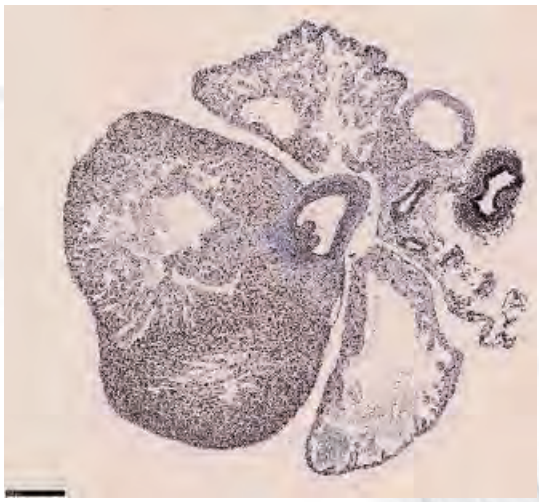
- Veterinary Medicine and Experimental Surgery Core (VMESC). The VMESC provides highly specialized expertise in the surveillance and monitoring of animal health status, disease follow-up, development of surgical animal models with enphasis on minimally invasive procedures, life support, setting up new experimental strategies that reproduce human cardiovascular diseases, and acquisition of pathophysiological data. The VMESC team is run by two clinical veterinarians with extensive expertise in laboratory animal science and four specialist veterinary technicians.

- Quality Control Core (QCC). The QCC follows the recommendations of the latest FELASA report (Laboratory Animals 2014, 48(3): 178-192).

The Comparative Medicine Unit maintains ISO 9001 accreditation for all five core work areas.

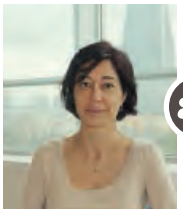


Atheroma plaques in a mouse aortic valve stained with Elastic Van Gieson



Anti Ki67 antibody immunostaining in a mouse neonate heart

Genomics



Head of Unit:
Ana Dopazo

Graduate Technicians:
Rebeca Álvarez
Alberto Benguría
Sergio Callejas
Estrella Esquivel

Technicians:
Eduardo Gil
Gema González
Álvaro Merchán

RESEARCH INTEREST

The Genomics Unit currently focuses on second generation sequencing (NGS) technologies for genome analysis using the Illumina HiSeq 2500 and MiSeq sequencers.

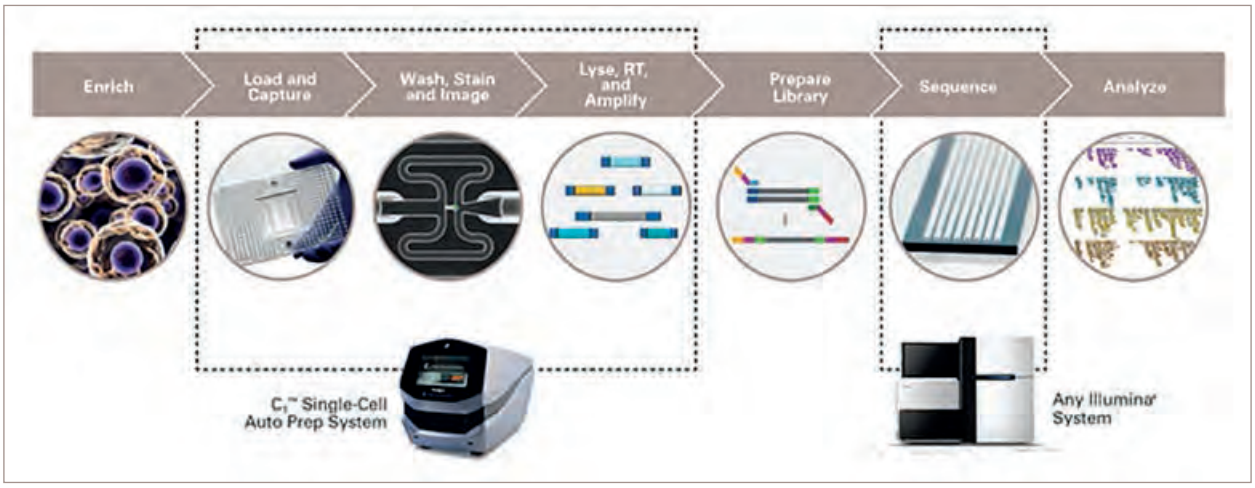
The Unit provides these cutting-edge genomic technologies to the scientific community at the CNIC and beyond, offering a wide variety of NGS applications (RNA Seq, Low input RNA Seq, small RNA-Seq, ChIP Seq, PCR Seq, Exome Sequencing, targeted resequencing, etc.). On each sequencing project the Unit's tasks include project consultation, sample quality control (QC), sample library preparation, and data generation. Several of the top CNIC scientific publications in 2015 and 2016 include NGS experiments performed in the Genomics Unit.

One of the team's scientific and technological research interests focuses on the study of the transcriptome at the single-cell level. The Unit has performed single-cell RNA seq in different cell types using the Fluidigm C1 Single-Cell Auto Prep System. This microfluidic device can isolate up to 96 cells and then process them to produce pre-amplified single-cell cDNA libraries for Illumina mRNA sequencing.

A key development of the Unit in 2016 was full automatization from cell capture to sequence-ready RNA seq libraries. This is essential when working at the single-cell level because automation allows to handle the required number of samples per experiment. By using an open liquid handling platform, the Unit's team has automated the downstream processing of C1 chips, from cDNA QC to the consolidation of samples from multiple chips to standard 96-well plates, followed by library construction, pooling, and QC. Captured cells can be selected for further RNA seq sequencing based on imaging data.

Other services include DNA fragmentation using a Covaris E220 ultrasonicator and the maintenance and management of the CNIC's real-time PCR instruments.

In addition to providing these high-quality genomics services, the Unit performs its own research.



Single cell trancriptome analysis workflow using Fluidigm's C1 Single-Cell Auto Prep System

MAJOR GRANTS

- Ministerio de Economía y Competitividad. FIS (PI14/02120)
- Ministerio de Economía y Competitividad. EXPLORA Tecnología (BFU2014-62250-EXP)

SELECTED PUBLICATIONS

Municio C, Soler Palacios B, Estrada-Capetillo L, Benguria A, Dopazo A, García-Lorenzo E, Fernández-Arroyo S, Joven J, Miranda-Carús ME, González-Álvaro I, Puig-Kröger A. **Methotrexate selectively targets human proinflammatory macrophages through a thymidylate synthase/p53 axis.** *Ann Rheum Dis* (2016) 75: 2157-65

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Microscopy and dynamic imaging

RESEARCH INTEREST

The Microscopy and Dynamic Imaging Unit is one of the largest light imaging core facilities in Spain. In addition to state-of-art light and confocal microscopes, it maintains and supports advanced technologies in super-resolution, FLIM, single molecule, non-linear, and mesoscopic imaging, linked to customized image analysis. In 2016 the Unit provided more than 20 000 hours of equipment time and supported more than 230 users, including scientists from outside Spain.

The Unit is part of the Advanced Infrastructure for Translational Imaging at the CNIC that has been selected for the Spanish Unique Scientific and Technical Infrastructure (ICTS-ReDib). This facility is accessible to national and international scientists wishing to use the large variety of equipment and high-end technologies in super-solution and FLIM imaging.

Our major scientific achievements of 2016 are related to original applications of super-resolution and FLIM imaging and post-processing image analysis. In collaboration with the CeSI Foundation at the University G. d'Annunzio, Chieti-Pescara, Italy, we used STED-FLIM imaging to demonstrate the direct interaction between CD9 and Trop2 localized in large domains on the plasma membrane of a variety of cancer cell lines. With the CNIC Molecular Cardiology group, we optimized STED imaging to define the organization of RyR2 clusters in wild type and mutant mice. With the Instituto de Ciencia de Materiales and the Hospital Univ. Ramón y Cajal (CSIC, Madrid), we have demonstrated, through a combination of SHG-FLIM imaging approaches in mice, the organ distribution and accumulation of thermal nanoprobes designed for biomedical applications.

Two ongoing super-resolution projects with the Ospedale San Raffaele in Milan, Italy examine cellular stress proteins and molecular markers of chronic lymphatic leukemia, with the aim of resolving the kinetics of assembly of signaling nanoclusters in the endoplasmic reticulum and in leukemia cells from patients.

The first Spanish National School in Super-Resolution Microscopy was organized in partnership with Leica Microsystems, the leading company in STED nanoscopy. Participants from a wide range of scientific backgrounds came from Spain and abroad, and included facilities managers, PhD students, and postdoctoral fellows.

The Unit also continued its training activities through one-to-one programs and workshops, and contributed to the CNIC-JOVEN training plan (ACERCATE, CICERONE and the Master Program) through theoretical and practical sessions.

Head of Unit:
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Staff Scientists:
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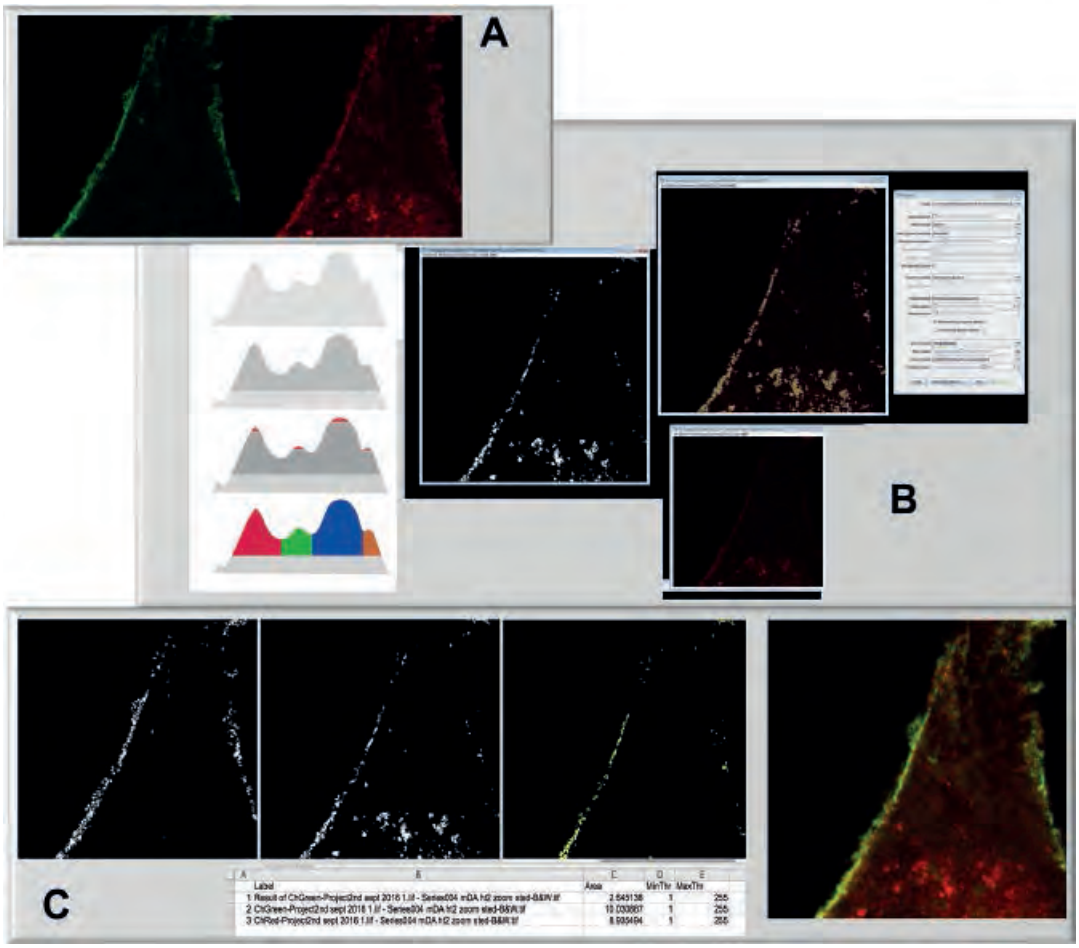
Antonio Manuel Santos Beneit
Elvira Arza
Veronica Labrador Cantarero

Visiting Scientists
Luca Pavesi
Paolo Ciufici
Jorge Ripoll



Quantitative analysis of coincident areas in STED images.
The nanostructured distribution of two membrane proteins in the cell membrane was quantified using recently published algorithms (1) that identify individual foci and clusters of each protein independently and measure the coincident ones.

A- Example of two STED images of proteins in MDA cell plasma membrane stained with 488/561-FAB-I fragments
B- Detection and quantification of clusters
C- Binary masks of the cluster areas detected in each image and quantification of the overlay (in yellow)
D- Composite STED image

(1) *Herbert AD, Carr AM, Hoffmann E (2014) PLoS ONE 9(12): e114749.*

SELECTED PUBLICATIONS

Bersini S, Gilardi M, Arrigoni C, Talo G, Zamai M, Zagra L, Caiolfa V, Moretti M. **Human in vitro 3D co-culture model to engineer vascularized bone-mimicking tissues combining computational tools and statistical experimental approach.** *Biomaterials* (2016) 76: 157-72

Garcia-Quintans, N., Sanchez-Ramos, C., Prieto, I., Tierrez, A., Arza, E., Alfranca, A., Redondo, J. M., and Monsalve, M. **Oxidative stress induces loss of pericyte coverage and vascular instability in PGC-1alpha-deficient mice.** *Angiogenesis* (2016) 19, 217-228

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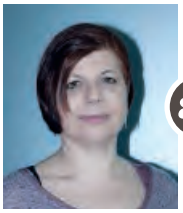
Pluripotent cell technology



RESEARCH INTEREST

The main focus of Pluripotent Cell Tehcnnoly Unit (PCTUnit) is to support CNIC scientists and their direct collaborators in their work with mouse and human stem cells. Our highly qualified staff members offer individualized training in successful stem cell culture, state-of-the-art protocols and expert advice and tecniques for proper maintenance and differentiation of stem cells and somatic cell reprogramming. In order to provide CNIC researchers with a suitable workspace, the PCTUnit houses two culture rooms, each devoted exclusively to mouse or human stem cells. Moreover, by supplying scientists with validated and standardized reagents we ensure experimentally reliability and reproducibility.

In 2016 the Unit continued to facilitate the generation of genetically-modified mice through homologous recombination in mouse embryonic stem cells (mESCs). Procedures for obtaining quality-controlled genetically modified mESCs are an essential requirement for germline transmission and the generation of mutant mice, but are labour-intensive and technically demanding. In this area, our staff takes charge of all the key steps of the gene targeting protocol: electroporation of the targeting vector, selection, karyotyping, and the preparation of cells for appropriate blastocyst microinjection. On request, we also assist researchers in the design of the targeting vector, screening stategy by Southern blot, and qPCR.

The Unit also applies its wide expertise in genetic modification using CRISPR/Cas technology and mESC derivation from mutant mouse lines to create in vitro pluripotent cell models. We use these technologies to supply CNIC researchers with knockout stem cell lines for a wide range of research projects. Our current goal is to improve the efficiency of gene editing using different genome insertion and deletion stategies based on different systems for CRISPR/cas9 complex delivery to stem cells.

Head of Unit:
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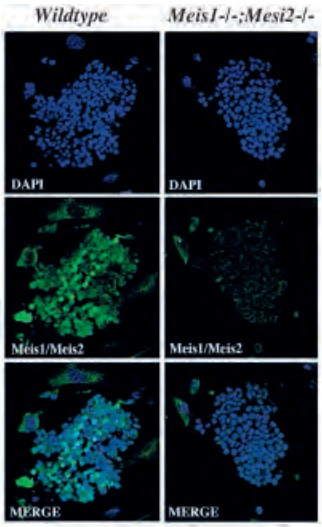
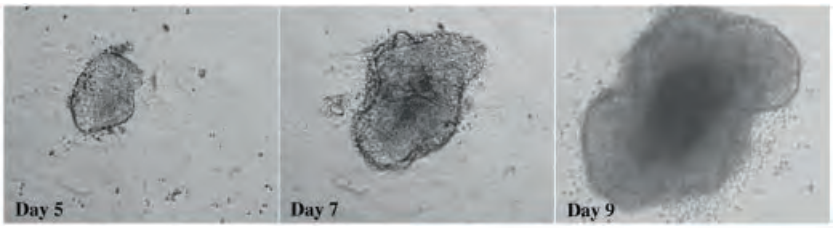
Carles Moreno



Immunocytochemistry analysis showing lack of Meis1/2 expression in diffretrentaied Meis1-/-; Mesi2-/- double knockout mESCs generated using the CRISPR/Cas9 system.



Phase contrast micrographs showing stages of the inner cell mass (ICM) outgrowth from an isolated blastocyst during the derivation of mouse embryonic stem cells.

SELECTED PUBLICATIONS

Gomez-Salinero JM, Lopez-Olaneta MM, Ortiz-Sanchez P, Larrasa-Alonso J, Gatto A, Felkin LE, Barton PJ, Navarro-Lerida I, Angel Del Pozo M, Garcia-Pavia P, Sundararaman B, Giovinazzo G, Yeo GW, Lara-Pezzi E. The calcineurin variant CnAbeta1 controls mouse embryonic stem cell differentiation by directing mTORC2 membrane localization and activation. *Cell Chem Biol* 23: 1372-82

Aguado T, Gutierrez FJ, Aix E, Schneider RP, Giovinazzo G, Blasco MA, Flores I. **Telomere length defines the cardiomyocyte differentiation potency of mouse induced pluripotent stem cells.** doi: 10.1002/stem.2497 (Epub 2016 Sep 26)

Proteomics/Metabolomics

RESEARCH INTEREST

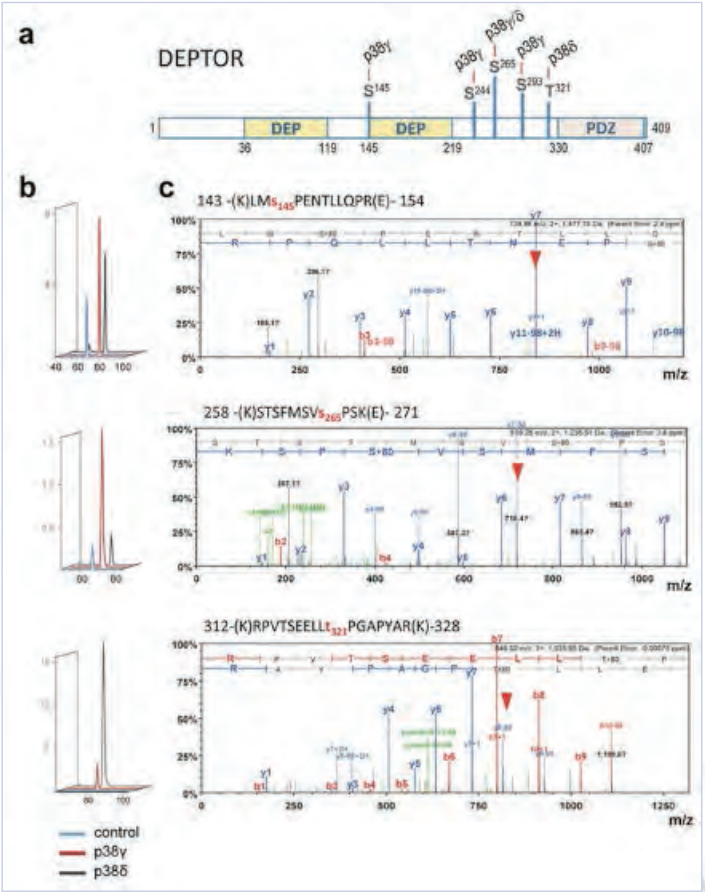
The CNIC Proteomics Unit is dedicated to technological innovation and the development of new methods of interest to the research community. Throughout 2016, the Unit worked on improvements to quantitative analysis of protein expression by shotgun and targeted proteomics using high-throughput technologies based on nanoHPLC coupled to mass spectrometry. The Proteomics Unit houses several nano-HPLC systems coupled to state-of-art mass spectrometers for deep proteome analysis.

During 2016 continuous progress was made in quantitative proteomics approaches, mainly using stable isobaric labeling (iTRAQ and TMT). Particular improvements were made in the development of chromatographic conditions for peptide fractionation, and optimization of the recently incorporated Orbitrap QExactive HF mass spectrometer. We also made progress in the statistical analysis of TMT-derived quantitative data and systems biology interpretation using algorithms developed in house.

These approaches are also being applied to the quantitative analysis of post-translational modifications, including analyses based on database searches and on peptide enrichment. For biomarker discovery in the clinical setting, we are analyzing dozens of plasma samples using depletion protocols of the most-abundant proteins and isobaric labeling. The use of non-depleted samples is under evaluation for the clinical setting.

We are also developing our technological and statistical methodologies for data-independent scanning acquisition mode, which mixes targeted and shotgun approaches, based on signal-independent fragmentation. This experimental approach has been applied to the analysis of the superassembly mechanism of mitochondrial respiratory complexes III and IV.

This robust analytical platform, together with our recognized experience in the field, enables us to manage large research projects that require qualitative and quantitative proteomic approaches to measure differential protein expression, characterize posttranslational modifications, and map protein-protein interactions in different biological systems. We have improved the quantitative proteomics pipeline at each stage, significantly improving the sensitivity and dynamic range for the analyzed biological systems.



Mass spectrometry analysis of DEPTOR phosphorylation by p38γ and p38δ kinases in vivo by. (a) DEPTOR phosphorylation sites. (b) Quantitative analysis of phosphorylation. (c) MS/MS spectra of each phosphopeptide, showing sequence and assignation of the modified sites.

Modified from González-Teran et al. *Nat Commun* (2016) 7: 10477.

Head of Unit:
Juan Antonio López

Support Scientists:
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Emilio Camafeita
Iakes Ezkurdia

Technicians:
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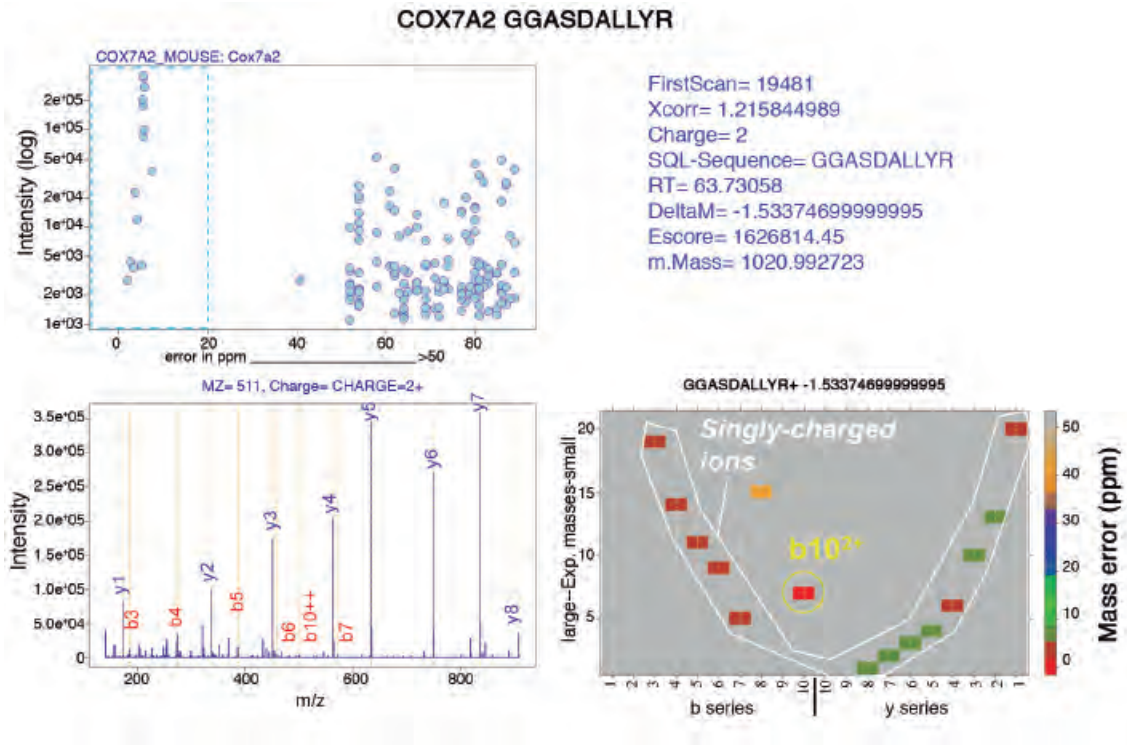
Rocío Campo
Ricardo Magni



Amino acid sequence of SCAF1. Specificity of MS/MS fragmentation series used to generate quantitative peptide profiles for COX7A2 peptide using Vseq, an in-house program written in R. Top: Intensity vs fragment mass error plot. *Bottom left*: representative MS/MS spectrum of the peptide, indicating the matched fragments. *Bottom right*: Color coded diagram of the mass error of fragments ranked according their m/z values and their correspondence with theoretical fragmentation series. Modified from Cogliati et al. *Nature* (2016) 539: 579–582.

SELECTED PUBLICATIONS

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Cogliati S, Calvo E, Loureiro M, Guarás AM, García-Poyatos C, Nieto-Arellano R, Ezkurdia I, Mercader N, Vázquez J, Enríquez JA. **Mechanism of superassembly between respiratory complexes III and IV**. *Nature* (2016) 539: 579–82

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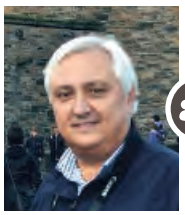
Latorre-Pellicer A, Moreno-Loshuertos R, Lechuga-Vieco AV, Sánchez-Cabo F, Torroja C, Acín-Pérez R, Calvo E, Aix E, González-Guerra A, Logan A, Bernad-Miana ML, Romanos E, Cruz R, Cogliati S, Sobrino B, Carracedo A, Pérez-Martos A, Fernández-Silva P, Ruiz-Cabello J, Murphy MP, Flores I, Vázquez J, Enríquez JA. **Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing**. *Nature* (2016) 535: 561-5

Transgenesis



RESEARCH INTEREST

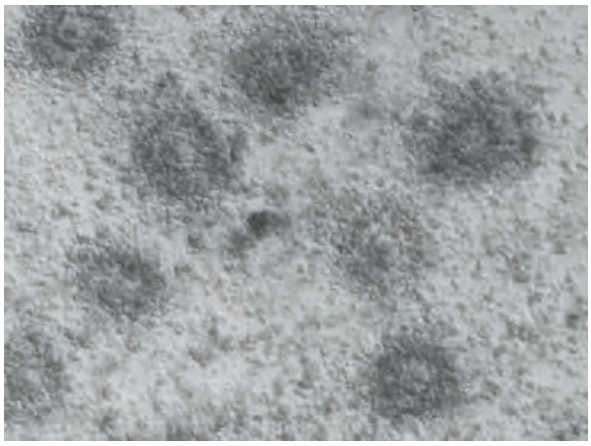
The Unit's main activities are rederivation of mouse strains, production of genetically modified mice, and cryopreservation of mouse strains. Rederivation, always done by embryo transfer, cleanses mouse strains of potential infective agents and is used to set up colonies in the SPF zone of the Comparative Medicine Unit. Genetically modified mice are produced according to the requirements of the CNIC's research groups, and are generated using well-established techniques: pronuclear and/or cytoplasmic injection of mouse zygotes, and injection of genetically modified mouse embryonic stem cells (ES-cells) into preimplantation mouse embryos at the 8-cell or blastocyst stages. We also offer gene editing using engineered nucleases (zinc finger nucleases, ZFN) and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system. Mouse strains are cryopreserved by freezing mouse embryos (2-cell or 8-cell stage) or mouse sperm. The Unit also carries out mouse in vitro fertilization (IVF) using fresh or frozen sperm.

The Unit also cryopreserves sperm from the zebrafish (*Danio rerio*) and offers IVF in this species.

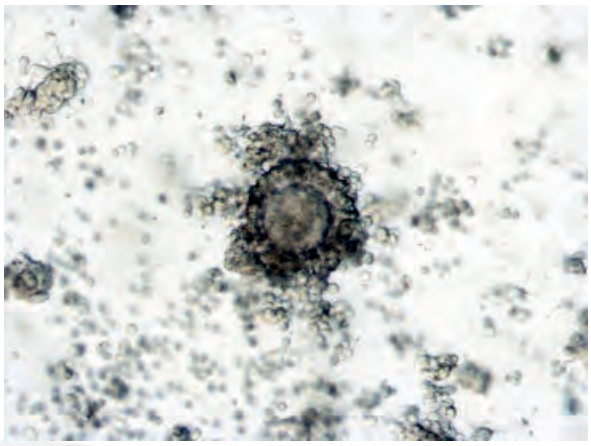
The Unit collaborates with several CNIC groups on specific aspects of their research programs, and participates in the CNIC's training programs by providing theoretical and practical sessions.

Head of Unit:
Luis-Miguel Criado Rodríguez

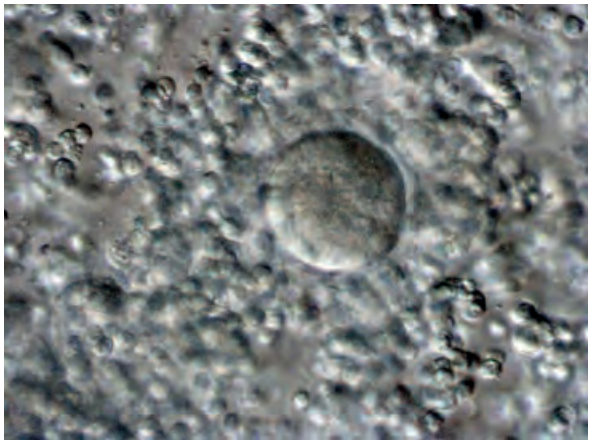
Support Scientists:
José Mª Fernández Toro
Juan de Dios Hourcade Bueno



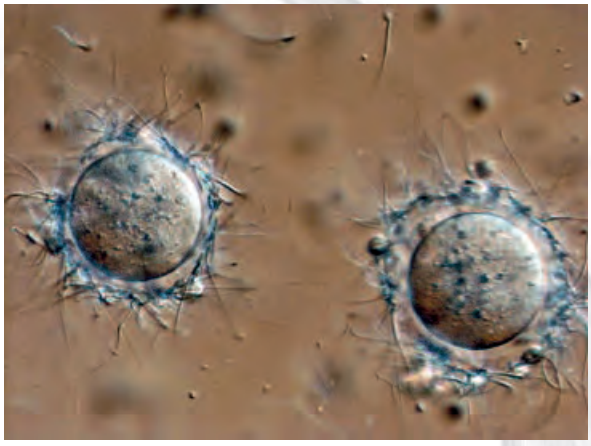
Eight mouse oocytes surrounded by cumulus cells, involved in coordining follicular development and oocyte maturation. Each mass contains a single oocyte surrounded by cumulus cells.



A mouse oocyte surrounded by cumulus cells (low magnification).

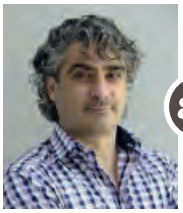


A mouse oocyte surrounded by cumulus cells (high magnification).



Two mouse oocytes surrounded by mouse spermatozoa trying to penetrate de zona pellucida, the glycoprotein layer that surrounds the oocyte (not visible in the picture).

Viral vectors



RESEARCH INTEREST

The main purpose of the Viral Vectors Unit (ViVU) is to provide investigators with the scientific resources needed to produce state-of-the-art recombinant viral vectors for in vivo and in vitro use in gene transfer experiments. The ViVU currently produces 2nd and 3rd generation lentivirus, adenovirus, and adeno-associated virus (AAV) serotypes 6, 8, DJ, and 9. The Unit also maintains a P2 facility with the appropriate expertise, equipment and permissions. We not only offer in-house services to CNIC researchers but also external services and collaborations to researchers from other institutions.

Viral vectors are widely used for gene transfer and gene expression in vitro, and our aim is to boost their use in vivo, in small and large animal models, by developing new tools for innovative applications. The use of viral vectors has several advantages over other methods: they have a high transduction efficiency and can be easily engineered for multiple purposes such as transgene expression, RNA silencing, and tandem CRISPR/Cas9 gRNA constructs, providing spatiotemporal control of any genetic modification and avoiding pitfalls common in traditional animal models.

We have developed an alternative to transgenic animals, in which AAV vectors, widely used for gene-therapy approaches, express disease-causing mutated genes to generate disease models in wild-type mice. We have also used AAV vectors to stain cellular compartments in vivo. AAV is more versatile, cost-effective, simpler, and time-efficient than transgenic approaches for generating this type of mutant model. These studies set the basis for our future vector development.

Head of Unit:
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Support Scientists:
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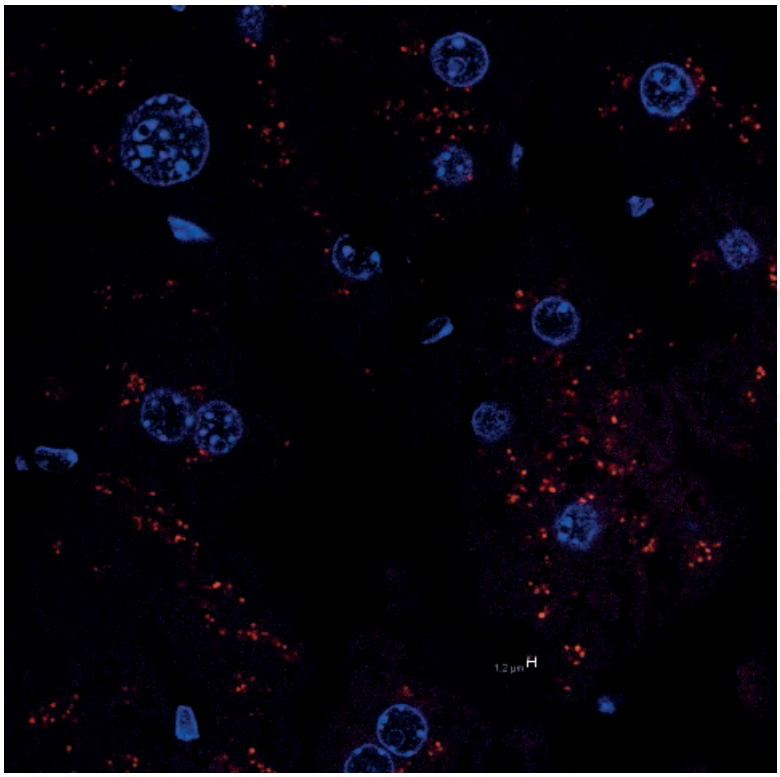
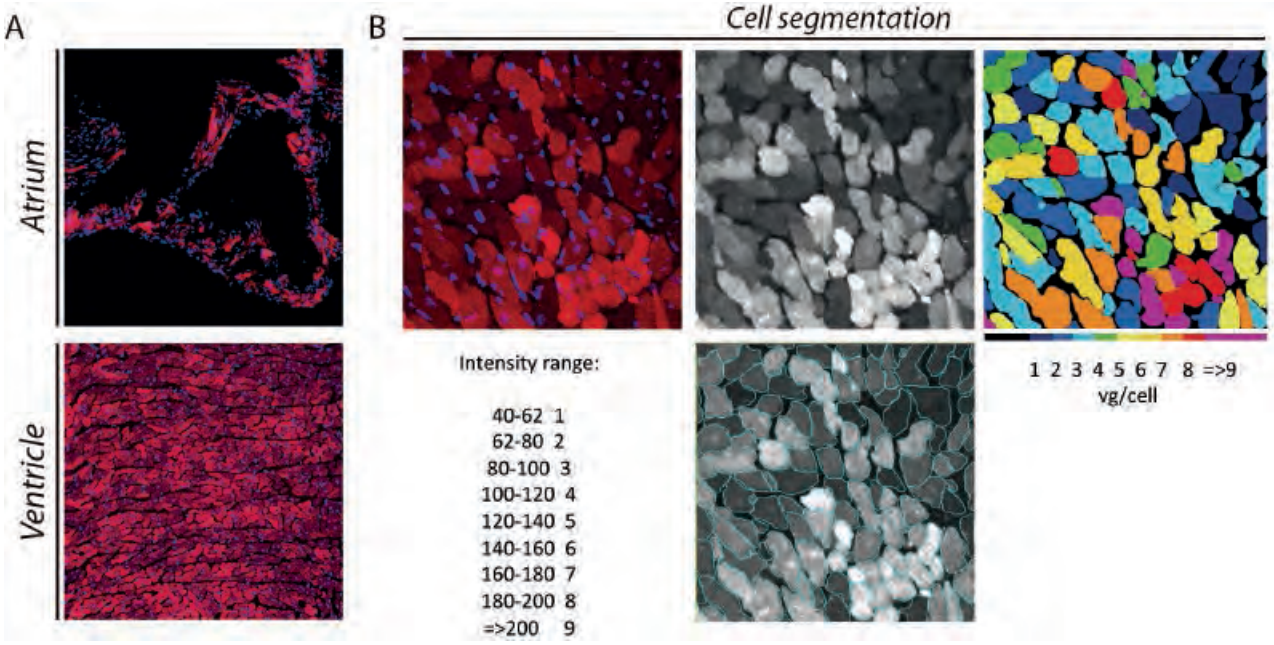
Daniel Martín-Pérez

Technicians:
Joan García
Cristina Márquez



Infection with AAV to identify mitochondria in vivo. Fluorescence imaging of mito-Keima transgene expression in hepatocytes of C57BL6J mice injected intravenously (femoral vein) with AAV2–based vector in packaging serotype 9 with $3.5x10^{10}$ viral genomes (vg). Images were acquired 4 weeks after inoculation.



Cardiac expression driven by the specific cardiac promoter TnT. (A) Representative fluorescence microscopy images of cross sections of AAV-transduced hearts, showing expression of EGFP throughout the left atrium and ventricle. **(B)** Magnified images show the mosaic cellular distribution of wild-type cardiac PKP2 expression. Fluorescence intensity segmentation and quantification of transduced protein expression, used to assign the number of integrated viral genomes per cardiomyocyte.

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Gallego-Colon E, Villalba M, Tonkin J, Cruz F, Bernal JA, Jiménez-Borreguero LJ, Schneider M, Lara-Pezzi E, Rosenthal N. **Intravenous delivery of adeno-associated virus 9-encoded IGF-1Ea propeptide improves post-infarct cardiac remodeling.** *npj Regen Med* (2016) 16001

Navarro E, Gonzalez-Lafuente L, Pérez-Liébana I, Buendia I, López-Bernardo E, Sánchez-Ramos C, Prieto I, Cuadrado A, Satrustegui J, Cadenas S, Monsalve M, López MG **Heme-oxygenase I and PCG-1α regulate mitochondrial biogenesis via microglial activation of alpha7 nicotinic acetylcholine receptors using PNU282987.** *Antioxid Redox Signal* doi: 10.1089/ars.2016.6698 2016 Sep 30

García-Quintans N, Sánchez-Ramos C, Prieto I, Tierrez A, Arza E, Alfranca A, Redondo JM, Monsalve M. **Oxidative stress induces loss of pericyte coverage and vascular instability in PGC-1α-deficient mice.** *Angiogenesis* (2016) 19: 217-28

García-Quintans N, Prieto I, Sánchez-Ramos C, Luque A, Arza E, Olmos Y, Monsalve M. **Regulation of endothelial dynamics by PGC-1α relies on ROS control of VEGF-A signaling.** *Free Radic Biol Med* (2016) 93: 41-51

Ruiz-Andres O, Suarez-Alvarez B, Sánchez-Ramos C, Monsalve M, Sanchez-Niño MD, Ruiz-Ortega M, Egido J, Ortiz A, Sanz AB. **The inflammatory cytokine TWEAK decreases PGC-1α expression and mitochondrial function in acute kidney injury.** *Kidney Int* (2016) 89: 399-410

see also additional publications on page 20

CLINICAL STUDIES

VF-3D-ESSOS

Fuster-CNIC-Ferrer Cardiovascular Polypill and SECURE Trial

ATHEROBRAIN H2H Study

PESA CNIC-SANTANDER

STEMI Trials: The Metoprolol program

TAN SNIP

VF-3D-ESSOS STUDY

MRI is the gold standard for studying cardiac anatomy and function.

Almost all hospitals are today equipped with MRI scanners and have cardiologists with the expertise to perform high quality studies.

A cardiac MRI takes about 45 minutes, and this long duration severely limits the number of scans that can be performed and therefore also limits the diagnostic power of the technique.

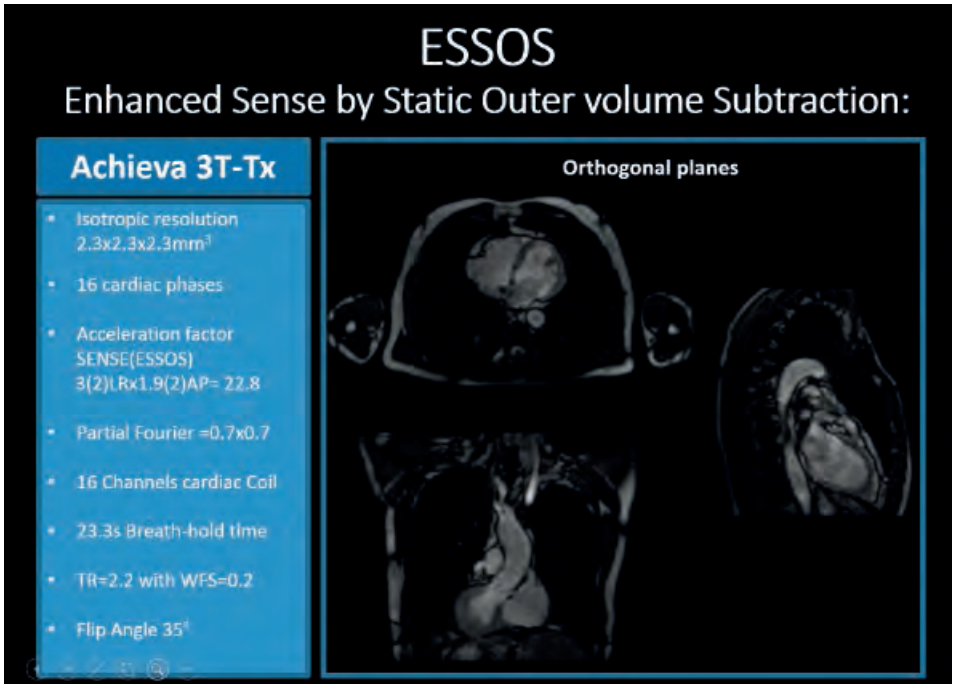
CNIC researchers are working on new MRI sequences to reduce the time of a conventional cardiac study. For this, they are using a novel 3D technology that is able to perform a scan in under 2 minutes.

The VF-3D-ESSOS (Enhanced SENSE by Static Outer volume Subtraction) study is conducted in Madrid. A total of 115 patients with different cardiac and aortic pathologies will be recruited by the participating hospitals:

- **Hospital Universitario Fundación Jiménez Díaz, Madrid**
- **Hospital Universitario Rey Juan Carlos, Móstoles, Madrid**
- **Hospital Universitario Infanta Elena, Valdemoro**
- **Hospital General de Villalba, Villalba, Madrid.**
- **Hospital Universitario Quirón, Madrid**

All participants will undergo an MRI at the CNIC core imaging facility. This MRI examination will include an additional 20-second breath-hold 3D sequence, in addition to the standard sequence. Both sequences will then be analyzed with the same hardware.

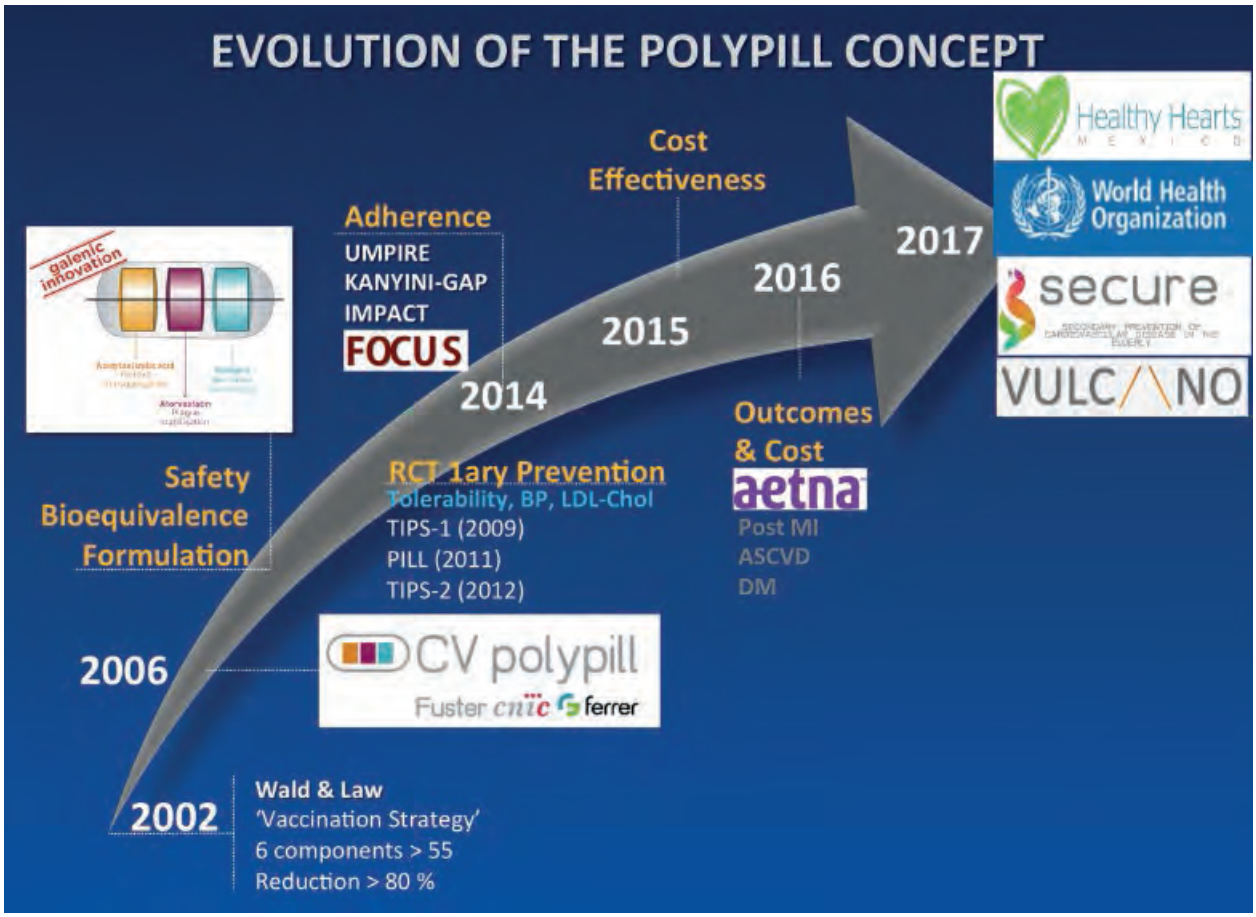
If the innovation is successful, all hospitals will be able to implement this technique and perform many more MRI scans, greatly increasing the amount and accuracy of the information obtained.



Axial, coronal and sagittal MRI of the same 3D cardiac cine sequence acquired in a breath-hold time of 23s.

Fuster-CNIC-Ferrer Cardiovascular Polypill and SECURE Trial

SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population): first clinical trial to investigate the efficacy of a Polypill in reducing cardiovascular mortality in secondary prevention.



10-years evolution of the Fuster-CNIC-Ferrer Cardiovascular Polypill Project

Cardiovascular disease (CVD) is the number one cause of death among men and women aged over 65 in Europe, and the CVD burden is expected to grow in parallel with the projected population aging. Moreover, the overall aging of the European population (the population over 65 years is projected to almost double by 2060, increasing from 85 million in 2008 to 151 million in 2060 in the EU) and the longer survival of patients with coronary heart disease (CHD) has created a large population of older adults eligible for secondary prevention.

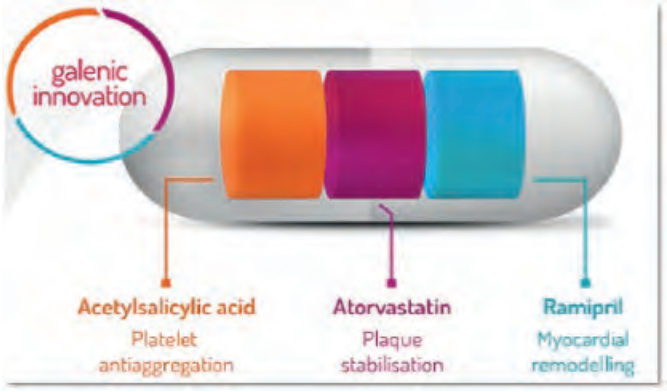
Despite ground-breaking advances in therapeutic interventions, rates of CVD mortality remain high mainly because patients are not receiving optimal medical treatment, either because of nonadherence or lack of access to medicines. A major barrier to adherence is treatment complexity, linked to the number of pills the patient has to take. The past decade has seen a surge of technical innovation in the development of a polypill strategy to improve adherence and accessibility in low and middle income countries.

The FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) study was the first to demonstrate that a polypill strategy significantly improves adherence in a secondary prevention population. The study was funded under the European Commission Seventh Framework Programme and coordinated by CNIC under the direction of Dr. Valentin Fuster.

The CNIC was recently awarded a H2020 grant to fund the first ever clinical trial testing the ability of a polypill strategy to reduce hard cardiovascular outcomes. The SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population) trial, led by Drs. Fuster and Castellano, will enroll 3600 patients over 65 years of age in Spain, Italy, Germany, France, the Czech Republic, Hungary, and Poland. Patients will be randomized to the Fuster-CNIC-Ferrer Cardiovascular Polypill vs. usual care and followed for 2-4 years. The kick-off meeting was held in Madrid in May 2015. Patient recruitment in all participating countries began in mid-2016. The results of SECURE will help shape clinical recommendations for the better use of medication in patients with ischemic heart disease across the world.

The Fuster-CNIC-Ferrer Cardiovascular Polypill has been approved for commercialization in more 25 countries and has been approved by the major regulatory agencies. After the success of FOCUS, SECURE will provide the final proof, so that millions of patients worldwide can enjoy simpler, more effective, and cost effective chronic treatment to decrease cardiovascular mortality and morbidity.

Fuster-CNIC-Ferrer Cardiovascular Polypill

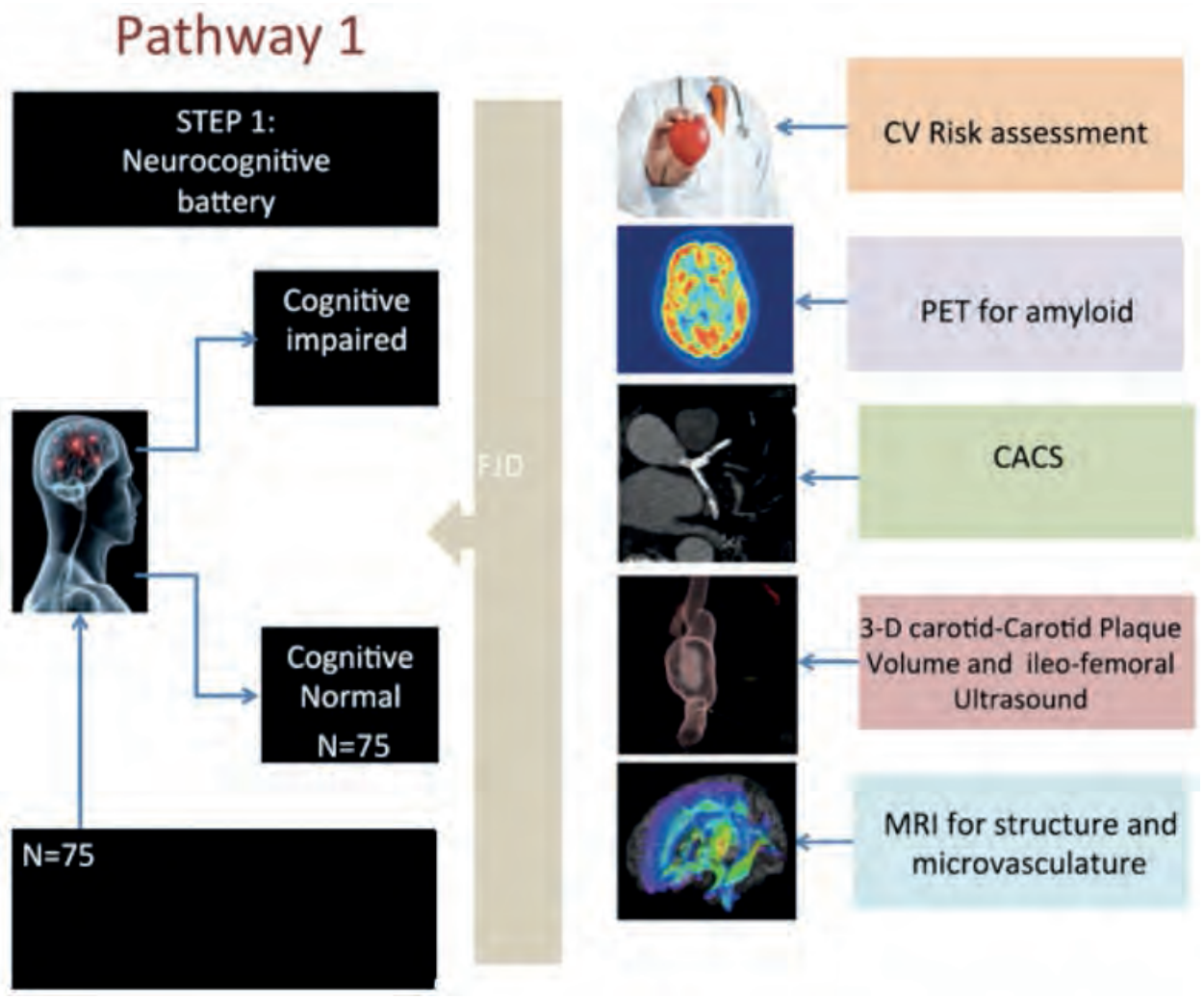


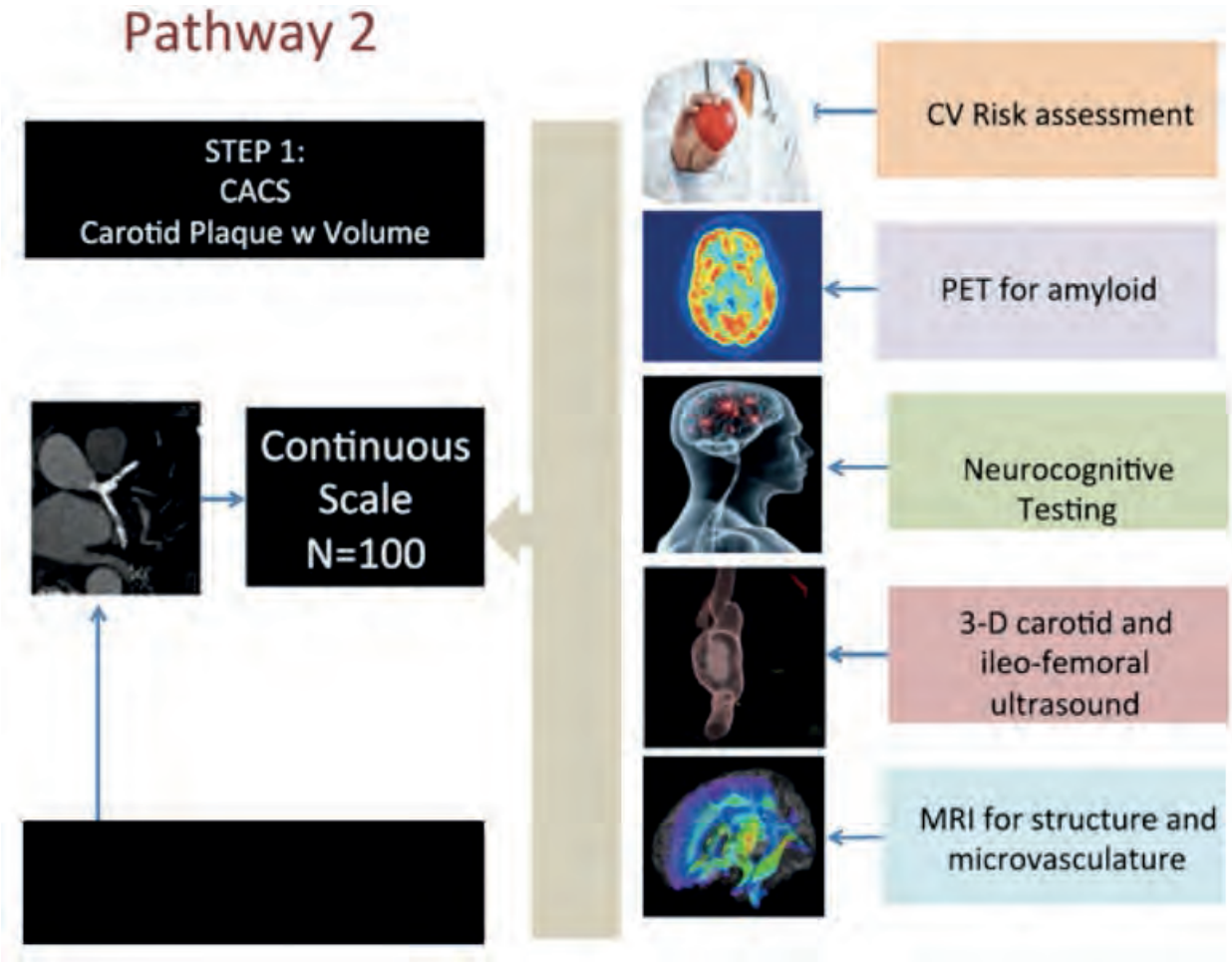
ATHEROBRAIN

Heart to Head (H2H) Spain Study

The Atherobrain - Heart to Head (**H2H**) study is a multicenter research project funded by the *Instituto de Salud Carlos III* (ISCIII) and run through partnership between the *Instituto de Investigación* at *Hospital 12 de Octubre* (i+12), the CNIC Human Imaging Unit, and several hospitals (*12 de Octubre, Gregorio Marañón, Clínico San Carlos, Fundación Jiménez Díaz, and Hospitales de Madrid*).

The H2H study is a prospective cohort study designed to unravel the relationship between subclinical atherosclerosis, cognitive decline, and Alzheimer's disease. The study will recruit 250 people aged 60 to 85 years with no cardiovascular or cerebrovascular disease, who will undergo exhaustive clinical and neurocognitive assessment as well as imaging evaluation, including anatomical and functional cerebral and carotid MRI, β-amyloid PET, 3D vascular ultrasound, and coronary calcium CT. Neurocognitive and MRI imaging will be repeated after 18 months. Two enrolment pathways have been designed: pathway 1 includes 75 participants with mild cognitive impairment and 75 control participants with normal cognition, whereas pathway 2 includes 100 patients with varying levels of coronary artery calcium score by cardiac CT.




Pathway 2
STEP 1:
CACS
Carotid Plaque w Volume
Continuous
Scale
N=100
CV Risk assessment
PET for amyloid
Neurocognitive
Testing
3-D carotid and
ileo-femoral
ultrasound
MRI for structure and
microvasculature

PESA CNIC- SANTANDER

(Progression of Early Subclinical Atherosclerosis)

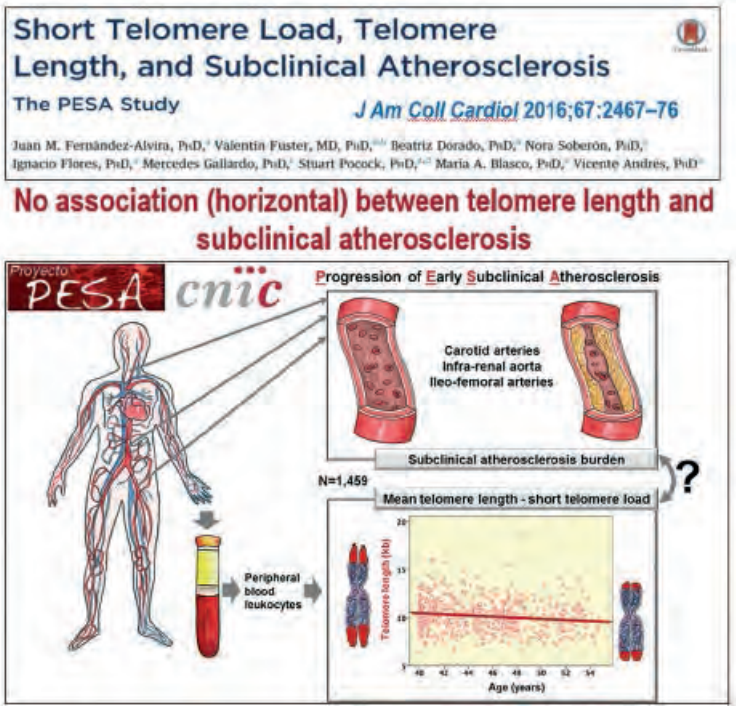
Strategies to identify individuals with subclinical alterations indicating increased risk of cardiovascular events have been boosted by the development of basic noninvasive imaging techniques (2D/3D vascular ultrasound and coronary calcium score by computed tomography) and advanced imaging techniques (magnetic resonance imaging and positron emission tomography) that can be applied to large populations. Several studies currently underway, such as the High-Risk Population (HRP) study led by Valentín Fuster in the USA, are pioneering the application of these techniques to population studies. Most studies to date have examined populations composed of individuals above the age of 60 years. Atherosclerotic disease in this group has already several decades of evolution and may be too advanced for prevention of future events.

The PESA CNIC-Grupo Santander is an ambitious study designed to identify new imaging and biological factors associated with the presence and progression of early phases of atherosclerosis. In 2014, PESA CNIC- Grupo Santander completed the prospective enrolment of 4184 healthy subjects aged 40 to 54 years (2.635 men and 1.549 women) who underwent a multi-territory screening for subclinical atherosclerosis by noninvasive 2D/3D ultrasound in the carotid, abdominal aorta and ilio-femoral arteries together with coronary artery calcium score by computed tomography. Participants were additionally assessed for a complete set of cardiovascular risk factors (including lifestyle and psychosocial factors) and provided blood samples for advanced “omics” and future analyses. In addition, advanced imaging assessment by18FDG PET/MRI technology was performed at the CNIC Advanced Imaging Unit during 2013 and 2014 in 940 individuals in whom a significant plaque burden was detected by ultrasound and CT.

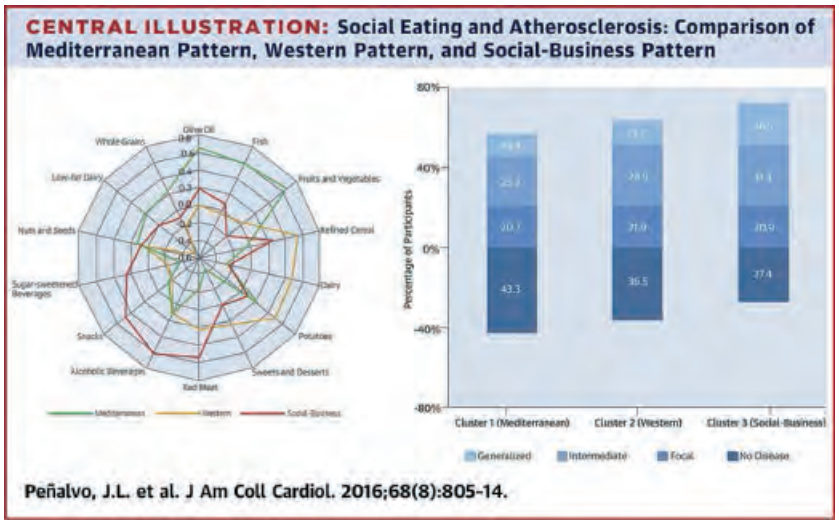
All PESA participants are followed-up at 3 and 6 years to assess the evolution of atherosclerotic plaques and to determine how the detection of subclinical disease may impact the risk of future cardiovascular events. By the end of 2016, more than 3700 participants have already undergone the 3-year follow up visit (visit 2). Similarly, more than 500 individuals have performed, the intermediate vascular MRI study at 3-year including cardiac MR sequences. These cardiac MR studies will allow a comprehensive characterization of subclinical myocardial disease.

The study also received approval for research into the association between atherosclerosis initiation/progression and telomere dysfunction in circulating leukocytes, and leukocyte samples were collected from a subgroup of 1.456 PESA participants. In May 2016 the article entitled “Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis in the PESA Study” with the results, was published in the **Journal of American College of Cardiology, Volume 67, Issue 21; Pages 2467-2476**. The conclusion is that in a cross-sectional study of a middle-aged population, average leucocyte telomere length and short telomere load are not significant independent determinants of subclinical atherosclerosis. However, the longitudinal follow-up of PESA participants will assess long-term associations between telomere length and progression of subclinical atherosclerosis.

Furthermore, in August 2016, the article entitled “Association between a Social-Business Eating Pattern and Early Asymptomatic Atherosclerosis” was published in the **Journal of American College of Cardiology. 2016, Volume 68, Issue 8; Pages 805-814**. This article describe a new social-business eating pattern, followed approximately by 1 in 5 participants enrolled in the PESA cohort, characterized by high consumption of red and processed meat, alcohol, and sugar-sweetened beverages, and by frequent snacking and eating out as part of an overall unhealthy life-style. This eating pattern is associated with an increased prevalence, burden, and multisite presence of subclinical atherosclerosis. These results suggest that diet and overall life-style habits are important in early atherosclerosis and could inform strategies to reduce the burden of CVD in similar populations. Ongoing PESA follow-ups will enable to study the associations between overall life style habits with subclinical disease and subsequent cardiovascular event.



No association (horizontal) between telomere length and subclinical atherosclerosis.



Social Eating and Atherosclerosis: Comparison of Mediterranean Pattern, Wester Pattern, and Social-Business Pattern.

SELECTED PUBLICATIONS

López-Melgar B, Fernández-Friera L, Sánchez-González J, Vilchez JP, Cecconi A, Mateo J, Peñalvo JL, Oliva B, García-Ruiz JM, Kauffman S, Jiménez-Borreguero LJ, Ruiz-Cabello J, Fernández-Ortiz A, Ibáñez B, Fuster V. **Accurate quantification of atherosclerotic plaque volume by 3D vascular ultrasound using the volumetric linear array method.** Atherosclerosis. 2016 May; 248; 230-7.

Fernández-Alvira JM, Fuster V, Dorado B, Soberón N, Flores I, Gallardo M, Pocock S, Blasco MA, Andrés V. **Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis in the PESA Study.** J Am Coll Cardiol. 2016 May 31;67(21):2467-76.

Peñalvo JL, Fernández-Friera L, López-Melgar B, Uzhova I, Oliva B, Fernández-Alvira JM, Laclaustra M, Pocock S, Mocoroa A, Mendiguren JM, Sanz G, Guallar E, Bansilal S, Vedanthan R, Jiménez-Borreguero LJ, Ibañez B, Ordovás JM, Fernández-Ortiz A, Bueno H, Fuster V. **Association between a social-business eating pattern and early asymptomatic atherosclerosis.** J Am Coll Cardiol. 2016 Aug 23;68(8):805-14.

STEMI Trials: The Metoprolol program

Acute myocardial infarction (AMI) is the main cause of death in western countries. The best strategy to limit myocardial damage is to perform an early coronary reperfusion. However, reperfusion itself comes at a price of additional myocardial damage, known as ischemia/reperfusion (I/R) injury.

The duration of ischemia can only be shortened through coordinated healthcare policies aimed at early detection and transfer of patients to hospitals with angioplasty capabilities. I/R injury, on the other hand, could potentially be reduced by pharmacological approaches; but despite great efforts, no therapy has been shown to consistently limit this phenomenon.

ß-blockers are a class of drugs that have been used to treat cardiovascular conditions for several decades. β-blockers reduce mortality when administered after an AMI, and are a class IA indication in this context. There is a lack of information on the infarct-limiting effect of β-blockers in patients undergoing reperfusion (current state-of-the-art treatment for infarction). Based on strong preclinical data, the CNIC initiated a program of clinical research with the long-term aim of demonstrating a reduction of events by the prereperfusion metoprolol administration in STEMI patients. The first trial was METOCARD-CNIC, recruiting patients with anterior STEMI presenting early (<6 hours from symptom onset). The EARLY BAMI trial is the validation study, recruiting a less restricted population with STEMI in any location presenting within 12 hours of symptom onset. In both trials, metoprolol or comparator (control/placebo) was administered before mechanical reperfusion.

The METOCARD-CNIC multicenter randomized clinical trial has already been completed. A total of 270 patients were recruited mainly by the emergency medical services. Metoprolol administration was associated with significantly smaller infarctions as evaluated by cardiac magnetic resonance (CMR) one week after infarction (Circulation 2013;128:1495-503), and with better long-term LVEF on 6-month CMR (J Am Coll Cardiol. 2014;63:2356-62). Metoprolol also significantly reduced the incidence of severe cardiac dysfunction and the incidence of heart failure readmissions.

The EARLY BAMI trial is a multinational randomized clinical trial conducted in Holland and Spain. More than 600 STEMI patients were recruited. The primary endpoint is infarct size evaluated by CMR one month after reperfusion. All CMR studies are being analyzed in the central core lab at the CNIC. Over 300 patients underwent CMR to meet the power calculation. The CNIC is coordinating the Spanish branch of the trial. EARLY BAMI is the result of a multidiciplinary effort bringing together several partners. Patients were recruited by the Emergency Medical Service SUMMA112 during transit to one of the following participating hospitals within the codigo infarto Madrid: Hospital Fundación Jiménez Díaz, Hospital 12 de Octubre, Hospital Clínico San Carlos, Hospital Puerta de Hierro, Hospital Gregorio Marañón, Hospital de la Princesa, Hospital Ramón y Cajal, Hospital Fundación Alcorcón, and Hospital Principe de Asturias. All CMR studies in Spain were performed at the CNIC using a unique magnet system.

Currently both trials are in the follow-up phase.

After these two trials testing the effect of early intravenous metoprolol on infarct size, the next step will be a larger multinational events-powered clinical trial led by the CNIC. More than 1200 STEMI patients will be recruited in more than 3 European countries.

Members of the METOCARD-CNIC and EARLY BAMI research group.

The TANSNIP-PESA randomized control trial: a 30-month worksite-based lifestyle program to promote cardiovascular health in middle-aged bank employees

Existing tools for characterizing atherosclerosis and determining the risk of its complications are inadequate. These deficiencies limit effective management across the spectrum of this disease, and therefore opportunities are lost for early, cost-effective interventions in sub-clinical disease, while high-risk populations with manifest disease are administered treatments almost indiscriminately. This leads to high 'numbers-needed-to-treat' (NNT), unnecessary patient risk, wasted resources, and unsustainable costs for health care purchasers.

In a relatively low-risk population (the PESA-CNIC cohort), we will study whether a personalized worksite based lifestyle intervention, driven by imaging data (2D and 3D-ultrasound of carotid and ilio-femoral arteries, and coronary artery calcification) results in changes in behavior, improved control of risk factors, and reduced progression of subclinical atherosclerosis plaque burden (SAPB).

TANSNIP is a randomized control trial (RCT) including middle–aged bank employees from the PESA cohort, stratified by SAPB (high SABP n=260; low SABP n= 590). Within each stratum, participants are randomized 1:1 to join a lifestyle program or receive standard care. The program consists of three elements: (1) 12 personalized lifestyle counseling sessions using motivational interviewing (MI) over a 30-month period; (2) a wrist-worn physical activity tracker, and (3) a sit-stand workstation. The primary outcome measure is a composite score of blood pressure (BP), physical activity, sedentary time, body weight, diet, and smoking (the adapted FUSTER-BEWAT score), measured at baseline and at 1-, 2-, and 3-year follow-up. Secondary outcomes are individual changes in lifestyle behaviors and specific changes in anthropometric measures, blood biomarkers, self-rated health, work-related outcomes (including work productivity and absenteeism), health care consumption, program process measures, and cost measures at different measurement points.

The expectation is that individual awareness of CVD risk stratification in the intervention group will lead to a reduction in the prevalence of CV risk factors related to lifestyle and an increase in physical activity compared with the control group. A second rationale is that the level of compliance with the comprehensive 3-year worksite-based lifestyle intervention will be higher among participants with a high imaging-defined CV risk.

TANSNIP-PESA started including participants in May 2015 and the first MI session took place in June 2015. So far, a total of 1027 participants have been included in the trial (484 from the control group and 477 from the intervention group). Of these, 286 participants belong to the high SAPB group and 675 to the low SAPB group. In the intervention group, 449 participants have already their first MI session; all participants are using the Fitbit activity monitor and 323 (68%) participants are willing to use the sit-stand workstation (60% already have the station installed at their workplaces). Inclusion is scheduled to finalize early in 2017, surpassing the sample size initially expected. The study is scheduled to end in September 2019.

Five focus group have been held with at least 5 intervention group participants who have completed their first 7 MI sessions. Overall, participants indicated that they were very satisfied with the intervention program.

To measure MI session quality and improve the content of the TANSNIP-PESA program, every 6 months random MIs are recorded and participants are surveyed by the study technicians. The overall results of these assessments have been very positive.

In 2016 the trial design paper was published in the American Heart Journal (doi: 10.1016/j.ahj.2016.11.002).

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Prof. Allard van der Beek
PhD. Jennifer Coffeng

Team SANTANDER

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MD. José María Mendiguren
MD. Juan Muñoz Gutiérrez
MD. Laura Gómez Paredes
Magdalena López García

Team ISMMS/ Madrid CNIC-PESA

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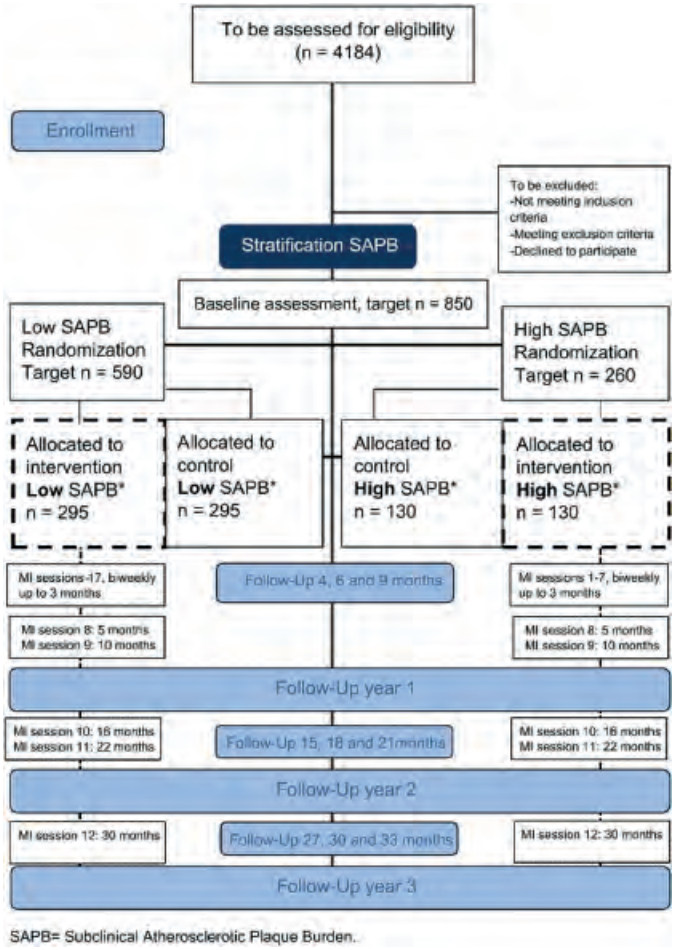
Study PI: PhD. MD. José M Castellano
Study PI: PhD. MD. Borja Ibañez
MD. Inés García Lunar
PhD.MD. Sameer Bansilal
PhD. MD. Antonio Fernández-Ortiz
PhD. Juan Miguel Fernández-Alvira
Laura García Leal
Evelyn Cárdenas
Sara García Ortega
Carolina Rojas
Mª Isabel Martínez
Silvia Santiago
Miriam Fernández Gallardo

Study figure TANSNIP-PESA



Scoring of different elements of the adapted FUSTER-BEWAT primary outcome measure.

SCORE	0	1	2	3	4
Score Systolic/diastolic blood pressure* (mm Hg)	≥140/90	134-139/87-89	128-133/84-86	121-127/81-83	≤120/80
Physical activity (steps/d)	<5500	5500-6999	7000-8499	8500-9999	≥10000
Sitting (h/d)	≥12.5	11-<12.5	9.5-<11	8-<9.5	<8
BMI (kg/m2) †	≥32	30-31.9	27-29.9	25-26.9	<25
Fruit & vegetable consumption (serves/d)	≤1	2	3	4	≥5
Smoking (units/d)	>20	10-20	1-9	<1	0

Total score range 0-24, with a higher score indicating a lower risk score.
* If systolic and diastolic blood pressure do not fall in the same group, then the participant is assigned to the group with the relatively highest blood pressure (i.e. systolic or diastolic)
† At follow-up visits, a >5% decrease in BMI will add 1 extra point in the BMI score except for those participants who have changed BMI categories since baseline or are already in the normal weight category (BMI<25). Similarly, a >5% increase in BMI at follow-up will mean 1 point less in the BMI score except for participants who have changed BMI categories since baseline or with BMI≥32.

TRANSLATION TO SOCIETY

Communications
Research Highlights

PRESS, RADIO, TV, ONLINE

*AVE INDICATES the ESTIMATED COST OF editorial coverage if it were advertising space

EUREKALERT

EurekAlert! The Global Source for Science News

82,525 HITS
23 PRESS RELEASES SUBMITTED

SOCIAL MEDIA MENTIONS

CNIC FLICKER ACCOUNT

flickr CNIC JOINED IN FEBRUARY 2016 AND HAS LOADED 748 IMAGES

CNIC TWITTER ACCOUNT

@CNIC_CARDIO TWITTER ACCOUNT has **5280** followers, including scientists, institutions and key figures in the scientific journalism community

TOTAL 2016 Tweet impressions (Number of people who saw a @cnic_cardio tweet): **217.006**

TOTAL 2016 Profile visits: **14.250**

TOP TWEET OF THE YEAR

Top Tweet earned 3,914 impressions

¿Conoces las cifras de las enfermedades cardiovasculares en Europa? #DíaMundialdelCorazón ❤ pic.twitter.com/4IMA7Qz2mO

	Tweet impressions (Number of people who saw a @cnic_cardio tweet)	Profile visits	Top Tweet of the month
JANUARY	7.803	1.058	**Top Tweet** earned 1,375 impressions Nuevo mecanismo para 'animar' al sistema inmune a que combata el #cancer goo.gl/WmVgZPI
FEBRUARY	11.400	1.106	**Top Tweet** earned 1,256 impressions Si eres estudiante de Máster y últimos cursos carreras de biomedicina puedes apuntarte al #ProgramaCicerone del CNIC bit.ly/1o5xPzR
MARCH	21.500	972	**Top Tweet** earned 1,877 impressions Crean un nuevo tipo de células para recuperar el corazón tras un infarto goo.gl/30Ip6M #cnic_news
APRIL	15.400	972	**Top Tweet** earned 1,078 impressions Silvia G. Priori' research group at @CNIC_CARDIO is searching a Postdoctoral Researcher goo.gl/wNSSrU #cnic_empleo
MAY	22.900	1.511	**Top Tweet** earned 1,645 impressions Cell Metabolism: Descubren los mecanismos moleculares que aseguran la estructura contráctil del corazón tinyurl.com/zcdnp24
JUNE	13.900	1.443	**Top Tweet** earned 1,976 impressions @CNIC_CARDIO Orgullosos de participar en este programa @BecarioslaCaixa - #SeveroOchoa goo.gl/i1l2yl
JULY	20.600	171	**Top Tweet** earned 1,313 impressions Todas las fotos de los estudiantes del programa #ACÉRCATE @CNIC_CARDIO #cnic_joven goo.gl/e7wIw3 pic.twitter.com/f7h1TBFdvF
AUGUST	10.300	593	**Top Tweet** earned 1,246 impressions Quieres que tu proyecto tenga la mejor imagen biomédica? convocatoria #ICTS ReDIB redib.net pic.twitter.com/7Iv6g1ybTb
SEPTEMBER	28.800	2.006	**Top Tweet** earned 3,914 impressions ¿Conoces las cifras de las enfermedades cardiovasculares en Europa? #DíaMundialdelCorazón ❤ pic.twitter.com/4IMA7Qz2mO
OCTOBER	16.600	1.195	**Top Tweet** earned 1,673 impressions #SemanaCienciaMadrid 'Un día en familia en CNIC' para niños y 'Jornada Acércate a la investigación' para estudiantes tinyurl.com/z6yfl6f pic.twitter.com/X0MTyVWlU
NOVEMBER	37.900	1.984	**Top Tweet** earned 3,056 impressions The CNIC proud hosting institution of the INPhINIT Fellowships Programme tinyurl.com/j34l46n @FundlaCaixa pic.twitter.com/N3u3du4hYU
DECEMBER	9.903	1.239	**Top Tweet** earned 892 impressions Disponible online el último número de CNICPulse. bit.ly/2HB1zd #cnic_news pic.twitter.com/O0NSL2XV0r

19 Dec 2016

2 million euros from the E.U. to David Sancho

21 Nov 2016

PhDay: Beyond PhD

16 Nov 2016

The CNIC is a host institution within the INPhINIT "la Caixa" Fellowships Programme

14 Nov 2016

A Family Day: Science up-close for children

10 Nov 2016

The CNIC Acércate Research Seminar welcomes 200 ESO and Bachillerato high school students

4 Nov 2016

Thai representatives visit the CNIC

2 Nov 2016

The CNIC Conference brings together international experts in mechanobiology

10 Oct 2016

The CNIC, "Setting the standard for research in Spain and Europe"

22 Sep 2016

Acciona's "Health and Wellbeing" program received the NAOS Award for 2015

8 Sep 2016

First call for proposals to access the ReDIB Unique Scientific-Technological Infrastructure (SSTI)

29 Jul 2016

Three CNIC projects selected for the BBVA Foundation's 2016 Fellowship and Grants Program

22 Jul 2016

Spain's future researchers train at the CNIC

20 Jul 2016

Dr. Fuster at Santander UIMP Summer Course for young cardiologists

11 Jul 2016

Madri+d Award for Best European R&D Cooperative Project awarded to the SECURE Project

29 Jun 2016

La Caixa-Severo Ochoa PHD fellowships award ceremony

27 Jun 2016

Isabel Fariñas: "Researchers must never let themselves be discouraged"

20 Jun 2016

The Pro CNIC Foundation celebrates 100 years of heparin

31 May 2016

Dr. Valentín Fuster awarded with the Severo Ochoa Prize for Biomedical Research

31 May 2016

The CNIC's 'Severo Ochoa' accreditation is reneweds

25 May 2016

Ido Amit: "To do 'good science' you must be constantly prepared to make mistakes and to learn from those mistakes"

24 May 2016

EPES 061 and CNIC sign a collaboration agreement

9 May 2016

Dan Roden: "Science is not only making discoveries, but also engaging society in them"

9 Mar 2016

Danone joins the Pro-CNIC Foundation in the fight to prevent cardiovascular diseases

3 Feb 2016

Fifty-Fifty project: a breakthrough in group therapy for cardiovascular research

8 Jan 2016

The *Hospital Universitario Fundación Jiménez Díaz* and the CNIC unite to fight cardiovascular diseases

CNIC PULSE MAGAZINE

For more information about the CNIC's contribution to this great enterprise of science and how we apply ourselves for the benefit of everyone, please check CNIC PULSE at www.cnic.es. This magazine is divided into four sections. In **Inside Science**, we present news of major, long-term scientific significance. **Train2Gain** highlights real-world examples from our training programs. Both the Pro-CNIC Foundation and I take a strong interest in these programs. The next two sections present interviews with important players in the cardiovascular field (**What's on**) and report on events related to our commitment to the public communication of science and medicine (**CNIC &Society**).

CLINICAL & EPIDEMIOLOGICAL RESEARCH

CNIC clinical researchers made significant contributions to atherosclerosis primary prevention last year. Primary prevention involves identifying individuals who do not yet have disease symptoms but who are at risk of having a cardiovascular event (myocardial infarction, stroke, sudden cardiac death, etc.) in the medium term. Major advances were made in the use of noninvasive imaging to identify the presence of atherosclerosis in different arterial territories and to use this information to estimate the risk of future cardiovascular events. Another area of progress was in programs examining lifestyle and behaviors that can be modified to improve cardiovascular health.

Our work with noninvasive imaging techniques forms the backbone of the Progression of Early Subclinical Atherosclerosis (PESA) study. This clinical study examines the level of asymptomatic atherosclerosis in participants with an intermediate cardiovascular risk profile and relates the findings to a range of biological and behavioral risk factors. The amount and location of atherosclerosis is assessed by coronary computed tomography (CT) and by 2D and 3D ultrasound of the carotid and femoral arteries and the aorta. CNIC researchers found that the presence of atherosclerotic plaques in the femoral arteries is a better indicator of risk in asymptomatic subjects than atherosclerosis in other territories (*Laclaustra et al. J Am Coll Cardiol 2016;67:1263-74*). This study complements previous CNIC studies showing that the femoral arteries are where atherosclerosis first develops (*Fernandez-Fiera et al. Circulation 2015;131:2104-13*). The imaging data from the PESA study were also used in a cross-sectional study that found no association between subclinical atherosclerosis in different arterial territories and the length of telomeres (the terminal structures that protect chromosomes from damage) in circulating leukocytes (*Fernández-Alvira et al. J Am Coll Cardiol 2016;67:2467-76*).

The CNIC's work with noninvasive imaging is contributing to a better stratification of cardiovascular risk among asymptomatic individuals, pointing the way to future interventions to halt disease progression after the identification of extensive subclinical atherosclerosis.

Our work on the links between lifestyle, atherosclerosis, and cardiovascular events builds on previous research led by Prof Fuster, showing that patients who adhere strictly to the prescribed medication program have better long term outcomes than those who don't (*Bansilal et al. J Am Coll Cardiol 2016; 68:789-801*). To improve medication adherence, the CNIC is leading a H2020-funded project testing the efficacy of a polypill combining the 3 most prescribed medications for cardiovascular problems in a single pill (SECURE project, http://www.secure-h2020.eu/). Another CNIC research project into lifestyle identified an association between a social-business eating pattern associated with extensive atherosclerosis (*Peñalvo et al. J Am Coll Cardiol 2016;68:805-14*).

The CNIC also investigates ways to modify behaviors, and thus stop the progression of cardiovascular disease (CVD). Last year we demonstrated that a group therapy intervention can significantly improve the risk profile among CVD patients (*Gómez-Pardo et al. J Am Coll Cardiol 2016;67:476-85*).

These contributions improve our understanding of how lifestyle determines the presence of atherosclerotic disease and of the several measures available to modify bad habits and improve long-term cardiovascular health.

BASIC RESEARCH

Basic research is a fundamental part of the CNIC's activity, generating new knowledge that underpins advances in patient treatment and prevention. 2016 was an extraordinary year for the CNIC basic research groups, with more articles published than ever before. Some of the highlights are summarized below.

Work on the roles of mitochondria in aging, metabolism, CVD, and the associated immune response revealed new mechanisms governing the superassembly of mitochondrial respiratory complexes (*Cogliati et al. Nature 2016; 539: 579-582*) and demonstrated that mitochondrial and nuclear DNA matching determines metabolism and healthy aging (*Latorre-Pellicer et al. Nature 2016; 535: 561-5*). These results also underline the importance of ensuring that the donor mitochondrial DNA in mitochondrial donation procedures, which produce children with three genetic parents, is an appropriate match for the recipient's nuclear genome. CNIC researchers also demonstrated that mitochondrial respiratory-chain adaptations in macrophages contribute to the body's defence against bacterial infections (*Garaude et al. Nat Immunol 2016; 17:1037-45*). These studies could help in the design of vaccines and provide new pharmacological targets for the treatment of infections and inflammatory metabolic disorders.

CNIC researchers last year identifid new mechanisms involved in the formation and morphogenesis of ventricular chambers (*D'Amato et al. Nat Cell Biol 2016; 18: 7-20*) and cardiac valves (*MacGrogan et al. Circ Res 2016; 118: 1480-97*). These studies demonstrate that perturbations of the ligand-dependent Notch signaling pathway during embryonic development cause abnormalities in heart chamber formation, thus opening a new research avenue into cardiomyopathies. These studies also identify a mechanism operating during valve morphogenesis that is linked to the origin of congenital heart defects associated with reduced NOTCH function.

Excessive growth of the heart (cardiac hypertrophy) increases the risk of illness and death due to diastolic and systolic heart failure and arrhythmia. A 2016 CNIC study (*Gonzalez-Terán et al. Nat Commun 2016; 7: 10477*) demonstrated that the kinases p38γ and p38δ are activated by pathological and physiological hypertrophic stimuli and promote cardiac physiological and pathological hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation. These results open a route to the development of new treatment strategies for this disease.

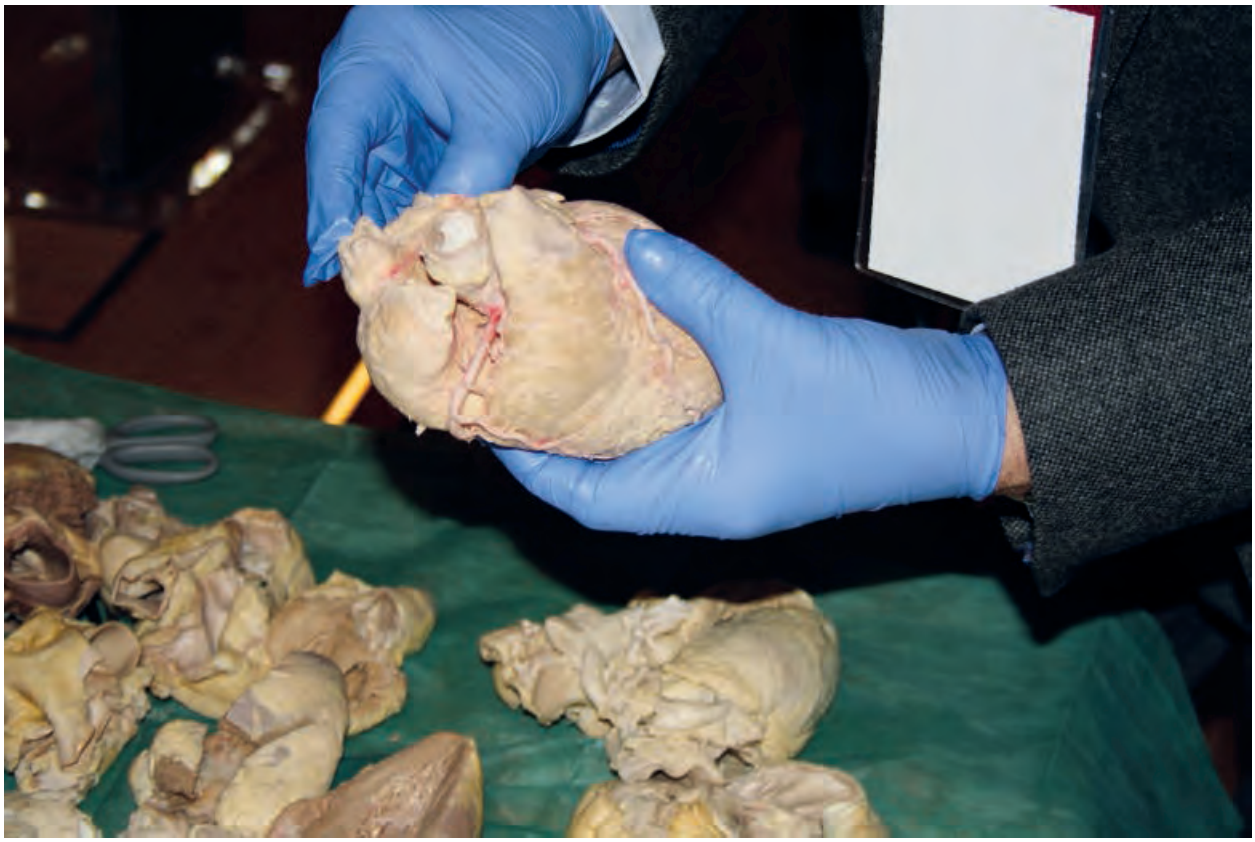
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable and highly debilitating disease that causes an estimated 15% of all unexplained sudden cardiac deaths in young people. However, the identity of the cardiac cells responsible for CPVT was unknown. A new CNIC study (*Willis et al. Circulation 2016; 133: 2348-59*) demonstrates for the first time a greater role of Purkinje cells in promoting arrhythmogenesis than ventricular myocytes. Although these are still preliminary results obtained in mouse models, they nonetheless introduce the Purkinje network as a potential target in CPVT and other cardiac diseases associated with calcium-linked arrhythmias.

Another study identified a population of cells expressing nestin in the vessel wall that promote the entry of inflammatory cells from the bloodstream and enhance atherosclerosis development (*Del Toro et al. Nat Commun 2016; 7: 12706*). This population of cells could represent a new therapeutic target.

CNIC researchers also identified the activation marker CD69 as a key mediator of psoriasis, a chronic inflammatory skin disease associated with a greater risk of early cardiovascular events (*Cibrián et al. Nat Immunol 2016; 17: 985-96*).

Heart and skeletal muscles are formed during embryonic development. Although they share structural similarities, they express different sets of genes to meet their distinct functions. A CNIC study (*Gomez-Del Arco et al. Cell Metab 2016; 23: 881-92*) found that the contractile structures of both muscle types depend on a mechanism involving the chromatin remodeling complex Chd4/NuRD. Loss of Chd4 in the heart triggers aberrant expression of the skeletal muscle genetic program, causing severe cardiomyopathy and sudden death. Conversely, Chd4 loss in skeletal muscle causes inappropriate expression of cardiac genes and myopathy. Thus, loss of Chd4-dependent regulation leads to hybrid striated muscle tissues incompatible with life.

In other projects, CNIC researchers identified mechanisms mediated by immune cells that could help in the design of new vaccines against a host of pathogens that cause infection via the skin or mucous membranes, such as flu, herpes, tuberculosis, HIV-1, dengue virus, cholera, and emerging viral diseases (*Iborra et al. Immunity 2016; 45: 847-60*), or against the ***Leishmania*** parasite, which causes leishmaniasis (*Iborra et al. Immunity 2016; 45: 788-801*).



20 Dec 2016

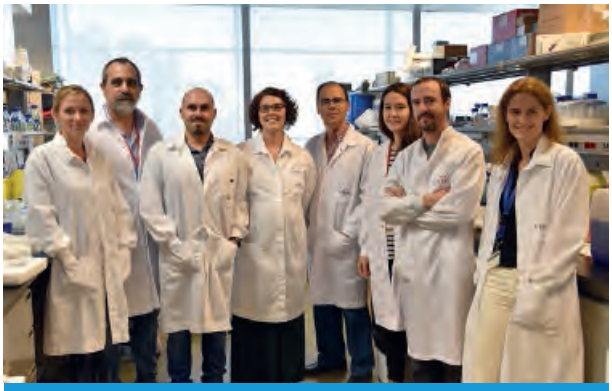
Developmental Cell: Hypoxia signaling plays a physiological role in the formation of the heart

25 Nov 2016

Nature Communications: Discover a key signal in intercellular communication

2 Nov 2016

PNAS: Heart defects identified in progeria patients that increase the risk of arrhythmias and premature death



26 Oct 2016

Nature: Scientists decipher the organization of the cellular mechanisms responsible for energy production

14 Oct 2016

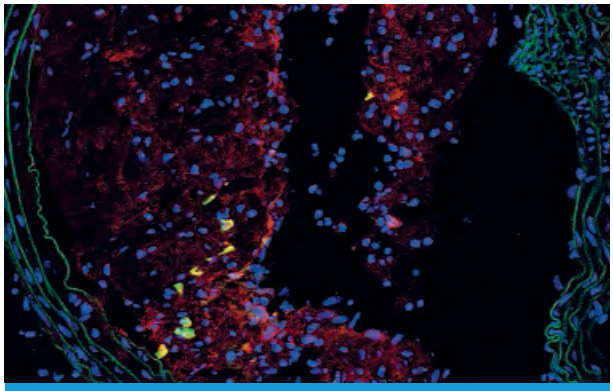
Immunity: Identify a mechanism through which the Leishmania parasite sabotages the immune response

28 Sep 2016

Immunity: CNIC investigators identify ways to improve vaccine design

20 Sep 2016

Circulation Research: The CNIC A Successful Vision in Cardiovascular Research



8 Sep 2016

Nature Communications: Identified a new mechanism involved in atherosclerosis

23 Aug 2016

JACC: MINERVA results demonstrate full adherence to guideline-recommended therapies associated with lower rate of a second major cardiovascular event and cost savings

7 Jul 2016

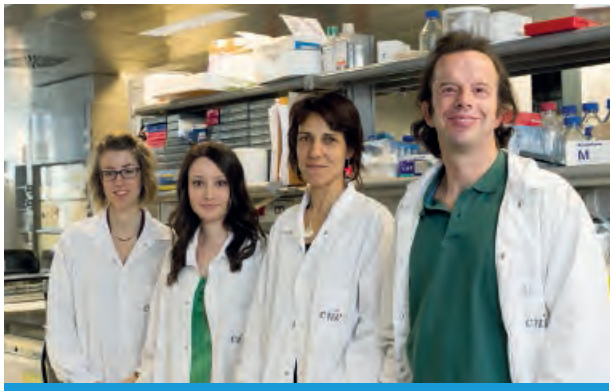
Nature: The interaction between our two genomes, nuclear and mitochondrial, is the key to healthy aging

5 Jul 2016

Nature Immunology: Scientists identify an essential role of the immune receptor CD69 in psoriasis

28 Jun 2016

Nature Immunology: Changes to mitochondrial metabolism allow the immune system to adapt to infection



1 Jun 2016

The Journal of Cell Biology: Telomere shortening limits the capacity of the heart to regenerate

24 May 2016

JACC: Telomere length in circulating blood cells does not predict asymptomatic atherosclerosis

11 May 2016

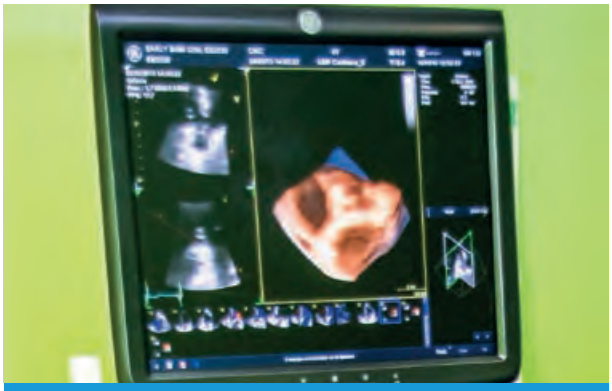
Cell Metabolism: CNIC researchers discover the molecular mechanisms that produce the heart's contractile structure

25 Apr 2016

Circulation Research: CNIC Researchers identify a new signaling mechanism implicated in congenital aortic valve disease

20 Apr 2016

Nature Communications: CNIC researchers define the key role of a protein in lymphocyte activation

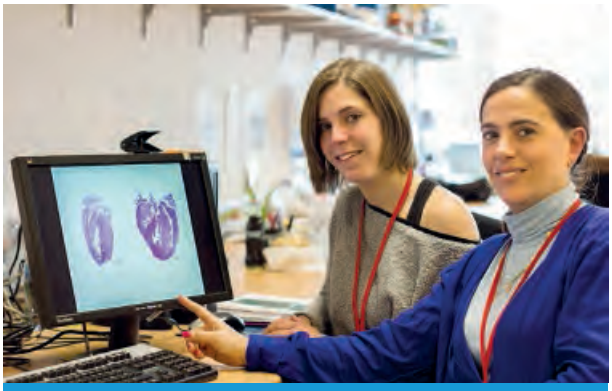


22 Mar 2016

JACC: New method for early diagnosis of atherosclerosis

3 Feb 2016

EMBO Journal: CNIC researchers discover a new target for the treatment of fatty liver disease



22 Jan 2016

Nature Communications: Two proteins control the growth of the heart and its adaptation to high blood pressure

8 Jan 2016

Nature Communications: Stem cells regulate their own proliferation and their microenvironment

ADMINISTRATION & SUPPORT SERVICES

ADMINISTRATION: General Management, Finance, Human Resources, Computing, Infrastructure & Installations, Science Management, Communication, TTO, Projects

SUPPORT SERVICES: Research Office, Library & Information, Scientific Editing

APPENDIX

There were 233 CNIC publications in 2016, 218 of them in JCR-listed journals with an Impact Factor (IF). Of the total publications, 64% were produced through collaboration with foreign institutions, 31% with national institutions, and 6% were authored solely by CNIC researchers.

A CNIC scientist was a main author on 55% of the publications. The average IF for all the articles was 8.498.

Articles with a CNIC Main Author

Cogliati S, Calvo E, Loureiro M, Guarás AM, Nieto-Arellano R, García-Poyatos C, Ezkurdia I, Mercader N, Vázquez J, Enríquez JA.
Mechanism of super-assembly of respiratory complexes III and IV.
Nature (2016) 539: 579-82
IF: 38.138

Latorre-Pellicer A, Moreno-Loshuertos R, Lechuga-Vieco AV, Sánchez-Cabo F, Torroja C, Acín-Pérez R, Calvo E, Aix E, González-Guerra A, Logan A, Bernad-Miana ML, Romanos E, Cruz R, Cogliati S, Sobrino B, Carracedo A, Pérez-Martos A, Fernández-Silva P, Ruiz-Cabello J, Murphy MP, Flores I, Vázquez J, Enríquez JA.
Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing.
Nature (2016) 535: 561-5
IF: 38.138

Torres M.
Regeneration: Limb regrowth takes two.
Nature (2016) 533: 328-30
IF: 38.138

Fernández LC, Torres M*, Real FX*. (MT and FXR are co-correspondig authors)
Somatic mosaicism: on the road to cancer.
Nat Rev Cancer (2016) 16: 43-55
IF: 34.244

Iborra S*, Martínez-López M*, Cueto FJ, Conde-Garrosa R, Del Fresno C, Izquierdo HM, Abram CL, Mori D, Campos-Martín Y, Reguera RM, Kemp B, Yamasaki S, Robinson MJ, Soto M, Lowell CA, Sancho D. (SI and MM-L contributed equally)
Leishmania Uses Mincle to Target an Inhibitory ITAM Signaling Pathway in Dendritic Cells that Dampens Adaptive Immunity to Infection.
Immunity (2016) 45: 788-801
IF: 24.082

Iborra S, Martínez-López M, Khouili SC, Enamorado M, Cueto FJ, Conde-Garrosa R, Del Fresno C, Sancho D.
Optimal Generation of Tissue-Resident but Not Circulating Memory T Cells during Viral Infection Requires Crosspriming by DNGR-1+ Dendritic Cells.
Immunity (2016) 45: 847-60
IF: 24.082

Di Scala M, Hidalgo A.
Angiogenin Defines Heterogeneity at the Core of the Hematopoietic Niche.
Cell Stem Cell (2016) 19: 284-6
IF: 22.387

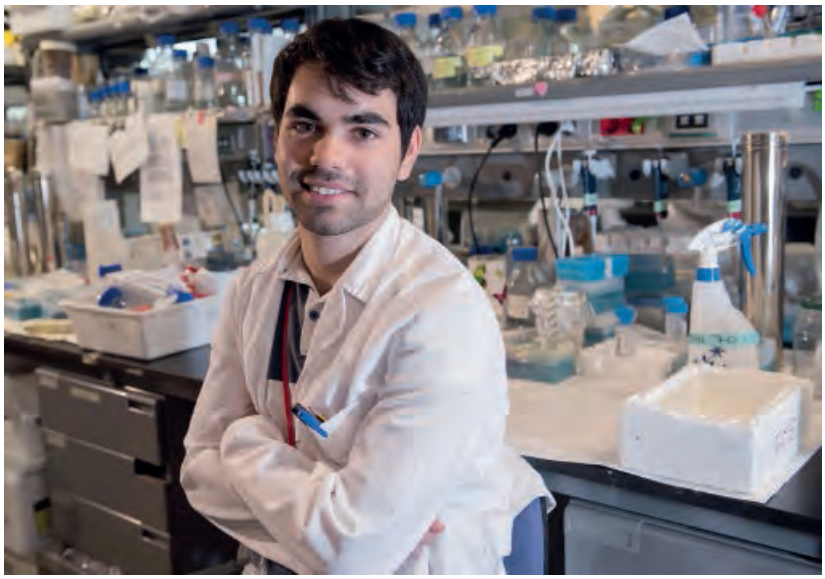
Sánchez-Paulete AR, Cueto FJ, Martínez-López M, Labiano S, Morales-Kastresana A, Rodríguez-Ruiz ME, Jure-Kunkel M, Azpilikueta A, Aznar MA, Quetglas JI, Sancho D*, Melero I*. (DS and IM are co-corresponding authors)
Cancer immunotherapy with immunomodulatory anti-CD137 and anti-PD-1 monoclonal antibodies requires Batf3-dependent dendritic cells.
Cancer Discov (2016) 6: 71-9
IF: 19.783

Cibrián D, Saiz ML, de la Fuente H, Sánchez-Díaz R, Moreno-Gonzalo O, Jorge I, Ferrarini A, Vázquez J, Punzón C, Fresno M, Vicente-Manzanares M, Daudén E, Fernández-Salguero PM, Martín P, Sánchez-Madrid F.
CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis.
Nat Immunol (2016) 17: 985-96
IF: 19.381

Garaude J, Acín-Pérez R, Martínez-Cano S, Enamorado M, Ugolini M, Nistal-Villán E, Hervás-Stubbs S, Pelegrín P, Sander LE, Enríquez JA*, Sancho D*. (JAE and DS are co-corresponding authors)
Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense.
Nat Immunol (2016) 17: 1037-45
IF: 19.381

D'Amato G, Luxán G, Del Monte-Nieto G, Martínez-Poveda B, Torroja C, Walter W, Bochter MS, Benedito R, Cole S, Martínez F, Hadjantonakis AK, Uemura A, Jiménez-Borreguero LJ, de la Pompa JL.
Sequential Notch activation regulates ventricular chamber development.
Nat Cell Biol (2016) 18: 7-20
IF: 18.699

Agüero J, Ishikawa K, Hadri L, Santos-Gallego CG, Fish KM, Kohlbrenner E, Hammoudi N, Kho C, Lee A, Ibáñez B, García-Álvarez A, Zsebo K, Maron BA, Plataki M, Fuster V, Leopold JA, Hajjar RJ.
Intratracheal Gene Delivery of SERCA2a Ameliorates Chronic Post-Capillary Pulmonary Hypertension: A Large Animal Model.
J Am Coll Cardiol (2016) 67: 2032-46
IF: 17.759



Arbab-Zadeh A, Fuster V.
The Risk Continuum of Atherosclerosis and its Implications for Defining CHD by Coronary Angiography.
J Am Coll Cardiol (2016) 68: 2467-78
IF: 17.759

Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, García-Alonso F, Lizano I, Arnold RJ, Rajda J, Steinberg G, Fuster V.
Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes.
J Am Coll Cardiol (2016) 68: 789-801
IF: 17.759

Bentzon JF.
Targeting Inflammation in Atherosclerosis.
J Am Coll Cardiol (2016) 68: 2794-6
IF: 17.759

Calvo E, García-Álvarez A, Vázquez J.
The Quest for Metabolic Biomarkers of Pulmonary Hypertension.
J Am Coll Cardiol (2016) 67: 190-2
IF: 17.759

Fernández-Alvira JM, Fuster V, Dorado B, Soberón N, Flores I, Gallardo M, Pocock S, Blasco MA, Andrés V.
Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis: The PESA Study.
J Am Coll Cardiol (2016) 67: 2467-76
IF: 17.759

Fernández-Jiménez R, Fuster V, Ibáñez B.
Reply: "Waves of Edema" Seem Implausible.
J Am Coll Cardiol (2016) 67: 1869-70
IF: 17.759

García-Ruiz JM, Fernández-Jiménez R, García-Álvarez A, Pizarro G, Galán-Arriola C, Fernández-Friera L, Mateos A, Nuño-Ayala M, Agüero J, Sánchez-González J, García-Prieto J, López-Melgar B, Martínez-Tenorio P, López-Martín GJ, Macías A, Pérez-Asenjo B, Cabrera JA, Fernández-Ortiz A, Fuster V, Ibáñez B.
Impact of the Timing of Metoprolol Administration During STEMI on Infarct Size and Ventricular Function.
J Am Coll Cardiol (2016) 67: 2093-104
IF: 17.759

Gómez E*, Fernández-Alvira JM*, Vilanova M, Haro D, Martínez R, Carvajal I, Carral V, Rodríguez C, de Miguel M, Bodega P, Santos-Beneit G, Peñalvo JL, Marina I, Pérez-Farinos N, DalRe M, Villar C, Robledo T, Vedanthan R, Bansilal S, Fuster V. (EG and JMF-A contributed equally)
A Comprehensive Lifestyle Peer-Group-Based Intervention on Cardiovascular Risk Factors: The Randomized Controlled Fifty-Fifty Program.
J Am Coll Cardiol (2016) 67: 476-85
IF: 17.759

Laclaustra M, Casasnovas JA, Fernández-Ortiz A, Fuster V*, León-Latre M, Jiménez-Borreguero LJ, Pocovi M, Hurtado-Roca Y, Ordovás JM, Jarauta E, Guallar E, Ibáñez B, Civeira F. (VF is corresponding author)
Femoral and Carotid Subclinical Atherosclerosis Association With Risk Factors and Coronary Calcium: The AWHS Study.
J Am Coll Cardiol (2016) 67: 1263-74
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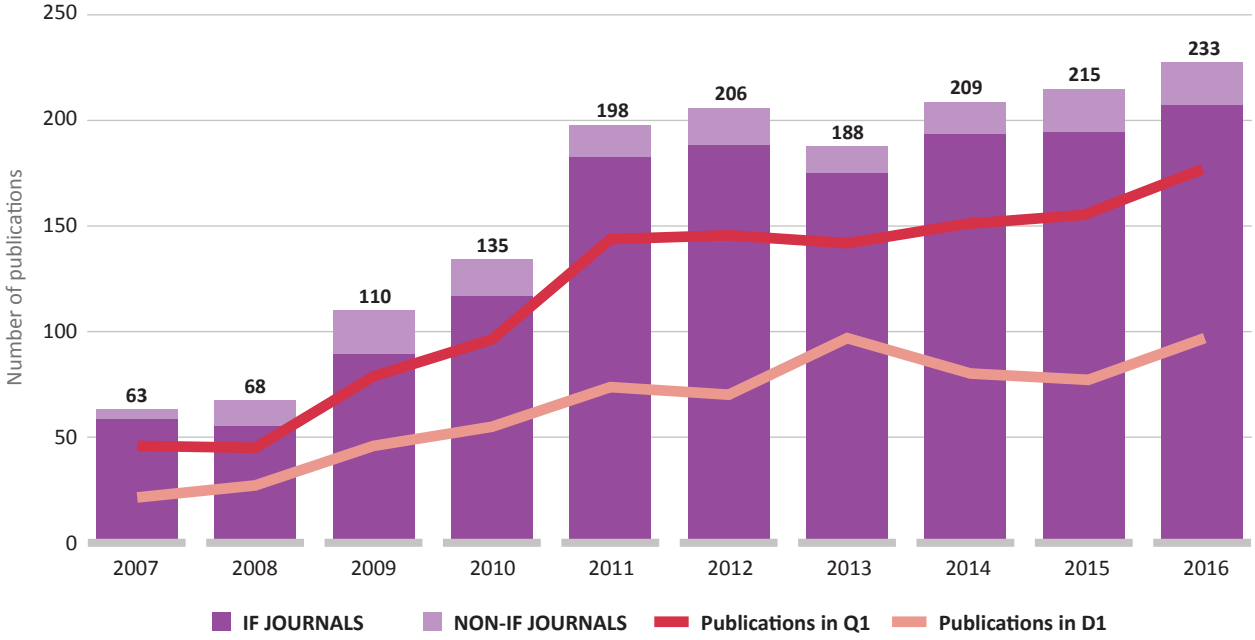

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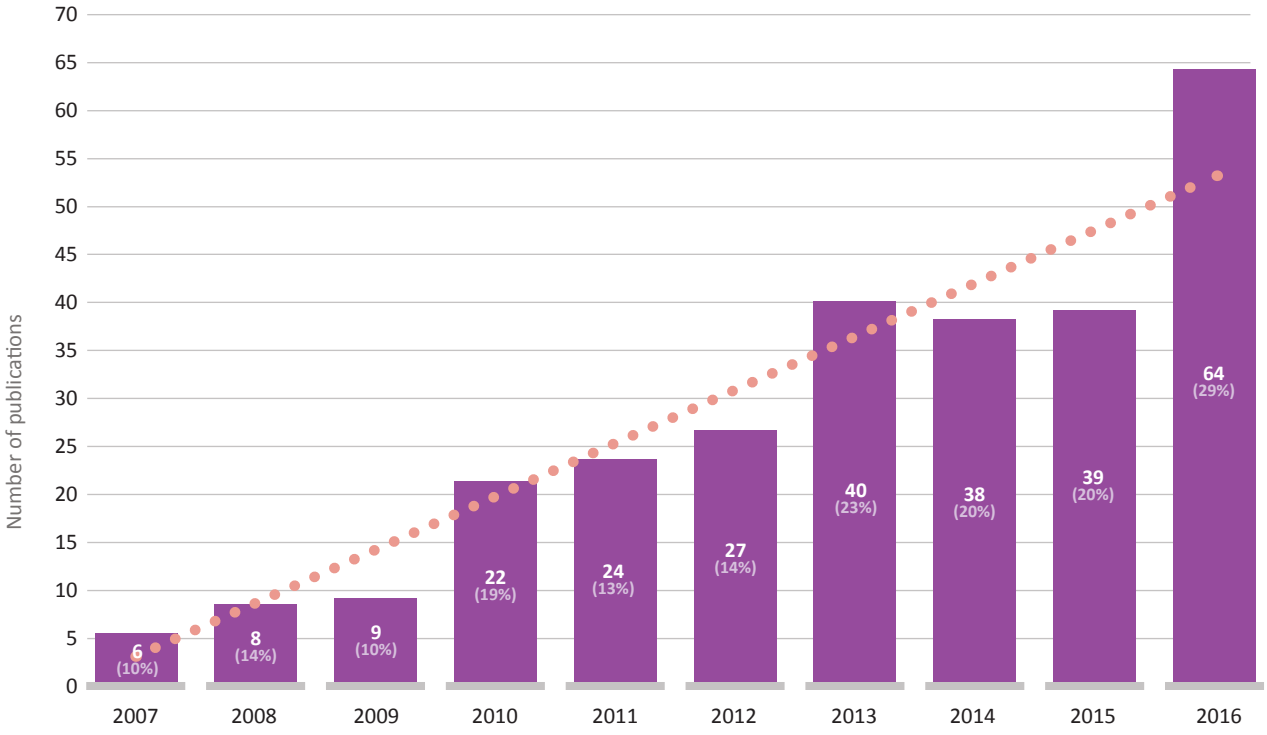

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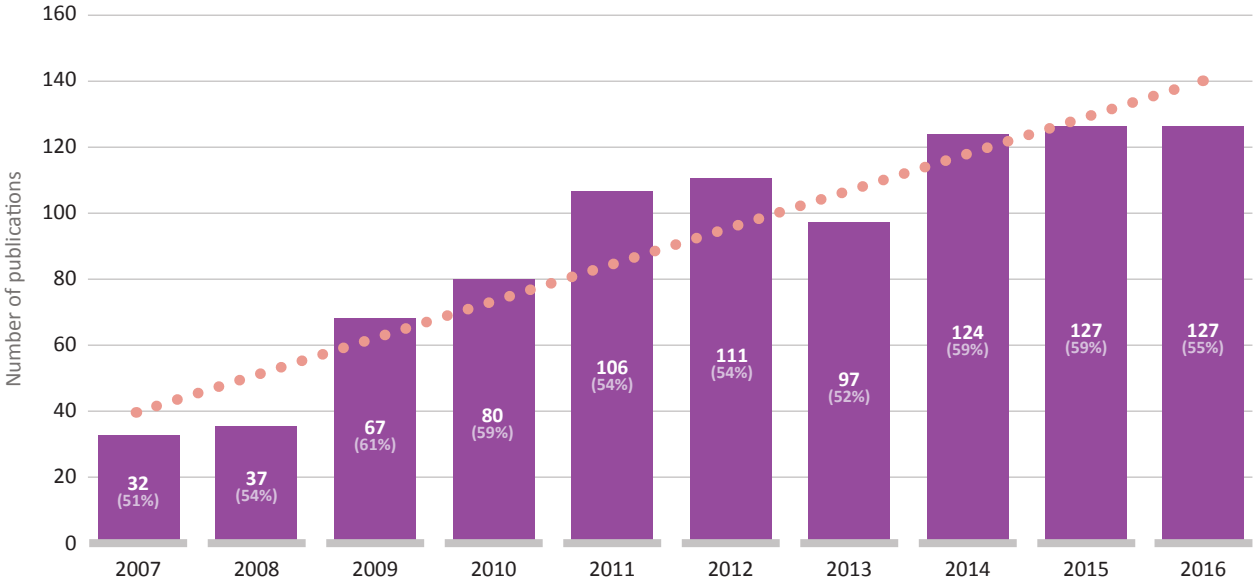

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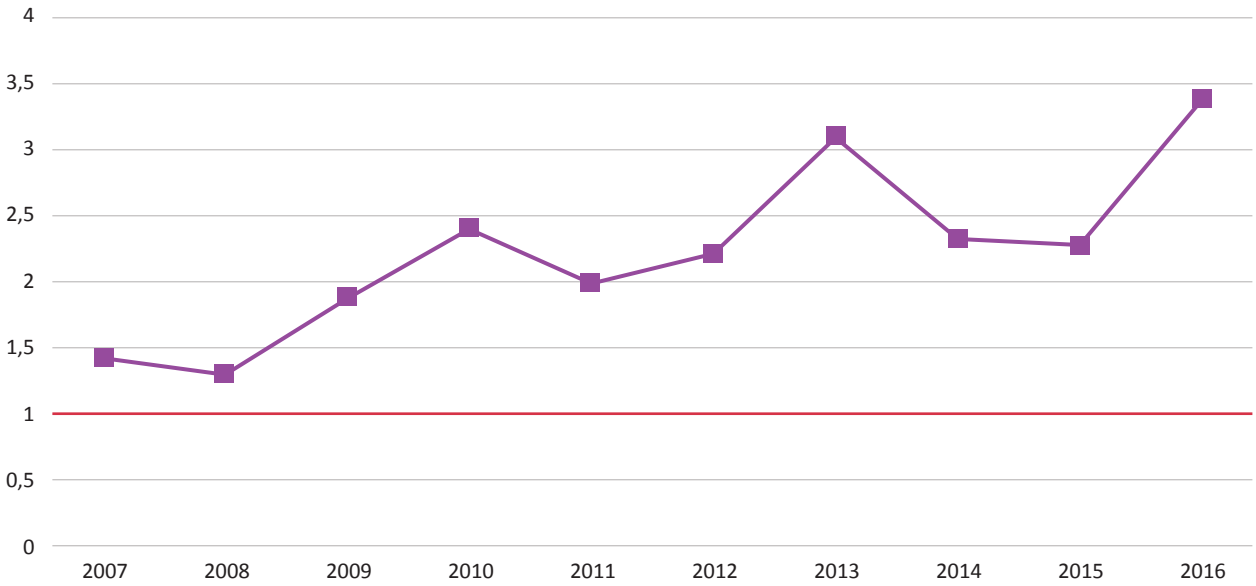

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Training is one of the CNIC's core activities, and the Center has devised a comprehensive training plan, **CNIC-JOVEN**, which includes programs for people at all levels, from senior high-school students to postdoctoral researchers and other professionals.

The CNIC-JOVEN Training Plan is designed to bring young people into biomedical research and create a strong base of talented researchers in the cardiovascular area.

Pre-university & Undergraduate Students

ACÉRCATE Program

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

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

Fellowships in 2016: 8

CICERONE Program

The CICERONE Program is open to Master´s and advanced undergraduate students studying toward a biomedicine-related university degree. Participants extend their scientific training through hands-on experience of laboratory-based biomedical research during the summer recess. In addition to carrying out a supervised research project, the students also attend CNIC seminars and workshops.

The aim of the program is to give students first-hand knowledge of biomedical research so that they can make informed choices about the possibility of pursuing a scientific career.

Fellowships in 2016: 24

Recent Graduates

CARDIOVASCULAR POSGRADUATE Program

The CNIC is developing a Cardiovascular Postgraduate Program, run through collaboration with Spanish universities. The first strand in this Program has been established through a formal agreement with the Universidad Autónoma de Madrid (UAM).

In the academic year 2015-2016, the CNIC partnered in the Masters in Molecular Biomedicine, offering a module in Cardiovascular Disease. This optional module provides a broad overview of cardiovascular biology, including perspectives from basic, clinical and translational research.

Dates: 12 January-17 February 2016
Venue: CNIC
UAM MSc Students: 14
CNIC PhD students: 17

MASTER Program

This grants program provides individual funding for study towards a Masters degree at a Spanish university. The program is directed at students who are going to study for a PhD in one of the CNIC's laboratories: completion of an official Masters (Máster Oficial) has been introduced as an obligatory stage towards a PhD in Spain, in accordance with the Bologna process to standardize academic qualifications across Europe.

Fellowships in 2016: 19

PREDOCTORAL (PhD) Program

The PREDOCTORAL Program provides a unified framework for all researchers at the CNIC who are working toward a doctoral degree. All predoctoral researchers are signed up to this program, independently of their funding source.

The aims of the program are as follows:

> To ensure uniform quality of predoctoral training at the CNIC
> To ensure fair and equal access of predoctoral researchers to training opportunities

Graduate students at the CNIC who obtained their PhD degrees in 2016: 9
Graduate students studying for their PhD theses at the CNIC during 2016: 101

LA CAIXA-SEVERO OCHOA INTERNATIONAL PhD Program

The *la Caixa* Foundation is a non-profit organisation funded by the third largest bank in Spain, the Caja de Ahorros y Pensiones de Barcelona (*la Caixa*). Since 1982, the *la Caixa* Foundation has run various fellowship programs to enable Spanish students to study postgraduate courses in Spain and abroad. Thanks to this support, thousands of students have been able to pursue their studies.

The *la Caixa* Foundation funds fellowships at the CNIC in recognition of the Center's status as one of the Spanish centers of excellence named in the first and second editions of the Severo Ochoa Award. In 2016 the *la Caixa* Foundation provided support for two highly qualified graduate students to carry out their experimental work towards obtaining a PhD degree at the CNIC within an International PhD Program.

***la Caixa* Fellowships in 2016: 2**

Graduates & Medical Professionals

RES@CNIC Program

The aim of the Res@CNIC Program is to offer medical professionals, during the first years of their specialization period as resident interns, the opportunity to learn about and become familiar with the latest techniques in cardiovascular research being used in the CNIC's laboratories, under the guidance of a CNIC scientist. Residents participating in RES@CNIC also receive training in theoretical aspects of cardiovascular research through a taught module run by experts. The Program also seeks to create links and collaborations so that on conclusion of their MIR specialization period, these professionals will have the chance to undertake research projects in their respective National Health System centers in partnership with the CNIC.
RES@CNIC was launched in 2012. Students selected for the fifth call will join the CNIC during January and February 2016.

Selected Candidates for the fourth call: 15

INVESMIR Program

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

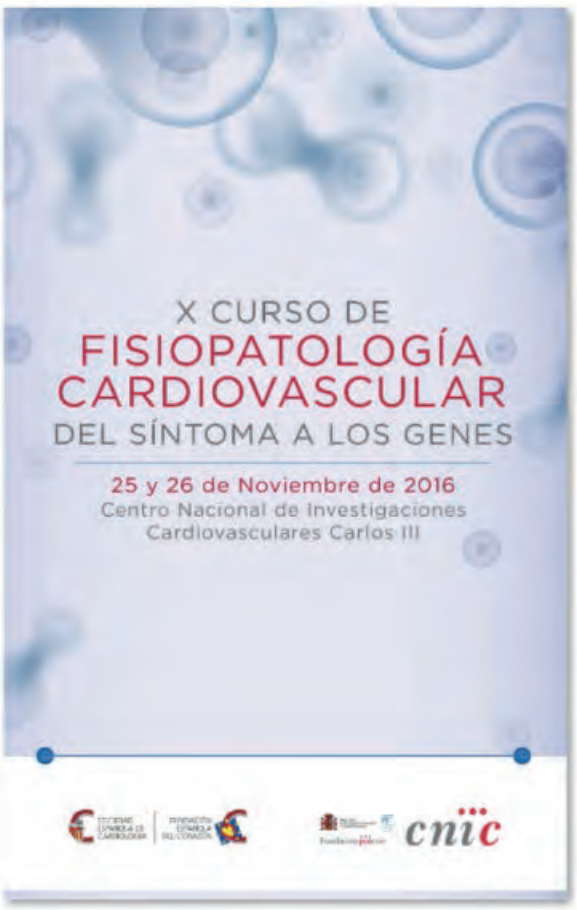
An important aim of the program is that participants establish contacts and collaborations in the CNIC that will support them, after completion of their MIR specialization training, in pursuing their own research projects at their centers within the Spanish National Health System.

Fellowships in 2016: 3

CARDIOVASCULAR PATHOPHYSIOLOGY Course: From symptoms to genes

The CARDIOVASCULAR PATHOPHYSIOLOGY course is offered in collaboration with the Sociedad Española de Cardiología. This course offers a translational vision of cardiology to medical specialists by introducing them to the study of pathophysiology and basic research. Participants are given an overview of the molecular and genetic factors that underlie cardiac diseases and gain an up-to-date vision of cardiac physiology.

Dates: November 25 and 29, 2016
Venue: CNIC Lecture Hall
Attendees: 76



VASCULAR BIOLOGY Course

Dr. Valentín Fuster delivers this lecture series, sponsored by FERRER, on "Vascular biology: basic and clinical research" as part of the summer program of the *Universidad Internacional Menéndez Pelayo* (UIMP).

Dates: July 18-19, 2016
Attendees: 280

Research Professionals

CNIC International Postdoctoral Program

The CNIC International Postdoctoral Program (CNIC IPP) is aimed at supporting transnational mobility of postdoctoral researchers and broadening and deepening their individual competence, particularly in relation to the acquisition of complementary skills needed to become an independent group leader in the future. The program offers fellowships for researchers who hold a PhD Degree at the time of the application deadline.

Fellowships awarded in 2016: 4

The CNIC-IPP is supported by the CNIC and the European Commission under the FP7 Marie Curie Actions- PEOPLE- COFUND Programme.

Research Staff and Students

CNIC Course in Statistics 2016-17

A series of 11 workshops aimed at giving attendees a deep understanding and practical knowledge of the tools used in statistics. Six of the workshops in this program were held in 2016:

Session 1- (21 Sept 2016) CNIC Statistics Course: Session 1- Introductory overview of statistics in medical research.
Attendees: 84

Session 2- (5 Oct 2016) Quantitative outcomes (1): Modeling uncertainty.
Attendees: 72

Session 3- (19 Oct 2016) Quantitative outcomes (II): Hypothesis testing.
Attendees: 42

Session 4- (2 Nov 2016) Design of animal model experiments and publication requirements.
Attendees: 30

Session 5- (19 Nov 2016) Design of clinical trials.
Attendees: 12

Session 6- (30 Nov 2016) Analysis of binary and time-to-event outcomes.
Attendees: 22

Seminars and Events

January

11 **Ido Amit**
Weizmann Institute
Rehovot, Israel

18 **Andrés J López-Contreras**
Center for Chromosome Stability. University of Copenhagen
Denmark

25 **Dennis Discher**
University of Pennsylvania
Philadelphia, USA

February

08 **Dianna M. Milewicz**
The University of Texas Health Science Center
Houston, USA

12 **Michael Potente**
Max Planck Institute for Heart and Lung Research Angiogenesis & Metabolism Laboratory
Bad Nauheim, Germany

22 **Dan Roden**
Vanderbilt University School of Medicine
Nashville, USA

March

07 **Brendan D. Manning**
Harvard School of Public Health
Boston, Massachusetts, USA

15 **Leica - CNIC 1st Practical School in Super-Resolution Microscopy**

April

04 **Ben Lehner**
Centre for Genomic Regulation
Barcelona, Spain

08 **Niroshana Anandasabapathy**
Harvard Skin Disease Research Center
Boston, Massachusetts, USA

11 **3rd CNIC-ZEISS Course**
Light Microscopy and Practical Application

18 **Yixian Zheng**
Carnegie Institution
Baltimore, Maryland, USA

21 **Ya Guo**
MRC Clinical Sciences Centre
Imperial College London
UK

28 **Invitrogen Course. Invitrogen™ EVOS™ imaging systems. Simply stunnihn**

28 **Sami Noujaim**
University of South Florida
Tampa, USA

May

09 **Stefan Neubauer**
Oxford Centre for Clinical Magnetic Resonance Research (OCMR) & Radcliffe Department of Medicine
University of Oxford
John Radcliffe Hospital
UK

23 **Isabel Fariñas**
Universidad de Valencia
Spain

June

02 **Andreas Schlitzer**
LIMES-Institute, University of Bonn
Germany

06 **Hiroshi Hamada**
RIKEN Center for Developmental Biology
Kobe, Japan

07 **Lai Guan Ng**
SIgN-Singapore Immunology Network
Singapore

10 **Israel Valverde**
Hospital Virgen del Rocío & Instituto de Biomedicina de Sevilla
Spain

August

08 **Mark A Febbraio**
Garvan Institute of Medical Research
Sydney, Australia

September

16 **Francesc Posas**
Universitat Pompeu Fabra
Barcelona, Spain

19 **Ludger Johannes**
Institute Curie
Paris, France

21 **CNIC Statistics Course**
Session 1- Introductory overview of statistics in medical research

October

03 **Michael Dustin, NDORMS**
The University of Oxford
Kennedy Institute of Rheumatology
Headington, UK

05 **CNIC Statistics Course**
Session 2: Quantitative outcomes (1): Modeling uncertainty

19 **CNIC Statistics Course**
Session 3: Quantitative outcomes (2): Hypothesis testing

27 **Caro Amezcua**
Yale University
New Haven, Connecticut
USA

November

02 **CNIC Statistic Course**
Session 4: Design of animal models experiments and publication requirements

03 **Vincent Christoffels**
Academic Medical Center University of Amsterdam
The Netherlands

04 **V CNIC Conference**
Mechanical forces in physiology and disease

08 **Semana de la Ciencia**
Jornada ACÉRCATE a la investigación del CNIC

11 **CNIC PhDay 2016**
The PhD and beyond

12 **Semana de la Ciencia**
Un día en familia en CNIC

14 **Francisco Javier Quintana**
Ann Romney Center for Neurologic Diseases
Brigham and Women's Hospital
Harvard Medical School
Boston, USA

16 **CNIC Statistics Course**
Session 5: Design of clinical trials

25 **X Curso de Fisiopatología Cardiovascular**
Del síntoma a los genes

28 **Gerald Dorn**
Washington University
St. Louis, USA

30 **CNIC Statistics Course**
Session 6: Analysis of binary and time-to-event outcomes

December

12 **Hugh Grosvenor Calkins**
The Johns Hopkins Hospital
Baltimore, USA

Awards 2016

Fuster, Valentín

- The Best European Research and Development in Cooperation (11th Edition) from the *Fundación para el Conocimiento madri+d*, for the SECURE project.
- *Premio Ciencias de la Salud*, from the *Fundación Caja Rural de Granad*a ,XII Edition, for his work on "The Progression of Early Subclinical Atherosclerosis".

Alonso Herranz, Laura

- Roche Prize for the best presentation at the XXXVIII *Sociedad Española de Bioquímica y Biología Molecular* Meeting, Salamanca, 5 to 8 September, for "Unraveling new roles for macrophages in cardiac repair upon myocardial infarction".

Ezkurdia, Iakes

- Juan Pablo Albar Prize from the *Sociedad Española de Proteómica* for the best paper published 2014-2015: "Multiple evidence strands suggest that there may be as few as 19000 human protein-coding genes" Human Molecular Genetics (2014) 15: 5866-78.

Sabio, Guadalupe

- *Sociedad Española de Bioquímica y Biología Molecular*-BIOTOOLS Young Investigator Prize, for her work on stress kinase signaling mechanisms involved in metabolic disease.

The CNIC consolidates and expands its alliances to investigate, train, innovate and transfer.

In 2016, the CNIC signed 47 interinstitutional agreements to create or consolidate partnerships.

In the education sector, the CNIC expanded its already wide academic network by signing new collaboration agreements with universities in Spain (Universidad Europea, Universidad CEU San Pablo, Universidad Pompeu Fabra, Universidad de Córdoba, Universidad de Barcelona, Universidad Miguel Hernández, Universidad de Sevilla, and Universidad Rey Juan Carlos). Moreover, the CNIC also strengthened its links with foreign universities, mostly through the establishment of student exchange programs and short visits for practical work in the CNIC's laboratories. Two new international agreements were signed last year (Université Paris Diderot, France, and University of Amsterdam, The Netherlands).

Links with the clinical sector have been consolidated through the signing of new agreements with Spanish clinical organizations such as the *Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz de Madrid* (IIS-FJD) to facilitate the development of clinical assays, exchange and training of medical professionals and scientists. This agreement is specifically focused on promoting the clinical application of research results in patients with acute myocardial infarction. Moreover, development of multicenter randomized clinical trials coordinated by the CNIC has been strengthenened by the establishment of a new partnership with the E*mpresa Pública de Emergencias Sanitarias* (EPES 061). This collaboration will act as a central contact point for better management and treatment of cardiac arrest in Spain.

Finally, thanks to the new strategic alliance established between the CNIC and the *Centro Vasco de Investigación Cooperativa en Biomateriales* (BiomaGUNE), the ReDIB (*Red Distribuida de Imagen Biomédica*) Singular Scientific-Tehcnological Infrastructure (SSTI) has launched its first 2 calls for proposals, offering the scientific and industrial communities a unique infrastructure in biomedical imaging.

From left to right: Dr. Petra Sanz (Head of Cardiology, Hospital Universitario Rey Juan Carlos), Dr. Vicente Andrés (Director of Basic Research Department, CNIC), D. Alberto Sanz (Managing Director, CNIC), Dr. Borja Ibáñez (Director of Clinical Research Department, CNIC and Head of Cardiology Research, Fundación Jiménez Díaz, FJD), Dr. Valentín Fuster (General Director, CNIC), D. Juan Antonio Álvaro de la Parra (Managing Director, Hospital Universitario FJD and Hospital General de Villalba), Dr. Carmen Ayuso (Director of Instituto de Investigación Sanitaria de la FJD and Head of Genetics Service, FJD), Dr. Felipe Navarro (Head of Cardiology of Hospital General de Villalba and Head of Intervention Cardiology, FJD) and Dr. Jose Angel Cabrera (Head of Cardiology, Hospital Quirón de Madrid-Pozuelo).

Public-Private Partnership

In December 2005, the Spanish Government signed an agreement with a group of some of the most important Spanish businesses (Pro CNIC Foundation, http://www.fundacionprocnic.es) to sponsor the CNIC.

Since the signing of this agreement, the CNIC's funding has been based on a public-private partnership (PPP) of a broad, socially-committed nature. The Pro CNIC Foundation does much more than provide the CNIC with money; it also contributes its accumulated managerial and business expertise. Representatives of the Pro CNIC Foundation sit on the CNIC's Board of Trustees and actively participate in the management, planning and decision taking related to the Center.

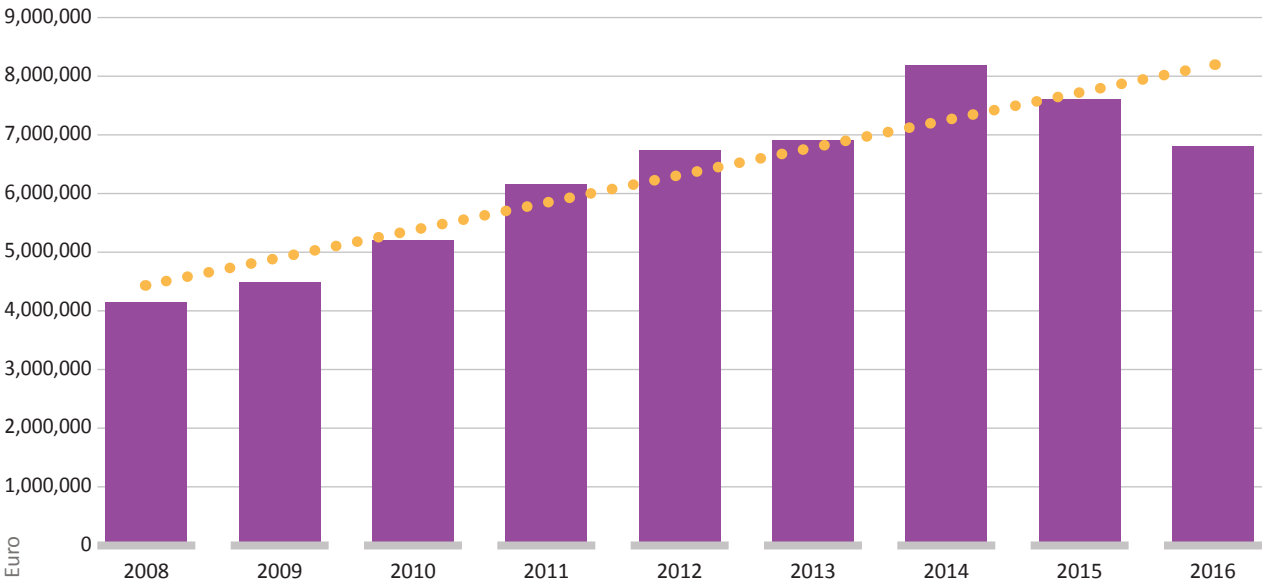
A major strength of this socially-committed PPP model is that it provides a more solid base than traditional forms of charitable financing, giving the CNIC a more stable financial base than it would have if it depended on sporadic donations from benefactors. This stability gives the CNIC greater freedom to commit itself to long-term, high-return research strategies in collaboration with public and private institutions, and allows for a more effective use of its own resources generated through competitive projects and the exploitation of intellectual property rights.

The current members of the Pro CNIC Foundation are **Acciona**, **BBVA**, **Endesa**, **Fundación Abertis**, **Fundación Mutua Madrileña**, **Fundación Mapfre**, **Santander**, **Fundación Ramón Areces**, **Fundación Repsol**, **Gas Natural Fenosa**, **Grupo Prisa**, **Inditex**, **la Caixa**, and **Telefónica**.

Private Funding

National Competitive Funding

Since 2006 the CNIC has attracted **more than €73 million from national competitive sources**. In 2016 alone the CNIC research attracted more than €11 million from public funding agencies, including renewal of the prestigious accreditation as a *Severo Ochoa* Center of Excellence for a further 4 years (2016-2019)



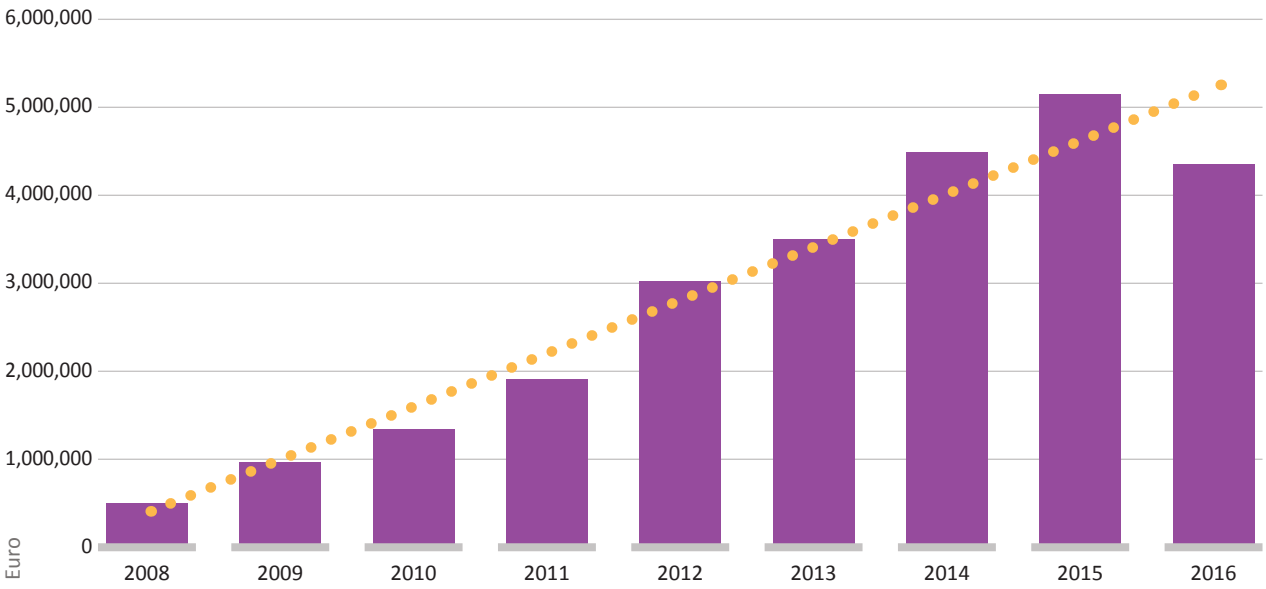
International Competitive Funding

Since 2006, the CNIC has attracted **more than €34 million from international competitive sources**.

The CNIC participated in **34 projects funded under the European Commission's Seventh Framework Programme (FP7)** and is engaged in **16 projects** funded under the EU Research and Innovation **Horizon 2020 (H2020)** programme. Moreover, the Center is the top-ranking Spanish institution for funding awarded under the EC Societal Challenge *Health, Demographic Change and Wellbeing* (H2020-2014 call).

The international scientific competitiveness of the CNIC's research groups is highlighted by their high representation in projects funded by the **European Research Council (ERC)**, which funds Europe's brightest minds to tackle innovative research challenges. The CNIC contributes to the achievement of this goal through **5 ERC projects awarded under FP7 and 4 awarded under H2020**.

The CNIC´s commitment to researcher training is confirmed by its prominent participation in the **Marie Curie-Skłodowska** programme: **21 projects in FP7** and **5 in H2020**, including **1 Coordinated Industrial Doctorate ITN**.



Sixteen inventions are currently being filed, nine of them in partnership with other institutions.

TECHNOLOGY OFFERS AVAILABLE FOR OUT-LICENSING

TITTLE	INVENTORS	APPLICANTS	PATENT APPLICATIONS
Methods of using the Calcineurin A variant CnAB1 for the treatment of cardiac hypertrophy	Enrique Lara Pezzi, Nadia Rosenthal, María López Olañeta, María Villalba Orero, Jesús Gómez Salinero.	CNIC, EMBL	PCT, US, EP
Uso de agonistas selectivos de receptores beta-3 adrenérgicos para el tratamiento de hipertensión pulmonar	Borja Ibañez Cabeza, Valentín Fuster Carulla, Ana García-Álvarez	CNIC , CLINIC	PCT, JP, US, EP
Terapia neuroregeneradora/neurocompensatoria para el tratamiento de las neoplasias mieloproliferativas	Simón Méndez Ferrer, Lorena Arranz Salas, Joan Isern Marín	CNIC	PCT, JP, US, EP
Single core radionuclide-metal oxide nanoparticles: a new biocompatible nanosystem for dual hot spot imaging	Jesús Ruiz-Cabello Osuna, Fernando Herranz Rabanal, Riju Bhavesh, Juan Pellico Sáez	CNIC, UCM	EP, PCT
Method of predicting or prognosticating neurological performance in patients who have suffered a cardiac arrest and optionally comatose status due to ventricular fibrillation	David Filgueiras Rama, Esteban López de Sá y Areses, José Millet Roig, Conrado Javier Calvo Sainz	CNIC, UPV, Hospital Universitario La Paz	EP, PCT
Method and system for generating MR images of a moving object in its environment	Javier Sanchez Gonzalez, Nils Dennis Nothnagel, Borja Ibáñez Cabeza, Rodrigo Fernández Jiménez, Valentín Fuster Carulla	Philips, CNIC	EP, PCT
Método de detección de predisposición a padecer cardiopatía dilatada	Pablo Garcia Pavía, Sofía Cuenca, Laura Padrón de Vaumas, Enrique Lara Pezzi	Fundación Investigación Hospital Puerta de Hierro; CNIC	ES
MiRNA compositions for the treatment of mature B-cell neoplasms	Almudena Rodríguez Ramiro, Nahikari Bartolomé Izquierdo, Virginia García de Yébenes Mena	CNIC	EP, PCT
p38 inhibitors for the treatment and prophylaxis of liver cancer	Ana Martinez Gil, Carmen Gil Ayuso-Gontán, Guadalupe Sabio Buzo, Antonia Tomás Loba, Bárbara González Terán, Elisa Manieri	CNIC, CSIC	EP, PCT
Procedimiento de obtención de datos útiles para el diagnóstico de cardiomiopatías	María Pilar Martín Fernández; Raquel Sánchez Díaz, Adela Matesanz Marín, Luis Jesús Jiménez Borreguero, Francisco Sánchez Madrid	CNIC	EP, PCT
Tratamiento y diagnóstico de Aneurisma Aórtico Torácico	Juan Miguel Redondo Moya, Nerea Méndez-Barbero, Jorge Oller Pedrosa, Miguel Ramón Campanero García	CNIC, CSIC, UAM	EP, PCT
Nuevos radiofármacos para el diagnóstico *in vivo*	Jesús Ruiz-Cabello, Jesús Mateo, Samuel España	CNIC	EP

Patent Applications:
ES - Spain
PCT - International
EP - Europe
US – USA
JP- Japan

ACTIVE LICENSED AGREEMENTS

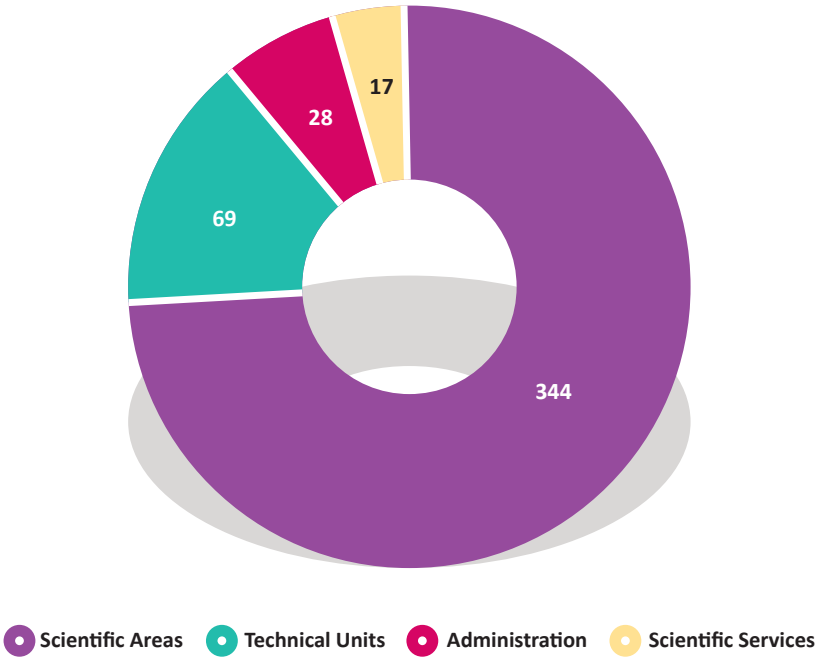
TITLE: "Capsule for the prevention of cardiovascular diseases"
APPLICANTS: CNIC, FERRER
LICENSEE: FERRER

TITLE: "Method for identifying senescent mesenchymal stem cells"
APPLICANTS: CNIC
LICENSEE: NIMGenetics

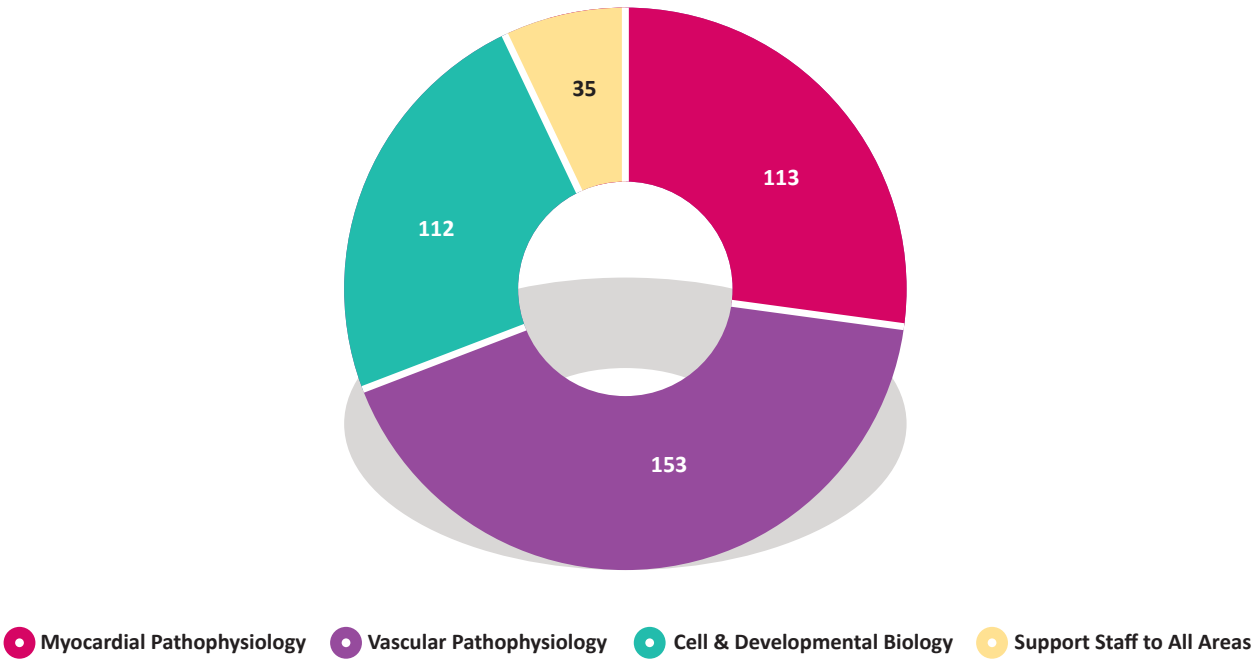
TITLE: "Vectores de expresión de proteínas: plásmidos pGEX-Calcineurina, pGEX-FKBP12 y pGEX-Ciclofilina A"
APPLICANTS: CNIC
LICENSEE: PROTEIN ALTERNATIVES S.L.

TITLE: "New biosafe viral vectors: non-integrating lentiviral episomes"
APPLICANTS: CNIC
LICENSEE: VIVEbio TECH S.L

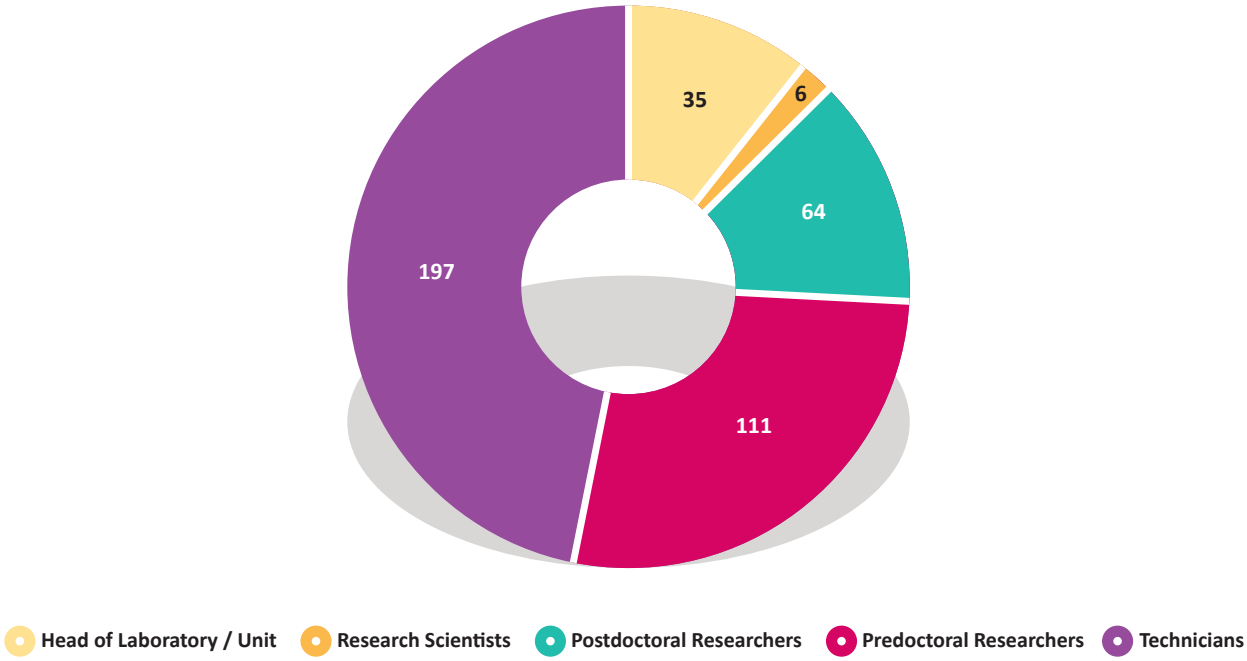
CNIC STAFF 2016 (458)



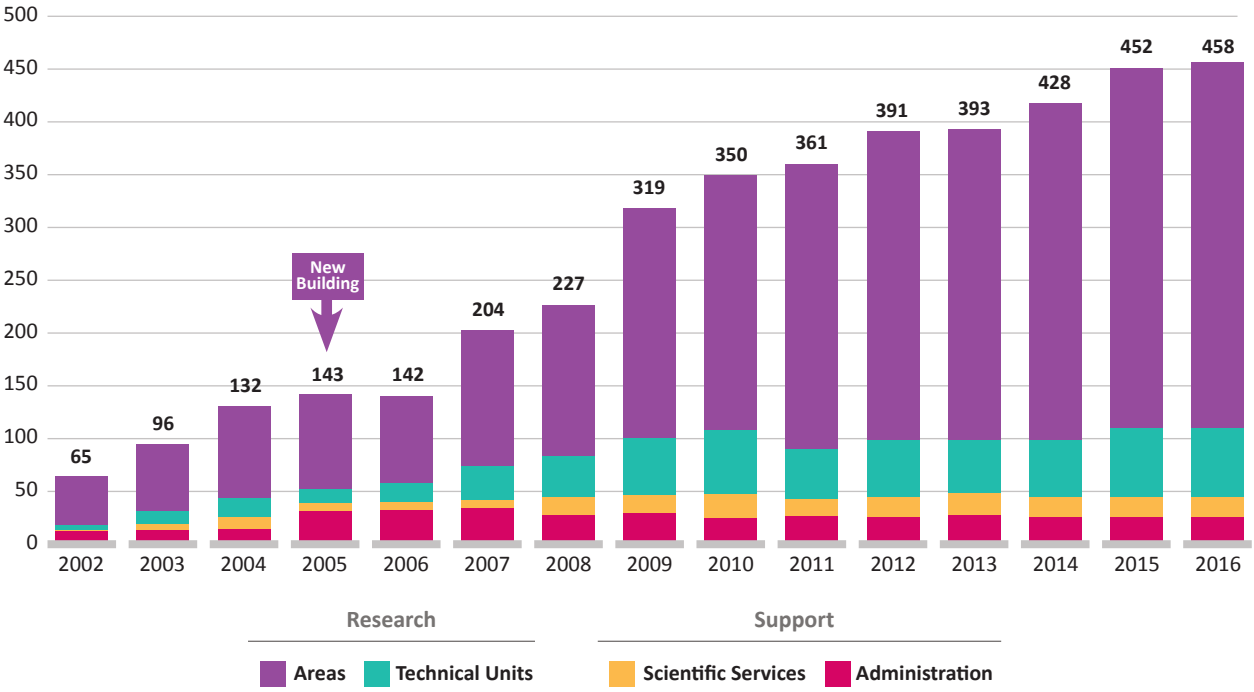
STAFF BY RESEARCH AREA 2016 (413)



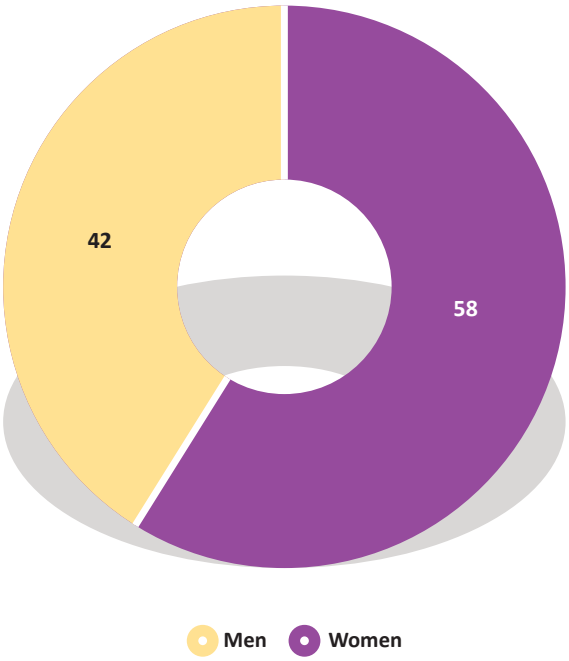
CNIC RESEARCH STAFF 2016 (413)



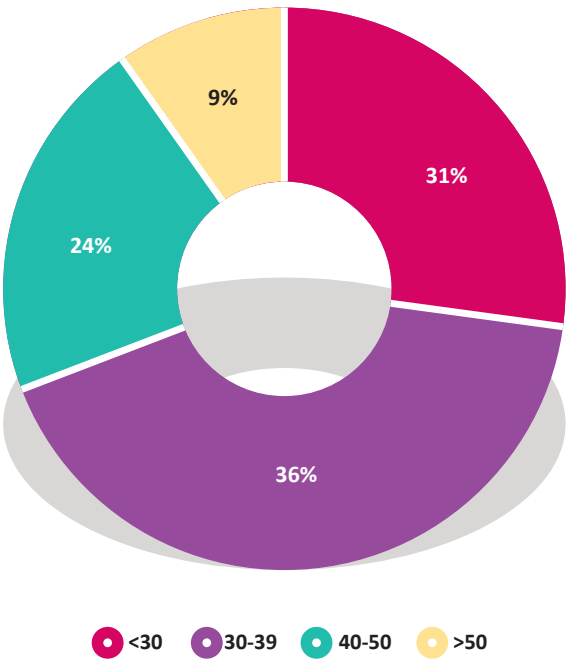
GRADUAL GROWTH CURRENT STATUS



GENDER DISTRIBUTION 2016



AGE DISTRIBUTION 2016



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