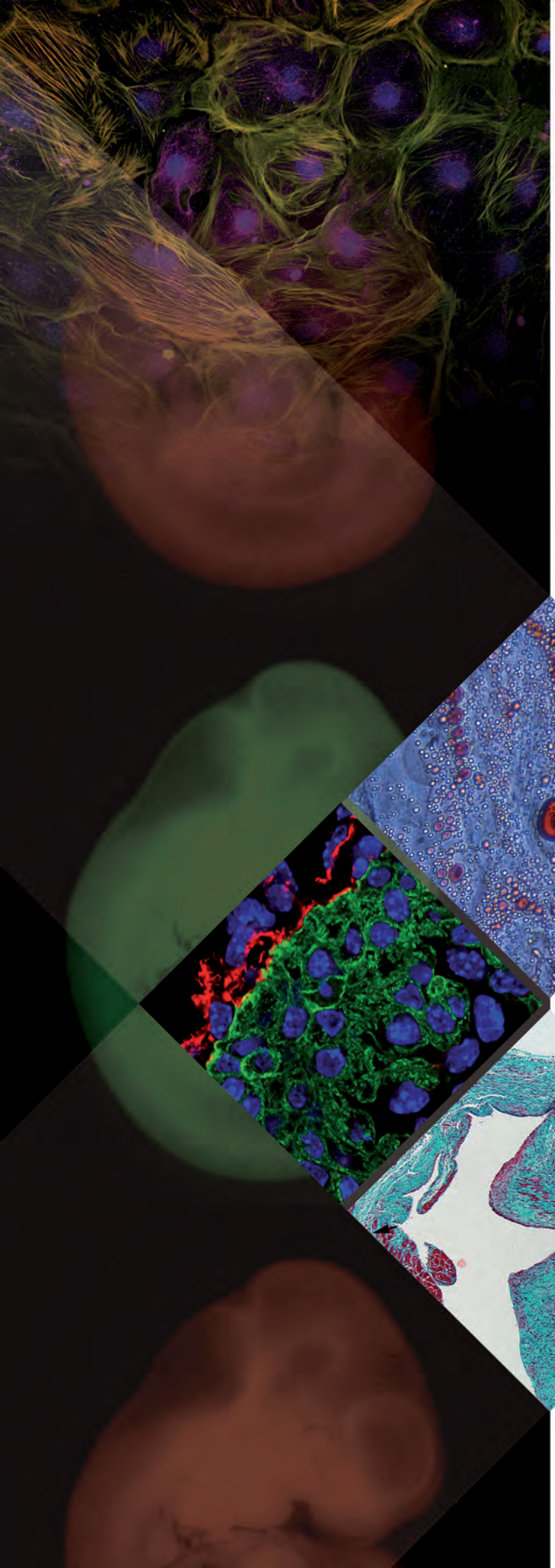
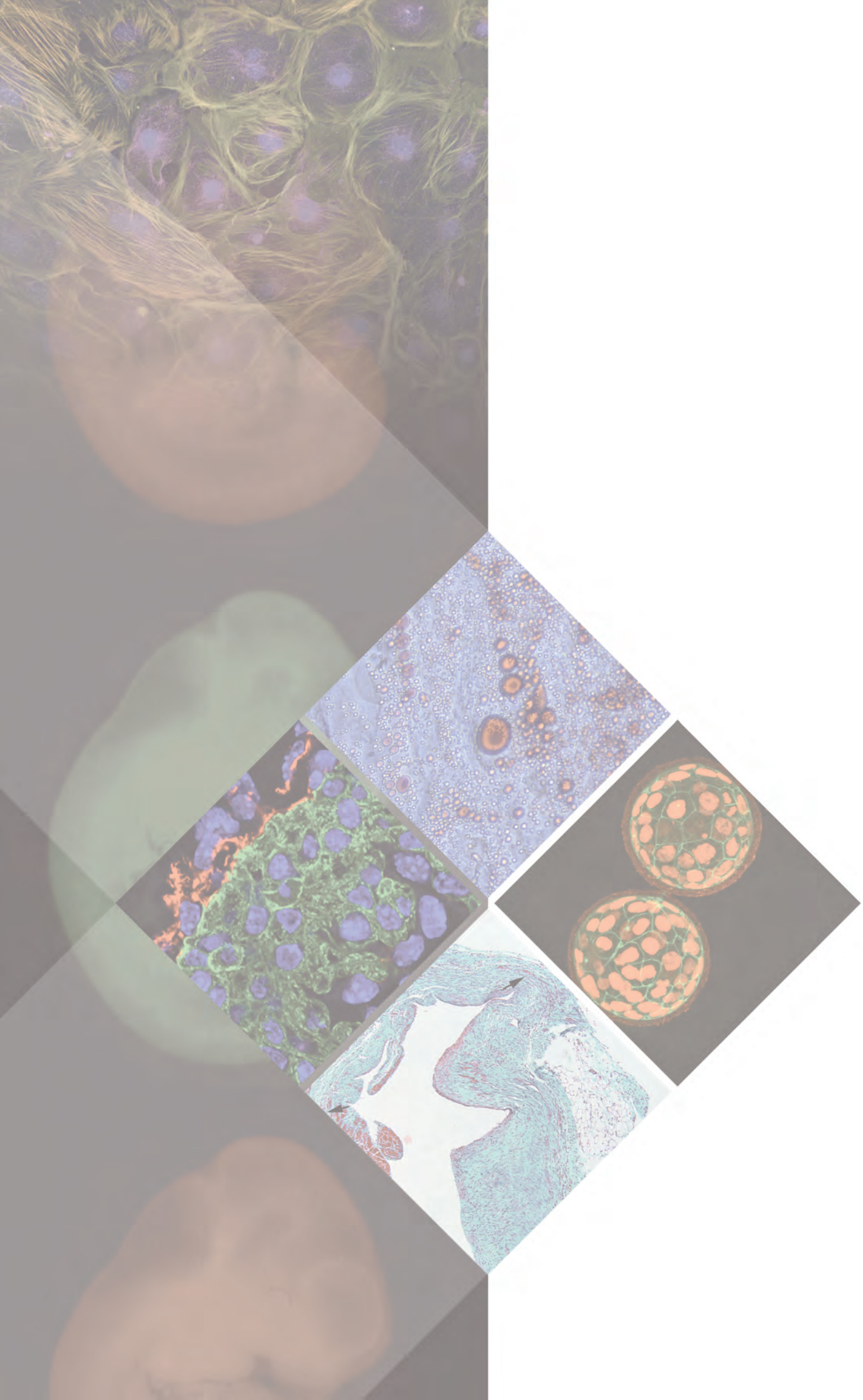


cnïc

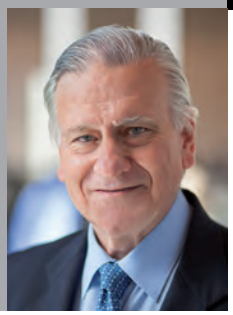
Fundación
Centro Nacional de
Investigaciones
Cardiovasculares
Carlos III

SCIENTIFIC REPORT 2013

EXCELENCIA
SEVERO
OCHOA



cnïc.es



Valentín Fuster

One of the most enjoyable aspects of 2013 was to witness the growing list of new CNIC articles making waves in top flight journals. And it was especially pleasing to see that while some of the hard hitters came from senior researchers, others were the work of groups led by younger investigators who have established their groups at the CNIC over the last few years.

It is also wonderful to witness the comprehensive scope of these publications, which span the arc of the CNIC's activity. We had articles investigating fundamental cellular processes—in energy metabolism (José Antonio Enriquez), the self-selection of the fittest cells early in embryonic development (Miguel Torres), and intercellular communication via the transfer of nanovesicle-encapsulated regulatory RNA molecules (Francisco Sánchez-Madrid). Meanwhile, other studies generated knowledge of developmental and physiological processes more directly related to cardiovascular disease, for example the role of heartbeat in the generation of the epicardial layer that envelops the heart (Nadia Mercader) or the role of diurnal cycles in regulating hematopoietic stem cell activity (Andrés Hidalgo). Studies with a more explicit clinical orientation included the identification of potential new avenues toward the treatment of atherosclerosis (Juan Miguel Redondo), Progeria aging disease (Vicente Andrés) and heritable cardiomyopathy (José Luis de la Pompa). Among studies with immediate clinical implications, a highlight was the first data from the METOCARD trial, led by Borja Ibañez and Valentín Fuster. The results, published in October, reveal an astounding ability to limit infarct size simply by administering a cheap off-the-shelf drug during transit of a heart attack patient to hospital.

Other developments in our translational clinical projects included the completion of baseline data for the PESA trial, run by the CNIC together with *Grupo Santander* and the *Fundación Botín*. The study is still in its early stages, but the preliminary results support the potential of non-invasive imaging analysis of multiple vascular territories to refine the diagnosis of atherosclerosis in asymptomatic patients. Advances were also made with the CNIC-Ferrer polypill project, with licencing of the first formulation extended to Nicaragua and the Dominican Republic. 2013 also saw the publication of the first results of Program SI!, a school intervention aimed at promoting cardiovascular health through the acquisition of healthy behaviors from early childhood. The findings show the importance of home environment and of involving parents in the intervention from the earliest stages.

The Center's performance was acknowledged in a very positive evaluation by the external Scientific Advisory Board, which also gave favorable verdicts for the Epidemiology, Atherothrombosis and Imaging department and one of our senior group leaders. The next Center evaluation will be on June 6 2014, when several more group leaders will be evaluated.

Further recognition came from the European Commission, which singled out the CNIC's employment policy within its Human Resources Strategy for Researchers (HRS4R) initiative. The CNIC is one of only four centers in Spain to carry the HRS4R logo, which recognizes researcher-centered employment policies that conform to the principles of the EU's European Charter for Researchers and The Code of Conduct for the Recruitment of Researchers. On the subject of recruitment, it was a pleasure to welcome David Filgueiras, who joined the Center as a new group leader in November. David previously worked at the renowned Center for Arrythmia Research at the University of Michigan, and brings his expertise in this area to the CNIC.

Our strategic alliances are integral to the CNIC mission, and it was with great pleasure last November 5 that we welcomed *Fundación Mapfre*, represented by Mapfre CEO Antonio Huertas, as the fourteenth member of the ProCNIC Foundation. The entry of another big player in Spanish civic life into this social covenant provides a further guarantee of excellence, and helps to weave the CNIC ever more closely into the social fabric of our nation. Also in November, the CNIC joined the *Fundación Jesús Serra* program for promoting scientific research in Spain, signaling the start of another mutually beneficial partnership. And earlier in the year we renewed our joint agreement with Spanish Society of Cardiology. Our partnership, which has supported training for resident cardiologists in Spain since 2009, is opening up new training opportunities internationally with the Mount Sinai Experience, held for the first time in May. In this program, the SEC and CNIC bring Spanish and US cardiologists together at Mt. Sinai Medical Center to share experiences and learn about systems of patient care operating at this world leading hospital.

Miguel Torres

A major highlight of our CNIC-Joven Training Program last year was the injection, in June, of €1.6 million from the European Commission to fund 30 postdoctoral fellowships. This funding, through the COFUND Programme, supplies 40% of the financing for our flagship postdoctoral program, which provides the best young talent with the support to start off a career in research. The program will create six three-year posts each year over the next five years. For earlier-stage researchers, the La Caixa-Severo Ochoa International PhD Program continued last year, with funding coming in for five new studentships to recruit from among the best graduates in Europe,

Another important element of our training program is our specialist areas of technological expertise. In March, the Center hosted and co-organized the international workshop 'Translational Aspects of Cardiovascular and Pulmonary Imaging', at which experts showcased the translational potential of diagnostic imaging technologies to researchers, clinicians and representatives of the pharmaceutical industry.

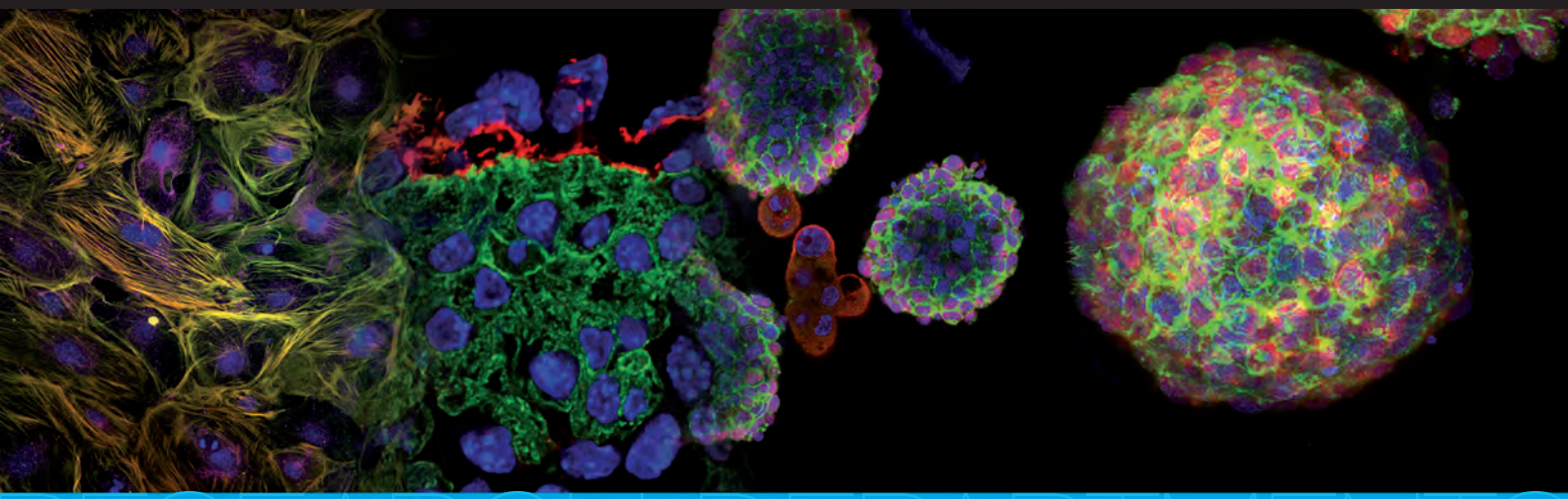
The innovative technologies in the CNIC's portfolio were also on display at BioAsia, held in Hyderabad in January. This biotech fair, the largest in India, gave our technology transfer office the opportunity to promote the CNIC at intergovernmental meetings and discuss possible areas of collaboration. Then, in May, it was the CNIC's turn to act as host, welcoming representatives from 11 Indian companies and institutions who met with teams from several of our research groups and Technical Units. India and China are projected to account for 20% of global scientific production by 2025, and this visit, organized by *Desarrollo Tecnológico Industrial* (CDTI), provided a valuable opportunity to present our technical capabilities.

In July, the CNIC hosted a one-day presentation by the European Research Council Executive Agency (ERCEA). Around 150 attendees learned about the opportunities and requirements for funding, benefitting from the experience of the CNIC and other centers with ERC support.

The highpoint of our meeting calendar was without doubt the third CNIC Conference, held in November. The meeting—'Cardiovascular Development, Disease and Repair'—was attended by 150 delegates, including key opinion leaders from Europe and North America. Areas covered included cardiac progenitor cells and transcriptional circuits in cardiac regeneration, cardiac mitochondria, the regulation of hematopoiesis by heartbeat, and new therapies in heart failure directed at Ca^{2+} cycling. The next CNIC Conference, in November, is titled 'Energy homeostasis and metabolic disease'. And in addition to that we will host the Weinstein Cardiovascular Conference in May 2014.

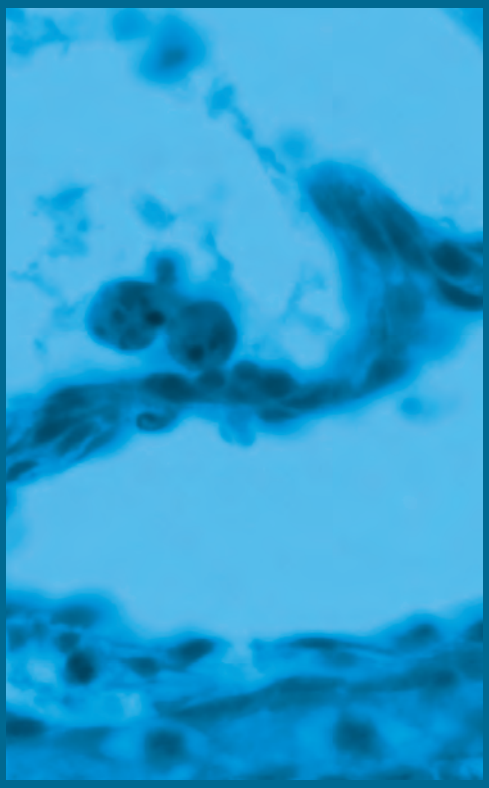
RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair



RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair



The Department of **Cardiovascular Development and Repair** seeks to understand how the cardiovascular system is built, maintained and in some instances repaired. Our research programs examine the molecular and cellular basis of cardiovascular development, cardiovascular homeostasis and repair, and the role of stem-cell biology in these processes.

Director:	Miguel Torres
Program Coordinators:	José Luis de la Pompa Miguel Manzanares José Antonio Enríquez
Department Managers:	Beatriz Ferreiro (coordinator) Ángel Ciprés
Project Manager:	Inga Dreville
Department Logistics:	Teresa Casaseca Mª Ángeles Oliva
Administrative Support:	Sandra Cillero Marta Ramón

A. Cardiovascular Developmental Biology Program

We study how cardiac lineage specification occurs and how proliferation and patterning of the different cardiac regions that will form the mature heart are regulated. We want to unravel how alterations to these mechanisms lead to cardiovascular disease and how they can be manipulated to repair the diseased heart.

Program Coordinator: José Luis de la Pompa

B. Stem Cell Biology

Our aim is to understand the role of stem and progenitor cells in the development and maintenance of the cardiovascular system, as well as their contribution to the repair of the diseased state. We study different stem-cell populations—including embryonic, mesenchymal, cardiac and hematopoietic populations—in order to understand common and type-specific aspects of stem-cell biology that can be translated to the cardiovascular setting.

Program Coordinator: Miguel Manzanares

C. Tissue Homeostasis and Repair

We aim to understand the molecular and cellular processes that control the response of the cardiovascular system to acute and chronic damage resulting from large and small scale injury. We are interested in how cells and tissues adapt to and regulate oxygen availability, how the cardiovascular system communicates with other body systems, and how innate cardiovascular repair mechanisms function and could be enhanced to treat disease.

Program Coordinator: José Antonio Enríquez

RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Genetic control of organ development and regeneration

Head of Laboratory:	Miguel Torres
Research Scientists:	Laura Carramolino Silvia Martín Puig
Postdoctoral Researchers:	Cristina Clavería Irene Delgado Daniel A. Félix Mónica González Lázaro
Predoctoral Researchers:	Covadonga Díaz Ghislaine Lioux Daniel Mateos San Martín Iván Menéndez Montes *(SMP research line)* Verónica Uribe *(JJSE research line)* Cristina Villa
Technicians:	Vanessa C. Cadenas Beatriz Escobar *(SMP research line)* Beatriz Palacios *(SMP research line)* Rocío Sierra Susana Temiño
Visiting Scientist:	Juan José Sanz-Ezquerro
Masters Student:	Noelia Muñoz Martín *(SMP research line)*

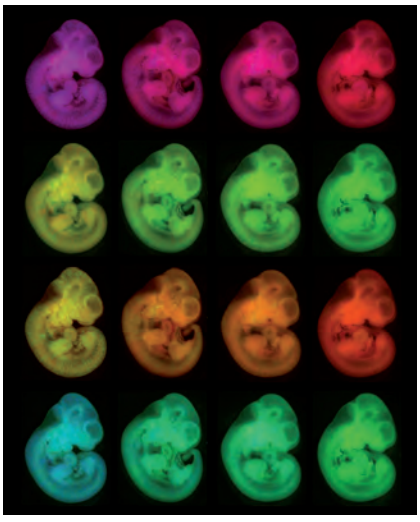
Research Interest

We are interested in understanding morphogenesis and cell differentiation in the mammalian embryo, with a special emphasis on the cardiovascular system.

We have developed methods for genetic mosaic induction *in vivo*. We are using these methods to describe the pattern of cell lineage diversification by clonal analysis during cardiac development and to study the physiological and instrumental relevance of cell competition in mammals. Our data suggest that cell competition is essential for maintaining the fitness of progenitor cell populations in the embryo. Currently we are exploring the relevance of cell competition in cardiogenesis and in cardiac tissue homeostasis and repair during adult life.

We also have a strong interest in the role of Meis transcription factors in cardiovascular and hemato-vascular development. Meis factors play redundant roles in hematopoietic stem cells, megakaryocytes, cardiac precursors and cardiomyocytes, but their exact functions and regulatory activities remain largely unknown. We combine molecular analysis of the pathways regulated by these transcription factors with genetic analysis of their functions in the mouse model.

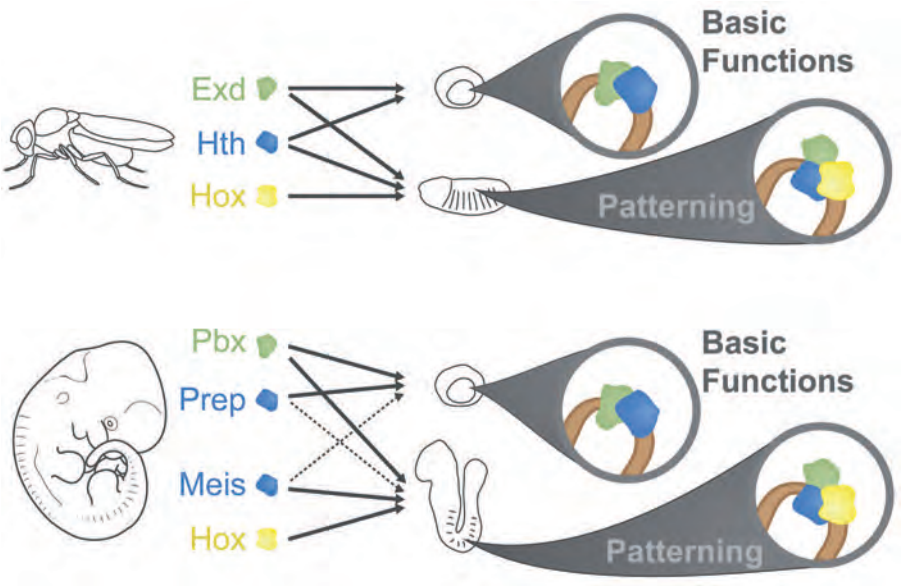
In addition we are investigating the impact of low oxygen tension and HIF-mediated responses on critical cardiovascular events such as chamber formation or coronary vasculature development. We have generated conditional mouse models to characterize the molecular mechanisms regulated by oxygen availability and canonical hypoxia pathways during heart development. We are now exploring the potential of these mouse lines as cardiovascular disease models.



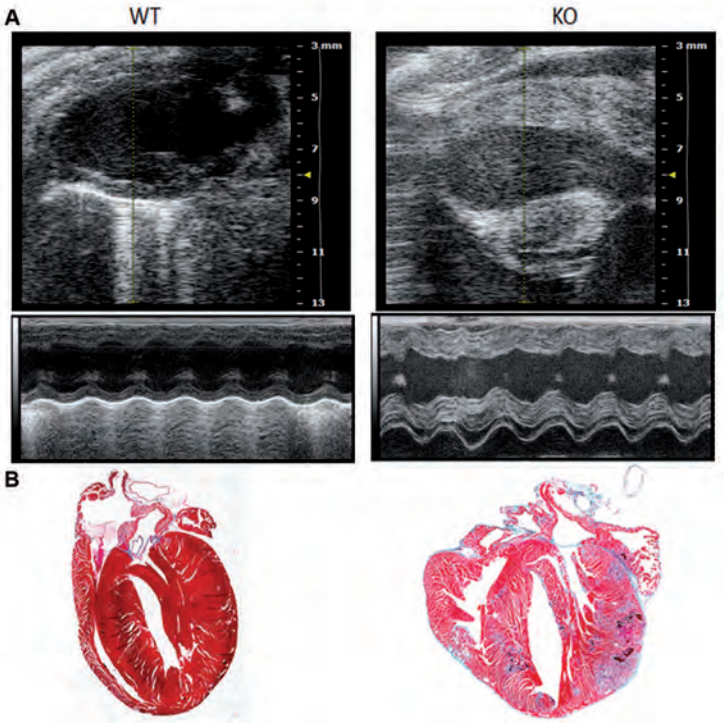
***Cell competition at work**. The pictures show mosaic embryos in which two cell populations with differing levels of MYC expression are confronted. The imbalance in MYC expression increases from left to right, which leads to a changing balance between the fluorescent dyes used to detect each of the two cell populations.*

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program



Extensive molecular "omic" analyses identifiy Meis factors as essential regulators of embryo patterning in vertebrates, while the closely related Prep factors mostly regulate housekeeping functions. This division of labor originated during evolution, and in drosophila both functions are provided by the Meis-related factor Hth, while Pbx and Exd are essential cofactors for Meis, Prep and Hth.



Hypoxia gain of function model in epicardial progenitors. A. *Echocardiographic analysis of 3-month-old normal (WT) and mutant (KO) mice, showing evident interventricular septum (IVS) and left ventricular wall (LVW) hypertrophy in the KO. Upper panels: 2D mode, long axis. Lower panels: M-mode.* ***B.*** *Masson's Trichrome staining of heart sections from WT (left) or KO (right) mice. Blue staining marks fibrotic areas, especially obvious in the IVS, LVW and subepicardium.*

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program

Major Grants

- COST – European Cooperation in the field of Scientific and Technical Research (EU RTD FP7, Ref. BM0805) PI and Action Chair: M.Torres
- EU FP7 Marie Curie EU (International Training Network28600)
- EU FP7. Marie Curie European Reintegration Grant (276891) PI: S. Martín Puig
- Ministerio de Economía y Competitividad. FIS. RETICS (Terapia Celular: RD12/0019/0005)
- Ministerio de Economía y Competitividad (BFU2012-31086)
- Ministerio de Economía y Competitividad (SAF2011-29830) PI: S. Martín Puig
- Ministerio de Economía y Competitividad. FIS (CP09/00100). PI: S. Martín Puig
- Ministerio de Economía y Competitividad. Juan de la Cierva (JCI-2011-10066). PI: Irene Delgado
- Comunidad de Madrid: (S2010/BMD-2315)
- Comunidad de Madrid: (S2010/BMD-2542) PI: S. Martín Puig

Selected Publications

Clavería C, Giovinazzo G, Sierra R, Torres M. **Myc-driven endogenous cell competition in the early mammalian embryo**. *Nature* (2013) 500: 39-44

Penkov D, Mateos San Martin D, Fernandez-Diaz LC, Rosselló CA, Torroja C, Sánchez-Cabo F, Warnatz HJ, Sultan M, Yaspo ML, Gabrieli A, Tkachuk V, Brendolan A, Blasi F, Torres M. **Analysis of the in vivo DNA-binding profile and function of TALE homeoproteins reveals their specialization and differential interactions with Hox genes and proteins**. *Cell Rep* (2013) 3: 1321-33

Richard C, Drevon C, Canto PY, Villain G, Bollerot K, Lempereur A, Teillet MA, Vincent A, Rossello CA, Torres M, Piwarzyk E, Speck NA, Souyri M, Jaffredo T. **Endothelio-mesenchymal interaction controls runx1 expression and modulates the notch pathway to initiate aortic hematopoiesis**. *Dev Cell* (2013) 24: 600-11

Kovacic JC, Mercader N, Torres M, Boehm M, Fuster V. **Epithelial- and endothelial- to mesenchymal transition: from cardiovascular development to disease**. *Circulation* (2012) 125: 1795-808

Martin-Puig S, Fuster V, Torres M. **Heart repair: From natural mechanisms of Cardiomyocyte production to the design of new cardiac therapies**. *Ann N Y Acad Sci*. (2012) 1254:71-81

RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Intercellular signaling in cardiac development, disease and repair

Head of Laboratory:	José Luis de la Pompa
Posdoctoral Researchers:	Donal Macgrogan Beatriz Martínez Poveda Meritxell Nus Belén Prados Mauro Sbroggio
Predoctoral Researchers:	Gaetano D'Amato Dimitrios Grivas Guillermo Luxán Juliane Münch Stanislao I. Travisano
Graduate Technician:	Patricia Martínez
Technicians:	Vanesa Bou Abel Galicia Martín Sara Perruca
Masters Students:	Paula Gómez Apiñaniz Marcos Siguero Álvarez

Research Interest

The interplay between the various tissues that form the heart is essential for cardiac development. The endocardium, myocardium and epicardium exchange signals and respond to them, eliciting finely orchestrated cellular proliferation, differentiation and patterning responses that give rise to the fully functional heart. Alterations to these signaling mechanisms can cause cardiac disease, manifested in the newborn or during adult life. In the last year, we have focused most of our efforts on the role in cardiogenesis, cardiac disease and repair of various signals, including Notch, Bmp2, midkine-a and caveolin-1. We address these questions through the use of mouse and zebrafish genetics, cell biology, biochemistry, NGS, imaging analysis and validation in human tissue samples.

Our work shows that during ventricular chamber development Notch is sequentially activated in a Fringe-dependent manner by the ligands Dll4, Jag1 and Jag2. Dll4 activates Notch in the endocardium of the early chamber, while Jag1 and Jag2 activate Notch in this tissue at later stages (Figure 1). Ligand signaling depends on their modification by the ubiquitin ligase Mind bomb1 (Mib1), whose disruption causes LVNC cardiomyopathy.

We have also studied the role of Notch in valve morphogenesis, where it is required for fine tuning cellular proliferation, ECM secretion and the remodeling process associated with valve sculpting (Figure 2). Bmp2 is another crucial signal for valve morphogenesis, as revealed by a novel gain-of-function model generated in the laboratory.

Our studies of the role of Notch in aortic valve disease center on the influence of endothelial inflammation—using mice doubly deficient for ApoE and Notch—and the role of other Notch-interacting signals in the onset of valve disease. Our findings show that Notch regulates inflammatory mechanisms involved in the modulation of adhesion of monocytes to the vascular endothelium.

In the zebrafish heart, Notch pathway expression is readily reactivated after cardiac damage. Functional studies indicate that Notch plays a crucial role in the modulation of cardiomyocyte proliferation and differentiation during cardiac repair (Figure 3).

We believe that advancing our knowledge of the signaling mechanisms underlying cardiac development and disease will help us to identify novel diagnostic or therapeutic strategies to treat the diseased heart.

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program

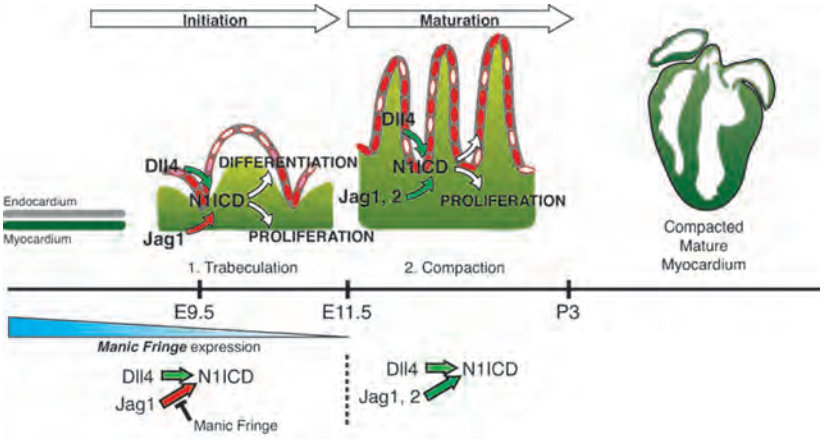


Figure 1. Working model of Notch function in murine ventricular chamber development. *During an early (initiation) phase, endocardial Fringe expression is high and favors Dll4-Notch activation, leading to trabeculae formation. At a later (maturation) phase, Fringe expression is down-regulated and the ligands Jag1 and Jag2 are able to activate Notch from the myocardium and regulate cardiomyocyte proliferation and differentiation and myocardial compaction.*

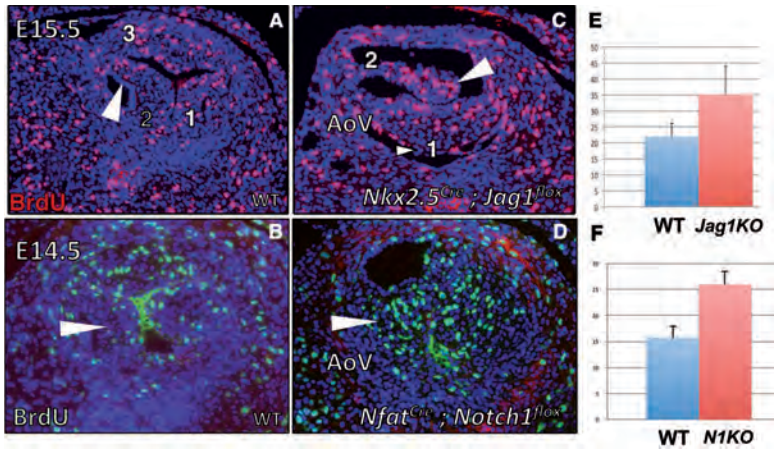


Figure 2. Notch pathway mutants show increased valve mesenchyme proliferation. *In wild type aortic valves (AoV), around 20% of mesenchyme cells are in proliferation (A,B,E,F). In contrast,* Nkx2.5-Cre*;* Jag1^{flox} *or* Nfatc1-Cre*;* Notch1^{flox} *valves (C,D) show an almost 100% increase in cellular proliferation (E,F). Arrowheads point to proliferating nuclei that are positive for BrdU staining.*

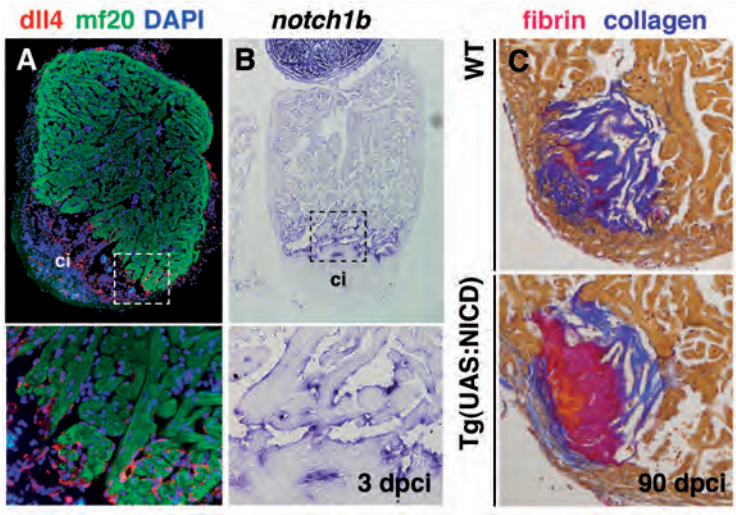


Figure 3. Endocardial Notch signaling activation in the regenerating zebrafish heart. *(A, B)* Dll4 *and* notch1b *are expressed in the endocardium after cryoinjury (ci). (C) Sustained overactivation of Notch signaling inhibits fibrin elimination and prevents regeneration.*

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program

Major Grants

- European Union (PITN-GA-2011-289600) (CardioNeT)
- Ministerio de Economía y Competitividad. FIS RETICS (TERCEL: RD12/0019/0003 and RIC: RD12/0042/0005)
- Ministerio de Economía y Competitividad. (SAF 2010-17555)
- Ministerio de Economía y Competitividad. (FIS CD08/00257). PI: B. Prados
- Ministerio de Economía y Competitividad. (FIS CD09/00452). PI: M. Nus
- Ministerio de Economía y Competitividad. (JCI 2010-06343). PI: B. Martínez Poveda

Selected Publications

Macgrogan D, Luxán G, de la Pompa JL. **Genetic and functional genomics approaches targeting the Notch pathway in cardiac development and congenital heart disease**. *Brief Funct Genomics* doi: 10.1093/bfgp/elt036. [Epub ahead of print]

Bolós V, Mira E, Martínez-Poveda B, Luxán G, Cañamero M, Martínez-A C, Mañes S, de la Pompa JL. **Notch activation stimulates migration of breast cancer cells and promotes tumor growth**. *Breast Cancer Res* (2013) 15: R54

Abdulla T, Luna-Zurita L, de la Pompa JL, Schleich JM, Summers R. E**pithelial to mesenchymal transition-the roles of cell morphology, labile adhesion and junctional coupling**. *Comput Methods Programs Biomed* (2013) 111: 435-46

Münch J, González-Rajal A, de la Pompa JL. **Notch regulates blastema proliferation and prevents differentiation during adult zebrafish fin regeneration**. *Development* (2013) 140: 1402-11

Luxán G, Casanova JC, Martínez-Poveda B, Prados B, D'Amato G, MacGrogan D, Gonzalez-Rajal A, Dobarro D, Torroja C, Martinez F, Izquierdo-García JL, Fernández-Friera L, Sabater-Molina M, Kong YY, Pizarro G, Ibañez B, Medrano C, García-Pavía P, Gimeno JR, Monserrat L, Jiménez-Borreguero LJ, de la Pompa JL. **Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy**. *Nat Med* (2013) 19: 193-201

RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

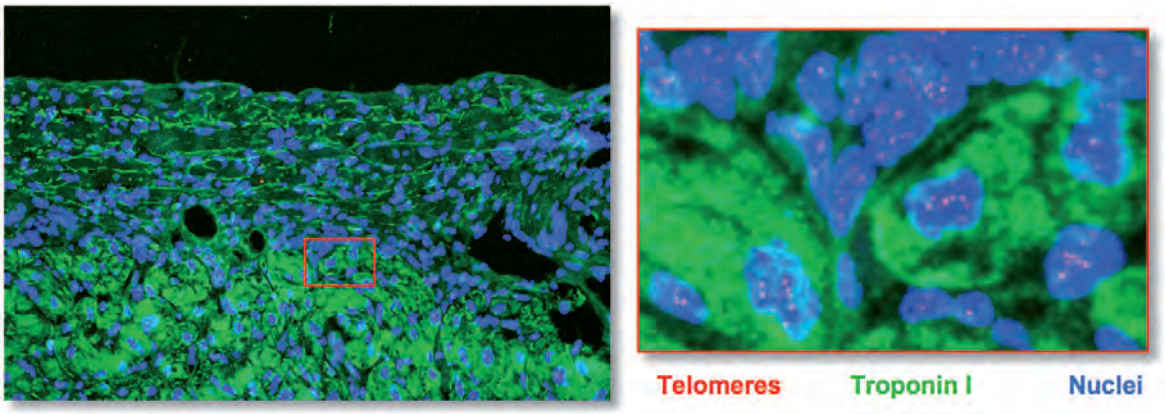
Regeneration and aging

Head of Laboratory:	Ignacio Flores
Posdoctoral Researchers:	Tania Aguado Cristina González Estévez
Predoctoral Researchers:	Esther Aix Dorota Bednarek Carlota Sánchez Ferrer
Technician:	Irene de Diego
Masters Students	Óscar Gutiérrez Gutiérrez Santiago Josa

Research Interest

Although recent advances have overturned the old view of the human heart as an inert postmitotic organ, it is clear that the human heart's capacity to proliferate, rejuvenate and regenerate is very limited. This presents a problem for strategies to treat damaged hearts after infarction, one of the leading causes of death worldwide.

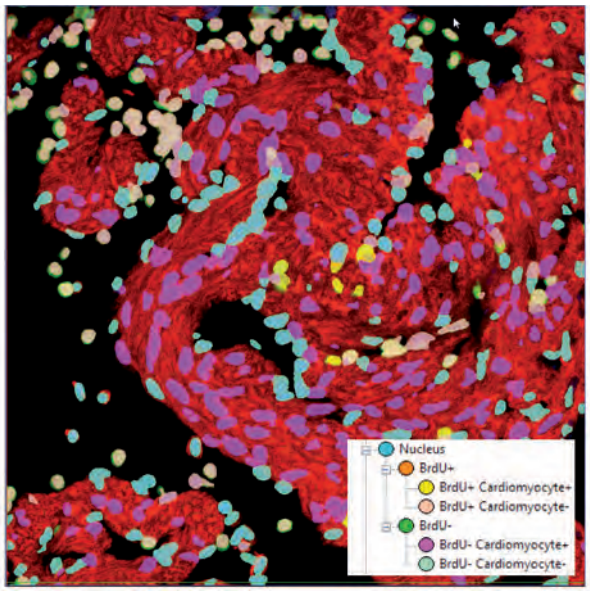
Our group aims to develop strategies to enhance cardiac regeneration. Towards this goal, we are characterizing the subpopulation of cardiac cells capable of regeneration. Based on this knowledge, we are currently exploring strategies to promote the repair of injured hearts. We have eliminated and reactivated telomerase, an anti-aging enzyme, in adult cardiac cells in order to assess the role of this enzyme in the re-expression of cardiac embryonic genes after infarction and 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% 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. Through these efforts, we hope to achieve a more complete knowledge of the role of endogenous cardiac progenitor cells and telomerase in heart rejuvenation and regeneration, which could eventually lead to the development of improved regeneration therapies.



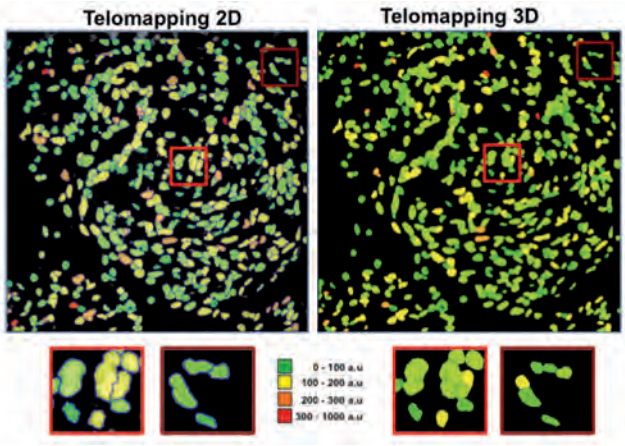
***Telomere length measurements in cardiomyocytes**. Staining of heart sections reveals telomeres (red), nuclei (blue) and the cardiomyocyte marker troponin I (green).*

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program



***Quantitative analysis of cardiac proliferation**. A specifically tailored image analysis program was used to segment, classify and quantify proliferation of different subtypes of cardiac cells after infarction. This work was done in collaboration with Hind Azegrouz of the Cellomics Unit.*



***Direct comparison of 2D and 3D telomapping**. Better telomere and nuclei segmentation and more accurate results are obtained when a Z stack of confocal images is analyzed instead of the classical 2D maximum projection image. This work was done in collaboration with Hind Azegrouz of the Cellomics Unit.*

Major Grants

- Ministerio de Economía y Competitividad (SAF2012-38449)
- Ministerio de Economía y Competitividad. FIS. RETICS (Red de Investigación Cardiovascular RD12/0042/0045)
- Ministerio de Economía y Competitividad. FIS. Miguel Servet (CP12/03214) PI: C. González-Estévez
- Asociación Española contra el Cáncer PI: Tania Aguado

Selected Publications

Schneider RP, Garrobo I, Foronda M, Palacios JA, Marión RM, Flores I, Ortega S, Blasco MA. **TRF1 is a stem cell marker and is essential for the generation of induced pluripotent stem cells**. *Nat Commun* (2013) 4:1946

Díaz-Alonso J, Aguado T, Wu CS, Palazuelos J, Hofmann C, Garcez P, Guillemot F, Lu HC, Lutz B, Guzmán M, Galve-Roperh I. **The CB1 Cannabinoid Receptor Drives Corticospinal Motor Neuron Differentiation through the Ctip2/Satb2 Transcriptional Regulation Axis**. *J Neurosci* (2012) 32: 16651-16665

González-Estévez C, Felix DA, Smith MD, Paps J, Morley SJ, James V, Sharp TV, Aboobaker A. **SMG-1 and mTORC1 act antagonistically to regulate response to injury and growth in planarians**. *PLoS Genet* (2012) 8: e1002619

González-Estévez C, Felix DA, Rodríguez-Esteban G, Aboobaker AA. **Decreased neoblast progeny and increased cell death during starvation-induced planarian degrowth**. *Int J Dev Biol* (2012) 56: 83-91

RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Development of the epicardium and its role during regeneration

Head of Laboratory: Nadia Mercader Huber

Postdoctoral Researcher: Inês João Dos Santos Marques

Predoctoral Researchers: Juan Manuel González-Rosa
Marina Peralta
Héctor Sánchez Iranzo

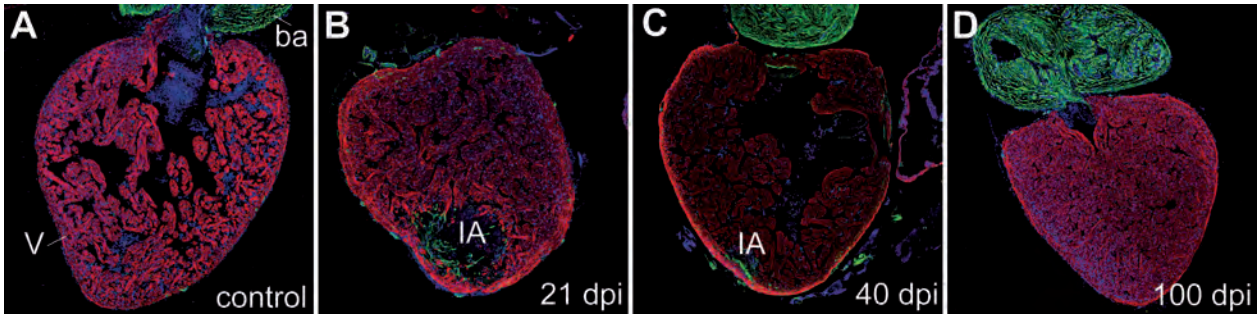
Technician: María Lozano Alonso

Masters Student: María Pérez

Visiting Scientists: Davide Seruggia
CNB-CSIC, Madrid, Spain
Ilse van Herck
Radboud University, Nijmegen, The Netherlands

Research Interest

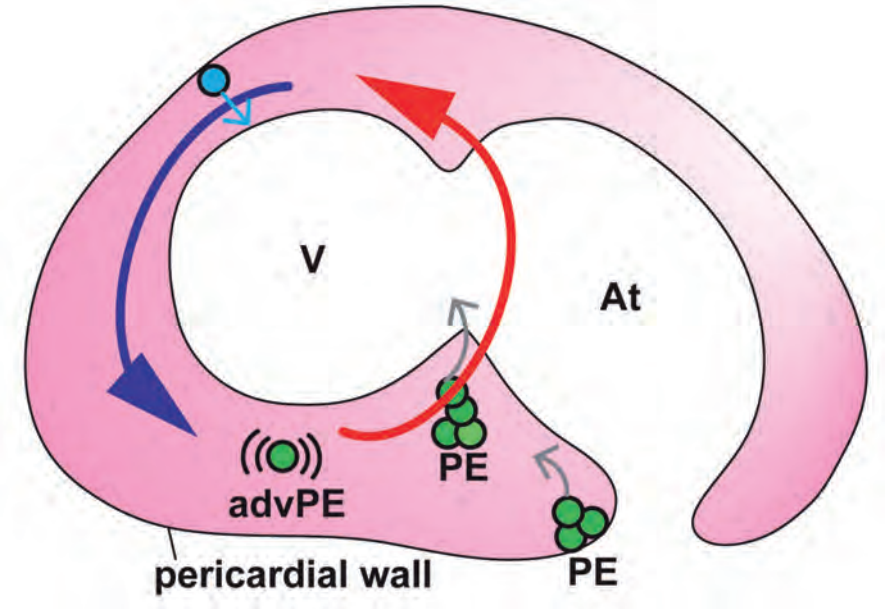
While in humans cardiac fibrosis is irreversible, other vertebrates have a remarkable capacity to regenerate damaged tissue. We recently established a zebrafish injury model mimicking the consequences of tissue loss upon MI and found that cardiac fibrosis is reversible and occurs as an intermediate step during regeneration. We aim to unravel the endogenous mechanisms of myofibroblast and extracelular matrix regression, as this might have implications for the design of antifibrotic strategies. One source of myofibroblasts is the epicardium, the outer layer covering the myocardium. The epicardium is an important source of trophic factors and progenitor cells, and a first step towards regeneration includes the reestablishment of the epicardial layer and the reexpression of developmental genes in epicardial derived cells. We are therefore also interested in analyzing its embryonic formation. Using live imaging in zebrafish embryos we are studying the mechanisms through which proepicardial cells emerge from the pericardial wall and attach to the myocardium. We found that proepicardium formation is dependent on pericardial fluid flow forces generated by the beating heart; we are now elucidating the underlying signaling pathways, which might also play an important role during disease and injury response.



Fibrotic tissue regression and cardiac regeneration upon ventricular cryoinjury in the zebrafish. *Immunostaining of cryoinjured hearts at different days postinjury (dpi). Cryoinjury leads to fibrotic tissue deposition (anit-MLCK, green) which gets eliminated and is no longer visible at 100 dpi. Myocardium is shown in red (anti-MHC antibody staining), and nuclei are counterstained in blue. ba, bulbus arteriosus; IA, injured area; V, ventricle.*

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program



Visualization of epicardium formation in vivo. *Summary of the results obtained from in vivo imaging of epicardium formation in the zebrafish embryo. In vivo imaging of epicardium formation in the zebrafish reveals that the beating heart triggers pericardial fluid flow forces, which are needed to transfer epicardial precursors from the pericardial wall to the myocardium. Proepicardial cells (PE) emerge from two regions of the dorsal pericaridal wall and are released into the pericardial cavity where they are advected until attaching to the myocardium. A second minor source of epicaridal precursors arises from the cranial pericardium (blue circle). Arrows indicate the direction of pericardial fluid flow and advected PE cells; red indicates high pericardial flow force and blue indicates low force. advPE, advected proepicardial cell; At, Atrium; PE, proepicardium; V, ventricle.*

Major Grants

- **Ministerio de Economia y Competividad (BFU2011-25297)**
- **Comunidad de Madrid (P2010/BMD-2321) (PI: E. Lara)**
- **Tercel (Red de Terapia Celular) (PI: M. Torres)**
- **European Commission. Marie Curie IEF. GA 330728. PI: Inês João Dos Santos Marques**

Selected Publications

Peralta M, Steed E, Harlepp S, Gonzalez-Rosa JM, Monduc F, Ariza-Cosano A, Cortes A, Rayon T, Gomez-Skarmeta JL, Zapata A, Vermot J, Mercader, N. **Heartbeat-driven pericardiac fluid forces contribute to epicardium morphogenesis**. *Curr Biol* (2013) 23: 1726-1735

Kovacic JC, Mercader N, Torres M, Boehm M, Fuster V. **Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease**. *Circulation* (2012) 125: 1795-1808

Gonzalez-Rosa JM, Peralta M, Mercader N, **Epicardial-derived cells give rise to myofibroblasts and perivascular cells but do not contribute to regenerated myocardium upon cryoinjury in zebrafish**. *Dev Biol* (2012) 370: 173-86

Gonzalez-Rosa JM, Mercader N. **Cryoinjury as a myocardial infarction model for the study of cardiac regeneration in the zebrafish**. *Nat Protoc* (2012) 7: 782-788

Neto A, Mercader N, Gomez-Skarmeta JL. **The Osr1 and Osr2 genes act in the pronephric anlage downstream of retinoic acid signaling and upstream of Wnt2b to maintain pectoral fin development**. *Development* (2012) 139: 301-311

RESEARCH DEPARTMENTS

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Molecular genetics of angiogenesis

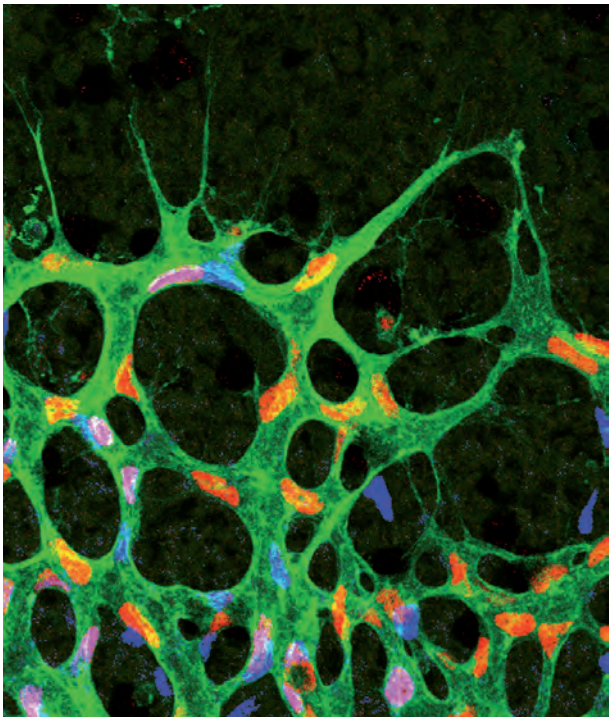
Head of Laboratory: Rui Miguel Benedito

Predoctoral Researchers: Samuel Pontes
Briane Laruy

Technicians: Adrian Galiana
Iker Rodríguez

Research Interest

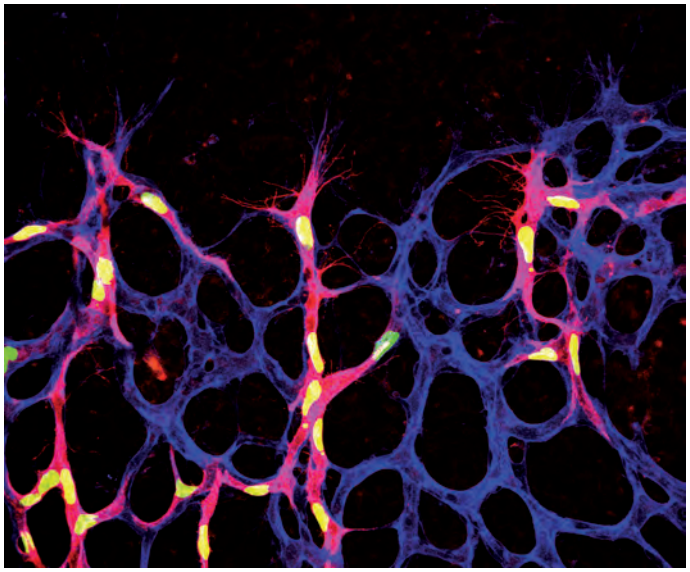
Angiogenesis, the formation of new blood vessels from pre-existing vessels, requires the coordination of several cellular and signaling mechanisms. The inner lining of blood vessels is formed by endothelial cells that express several surface receptors that are able to sense different extracellular molecular cues. The vascular endothelial growth factor (VEGF) family of secreted ligands and receptors are among the most important and are specific regulators of endothelial cell sprouting, proliferation and survival in a variety of organs and pathological processes. In addition to being influenced by external factors, endothelial cells also have endogenous signaling mechanisms that can modulate their response to the surrounding environment. One such mechanism is the Notch signaling pathway, where both ligands and receptors are transmembrane proteins and, upon cell-to-cell ligand-receptor activation, elicit a transcriptional program that leads to changes in cell status and behavior. Contrary to the previous understanding of Notch function, we recently found that Notch can regulate angiogenesis independently of VEGF signaling. The general goal of our lab is to define in high detail the role of Notch in vascular proliferation, differentiation and maturation, and characterize some of the downstream molecular mechanisms. We use a combination of advanced mouse models, several in vitro systems, quantitative gene expression analysis and the latest imaging technologies to gain deeper understanding of the biology of blood vessels during development and disease.



Thin optical section of the angiogenic vascular network (green), where some cells sprout towards the surrounding environment. The capillary endothelial nuclei are shown in red, the membrane in green (IsolectinB4+) and the nuclei of cells in S-phase in blue. Th nuclei of proliferating endothelial cells in S-phase are pink because of the overlap of the red and blue signals.

RESEARCH DEPARTMENTS

A. Cardiovascular Developmental Biology Program



Retinal vasculature of a mouse line recently generated in our lab. The membrane of some endothelial cells is labeled with the fluorescent protein MTomato (red) and nuclei with green fluorescent protein fused to histone 2B (H2B-GFP, yellow). In this case we used incomplete Cre induction, and the membranes of non-recombined cells are visible in blue (IsolectinB4 staining).

Major Grants

- **Europa Excelencia 2013 MINECO (MIN/SAF1301)**
- **COFUND Incoming Fellowship (UEO/COF1002)**

Selected Publications

Benedito R. **Werner Risau Prize 2013**. *DGZ Journal Cell News* (2013) 2: 10-13

Ehling M, Adams S, Benedito R, Adams RH. **Notch controls retinal blood vessel maturation and quiescence**. *Development* (2013) 140: 3051-61

Benedito R, Hellstrom M. **Notch as a hub for signaling in angiogenesis**. *Exp Cell Res* (2013) 319: 1281-8

Wang L, Benedito R, Bixel MG, Zeuschner D, Stehling M, Sävendahl L, Haigh JJ, Snippert H, Clevers H, Breier G, Kiefer F, Adams RH. **Identification of a clonally expanding haematopoietic compartment in bone marrow**. *Embo J* (2013) 32: 219-30

Gaengel K, Niaudet C, Hagikura K, Siemsen BL, Muhl L, Hofmann JJ, Ebarasi L, Nyström S, Rymo S, Chen LL, Pang MF, Jin Y, Raschperger E, Roswall P, Schulte D, Benedito R, Larsson J, Hellström M, Fuxe J, Uhlén P, Adams R, Jakobsson L, Majumdar A, Vestweber D, Uv A, Betsholtz C. **The sphingosine-1-phosphate receptor S1PR1 restricts sprouting angiogenesis by regulating the interplay between VE-cadherin and VEGFR2**. *Dev Cell* (2012) 23: 587-99

Benedito R*, Rocha SF, Woeste M, Zamykal M, Radtke F, Casanovas C, Duarte A, Pytowski B, Adams RH. **Notch–dependent VEGFR3 upregulation allows angiogenesis without VEGF-VEGFR2 signaling**. *Nature* (2012) 484: 110-114
**Corresponding author*

Functional genomics of embryonic pluripotency and heart development

Head of Laboratory: Miguel Manzanares

Postdoctoral Researchers: Luis Augusto Aguirre
Cristina Arias Sánchez
Elena López

Predoctoral Researchers: Teresa Rayón
Melisa Gómez Velázquez
Julio González Sainz de Aja
Sergio Menchero

Graduate Technician: Isabel C. Rollán

Technicians: Claudio Badía
Inmaculada Ors

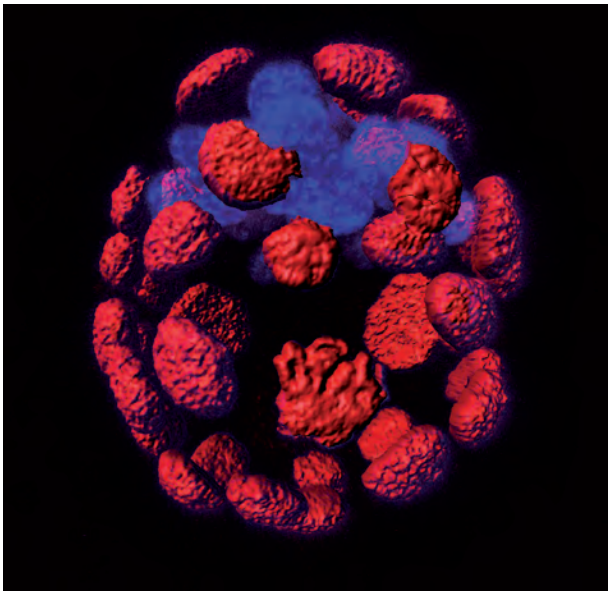
Masters Student: Raquel Rouco
Eva Fernández Cáceres

Research Interest

Our lab studies 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.

Current projects include the study of the regulatory events leading to the first differentiation event during mammalian development, the split between the extraembryonic trophectoderm and the pluripotent inner cell mass. By studying the regulation of the key trophectodermal regulator *Cdx2*, we have shown how the integration of multiple signaling pathways establishes this lineage in the blastocyst. We are also analyzing how the embryo makes the decision to escape from the pluripotent state, leading to the differentiation of the definitive embryonic lineages and germ layers.

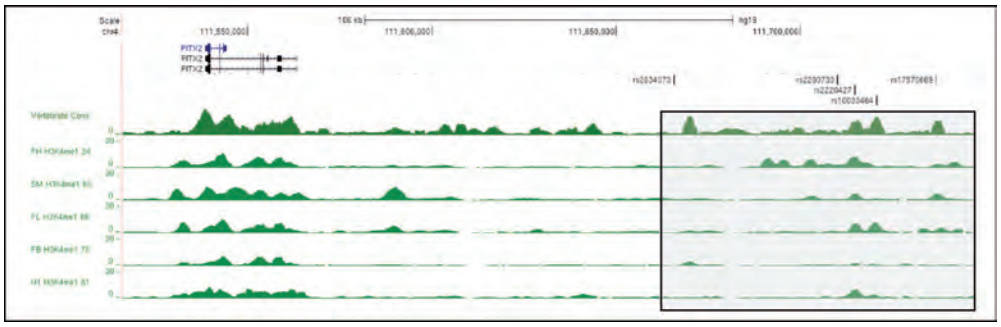
We are also interested in how regulatory variation in developmental loci is important for common human diseases. By exploring the findings of genome-wide association studies, we have found that regulatory elements distal to the *PITX2* gene lie in a genomic region associated with an increased risk of atrial fibrillation. We are exploring the genomic architecture of this locus and have found unsuspected interactions with other genes in the region. Using mouse genetic models, we are conducting a genome-wide study of how chromatin structure crucially regulates proper gene expression in the heart, and how this could underlie certain cases of human cardiovascular disease.



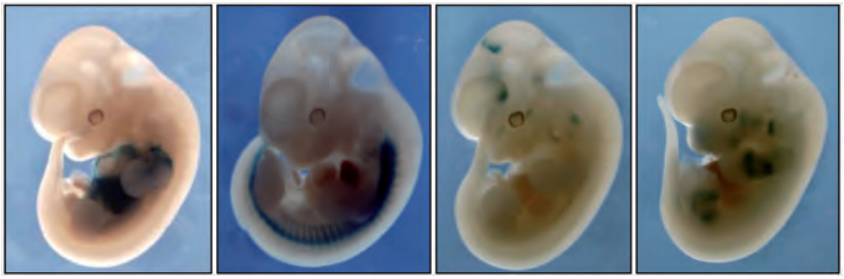
Confocal image of a mouse blastocyst showing activity of a red fluorescent protein under the control of a trophectoderm specific enhancer of Cdx2. *Other nuclei are stained blue.*

RESEARCH DEPARTMENTS

B. Stem Cell Biology Program



Genomic landscape of the human 4q25 atrial fibrillation risk locus, showing the evolutionary conservation and different epigenetic marks of the PITX2 *gene and the region where atrial-fibrillation-associated SNPs have been mapped (boxed).*



A series of transgenic mouse embryos where reporter activity (in blue) is driven by cis-regulatory elements present in the 4q25 atrial fibrillation risk locus. These elements reproduce subsets of the endogenous expression of Pitx2 *in the mouse embryo.*

Major Grants

- **CNIC Translational Projects (CNIC-08-2009).**
- **Comunidad Autónoma de Madrid (CAM), S2010/BMD-2315**
- **Ministerio de Ciencia e Innovación (MICINN), BFU2011-23083**

Selected Publications

Lara-Pezzi E, Dopazo A, Manzanares M. **Understanding cardiovascular disease: a journey through the genome (and what we found there).** *Dis Model Mech* (2012) 5: 434-43

Manzanares M, Rodriguez TA. **Development: Hippo signalling turns the embryo inside out.** *Curr Biol* (2013) 23: R559-61

Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayon T, Ors I, Graña O, Megías D, Domínguez O, Martínez D, Manzanares M, Ortega S, Serrano M. **Reprogramming in vivo produces teratomas and iPS cells with totipotency features.** *Nature* (2013) 502: 340-5

Peralta M, Steed E, Harlepp S, González-Rosa JM, Monduc F, Ariza-Cosano A, Cortés A, Rayón T, Gómez-Skarmeta JL, Zapata A, Vermot J, Mercader N. **Heartbeat-driven pericardiac fluid forces contribute to epicardium morphogenesis.** *Curr Biol* (2013) 23: 1726-35

Manzanares M. **Functional genomics of cardiovascular development and disease.** *Brief Funct Genomics* (accepted)

Regulation of gene expression & genetic stability in somatic stem cells

Head of Laboratory: Antonio Bernad Miana
Research Scientist: Manuel Ángel González de la Peña
Postdoctoral Researchers: Isabel Moscoso Galán, Juan A Bernal Rodríguez, José Luis Torán García, Susana Cañón Sánchez
Predoctoral Researchers: Juan Camilo Estrada Rodríguez, María Tomé Pizarro, Íñigo Valiente Alandi, Francisco Miguel Cruz Urende, Diego Herreros
Scientific Support: Candelas Carreiro Quintana, Carmen Albo Castellanos
Technicians: Juan Carlos Sepúlveda Muñoz, Yaima Torres Rodríguez, Rosa María Carmona Canorea, Susana Aguilar García, Juan A. Quintana Fernández
Visiting Scientist: Enrique Samper

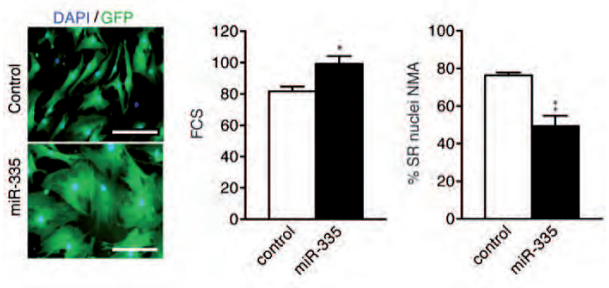
Research Interest

Adult organ function depends on the concerted and regulated action of specialized stem cells. We study mouse and human mesenchymal stem cells (MSCs) and cardiac progenitor cells (CPCs) isolated from the adult mammalian heart.

hMSCs have become an increasingly important resource for regenerative medicine as they can be obtained using minimally invasive techniques and can be easily expanded and differentiated *in vitro* to different cell linages. However, yields from the original sources are typically modest, and hMSCs must therefore be expanded *ex vivo*. It is currently suspected that, unless carefully optimized, this *ex vivo* expansion of primary cells compromises their biological activity.

Differential analysis of miRNA expression has established a set of miRNAs that are associated with the replicative senescence of hMSC cultures. miR-335 is required to maintain hMSCs in the undifferentiated state, its downregulation being critical for the acquisition of reparative MSC phenotypes. In contrast, progressive overexpression of miR-335—during *ex vivo* culture or with donor age—correlates with senescence and reduced therapeutic potential (Figure 1). We additionally found that 69% of miRNAs upregulated during hMSC senescence map to the unique imprinted locus 14q32-31 (Figure 2).

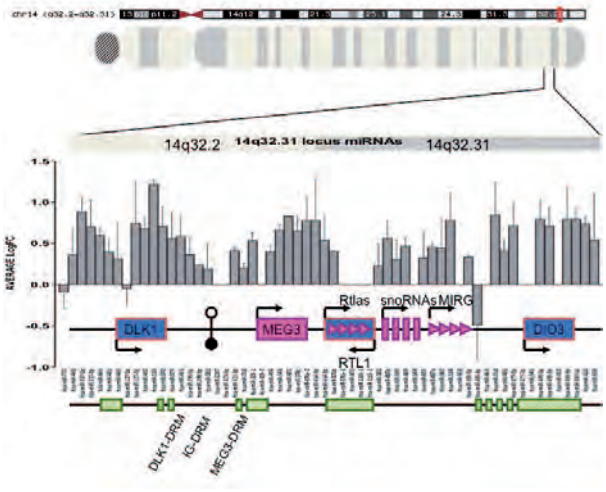
A precise definition of cardiac precursor and stem cells is still lacking. Mouse, pig and human CPCs have been characterized as MSC-like populations. We have demonstrated that the polycomb transcription factor Bmi-1 is an important marker of mouse CPCs. The Bmi-1+ CPC subpopulation (B-CPC) contributes both to homeostatic cardiac turnover and to repair after acute injury, and fulfils the criteria for definition as a population of long-term resident cardiac stem cells (Figure 3).



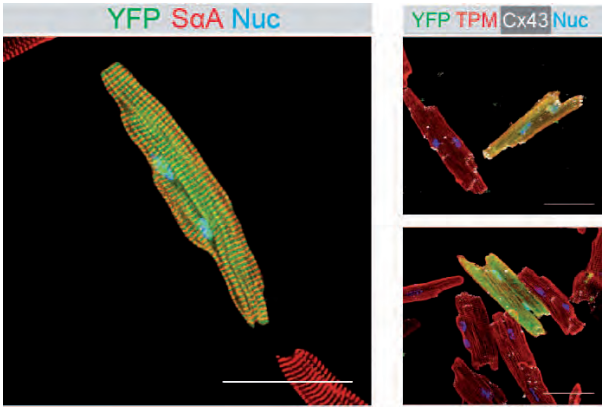
Forced expression of miR-335 promotes hMSC senescence. Comparative analysis of naive (control) hMSCs with those overexpressing miR-335, simultaneously labeled with GFP (green), demonstrates morphological alterations, including larger cell size, more vacuoles (left and central panels) and nuclear irregularity, revealed as a lower percentage of small and regular nuclei (SR; right panel).

RESEARCH DEPARTMENTS

B. Stem Cell Biology Program



The genomic locus 14q32.31. The figure shows the location of the large cluster of miRNAs in relation to other coding (DLK1, DIO3) and non-coding (MEG3) RNAs; the lower line shows some of the regulatory units.



B-CPCs contribute to adult mammalian heart homeostasis in vivo. *Two months after induction with tamoxifen, individual cardiomyocytes (CM) were isolated and analyzed by immunohistochemistry. A significant proportion of binucleated mature YFP+CMs (yellow), derived from B-CPCs (YFP; green), co-stained for sarcomeric α-actinin (SαA; red), tropomyosin (TPM; red) or connexin 43 (Cx43; white). Nuclei were stained with DAPI. Bars, 50μm.*

Major Grants

- **European Commission (ref: FP7-HEALTH-SINGLE-STAGE-2009/CARE-MI-242038). Antonio Bernad (Coordinator).**
- **Ministerio de Economía y Competitividad (MICINN) Plan Nacional de I + D + I (ref: SAF2012-34327). .**
- **Red de Investigación Cooperativa Terapia Celular (TerCel) ISCIII (ref: RD12/0019/0018).**
- **Grupos de investigación Cooperativa de la Comunidad de Madrid en Biomedicina (GRUPOSCAM10/ CELLCAM) (Ref: S2011/BMD-2420).**
- **MICINN (ref: IPT-2011-1307-010000) Antonio Bernad (Subproject Coordinator)**
- **MICINN. Programa Nacional de Internacionalización de la I+D. (ref: PLE2009-0147 (CARDIO-STEM). Dr. Juan Carlos Izpisua (Coordinator); Dr. Antonio Bernad (Subproject Coordinator)**
- **MICINN. Programa Nacional de Internacionalización de la I+D. (ref: PLE2009-0100). Dr. Juan A. Bueren (Coordinator); Dr. Antonio Bernad (Subproject Coordinator)**

Selected Publications

Estrada JC, Torres Y, Benguria A, Dopazo A, Roche E, Carrera-Quintanar L, Perez RA, Enriquez JA, Torres R, Ramirez JC, Samper E, Bernad A. **Human mesenchymal stem cell-replicative senescence and oxidative stress are closely linked to aneuploidy**. (2013) *Cell Death Dis* 4: e691

Lucas D, Delgado-Garcia J M, Escudero B, Albo C, Aza A, Acin-Perez R, Torres Y, Moreno P, Enriquez JA, Samper E, Blanc, L, Fairen A, Bernad A*, Gruart A*. **Increased Learning and Brain Long-Term Potentiation in Aged Mice Lacking DNA Polymerase mu** (2013) *PLoS One* 8:e53243
**Co-corresponding authors*

Moscoso I, Tejados N, Barreiro O, Sepúlveda P, Izarra A, Calvo E, Dorronsoro A, Salcedo JM, Sádaba, R, Díez-Juan A, Trigueros C, Bernad A. **Podocalyxin-like protein 1 is a relevant marker for human c-kit^{pos} cardiac stem cells**. (2013) *J Tissue Eng Regen Med* doi: 101002/term1795 [Epub ahead of print]

Bernal JA. **RNA-based tools for nuclear reprogramming and lineage conversion: towards clinical applications**. (2013) *J Cardiovasc Transl Res* 6: 956-968

Sepúlveda JC, Tomé M, Fernández ME, Delgado M, Campisi J, Bernad A*, González MA*. **Cell senescence abrogates the therapeutic potential of human mesenchymal stem cells in the lethal endotoxemia model**. (2014) *Stem Cells* (accepted)
**Co-corresponding authors*

Stem cell niche pathophysiology

Head of Laboratory: Simón Méndez-Ferrer

Postdoctoral Researchers: Joan Isern
Abel Sánchez-Aguilera
Raquel del Toro
Lorena Arranz

Predoctoral Researchers: Andrés García

Masters Student: Carmen Mora

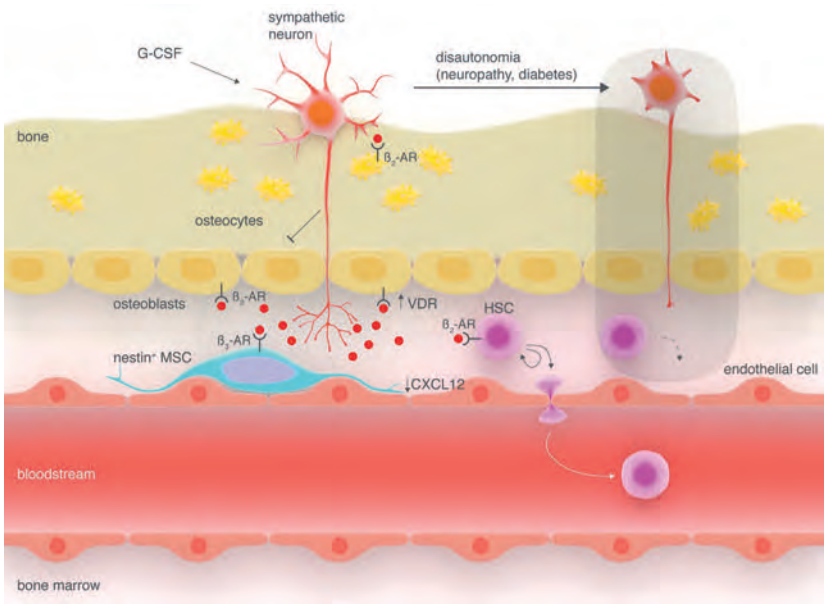
Technicians: Ana M. Martín
Daniel Martín
Sandra Martín
Xavier Langa

Research Interest

Our group studies the niche micoenvironment that maintains and regulates stem cells and how its deregulation can contribute to disease. Our earlier work described a tight regulation of the bone marrow (BM) stem cell niche by circadian oscillations of sympathetic activity, alteration of which disrupts the traffic of hematopoietic stem cells (HSCs) in and out of the BM (Figure 1).

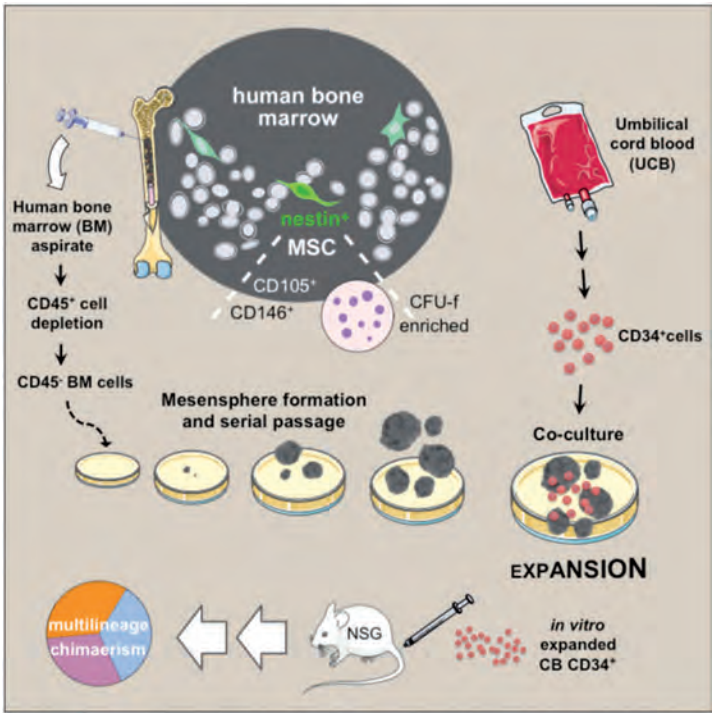
Increasing the numbers of stem cells for transplantion is a major challenge in cell therapy. Hematopoietic stem cells from umbilical cord blood have several advantages, but their low abundance effectively limits their use to children or adults with a low body weight. A method for increasing their numbers would make this procedure viable for many more patients and would also increase the chances of patient survival after this treatment. One strategy is to co-cultivate with mesenchymal stem cells (MSCs), the cells that maintain HSCs in their natural microenvironment or niche. However, published studies suggest that standard MSC cultures are unable to support the expansion of HSCs from human cord blood.

We have developed a new method for the isolation of human MSCs as non-adherent clonal spheres. These "mesenspheres" can be easily cultivated from CD45- cells isolated from human bone marrow. Under conditions that preserve their own stem-cell properties, MSCs are able to promote the expansion of hematopoietic stem cells from human umbilical cord blood (Figure 2). This activity of MSCs is mediated by factors secreted into the culture medium (Figure 3), which could facilitate eventual clinical application of the findings.

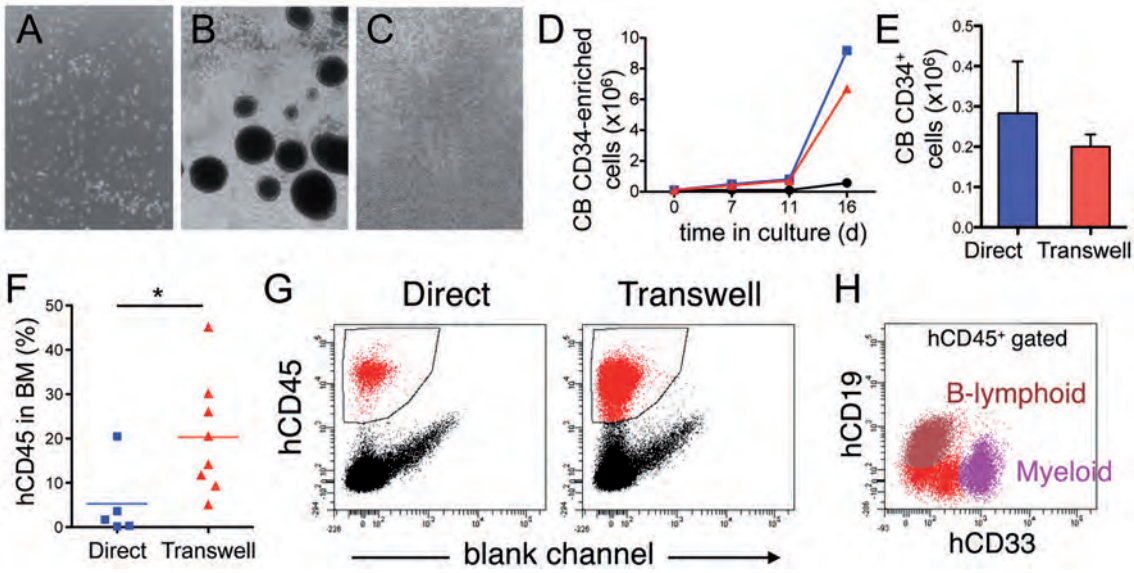


***Sympathetic regulation of BM HSC egress and mobilization**. G-CSF elicits HSC mobilization in part through stimulation of sympathetic activity, which is propagated along osteocytes and leads to increased VDR expression and suppression of osteoblasts, CXCL12 downregulation in osteoblasts and nestin+ MSCs, and HSC proliferation and migration to the bloodstream. Neuropathy/disautonomia caused by chemotherapy or diabetes impairs HSC mobilization. G-CSF, granulocyte colonystimulating factor; HSC: hematopoietic stem cell; MSC: mesenchymal stem cell; VDR: vitamin D receptor; AR: adrenergic receptor (del Toro R & Méndez-Ferrer S.* Haematologica *(2013) 98: 1663-6).*

B. Stem Cell Biology Program



New method for isolation and expansion of human mesenchymal and hematopoietic stem cells. *(Isern J et al.* Cell Rep *(2013) 3: 1714-24).*



Human BM mesenspheres support cord blood HSCs mainly through secreted factors. ***A-E****, CD34⁺ cord blood cells were cultured for 16 days in serum-free medium containing cytokines (**A**) in the absence or (**B-C**) in co-culture with human fetal mesenspheres, either (**B**) in direct contact or (**C**) separated by transwell filters.* ***D****, Growth curve of cord blood CD34-enriched cells cultured alone (black line), in contact with human mesenspheres (blue line) or separated by transwell filters (red line).* ***E****, Number of CD34⁺ cells measured by FACS (n = 3).* ***F-H****, Soluble secreted factors produced by human BM mesenspheres expand cord blood HSCs capable of long-term reconstitution and multilineage differentiation in immunodeficient mice.* ***F****, Percentage of human CD45⁺ cells in the BM of NSG mice 16 weeks after transplantation of CD34⁺ cord blood cells cultured for 3 weeks with human BM mesenspheres in direct contact or separated by transwell filters. * $p < 0.05$; unpaired two tailed t test.* ***G****, Representative FACS diagrams of hCD45-stained BM cells from NSG mice 4 moths after transplantation of CD34⁺ cells cultured in both conditions.* ***H****, Representative FACS diagram showing long-term multilineage reconstitution. BM cells were stained with anti-hCD45 (hematopoietic), -hCD19 (B-lymphoid) and -hCD33 (myeloid) antibodies (Isern J et al.* Cell Rep *(2013) 3: 1714-24).*

RESEARCH DEPARTMENTS

B. Stem Cell Biology Program

Major Grants

- Howard Hughes Medical Institute. International Early Career Scientist. (HHMI 55007426)
- Convocatoria de Programas de I+D en Biomedicina. Comunidad de Madrid. (S2011/BMD-2542)
- Ministerio de Economía y Competitividad (RYC-2009-04703)
- Ministerio de Economía y Competitividad (RYC-2011-09726) PI: Abel Sánchez-Aguilera
- Ministerio de Economía y Competitividad. (RYC-2011-09209) PI: Joan Isern
- Ministerio de Economía y Competitividad (SAF-2011-30308)
- Ministerio de Economía y Competitividad (BFU2012-35892) PI: Joan Isern
- Ministerio de Economía y Competitividad. FIS. RETICS (Terapia Celular: RD12/0019/0030)
- European Commission FP7. Marie Curie Career Integration Grant (294262)
- European Commission FP7. Marie Curie Career Integration Grant (294096) PI: Abel Sánchez-Aguilera
- European Hematology Association. Research Award. PI: Abel Sánchez-Aguilera

Selected Publications

Isern J, Martín-Antonio B, Ghazanfari R, Martín AM, del Toro R, Sánchez-Aguilera A, Arranz L, Martín-Pérez D, López JA, Suárez-Lledó M, Marín P, Van Pel M, Vázquez J, Fibbe WE, Scheding S, Urbano-Ispizúa A, Méndez-Ferrer S. **Self-renewing human mesenspheres promote hematopoietic stem cell expansion**. *Cell Rep* (2013) 3: 1714-24

del Toro R, S. Méndez-Ferrer. **Autonomic regulation of haematopoiesis and cancer**. *Haematologica* (2013) 98: 1663-6

Zaidi M, Méndez-Ferrer S. **Cell biology: tumour stem cells in bone**. *Nature* (2013) 499: 414-6

Arranz L, Urbano-Ispizúa A, S. Méndez-Ferrer. **Mitochondria underlie different metabolism of hematopoietic stem and progenitor cells**. *Haematologica* (2013) 98: 993-5

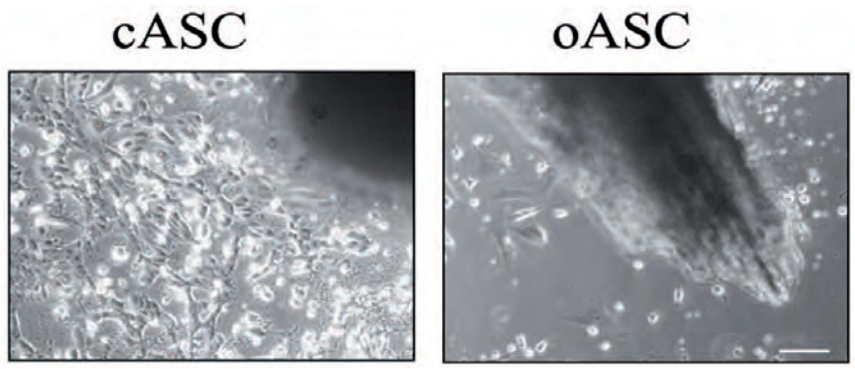
Arranz L, Sánchez-Aguilera A, Martín-Pérez D, Isern J, Langa X, Tzankov A, Lundberg A, Muntión A, Tzeng Y-S, Lai D-M, Schwaller J, Skoda RC and Méndez-Ferrer S. **Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms**. Nature (in press).

Pathophysiology of adipose and cardiac tissues

Head of Laboratory: Beatriz G. Gálvez
Predoctoral Researchers: Aurora Bernal, Laura Martín
Masters Student: Beatriz De Lucas
Technician: Nuria San Martín
Visiting scientist: Manuel Lobo

Research Interest

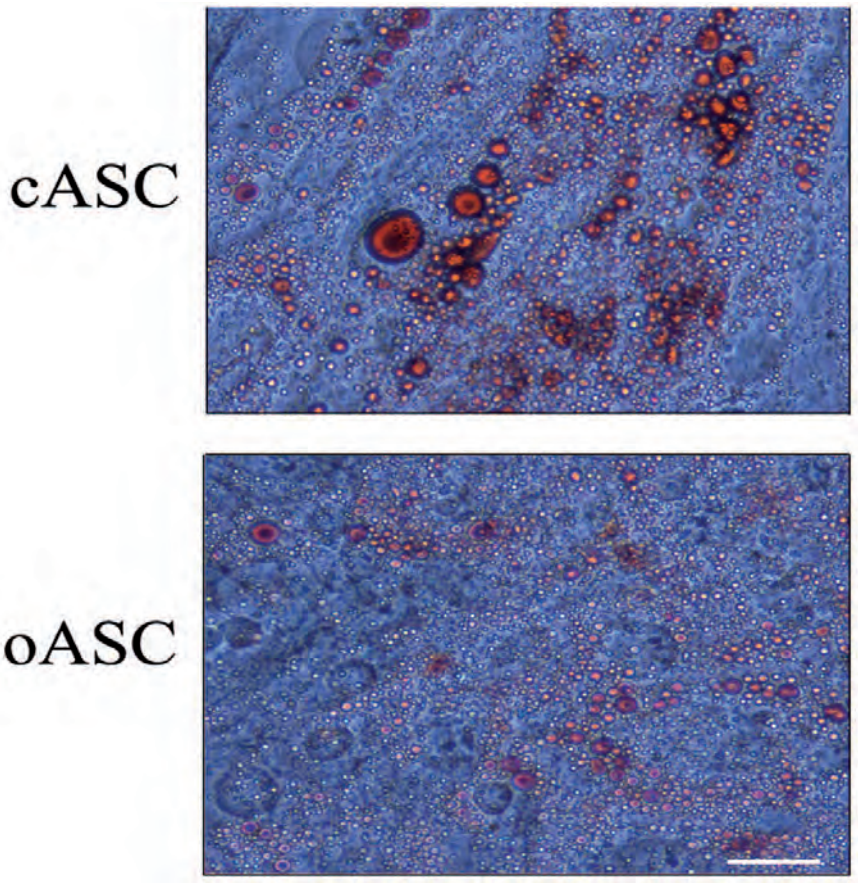
Adipose-derived stem cells (ASCs) are promising candidates for autologous cell-based regeneration therapies by virtue of their multilineage differentiation potential and immunogenicity. However, relatively little is known about their role in adipose tissue physiology and dysfunction. Our group has been evaluating whether ASCs isolated from non-obese and obese tissue differ in their metabolic characteristics and differentiation potential. During differentiation to mature adipocytes, mouse and human ASCs derived from non-obese tissues increase their insulin sensitivity and inhibition of lipolysis, whereas obese-derived ASCs are insulin-resistant, showing impaired insulin-stimulated glucose uptake and resistance to the antilipolytic effect of insulin. Furthermore, obese-derived ASCs show enhanced release of proinflammatory cytokines and impaired production of adiponectin. Interestingly, the transfer of cytosol from control ASCs into obese-derived ASCs using a lipid-based protein-capture methodology restores insulin sensitivity of glucose and lipid metabolism and reverses the proinflammatory cytokine profile, in part through the restoration of Lin28 protein levels. Our results thus show that glucose and lipid metabolism and ASC maturation are truncated in an obese environment. The reversal of the altered pathways in obese cells by delivery of normal subcellular fractions offers a potential new tool for cell therapy.



Isolation of adipose stem cells from control mice (cASCs) and obese mice (oASCs)

RESEARCH DEPARTMENTS

B. Stem Cell Biology Program



Differentiation of ASCs into mature adipocytes

Major Grants

- **Ministerio de Economia y Competitividad (SAF2010-15239)**

Selected Publications

Pérez LM, Bernal A, San Martín N, Lorenzo M, Fernández-Veledo S, Gálvez BG. **Metabolic rescue of obese adipose-derived stem cells by Lin28/Let7 pathway**. *Diabetes* (2013) 62: 2368-79

Bernal A, Gálvez BG. **The potential of stem cells in the treatment of cardiovascular diseases**. *Stem Cell Rev* (2013) 9: 814-32

Pérez LM, Bernal A, San Martín N, Gálvez BG. **Obese-derived ASCs show impaired migration and angiogenesis properties**. *Arch Physiol Biochem* (2013) 119: 195-201

Bernal A, Fernández M, Pérez LM, San Martín N, Gálvez BG. **Method for obtaining committed adult mesenchymal precursors from skin and lung tissue**. *PLoS One* (2012) 7:e53215

Bernal A, San Martín N, Fernández M, Covarello D, Molla F, Soldo A, Latini R, Cossu G, Gálvez BG. **L-selectin and SDF-1 enhance the migration of mouse and human cardiac mesoangioblasts**. *Cell Death Differ* (2012) 19: 345-55

Cellular signaling

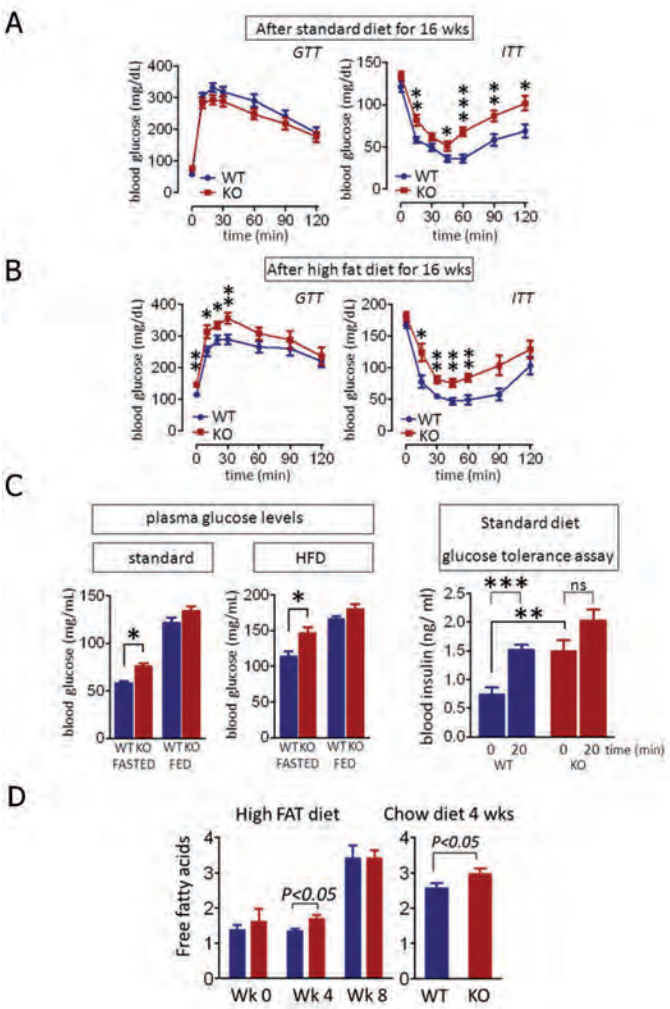
Head of Laboratory: Kenneth J. McCreath
Research Scientist: Ana Mª Cervera

Research Interest

Our laboratory is interested in impaired cellular metabolism and the adaptive responses to oxidative stress, which are hallmarks of many disease states and can affect homeostatic signaling processes. G protein-coupled receptors are cell-surface signaling proteins tasked with the recognition and transduction of messages from the external environment. SUCNR1, a recently de-orphanized GPCR, is activated by binding of its natural ligand succinate, a Kreb's cycle intermediate. Levels of succinate, a cellular danger signal, increase after dysregulated energy metabolism (such as hypoxia or hyperglycemia), and thus SUCNR1 is a metabolic sensor of cell homeostasis.

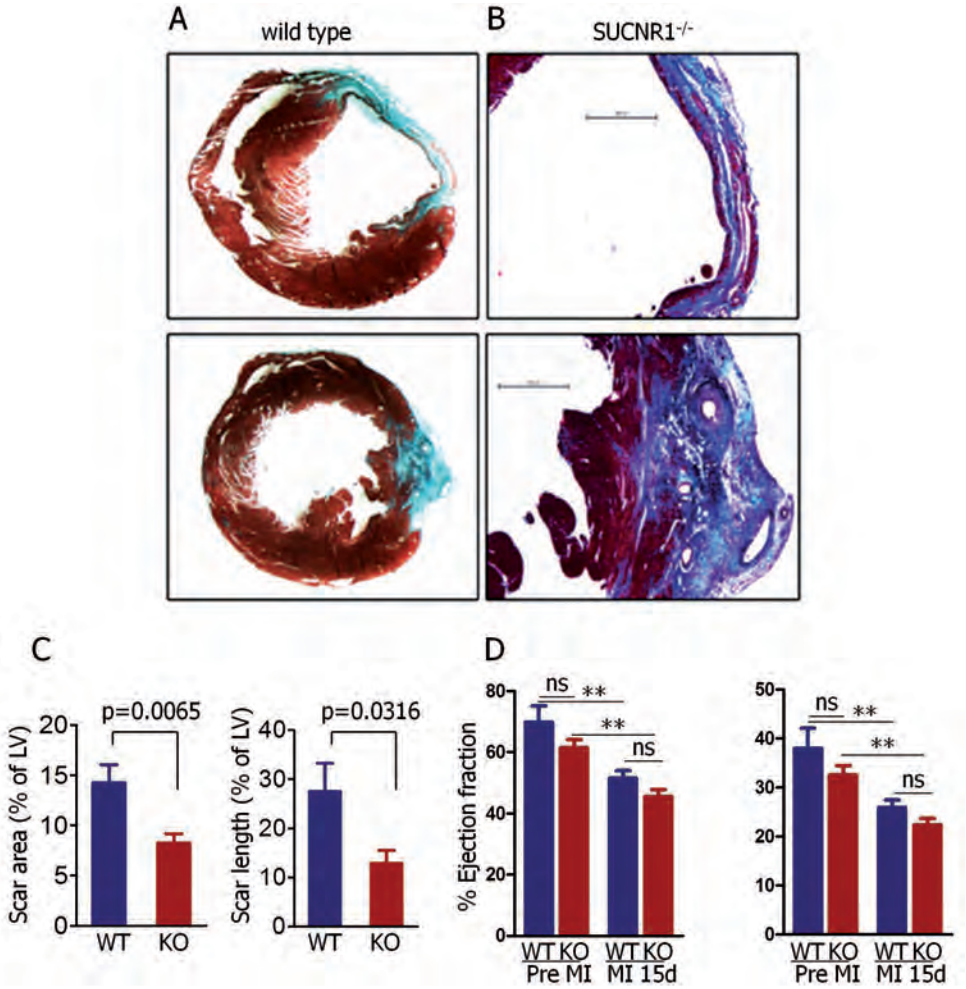
High expression of SUCNR1 can be found in adipose tissue, suggesting a possible role in adipocyte homeostasis. Interestingly, although apparently normal at birth, SUCNR1-knockout mice very quickly gain weight under both normal and high fat diet (HFD) regimes, resulting in preferential weight gains in the adipocyte compartments with accompanying adipocyte hypertrophy. These changes are also reflected in higher fasting levels of serum fatty acids, together with higher serum glucose and insulin concentrations. Intraperitoneal glucose and insulin tolerance tests in SUCNR1-knockout mice reveal a moderate decrease in insulin sensitivity together with a decrease in glucose tolerance, especially in HFD-fed animals. Together these results suggest that SUCNR1-knockout animals show hallmarks of diabetes.

Results of a separate study show that the loss of SUCNR1 in mice leads to a reduction in the formation of the fibrotic scar tissue after myocardial infarction, possibly due to a reduction in the inflammatory response. These findings point to the possibility of SUCNR1 as a novel therapeutic target in myocardial injury.



SUCNR1 *deletion alters metabolic homeostasis. (**A,B**) A glucose tolerance test (GTT) was carried out in animals (n=11) after an overnight fast, and an insulin tolerance test (ITT) was carried out in animals after a 2 h fast. (C) Basal plasma glucose levels were measured in fasted animals (left), and blood insulin was measured by ELISA before and during a GTT (right). (D) Serum levels of FA are consistently increased in KO animals.*

B. Stem Cell Biology Program



SUCNR1 *deletion results in reduced scar formation following myocardial infarction. Myocardial infarction (MI) in animals (n=12 per genotype) was performed by surgical ligation of the LAD artery. (**A,B**) 15d post MI both WT and KO animals developed fibrotic scarring as shown by Masson's trichrome staining, with collagen deposition. (**C**) A pronounced (50%) reduction in scarring was observed in KO animals compared with WT animals. (**D**) Assessment of cardiac function at 15d post MI showed similar reductions in performance in both genotypes.*

Selected Publications

Redpath SA, van der Werf N, Cervera AM, MacDonald AS, Gray D, Maizels RM, Taylor MD. **ICOS controls Foxp3(+) regulatory T-cell expansion, maintenance and IL-10 production during helminth infection**. *Eur J Immunol* (2013) 43: 705-15

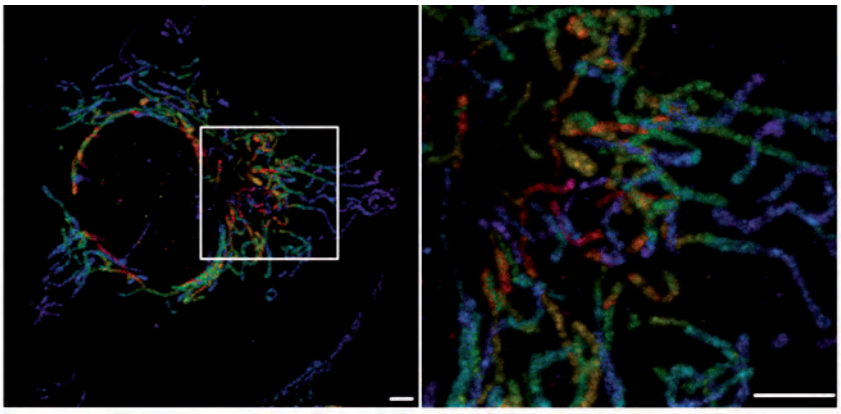
San Martin N, Cervera AM, Cordova C, Covarello D, McCreath KJ, Galvez BG. **Mitochondria determine the differentiation potential of cardiac mesoangioblasts**. *Stem Cells* (2011) 29: 1064-74

Functional genetics of the oxidative phosphorylation system

Head of Laboratory: José Antonio Enríquez
Research Scientist: Rebeca Acín
Postdoctoral Researchers: Carmen Colas, Cristiane Benincá, Umut Cagin, Sara Cogliati
Predoctoral Researchers: Adela Guaras, Ana Latorre, Rocío Nieto
Support Scientist: Mª Concepción Jiménez
Technicians: Isabel Martínez, Andrés González
Visiting Scientists: Patricio Fernández-Silva, Eduardo Balsa, Rosa Bretón, Pedro Martínez, Victoria Chaves, Elena Martín, Blanca Bello, Ana V. Lechuga, Laura Díaz, María Sánchez

Research Interest

We are interested in the biogenesis, structural organization and functional regulation of the oxidative phosphorylation (OXPHOS) system, and the consequences that impairment of its function has in disease. We are especially interested in the roles of mitochondria and the OXPHOS system in metabolic and cellular homeostasis, adaptation to ischemia/reperfusion, and aging and the initiation and progression of cardiovascular and neurodegenerative diseases. We pay special attention to two unique characteristics of the OXPHOS system: its double genetic origin (mtDNA and nuclear DNA) and the convergence of three critical processes in the same structure (electron transport, proton pumping and ATP synthesis). These processes are central to both anabolic and catabolic metabolism, and the optimization of one could be detrimental to the others. We are currently conducting a series of high-throughput screens based on a genome-wide lentiviral siRNA library, gene-trap technologies, and mitochondrial proteomics, with the goal of identifying and characterizing genes required for the correct biogenesis and performance of the OXPHOS system. We are also studying the functional consequences of allelic variants of mtDNA and their influence on disease susceptibility and development.



Mouse Fibroblasts (C57) were fixed and labeled with anti-Fp70 (mitochondrial complex II) to reveal the mitochondrial network surrounding the nucleus. The left-hand image was acquired with an SP5 confocal microscope and the boxed area is shown at a higher magnification on the right. 3D-projections were generated with LAS-AF software; color code represents Z-positions, with low positions represented by cold colors and high positions by hot colors. Scale bar: 2.5 um.

RESEARCH DEPARTMENTS

C. Tissue Homeostasis and Repair Program

Major Grants

- Ministerio de Economía y Competitividad (SAF2012-32776)
- Comunidad de Madrid. GRUPOSCAM10 (P2010/BMD-2402)
- Marie Curie Initial Training Network (ITN): Mitochondrial European Educational Training. (GA Nº 317433)
- Ministerio de Economía y Competitividad (RyC 2011-07826). PI: Rebeca Acín

Selected Publications

Acín-Perez R, Enriquez JA. **The function of the respiratory supercomplexes: The plasticity model**. *Biochim Biophys Acta* (accepted)

Cogliati S, Frezza C, Soriano ME, Varanita T, Quintana-Cabrera R, Corrado M, Cipolat S, Costa V, Casarin A, Gomes LC, Perales-Clemente E, Salviati L, Fernandez-Silva P, Enriquez JA*, Scorrano L*. **Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency**. *Cell* (2013) 155: 160-71
**Co-correponding authors*

Lapuente-Brun E, Moreno-Loshuertos R, Acín-Pérez R, Latorre-Pellicer A, Colás C, Balsa E, Perales-Clemente E, Quirós PM, Calvo E, Rodríguez-Hernández MA, Navas P, Cruz R, Carracedo Á, López-Otín C, Pérez-Martos A, Fernández-Silva P, Fernández-Vizarra E, Enríquez JA. **Supercomplex assembly determines electron flux in the mitochondrial electron transport chain**. *Science* (2013) 340: 1567-70

Villa-Bellosta R, Rivera-Torres J, Osorio FG, Acín-Pérez R, Enriquez JA, López-Otín C, Andrés V. **Defective extracellular pyrophosphate metabolism promotes vascular calcification in a mouse model of Hutchinson-Gilford progeria syndrome that is ameliorated on pyrophosphate treatment**. *Circulation* (2013) 24: 2442-51

Balsa E, Marco R, Perales-Clemente E, Szklarczyk R, Calvo E, Landázuri MO, Enríquez JA. **NDUFA4 Is a subunit of complex IV of the mammalian electron transport chain**. *Cell Metab* (2012) 16: 378-86

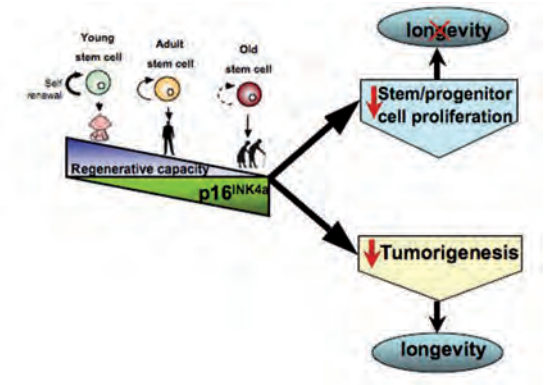
Stem cell aging

Head of Laboratory: Susana González
Postdoctoral Researcher: Antonio Herrera
Predoctoral Researchers: Isabel Hidalgo, Ileana González
Technician: Rebeca Diges
Masters Students: Arturo Bujarrabal, Inmaculada Martos

Research Interest

The INK4b-ARF-INK4a locus encodes three tumour suppressors, p15INK4b, ARF, and p16INK4a. Together, these factors constitute one the most important sources of cancer protection in mammals, equalled in importance only by p53. These tumour suppressors have taken on additional importance in the light of recent evidence that at least one product of the locus, p16INK4a, also contributes to the decline in the replicative potential of self-renewing cells with age. Thus, on the one hand, p16INK4a promotes longevity through its action as a potent tumour suppressor, while on the other hand the increased expression of p16INK4a with age reduces stem and progenitor cell proliferation, ultimately reducing longevity. In other words, p16INK4a appears to balance the need to prevent cancer against the need to sustain regenerative capacity throughout life. These observations suggest the provocative but unproven notion that mammalian aging results in part from the effectiveness of tumour suppressor proteins at preventing cancer.

Our group is investigating the role and molecular regulation of the INK4b-ARF-INK4a locus in the context of self-renewal, proliferation and aging of hematopoietic stem cells in vitro and in vivo, with planned extension of these studies to cardiac stem cells. In parallel, we are developing tools for the study of the genetic and epigenetic mechanisms that regulate stem cells, and how these unique cells differentiate from a pluripotent to a more restricted state.



The INK4/ARF locus regulates cancer cell proliferation and stem cell aging, and in this way may control the balance between the needs for regenerative capacity and for protection against the increased risk of risk of neoplasms with age.

Major Grants

- **Ministerio de Ciencia e Innovación (SAF2010-15386)**

Selected Publications

Hidalgo I, Gonzalez S. **New epigenetic pathway for stemness maintenance mediated by the histone methyltransferase Ezh1**. *Cell Cycle* (2013) 12: 383-4

Hidalgo I, Herrera-Merchan A, Ligos JM, Carramolino L, Nuñez J, Martinez F, Dominguez O, Torres M, Gonzalez S. **Ezh1 Is Required for Hematopoietic Stem Cell Maintenance and Prevents Senescence-like Cell Cycle Arrest**. *Cell Stem Cell* (2012) 11: 649-62

Herrera-Merchan A, Arranz L, Ligos JM, de Molina A, Dominguez O, Gonzalez S. **Ectopic expression of the histone methyltransferase Ezh2 in haematopoietic stem cells causes myeloproliferative disease**. *Nat Commun* (2012) 3: 623

Arranz L, Herrera-Merchan A, Ligos JM, de Molina A, Dominguez O, Gonzalez S. **Bmi1 is critical to prevent Ikaros-mediated lymphoid priming in hematopoietic stem cells**. *Cell Cycle* (2012) 11: 65-78

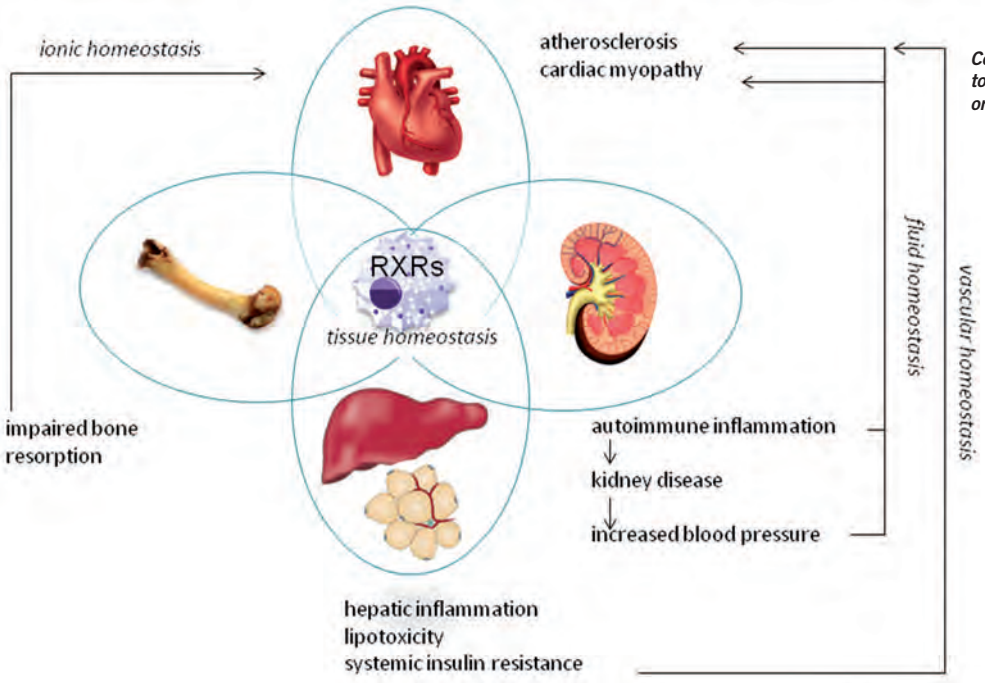
Arranz L, Herrera-Merchan A, Gonzalez S. **Therapeutic Polycomb targeting in human cancer**. *Recent Pat Reg Med* (2012) 2: 22-29

Nuclear receptor signaling

Head of Laboratory: Mercedes Ricote
Postdoctoral Researchers: Piedad Menéndez, Tamás Röszer
Predoctoral Researchers: Daniel Alameda, Marta Cedenilla, Anna Kwasniewska, Wencke Walter
Technician: Vanessa Núñez
Masters Student: Laura Alonso

Research Interest

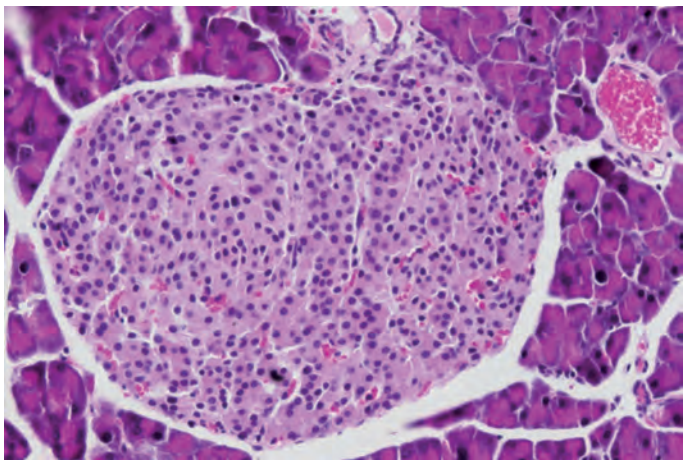
Macrophages are immune cells with important functions in development, immunity, tissue homeostasis and disease. Projects in our laboratory focus on elucidating the transcriptional control of these functions, with special emphasis on their possible medical utility in the treatment of metabolic and cardiovascular diseases. Our recent studies have demonstrated the central role of a family of transcription factors, the retinoid X receptors (RXRs), in macrophage biology. Our findings underscore the importance of RXR ligands in the treatment of macrophage-associated pathologies, such as autoimmunity, insulin resistance and atherosclerosis. We have developed mouse lines with conditional deletion of RXRs in myeloid cells and used next generation sequencing to identify RXR-controlled transcriptional networks. This analysis has provided evidence that macrophage RXRs play an important role in the development of insulin resistance. We have also demonstrated that RXR ligands have clinical potential, since pharmacological RXR activation mitigates insulin resistance and inhibits the differentiation of osteoclast precursors. RXRs may thus be promising targets for interventions to increase insulin sensitivity or treat osteoporosis, a frequent comorbidity of insulin resistance. Interestingly, mice lacking macrophage RXRs develop high arterial blood pressure and cardiac hypertrophy, suggesting the contribution of macrophage RXRs to hypertension and cardiac disease. Our studies identify myeloid cell RXRs as key players in tissue and organ homeostasis, and open new perspectives on the use of RXR ligands as potential regulators of pathologies associated with altered myeloid cell differentiation and function.



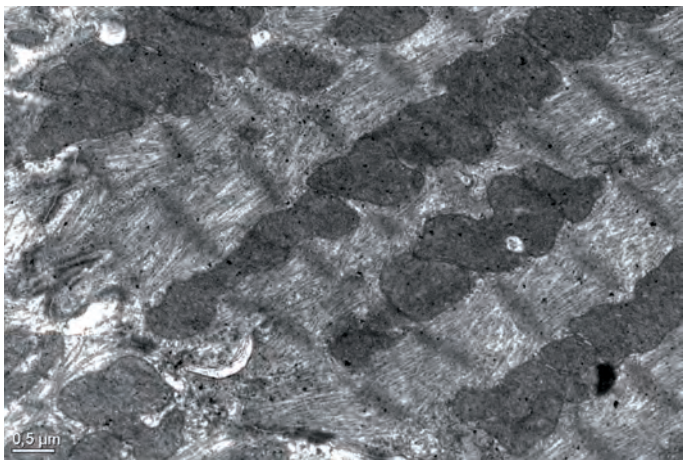
Contribution of macrophage RXRs to the integration of tissue and organ homeostasis.

RESEARCH DEPARTMENTS

C. Tissue Homeostasis and Repair Program



***Hematoxylin and eosin stained section of a pancreatic islet**. A high-fat diet results in insulin resistance, which induces compensatory hyperplasia of the pancreatic islets.*



***Transmission electron micrograph of hypertrophic cardiomyocytes.** The image shows hypertrophic cardiomyocytes from the left ventricle, showing enlarged mitochondria and disordered microfilaments.*

Major Grants

- **European Union (PITN-GA-2013-608027) (CardioNext)**
- **Fundación la Marató TV3 (MTV3012)**
- **Ministerio de Economía y Competitividad (SAF2012-31483)**
- **European Foundation for the Study of Diabetes/Lilly Research Fellowship (T. Röszer, EFSDF2012)**

Selected Publications

Ballesteros I[1], Cuartero MI, Pradillo JM, de la Parra J, Pérez-Ruiz A, Corbí A, Ricote M, Hamilton JA, Sobrado M, Vivancos J, Nombela F, Lizasoain I, Moro MA. **Rosiglitazone-induced CD36 up-regulation resolves inflammation by PPARγ and 5-LO-dependent pathways**. *J Leukoc Biol*. 2013 Dec 12. [Epub ahead of print]

Röszer T, Menéndez-Gutierrez MP, Cedenilla M, Ricote M. **Retinoid X receptors in macrophage biology**. *Trends Endocrinol Metab* (2013) 24: 460-8

Menéndez-Gutierrez MP, Röszer T, Ricote M. **Biology and therapeutic applications of peroxisome proliferator-activated receptors**.*Curr Topics Med Chem* (2012) 12: 548-84

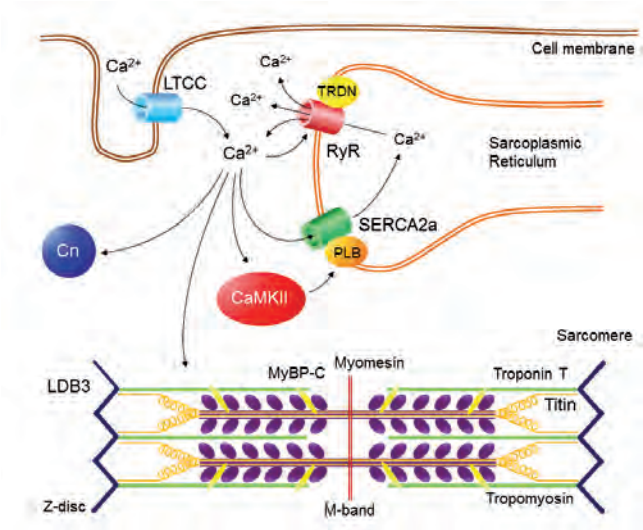
Molecular regulation of heart development and disease

Head of Laboratory: Enrique Lara-Pezzi
Predoctoral Researchers: Jesús Gómez Salinero, Alberto Gatto, Enda Clinton, Girolamo Giudice
Graduate Technician: Maria Villalba Orero
Technician: Marina López Olañeta
Masters Student: Paula Ortiz Sánchez
Visiting Scientist: José González Santamaría

Research Interest

Following myocardial infarction, dead cardiomyocytes are substituted by a collagen scar. Although this response prevents heart rupture, it also leads to a progressive remodeling of the heart and eventually to heart failure. The molecular mechanisms underlying this process are unclear and are the main focus of our lab. In particular, we are interested in the role and regulation of alternative splicing, the main mechanism responsible for protein diversity. The role of alternative splicing in the response to myocardial infarction is unknown. For our approach, we have developed a new analysis pipeline that considerably increases the precision of read alignment in RNA-Seq experiments. This allows a more accurate analysis of exon junction expression and alternative splicing regulation. Using this analysis pipeline we have identified splicing factors that may play regulatory roles in the infarcted heart. We are now analyzing the role of these factors through different gain- and loss-of-function approaches in mice.

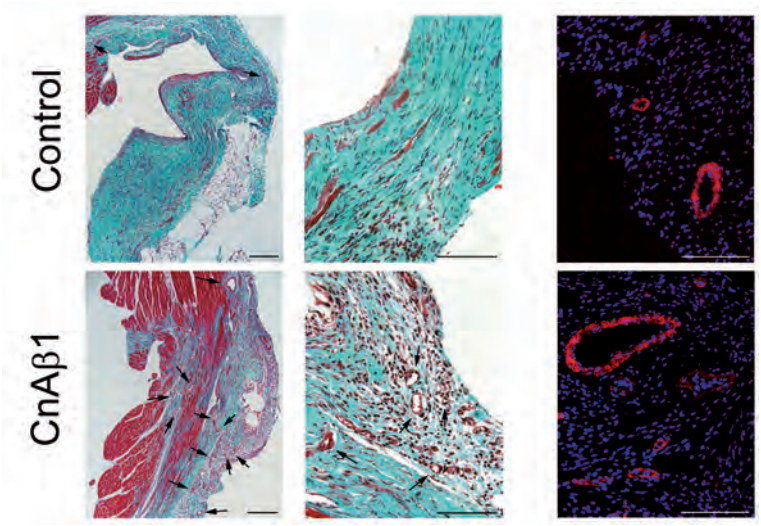
We are particularly interested in a calcineurin splicing isoform called CnAβ1. CnAβ1 is highly expressed in stem cells and regenerating tissues, and our results suggest that it regulates the differentiation of embryonic stem cells to the mesodermal lineage. Unlike other calcineurin isoforms, which play a pathological role in the heart, CnAβ1 improves cardiac function after myocardial infarction by reducing infarct expansion. We are now investigating its effect on the heart in a mouse model of diabetic cardiomyopathy. As part of a new European Network (CardioNext), also involving other CNIC groups, we will explore the therapeutic potential of CnAβ1 in a preclinical myocardial infarction model in the pig.



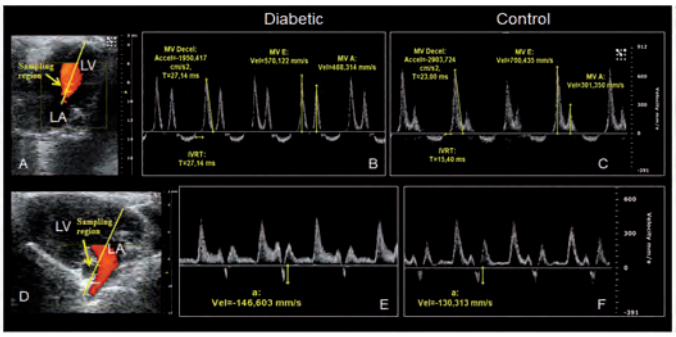
***Calcium handling and sarcomere contraction is regulated by alternative splicing**. Proteins regulated by alternative splicing and involved in calcium mobilization, cell signaling and sarcomere contraction are shown (except for phospholamban, PLB). Calcium entry through voltage-gated L-type calcium channels (LTCC) promotes calcium release from the sarcoplasmic reticulum through the ryanodine receptor (RyR). This promotes muscle contraction until calcium is pumped back into the sarcoplasmic reticulum by the SERCA2 ATPase. Calcium also activates calcineurin (Cn) and calcium/calmodulin-dependent protein kinase II (CaMKII), which modulates different processes in the cardiomyocyte. Some of the alternative splicing changes in the mRNAs encoding these proteins are associated with cardiomyopathies and heart failure, while others have a positive effect on the heart (adapted from Lara-Pezzi et al, 2013).*

RESEARCH DEPARTMENTS

C. Tissue Homeostasis and Repair Program



CnAβ1 improves vascularization of the infarcted region. *Overexpression of the calcineurin isoform CnAβ1 in transgenic mice after myocardial infarction increases the number of blood vessels in the infarcted region compared with control mice, thereby preventing cell death and infarct expansion. Left and center, Masson's trichrome staining of the infarcted region in the heart. Blue indicates collagen. Vessels are indicated by an arrow. Right, Immunostaining of the infarcted region. Red, α-smooth muscle actin; blue, nuclei stained with DAPI; green. Bar, 100 μm.*



Diastolic dysfunction in diabetic cardiomyopathy. *Color (CD) and pulsed-wave (PW) Doppler imaging of a four apical chamber heart view (A-C) and a parasternal long axis-modified view (D-F) 4 weeks after diabetes induction with streptozotocin. A, D, Representative CD images showing the mitral (A) and the pulmonary vein (D) flow (red) in the sampling region used to obtain the PW. B,C, Mitral inflow pattern in diabetic (B) and control mice (C). Diabetic mice have an increased isovolumic relaxation time (IVRT) and a decreased mitral valve (MV) deceleration and E/A ratio, suggesting diastolic dysfunction. E, F, Pulmonary flow velocity pattern in diabetic (E) and control mice (F). The reverse flow velocity during atrial contraction (a) is increased in diabetic mice. LV, Left ventricle; LA, left atrium; E, Peak early flow velocity; A, Peak active flow velocity.*

Major Grants

- European Union (PITN-GA-2013-608027) (CardioNext)
- European Union (PITN-GA-2011-289600) (CardioNeT)
- Comunidad de Madrid (GRUPOSCAM10, "Fibroteam" (S2010/BMD-2321)
- Ministerio de Economía (SAF2012-31451)
- Ministerio de Ciencia e Innovación. FIS (CP08/00144)

Selected Publications

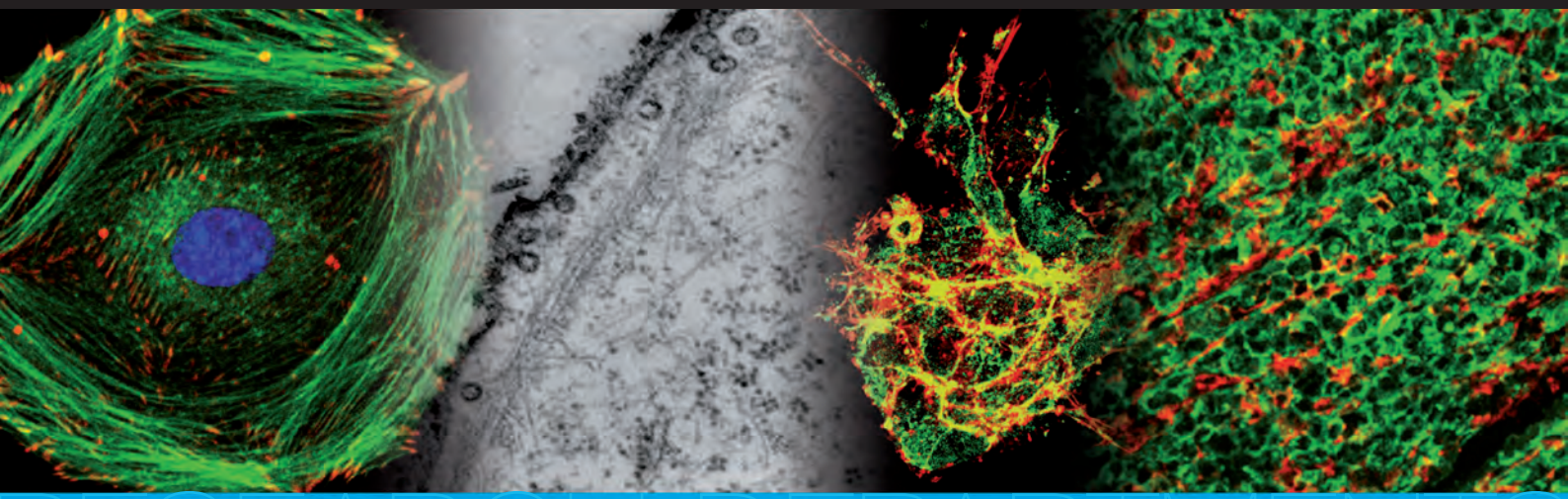
Lara-Pezzi E, Gómez-Salinero J, Gatto A, García-Pavía P. **The alternative heart: impact of alternative splicing in heart disease**. *J Cardiovasc Transl Res* (2013) 6: 945-55

Panse KD, Felkin LE, López-Olañeta MM, Gómez-Salinero J, Villalba M, Muñoz L, Nakamura K, Shimano M, Walsh K, Barton PJ, Rosenthal N, Lara-Pezzi E. **Follistatin-Like 3 Mediates Paracrine Fibroblast Activation by Cardiomyocytes**. *J Cardiovasc Transl Res* (2012) 5: 814-826

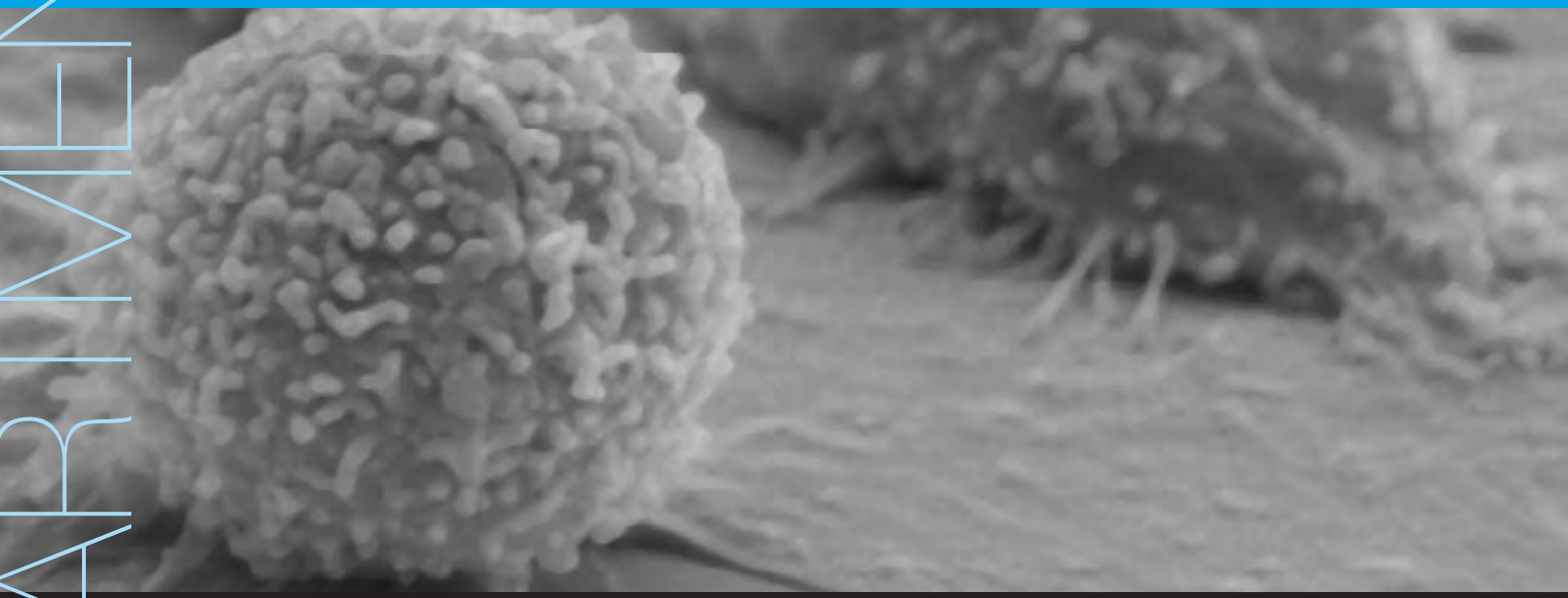
Gómez-Gaviro MV, Lovell-Badge R, Fernández-Avilés F, Lara-Pezzi E. **The Vascular Stem Cell Niche**. *J Cardiovasc Transl Res* (2012) 5: 618-630

Lara-Pezzi E, Dopazo A, Manzanares M. **Understanding cardiovascular disease: a journey through the genome (and what we found there)**. *Dis Model Mech* (2012) 5: 434-4

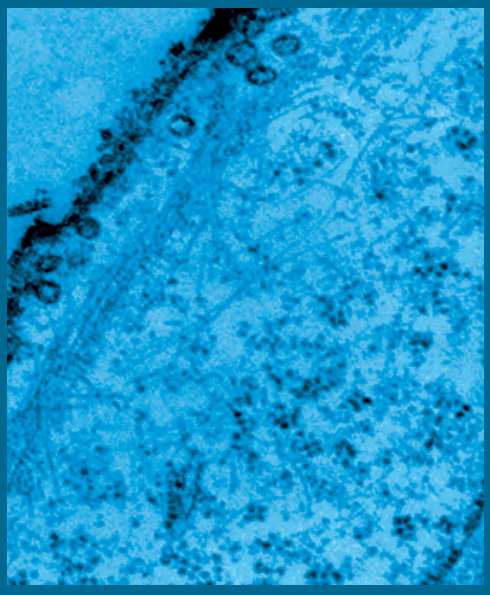
2 Vascular Biology and Inflammation



RESEARCH DEPARTMENTS



2 Vascular Biology and Inflammation



Research in the **Department of Vascular Biology and Inflammation** (DVBI) is focused on the interactions between cells of the vascular system. The groups in the department work along the following strategic research lines: 1) Vascular Wall Remodeling; 2) Inflammation and Autoimmunity; and 3) Cell Biology and Signaling in Metabolism and Disease. DVBI research groups use a wide variety of techniques, including animal, tissue, cellular and molecular models, to investigate normal vascular function and the key steps in the vascular alterations that underlie cardiovascular diseases. Cardiovascular proteomics is also a major interest.

Department Director:	Juan Miguel Redondo
Department Managers:	Antonio Jesús Quesada Laura Grau
Project Manager:	Lilit Manukyan
Technicians:	Andrea Quintana Juan José Lazcano María José Gómez Bahia El Maimouni (Charles River) Elisabeth Daniel (Charles River)
Administrative Support:	Almudena Fernández Eduardo Bieger

Gene regulation in cardiovascular remodelling and inflammation

Head of Laboratory: Juan Miguel Redondo
Research Scientists: Pablo Gómez-del Arco, Sara Martínez-Martínez
Predoctoral Researchers: Amelia Escolano, Nerea Méndez, Noelia Lozano, Jorge Oller
Masters Student: Silvia Villahoz
Technicians: Dolores López Maderuelo, Beatriz Carolina Ornés, Ruth Alberca, Alicia Peral
Visiting Scientist: Ángel Luis Armesilla

Research Interest

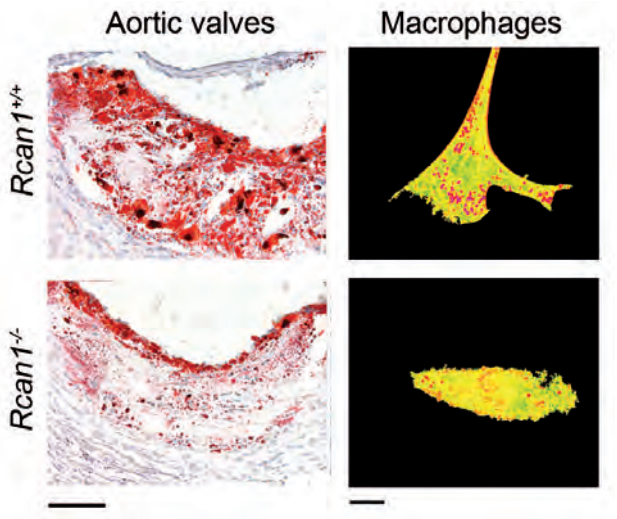
The calcineurin (CN)-NFAT pathway regulates many important biological processes, including the function and development of the immune and cardiovascular systems, the morphogenesis of the heart valves, muscle development, and the functions of pancreatic β-cells.We study the regulation and function of this pathway in inflammation and cardiovascular and inflammatory diseases.

We are analyzing gene expression triggered by both expression overload and angiotensin II (AngII) in cardiac tissue. This work is aimed at identifying molecular mediators of cardiac hypertrophy. We have found several CN-regulated genes in models of cardiac hypertrophy, and plan to characterize their roles in this disease.

We recently identified CN and its downstream effector RCAN1 as mediators of diseases characterized by pathological vascular wall remodeling. This work shows that CN inhibition prevents restenosis and abdominal aortic aneurysm (AAA), and that RCAN1 deficient mice are resistant to these diseases. We are now characterizing cellular and molecular mechanisms involved in RCAN-1–mediated vascular wall remodeling by using lentiviral vectors encoding the Rcan isoforms and by studying recently generated conditional KO mice for each isoform.

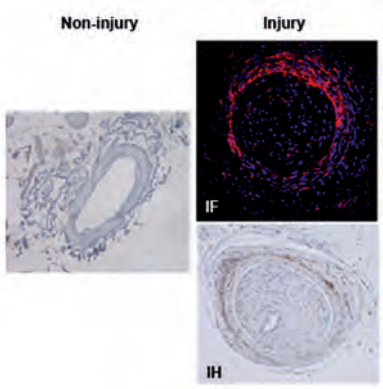
Through in vivo infection with lentiviral vectors encoding motifs important for CN-NFAT interactions, we can prevent or retard the development of arthritis in mice. In our system, inflammation is curtailed by infection of macrophages at distinct locations and their subsequent migration to inflammation sites.

All the work in our laboratory is focused on gaining a better understanding of molecular and cellular mechanisms underlying inflammatory diseases and diseases that occur with pathological vascular wall or cardiac remodeling, and our longer term goal is that these findings will lead to the identification of prognostic or diagnostic markers and therapeutic targets.



Genetic inactivation of Rcan1 reduces LDL cholesterol accumulation (red staining) in aortic valves and macrophages, the most important inflammatory cells in atherosclerotic plaques.

RESEARCH DEPARTMENTS



Lymphocyte infiltration in a mouse model of neointima thicknening upon femoral injury. Images show CD3 immunofluorescence (IF) and immunostaining (IH) in cross sections of femoral injured arteries.

Major Grants

- **Ministerio de Economía y Competitividad (SAF2012-34296)**
- **Ministerio de Economía y Competitividad. FIS RETICS (Red de Investigación Cardiovascular: RD12/0042/0022)**
- **Fundació La Marató TV3 (264/C/2012) (PI: Sara Martínez)**

Selected Publications

Escolano A, Martínez-Martínez S, Alfranca A, Urso K, Izquierdo HM, Delgado M, Martín F, Sabio G, Sancho D, Gómez-del Arco P and Redondo JM. **Specific calcineurin-targeting in macrophages confers resistance to inflammation via MKP-1 and p38**. *EMBO J* (accepted)

Silvestre-Roig C, Fernández P, Esteban V, Pello ÓM, Indolfi C, Rodríguez C, Rodríguez-Calvo R, López-Maderuelo MD, Bauriedel G, Hutter R, Fuster V, Ibáñez B, Redondo JM, Martínez-González J, Andrés V. **Inactivation of nuclear factor-Y inhibits vascular smooth muscle cell proliferation and neointima formation**. *Arterioscler Thromb Vasc Biol*. (2013) 33(5):1036-45

Méndez-Barbero N, Esteban V, Villahoz S, Escolano A, Urso K, Alfranca A, Rodríguez C, Sánchez SA, Osawa T, Andrés V, Martínez-González J, Minami T, Redondo JM* Campanero MR*. **A major role for RCAN1 in atherosclerosis progression**. *EMBO Mol Med* (2013) 5(12):1901-17

Garaulet G, Alfranca A, Torrente M, Escolano A, López-Fontal R, Hortelano S, Redondo JM, Rodríguez A. **IL10 released by a new inflammation-regulated lentiviral system efficiently attenuates zymosan-induced arthritis**. *Mol Ther* (2013) 21(1):119-30

Salvado MD, Alfranca A, Haeggström JZ, Redondo JM. **Prostanoids in tumor angiogenesis: therapeutic intervention beyond COX-2**. *Trends Mol Med* (2012) 18: 233-43

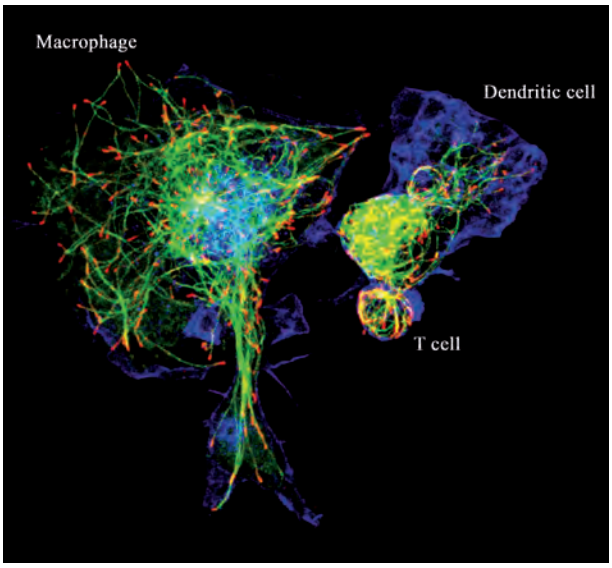
CNIC-UAM COLLABORATIVE PROGRAM
Intercellular communication in the inflammatory response

Head of Laboratory:	Francisco Sánchez Madrid
Research Scientist:	Gloria Martínez del Hoyo
Postdoctoral Researchers:	Olga Barreiro Hortensia de la Fuente Noa B. Martín María Mittelbrunn Vera Rocha Danay Cibrian
Predoctoral Researchers:	Francesc Baixauli Cristina Gutierrez Giulia Morlino Norman Núñez Mª Laura Saiz Carolina Villarroya Olga Moreno Noelia Blas Eugenio Bustos
Masters Student:	Ángel Luis Jaso
Technicians:	Marta Esther Ramirez María José López

Research Interest

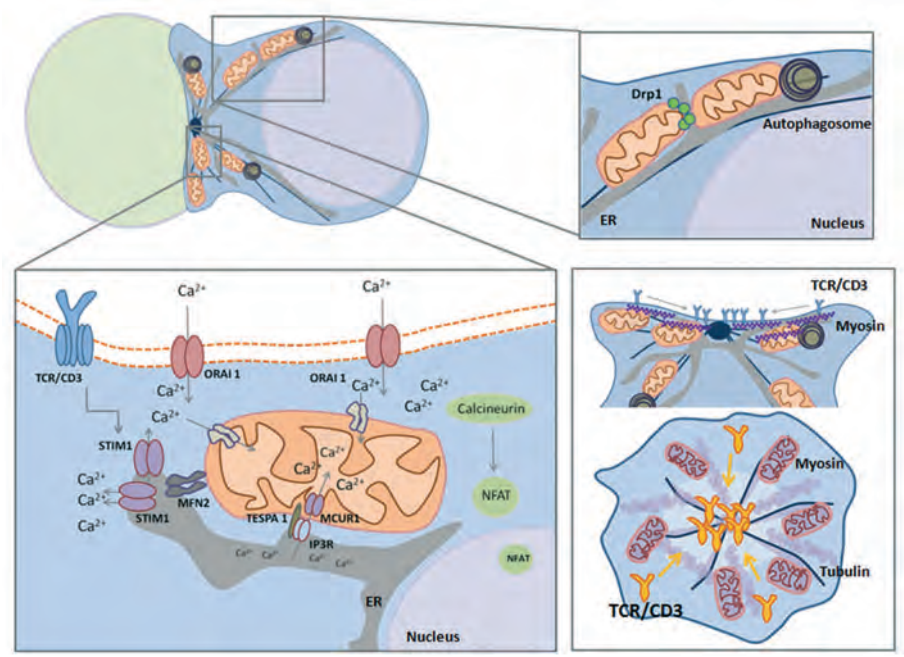
Communication between antigen-presenting cells (APCs) and T cells can be established through the formation of the immune synapse (IS). The IS has a specific molecular architecture, which is organized and maintained through the dynamics of cytoskeleton components. A key cell marker for lymphocyte polarization is the localization of the centrosome, or MTOC (microtubule-organizing centre), which acts as a cell-polarity maintenance organelle (Martín-Cófreces et al., 2013).

We have found that localization of the tetraspanin CD81 at the contact area between the APC and the T cell marks the degree of maturation of an IS (Perugini-Rocha et al., 2013). We have analyzed the role of the MTOC and microtubules (MT) as key components in T cell activation. MTOC translocation stimulates and regulates the transport of several organelles towards the IS, including mitochondria. The EB1-dependent nucleation of MT from the MTOC permits the organization of an intense vesicular trafficking that supports T cell receptor downstream signaling at the IS (Martín-Cófreces et al., 2012). Multivesicular bodies (MVB) concentrate at the IS upon MTOC translocation, favoring the exocytosis of small membrane vesicles (exosomes) that mediate an original mode of cell-cell communication with the APC (Gutierrez et al., 2013). Our results support specific roles for miRNAs released from exosomes as messengers in the target APC (Mittelbrunn and Sanchez-Madrid, 2012). Specific miRNAs are sorted to exosomes through the binding via specific nucleotide motifs to proteins such as ROA2 (hnRNPA2B1). The localization of ROA2 in exosomes is regulated by sumoylation (Villarroya-Beltri et al., 2013).

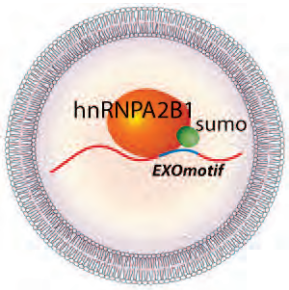


***Skeletons at the immune synapse**. Macrophages (left) and dendritic cells (right) act as antigen presenting cells for OVA-specific, CD4+ T lymphocytes. Tubulin (green), actin filaments (blue), end-binding 1 (EB1, red).*

RESEARCH DEPARTMENTS



Fueling the IS. *The mitochondrial fission factor Drp1 controls the localization of the mitochondria at the nascent IS to regulate ATP levels and the actomyosin centripetal flux of the TCR.*



hnRNPA2B1 exosomal sorting. *Sumoylated hnRNPA2B1 controls the sorting of exosomal microRNAs through binding to specific sequence motifs.*

Major Grants

- **ERC Advanced Investigators Grant (ERC-2011-AdG 20110310) (GENTRIS)**
- **Ministerio de Economía y Competitividad (SAF2011-25834)**
- **Ministerio de Economía y Competitividad. FIS RETICS (RIC: RD12/0042/0056)**
- **Redes de Excelencia de la Comunidad de Madrid (P2010/BMD-2332)**
- **Ministerio de Economía y Competitividad. FIS (PI11/00939) PI: Gloria Martínez del Hoyo**

Selected Publications

Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, Pérez-Hernández D, Vázquez J, Martin-Cofreces N, Martinez-Herrera DJ, Pascual-Montano A, Mittelbrunn M, Sánchez-Madrid F. **Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs**. *Nat Commun* (2013) 4:2980

Martín-Cófreces NB, Baixauli F, Sánchez-Madrid F. **Immune synapse: conductor of orchestrated organelle movement**. *Trends Cell Biol* (2013) 24:61-72

Rocha-Perugini V, Zamai M, González-Granado JM, Barreiro O, Tejera E, Yañez-Mó M, Caiolfa VR, Sanchez-Madrid F. **CD81 controls sustained T cell activation signaling and defines the maturation stages of cognate immunological synapses**. *Mol Cell Biol*. (2013) 33:3644-58

Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M, Sánchez-Madrid F. **Transfer of extracellular vesicles during immune cell-cell interactions**. *Immunol Rev* (2013) 251:125-42

Mittelbrunn M, Sánchez-Madrid F. **Intercellular communication: diverse structures for exchange of genetic information**. *Nat Rev Mol Cell Biol* (2012) 13:328-35

2 Vascular Biology and Inflammation

Integrin signaling

Head of Laboratory: Miguel Angel Del Pozo

Research Scientists: Asier Echarri
Inés Martin Padura

Postdoctoral Researchers: Raffaele Strippoli
Inmaculada Navarro
Teijo Pellinen
Fidel Lolo Romero
Marta C. Guadamillas
Silvia Fernández-Soriano

Predoctoral Researchers: Roberto Moreno Vicente
Lucas Albacete

Masters Student: Alberto Díez

Technicians: Sara Sánchez Perales
Dácil M. Pavón
Teresa Osteso Ibáñez
Mauro Catalá

Visiting Scientist: Marco Cordani

Research Interest

Caveolae are actin-linked plasma membrane nano-invaginations, abundant in mechanically stressed tissues. They are involved in signaling, viral entry, membrane trafficking and lipid metabolism; however, controversy surrounds these actions, and the precise functions of caveolae and their main proteins caveolins (Cav 1-3) and cavins (1-4) remain unresolved. Cav-deficient mice show tissue abnormalities, and caveolar disorders are associated with lipodystrophy and muscular dystrophy, cardiovascular disease and cancer, suggesting a role as homeostatic regulators. Preliminary evidence suggests that caveolae sense mechanical cues. Indeed, we have shown that Cav1 can modulate cell shape and responses via force-dependent remodeling of the 3D microenvironment. Many cancer associated fibroblasts (CAFs) express high levels of Cav1, which activates Rho signaling, causing cells to stretch out and remodel the matrix. The elongated Cav1-CAFs form stiff, parallel-fiber networks through which cancer cells move rapidly, promoting local invasion and subsequently distant metastasis (Figure1). We now aim to identify other stromal stromal genes involved in biomechanical cell responses that foster cancer progression, by performing an image-and-RNAi-based high content screening (Figure 2).

Our work shows that stromal-Cav1 drives not only pathological remodeling of the tumor microenvironment, but also physiological remodeling, for example in breast and skin. We are now addressing the role of Cav1 and the phosphorylation of its Tyr14 in cardiac remodeling after acute myocardial infarction using the LAD (left anterior descending) artery permanent ligation model (Figure 3).

Our recent work has also established tight links between the actin cytoskeleton and caveolar plasticity and trafficking. We are now addressing the role of newly identified caveolar components in the organization and dynamics of the actin cytoskeleton (Figure 4).

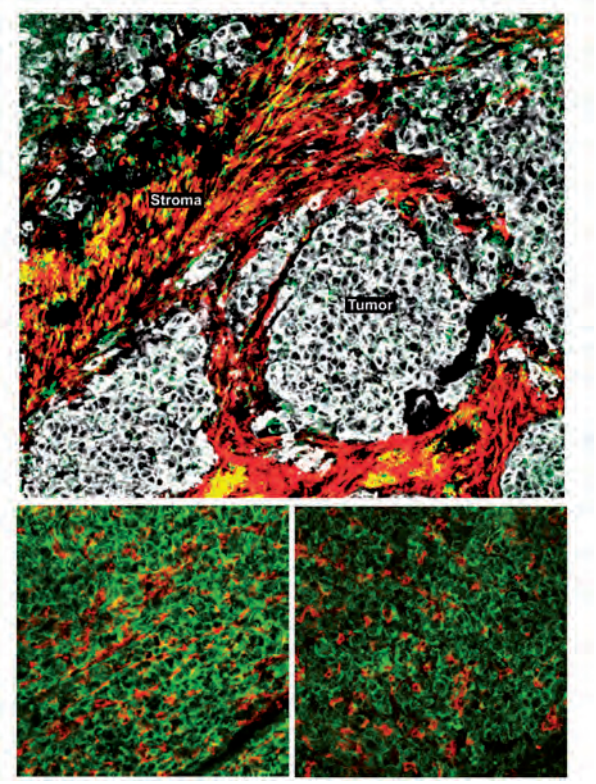


Figure 1. Caveolin-1^{hi} stroma promotes tumor invasion. **Top** *Multicolor confocal image of a melanoma metastatic lession stained for Hmb45 (tumor cells) in white, CD90 (CAFs) in red, and Cav1 in green. The stroma of this aggressive tumor is highly positive for Cav1.* **Bottom** *Extracted tumors from xenografted mice stained for Cav1 (green) and SMA (CAFs, in red). Cav1-positive CAFs (left), but not Cav1-deficient CAFs (right), remodel the stroma to organize highly parallel and stiff avenues that promote directional migration and invasion of tumor cells (labeled also by Cav1 in green).*

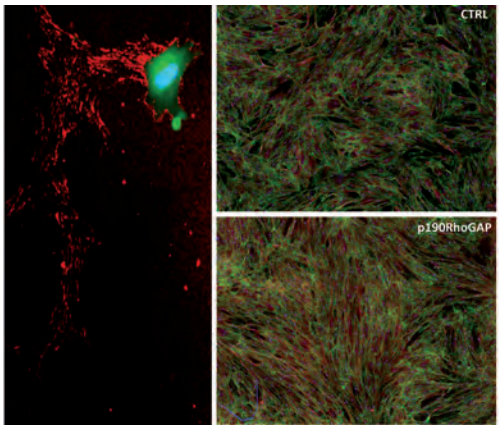


Figure 2. Remodeling of a fibronectin (Fn) matrix by cancer associated fibroblasts (CAFs). **Left** *A human fibroblast walking on and remodeling a Fn-coated plate.* **Right** *Human CAFs were seeded onto FITC-Fn (green) and after 48h fixed and stained for actin cytoskeleton (red) and nuclei (blue). Silencing of p190RhoGAP in CAFs (bottom) renders a highly organized and parallel Fn matrix, as compared with control siRNA (up). Quantitative assessment of Fn fiber orientations and texture patterns through advanced image analysis will be used in an RNAi-based high content screening to identify genes involved in biomechanical stroma remodeling.*

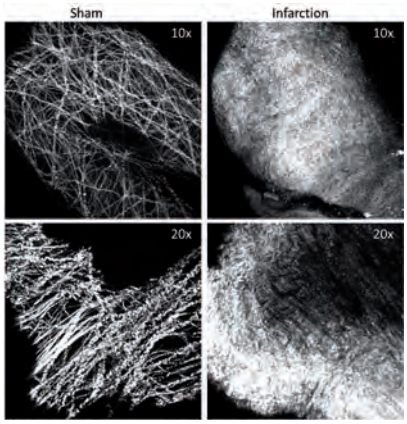


Figure 3. Collagen fiber remodeling after myocardial infarction imaged by second harmonic generation (SHG). *Native (non-fixed) hearts from wild-type mice were imaged for SHG. Whereas collagen fibers are highly ordered under basal conditions (left), after permanent ligation of the LAD strong collagen deposition is observed (right).*

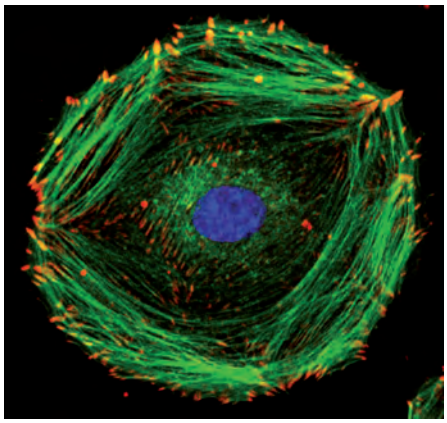


Figure 4. Caveolar proteins regulate the actin cytoskeleton. *The image shows the architecture of the actin cytoskeleton (phalloidin, green) and focal adhesions (vinculin, red) in a cell devoid of a caveolar component. The cells exhibit loss of polarity and an atypical concentrical distribution of stress fibers, very different from the polarized wild-type cells.*

Major Grants

- Ministerio de Economía y Competitividad (SAF2011-25047)
- Ministerio de Economía y Competitividad. Consolider COAT (CSD2009-00016)
- Fundació La Marató TV3 (674/C/2013)

Selected Publications

Azegrouz H, Karemore G, Torres A, Alaíz CM, Gonzalez AM, Nevado P, Salmerón A, Pellinen T, Del Pozo MA, Dorronsoro JR, Montoya MC. **Cell-based fuzzy metrics enhance high-content screening (HCS) assay robustness**. *J Biomol Screen* (2013) 18: 1270-1283

Samaniego R, Estecha A, Relloso M, Longo N, Escat JL, Longo-Imedio I, Avilés JA, Del Pozo MA, Puig-Kröger A, Sánchez-Mateos P. **Mesenchymal contribution to recruitment, infiltration, and positioning of leukocytes in human melanoma tissues**. *J Invest Dermatol* (2013) 133: 2255-2264

Parton RG, Del Pozo MA. **Caveolae as plasma membrane sensors, protectors and organizers**. *Nat Rev Mol Cell Biol* (2013) 14: 98-112

Echarri A, Muriel O, Pavón DM, Azegrouz H, Escolar F, Terrón MC, Sanchez-Cabo F, Martínez F, Montoya MC, Llorca O, Del Pozo MA. **Caveolar domain organization and trafficking is regulated by Abl kinases and mDia1**. *J Cell Sci* (2012) 125: 3097-3113.

Navarro-Lérida I, Sánchez-Perales S, Calvo M, Rentero C, Zheng Y, Enrich C, Del Pozo MA. **A palmitoylation switch mechanism regulates Rac1 function and membrane organization**. *EMBO J* (2012) 31: 534-51

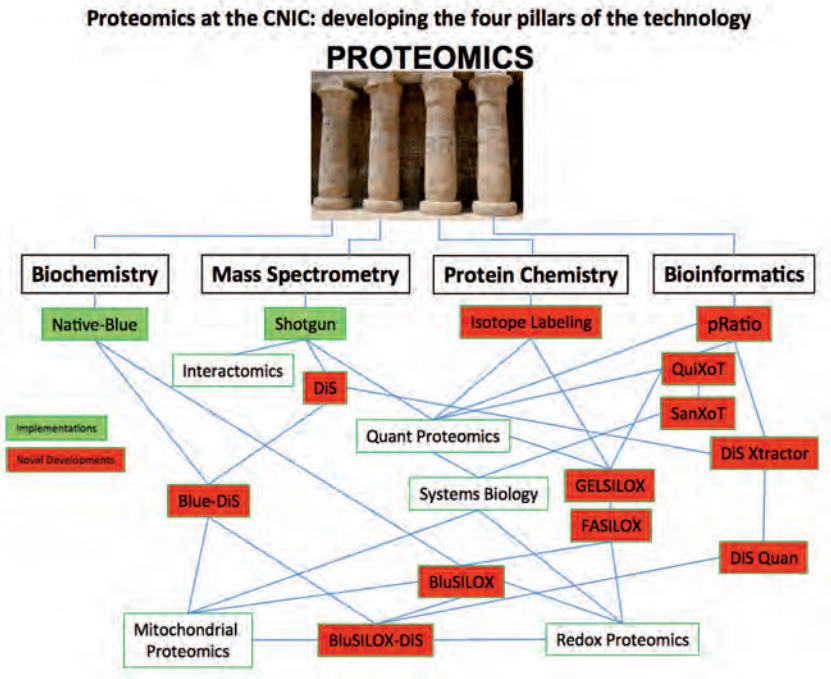
2 Vascular Biology and Inflammation

Cardiovascular proteomics

Head of Laboratory:	Jesús Mª Vázquez Cobos
Postdoctoral Researchers:	Estefanía Núñez Sánchez Elena Bonzón Kulichenko Inmaculada Jorge Cerrudo
Predoctoral Researchers:	Fernando García Marqués Marco Trevisan Herraz Aleksandra Binek
Masters Student:	Marta Loureiro
Technician:	Raquel Mesa Carrasco
Visiting Scientists:	Mariano Ortega Múñoz Adela Ramírez Torres Elena Burillo

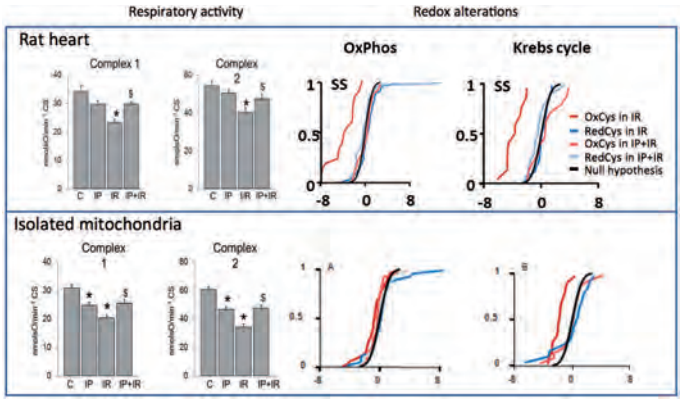
Research Interest

Our group works on the development of high-throughput quantitative approaches for the dynamic analysis of the deep proteome and their application to cardiovascular projects. We have recently developed a generic integration algorithm (SanXoT) that serves as the basis for systems biology analysis of highthroughput quantitative proteomics experiments. By using a novel redox proteomics technology (GELSILOX) recently developed in our laboratory, we have also demonstrated that ischemia-reperfusion and infarct increases oxidation of Cys sites in mitochondrial proteins and that this effect is inhibited by ischemic or pharmacological preconditioning. These studies are being extended to models of aging, hypertrophy and animal models of deletion or overexpression of several protein factors. We have developed a novel data-independent mass spectrometry scanning technique (DiS) that improves on the performance of conventional shotgun approaches and also allows in-silico-targeted quantification of any suspected peptide, including post-translationally-modified species (PTM). We are using an extension of this technique (Blue-DiS) to generate an extremely detailed structural map of components of mitochondrial oxidative phosphorylation supercomplexes in several models, which include characterization of PTMs that may act as molecular determinants of assembly. We have also used advanced interactomics to study the supramolecular structure of human T-cell derived exosomes. We have found evidence that the network of intramolecular interactions with tetraspanins may act as a sorting machinery to determine the protein components of exosomes. In an extension of these studies, we have contributed to the discovery of a novel molecular mechanism by which miRNAs are selectively transported from cell to cell within exosomes.

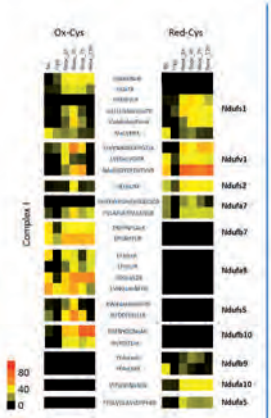


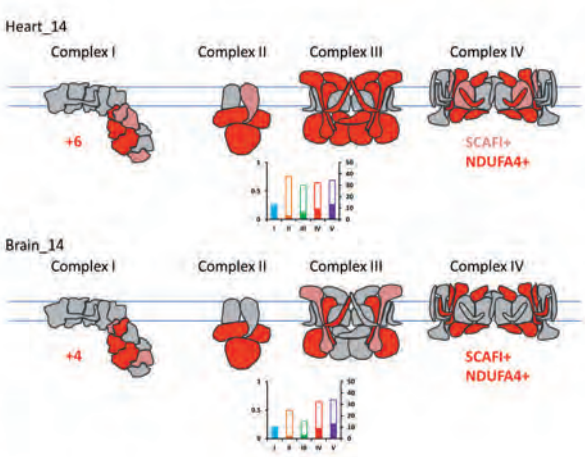
Recent developments in proteomics at the CNIC

RESEARCH DEPARTMENTS



Evidence that ischemic preconditioning inhibits ischemia/reperfusion-induced oxidative damage in mitochondria and may take place in mitochondria in the absence of cytosolic signals.





Time-course of oxidative damage at specific Cys sites in a model of complex-I degradation by reoxygenation, measured by combining the GELSILOX and DiS techniques (left). Characterization of the protein components of one of the supercomplexes of the OxPhos system in two different tissues using Blue-DiS (right).

Major Grants

- **Ministerio de Economía y Competitividad (BIO2012-37926)**
- **Ministerio de Economía y Competitividad. FIS RETICS (RIC: RD12/0042/0056)**
- **Unión Europea: 7th Framework Programme for Research (FP7-PEOPLE-ITN-2013)**

Selected Publications

Ruiz-Meana M, Núñez E, Miró-Casas E, Martínez-Acedo P, Barba I, Rodriguez-Sinovas A, Fernandez-Sanz C, Vázquez J*, David Garcia-Dorado*. **Ischemic preconditioning protects cardiomyocyte mitochondria through mechanisms independent of cytosol**. *J Mol Cell Cardiol* (2014) 68:79-88
*Co-corresponding authors

Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, Pérez-Hernández D, Vázquez J, Martin-Cofreces N, Martinez-Herrera DJ, Pascual-Montano A, Mittelbrunn M, Sánchez-Madrid F. **Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs**. *Nat Commun* (2013) 4:2980

Perez-Hernandez D, Gutiérrez-Vázquez C, Jorge I, López-Martín S, Ursa A, Sánchez-Madrid F, Vázquez J, Yáñez-Mó M. **The intracellular interactome of tetraspanin-enriched microdomains reveals their function as sorting machineries toward exosomes**. *J Biol Chem* (2013) 288:11649-61

Gordón-Alonso M, Sala-Valdés M, Rocha-Perugini V, Perez-Hernandez D, López-Martín S, Ursa A, Kolesnikova TV, Vázquez J, Sánchez-Madrid F, Yáñez-Mó M. **EWI-2 association with alpha-actinin regulates T-cell immune synapses and HIV viral infection**. *J Immunol* (2012) 189: 689-700

Martínez-Acedo P, Núñez E, Gómez FJ, Moreno M, Ramos E, Izquierdo-Álvarez A, Miró-Casas E, Mesa R, Rodriguez P, Martínez-Ruiz A, Dorado DG, Lamas S, Vázquez J. **A novel strategy for global analysis of the dynamic thiol redox proteome**. *Mol Cell Proteomics* (2012) 9: 800-13

2 Vascular Biology and Inflammation

Matrix metalloproteinases in angiogenesis and inflammation

Head of Laboratory: Alicia G. Arroyo

Research Scientist: Pilar Gonzalo

Postdoctoral Researchers: Vanessa Moreno, Susana Rocha, Agnieszka Koziol

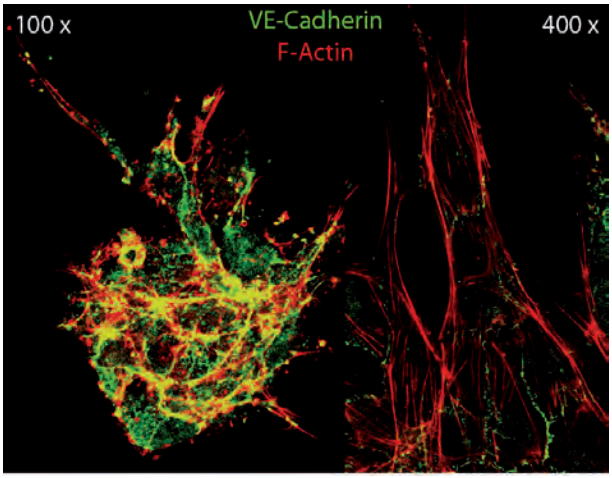
Predoctoral Researchers: Cristina Clemente, Jesús Gómez Escudero, Mara Martín Alonso, Magdalena Maria Zak, Sergio Esteban

Technicians: Ángela Pollán, Laura Balonga

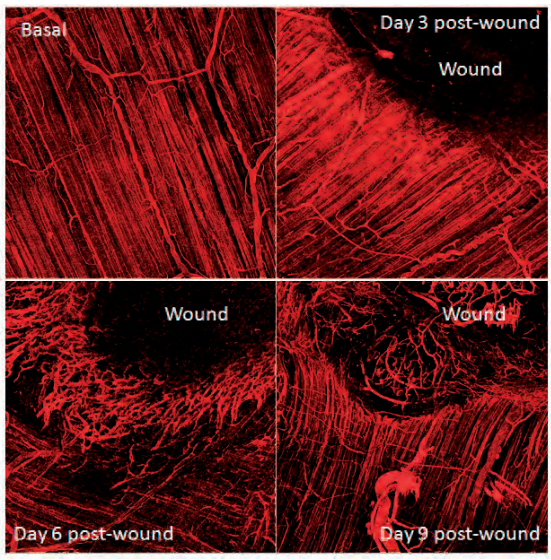
Visiting Scientist: Cristina Sánchez-Camacho

Research Interest

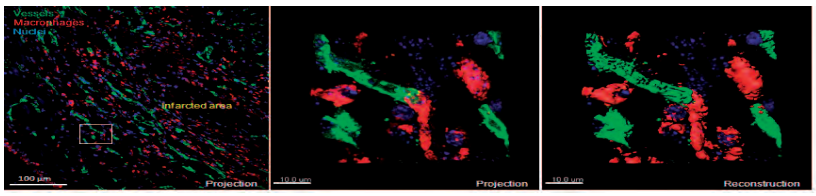
Angiogenesis in adults is often coupled to inflammation, and its deregulation can result in failed tissue repair after acute injury or in the progression of chronic inflammatory disorders. One of the first steps in the transition from a quiescent to an angiogenic vasculature is the remodeling of the basement membrane and the perivascular extracellular matrix. Our previous work on the regulation and function of members of the matrix metalloproteinase family, in particular membrane-type MT1-MMP and MT4-MMP, identified specific functions for these proteases and highlighted the complexity of the spatio-temporally orchestrated multi-cellular response during inflammation-driven angiogenesis. We have recently set up in vitro and ex vivo 2D and 3D angiogenic models and have generated new animal models, including animals genetically modified as molecular/cellular reporters or deficient in molecules of interest and mouse models of acute and chonic inflammation. We use an armoury of cutting edge technologies—including high-resolution confocal microscopy, mathematical analysis (MatLab), image analysis and 3D reconstruction (Image J, Metamorph, Imaris), advanced proteomics (iTRAQ), and novel lentivirus-based gene therapy strategies—to gain greater understanding of how angiogenesis occurs in the inflammatory context and to identify new molecules or cell subsets whose modulation might impact the angiogenic process. In this way we aim to contribute to the goals of improving wound healing and ameliorating the development of diseases such as myocardial infarction, inflammatory bowel disease and others that involve an alteration of vascular function.



Analysis of single cell endothelial responses during capillary formation. *Staining of endothelial cells (VE-cadherin, green; F-actin, red) embedded in a fibrin gel and stimulated with VEGF in the 'hanging drop' model allows investigation of single cell responses (junction remodeling, and actin polymerization) during the formation of 3D capillaries in response to angiogenic factors.*



***Imaging in vivo vascular responses to inflammation**. Whole-mount staining of skin (collagen IV for perivascular basement membrane, red) shows the changes in organization and structure of the vasculature during wound-healing compared with quiescent vessels under basal conditions.*



***Imaging cellular crosstalk in inflammation-driven angiogenesis**. Confocal microscopy imaging of thick sections from heart and 3D reconstruction with Imaris software show the close association of vessels (green) and macrophages (red) in a mouse model of myocardial infarction (7 days after ligation of the coronary artery).*

Major Grants

- Ministerio de Economía y Competitividad (SAF2011-25619)
- Ministerio de Economía y Competitivad (RD12/0042/0023)
- Comunidad Autónoma de Madrid (S2010/BMD-2312)
- Fundació La Marató TV3 (165/C/2012)
- European Union (PITN-GA-2013-608027) (CardioNext)

Selected Publications

Koziol A, Martín-Alonso M, Clemente C, Gonzalo P, Arroyo AG. **Site-specific cellular functions of MT1-MMP**. *Eur J Cell Biol* (2012) 11-12: 889-95

Koziol A, Gonzalo P, Mota A, Pollán A, Lorenzo C, Colomé N, Montaner D, Dopazo J, Arribas J, Canals F, Arroyo AG. **The protease MT1-MMP drives a combinatorial proteolytic program in activated endothelial cells**. *FASEB J* (2012) 26: 4481-94

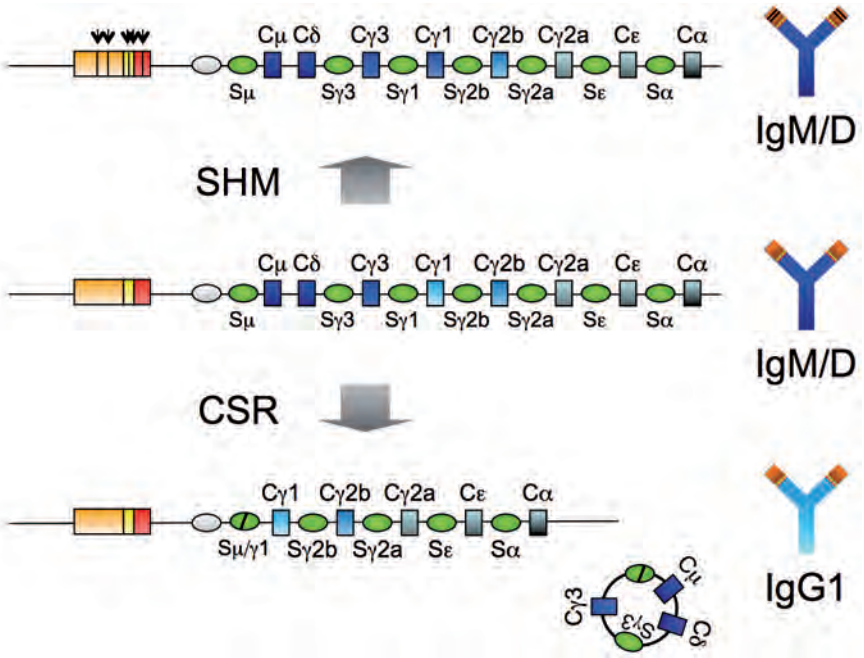
B lymphocyte biology

Head of Laboratory:	Almudena R Ramiro
Research Scientists:	Virginia G de Yébenes Maria Pilar Delgado
Postdoctoral Researchers:	Regina González Dosal
Predoctoral Researchers:	Nahikari Bartolomé Arantxa Pérez-García Ángel F. Álvarez
Masters Student:	Ester Marina
Technician:	Sonia Mur

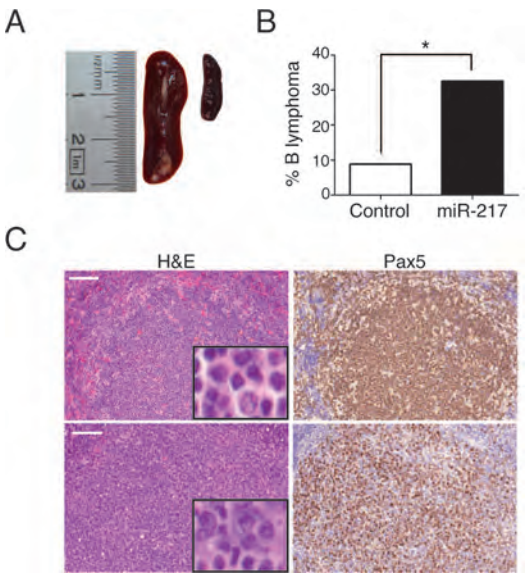
Research Interest

B lymphocytes protect the organism against infection through the generation of a diversity of antibodies that can recognize virtually any pathogen in a specific fashion. However, misregulation of B lymphocyte function can lead to multiple health conditions, including immune deficiencies, autoimmunity and cancer. Our lab is interested in various aspects of B cell biology, in particular the regulatory and diversification events that take place in germinal centers. Diversification in germinal centers entails the remodeling of immunoglobulin genes through somatic hypermutation (SHM) and class switch recombination (CSR), allowing the generation of high-affinity, specialized antibodies. SHM and CSR are initiated by activation-induced deaminase (AID) (Figure 1), whose activity can also promote deleterious lesions in DNA, such as mutations and chromosome translocations.

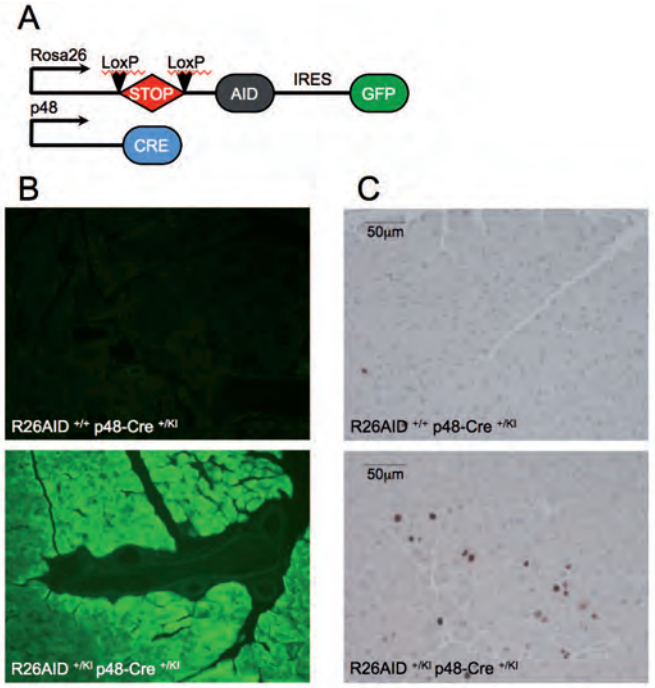
Over the past few years we have focused on AID function and microRNA-regulated mechanisms in germinal centers (Belver et al., Curr Opin Immunol 2011; de Yébenes et al. Immunol Rev 2013). We have found that microRNAs play a crucial role in the establishment of tolerance during late B cell differentiation (Belver et al. Immunity 2010). We have also shown that miR-181b (de Yébenes et al J Exp Med 2008) is a negative regulator of AID expression and that miR-217 is a positive regulator of germinal centers, thereby promoting B cell lymphomagenesis (Figure 2). In addition, we have developed conditional mouse models of AID expression to address the contribution of this enzyme to B cell mediated immunity and B cell transformation (Figure 3).



AID activity in germinal center B lymphocytes. Antibody diversification in germinal centers occurs through somatic hypermutation (SHM) and class switch recombination (CSR) and allows the generation of specialized antibody isotypes with high affinity for antigen. However, AID activity can also promote chromosome translocations and mutations outside immunoglobulin genes, potentially leading to oncogenic transformation.



miR-217 expression promotes B cell lymphomagenesis. (A) miR-217 transgenic mice display splenomegaly. (B) miR-217 overexpression increases the incidence of B cell lymphoma. (C) Representative spleen images from control (top) and miR-217 transgenic mice (bottom).



Heterologous AID expression promotes proliferation. (A) Representation of constructs for a mouse model of conditional AID expression in pancreas (R26AID$^{+/KI}$; p48Cre$^{+/KI}$). (B) GFP immunofluorescence analysis shows that R26AID$^{+/KI}$ p48Cre$^{+/KI}$ mice susccessfully express the conditional construct in pancreas. (C) Ki67 staining shows that pancreata from R26AID$^{+/KI}$ p48Cre$^{+/KI}$ mice are more proliferative than R26AID$^{+/+}$ p48Cre$^{+/KI}$ littermate controls.

Major Grants

- Ministerio de Economía y Competitividad (SAF2010-21394)
- European Commission. European Research Council Starting Independent Researcher Grant (ERC-BCLYM 2007)

Selected Publications

de Yébenes VG, Bartolomé-Izquierdo N, Ramiro AR. **Regulation of B-cell development and function by microRNAs**. *Immunol Rev* (2013) 253:25-39

Pérez-Durán P, Belver L, de Yébenes VG, Delgado P, Pisano DG, Ramiro AR. **UNG shapes the specificity of AID-induced somatic hypermutation**. *J Exp Med* (2012) 209:1379-89

Immunobiology of inflammation

Head of Laboratory: David Sancho Madrid
Postdoctoral Researchers: Salvador Iborra Martín
Johan J.B. Garaude
Carlos del Fresno Sánchez
Laura Conejero Hall
Predoctoral Researchers: Noelia Blanco Menéndez
Helena M. Izquierdo Fernández
María Martínez López
Neris M. Enamorado Escalona
Masters student: Francisco Javier Cueto Rodriguez
Technician: Ruth Conde Garrosa
Sarai Martinez Cano

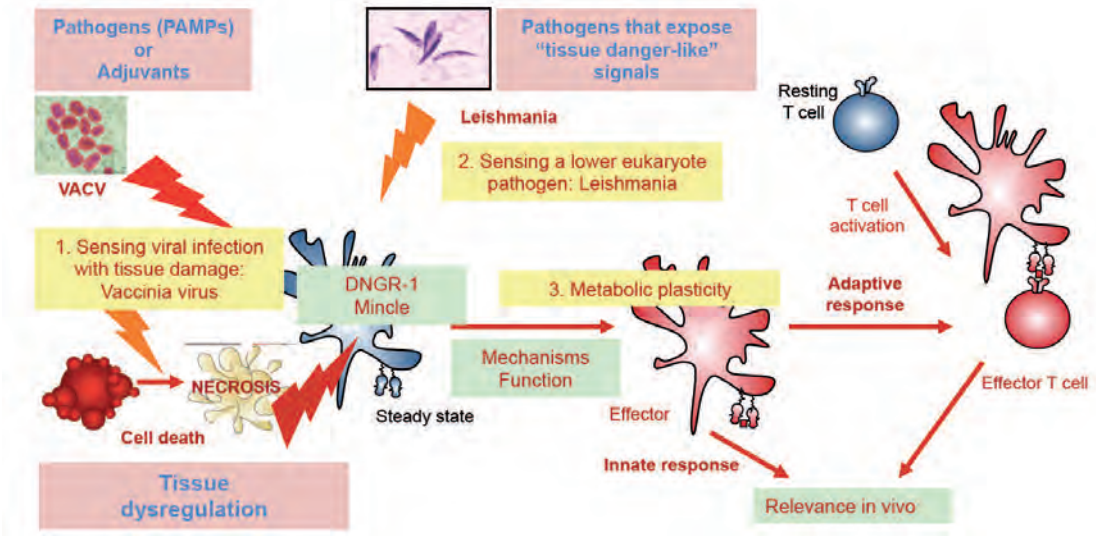
Research Interest

We are working on innovative approaches to the study of the immune and inflammatory responses to infection and tissue damage (Fig. 1). We believe that this research has potential for the development of new vaccines and immunotherapy strategies.

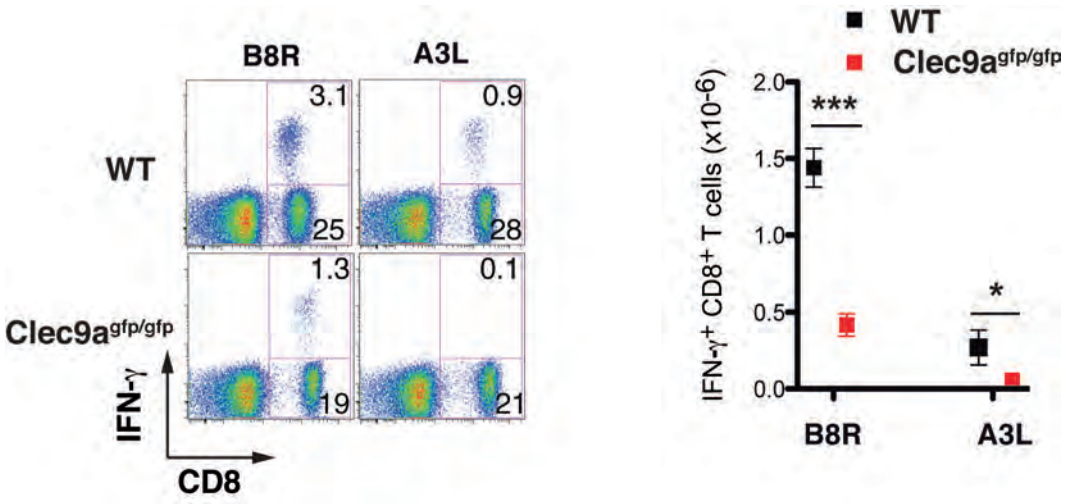
Infection is frequently associated with tissue damage, but knowledge is limited about how concomitant sensing of cell death by myeloid cells affects the immune and inflammatory response to infection. Some myeloid C-type lectin receptors (CLRs) have been identified as receptors for necrotic cells that couple to Syk signaling, potentially triggering innate and adaptive immune responses. DNGR-1 (CLEC9A), expressed on dendritic cells, and Mincle (CLEC4E), expressed broadly in myeloid cells, detect ligands exposed upon necrosis and potentially modulate signals from other pattern-recognition receptors during infection.

Viral agents such as vaccinia virus (VACV) have cytopathic effects, and we have found that sensing of tissue damage through DNGR-1 during VACV infection controls viral antigen cross-presentation (Fig. 2). We are currently investigating how control of cross-presentation via DNGR-1 can be crucial for shaping the CD8+ T cell memory response during VACV infection, with potential implications for novel vaccination strategies. We are also exploring the effects of sensing tissue damage in other models of infection and inflammation.

We are also interested in how sensing of infection and tissue damage affects the metabolic status of the myeloid cell. Our preliminary data show that the sensing of the nature of internalized cargo upon phagocytosis dictates a metabolic re-programming, and we are interested in the mechanisms driving this change in myeloid cells and the functional consequences for immunity and inflammation.



Main branches of research developed in the Immunobiology of Inflammation laboratory. Our research focuses on how infection and tissue damage interact for generation of signals that can impact myeloid cell metabolism. Sensing infection and cell death may influence the development of inflammation and immunity in models of disease that we are analyzing in order to explore the translational potential of our findings.



*Generation of antigen specific T cells during vaccination is impaired in the absence of DNGR-1/CLEC9A. The antigen-specific CD8 T cells producing IFN-γ in response to VACV peptides B8R and A3L are reduced in the absence of DNGR-1 (Clec9a$^{gfp/gfp}$). Left: Dot plots showing antigen-specific CD8 T cells from one representative mouse. Right: Mean results are shown from 5 mice in one representative experiment out of three performed. *, p<0.05; ***, p<0.001, Student's t test.*

Major Grants

- Ministerio de Economía y Competitividad (SAF2010-15120)
- European Commission. European Research Council Starting Independent Researcher Grant (ERC-StG-260414)
- Ministerio de Economía y Competitividad (RYC2009-04235)
- Research cooperation agreement with MedImmune (Cambridge, UK)

Selected Publications

del Fresno C, Soulat D, Roth S, Blazek K, Udalova I, Sancho D, Ruland J, Ardavín C. **Interferon-β production via Dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to C. albicans**. *Immunity* (2013) 38(6):1176-86.

Sancho D, Reis e Sousa C. **Sensing of cell death by myeloid C-type lectin receptors**. *Curr Opin Immunol* (2013) 25(1):46-52.

Zelenay S, Keller AM, Whitney PG, Schraml BU, Deddouche S, Rogers NC, Schulz O, Sancho D, Reis e Sousa C. **The dendritic cell receptor DNGR-1 controls endocytic handling of necrotic cell antigens to favor cross-priming of CTLs in virus-infected mice**. *J Clin Invest* (2012) 122:1615-27

Iborra S, Izquierdo HM, Martínez-López M, Blanco-Menéndez N, Reis e Sousa C, Sancho D. **The DC receptor DNGR-1 mediates cross-priming of CTLs during vaccinia virus infection in mice**. *J Clin Invest* (2012) 122:1628-43

Sancho D, Reis e Sousa C. **Signaling by myeloid C-type lectin receptors in immunity and homeostasis**. *Annu Rev Immunol* (2012) 30: 491-529

2 Vascular Biology and Inflammation

Stress kinases in diabetes, cancer and cardiovascular disease

Head of Laboratory: Guadalupe Sabio

Postdoctoral Researchers: Nuria Matesanz
Antonia Tomás Loba

Predoctoral Researchers: Edgar Bernardo
Bárbara González
Elisa Manieri
María Ángeles Verdugo

Technicians: Elena González
Luis Leiva

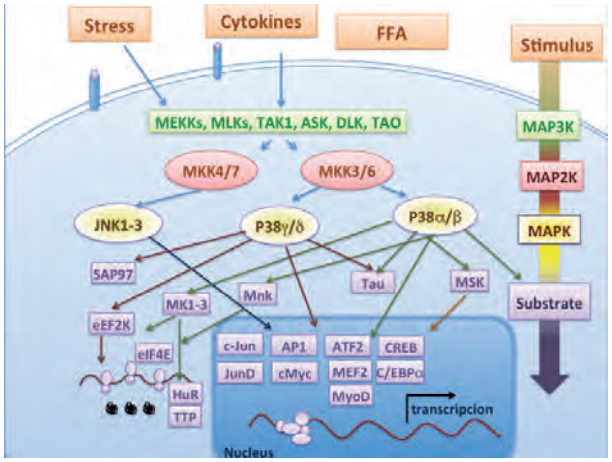
Masters Students: Sara Bernardez
Maria del Valle Montalvo

Research Interest

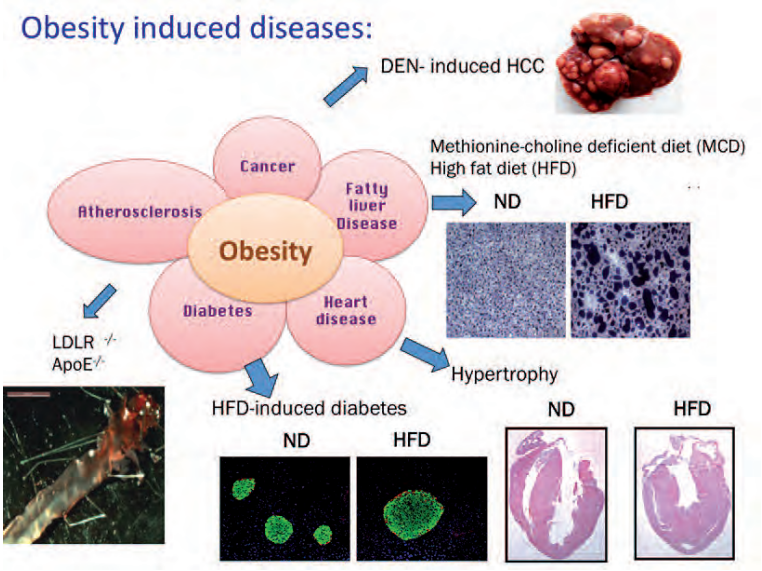
Metabolic syndrome is a medical disorder defined by the co-occurrence of obesity, impaired glucose tolerance, dyslipidemia and hypertension. The condition is associated with proinflammatory and prothrombotic states, and clinical outcomes include cardiovascular disease and type 2 diabetes. Moreover, metabolic syndrome may be a predisposing factor for the development of some types of cancer, such us hepatocellular carcinoma.

The high cardiovascular risk associated with metabolic syndrome and type 2 diabetes suggests that common mechanisms are involved in the etiology of these conditions, and that agents acting on the same therapeutic targets might improve disease parameters in both. Research suggests that one such target might be the stress activated protein kinases (SAPKs), an important family of kinases implicated in the transduction of stress signals into the cell.

Our group investigates the involvement of SAPKs in the development of cancer, diabetes, cardiac hypertrophy and atherosclerosis induced by obesity. Our research is conducted with a number of disease models in combination with whole-body and tissue-specific knockout mice, and has already shown that the p38γ/δ isoforms control IL6 and TNF production in myeloid cells. We are now studying how the regulation of inflammation by these kinases affects the development of metabolic syndrome. We are also studying the function of these kinases in other tissues, such us muscle, heart, the central nervous system and adipose tissue, in order to elucidate the role of these kinases in the development of different diseases associated with obesity (steatosis, diabetes, cardiovascular diseases and some types of cancer)



MAPK signaling pathway



Obesity related diseases and mouse models

Major Grants

- European Commission. European Research Council Starting Independent Researcher Grant (ERC-StG-260464)
- Comunidad de Madrid. INMUNOTHERCAN (S2011/BMD-2326)
- Ministerio de Economía y Competitividad (SAF2010-19347)
- Ministerio de Economía y Competitividad (RYC-2009-04972)

Selected Publications

González-Terán B, Cortés JR, Manieri E, Matesanz N, Verdugo A, Rodríguez ME, González-Rodríguez A, Valverde A, Martín P, Davis RJ, Sabio G. **Eukaryotic elongation factor 2 controls TNF-α translation in LPS-induced hepatitis**. *J Clin Invest* (2013) 123:164-78

Imbernon M, Beiroa D, Vázquez MJ, Morgan DA, Veyrat-Durebex C, Porteiro B, Díaz-Arteaga A, Senra A, Busquets S, Velásquez DA, Al-Massadi O, Varela L, Gándara M, López-Soriano FJ, Gallego R, Seoane LM, Argiles JM, López M, Davis RJ, Sabio G, Rohner-Jeanrenaud F, Rahmouni K, Dieguez C, Nogueiras R. **Central melanin-concentrating hormone influences liver and adipose metabolism via specific hypothalamic nuclei and efferent autonomic/JNK1 pathways**. *Gastroenterol* (2013) 144:636-649

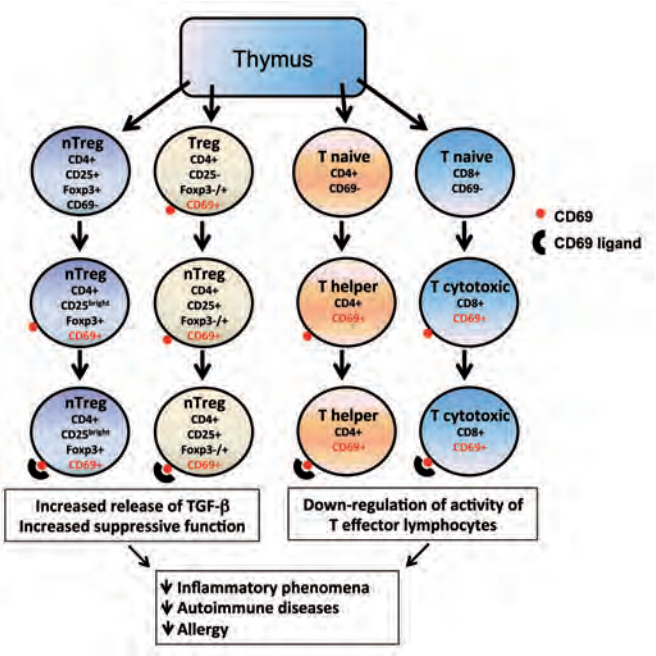
Regulatory molecules of inflammatory processes

Head of Laboratory: Pilar Martín
Postdoctoral Researcher: José Rodríguez Cortés *(until march 2013)*
Predoctoral Researchers: Adela Matesanz Marín *(until august 2013)*
Elena G. Rodríguez Bovolenta *(until august 2013)*
Raquel Sánchez Díaz
Masters Student: Manuel Daza Martín *(until february 2013)*
Technician: Sara Salvanés *(until february 2013)*
Amada Elia Beltrán
Visiting Scientist: Georgios Liappas
Guadalupe González Tirma

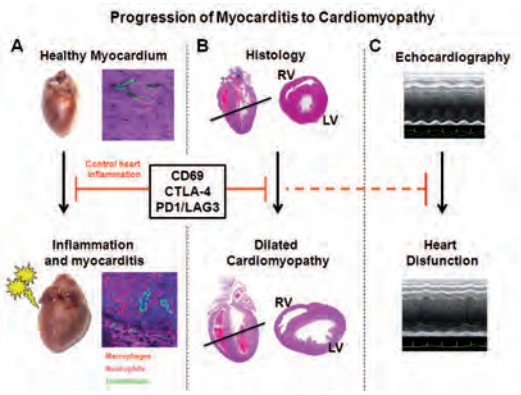
Research Interest

Early studies described CD69 as a leukocyte activation marker, and suggested its involvement in the activation of different leukocyte subsets as well as in the pathogenesis of chronic inflammation. Recent investigations, however, have shown that CD69 knockout mice exhibit an enhanced susceptibility to different inflammatory diseases, mainly those mediated by Th17 lymphocytes. In this regard, the expression of CD69, both in Th17 lymphocytes and in a subset of regulatory T cells, has an important role in the control of the immune response and inflammation. The evidence thus indicates that CD69 exerts a complex immunoregulatory role in humans, and that it could be considered as a target molecule for the treatment of immune-mediated diseases.

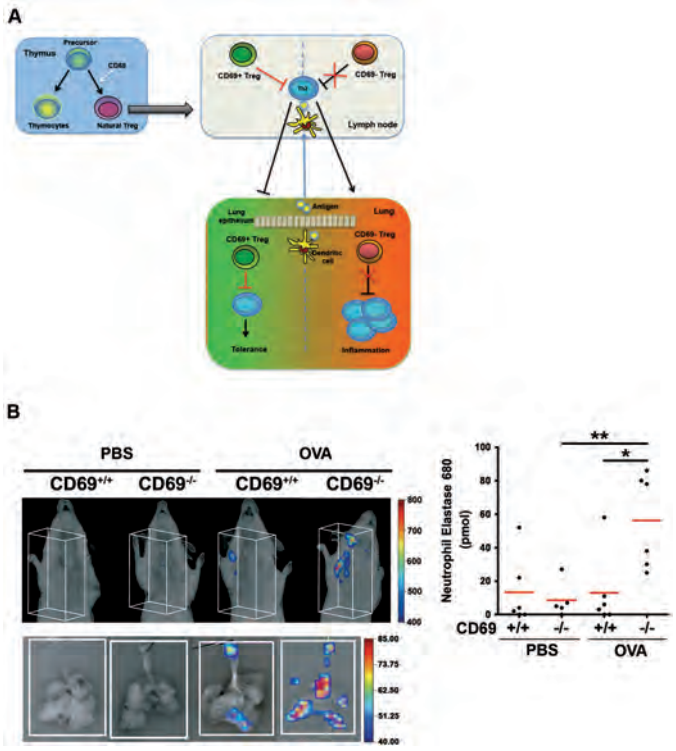
Our group investigates the role of regulatory molecules in the maintenance of immune tolerance by FoxP3$^+$ regulatory T cells in cardiorespiratory systems in mice and humans. We and others have previously shown that CD69 expression protects against arthritis, allergic asthma, contact hypersensitivity and autoinmune cardiomyopathy. We are now investigating the role of CD69 in the balance between Th17 and regulatory T cells in these pathologies in mice and humans, focusing on miRNAs as regulatory molecules and putative biomarkers.



The complex immunoregulatory role of CD69. *Natural T regulatory lymphocytes, which do not constitutively express CD69, can synthesize this molecule when activated in the periphery. Intracellular signals generated through CD69 would enhance the immunosuppressive activity of nTreg cells and increase synthesis of TGF-β. Another subset of Treg lymphocytes (CD4$^+$ CD25$^-$) expresses CD69 constitutively. Upon activation, these cells become CD25$^+$ and increase their immunoregulatory activity after engagement of CD69. In naïve non-regulatory CD4$^+$ and CD8$^+$ T cells, CD69 behaves as an activation molecule, appearing on the cell surface when these cells are activated by APCs or other stimuli. When these cells are differentiated into effector (helper and cytotoxic) lymphocytes, they remain CD69$^+$, and engagement of this molecule diminishes their pro-inflammatory activity.*



***Progression of myocarditis to dilated cardiomyopathy and heart failure**. (A) Myocarditis is initiated after cardiac injury by the recruitment of leukocytes (mainly macrophages and neutrophils) to the heart, where they induce myocyte damage, degrade collagen and destroy cardiac muscle. Exacerbated inflammation in the heart can be regulated by T cell immunoregulatory molecules such as CD69, CTLA-4, PD1 and LAG-3. (B) Myocardial damage causes impaired of left ventricle (LV) function leading to a ventricular dilation. Immunoregulatory molecules control matrix remodeling, thereby limiting myocardial damage and blocking progression of fibrosis and impaired ventricular function to dilated cardiomyopathy. (C) Uncontrolled inflammation leads to necrosis of cardiac muscle and ventricular dysfunction, resulting in chronic dilated cardiomyopathy and deficient contractile function. The control of inflammation in the myocardium in the first phase of myocarditis is essential for the control of the progression of the disease to heart failure (dotted red line).*



Cd69$^{-/-}$ *mice show impaired ability to maintain immune lung tolerance*. *(A) The immunoregulatory role of CD69 in nTregs and the maintenance of immune tolerance in lungs after exposure to harmless antigens. ***(B)** Mice were treated with OVA i.t. before PBS or OVA-aerosolized challenge. Detection of activated neutrophils in airways or in resected lungs and tracheas was analyzed by three-dimensional tomographic imaging (FMT: Fluorescence Molecular Tomography).*

Major Grants

- Ministerio de Economía y Competitividad (SAF2011-27330)
- Redes de Excelencia de la Comunidad de Madrid (P2010/BMD-2332)
- Instituto de Salud Carlos III Red Cardiovascular (RD12-0042-0056)

Selected Publications

López-Bravo M, Minguito de la Escalera M, Domínguez PM, González-Cintado L, Del Fresno C, Martín P, Martínez Del Hoyo G, Ardavín C. **IL-4 blocks TH1-polarizing/inflammatory cytokine gene expression during monocyte-derived dendritic cell differentiation through histone hypoacetylation**. *J Allergy Clin Immunol*. (2013)132:1409-1419

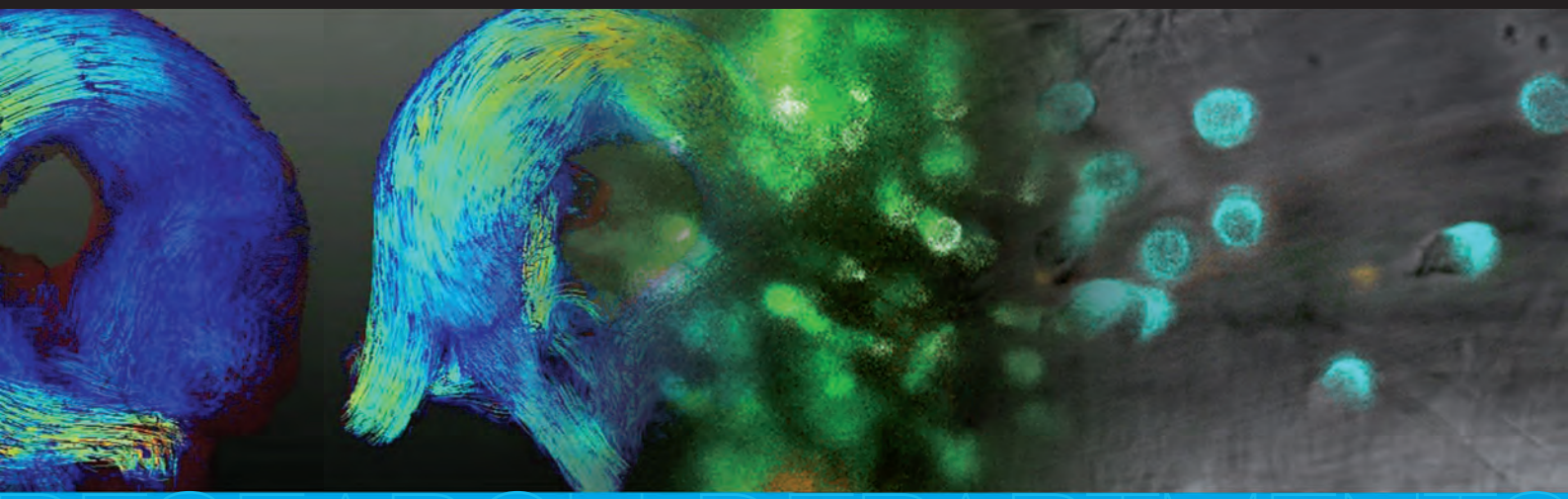
González-Amaro R, Cortés JR, Sánchez-Madrid F, Martín P. **Is CD69 an effective brake to control inflammatory diseases?** *Trends Mol Med*. (2013) 19:625-32

Leskela S, Rodríguez-Muñoz A, de la Fuente H, Figueroa-Vega N, Bonay P, Martín P, Serrano A, Sánchez-Madrid F, González-Amaro R, Marazuela M. **Plasmacytoid dendritic cells in patients with autoimmune thyroid disease**. *J Clin Endocrinol Metab*. (2013) 98:2822-33

González-Terán B, Cortés JR, Manieri E, Matesanz N, Verdugo A, Rodríguez ME, González-Rodríguez A, Valverde A, Martín P, Davis RJ, Sabio G. **Eukaryotic elongation factor 2 controls TNF-α translation in LPS-induced hepatitis**. *J Clin Invest* (2013) 123:164-78

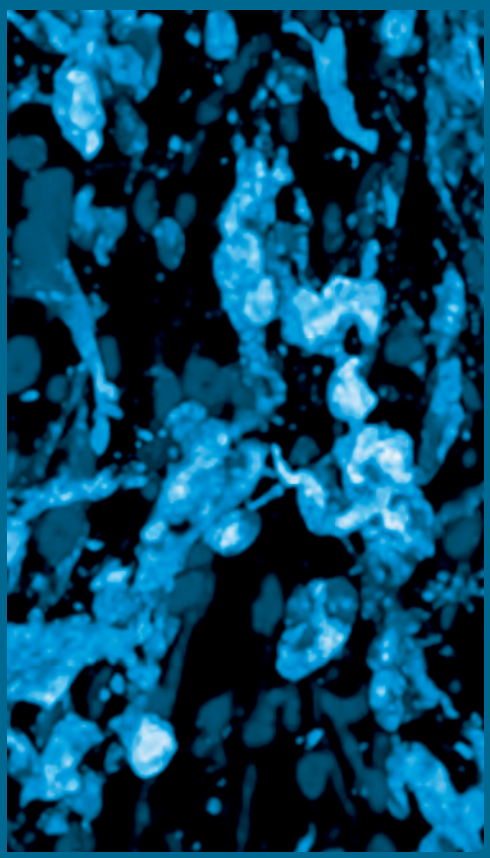
Luque-Garcia JL, Sanchez-Diaz R, Lopez Heras I, Martin P, Camara C. **Bioanalytical strategies for in-vitro and in-vivo evaluation of the toxicity induced by metallic nanoparticles**. *Trends in Analytical Chemistry* (2013) 43:254-26

3 Atherothrombosis, Imaging and Epidemiology



RESEARCH DEPARTMENTS

3 Atherothrombosis, Imaging and Epidemiology



Our department integrates basic science, clinical data, and population-level studies to better understand the occurrence, natural history and prognosis of cardiovascular disease and therapeutic alternatives. Our programs include studies into the molecular and cellular mechanisms underlying atherosclerosis, restenosis and aging; the role of neutrophils and other myeloid leukocytes in various aspects of the inflammatory response; the actions of vasoactive factors and proteolytic enzymes during the early steps of vascular remodeling, cardioprotection during myocardial infarction, and complex cardiac arrhythmias including studies in animal models and humans using latest-generation advanced imaging techniques.

For this work, the department works closely with the Advanced Imaging Unit, bringing in expertise in imaging, nanomedicine, radiochemistry and metabolomics. The department also coordinates epidemiolgical studies on the distribution and progression of atherosclerosis and the genetic, environmental, lifestyle, and social determinants in human populations.

Department Director:	Valentín Fuster
Department Manager:	Ana Isabel Castillo
Project Manager:	Eeva Inari Soininen
Technicians:	Javier Mateos Inés Ortega Virginia Zorita Gonzalo Javier López Ángel Macías Braulio Pérez Asenjo Ana Vanesa Alonso Lorena Flores Ruiz
Study Nurse:	Maite Dubraska Rodríguez Cabrera
Administrative Support:	Ana Gutiérrez

3 Atherothrombosis, Imaging and Epidemiology

Atherothrombosis and clinical imaging

Head of Laboratory: Valentín Fuster Carulla
(CNIC, Mt. Sinai Medical Center, New York)

Research Scientists:
Luis Jesús Jiménez Borreguero
(CNIC, Hospital de la Princesa Research Agreement)
Antonio Fernández-Ortiz
(CNIC, Hospital Clínico San Carlos Research Agreement)
Jesús Mateo de Castro
(CNIC)
Javier Sánchez González
(CNIC, Philips Healthcare)
Leticia Fernández Friera
(CNIC, Hospital Monte Príncipe)
Beatriz López-Melgar

Project Managers:
Laura García Leal
Evelyn Cárdenas Marín

Technicians:
Aurora Del Barrio Mantecas
Alberto Ávila Morales
Rosario Pérez Rubiño
Sergio Cárdenas Melero

Res@CNIC Fellows:
Jose Antonio de la Chica, Sánchez
Eva García Piney
Manuel Lobo González

Visiting Scientists:
Vicente Martínez de Vega
Juan Carlos Alonso Farto
Ana Álvarez Vázquez
Estefanía Fernández Delgado
Claudia Susana Linares González
Gabriela Guzmán Martínez
John Patrick Pikington

Research Interest

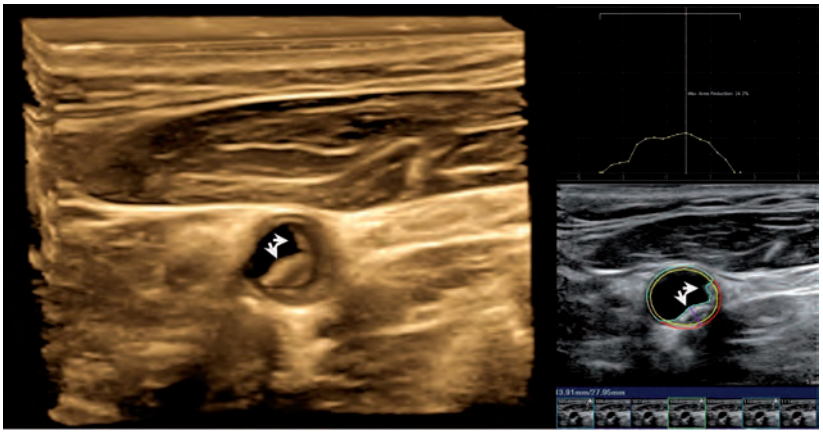
Our group works on the development and research applications of non-invasive, high-resolution and high-sensitivity imaging technologies. Established and new imaging technologies are playing an increasingly important role in early diagnostic and prognostic assessments of cardiovascular diseases, yielding novel information about the origin and development of disease, and through this providing ways to diagnose asymptomatic disease and monitor treatment outcomes.

We are directly involved in two large cohort studies (PESA and AWHS; see Multidepartamental Projects), where we are evaluating the use of non-invasive imaging to track atherosclerosis development and stratify risk in asymptomatic populations. During 2013 we started the second round of visits by participants in the PESA study, three years after their initial assessment. Final follow-up examinations are scheduled for six years after joining the study. Through these projects we have established a strong network of international partners who use imaging technologies to study subclinical atherosclerosis.

We also worked in partnership with other CNIC groups and centers throughout Spain in the METOCARD-CNIC trial (see Multidepartamental Projects), which compared the effect of early and delayed β-blocker treatment on infarct size and clinical outcome in patients with acute myocardial infarction. Data on the primary endpoint was published in 2013, and further analysis will be reported in 2014.

During the last year we fine-tuned the new imaging equipment in our human imaging facility, which is being used for hybrid PET/MR evaluation of subclinical atherosclerosis in the PESA study. The equipment available for our ambitious advanced imaging program includes a wide range of state-of-the-art imaging modalities for small animals (ultrasonography, high field 7T MR, nano PET/CT), large animals (3T MR Tx, PET/CT, intravascular OCT), and humans (256 row MDCT and PET/MR system). Close collaboration with the new Advanced Imaging Unit is fully established, and we are developing novel agents and probes that are being tested in our preclinical models.

RESEARCH DEPARTMENTS



Assessment of atherosclerosis burden in carotid and femoral arteries using non-invasive 3D ultrasound in a low CV risk population (PESA study). Left: 3D image of a right carotid artery. Right: Multi-slice axial view of the vessel for semiautomatic segmentation and quantification of plaque volume. The calculated plaque volume was 77 mm^3, with a maximum luminal area reduction of 24%. Arrows mark atherosclerotic plaques.

Major Grants

- **European Commission FP7 (241559 FOCUS)**
- **European Commission FP7-ICT-2011-8 (LIPHOS)**
- **Ministerio de Sanidad y Política Social (EC10-042 Metocard, CNIC Translational Projects)**
- **Departamento de Salud y Consumo of the regional government of Aragon, General Motors Spain and CNIC (AWHS)**
- **NIH Grant (U01 HL-071988-01A1)**
- **NIH Grant Project: (U01HL-114200-02)**
- **NIH Grant (R01 HL-092989). Co-Investigator**
- **NIH Grant (298201000045-C-0-1). Co-Investigator**

Selected Publications

Fernandez-Ortiz, A., Jimenez-Borreguero, L. J., Penalvo, J. L., Ordovas, J. M., Mocoroa, A., Fernandez-Friera, L., Laclaustra, M., Garcia, L., Molina, J., Mendiguren, J. M., Lopez-Melgar, B., de Vega, V. M., Alonso-Farto, J. C., Guallar, E., Sillesen, H., Rudd, J. H., Fayad, Z. A., Ibanez, B., Sanz, G. and Fuster, V. **The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: Rationale and design**. *Am Heart J* (2013) 166: 990-998

Ibanez, B., Macaya, C., Sanchez-Brunete, V., Pizarro, G., Fernandez-Friera, L., Mateos, A., Fernandez-Ortiz, A., Garcia-Ruiz, J. M., Garcia-Alvarez, A., Iniguez, A., Jimenez-Borreguero, J., Lopez-Romero, P., Fernandez-Jimenez, R., Goicolea, J., Ruiz-Mateos, B., Bastante, T., Arias, M., Iglesias-Vazquez, J. A., Rodriguez, M. D., Escalera, N., Acebal, C., Cabrera, J. A., Valenciano, J., Perez de Prado, A., Fernandez-Campos, M. J., Casado, I., Garcia-Rubira, J. C., Garcia-Prieto, J., Sanz-Rosa, D., Cuellas, C., Hernandez-Antolin, R., Albarran, A., Fernandez-Vazquez, F., de la Torre-Hernandez, J. M., Pocock, S. J., Sanz, G. and Fuster, V. **Effect of Early Metoprolol on Infarct Size in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary PCI: The METOCARD-CNIC Trial**. *Circulation* (2013) 128: 1495-1503

Farkouh, M. E., Boden, W. E., Bittner, V., Muratov, V., Hartigan, P., Ogdie, M., Bertolet, M., Mathewkutty, S., Teo, K., Maron, D. J., Sethi, S. S., Domanski, M., Frye, R. L. and Fuster, V. **Risk factor control for coronary artery disease secondary prevention in large randomized trials**. *J Am Coll Cardiol* (2013) 61: 1607-1615

García-Alvarez, A., Fernandez-Friera, L., Garcia-Ruiz, J. M., Nuno-Ayala, M., Pereda, D., Fernandez-Jimenez, R., Guzman, G., Sanchez-Quintana, D., Alberich-Bayarri, A., Pastor-Escuredo, D., Sanz-Rosa, D., Garcia-Prieto, J., Mirelis, J. G., Pizarro, G., Jimenez-Borreguero, L. J., Fuster, V., Sanz, J. and Ibanez, B. **Noninvasive Monitoring of Serial Changes in Pulmonary Vascular Resistance and Acute Vasodilator Testing using Cardiac Magnetic Resonance**. *J Am Coll Cardiol* (2013) 62: 1621-1631

Gorog DA, Fuster V. **Platelet function tests in clinical cardiology: unfulfilled expectations**. *J Am Call Cardiol* (2013) 61: 2115-2129.

3 Atherothrombosis, Imaging and Epidemiology

Atherothrombosis and experimental imaging

Head of Laboratory: **Borja Ibáñez**
(CNIC, Hosp. Clínico San Carlos)

Postdoctoral Researchers: David Sanz-Rosa
Leticia Fernández Friera
(CNIC,Hospital Monte Principe)
Gonzalo Pizarro Sánchez
(CNIC, Hospital Quirón Madrid)
Ana García-Álvarez
(CNIC, Hospital Clinic Barcelona)
Rodrigo Fernández-Jiménez
José Manuel García Ruíz
(CNIC, Hospital Univ. Central de Asturias)

Predoctoral Researchers: Jaime García-Prieto Cuesta
Andrés Pun García
Jaume Agüero Ramón-Llin

Research Coordinator: Noemí Escalera Biendicho

Technicians: Mario Nuño Ayala
Parvin Rupa Khaton

Res@CNIC Fellows: David del Val Martín
Fernando Macaya Ten

Invesmir Fellow: Francisco Javier Rosselló Lozano

Masters Students: Carlos Galán Arriola
Federico Sierra Rodríguez de la Rubia

Visiting Scientists: Alonso Antonio Mateos Rodríguez
Daniel Pereda Arnau
Jacobo Silva Guisasola
Jesús González Mirelis
María del Trigo Espinosa
Javier Escaned Barbosa
Jorge Solís Martín
Alberto Cecconi
Javier Sánchez González
Timothy Wai
María Gallego Delgado
Jean Paul Vilchez Tschischke
Inés García Lunar
Javier Sanz
Rocío Villena Gutiérrez

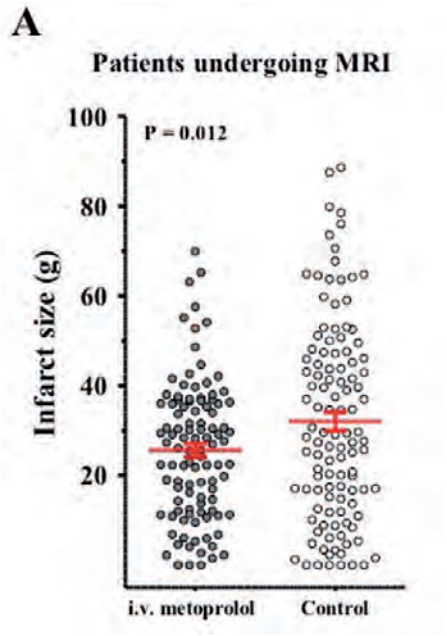
Research Interest

Our laboratory focuses on the study of myocardial diseases, ranging from ischemia/reperfusion to heart failure. Our studies span the molecular origins of disease and their manifestations at the macro-anatomical and physiological levels, and our group includes experts in molecular biology, clinical cardiology and cardiovascular imaging. Our evaluation of experimental animal models makes use of advanced imaging techniques that can also be applied to humans, strengthening the translational potential of our research. To exploit this potential, we work on multidisciplinary programs in close collaboration with hospitals and clinical researchers.

A major interest of the group is cardioprotection during myocardial infarction (MI). We have established models of MI in rodents and large animals, and we are using these to study the mechanisms underlying the beneficial effects of various cardioprotective strategies, mainly related to modulation of the adrenergic system. We are 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.

In the clinical setting, our team is a key participant in the METOCARD-CNIC trial, which uses magnetic resonance imaging to evaluate the effectiveness of a cardioprotective strategy based on beta adrenergic modulation in patients suffering a myocardial infarction. Last year we reported the primary outcome of the trial, which shows that this strategy can reduce infarct size in patients undergoing primary angioplasty. During 2014 we will analyze the follow-up data

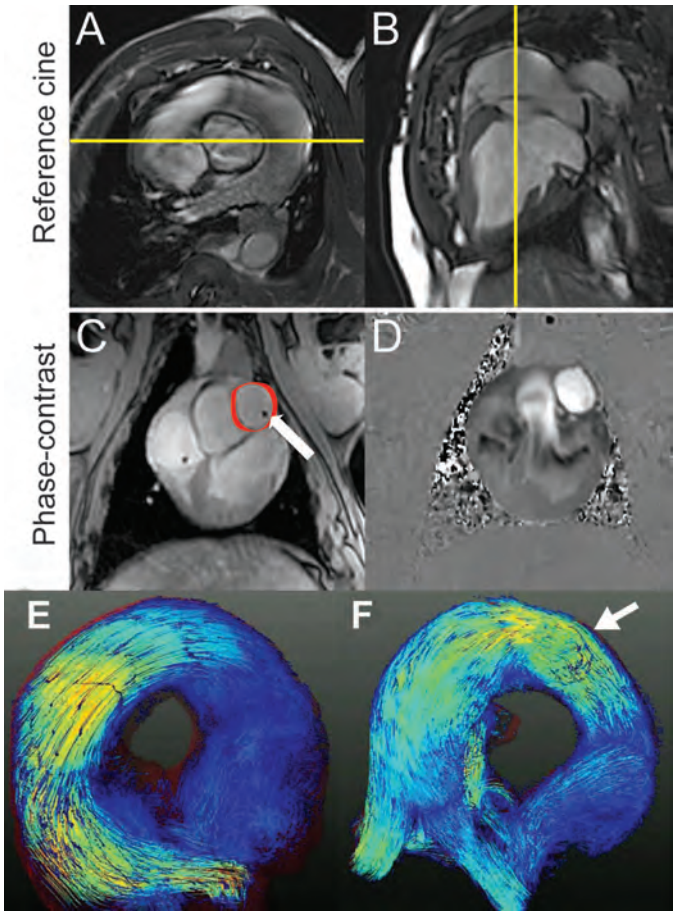
of this trial to evaluate the effect of the therapy on long term myocardial performance and clinical events. The METOCARD-CNIC trial serves as the platform for a future large trial in myocardial infarction patients that will test the effect of the therapy on hard clinical endpoints. This trial will be coordinated by us and will have more than six European partners. Finally, we are evaluating diffuse fibrosis within the myocardium by novel magnetic resonance imaging sequences, and are currently recruiting patients with different cardiomyopathies for this endeavour.



Main results of the METOCARD-CNIC trial: administration of pre-reperfusion metoprolol significantly reduces infarct size in patients undergoing primary angioplasty.

Effect of early pre-reperfusion i.v. metoprolol administration on infarct size evaluated by magnetic resonance imaging (MRI) 5-7 days post-infarction.

Infarct size assessed by delayed gadolinium enhancement in all patients undergoing MRI. Red lines represent means (±SEM). Circles are individual patient data.



Magnetic resonance imaging evaluation of pulmonary hypertension in a pig model.

Our group is a pioneer in the development of non-invasive imaging protocols for improving diagnosis and monitoring of Pulmonary Hypertension. With the MRI protocols developed at the CNIC it is possible to accurately quantify pulmonary vascular resistances, arterial elastance, and right ventricular performance.

A to D correspond to phase contrast imaging of the main pulmonary artery.

A-B, Double-oblique orthogonal views oriented along the main axis of the PA trunk acquired with a steady-state free precession cine sequence; C-B, Phase-contrast imaging on the main PA (C: anatomic view, D: flow-encoded view). White arrow= Swan-Ganz catheter.

E and F: Three-dimensional phase contrast imaging of the main pulmonary artery. E, Control animal without pulmonary hypertension showing laminar flow; F, Case of postcapillary pulmonary hypertension showing turbulent flow and formation of a flow vortex in the main pulmonary artery (arrow).

Major Grants

- Ministerio de Ciencia e innovación. FIS (PI13/01979)
- Ministerio de Economía y Competitividad. ISCIII RETICS (RiC, RD12/0042/0054)
- European Commision FP7-ICT-2011-8 (LIPHOS-317916)
- Maratón, Fundación TV3 (REF: 70/C/2012)
- Fundacion Mutua Madrileña (AP8695-2011)
- CNIC Translational Grants (01-2009)
- Ministerio de Sanidad y Politica Social. FICI (EC10-042)
- Ministerio de Ciencia e innovación. FIS (PI10/02268)

Selected Publications

Ibanez B, Macaya C, Sánchez-Brunete V, Pizarro G, Fernández-Friera L, Mateos A, Fernández-Ortiz A, García-Ruiz JM, García-Álvarez A, Iñiguez A, Jiménez-Borreguero LJ, López-Romero P, Fernández-Jiménez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vázquez JA, Rodriguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Pérez de Prado A, Fernández-Campos MJ, Casado I, García-Rubira JC, García-Prieto J, Sanz-Rosa D, Cuellas C, Hernández-Antolín R, Albarrán A, Fernández-Vázquez F, de la Torre-Hernández JM, Pocock S, Sanz G, Fuster V. **Effect of early metoprolol on infarct size in ST-segment elevation myocardial infarction patients undergoing primary PCI: the METOCARD-CNIC trial**. *Circulation* (2013) 128:1495-1503

García-Álvarez A, Fernández-Friera L, García-Ruiz JM, Nuño-Ayala M, Pereda D, Fernández-Jiménez R, Guzmán G, Sanchez-Quintana D, Alberich-Bayarri A, Pastor-Escuredo D, Sanz-Rosa D, García-Prieto J, Mirelis JG, Pizarro G, Jimenez-Borreguero LJ, Fuster V, Sanz J, Ibáñez B. **Noninvasive monitoring of serial changes in pulmonary vascular resistance and acute vasodilator testing using cardiac magnetic resonance**. *J Am Coll Cardiol* (2013) 62:1621-31

Echavarria-Pinto M, Escaned J, Macías E, Medina M, Gonzalo N, Petraco R, Sen S, Jimenez-Quevedo P, Hernandez R, Mila R, Ibañez B, Nuñez-Gil IJ, Alfonso F, Bañuelos C, García E, Davies J, Fernández-Ortiz A, Macaya C. **Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve. A combined analysis of epicardial and microcirculatory involvement in ischemic heart disease**. *Circulation* (2013) 128: 2557-66

Hadri L, Kratlian R G, Benard L, Maron B A, Dorfmüller P, Ladage De, Guignabert C, Ishikawa K, Aguero J, Ibanez B, Turnbull IC, Kohlbrenner E, Liang L, Zsebo K, Humbert M, Hulot J-S, Kawase Y,. Hajjar RJ, Leopold JA. **Therapeutic Efficacy of AAV1.SERCA2a in Monocrotaline-Induced Pulmonary Arterial Hypertension**. *Circulation* (2013)128:512-23

Fernandez-Friera L, García-Alvarez A, Ibañez B. **Imagining the future of diagnostic imaging**. *Rev Esp Cardiol* (2013) 66:134-143

Imaging cardiovascular inflammation and the immune response

Head of Laboratory: Andrés Hidalgo Alonso

Postdoctoral Researchers: Vinatha Sreeramkumar
Noelia Alonso González
Magdalena Leiva Arjona

Predoctoral Researcher: María Casanova Acebes

Technicians: Christophe Pitaval
Juan Antonio Quintana Fernández

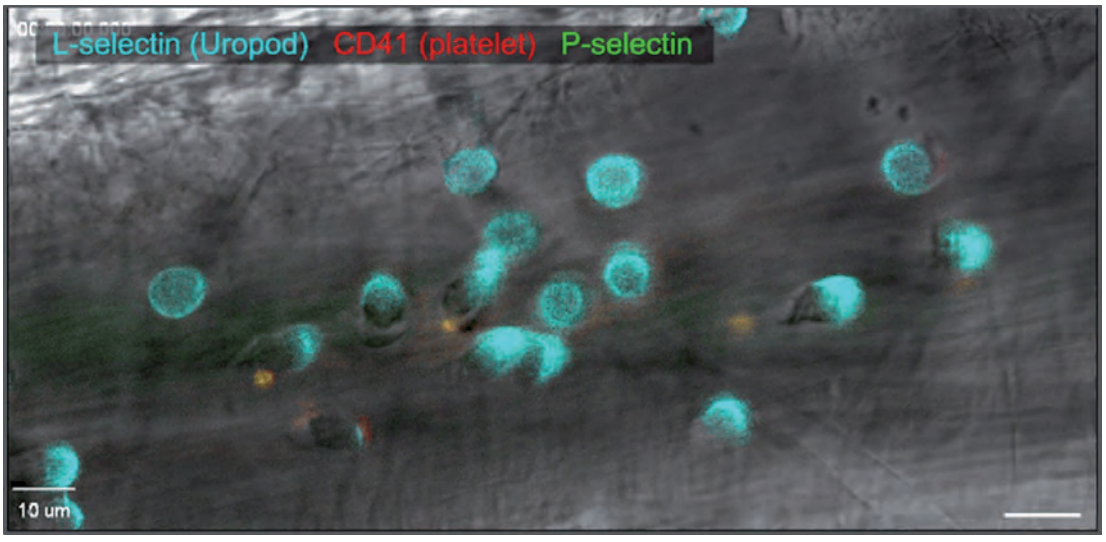
Res@CNIC Fellow: Gonzalo Luis Alonso Salinas

Master Students: Ane Miren Salvador Garikano
Jose Ángel Nicolás Ávila
Paola Brandi

Visiting Scientist: Linnea A. Weiss

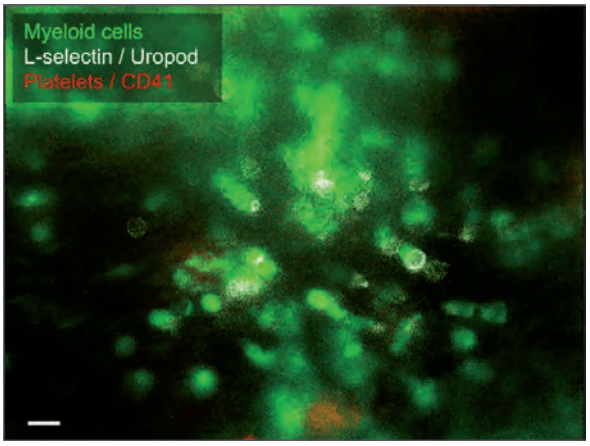
Research Interest

Leukocytes are essential mediators of the organism's immunity. They originate from specialized precursors in the bone marrow termed hematopoetic stem cells (HSCs). Our lab is interested in the mechanisms by which leukocytes and HSCs carry out their functions not only in the context of disease, but also during normal homeostatic situations. We have recently completed studies demonstrating that during inflammatory disease neutrophils use a poorly characterized receptor (ESL-1) to roll on the vasculature and to migrate to areas of injury. Notably, the same receptor plays an even more prominent role in the migration of HSCs to the bone marrow. Our lab is also interested in using and developing high-end imaging techniques to track the behavior of leukocytes *in vivo*. We have developed a method to visualize the formation and growth of the atherosclerotic plaque in mice. This method uses reporter mice and fluorescent probes to image multiple leukocyte subsets and platelets as they accumulate in the growing plaque. Finally, in the past year we have characterized interesting aspects of the biology of neutrophils in the absence of inflammation, and shown that clearance of a population of aged neutrophils in the bone marrow causes important changes in the hematopoietic niches present in this organ, resulting in alterations in the retention of HSCs. Our current studies explore how this phenomenon of clearance regulates the function of other organs, as well as the cells and molecules that mediate these processes.



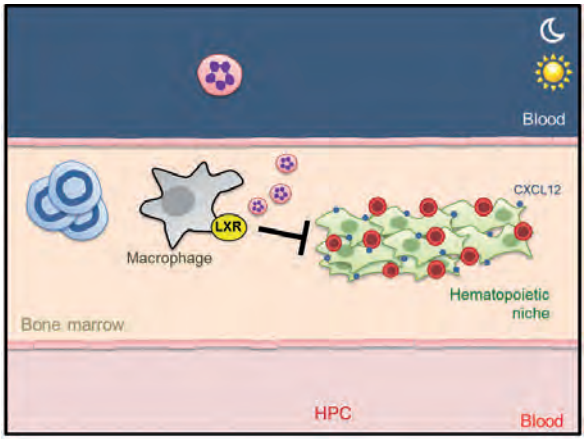
Capture of platelets by inflammatory neutrophils
Intravital image of an inflamed venule displaying adhered neutrophils (blue) and platelets captured from the circulation (red), in the context of a venule (brightfield).

RESEARCH DEPARTMENTS



Imaging inflammation in the atherosclerotic plaque in vivo

Still-frame of myeloid leukocytes (green) accumulated in a developing plaque, together with platelets (red) during the initial phases of plaque formation.



Rhythmic modulation of the hematopoietic niche within the bone marrow

Neutrophils cleared from the circulation infiltrate the marrow and trigger reductions in the stem cell niche.

Major Grants

- **Comunidad de Madrid (P2010-BMD-2314)**
- **Ministerio de Economía y Competitividad (SAF2012-31142)**
- **Ministerio de Ciencia e Innovación (RYC-2007-00697-11037)**
- **European Commission FP7 (246655 LEMPIT 2009)**
- **BAYER HealthCare Grants 2013 (ID 2012-08-0751)**

Selected Publications

Casanova-Acebes M, Pitaval C, Weiss LA, Nombela-Arrieta C, Chèvre R, A-González N, Kunisaki Y, Zhang D, van Rooijen N, Silberstein LE, Weber C, Nagasawa T, Frenette PS, Castrillo A, and Hidalgo A. **Rhythmic modulation of the hematopoietic niche through neutrophil clearance**. *Cell* (2013) 153:1025-35

A-González N, Guillén JA, Gallardo G, Diaz M, de la Rosa JV, Casanova-Acebes M, Hong C, Lara PC, Andujar M, Arai S, Miyazaki T, Li S, Corbí AL, Tontonoz P, Hidalgo A and Castrillo A. **The nuclear receptor LXRα controls the functional specialization of splenic macrophages**. *Nature Immunol* (2013) 14:831-39

Devi S, Wang Y, Chew WK, Lima R, A-González N, Mattar CN, Chong SZ, Schlitzer A, Bakocevic N, Chew S, Keeble JL, Goh CC, Li JL, Evrard M, Malleret B, Larbi A, Renia L, Haniffa M, Tan SM, Chan JK, Balabanian K, Nagasawa T, Bachelerie F, Hidalgo A. Ginhoux F, Kubes P, Ng LG. **Neutrophil mobilization via CXCR4 inhibition arises from lung de-margination and blockade of bone marrow neutrophil homing**. *J Exp Med* (2013) 210:2321-2336

Sreeramkumar V, Leiva M, Stadtmann A, Pitaval C, Ortega-Rodríguez I, Wild MK, Lee B, Zarbock A and Hidalgo A. **Coordinated and unique functions of the E-selectin ligand ESL-1 during inflammatory and hematopoietic recruitment in mice**. *Blood* (2013) 122:3993-4001

Chèvre R, González-Granado JM, Megens RT, Sreeramkumar V, Silvestre-Roig C, Molina-Sánchez P, Weber C, Soehnlein O, Hidalgo A* and Andrés V*. High-Resolution Imaging of Intravascular Atherogenic Inflammation in Live Mice. Circ Res (accepted)
**Co-corresponding authors*

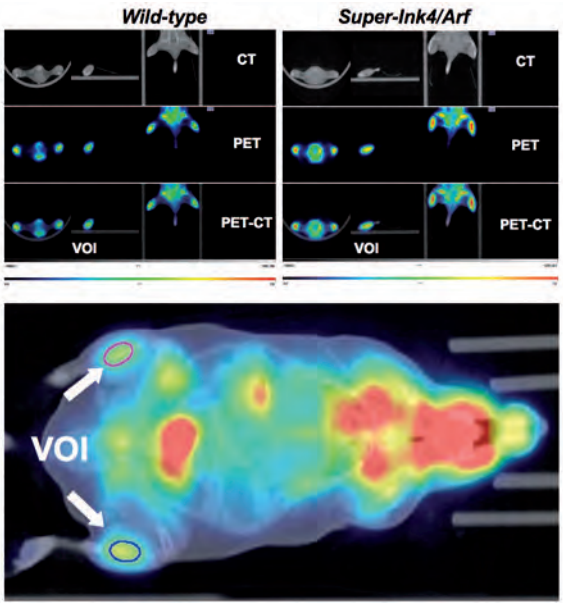
Molecular and genetic cardiovascular pathophysiology

Head of Laboratory:	Vicente Andrés García
Postdoctoral Researchers:	Lara del Campo Milán Raphaël Chèvre José María González Granado *(Miguel Servet Programme)* Oscar Muñiz Pello Cristina Rius Leiva José Rivera Torres Ricardo Villa Bellosta
Predoctoral Researchers:	Pedro Molina Sánchez Magda Rita Hamczyk Carlos Silvestre Roig
Technicians:	Beatriz Julia Dorado de la Corte *(Lab. Manager)* María Jesús Andrés Manzano Marta Blanco Berrocal Alba de Juan Guillén Cristina González Gómez
Res@CNIC Fellow:	Jorge Vázquez López-Ibor
Invesmir Fellow:	Luis González Torres
Masters Students:	Alberto del Monte Monge Victor Fanjul Hevia
Visiting Scientists:	Veronica Bignone Paola Brandi Marcelo Alarcón Lozano Andreu Llobera Adán Francesc Xavier Muñoz Berbel

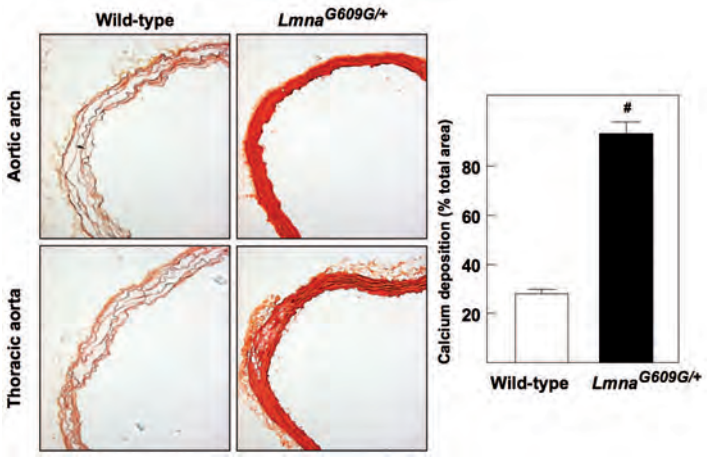
Research Interest

Aging is the main risk factor for cardiovascular disease (CVD), which is responsible for 1 in 3 deaths in developed countries. The World Health Organization has estimated that CVD will by 2020 be the main health and socio-economic problem worldwide, in part due to the progressive aging that the world population is experiencing. Atherosclerosis and vascular calcification (VC) are very complex degenerative processes that contribute significantly to CVD-related morbimortality in the elderly. These anomalies and the aging process are much accelerated in Hutchinson-Gilford progeria syndrome (HGPS), a rare genetic disorder caused by the expression of progerin. Aging-associated symptoms in HGPS patients include alopecia, wrinkled skin, reduced subcutaneous fat, joint abnormalities, bone fractures, and osteoporosis. The most serious aspect of HGPS is extensive atherosclerosis and VC which are associated with early death (average lifespan: 13yr, range: 8-21yr), predominantly from myocardial infarction, heart failure or stroke. Although several palliative therapies have shown efficacy in cell and animal models of HGPS and some are currently under evaluation in clinical trials, a better understanding of the molecular alterations produced by progerin is essential to develop efficient treatments and to find a cure for this devastating disease. 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 physiological aging.

Our research currently focuses on four main areas: 1. Mechanisms of CVD induced by defective phosphorylation of p27 at serine 10; 2. Mechanisms of VC and its regulation by ATP, pyrophosphate, macrophages and aging; 3. Mechanisms through which lamin A/C and progerin regulate CVD and aging; and 4. Specific and shared molecular mechanisms involved in premature and physiological aging.



^{18}F-FDG uptake in mice. *Representative PET scans from* Wild-type *and* Super-Ink4/Arf *mice showing transaxial images of the lower section of the mouse body. The image in the bottom shows whole-body PET.*



Excessive calcification in aorta from progerin-expressing LmnaG609G/+ mice. *Representative images of Alizarin red staining and quantification of calcium deposition.*

Major Grants

- Ministerio de Economía y Competitividad. FIS RETICS (RECAVA, RD06/0014/0021)
- Ministerio de Economía y Competitividad. FIS RETICS (RiC, RD12/0042/0028)
- Ministerio de Economía y Competitividad (SAF2010-16044)
- Progeria Research Foundation (Innovator Award PRF 2012-42)
- European Commission FP7-ICT-2011-8 (LIPHOS-317916)
- European Commission. Marie Curie Career Integration Grant (PCIG10-GA-2011-303850) PI, O.M. Pello
- Ministerio de Economía y Competitividad. FIS (CP11/00145) PI, J.M. Gonzalez Granado

Selected Publications

Silvestre-Roig, C, Fernández, P, Esteban, V, Pello, OM, Indolfi, C, Rodríguez, C, Rodríguez-Calvo, R, López-Maderuelo, MD, Bauriedel, G, Hutter, R, Fuster, V, Ibáñez, B, Redondo, JM, Martínez-González, J, Andrés, V. **Inactivation of NF-Y inhibits vascular smooth muscle cell proliferation and neointima formation**. *Arterioscl Thromb Vas. Biol* (2013) 33: 1036-45

González-Navarro, H, Vinué, A, Sanz, MJ, Delgado, M, Pozo, MA, Serrano, M, Burks, DJ, Andrés, V. **Increased dosage of Ink4/Arf protects against glucose intolerance and insulin resistance associated with aging**. *Aging Cell* (2013) 12:102-11

Rivera-Torres, J, Acín-Perez, R, Cabezas-Sánchez, P, Osorio, FG, González, C, Megías, D, Cámara, C, López-Otín, C, Enríquez, JA, Luque-García, JL, Andrés, V. **Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labelling with amino acids in cell culture**. *J Proteom* (2013) 91C:466-77

Villa-Bellosta, R, Rivera-Torres, J, Osorio, FG, Acín-Pérez, R, Enriquez, JA, López-Otín, C, Andrés, V. **Defective extracellular pyrophosphate metabolism promotes vascular calcification in a mouse model of Hutchinson-Gilford progeria syndrome that is ameliorated on pyrophosphate treatment**. *Circulation* (2013) 127: 2442-51

Chèvre R, González-Granado JM, Megens RT, Sreeramkumar V, Silvestre-Roig C, Molina-Sánchez P, Weber C, Soehnlein O, Hidalgo A and Andrés V. **High-Resolution Imaging of Intravascular Atherogenic Inflammation in Live Mice**. *Circ Res* (accepted)

3 Atherothrombosis, Imaging and Epidemiology

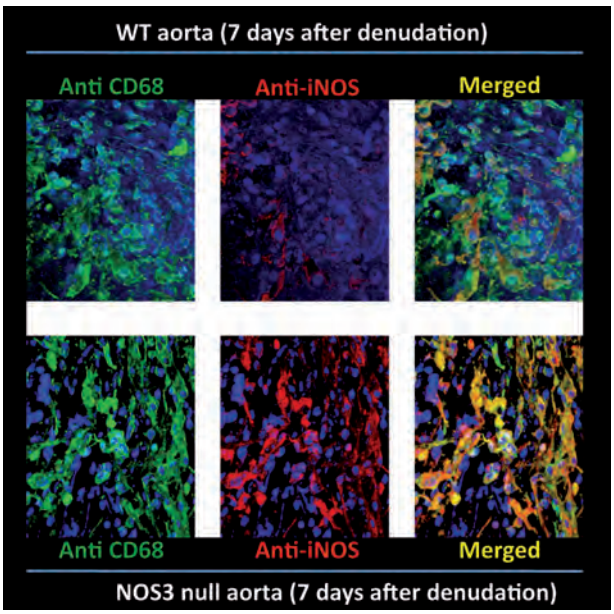
Vascular wall remodeling and cardiovascular disease

Head of Laboratory: Carlos Zaragoza Sánchez
Postdoctoral Researcher: Beatriz Herranz Sánchez
Predoctoral Researcher: Begoña Lavin Plaza
Technician: Mónica Gómez Parrizas
Visiting Scientists: Irene Herruzo Priego
María José García-Miguel Piedras
María del Carmen Turpín Sevilla

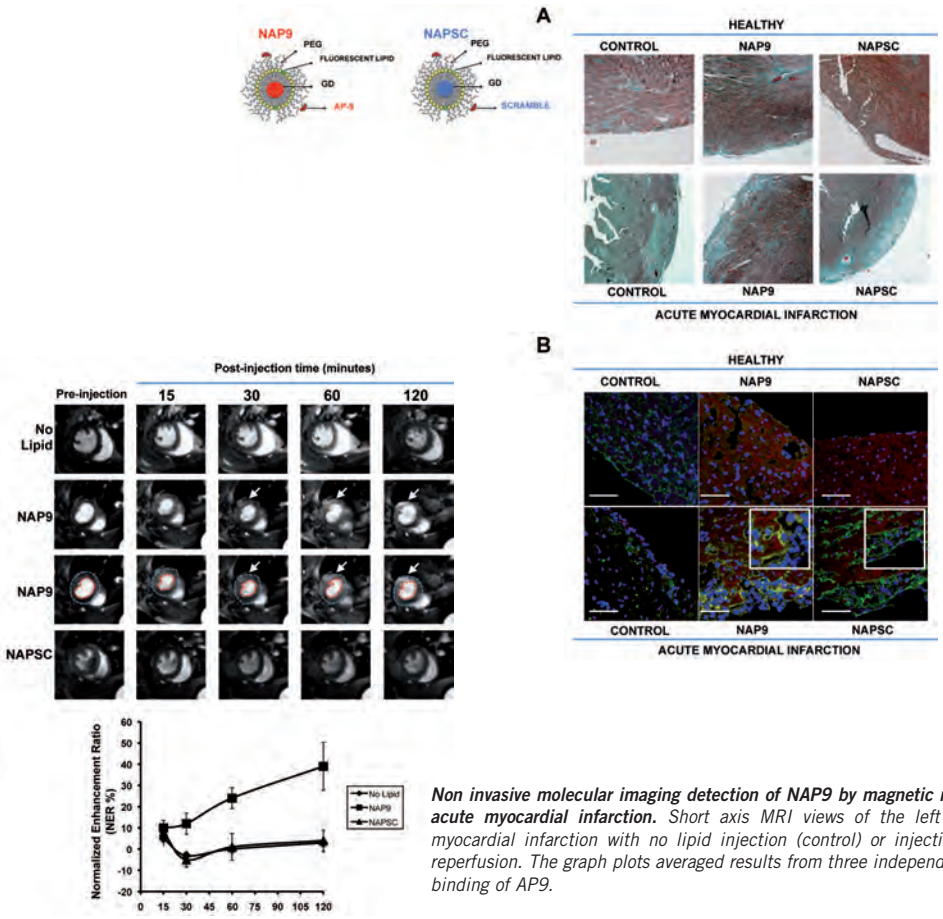
Research Interest

Our laboratory studies atherothrombotic and cardiac diseases, with special attention on the early steps of arterial neointima hyperplasia and cardiac myocyte necrosis. Our primary goal is to understand the signals that trigger the activation of signaling cascades leading to tissue proliferation and degradation at the subclinincal level. Our work has shown the importance of endothelial production of the vasoactive factor nitric oxide (NO) in the regulation of inflammation. Endothelial NO production preceeds the abnormal proliferation of muscle and endothelial cells (neointilmal hyperplasia) triggered by vascular denudation, a frequent consequence of mechanical intervention to clear occluded vessels. We have found that inflammatory macrophages polarize toward a resolving phenotype in damaged vessels through NO-dependent inhibiton of proteolysis, thus preventing neointima formation. The molecular mechanisms leading to abnormal macrophage polarization are now under investigation.

Building on our findings on the cardioprotective effect of NO, we are continuing with our search for strategies to inhibit the enzymatic activity of a cardiac proteolytic activator induced in ischemic coronary arteries. Our preclinical research in mouse models of acute myocardial infarction allowed us to protect our results under a patent in the United States and Europe. During the next year, with backing from private enterprise, our goal is to validate our cardiac protection strategy in porcine models of acute myocardial infarction, in preparation for evaluation in patients.



Lack of endothelial nitric oxide promotes infiltration of pro-inflammatory M1 macrophages after aortic denudation in mice. *Images show "en face" confocal microscopy detection of CD68+ (FITC, green), iNOS+ (Cy3, red), and nuclei (Hoecht, blue) in mouse aortas 7 days after endothelial denudation. Colocalization of CD68 and iNOS (yellow in the merged panels) marks proinflammatory (M1) macrophages.*



Injected nanoparticles containing AP9 peptide (NAP9) protect against cardiac cell death in mice subjected to left anterior descending coronary artery occlusion. Left panel. *Configuration of gadolinium-containing nanoparticles. Conjugated AP9 (NAP9) is in red, whereas scrambled AP9 peptide (NAPSC) used as negative control is in blue. NAP9 and NAPSC nanoparticles both contain a conjugated fluorochrome for fluorescence microscopy detection in ex vivo samples. GD, gadolinium; PEG, polyethylene glycol.* ***A****. Masson's Trichrome staining of healthy hearts (top) or hearts isolated two days after acute myocardial infarction (bottom), and injected with NAP9 or NAPSC nanoparticles at the time of reperfusion.* ***B****. Confocal microscopy detection of endogenous EMMPRIN (endogenous AP9 target; green), and injected nanoparticles (red), in the same mice as in A. Colocalization of the two signals (yellow) is only observed in hearts subjected to acute myocardial infarction and injected with NAP9*

Non invasive molecular imaging detection of NAP9 by magnetic resonance imaging in mice subjected to acute myocardial infarction. *Short axis MRI views of the left ventricle of mice subjected to acute myocardial infarction with no lipid injection (control) or injection of NAP9 or NAPSC at the time of reperfusion. The graph plots averaged results from three independent experiments, indicating the specific binding of AP9.*

Major Grants

- **Ministerio de Economía y Competitividad (SAF 2011-28375)**
- **European Commission FP7 (TD1007 COST). Work package leader: C. Zaragoza.**
- **Universidad Francisco de Vitoria, intramural grants.**

Selected Publications

Fernández-Velasco M, Prieto P, Terrón V, Benito G, Flores JM, Delgado C, Zaragoza C, Lavin B, Gómez-Parrizas M, López-Collazo E, Martín-Sanz P, Boscá L. **NOD1 activation induces cardiac dysfunction and modulates cardiac fibrosis and cardiomyocyte apoptosis**. *PLoS One* (2012) 7: e45260

Zaragoza C, Márquez S, Saura M. **Endothelial mechanosensors of shear stress as regulators of atherogenesis**. *Curr Opin Lipidol* (2012) 23: 446-52

Herranz B, Marquez S, Guijarro B, Aracil E, Aicart-Ramos C, Rodriguez-Crespo I, Serrano I, Rodríguez-Puyol M, Zaragoza C*, Saura M*. Integrin-linked kinase regulates vasomotor function by preventing endothelial nitric oxide synthase uncoupling: role in atherosclerosis. *Circ Res* (2012) 110: 439-49 Erratum in: *Circ Res* (2012) 110: e48
**Co-corresponding authors*

Fuster JJ, Castillo AI, Zaragoza C, Ibáñez B, Andrés V. Animal models of atherosclerosis. *Prog Mol Biol Transl Sci* (2012) 105: 1-23

Chen W, Cormode DP, Vengrenyuk Y, Herranz B, Feig JE, Klink A, Mulder WJ, Fisher EA, Fayad ZA. Collagen-specific peptide conjugated HDL nanoparticles as MRI contrast agent to evaluate compositional changes in atherosclerotic plaque regression. *JACC Cardiovasc Imaging* (2013) 6: 373-84

3 Atherothrombosis, Imaging and Epidemiology

Advanced development in arrhythmia mechanisms and therapy

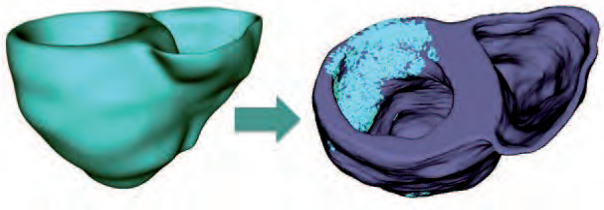
Head of Laboratory: David Filgueiras Rama
Visiting Scientist: Jorge García Quintanilla

Research Interest

The laboratory focuses on investigating the mechanisms underlying complex cardiac arrhythmias that occur in highly prevalent cardiovascular diseases in the general population, as well as in specific subsets at particular risk of sudden cardiac death. Atrial fibrillation (AF) and infarct scar-related ventricular tachycardia (VT) represent two of the most prevalent cardiac rhythm disorders, in which the capacity of current therapeutic strategies to accurately eliminate the arrhythmogenic substrate is limited. Our goal is to achieve in-depth insight into AF and VT mechanisms through the use of appropriate experimental and numerical models, which could then be used to improve patient care and to develop new and more specific therapies.

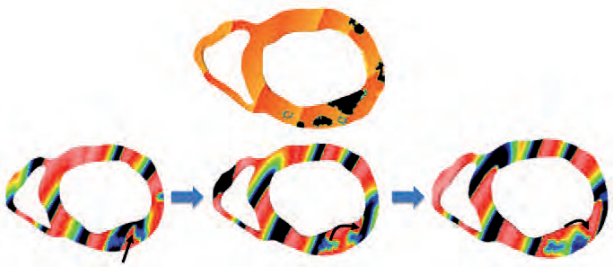
We use a translational approach to study infarct scar-related VT in pigs and clinical infarct-related reentrant VT. High-resolution MRI images, both in humans (*in vivo*) and animals (*ex vivo*) provide the structural details to construct patient and animal-specific 3D anatomical models of the ventricles. Electrophysiologically realistic numerical simulations can be incorporated in 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 humans.

We are also involved in characterizing the differences in the transcriptome, ion channel density and function, as well as the molecular and gross anatomical structure of relevant regions of the atria of pigs with paroxysmal, persistent and long-standing persistent AF. Such differences provide information essential for the understanding of AF maintenance and patterns of electrical activation observed during the arrhythmia.



3D ventricular reconstruction.

Patient-specific 3D reconstruction of right and left ventricular cavities (left side) and infarct-related scar areas (right).



Reentry simulation.

Reentry simulation around an infarct-related scar area (upper image) after virtual stimulation using a S1-S2 protocol. The lower image sequence shows the propagation of the wavefront around the scar area (black arrow).

Major Grants

- **Eugenio Rodríguez Pascual Foundation.**
- **Salud 2000 Foundation (NOT CNIC).**

Selected Publications

Raphael P. Martins, Kuljeet Kaur, Elliot Hwang, Rafael J. Ramirez, B. Cicero Willis, David Filgueiras-Rama, Steven R. Ennis, Yoshio Takemoto, Daniela Ponce-Balbuena, Manuel Zarzoso, Ryan P. O'Connell, Hassan Musa, Guadalupe Guerrero-Serna, Uma Mahesh R. Avula, Michael F. Swartz, Sandesh Bhushal, Makarand Deo, Sandeep V. Pandit, Omer Berenfeld, José Jalife. **Dominant Frequency Increase Rate Predicts Transition from Paroxysmal to Long-Term Persistent Atrial Fibrillation**. *Circulation* (accepted)

Prefasi D, Martínez-Sánchez P, Rodríguez-Sanz A, Fuentes B, Filgueiras-Rama D, Ruiz-Ares G, Sanz-Cuesta BE, Díez-Tejedor E. **Atrial fibrillation in young stroke patients: do we underestimate its prevalence?** *Eur J Neurol*. (2013) 20: 1367-74

David Filgueiras-Rama and Jose L Merino. **The Future of Pulmonary Vein Isolation – Single-shot Devices, Remote Navigation or Improving Conventional Radiofrequency Delivery by Contact Monitoring and Lesion Characterisation?** *Arrhythmia & Electrophysiology Review* (2013) 2: 59–64

David Filgueiras-Rama*, Miguel A. Arias, Ángel Iniesta, Eduardo Armada, José L.Merino, Rafael Peinado, and J. L. López-Sendón. **Atrial arrhythmias in obstructive sleep apnea: underlying mechanisms and implications in the clinical setting**. *Pulmonary Medicine* (2013) Article #426758. dx.doi.org/10.1155/2013/426758.
** Corresponding author*

David Filgueiras-Rama, Alejandro Estrada, Josh Shachar, Sergio Castrejón, David Doiny, Marta Ortega, Eli Gang, José L. Merino. **Remote magnetic navigation for accurate, real-time catheter positioning and ablation in cardiac electrophysiology procedures**. *J Vis Exp* (2013) 74: e3658

Atherothrombosis and cardiovascular epidemiology

Head of Laboratory:	**Valentín Fuster** *(CNIC, Mt. Sinai Medical Center, New York)*
Research Scientists:	Ginés Sanz José Luis Peñalvo Martín Laclaustra
Predoctoral Researcher:	Belén Moreno
Project Manager:	Luz Álvarez
Biostatistician:	Belén Oliva
Technicians:	Natalia Serrano Mª José Diego Estrella Rubio Carolina Rojas Ricardo Ponce
Invesmir Fellow:	Gabriela Saravia
Visiting Scientists:	José Mª Ordovás *(CNIC, Tufts University, Boston, IMDEA-FOOD, Madrid)* Stuart Pocock *(CNIC, London School of Hygiene and Tropical Medicine, London)* Manuel Franco *(University of Alcalá, Madrid)* Antonio Sarría *(Instituto de Salud Carlos III, Madrid)* Mercedes Sotos *(Fundación SHE, Barcelona)* Gloria Santos *(Fundación SHE, Barcelona)* Patricia Bodega *(Fundación SHE, Barcelona)* Jenny Guadamuz *(St. Louis University, USA)*

Research Interest

The group conducts high-quality and high-impact population research studies into the environmental, individual and genetic risk factors that are causally related to cardiovascular disease (CVD). The group works closely with other department areas on the design and coordination of the CNIC's population studies, such as the Aragon Workers' Health Study (AWHS), PESA (Progression of Subclinical Atherosclerosis), IMJOVEN, FOCUS/Polypill, and Program SI! (Salud Intergral; Comprehensive Health). Program SI! moves the department into the direct promotion of cardiovascular health from early in life. This multidimensional school-based intervention works with children from the ages of 3 to 16 and key figures in their proximal environment (family and school). The program encourages a comprehensive awareness of health, with the aim of instilling appropriate lifestyle behaviors for CVD prevention that will be maintained throughout life.

The multidisciplinary group pursues highly innovative research that covers the major risk factors for CVD, including diet, genetics and epigenetics, metabolic factors, the environment, and psychosocial factors. We are also developing expertise in the analysis of high-throughput data and in the evaluation of novel and established cardiovascular risk factors in studies of populations with subclinical measures of atherosclerosis. Through these approaches, the group is making significant contributions to the understanding and control of the current epidemic of CVD.

The members of the group also continue to make significant contributions to leading international studies such as the Framingham Heart Study, the Atherosclerosis Risk in Communities (ARIC) Study, the Multiethnic Study of Atherosclerosis (MESA), the Strong Heart Study, the US National Health and Nutrition Examination Survey, and the UK National Diet and Nutrition Survey.

Major Grants

- **Instituto de Salud Carlos III (CP08/112). PI: M Laclaustra**
- **Comunidad de Madrid (P2009/AGR-1469). PI: JL Peñalvo**
- **Instituto de Salud Carlos III (PI10/21). PI: M Laclaustra**
- **Instituto de Salud Carlos III (PI11/00403). PI: JL Peñalvo**
- **Instituto de Salud Carlos III (PI11/01885). PI: J Redondo**

Selected Publications

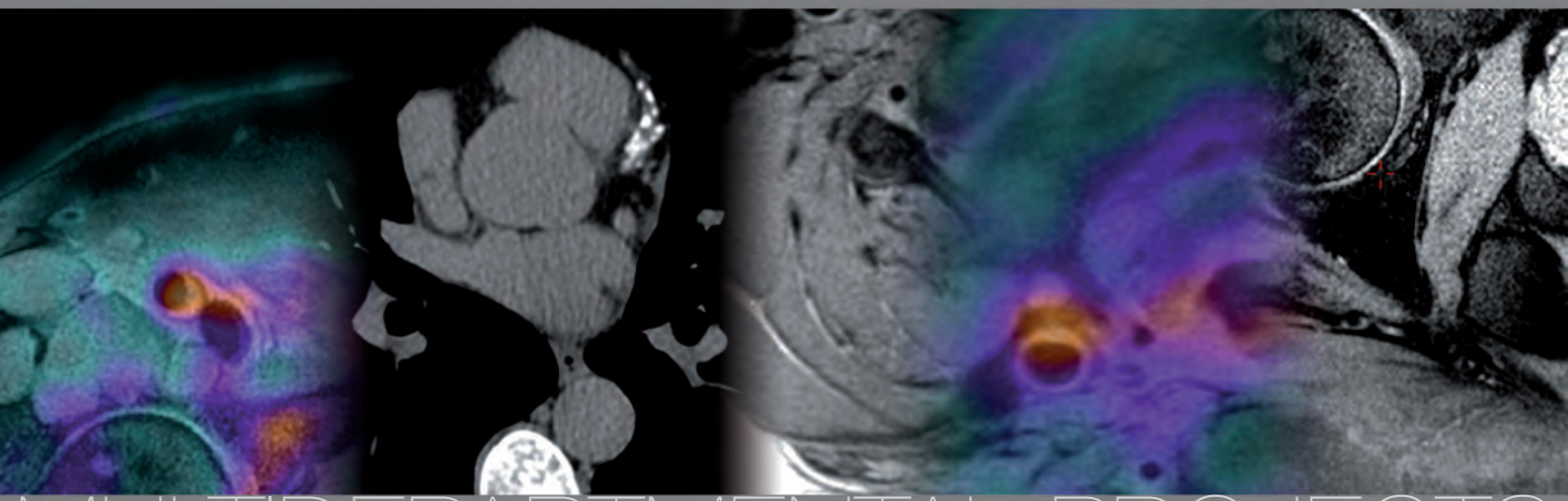
Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, Ordovás JM, Mocoroa A, Fernández-Friera L, Laclaustra M, García L, Molina J, Mendiguren JM, López-Melgar B, de Vega VM, Alonso-Farto JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibañez B, Sanz G, Fuster V. **The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design**. *Am Heart J* (2013) 166: 990-8

Franco M, Bilal U, Orduñez P, Benet M, Morejón A, Caballero B, Kennelly JF, Cooper RS. **Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends**. *BMJ* (2013) 346: f1515

Céspedes J, Briceño G, Farkouh ME, Vendanthan R, Baxter J, Leal M, Boffetta P, Hunn M, Dennis R, Fuster V. **Promotion of cardiovascular health in preschool children: 36-month cohort follow up**. *Am J Med* (2013) 126: 1122-1226.

Corella D, Carrasco P, Sorlí JV, Estruch R, Rico-Sanz J, Martínez-González MÁ, Salas-Salvadó J, Covas MI, Coltell O, Arós F, Lapetra J, Serra-Majem L,Ruiz-Gutiérrez V, Warnberg J, Fiol M, Pintó X, Ortega-Azorín C, Muñoz MÁ,Martínez JA, Gómez-Gracia E, González JI, Ros E, Ordovás JM. **Mediterranean diet reduces de adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population**. *Diabetes Care* (2013) 36: 3803-11

Sanz G, Fuster V. **Prevention: Polypills for cardiovascular prevention: a step forward?** *Nat Rev Cardiol* (2013) 10: 683-4



MULTIDEPARTMENTAL PROJECTS

IMJOVEN

Although heart disease in young women causes many deaths, it has been virtually ignored by the medical profession because it represents only a small fraction of the total incidence of atherosclerotic heart disease. However, young women who suffer an acute myocardial infarction (AMI) have a mortality risk markedly higher than that of young men, and the limited data on young women from minority groups in the USA suggest that this population may have the highest risk of any young subgroup. There have been no large prospective studies of ischemic heart disease in young women, even though the death toll is comparable to that due to breast cancer. Findings from the small number of studies that have been published suggest that the biology, epidemiology, care, and outcomes of heart disease in women differ from those of men. The IMJOVEN study is the Spanish counterpart of the VIRGO study, an NIH-sponsored investigation led by Harlan Krumholz of Yale University into the excess risk in young women with AMI.

The specific aims of VIRGO and IMJOVEN are as follows. 1) To characterize sex differences after hospitalization for AMI for a broad range of outcomes including mortality, all-cause readmission, rehospitalization for cardiovascular causes, and adverse health status. 2) To evaluate the influence of demographic, clinical, metabolic, biochemical, genetic, psychosocial, and lifestyle factors on outcomes for young women and men with AMI and to examine whether sex-based variation in these factors is associated with variation in outcomes. 3) To compare the clinical treatment of young men and women who present at hospital with AMI and determine whether differences in quality of care are associated with differences in outcome. 4) To describe the relationship of female-specific factors—including genetic variants, sex hormones, reproductive history, prior use of estrogens and menstrual cycle history—with disease outcomes for women. 5) To develop comprehensive prognostic scores to stratify risk in this young population and identify predictors of early (within 1 month of discharge) and longer-term (1 year) outcomes. 6) To create a blood and DNA repository as a resource for future studies. 7) To partner with national and international organizations to disseminate study findings in order to improve the prevention, care, and outcomes for young patients with AMI.

Our aim with IMJOVEN was to study 450 patients (300 women and 150 men) with a previous history of AMI, using the same protocol as the VIRGO study. We finally recruited 529 patients (359 women and 170 men) in 24 hospitals in Spain, and recruitment was completed in October 2011. IMJOVEN is coordinated by the Translational Platform at the CNIC, the Spanish Society of Cardiology and the RECAVA and Heracles networks. Funding comes from a FIS grant, the NIH and the CNIC.The database cleaning was completed in 2013, and data analysis is scheduled for completion in the fall of 2014.

The following substudies have been started in collaboration with the indicated partners:

- ***Angiographic substudy. Hospital Clinic, Barcelona.***
- ***Electrocardiographic substudy. Vall d´Hebrón Hospital, Barcelona.***
- ***RNA substudy. CNIC Genomics Unit.***

The Aragon Workers Health Study (AWHS) is an ongoing project conducted in collaboration with the Instituto Aragonés de Ciencias de la Salud (IACS) and the General Motors factory in Zaragoza. The AWHS has been designed to evaluate the trajectories of traditional and emergent CVD risk factors and their association with the prevalence and progression of subclinical atherosclerosis in a population of middle-aged men and women in Spain. The study examines the development of cardiovascular disease and its risk factors by monitoring factory workers at their annual medical checkups.

The AWHS is an observational, prospective cohort study including more than 5000 participants. Recruitment began in 2009 and all workers at the factory fulfilling the inclusion criteria and willing to participate have now made their initial visit. Current planned follow-up will continue to 2018.

The initial visit consisted of a clinical examination, biochemical and hematologic tests and sample collection. Sample aliquots of serum, plasma, whole blood, DNA, and urine have been frozen and stored. All laboratory procedures conform to the ISO9001:2008 quality standard. After inclusion, workers' health data and biochemistry tests are collected at each annual health check-up.

In 2011, a screen was begun to detect subclinical atherosclerosis among 40-54 years-old participants, based on vascular 2D and 3D ultrasound in carotid, aorta and ilio-femoral arteries and on measurement of coronary artery calcification by computed tomography (CT). Completion of the whole screen is scheduled for 2014. More than 1500 participants have already been studied.

In 2012, the study's general methods were published* in an open access journal to support a more focused future publication of the on-going research subprojects and to provide a clear description of the study to support fund-attracting strategies.

* *Casasnovas JA, Alcaide V, Civeira F, Guallar E, Ibañez B, Borreguero JJ, Laclaustra M, León M, Peñalvo JL, Ordovás JM, Pocovi M, Sanz G, Fuster V. Aragon workers' health study--design and cohort description.* BMC Cardiovasc Disord *(2012) Jun 19;12:45. doi: 10.1186/1471-2261-12-45.*

Additional external funding has been raised for the following sub-studies on the cohort, which are being conducted by CNIC-based researchers:

- Insulin resistance and inflammatory response to oxidative stress: Study of determinants and interactions (ISCIII CP08/112)
- Identification of the genetic determinants of mitochondrial DNA content in a working population, and its relationship with oxidative stress and subclinical atherosclerosis (ISCIII PI10/21)
- Cadmium exposure, metallothionein levels, and kidney disease in a General Motors company assembly plant (Johns Hopkins NIOSH Education and Research Center Research Project Award)
- DNA methylation and the association of cadmium exposure with chronic kidney disease in a population-based occupational study (Johns Hopkins NIEHS Center in Urban Environmental Health Award)
- Polymorphism APOA2 -265T>C in relation to dietary patterns and cardiovascular risk factors (ISCIII PI11/403)

Table 2
Prevalence of subclinal atherosclerosis in the initial 587 AWHS participants completing all imaging procedures

	Age 40 - 50	Age 50 - 56	Overall
Age, years	47.0 (2.5)	52.9 (2.5)	50.0 (3.6)
Carotid plaque	46 (18.5)	194 (35.7)	240 (30.3)
Femoral plaque	101 (39.6)	317 (56.0)	418 (50.9)
Coronary calcium			
Agatston score >1 to 100	48 (20.0)	159 (30.5)	207 (27.2)
Agatston score >100	8 (3.3)	59 (11.3)	67 (8.8)

Values in the Table are numbers (%), except for age [mean (SD)].

Casasnovas et al. BMC Cardiovascular Disorders 2012 12:45 doi:10.1186/1471-2261-12-45

PESA CNIC GRUPO SANTANDER AND FUNDACIÓN BOTÍN

(Progression of Early Subclinical Atherosclerosis)

The ongoing PESA CNIC-Grupo Santander and Fundación Botín study will achieve early diagnosis of atherosclerosis before the appearance of symptoms and help to identify risk factors and daily habits that influence the onset and development of atherosclerosis. Future follow-up of this population may identify new and more effective predictors for cardiovascular events.

Strategies to identify individuals with subclinical alterations indicating increased risk of cardiovascular disease have been boosted by the development of basic imaging techniques (3D ultrasound) and advanced non-invasive imaging techniques (magnetic resonance imaging, positron emission tomography, and computerized 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. Atherosclerotic disease in this age group has already been developing for several decades and it may be too late to prevent future events. To assess the early phases of atherosclerosis, longitudinal vascular imaging studies on middle-aged asymptomatic populations are needed.

The PESA study is an observational, prospective, cohort study in a target population of 4000 healthy middle-aged individuals (40-54 years old, 35% women) based in Madrid. Participant inclusion began in June 2010 and will be completed in February 2014. All participants will be followed for 6 years. Recruitment of study participants is based on volunteer participation after completion of the annual medical checkup by the Banco Santander medical services. Subclinical atherosclerosis is first assessed by vascular 2D and 3D ultrasound in carotid, aorta and ilio-femoral arteries. Each participant is also explored for coronary artery calcification by computed tomography (CT) and is interviewed to identify classical and new cardiovascular risk factors (including lifestyle and psychosocial factors). In addition, plasma, serum, RNA, DNA and leukocyte samples are obtained, frozen, and stored for future biomarker and omics discovery studies. Follow-up visits at 3 and 6 years will include repetition of all these baseline measurements. In addition, advanced imaging by contrast-enhanced magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose–positron emission tomography (18FDG PET) for carotid and ilio-femoral plaques will be offered at baseline and at 6 years to a selected group of 1300 participants with subclinical disease. A new PET-MRI system deployed at the CNIC allows advanced sequential acquisition of PET and MRI data for atheroma plaques. These imaging techniques enable early detection of subclinical atherosclerosis, characterization of the atherosclerotic burden, and monitoring of disease progression. The study will run for a total of 9 years, ending in 2019.

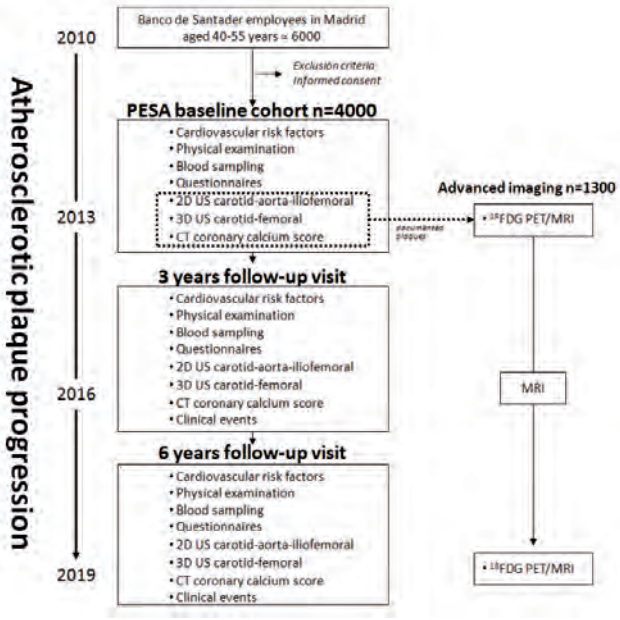
By the end of 2013, the PESA study had recruited more than 3895 volunteers (2476 men and 1419 women). All these participants have been assessed for subclinical atherosclerosis by vascular 2D and 3D ultrasound, and advanced RMN-PET imaging studies have been performed on 595 participants who have atheroma plaques. Anonymized data are being recorded in the PESA study database, and biological samples from all study participants are being stored at the CNIC Biobank for future analysis. All participants receive a report with their test results, together with healthy lifestyle recommendations. In addition, approval has been granted to investigate the association between atherosclerosis and telomere dysfunction and progerin expression in circulating leukocytes, and leukocyte samples from more than 1200 PESA study participants were collected and stored for this analysis in 2013.

In July 2013 the project PESA CNIC-Santander was ISO 9001:2008 certified by Bureau Veritas. This certification allows external validation of quality management and control and traceability of the data.

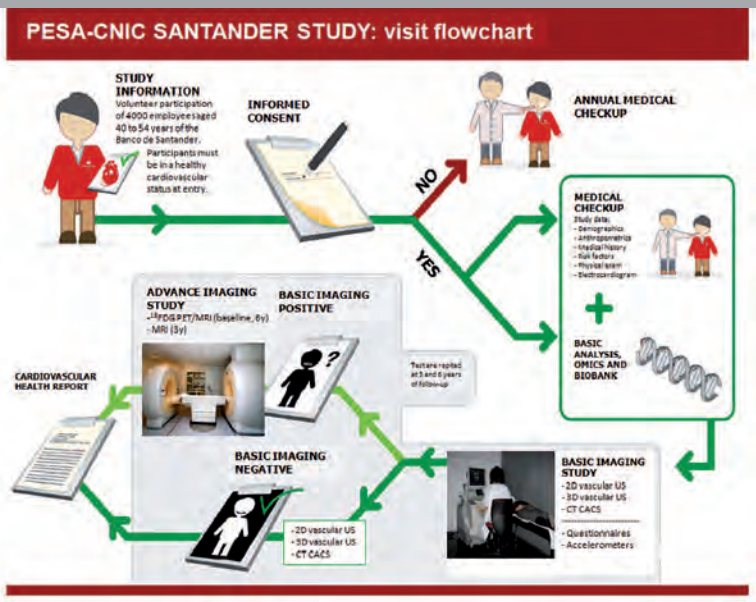
Rationale and design for the PESA study were published on the December 2013 issue of the American Heart Journal *(Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, Ordovás JM, Mocoroa A,Fernández-Friera L, Laclaustra M, García L, Molina J, Mendiguren JM, López-Melgar B, de Vega VM, Alonso-Farto JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibañez B, Sanz G, Fuster V. The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design. Am Heart J. 2013 Dec;166(6):990-8).*

PESA CNIC SANTANDER ACIÓN BOTÍN

Flowchart for the procedures performed on PESA participants during each visit (US: ultrasound).

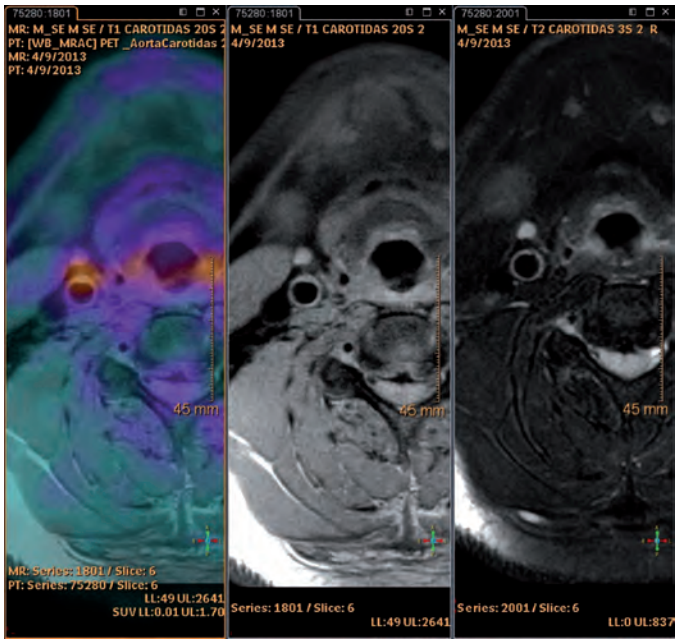


Visit flowchart for the PESA study. The rationale and design of the PESA study were published in the December 2013 issue of the American Heart Journal: Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, Ordovás JM, Mocoroa A,Fernández-Friera L, Laclaustra M, García L, Molina J, Mendiguren JM, López-Melgar B, de Vega VM, Alonso-Farto JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibañez B, Sanz G, Fuster V. The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design. Am Heart J (2013) 166: 990-8

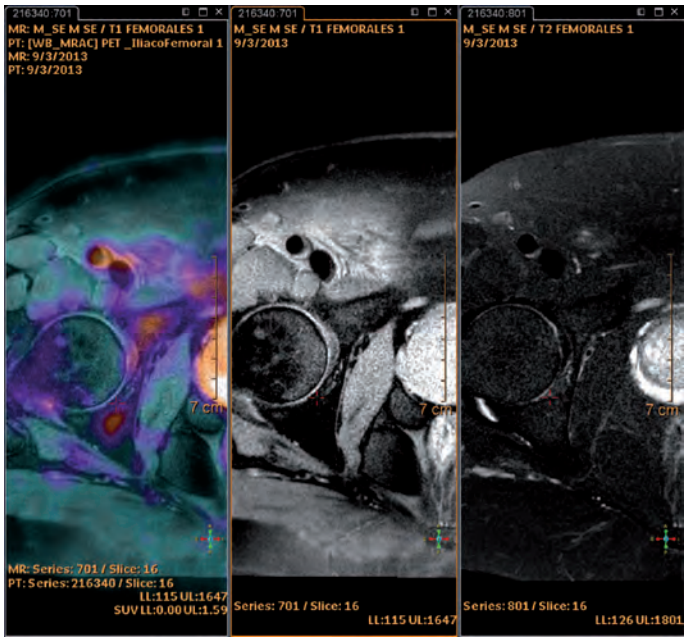


PESA CNIC GRUPO SANTANDER AND FUNDACIÓN BOTÍN

PET/MRI (positron emission tomography/magnetic resonance imaging) of a right carotid artery, showing uptake of ^{18}FDG (fluorodeoxyglucose).



PET/MRI of a right common femoral artery, showing uptake of ^{18}FDG



POLYPILL CNIC-FERRER

The prevention of cardiovascular disease is hampered by several factors, including wide variability in the pattern of prescription among physicians, limited access to expensive drugs in emerging countries, and poor adherence to medication. The use of a fixed dose drug combination (polypill) has been recommended to improve accessibility and adherence to treatment. The CNIC, working in a private-public partnership with Ferrer International, has devised two fixed-dose polypills for secondary prevention, one comprising aspirin, simvastatin and ramipril *(ASR)*, the other containing atorvastatin instead of simvastatin *(AAR)*. The CNIC-Ferrer polypill project is led by Valentín Fuster and is coordinated by the CNIC Translational Platform.

Several clinical trials have been completed to confirm the quality and safety of the polypill. The Spanish pharmacodynamic interactions study with simvastatin in 100 patients showed that this polypill significantly reduces blood levels of LDL and total cholesterol to the same extent as its comparator, and the number of adverse events recorded with polypill treatment did not differ significantly from that for participants receiving aspirin, simvastatin and ramipril separately. In 2013 the *AAR* polypill (with atorvastatin instead of simvastatin) was extensively tested in preclinical studies, demonstrating its bioequivalence.

Interest in the polypill subject is increasing steadily, and was evident during the "Global Summit on Combination Polypharmacy for CV Disease" held September 25-26 2012 in Hamilton, Canada. The meeting gathered physicians, public health experts, members of health agencies (WHO and WHF), representatives from regulatory agencies (FDA and EMA), lawyers, executives of several health maintenance organizations and insurance companies, and representatives of pharmaceutical companies involved in the development of cardiovascular polypills. This forum fostered a comprehensive, open, in-depth discussion on the potential clinical applications of the polypill and associated legal, regulatory and financial aspects. Dr. Valentín Fuster presented the aims and design of FOCUS, a project regarded as the most promising study in this field, whose results are eagerly awaited. No other study is conducting such a comprehensive analysis of the role of a polypill on patient treatment adherence. This multinational trial examines the efficacy of the CNIC-FERRER polypill and explores the factors that determine poor treatment adherence in a cohort of 2000 patients across 80 centers and five countries. Recruitment to the FOCUS trial is scheduled for completion in January 2014.

The CNIC-FERRER *ASR* polypill has been approved for prescription in patients with a previous history of acute myocardial infarction in Guatemala, Argentina, México, Nicaragua and the Dominican Republic, under the name Trinomia/SincroniumR. The *AAR* polypill has just been approved for commercialization in Spain, Romania, Greece and Sweden. CNIC and FERRER continue to work on new fixed-dose combinations to provide physicians and patients with more effective therapeutic tools.

METOCARD-CNIC trial

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.

β-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 (the current state-of-the-art treatment for infarction). Building on strong pre-clinical data, the CNIC led the METOCARD-CNIC trial, the first randomized trial testing the effect of i.v. β-blockers on infarct size in patients undergoing primary angioplasty.

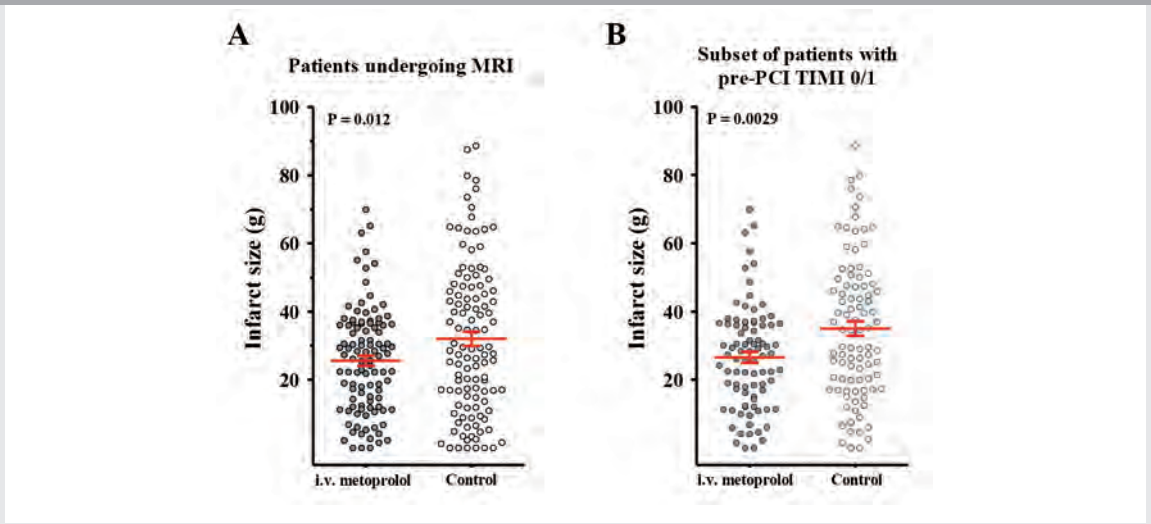
METOCARD-CNIC was a multicenter randomized clinical trial comparing the effect of early and delayed metoprolol initiation on infarct size and clinical events. The trial has already been completed, with a total of 270 patients recruited by the emergency medical services (55%) and participating hospitals (45%). A total of 220 patients underwent a magnetic resonance imaging (MRI) scan five days after infarction, and 202 patients underwent follow-up MRI at six months. All patients underwent one year clinical follow-up. Studies of patients recruited in Madrid were performed at the CNIC's human imaging facility, where the advanced imaging protocol is performed with a pioneering MRI system. MRI scan data were analyzed in a core laboratory at the CNIC.

The primary endpoint of the trial (infarct size as evaluated by MRI) was published last year (Circulation 2013;128:1495-503). The report showed that early administration of metoprolol before reperfusion significantly reduced infarct size in the days following AMI (see Figure). This effect was accompanied by a significantly higher left ventricular ejection fraction than in untreated patients. Follow-up MRI scans and clinical data collection are complete and will be reported in 2014.

METOCARD-CNIC is the result of a multidisciplinary effort requiring close cooperation between investigators at the CNIC, hospitals across Spain, and, importantly, the emergency medical services. The hospitals participating in the METOCARD-CNIC trial are the Hospital Clínico San Carlos, Hospital Puerta de Hierro, Hospital de la Princesa, Hospital 12 de Octubre and Hospital Quirón in Madrid; the Hospital Meixoeiro in Vigo; the Hospital Marqués de Valdecilla in Santander, and the Hospital de León. Emergency medical services actively participating as co-investigators are SUMMA112, 061 Galicia, and SAMUR. The randomization center was located in the headquarters of SUMMA112 and was run 24/7 by trained full-time staff.

The CNIC is already working on the design of a multinational clinical trial based on the design of METOCARD-CNIC but powered to detect differences in clinical endpoints (mortality, heart failure, and arrhythmias). More than 3500 patients will be recruited for the new trial in six countries across Europe.

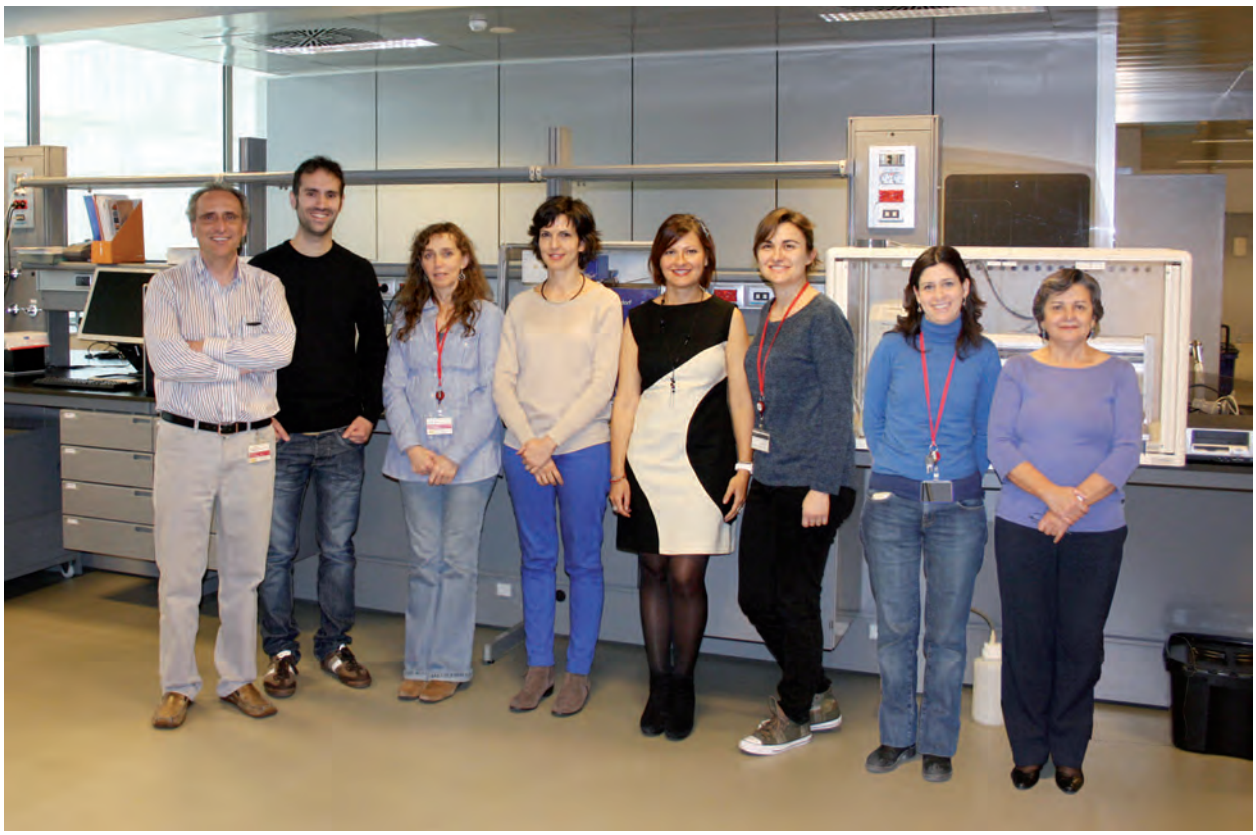
Effect of early pre-reperfusion i.v. metoprolol administration on infarct size evaluated by magnetic resonance imaging (MRI) 5-7 days post-infarction.



Infarct size assessed by delayed gadolinium enhancement in (A) all patients undergoing MRI and (B) in the subset of patients with TIMI flow grade 0/1 before primary percutaneous coronary intervention (PCI). Red lines represent means (±SEM); circles are individual patient data. (Picture taken from Circulation 2013;128:1495-503: METOCARD-CNIC results publication.)

Members of the METOCARD-CNIC research team.

TRANSLATIONAL PLATFORM



Translational Platform

The Technology Transfer & Translational Research Platform ([T]$_3$RP) runs initiatives that foster translational research at the CNIC, in Spanish clinical facilities, and with international partners. The Platform also identifies, promotes, and co develops CNIC research with potential for industrial application by facilitating the granting of patents and their subsequent development or licensing.

The [T]$_3$RP also runs its own Clinical Research Program in coordination with the Atherothrombosis, Imaging and Epidemiology Department. This program provides logistical and methodological support to CNIC researchers and to collaborating institutions and healthcare companies requesting assistance in this area. The [T]$_3$RP has also established a Biobank to support specialized state-of-the-art cardiovascular research.

The [T]$_3$RP's main goal is to promote the research carried out at the Center by stimulating early IP protection, facilitating initial decision making, and assisting with the exploitation of the protected results. The activity of the [T]$_3$RP is divided into the following areas.

1.-Technology Development Unit

The mission of the Technology Development Unit is to shorten the period between registration of CNIC inventions and their uptake and exploitation by industry. Part of the Unit's task is to select projects (the core of which will be CNIC inventions) that show strong potential for establishing proof-of-concept in preclinical studies. Project selection is subject to a feasibility analysis and approval by the [T]$_3$RP Scientific Advisory Committee.

The legal basis for the Unit's activity is being designed in conjunction with the spin off-support policies.

2.- Technology Transfer Office

The CNIC TTO is the interface between our research groups and agencies in the research and development sphere and society at large. The TTO's main activities are as follows:

1.- To encourage the exploitation of research results generated at the CNIC:

- Promoting and publicizing the CNIC´s R&D assets.
- Providing researchers with professional advice about the potential for patenting their research results.
- Helping in the design, preparation and presentation of patents.

2.- To promote and coordinate relations between the CNIC and partners in the fields of research and technological innovation:

- Stimulating collaboration between CNIC researchers and companies interested in their work through formal collaboration agreements or research contracts at regional, national and international level.
- Promoting participation by CNIC research groups in collaborative research and technology-development programs at regional, national, and European level.

2.1.- Patent Filing & Technology Transfer

The past two years have seen a significant increase in the number of new invention disclosures assessed, confirming the interest of CNIC researchers in translating their laboratory results into technologies for transfer to clinical practice and the market. The culture of innovation at the CNIC has encouraged several researchers who had not previously filed a patent application to approach the Technology Transfer Office in order to study the patentability of their inventions.

Fourteen new invention disclosures were assessed in 2013, and five of these were filed as priority applications. In addition, five priority applications were extended to PCT and one PCT application was extended to the EPO (to be filed in February 2014).

The CNIC portfolio currently includes 16 active patent families at various stages. This includes the five new applications filed in 2013 (Figure 2), and seven that are shared with other institutions.

Figure 1. New invention disclosures assessed & filed

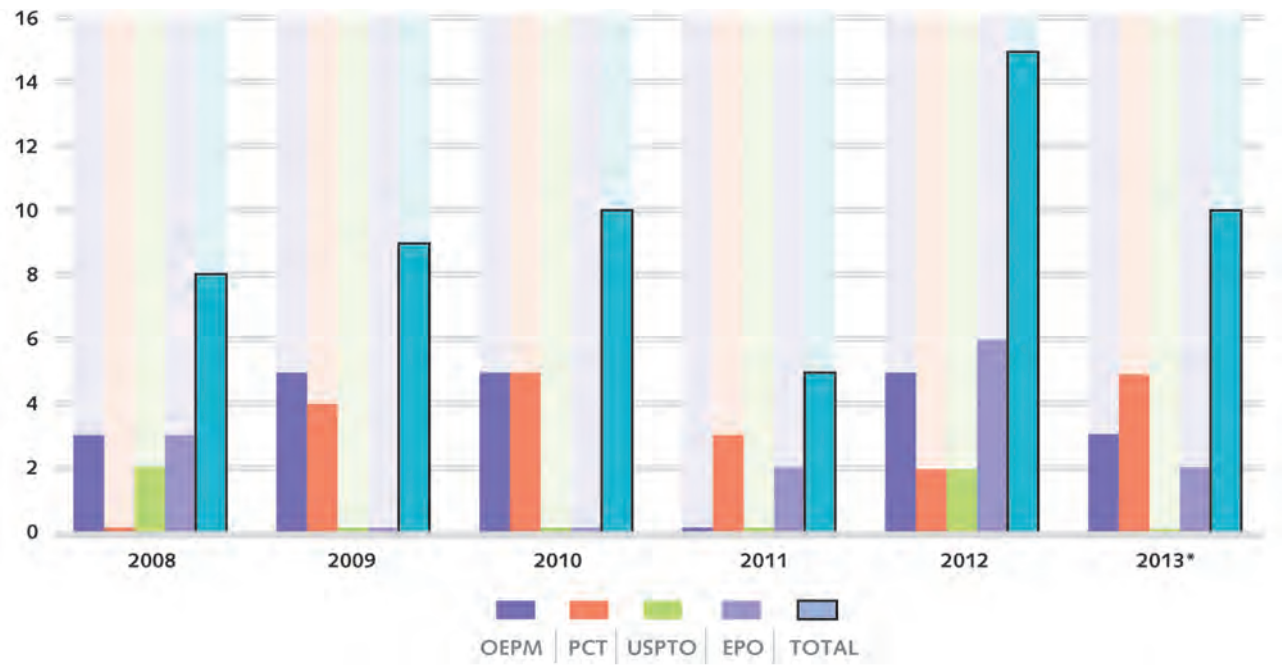


Figure 2. Types of applications filed in the last five years. OEPM: Oficina Española de Patentes y Marcas. PCT: Patent Cooperation Treaty: under a PCT, an "international application" can be filed in several offices; we normally use the EPO or OEPM. USPTO: United States Patents and Trademarks Office. EPO: European Patent Office.

In 2013 we also licensed three new inventions and assigned another (to the inventors). We are also working on new procedures and policies, to be implemented in 2014, to support the development of spin-offs.

2.2.- Research Cooperation:

2.2.1.- Research Cooperation Agreements (RCAs)

Five new RCAs were signed in 2013 with different companies and academic institutions, and another two are scheduled for the first trimester of 2014.

2.2.2.- Material Transfer Agreements (MTAs) and Confidential Disclosure Agreements (CDAs)

In 2013 we signed 67 MTAs and 20 new CDAs (also called non-disclosure agreements: NDAs).

3.- Projects Office

The Projects Office (PO) promotes the CNIC's research activity by facilitating access to external sources of funding. A major task of the PO is thus to supply CNIC staff with tailored, up-to-date information about public and private sources of funding for research, including grants, contracts, research projects, scientific infrastructure, etc. The PO also helps with the organization, preparation and processing of funding proposals, administers grants and other funding awarded to CNIC personnel, and prepares and processes proposals for core CNIC funding and one-off calls.

The CNIC's success in securing competitive funding is summarized in the Appendix.

In addition to the funding listed in the Annex, the PO has also been working on two applications related to the CNIC's Advanced Imaging Unit. One is aimed at securing Spanish government accreditation for ICTS (*Infraestructura Científica y Técnica Singular*); the results will be published in the first trimester of 2014. The second is the preparatory phase of the EC-funded Eurobioimaging Project.

In addition to the funding listed in the Annex, the PO has also been working on two applications related to the CNIC's Advanced Imaging Unit. One is aimed at obtaining Spanish government accreditation for ICTS (*Infraestructura Científica y Técnica Singular*); the results will be published in the first trimester of 2014. The second is the preparatory phase of the pan?European Eurobioimaging infrastructure project, on the European Strategy Forum on Research Infrastructures (ESFRI) roadmap.

4.- Biobank

The CNIC Biobank (CB_b) was created and began to collect samples in 2012. The CBb facilities have the capacity to securely store more than 200,000 independent human samples at -80ºC and around 25,000 in liquid nitrogen. The CB_b is currently the main repository for samples collected in the longitudinal PESA study (Progression of Early Subclinical Atherosclerosis), and also holds a backup collection for the AWHS (Aragon Workers Health Study). The CBb currently holds 25,922 samples, including whole blood, serum, plasma, buffy coats, DNA, RNA (PAXgene tubes), and urine.

The CB_b has completed the documentation for certification as an official biobank under current national regulations (*Ley 14/2007 de Investigación biomedical y Real Decreto 1716/2011 de Biobancos*).

5.- Translational Research & Epidemiology

The Translational Platform works closely with the CNIC's clinical researchers and leads some of Center's population studies. For further information, see the Atherothrombosis, Imaging and Epidemiology Department.

Platform Staff

PLATFORM COORDINATOR:
Antonio Bernad

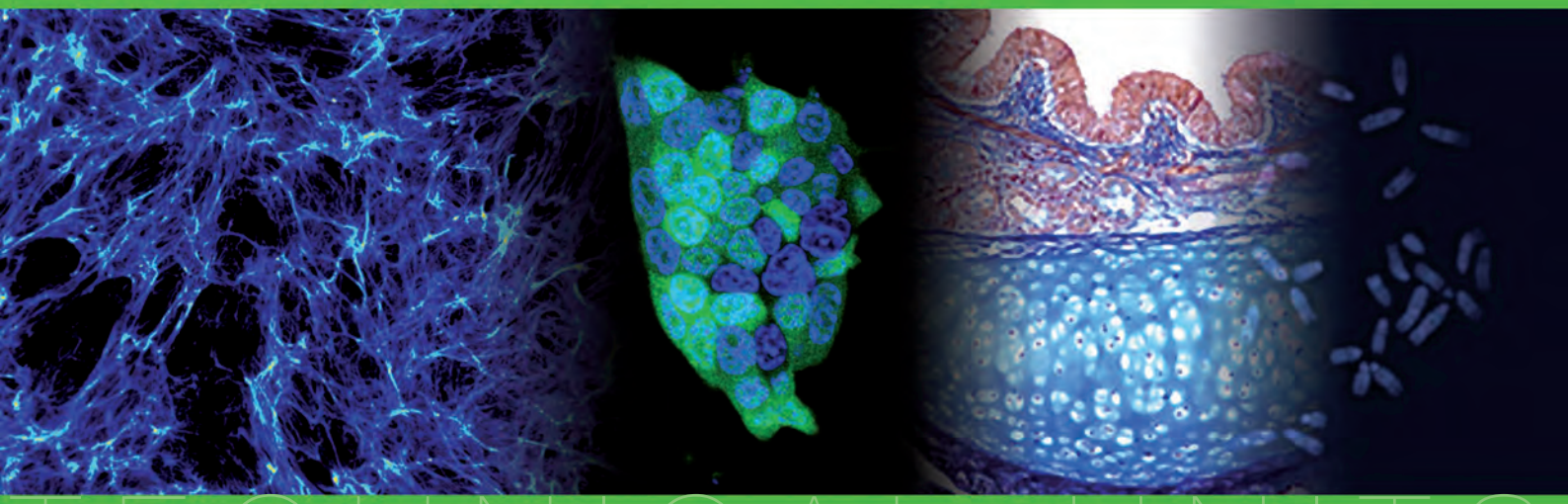
HEAD OF PROJECT OFFICE AND TECHNOLOGY TRANSFER AREA:
Luzma García

PROJECT OFFICE AND TECHNOLOGY TRANSFER AREA:
Noelia López (TTO – IPR & TT Manager)
Candelas Carreiro (TTO – National Projects Manager)
Marta Abelleira (TTO – International Projects Manager)

TECHNOLOGY DEVELOPMENT GROUP:
Ricardo Ponce (CBb. Senior Technician)

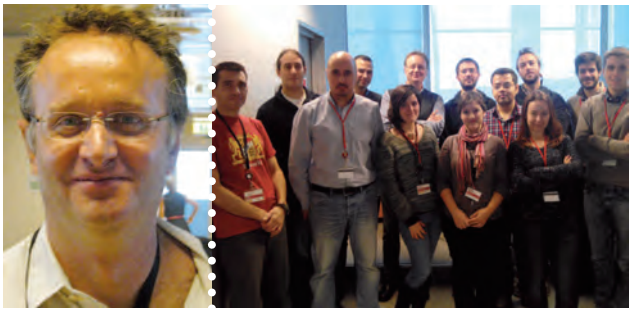
TRANSLATIONAL RESEARCH & EPIDEMIOLOGY
Laura García (Project Manager)

ADMINISTRATIVE SUPPORT:
Piedad Fernández



TECHNICAL UNITS

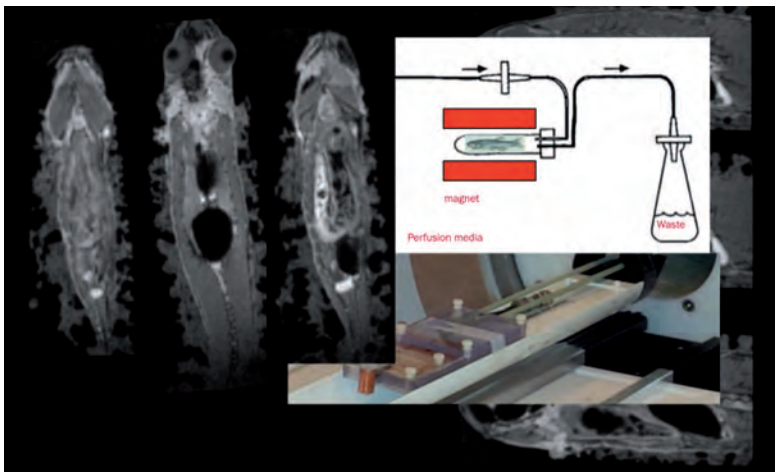
Advanced Imaging



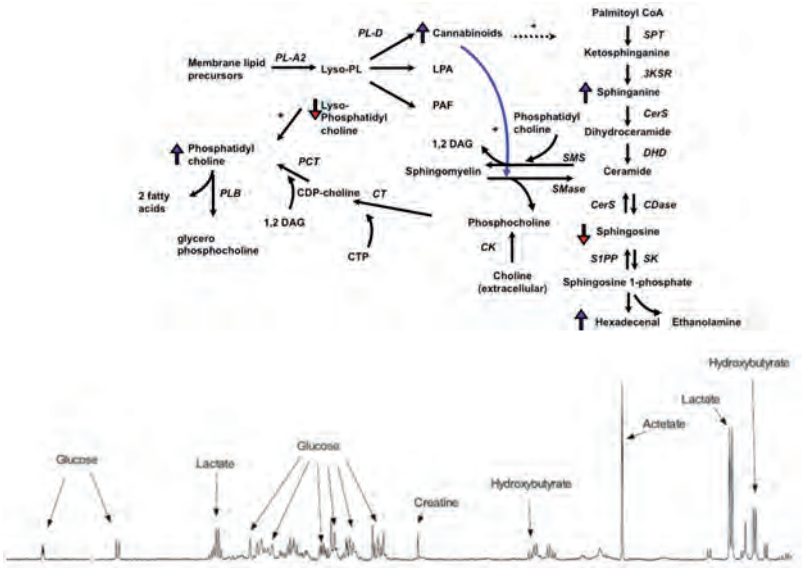
Head of Unit:	Dr. Jesús Ruiz-Cabello Osuna
Postdoctoral Researchers:	Fernando Herranz Rabanal Jesús Mateo de Castro Samuel España Palomares
Predoctoral Researchers:	Ana Victoria Lechuga Vieco Hugo Groult Juan Pellico Sáez Riju Bhavesh Nils Dennis Nothnagel
Technicians:	Izaskun Bilbao Luri Marina Benito Vicente
CardioImage Fellows:	Carlos Pérez Medina Jose Manuel Pérez Sánchez
Res@CNIC Fellows	Alberto Ullate de la Torre Jorge Sanz Sánchez Juan Carlos Gomez Polo David Cordero Pereda
Visiting Scientists:	Ignacio Rodríguez Ramírez de Arellano Palmira Villa Valverde Juan Manuel García-Segura Marco Filice Sandra Pérez Rial

Research Interest

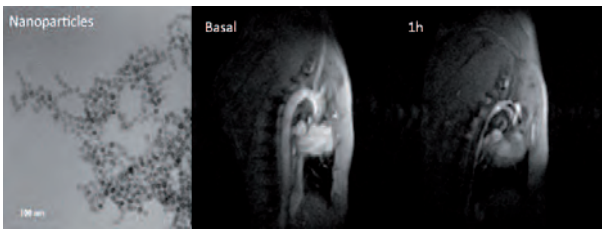
The Advanced Imaging Unit (AIU), established early in 2012, is a multidisciplinary group focused on the development of new imaging applications and tools that will expand molecular and cellular knowledge of cardiovascular disease. The AIU conducts research and provides services in cardiovascular imaging, nanomedicine and radiochemistry, and metabolomics. The cardiovascular imaging technology offered by the AIU is state-of-the-art and encompasses five modalities: MRI, X-ray CT, nuclear imaging (PET), ultrasound (echocardiography) and optical (two and three-dimensional luminescence and fluorescence). For the nanomedicine program, the AIU has a dedicated nanotechnology and organic chemistry laboratory in which we develop new nanoparticles, molecular probes and biofunctionalization techniques for the diagnosis and treatment of cardiovascular diseases. The unit currently produces multifunctional nanoparticles for all imaging techniques available at the CNIC—for example, iron oxide, liposomes, upconverting nanophosphors and gold nanoparticles—all of them functionalized by combination with specific cardiovascular biomarkers. Additionally, a new radiochemistry laboratory is now fully operational for work with ^{68}Ga, and capacity for ^{89}Zr will come on line early in 2014. This facility provides the Center with specific PET radiotracers for cardiovascular nuclear imaging. Finally, the unit also has a long experience in the application of metabolic analysis to the study of different pathologies, by the use of Magnetic Resonance Spectroscopy and Mass Spectrometry and different statistical tools developed within the group. Our research projects range from technical developments and chemistry advances to in vitro studies and tracking of biological processes *in vivo*.



High resolution MRI of zebrafish. These images were acquired with a specifically designed perfusion system and a customized radiofrequency coil.



Representative aliphatic portion of the ^{1}H-NMR spectrum of bronchoalveolar fluid samples and representation of membrane lipid metabolism affected after an inflammatory challenge.



Iron oxide nanoparticles for selective accumulation in atherosclerosis plaque in a mouse model

Major Grants

- **European Commission FP7-PEOPLE-2010-ITN (CIBERES 264864) (NO CNIC)**
- **European Commission FP7-PEOPLE-2013-ITN (CardioNext PITN-GA-2013-608027)**
- **Fundació La Marató TV3 (70/C/2012) PI WP2, Borja Ibañez Colaborador Jesus Ruiz Cabello**
- **Ministerio de Economía y Competitividad (SAF2011-25445) PI, Ignacio Rodriguez Ramirez de Arellano (UCM- NO CNIC) - Colaborador Jesus Ruiz Cabello**

Selected Publications

Bujak R, García-Alvárez A, Rupérez FJ, Nuño-Ayala M, García A, Ruiz-Cabello J, Fuster V, Ibañez B, Barbas C. **Metabolomics reveals metabolite changes in acute pulmonary embolism**. *J Proteome Res* (accepted)

Izquierdo-García JL, Naz S, Nin N, Rojas Y, Erazo M, Martínez-Caro L, García A, de Paula M, Fernández-Segoviano P, Casals C, Esteban A, Ruiz-Cabello J, Barbas C, Lorente JA. **A metabolomic approach to the pathogenesis of ventilator-induced lung injury**. *Anesthesiology* [Epub ahead of print]

Ferrarini A, Rupérez FJ, Erazo M, Martínez MP, Villar-Álvarez F, Peces-Barba G, González-Mangado N, Troncoso MF, Ruiz-Cabello J, Barbas C. **Fingerprinting-based metabolomic approach with LC-MS to sleep apnea and hypopnea syndrome: a pilot study**. *Electrophoresis.* (2013) 34: 2873-81

Bini J, Izquierdo-García D, Mateo J, Machac J, Narula J, Fuster V, Fayad ZA. **Preclinical evaluation of MR attenuation correction versus CT attenuation correction on a sequential whole-body MR/PET scanner**. *Invest Radiol* (2013) 48: 313-22

Ruiz A, Salas G, Calero Y, Hernández Y, Villanueva A, Herranz F, Veintemillas-Verdaguer S, Martínez E, Barber DF, Morales MP. **Short-chain PEG molecular strongly bound to magnetic nanoparticle for MRI long circulating agents**. *Acta Biomaterialia* (2013), 9: 6421-30

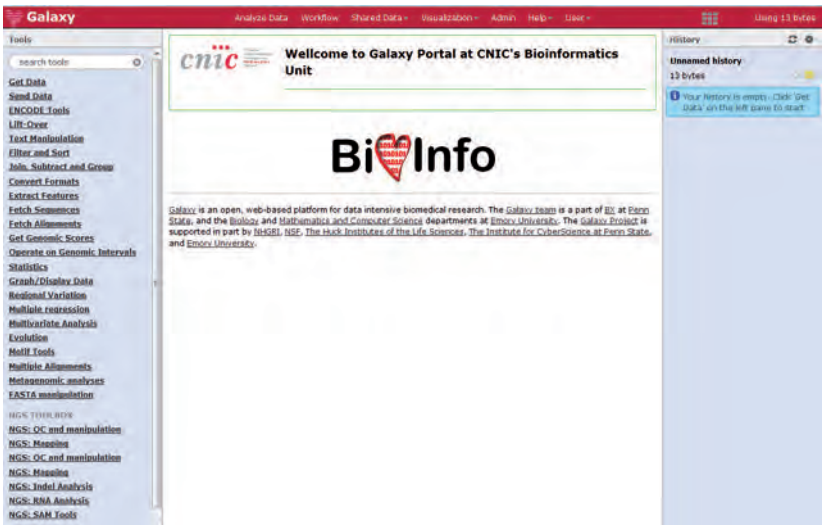
Bioinformatics

Head of Unit: Fernando Martínez

Support Scientists: Fátima Sánchez Cabo
Carlos Torroja
Manuel José Gómez Rodríguez

Research Interest

The CNIC Bioinformatics Unit was established in the last quarter of 2010. The main goal of the Unit is to establish a collaborative environment within which to contribute to CNIC research projects, thereby providing CNIC researchers with ad-hoc, state-of-the-art bioinformatics and computational biology solutions to support and enhance their research.



Main page of the CNIC Bioinformatics Unit's Galaxy Portal

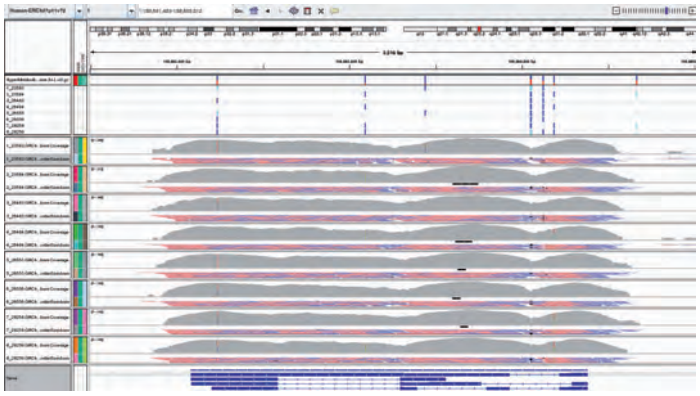
The Bioinformatics Unit has established four main support channels:

1. Standardized data analysis methods and ad-hoc solutions. The Unit focuses on the analysis and interpretation of high-throughput biological data from CNIC research projects, with special emphasis on next generation sequencing data. One of the Unit's main aims is to develop and implement analysis pipelines using state-of-the-art algorithms specific for each type of data.

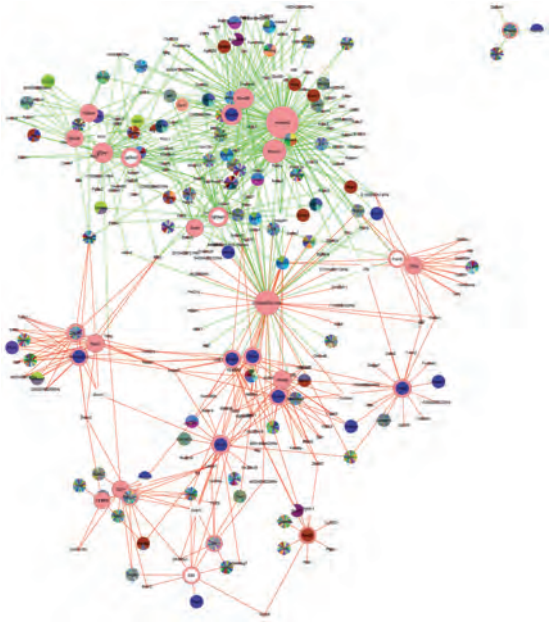
   2.Web-based analysis tools. The Unit aims to locally implement genome-related software (for example, genomics browsers such as GBrowse) and makes its standardized analysis tools and implemented pipelines available to researchers through a user-friendly web-based interface (the CNIC Galaxy server, in development) so that they can conduct their own analysis if desired.

3. Advice and training. The Unit also provides customized advice and training to CNIC researchers in the analysis and interpretation of their experimental data. We have implemented four training modules through the year to help scientists learn how to analyze their data and understand the results.

4. Support and guidelines for PhD students. New high-throughput technologies are now becoming affordable for most labs, and CNIC researchers are aware that their labs now need not only wet-lab researchers but also computational biology researchers. The Unit therefore contributes support and guidance to new PhD students working on boinformatics projects in CNIC groups.



IGV caption of a C-reactive protein region in an Exome-Seq of 8 members of a family with a history of hypermetabolism, analyzed with the GATK Variation Analysis Pipeline.



Reconstruction of the regulatory network of alternative splicing in fibroblasts. The nodes are colored according to Gene Ontology enrichment terms.

Selected Publications

Aguilera-Montilla N, Chamorro S, Nieto C, Sanchez-Cabo F, Dopazo A, Fernandez-Salguero PM, Rodriguez-Fernandez JL, Pello OM, Andres V, Cuenda A, Alonso B, Dominguez-Soto A, Sanchez-Ramon S and Corbi AL. **Aryl hydrocarbon receptor contributes to the MEK/ERK-dependent maintenance of the immature state of human dendritic cells**. *Blood* (2013) 121: e108-17

Penkov D, San Martin DM, Fernandez-Diaz LC, Rossello CA, Torroja C, Sanchez-Cabo F, Warnatz HJ, Sultan M, Yaspo ML, Gabrieli A, Tkachuk V, Brendolan A, Blasi F and Torres M. **Analysis of the DNA-binding profile and function of TALE homeoproteins reveals their specialization and specific interactions with Hox genes/proteins**. *Cell Rep* (2013) 3: 1321-33

Villarroya-Beltri C, Gutierrez-Vazquez C, Sanchez-Cabo F, Perez-Hernandez D, Vazquez J, Martin-Cofreces N, Martinez-Herrera DJ, Pascual-Montano A, Mittelbrunn M and Sanchez-Madrid F. **Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs**. *Nat Commun* (2013) 4: 2980

Luxan G, Casanova JC, Martinez-Poveda B, Prados B, D'Amato G, Macgrogan D, Gonzalez-Rajal A, Dobarro D, Torroja C, Martinez F, Izquierdo-Garcia JL, Fernandez-Friera L, Sabater-Molina M, Kong YY, Pizarro G, Ibanez B, Medrano C, Garcia-Pavia P, Gimeno JR, Monserrat L, Jimenez-Borreguero LJ and de la Pompa JL. **Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy**. *Nat Med* (2013) 19: 193-201

Howe K, Clark MD, Torroja CF, Torrance J, Berthelot C, Muffato M, Collins JE, Humphray S, McLaren K, Matthews L, McLaren S, Sealy I, Caccamo M, Churcher C, Scott C, Barrett JC, Koch R, Rauch GJ, White S, Chow W, Kilian B, Quintais LT, Guerra-Assuncao JA, Zhou Y, Gu Y, Yen J, Vogel JH, Eyre T, Redmond S, Banerjee R, Chi J, Fu B, Langley E, Maguire SF, Laird GK, Lloyd D, Kenyon E, Donaldson S, Sehra H, Almeida-King J, Loveland J, Trevanion S, Jones M, Quail M, Willey D, Hunt A, Burton J, Sims S, McLay K, Plumb B, Davis J, Clee C, Oliver K, Clark R, Riddle C, Eliott D, Threadgold G, Harden G, Ware D, Mortimer B, Kerry G, Heath P, Phillimore B, Tracey A, Corby N, Dunn M, Johnson C, Wood J, Clark S, Pelan S, Griffiths G, Smith M, Glithero R, Howden P, Barker N, Stevens C, Harley J, Holt K, Panagiotidis G, Lovell J, Beasley H, Henderson C, Gordon D, Auger K, Wright D, Collins J, Raisen C, Dyer L, Leung K, Robertson L, Ambridge K, Leongamornlert D, McGuire S, Gilderthorp R, Griffiths C, Manthravadi D, Nichol S, Barker G, Whitehead S, Kay M, Brown J, Murnane C, Gray E, Humphries M, Sycamore N, Barker D, Saunders D, Wallis J, Babbage A, Hammond S, Mashreghi-Mohammadi M, Barr L, Martin S, Wray P, Ellington A, Matthews N, Ellwood M, Woodmansey R, Clark G, Cooper J, Tromans A, Grafham D, Skuce C, Pandian R, Andrews R, Harrison E, Kimberley A, Garnett J, Fosker N, Hall R, Garner P, Kelly D, Bird C, Palmer S, Gehring I, Berger A, Dooley CM, Ersan-Urun Z, Eser C, Geiger H, Geisler M, Karotki L, Kirn A, Konantz J, Konantz M, Oberlander M, Rudolph-Geiger S, Teucke M, Osoegawa K, Zhu B, Rapp A, Widaa S, Langford C, Yang F, Carter NP, Harrow J, Ning Z, Herrero J, Searle SM, Enright A, Geisler R, Plasterk RH, Lee C, Westerfield M, de Jong PJ, Zon LI, Postlethwait JH, Nusslein-Volhard C, Hubbard TJ, Crollius HR, Rogers J and Stemple DL. **The zebrafish reference genome sequence and its relationship to the human genome**. *Nature* (2013) 469: 498-503

Cellomics

Head of Unit: María Montoya
Support Scientists: Jose Manuel Ligos, Hind Azegrouz, Gopal Karemore
Technicians: Raquel Nieto, Mariano Vitón, Irene Palacios Doiztua

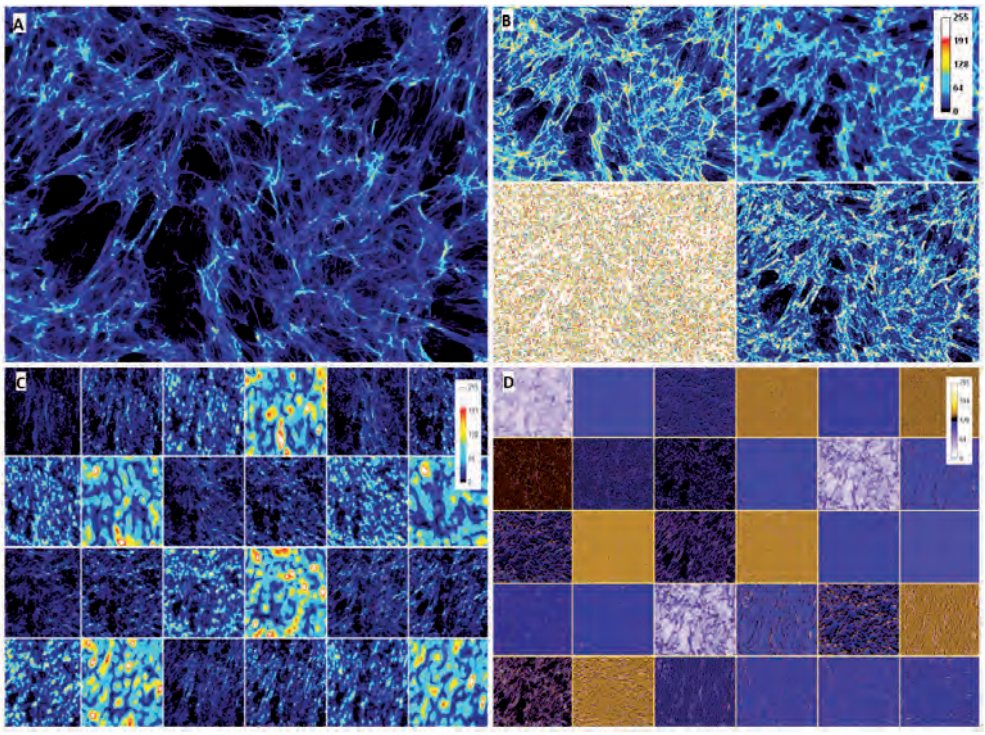
Research Interest

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.

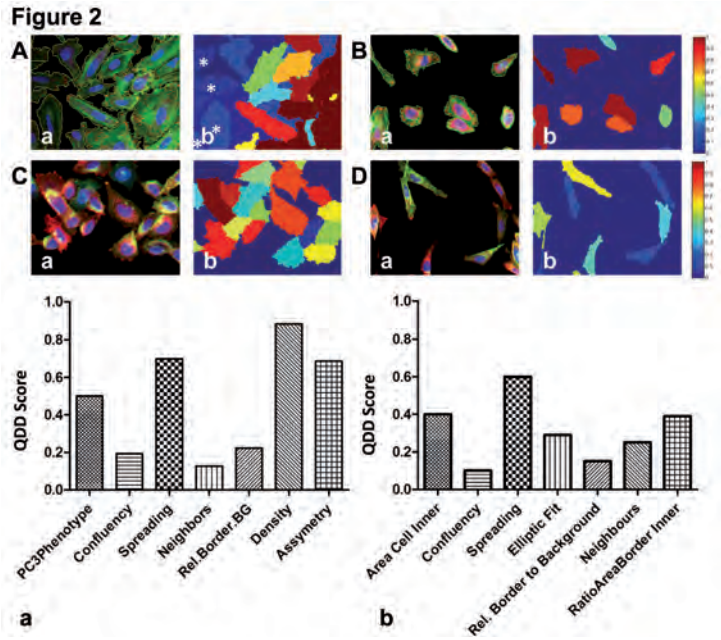
The Unit has expanded its flow-sorting capabilities with the acquisition of a dual Sy3200 cell sorter (SonyBiotechnology), allowing sorting of samples that require BSL2 biosecurity. The FACSAria Cell sorter has been upgraded with a 405nm laser for exciting new-generation fluorochromes (Brilliant Violet, Qdots, eFluor NanoCristal, etc.) expanding its multiparametric capacity. This allows the excitation of new violet fluorochormes and sorting of rare populations identified by the presence of a large number of markers such as hematopoietic precursors obtained from mice expressing fluorescent proteins.

The confocal-HCS-dedicated microplate reader has been updated with brightfield capability based on digital phase contrast and a 4x magnification air objective for whole-well imaging of small animals (zebrafish embryos) and optimized detection of rare events. The Unit has developed an assay for the quantification of extracellular matrix organization (Figure 1) which is being moved into the screening phase.

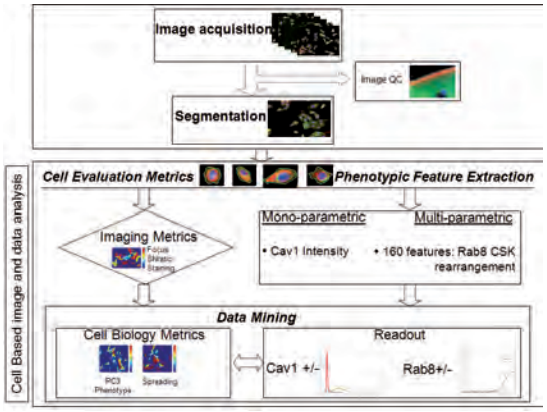
The Unit also conducts research into HCS image and data analysis bioinformatics tools (Azegrouz et al 2013). A suite of cell-based metrics was developed to either filter HCS data in a cell-specific manner (imaging metrics) or evaluate biologically relevant cell characteristics (cell biology metrics) to stratify cellular data in homogeneous cell subpopulations (Figure 2). These metrics were implemented in a novel exploratory HCS data analysis pipeline (Figure 3) that was shown to improve assay robustness in HCS assay development and optimization.



***Quantitative assessment of collagen fiber orientations and patterns by advanced image analysis**. A) Confocal image of collagen fiber organization, courtesy of the Integrin Signaling group. B) Projecting input image into various texture subspaces: coherence enhancing diffusion space, edge enhancing diffusion space, Hessian space, Laplacian space. C) Input image projected into Gabor space formed by six bands of four orientations in a Fourier domain. D) Input image projected onto Gaussian derivative space, commonly called "n-JET" space. n-JET space is formed by various combinations of derivatives with respect to the x and y coordinates of the input image frame. Derivatives are taken up to order of degree three after Gaussian smoothing with four different scales.*



Influence of cell evaluation metrics on screen readouts. A, B)*: Left panels (a) are confocal fluorescence images of Hela cells stained with Hoechst (blue), phalloidin (green) and anti-vinculin (red). Right panels (b) show pseudocolor image representations of* Focus Ab) and Spreading Bb) *metric values.* ***(C,D)*** *Left panels (a) show confocal images of PC3 cells stained with Hoechst (blue), anti-B1 integrin (red) and anti-CAV1 (green). Right panels (b) show pseudocolor image representations of* PC3 phenotype *metric values.* ***(E)*** *Quantile-dependent deviation (QDD) of (a) classification output of Hela CSK rearrangement assay and b) caveolin intensity.*



Outline of the image and data processing pipeline*. Screening images are acquired and quality checked to discard outliers. Segmentation then identifies cells as individual entities for further analysis. At the cellular level, feature sets are extracted as evaluators, among which are imaging and cell-biology metrics. Phenotypic features of the monoparametric (CAV1) and multiparametric (RAB8A CSK rearrangement) assays are extracted at the cellular level to obtain assay readouts. Imaging metrics are used as filtering criteria to remove poorly imaged cells, and cell-biology evaluators are used to data mine the screen readout.*

Selected Publications

Azegrouz H, Karemore G, Torres A, Alaíz CM, Gonzalez AM, Nevado P, Salmerón A, Pellinen T, del Pozo MA, Dorronsoro JR, and Montoya MC. **Cell-based fuzzy metrics enhance High Content Screening (HCS) assay robustness**. J. Biomol Screen. 2013. 18(10):1270-83

Echarri A, Muriel O, Pavon DM, Azegrouz H, Escolar F, Terron MC, Sanchez-Cabo F, Martinez F, Montoya MC, Llorca O, Del Pozo MA. **Caveolar domain organization and trafficking is regulated by Abl kinases and mDia1**. *J Cell Sci* (2012) 125: 3097-113

Hidalgo I, Herrera-Merchan A, Ligos JM, Carramolino L, Nunez J, Martinez F, Dominguez O, Gonzalez S. **Ezh1 is required for hematopoietic stem cell maintenance and prevents senescence-like cell cycle arrest**. *Cell Stem Cell* (2012) 11: 649-62

Herrera-Merchan A, Arranz L, Ligos JM, de Molina A, Dominguez O, Gonzalez S. **Ectopic expression of the histone methyltransferase Ezh2 in haematopoietic stem cells causes myeloproliferative disease**. *Nat Commun* (2012) V3: doi:10.1038/ncomms1623

Arranz L, Herrera-Merchan A, Ligos JM, de Molina A, Dominguez O, Gonzalez S. **Bmi1 is critical to prevent Ikaros-mediated lymphoid priming in hematopoietic stem cells**. *Cell Cycle* (2012) 11: 65-78

Comparative Medicine

The Comparative Medicine Unit supports in vivo work at the CNIC, and is organized into five core work areas.

- Animal Husbandry. This area is staffed by dedicated animal technicians, managers and veterinarians who take charge of the daily husbandry and welfare of animals. We have implemented conditions for environmental enrichment to improve the welfare of animals.

- The 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 scanner 3001 and general support to CNIC researchers with phenotyping and histopathological evaluation of their animal models.

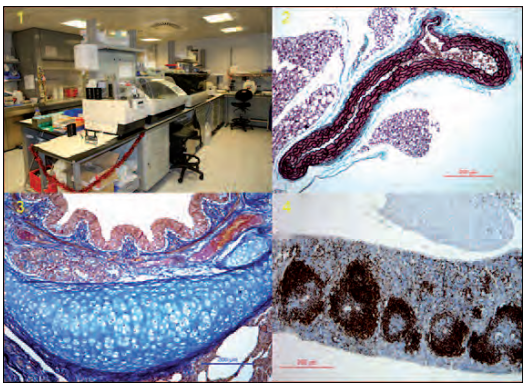
- The Phenotyping Core (PhC) is involved in the development of standardized protocols for cardiovascular phenotyping of different species. The clinical pathology service has adapted several of the well established technologies utilized in human biomedical science to overcome the challenges involved in working with a variety of species, for example the small sample volumes obtained from mice.

- The Veterinary Medicine and Experimental Surgery Core (VMESC) provides highly specialized expertise in animal medical problems, disease follow-up, surgical procedures, minimally invasive intervention, and life support. The VMESC is run by two clinical veterinarians with extensive expertise in anesthesia of small and large animals and four veterinary asistants.

- The Quality Control Core (QCC). Each quarter, health screens are performed in an external laboratory of proven reliability to monitor the health of the animals. The QCC produces a FELASA report.

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

Hematology analyzer



1. Histopathology laboratory, 2. Mouse aorta stained with Masson's Trichrome and Elastic Van Gieson stains, 3. Acid Fuchsin Orange G staining of a pig bronchium, 4. Immunostaining of the CD3 marker in a mouse spleen.

Clinical biochemistry analyzer

Genomics

Head of Unit: Ana Dopazo
Support Scientists: Sergio Callejas, Alberto Benguría
Technician: Rebeca Álvarez

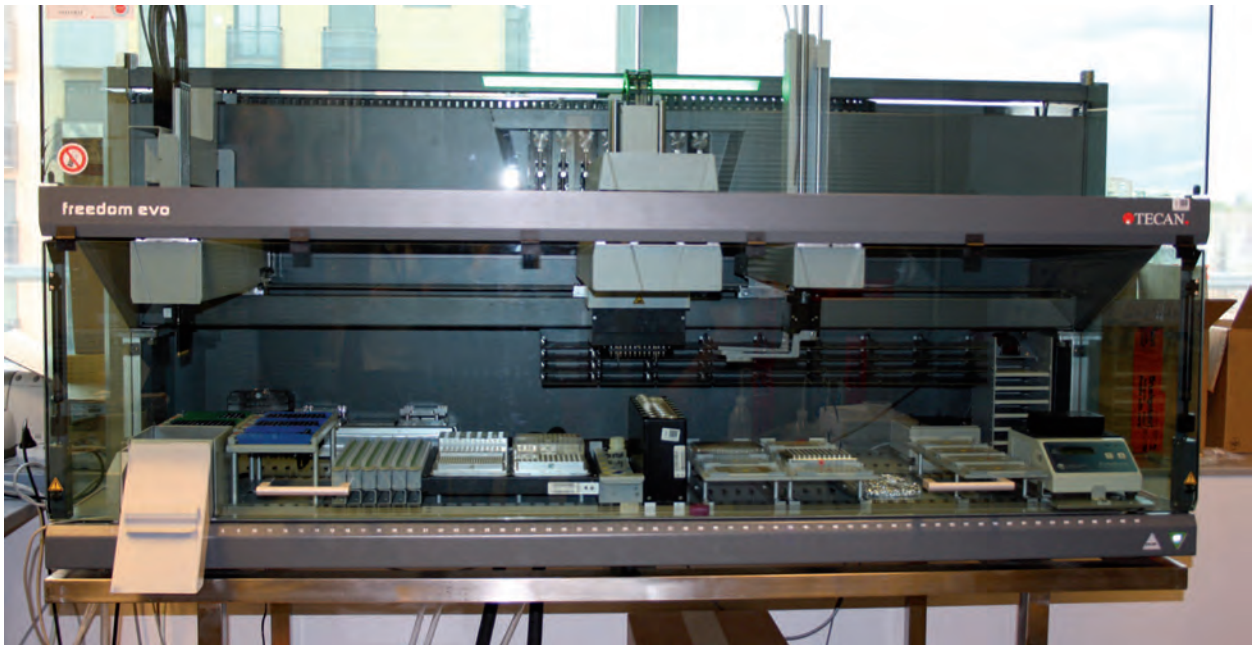
Research Interest

The Genomics Unit focuses its efforts on the use of second generation sequencing (NGS) technologies for genome analysis by means of an Illumina Genome Analyzer IIx sequencer.

The Unit provides these cutting-edge genomic technologies to the scientific community at the CNIC and beyond, offering NGS applications including RNA Seq, small RNA-Seq, ChIP Seq and PCR Seq. The Unit's capabilities expanded in 2013 to incorporate new NGS applications for Exome Analysis and solutions for targeted resequencing. On each sequencing project the Unit's tasks include project consultation, sample quality check, sample library preparation and data generation.

The team continues to improve methods for low-input RNA Seq applications, in which RNA Seq can be performed from very tiny amounts of starting biological material or even directly from cells. Using an open liquid handling platform, the Unit also continues to develop informatics applications that allow the automation of the different Illumina-NGS steps. By progressively automating the time-consuming processes of an NGS experiment, the Unit has considerably speeded up the throughput of NGS library preparation, avoiding the bottleneck created by the high sample number typically included in a single sequencing run and, additionally, reducing the risk of human error during this step.

On request, the Unit continues to offer microarray analysis services using Agilent and Affymetrix microarray platforms. The most demanded microarray-based application in 2013 was microRNA expression profiling, because the amount of starting RNA needed is considerably smaller using microarrays than using NGS. Other services include the maintenance and management of real-time PCR instruments (one AB 7000 and two ABI 7900HT machines) and a TaqMan array processing service.



Liquid handling platform used for the automation of Illumina-NGS steps

Major Grants

- Ministerio de Economía y Competitividad. FIS (PI10/01124)

Selected Publications

Rallon NI, Lopez-Fernandez LA, Garcia MI, Benguría A, Fiorante S, Soriano V, Benito JM **Interferon-stimulated genes are associated with peginterferon/ribavirin treatment response regardless of IL28B alleles in hepatitis C virus/HIV-coinfected patients**. AIDS (2013) 27: 687-96

Estrada JC, Torres Y, Benguría A, Dopazo A, Roche E, Carrera-Quintanar L, Pérez RA, Enríquez JA, Torres R, Ramírez JC, Samper E, Bernad A. **Human mesenchymal stem cell-replicative senescence and oxidative stress are closely linked to aneuploidy**. *Cell Death Dis* (2013) 4:e691

Trigueros-Motos L, González-Granado JM, Cheung C, Fernández P, Sánchez-Cabo F, Dopazo A, Sinha S, Andrés V. **Embryological-Origin-Dependent Differences in Homeobox Expression in Adult Aorta: Role in Regional Phenotypic Variability and Regulation of NF-κB Activity**. *Arterioscler Thromb Vasc Biol* (2013) 33:1248-56

Aguilera-Montilla N, Chamorro S, Nieto C, Sánchez-Cabo F, Dopazo A, Fernández-Salguero PM, Rodríguez-Fernández JL, Pello OM, Andrés V, Cuenda A, Alonso B, Domínguez-Soto A, Sánchez-Ramón S, Corbi AL. **Aryl hydrocarbon receptor contributes to the MEK/ERK-dependent maintenance of the immature state of human dendritic cells**. *Blood* (2013) 121:e108-17

Bhardwaj D, Nager M, Camats J, David M, Benguria A, Dopazo A, Canti C and Herreros J. **Chemokines induce axon outgrowth downstream of Hepatocyte Growth Factor and TCF/beta-catenin signaling**. *Front Cell Neurosci* (2013) 7: 52

Microscopy and Dynamic Imaging

Head of Unit: Valeria R. Caiolfa

Support Scientists: Moreno Zamai
Antonio Manuel Santos Beneit
Elvira Arza
Susana Sanchez Donoso

Postdoctoral Researchers Andrea Orsi
Antonio Trullo
Valeria Corti

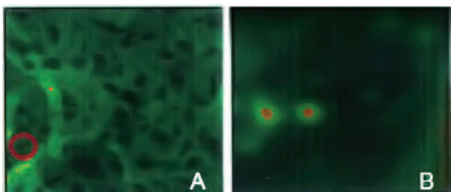
Research Interest

The Unit houses a large number of state-of-art bright-field, wide-field and confocal microscopes that are fully equipped for multicolor immunofluorescence and for a variety of live-cell and in-tissue applications. The Unit's capabilities also include two multiphoton platforms for live cells and in vivo imaging studies. The Unit has developed many customized applications, including dedicated software routines for very large image tiling, cell tracking, shape recognition and 3D-multicolor rendering applied to thick tissues and model organisms such as mouse and zebrafish. The Unit is also strongly committed to technological innovation and development of new applications of interest to scientists at the CNIC and beyond.

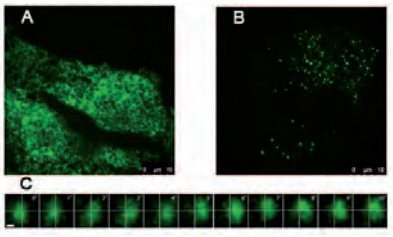
Ongoing research collaborations with all CNIC Departments and a number of external groups have led to the submission of three joint grant applications in 2013. In collaboration with the Advanced Imaging Unit, we have continued the study of a new class of nanoscale carriers based on albumin-coated upconverting nanophosphors (UCNPs). These nanoparticles have the unique feature of converting low energy near infrared (NIR) light into higher visible light and/or NIR emission, thereby overcoming the typical problems of fluorescent probes (autofluorescence, low penetration depth, photobleaching, high costs and toxicity). UCNPs can also be used as probes in magnetic resonance imaging studies (Figure 1).

We have also begun a new research program on the unfolded protein response (UPR) and cellular stress, studying the UPR sensors IRE1 and PERK, which signal ER stress by forming clusters. We have developed visualization tools to monitor UPR sensor clustering, and have perfected a protocol for fluorescence fluctuation imaging (TIRFM-Number & Brightness) to assess stoichiometry and dynamics of clustering/aggregation in vivo, enabling us to determine how stress-driven clustering of IRE1 and PERK is coordinated at the single molecule level (Figure 2).

The Unit provides daily individual training to all users, and Unit staff members participate actively in the ongoing CNIC-JOVEN training plan (ACERCATE, CICERONE and the Masters Program) through the provision of theoretical and practical sessions. In partnership with Carl Zeiss Microscopy S.L., the Unit has organized the 1st Course on Microscopy and Advanced Application that has registered more than 65 participants from Spain and abroad, who attend a total of 6 days of lectures and hands-on sessions at the CNIC.



***Detection of nanoparticles accumulated in lung alveoli**. Multiphoton fluorescence images of stained 7-micron-thick lung tissue from healthy female Balb/c mice i.v. injected with UCNP particles. (A) Low-magnification view of the alveolar structure; (B) High-magnification view of the circled region in A, showing nanoparticles inside a single alveolus. Excitation was at 995 nm and the emission was collected at 610/50 nm (tissue) and 460/54 nm (UCNPs).*



***Cell stress kinetics tracked by IRE1 clustering in the endoplasmic reticulum**. (A) N&B analysis shows that in unstressed cells IRE1 is mostly monomeric. (B) In response to ER stress signals, IRE1 forms clusters. (C) Sub-clusters of at least dimeric nature are mobile with respect to each other. IRE1 was expressed in Hela cells under the Tet promoter. Tail Anchor (TA) was used to target the protein to the ER. TIRF images were taken at 150 nm depth.*

Selected Publications

Trullo A, Corti V, Arza E, Caiolfa VR, Zamai M, **Application limits and data correction in number of molecules and brightness analysis**. *Microsc Res Tech* (2013) 76: 1135-46

Rocha-Perugini V, Zamai M, Gonzalez-Granado JM, Barreiro O, Tejera E, Yanez-Mo M, Caiolfa VR, Sanchez-Madrid F,.**CD81 controls sustained T cell activation signaling and defines the maturation stages of cognate immunological synapses**. *Mol Cell Biol* (2013) 33: 3644-58

Mendez-Barbero N, Esteban V, Villahoz S, Escolano A, Urso K, Alfranca A, Rodriguez C, Sanchez SA, Osawa T, Andres V, Martinez-Gonzalez J, Minami T, Redondo JM, CampaneroMR. **A major role for RCAN1 in atherosclerosis progression**. *EMBO Mol Med* (2013) 5: 1901-17

Quintana-Bustamante O, Grueso E, Garcia-Escudero R, Arza E, Alvarez-Barrientos A, Fabregat I, Garcia-Bravo M, Meza NW, Segovia JC. **Cell fusion reprogramming leads to a specific hepatic expression pattern during mouse bone marrow derived hepatocyte formation in vivo**. *PloS One* (2012) 7: e33945

Aguilar LF, Pino JA, Soto-Arriaza MA, Cuevas FJ, Sanchez S, Sotomayor CP. **Differential dynamic and structural behavior of lipid-cholesterol domains in model membranes**. *PloS One* (2012) 7: e40254

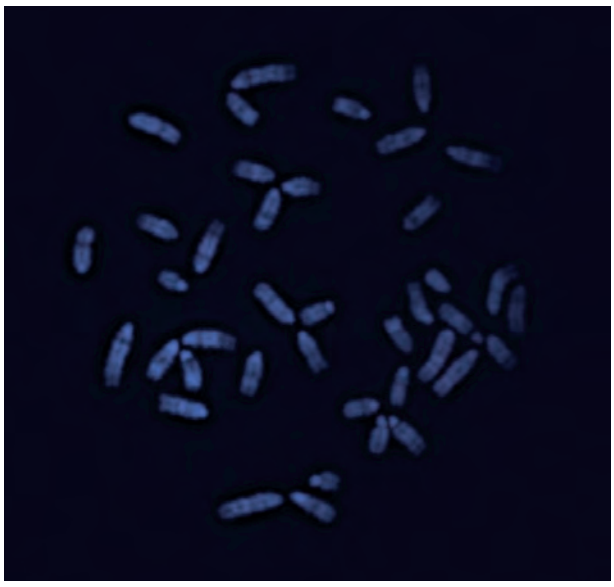
Pluripotent Cell Technology

Head of Unit: Giovanna Giovinazzo
Support Scientists: Francisco Gutierrez
Elisa Santos
Technician: María Ángeles Sanguino

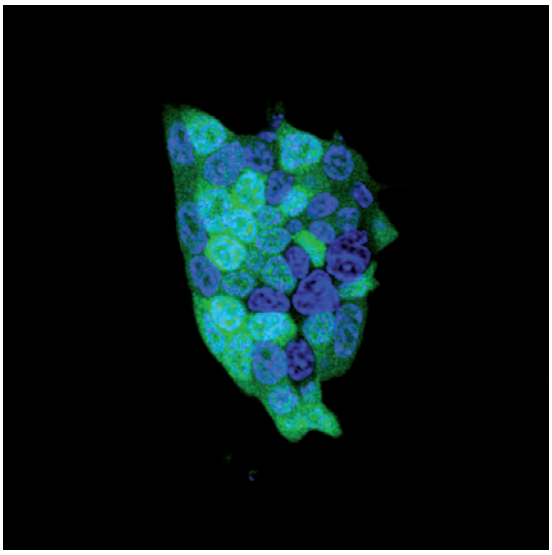
Research Interest

The Pluripotent Cell Technology Service (PCTS) is dedicated to supporting CNIC researchers whose research involves mouse or human embryonic stem cells (mESCs and hESCs) or induced pluripotent stem cells. Our staff offers individualized training for successful stem cell culture, supplies protocols and expert advice in the maintenance and differentiation of stem cells, and provides validated reagents. An appropriate environment for work with stem cells is provided by two supervised culture rooms, one devoted to human cells and the other to mouse cells.

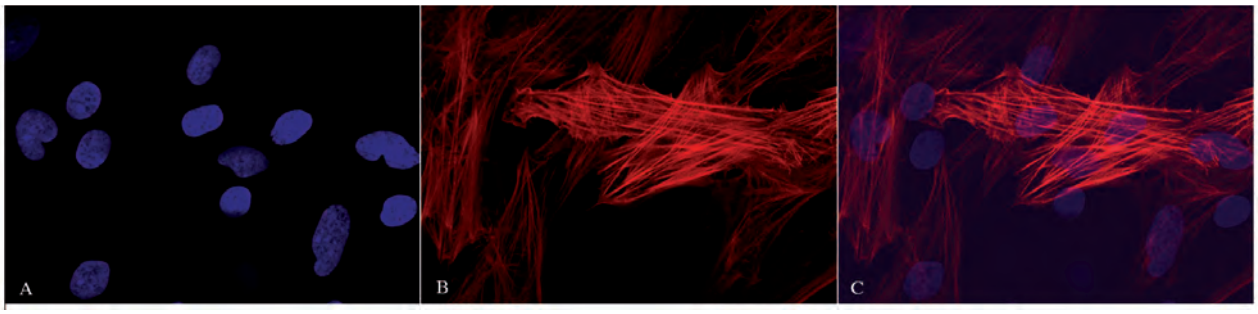
A core function of the PCTS is to facilitate gene-targeting experiments to produce quality-controlled genetically modified mESCs, an essential requirement for germline transmission and the generation of knockout, knockin and conditional mutant mice. The PCTS undertakes all key steps in the gene-targeting protocol: electroporation of the targeting vector, selection, karyotyping, culture, and the preparation of cells for blastocyst injection. The recruitment of new staff at the beginning 2013 has enabled us to add neo removal, random insertion and screening by Southern blot to the PCTS's service portfolio. On request, we can also assist CNIC researchers with the design of targeting vectors and screening strategies. With the methodologies available in the PCTS, we are able to identify homologous recombination events using a small number of clones. This, combined with the high efficiency of germline transmission achieved, brings time and cost savings. We continue to provide support in mESC derivation from mutant mice, and in 2013, through collaboration with the Transgenesis Unit, we derived mESC lines from C57Bl6/J wild type mice. We hope to obtain our own Bl6/J-mESC line suitable, after confirming germiline transmission, for use in gene targeting experiments. The PCTS staff is also able to provide expert advice on the design of experiments involving human pluripotent stem cells (hPSCs) and strives to implement emerging technologies such as ZNF or the CRISPR/cas system to modify genome and generate in vitro models of cardiovascular disease.



Metaphase spread of mESC derived from iMOS *blastocyst. Chromosomes are counterstained with DAPI.*



Confocal image of the iMOS *mESC line showing EYFP expression (green) and DAPI (blue).*



Immunocytochemistry of differentiated cardiac cells. A) DAPI, B Troponin I; C) Merged view.

Selected Publications

Hidalgo-Figueroa, M, Bonilla S, Gutiérrez F, Pascual A, López-Barneo J. **GDNF is predominantly expressed in the PV+ neostriatal interneuronal ensemble in normal mouse and after injury of the nigrostriatal pathway**. *J Neurosci* (2012) 32: 864-87

Claveria C, Giovinazzo G, Sierra R, Torres M. **Myc-driven endogenous cell competition in the early mammalian embryo**. *Nature* (2013) 500: 39-44

Proteomics

Head of Unit: Juan Antonio López

Support Scientists: Enrique Calvo
Emilio Camafeita
Iakes Ezkurdia

Research Interest

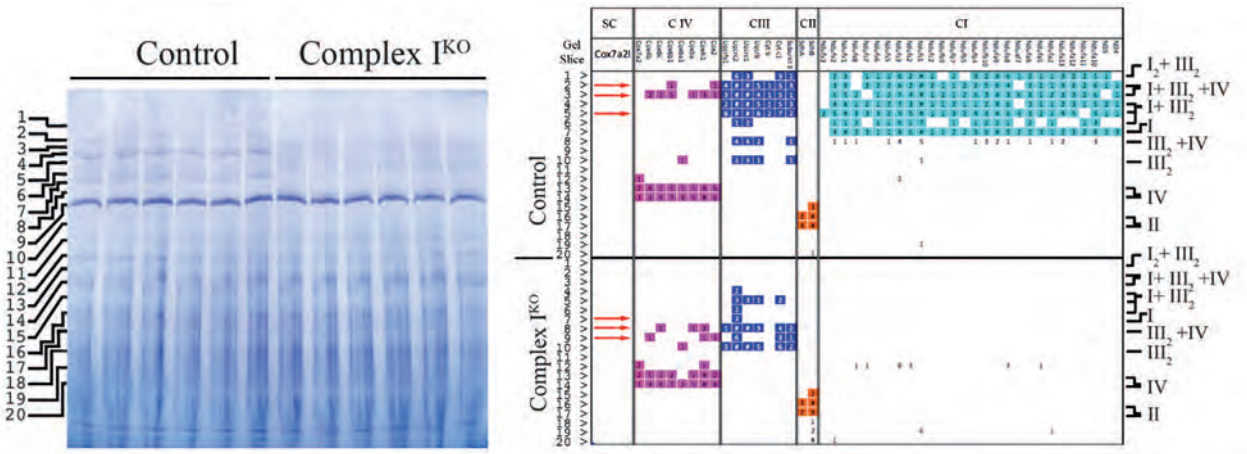
The Proteomics Unit has broad experience in proteomics approaches aimed at the separation, quantification, identification and characterization of proteins in biological systems, and maintains a program of continuous development and improvement of technologies and protocols to meet the challenging requirements of the research community. During 2013 substantial progress was made in quantitative proteomics approaches with fully operational state-of-the-art mass spectrometers.

Continuous improvements are being made in the separation and quantitative analysis of protein expression by shotgun proteomic analyses using high-throughput technologies based on nanoHPLC coupled to mass spectrometry. Proteins and peptides, and their post-translational modifications, are identified and characterized by mass spectrometry. Particular improvements have been made in the development of the chromatographic conditions for peptide separation, optimization of fragmentation parameters, and post-acquisition analysis and data visualization employing several validation programs.

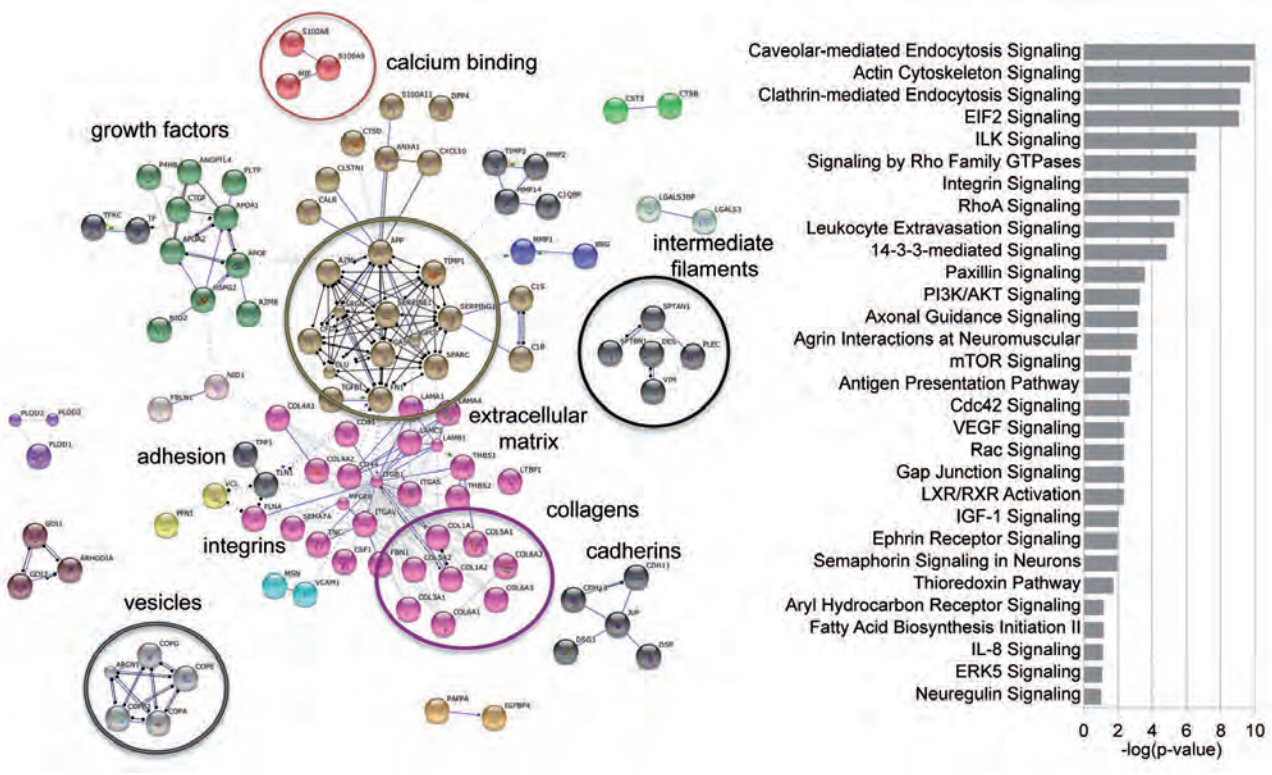
We are increasing analytical sensitivity to the level where it can reliably quantify and detect low-abundance proteins in complex biological specimens such as cell extracts or tissues. Protein quantification using mass spectrometry-based techniques, including label-free and stable isobaric labeling (mainly iTRAQ), allows us to analyze thousands of proteins in a single experiment. This past year we have exploited the latest Thermo Orbitrap Elite and Thermo QExactive mass spectrometers for ultra-deep proteome analysis.

One of the most interesting developments is a new acquisition mode that mixes targeted and shotgun approaches, based on a signal-independent fragmentation. This novel approach is being extensively explored in selected subproteomes to increase the coverage and number of identified peptides, and is allowing us to conduct targeted analyses *in silico* of selected peptide sequences.

This robust analytical platform together with our recognized experience in the field enables us to manage large research projects with a high technology content and which require qualitative and quantitative proteomic approaches for measuring differential protein expression, studying chemical and posttranslational modifications, and mapping protein-protein interactions in different biological systems.



Cox7a2l is present in respiratory supercomplexes (SC) but not in individual complexes. (Left) *Blue native polyacrylamide gel electrophoresis (BNGE) of control and complex I-KO cell lines. After Coomassie staining, 20 gel bands were excised per control and mutant cell lane for further in-gel protein trypsin digestion and protein identification by LC-MS/MS analysis using an LTQ Orbitrap XL mass spectrometer.* (Right) *Composition of the OXPHOS proteins from complexes I to IV at each band for control and the complex I-KO cell lines. The complex I-KO cell line loses SC(I+III+IV) but retains SC(III+IV). Pink indicates components of complex IV (CIV), dark blue CIII, orange CII, and light blue CI. Note that Cox7a2l peptides (red arrows) were identified only in gel areas showing interaction of CIII and CIV. Modified from Lapuente-Brun* et al., Science *(2013) 340: 1567-15.*



Human bone marrow (BM) mesenspheres support cord blood HSCs mainly through secreted factors. (Left) *Protein-protein interactions predicted from the list of proteins identified in the secretome of human chicken embryo extract (CEE) BM mesenspheres (n = 3 independent donors). Only proteins for which two or more peptides were identified in two or more samples were considered for the analyses using STRING 9.0. Interactions were identified from experimental data and databases using a high confidence level (0.700). The clustering was performed using the MCL algorithm (inflation parameter set at 2). (Right) Enrichment in relevant canonical pathways detected using Ingenuity Pathway Analysis software. Modified from Isern* et al., Cell Reports, *(2013) 3: 1714-24.*

Selected Publications

Alvarez-Llamas G, Martín-Rojas T, de la Cuesta F, Calvo E, Gil-Dones F, Dardé VM, Lopez-Almodovar LF, Padial LR, Lopez JA, Vivanco F, Barderas MG. **Modification of the secretion pattern of proteases, inflammatory mediators, and extracellular matrix proteins by human aortic valve is key in severe aortic stenosis**. *Mol Cell Proteomics* (2013) 12: 2426-39

Isern J, Martin-Antonio B, Ghazanfari R, Martin AM, Lopez JA, Del Toro R, Sanchez-Aguilera A, Arranz L, Martin-Perez D, Suarez-Lledo M, Marin P, Van Pel M, Fibbe WE, Vazquez J, Scheding S, Urbano-Ispizua A and Mendez-Ferrer S. **Self-renewing human bone marrow mesenspheres promote hematopoietic stem cell expansion**. *Cell Rep* (2013) 3: 1714-24

Lapuente-Brun E, Moreno-Loshuertos R, Acín-Pérez R, Latorre-Pellicer A, Colás C, Balsa E, Perales-Clemente E, Quirós PM, Calvo E, Rodríguez-Hernández MA, Navas P, Cruz R, Carracedo Á, López-Otín C, Pérez-Martos A, Fernández-Silva P, Fernández-Vizarra E, Enríquez JA. **Supercomplex assembly determines electron flux in the mitochondrial electron transport chain**. *Science* (2013) 340: 1567-70

Lopez-Huertas MR, Mateos E, Sanchez Del Cojo M, Gomez-Esquer F, Diaz-Gil G, Rodriguez-Mora S, Lopez JA, Calvo E, Lopez-Campos G, Alcami J and Coiras M. **The Presence of HIV-1 Tat Second Exon Delays Fas-Mediated Apoptosis in CD4+ T lymphocytes: a Potential Mechanism for Persistent Viral Production**. *J Biol Chem* (2013) 288: 7626-44

Martinez-Pinna R, Madrigal-Matute J, Tarin C, Burillo E, Esteban M, Pastor-Vargas C, Jes S. Lindholt, Lopez JA, Calvo E, Vega de Ceniga M, Meilhac O, Egido J, Blanco-Colio, Michel JB, Martin-Ventura JL. **Proteomics analysis of intraluminal thrombus highlights complement activation in human abdominal aortic aneurisms**. *Arterioscler Thromb Vasc Biol* (2013) 33: 2013-20

Transgenesis

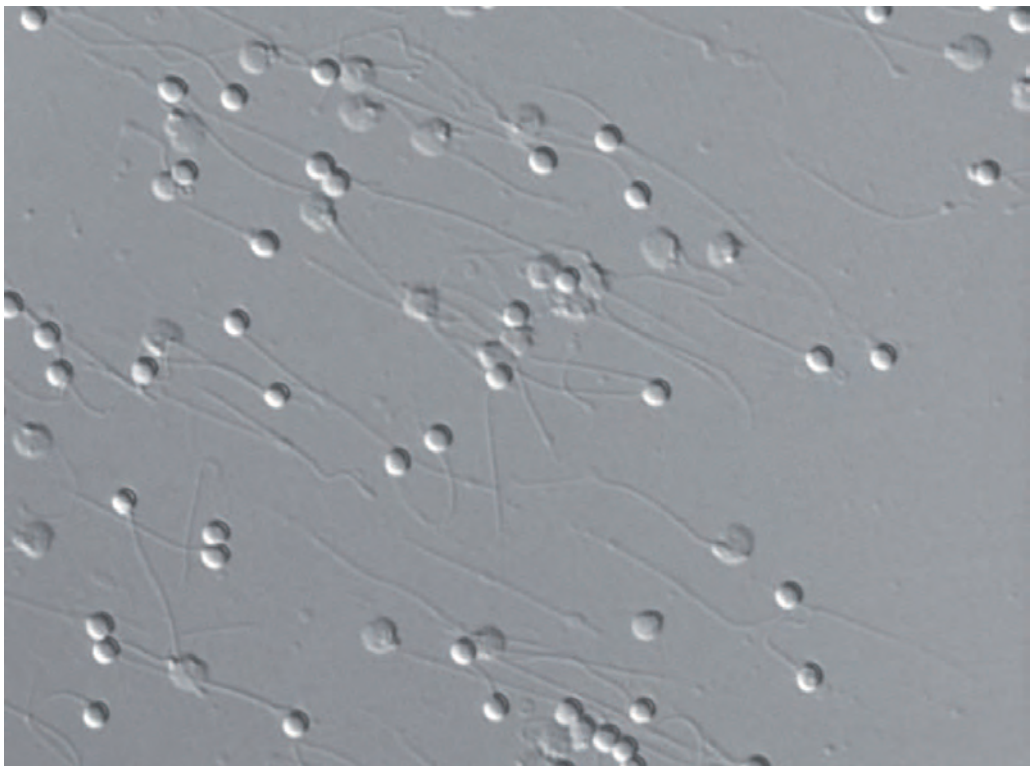
Head of Unit: Luis-Miguel Criado Rodríguez
Support Scientists: José Mª Fernández Toro
Juan de Dios Hourcade Bueno

Research Interest

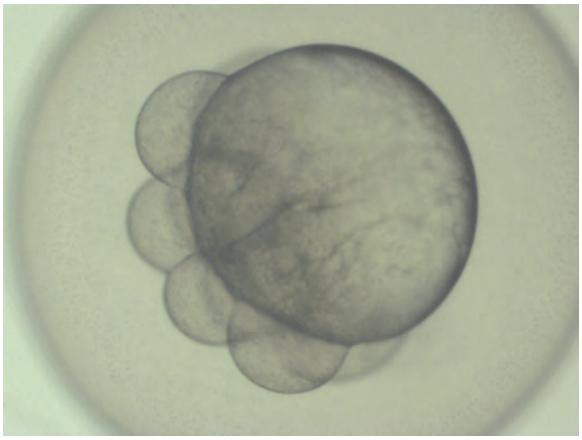
Most of the Transgenesis Unit's work to date has been done in the mouse (Mus musculus). The unit produces genetically modified mouse strains to meet the needs of the Center's researchers using standard, well-established techniques: pronuclear microinjection with DNA and microinjection of embryonic stem cells (ESCs) into mouse 8-cell embryos and blastocysts. Another important activity is the rederivation of mouse and rat strains by embryo transfer to set up colonies in the SPF zone of the Comparative Medicine Unit. Other procedures performed in the mouse are the production of chimeras by 8-cell embryo aggregation, the cryopreservation of strains by freezing sperm and embryos, in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI).

The zebrafish (Danio rerio) is other important vertebrate model organism used in research at the CNIC, and over the past year the Unit has set up protocols for cryopreserving sperm from this species and for IVF with fresh and frozen sperm.

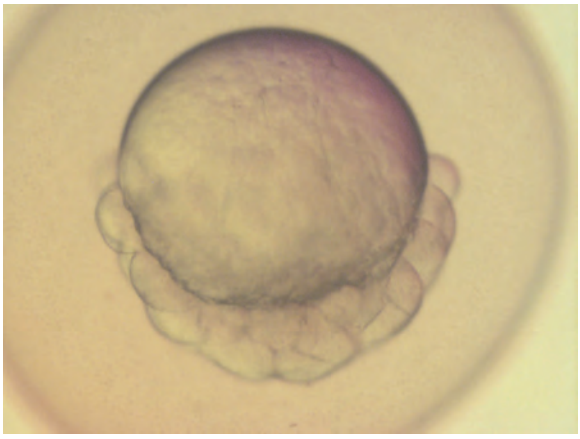
In addition to its routine work, the Unit collaborates with several CNIC groups on specific aspects of their research programs, and Unit members participate in the training programs at the CNIC by providing theory and practical classes.



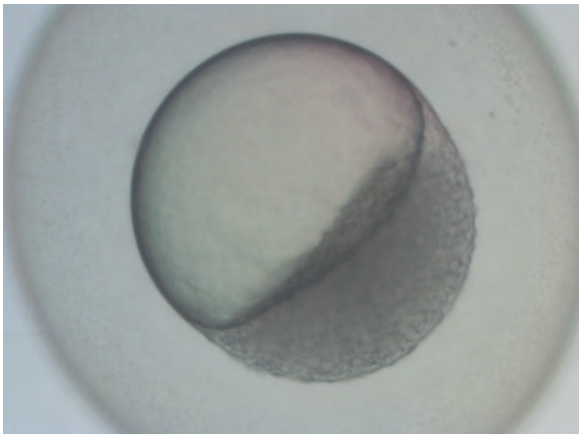
Differential interference contrast (DIC) image of zebrafish sperm



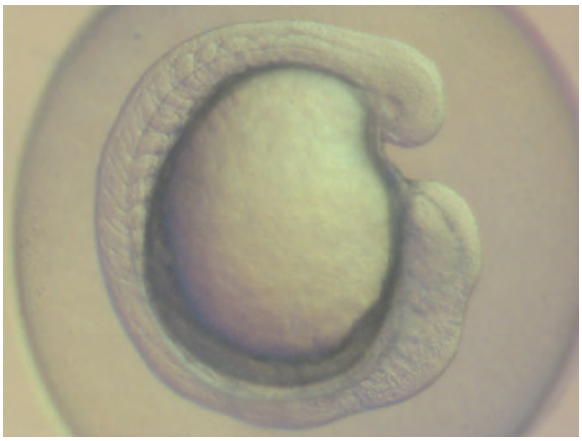
8-cell zebrafish embryo (1.25 hours postfertilization)



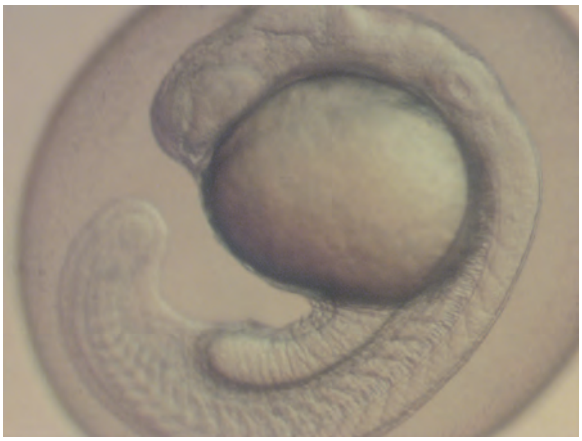
32-cell zebrafish embryo (1.75 hours postfertilization)



Oblong zebrafish embryo (3.7 hours postfertilization)



14-somite zebrafish embryo (16 hours postfertilization)



24-somite zebrafish embryo (21 hours postfertilization)

Selected Publications

Alfaro J, Grau M, Serrano M, Checa AI, Criado LM, Moreno E, Paz-Artal E, Mellado M, Serrano A. **Blockade of endothelial Gi protein enhances early engraftment in intraportal cell transplant to mouse liver**. *Cell Transplant* (2012) 21: 1383-96

Hourcade JD, Pérez-Crespo M, Serrano A, Gutiérrez-Adán A, Pintado B. **In vitro and in vivo development of mice morulae after storage in non-frozen conditions**. *Reprod Biol Endocrinol* (2012) 10: 62

Viral Vectors

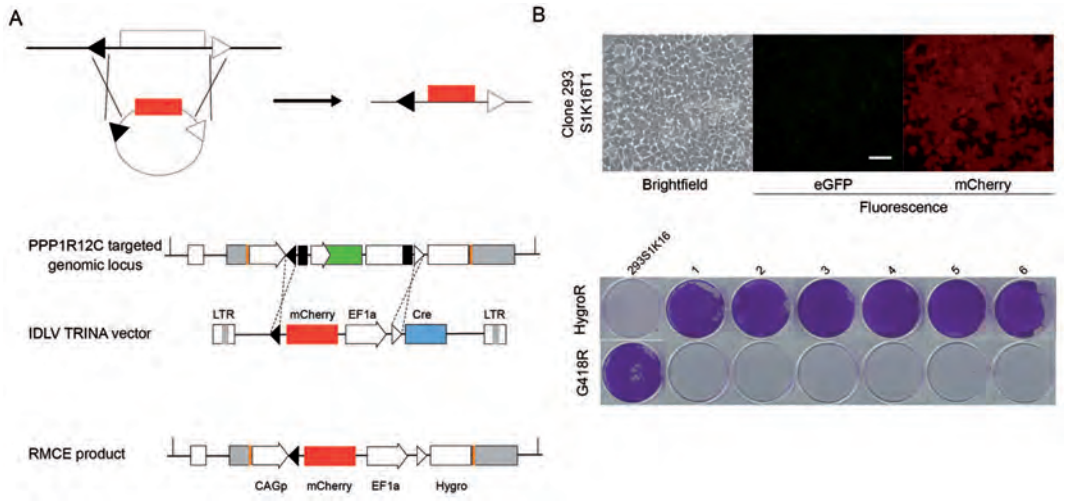
Head of Unit: Juan C. Ramírez
Support Scientist: Raúl Torres
Technician: Aida García
Visiting Scientists: Catarina Reis (CNIO)
Mariona Terradas (UAB)

Research Interest

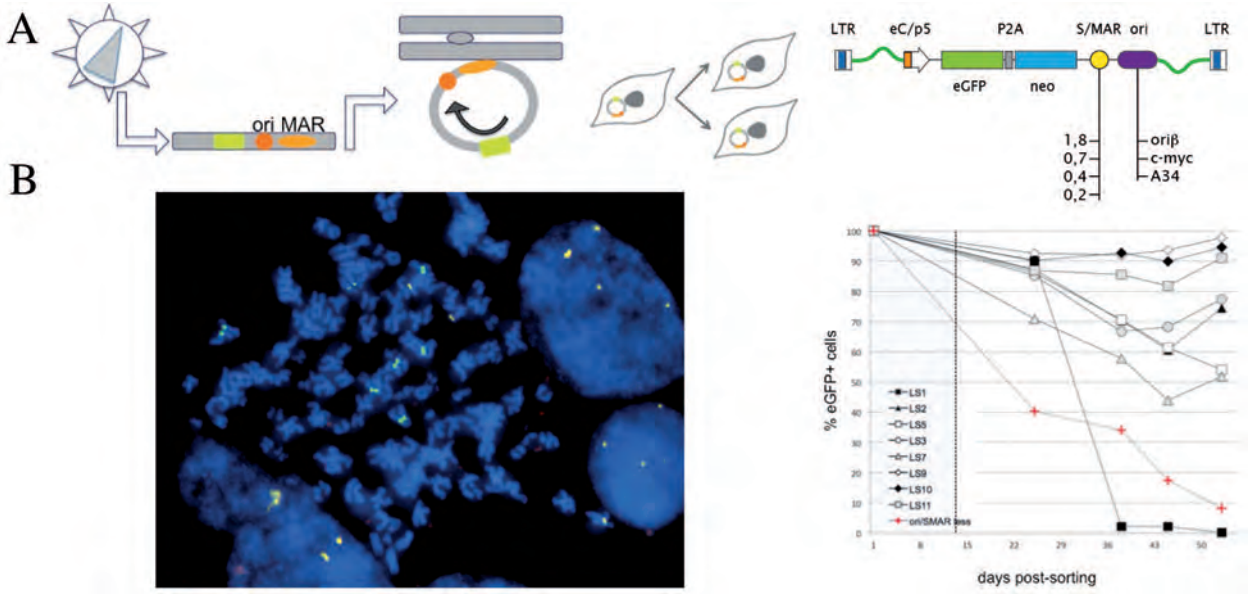
Gene-transfer-based strategies play a central role in biomedical research and cutting edge molecular medicine, and provide a resource for gaining unambiguous insights into the roles of genes in health and disease. While there are many available approaches for introducing genes in vivo and in vitro, recombinant viral vectors remain the most common and efficient vehicles for gene delivery.

The Viral Vectors Unit provides non-clinical grade recombinant viral vectors to researchers at the CNIC. The service launched in 2008 and since then hundreds of stocks of recombinant vectors have been produced and delivered. The Unit provides second and third generation integrative and non-integrative lentivirus, adenovirus and adeno-associated virus (AAV), covering most of the needs for integrative and non-integrative gene transfer strategies in vitro and in pre-clinical animal models. A portfolio of more than 50 ready-to-use shuttle vectors is available to accommodate most investigators' needs. State-of-the-art quality control checks are run on all batches produced. The Unit also provides support and advice on the choice of vector, promoters and customized genetic building blocks, and also on the global experimental strategy to be followed.

The Unit is also building a platform based on integrase-deficient lentiviruses, aimed at increasing biosafety, reproducibility and stability. The platform is currently composed of three exchangeable strategies able to 1) generate isogenic cell lines by recombinase-mediated cassette exchange (RMCE), 2) deliver functional proteins in lentiviral particles, and 3) deliver a novel-replicative episome based vector derived from lentiviral replication-intermediates submitted for patent (P9994EP00-28Nov2013). Finally, in collaboration with the Molecular Cytogenetics group at the CNIO, we have explored the potential of the gene editing CRISPR/Cas9 system to engineer human tumor-associated chromosomal translocations.



Lentivirus-mediated RMCE. (A) *Anticipated RMCE reaction in HEK293 cells bearing the KAS2.0 cassette integrated by ZFN in the* AAVS1 *locus (*PPP1R12C*), upon transduction with the integrase-deficient lentivirus (IDLV) TRINA. The upper scheme is a simplified overview of the anticipated RMCE reaction detailed in the lower scheme. The red and blue boxes in IDLV-TRINA depict the mCherry and Cre expression components of the promoterless cassette. The scheme of the RMCE product highlights the promoter trapping strategy, in which the integration of TRINA components places mCherry under the control of the PGK promoter in the KAS2.0 cassette (displacing eGFP and Neo^R) and introduces the EF1α promoter to activate hygromycin B resistance.* ***(B)*** *The micrographs show fluorescence microscopy analysis of TRINA-derived clone* K16T1 *subsequently grown without selection for two weeks, confirming expression of mCherry instead of eGFP. Viability of the TRINA-derived clone* K16T1-6 *in hygromicin B but not in G418 reveals Cre-driven promoter trapping and legitimate RMCE between KAS and TRINA cassettes in the parental clone 293*S1K16.



LentiSome, a novel lentiviral vector consisting of a replicative episome that does not integrate in chromosomes. (A) *Elements present in lentisomal backbone and the expected outcome upon transduction in a rapidly dividing cell. S/MAR, scaffold/matrix attachment region; ori, eukaryotic origin of DNA replication.* ***(B)*** *Stable maintenance of GFP+ phenotype by LentiSome in HEK293 cells after two months in culture, equivalent to ~70 population doublings. On the left are shown FISH-visualization of transgenes (red) in metaphase spreads at 50 days post-transduction. Intense signals are revealed, indicating the typical extra chromosome copies, in contrast with doublets in both chromatids upon integration.*

Major Grants

- **Ministerio de Economía y Competitividad (BIO2011-13944-E)**
- **Ministerio de Economía y Competitividad (PI11/02041)**

Selected Publications

R. Torres, A. Garcia, M. Jimenez, S Rodriguez-Perales and J. C. Ramirez. **An integration-defective lentivirus-based resource for site-specific targeting of an edited safe-harbour locus in the human genome**. *Gene Therapy* (accepted)

J.M. Rojas, H. Moreno, A. Garcia, J.C. Ramirez, N. Sevilla, and V. Martin. **Two replication-defective adenoviral vaccine vectors for the induction of immune responses to PPRV**. *Vaccine* (accepted)

J.C. Estrada, Y. Torres, A. Benguría, A. Dopazo, E. Roche, L. Carrera-Quintanar, R.A. Pérez RA, J.A. Enríquez, R. Torres, J.C. Ramírez, E. Samper, A. Bernad. **Human mesenchymal stem cell-replicative senescence and oxidative stress are closely linked to aneuploidy**. *Cell Death Dis* (2013) 4: e691

C. Belmar-López, G. Mendoza, D. Öberg, J. Burnet, C. Simon, I. Cervello, M. Iglesias, J.C. Ramirez, P. López-Larrubia, M. Quintanilla, and P. Martin-Duque. **Tissue-derived mesenchymal stromal cells used as vehicles for anti-tumor therapy exert different in vivo effects on migration capacity and tumor growth**. *BMC Med* (2013) 11: 139

APPENDIX

Publications

Training Programs and Courses

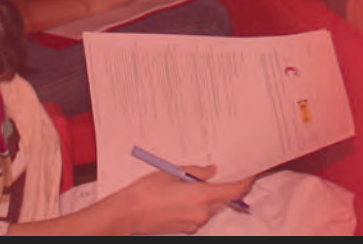
Seminars, Events and Awards

Strategic Alliances

Funding

Patent Portfolio

Staff Figures



APPENDIX

PUBLICATIONS 2013

The number of CNIC publications stabilized during 2013, reflecting the stabilization in the number of researchers working at the Center. The impact of CNIC publications, however, significantly improved.

CNIC scientists published 192 articles in 2013, 170 of them in JCR-listed journals with an Impact Factor (IF). Of all published articles, 67% were studies done in collaboration with foreign institutions, 27% with national institutions, and 6% solely by CNIC researchers.

The average IF for all articles was 8.949. Articles with a CNIC scientist as a main author (52% of the total) had an average IF of 9.875, marking the added value of CNIC leadership.

Articles with a CNIC Main Author

Articles with an IF

Arranz L, Urbano-Ispizua A and Méndez-Ferrer S.
Mitochondria underlie different metabolism of hematopoietic stem and progenitor cells.
Haematologica (2013) 98: 993-5
IF: 5.935

Azegrouz H, Karemore G, Torres A, Alaiz CM, González AM, Nevado P, Salmerón A, Pellinen T, Del Pozo MA, Dorronsoro JR and Montoya MC.
Cell-Based Fuzzy Metrics Enhance High-Content Screening (HCS) Assay Robustness.
J Biomol Screen (2013) 18: 1270-83
IF: 2.207

Benedito R and Hellstrom M.
Notch as a hub for signaling in angiogenesis.
Exp Cell Res (2013) 319: 1281-8
IF: 3.557

Bernal A and Gálvez BG.
The Potential of Stem Cells in the Treatment of Cardiovascular Diseases.
Stem Cell Rev (2013) 9: 814-32
IF: 4.523

Bernal JA.
RNA-Based Tools for Nuclear Reprogramming and Lineage-Conversion: Towards Clinical Applications.
J Cardiovasc Transl Res (2013) 6: 956-68
IF: 2.611

Bolos V, Mira E, Martínez Poveda B, Luxán G, Cañamero M, Martínez AC, Manes S and de la Pompa JL.
Notch activation stimulates migration of breast cancer cells and promotes tumor growth.
Breast Cancer Res (2013) 15: R54
IF: 5.872

Casanova JC, Travisano S and de la Pompa JL.
Epithelial-to-mesenchymal transition in epicardium is independent of Snail1.
Genesis (2013) 51: 32-40
IF: 2.584

Casanova-Acebes M, Pitaval C, Weiss LA, Nombela-Arrieta C, Chèvre R, A-González N, Kunisaki Y, Zhang D, van Rooijen N, Silberstein LE, Weber C, Nagasawa T, Frenette PS, Castrillo A and Hidalgo A.
Rhythmic Modulation of the Hematopoietic Niche through Neutrophil Clearance.
Cell (2013) 153: 1025-35
IF: 31.957

Castellano JM, Vaishnava P, Castillo JG, Anyanwu AC and Fuster V.
Coronary vasospasm attributable to fibromuscular dysplasia: the long bridge to transplant.
Circ Heart Fail (2013) 6: e31-2
IF: 6.684

Céspedes J, Briceno G, Farkouh ME, Vedanthan R, Baxter J, Leal M, Boffetta P, Hunn M, Dennis R and Fuster V.
Promotion of Cardiovascular Health in Preschool Children: 36-Month Cohort Follow-up.
Am J Med (2013) 126: 1122-6
IF: 4.768

Céspedes J, Briceno G, Farkouh ME, Vedanthan R, Baxter J, Leal M, Boffetta P, Woodward M, Hunn M, Dennis R and Fuster V.
Targeting Preschool Children to Promote Cardiovascular Health: Cluster Randomized Trial.
Am J Med (2013) 126: 27-35
IF: 4.768

APPENDIX

PUBLICATIONS 2013

Chinitz JS, Vaishnava P, Narayan RL and Fuster V.
Atrial fibrillation through the years: contemporary evaluation and management.
Circulation (2013) 127: 408-16
IF: 15.202

Clavería C, Giovinazzo G, Sierra R and Torres M.
Myc-driven endogenous cell competition in the early mammalian embryo.
Nature (2013) 500: 39-44
IF: 38.597

Cogliati S, Frezza C, Soriano ME, Varanita T, Quintana-Cabrera R, Corrado M, Cipolat S, Costa V, Casarin A, Gomes LC, Perales-Clemente E, Salviati L, Fernández-Silva P, Enríquez JA and Scorrano L.
Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency.
Cell (2013) 155: 160-71
IF: 31.957

Corella D, Carrasco P, Sorli JV, Estruch R, Rico-Sanz J, Martínez-González MA, Salas-Salvado J, Covas MI, Coltell O, Aros F, Lapetra J, Serra-Majem L, Ruiz-Gutiérrez V, Warnberg J, Fiol M, Pinto X, Ortega-Azorín C, Muñoz MA, Martínez JA, Gómez-Gracia E, González JI, Ros E and Ordovás JM.
Mediterranean Diet Reduces the Adverse Effect of the TCF7L2-rs7903146 Polymorphism on Cardiovascular Risk Factors and Stroke Incidence: A randomized controlled trial in a high-cardiovascular-risk population.
Diabetes Care (2013) 36: 3803-11
IF: 7.735

Corella D and Ordovás JM.
Can genotype be used to tailor treatment of obesity? State of the art and guidelines for future studies and applications.
Minerva Endocrinol (2013) 38: 219-35
IF: 1.396

De Yébenes VG, Bartolomé-Izquierdo N and Ramiro AR.
Regulation of B-cell development and function by microRNAs.
Immunol Rev (2013) 253: 25-39
IF: 12.155

Del Toro R and Méndez-Ferrer S.
Autonomic regulation of hematopoiesis and cancer.
Haematologica (2013) 98: 1663-6
IF: 5.935

Echavarría-Pinto M, Escaned J, Bañuelos C and Gonzalo N.
Optical coherence tomography findings in an acquired coronary fistula.
Circulation (2013) 127: e865-7
IF: 15.202

Echavarría-Pinto M, Escaned J, Macias E, Medina MA, Gonzalo N, Petraco R, Sen S, Jiménez-Quevedo P, Hernández R, Mila R, Ibáñez B, Nuñez-Gil IJ, Fernández C, Alfonso F, Banuelos C, García E, Davies JE, Fernández-Ortiz A and Macaya C.
Disturbed Coronary Hemodynamics in Vessels with Intermediate Stenoses Evaluated with Fractional Flow Reserve: A Combined Analysis of Epicardial and Microcirculatory Involvement in Ischemic Heart Disease.
Circulation (2013) 128: 2557-66
IF: 15.202

Estrada JC, Torres Y, Benguría A, Dopazo A, Roche E, Carrera-Quintanar L, Pérez RA, Enríquez JA, Torres R, Ramírez JC, Samper E and Bernad A.
Human mesenchymal stem cell-replicative senescence and oxidative stress are closely linked to aneuploidy.
Cell Death Dis (2013) 4: e691
IF: 6.044

Farkouh ME, Boden WE, Bittner V, Muratov V, Hartigan P, Ogdie M, Bertolet M, Mathewkutty S, Teo K, Maron DJ, Sethi SS, Domanski M, Frye RL and Fuster V.
Risk factor control for coronary artery disease secondary prevention in large randomized trials.
J Am Coll Cardiol (2013) 61: 1607-15
IF: 14.086

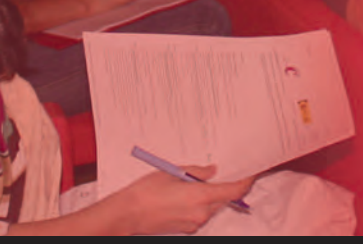
Farkouh ME, Domanski M and Fuster V.
Revascularization strategies in patients with diabetes.
N Engl J Med (2013) 368: 1455-6
IF: 51.658

Fernández-Friera L, García-Álvarez A and Ibáñez B.
Imagining the Future of Diagnostic Imaging.
Rev Esp Cardiol (2013) 66: 134-43
IF: 3.204

Fernández-Jiménez R and Fernández-Ortiz A.
Multimarker Panel for Patients With Chest Pain: Case Closed?
Rev Esp Cardiol (2013) 66: 523-5
IF: 3.204

Fernández-Jiménez R, Kempny A, Swan L, Uebing A, Diller GP, Dimopoulos K, Rubens MB and Gatzoulis MA.
Paracardiac mass on chest X-ray in a patient with Eisenmenger syndrome.
Int J Cardiol (2013) 165: e6-8
IF: 5.509

Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, Ordovás JM, Mocoroa A, Fernández-Friera L, Laclaustra M, García L, Molina J, Mendiguren JM, López-Melgar B, de Vega VM, Alonso-Farto JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibáñez B, Sanz G and Fuster V.
The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: Rationale and design.
Am Heart J (2013) 166: 990-8
IF: 4.497



APPENDIX

PUBLICATIONS 2013

Franco M, Bilal U, Orduñez P, Benet M, Morejón A, Caballero B, Kennelly JF and Cooper RS.
Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends.
BMJ (2013) 346: f1515
IF: 17.215

Garaude J.
[Control of innate immune system for cancer therapy].
Med Sci (Paris) (2013) 29: 985-90
IF: 0.556

Garaulet G, Alfranca A, Torrente M, Escolano A, López-Fontal R, Hortelano S, Redondo JM and Rodríguez A.
IL10 Released by a New Inflammation-regulated Lentiviral System Efficiently Attenuates Zymosan-induced Arthritis.
Mol Ther (2013) 21: 119-30
IF: 7.041

García-Álvarez A, Fernández-Friera L, García-Ruiz JM, Nuño-Ayala M, Pereda D, Fernández-Jiménez R, Guzmán G, Sánchez-Quintana D, Alberich-Bayarri A, Pastor-Escuredo D, Sanz-Rosa D, García-Prieto J, Mirelis JG, Pizarro G, Jiménez-Borreguero LJ, Fuster V, Sanz J and Ibáñez B.
Noninvasive Monitoring of Serial Changes in Pulmonary Vascular Resistance and Acute Vasodilator Testing using Cardiac Magnetic Resonance.
J Am Coll Cardiol (2013) 62: 1621-31
IF: 14.086

González-Amaro R, Cortes JR, Sánchez-Madrid F and Martín P.
Is CD69 an effective brake to control inflammatory diseases?
Trends Mol Med (2013) 19: 625-32
IF: 9.571

González-Navarro H, Vinué A, Sanz MJ, Delgado M, Pozo MA, Serrano M, Burks DJ and Andrés V.
Increased dosage of Ink4/Arf protects against glucose intolerance and insulin resistance associated with aging.
Aging Cell (2013) 12: 102-11
IF: 5.705

González-Teran B, Cortés JR, Manieri E, Matesanz N, Verdugo A, Rodríguez ME, González-Rodríguez A, Valverde A, Martín P, Davis RJ and Sabio G.
Eukaryotic elongation factor 2 controls TNF-alpha translation in LPS-induced hepatitis.
J Clin Invest (2013) 123: 164-78
IF: 12.812

Gordon-Alonso M, Rocha-Perugini V, Álvarez S, Ursa A, Izquierdo-Useros N, Martínez-Picado J, Muñoz-Fernández MA and Sánchez-Madrid F.
Actin-binding protein drebrin regulates HIV-1-triggered actin polymerization and viral infection.
J Biol Chem (2013) 288: 28382-97
IF: 4.651

Gorog DA and Fuster V.
Platelet function tests in clinical cardiology: unfulfilled expectations.
J Am Coll Cardiol (2013) 61: 2115-29
IF: 14.086

Guallar E, Manson JE, Laine C and Mulrow C.
Postmenopausal hormone therapy: the heart of the matter.
Ann Intern Med (2013) 158: 69-70
IF: 13.976

Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M and Sánchez-Madrid F.
Transfer of extracellular vesicles during immune cell-cell interactions.
Immunol Rev (2013) 251: 125-42
IF: 12.155

Hidalgo I and González S.
New epigenetic pathway for stemness maintenance mediated by the histone methyltransferase Ezh1.
Cell Cycle (2013) 12: 383-4
IF: 5.243

Ibáñez B, Macaya C, Sánchez-Brunete V, Pizarro G, Fernández-Friera L, Mateos A, Fernández-Ortiz A, García-Ruiz JM, García-Álvarez A, Íñiguez A, Jiménez-Borreguero J, López-Romero P, Fernández-Jiménez R, Goicolea J, Ruiz-Mateos B, Bastante T, Arias M, Iglesias-Vázquez JA, Rodríguez MD, Escalera N, Acebal C, Cabrera JA, Valenciano J, Pérez de Prado A, Fernández-Campos MJ, Casado I, García-Rubira JC, García-Prieto J, Sanz-Rosa D, Cuellas C, Hernández-Antolín R, Albarrán A, Fernández-Vázquez F, de la Torre-Hernández JM, Pocock SJ, Sanz G and Fuster V.
Effect of Early Metoprolol on Infarct Size in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary PCI: The METOCARD-CNIC Trial.
Circulation (2013) 128: 1495-503
IF: 15.202

Lapuente-Brun E, Moreno-Loshuertos R, Acín-Pérez R, Latorre-Pellicer A, Colás C, Balsa E, Perales-Clemente E, Quirós PM, Calvo E, Rodríguez-Hernández MA, Navas P, Cruz R, Carracedo A, López-Otín C, Pérez-Martos A, Fernández-Silva P, Fernández-Vizarra E and Enríquez JA.
Supercomplex assembly determines electron flux in the mitochondrial electron transport chain.
Science (2013) 340: 1567-70
IF: 31.027

Lara-Pezzi E, Gómez-Salinero J, Gatto A and García-Pavía P.
The Alternative Heart: Impact of Alternative Splicing in Heart Disease.
J Cardiovasc Transl Res (2013) 6: 945-55
IF: 3.062

Lolo FN, Tinto SC and Moreno E.
How winner cells cause the demise of loser cells: Cell competition causes apoptosis of suboptimal cells: Their dregs are removed by hemocytes, thus preserving tissue homeostasis.
Bioessays (2013) 35: 348-53
IF: 5.423

Lopez-Collazo E and Del Fresno C.
Pathophysiology of endotoxin tolerance: mechanisms and clinical consequences.
Crit Care (2013) 17: 242
IF: 4.718

Lucas D, Delgado-García JM, Escudero B, Albo C, Aza A, Acín-Pérez R, Torres Y, Moreno P, Enríquez JA, Samper E, Blanco L, Fairen A, Bernad A and Gruart A.
Increased Learning and Brain Long-Term Potentiation in Aged Mice Lacking DNA Polymerase mu.
PLoS One (2013) 8: e53243
IF: 3.730

Luque-García JL, Sánchez-Díaz R, López-Heras I, Cámara C and Martín P.
Bioanalytical strategies for in-vitro and in-vivo evaluation of the toxicity induced by metallic nanoparticles.
TrAC Trends in Analytical Chemistry (2013) 43: 254-68
IF: 6.351

Luxán G, Casanova JC, Martínez-Poveda B, Prados B, D'Amato G, Macgrogan D, González-Rajal A, Dobarro D, Torroja C, Martínez F, Izquierdo-García JL, Fernández-Friera L, Sabater-Molina M, Kong YY, Pizarro G, Ibáñez B, Medrano C, García-Pavía P, Gimeno JR, Monserrat L, Jiménez-Borreguero LJ and de la Pompa JL.
Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy.
Nat Med (2013) 19: 193-201
IF: 22.864

Manzanares M and Rodríguez TA.
Development: hippo signalling turns the embryo inside out.
Curr Biol (2013) 23: R559-61
IF: 9.494

Marcos-Contreras OA, Ganguly K, Yamamoto A, Shlansky-Goldberg R, Cines DB, Muzykantov VR and Murciano JC.
Clot penetration and retention by plasminogen activators promote fibrinolysis.
Biochem Pharmacol (2013) 85: 216-22
IF: 4.576

Méndez-Barbero N, Esteban V, Villahoz S, Escolano A, Urso K, Alfranca A, Rodríguez C, Sánchez SA, Osawa T, Andrés V, Martínez-González J, Minami T, Redondo JM and Campanero MR.
A major role for RCAN1 in atherosclerosis progression.
EMBO Mol Med (2013) 5: 1901-17
IF: 7.795

Mirelis JG, García-Álvarez A, Fernández-Friera L, Sawit S, Hinojar R, Fuster V, García MJ and Sanz J.
Respiratory ventricular area changes measured with real-time cardiac magnetic resonance: A new, accurate, and reproducible approach for the diagnosis of pericardial constriction.
Int J Cardiol (2013) 166: 267-71
IF: 5.509

A-González N, Guillén JA, Gallardo G, Díaz M, de la Rosa JV, Hernández IH, Casanova-Acebes M, López F, Tabraue C, Beceiro S, Hong C, Lara PC, Andujar M, Arai S, Miyazaki T, Li S, Corbi AL, Tontonoz P, Hidalgo A and Castrillo A.
The nuclear receptor LXRalpha controls the functional specialization of splenic macrophages.
Nat Immunol (2013) 14: 831-9
IF: 26.199

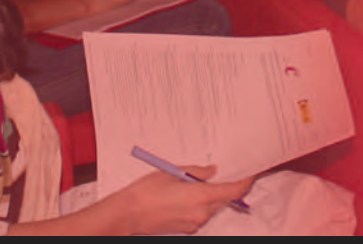
Olmos Y, Sánchez-Gómez FJ, Wild B, García-Quintans N, Cabezudo S, Lamas S and Monsalve M.
SirT1 regulation of antioxidant genes is dependent on the formation of a FoxO3a/PGC-1alpha complex.
Antioxid Redox Signal (2013) 19: 1507-21
IF: 7.189

Moreno-Loshuertos R, Pérez-Martos A, Fernández-Silva P and Enríquez JA.
Length variation in the mouse mitochondrial tRNA DHU loop size promotes OXPHOS functional differences.
FEBS J (2013) 280: 4983-98
IF: 4.250

Münch J, González-Rajal A and de la Pompa JL.
Notch regulates blastema proliferation and prevents differentiation during adult zebrafish fin regeneration.
Development (2013) 140: 1402-11
IF: 6.208

Parton RG and Del Pozo MA.
Caveolae as plasma membrane sensors, protectors and organizers.
Nat Rev Mol Cell Biol (2013) 14: 98-112
IF: 37.162

Peñalvo JL, Santos-Beneit G, Sotos-Prieto M, Martínez R, Rodríguez C, Franco M, López-Romero P, Pocock S, Redondo J and Fuster V.
A cluster randomized trial to evaluate the efficacy of a school-based behavioral intervention for health promotion among children aged 3 to 5.
BMC Public Health (2013) 13: 656
IF: 2.076



APPENDIX

PUBLICATIONS 2013

Peñalvo JL, Sotos-Prieto M, Santos-Beneit G, Pocock S, Redondo J and Fuster V.
The Program SI! intervention for enhancing a healthy lifestyle in preschoolers: first results from a cluster randomized trial.
BMC Public Health (2013) 13: 1208
IF: 2.076

Peralta M, Steed E, Harlepp S, González-Rosa JM, Monduc F, Ariza-Cosano A, Cortes A, Rayon T, Gómez-Skarmeta JL, Zapata A, Vermot J and Mercader N.
Heartbeat-Driven Pericardiac Fluid Forces Contribute to Epicardium Morphogenesis.
Curr Biol (2013) 23: 1726-35
IF: 9.494

Pérez LM, Bernal A, San Martín N, Lorenzo M, Fernández-Veledo S and Gálvez BG.
Metabolic rescue of obese adipose-derived stems cells by Lin28/Let7 pathway.
Diabetes (2013) 62: 2368-79
IF: 7.895

Pérez-Hernández D, Gutiérrez-Vázquez C, Jorge I, López-Martín S, Ursa A, Sánchez-Madrid F, Vázquez J and Yáñez-Mo M.
The intracellular interactome of tetraspanin-enriched microdomains reveals their function as sorting machineries to exosomes.
J Biol Chem (2013) 288: 11649-61
IF: 4.651

Regueiro A, García-Álvarez A, Sitges M, Ortiz-Pérez JT, De Caralt MT, Pinazo MJ, Posada E, Heras M, Gascón J and Sanz G.
Myocardial involvement in Chagas disease: Insights from cardiac magnetic resonance.
Int J Cardiol (2013) 165: 107-12
IF: 5.509

Richardson K, Nettleton JA, Rotllan N, Tanaka T, Smith CE, Lai CQ, Parnell LD, Lee YC, Lahti J, Lemaitre RN, Manichaikul A, Keller M, Mikkila V, Ngwa J, van Rooij FJ, Ballentyne CM, Borecki IB, Cupples LA, García M, Hofman A, Ferrucci L, Mozaffarian D, Perala MM, Raitakari O, Tracy RP, Arnett DK, Bandinelli S, Boerwinkle E, Eriksson JG, Franco OH, Kahonen M, Nalls M, Siscovick DS, Houston DK, Psaty BM, Viikari J, Witteman JC, Goodarzi MO, Lehtimaki T, Liu Y, Zillikens MC, Chen YD, Uitterlinden AG, Rotter JI, Fernández-Hernando C and Ordovás JM.
Gain-of-Function Lipoprotein Lipase Variant rs13702 Modulates Lipid Traits through Disruption of a MicroRNA-410 Seed Site.
Am J Hum Genet (2013) 92: 5-14
IF: 11.202

Rivera-Torres J, Acín-Pérez R, Cabezas-Sánchez P, Osorio FG, González-Gómez C, Megias D, Camara C, López-Otín C, Enríquez JA, Luque-García JL and Andrés V.
Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labeling with amino acids in cell culture.
J Proteomics (2013) 91: 466-77
IF: 4.088

Rocha-Perugini V, Zamai M, González-Granado J, Barreiro O, Tejera E, Yáñez-Mo M, Caiolfa V and Sánchez-Madrid F.
CD81 controls sustained T cell activation signaling and defines the maturation stages of cognate immunological synapses.
Mol Cell Biol (2013) 33: 3644-58
IF: 5.372

Roszer T, Menéndez-Gutiérrez MP, Cedenilla M and Ricote M.
Retinoid X receptors in macrophage biology.
Trends Endocrinol Metab (2013) 24: 460-8
IF: 8.901

Sancho D and Reis ESC.
Sensing of cell death by myeloid C-type lectin receptors.
Curr Opin Immunol (2013) 25: 46-52
IF: 8.771

Santos-Gallego CG, Badimon JJ and Ibáñez B.
Experimental models of atherosclerosis.
Rev Esp Cardiol (2013) 13: 3-12
IF: 3.204

Sanz G and Fuster V.
Prevention: Polypills for cardiovascular prevention: a step forward?
Nat Rev Cardiol (2013) 10: 683-4
IF: 10.400

Sanz J, Moreno P and Fuster V.
The Year in Atherothrombosis 2012.
J Am Coll Cardiol (2013) 62: 1131-43
IF: 14.086

Sillesen H, Entrekin R, García M, Falk E and Fuster V.
Reply to: Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study
JACC Cardiovasc Imaging (2013) 6: 130
IF: 6.164

Silvestre-Roig C, Fernández P, Esteban V, Pello OM, Indolfi C, Rodríguez C, Rodríguez-Calvo R, López-Maderuelo MD, Bauriedel G, Hutter R, Fuster V, Ibáñez B, Redondo JM, Martínez-González J and Andrés V.
Inactivation of Nuclear Factor-Y Inhibits Vascular Smooth Muscle Cell Proliferation and Neointima Formation.
Arterioscler Thromb Vasc Biol (2013) 33: 1036-45
IF: 6.338

Smith CE, Tucker KL, Arnett DK, Noel SE, Corella D, Borecki IB, Feitosa MF, Aslibekyan S, Parnell LD, Lai CQ, Lee YC and Ordovás JM.
Apolipoprotein A2 Polymorphism Interacts with Intakes of Dairy Foods to Influence Body Weight in Two U.S. Populations.
J Nutr (2013) 143: 1865-71
IF: 4.196

Sotos-Prieto M and Peñalvo JL.
Genetic Variation of Apolipoproteins, Diet and Other Environmental Interactions; an Updated Review.
Nutr Hosp (2013) 28: 999-1009
IF: 1.305

Sreeramkumar V, Leiva M, Stadtmann A, Pitaval C, Ortega-Rodríguez I, Wild MK, Lee B, Zarbock A and Hidalgo A.
Coordinated and unique functions of the E-selectin ligand ESL-1 during inflammatory and hematopoietic recruitment in mice.
Blood (2013) 122: 3993-4001
IF: 9.060

Strippoli R, Caiello I and De Benedetti F.
Reaching the Threshold: A Multilayer Pathogenesis of Macrophage Activation Syndrome.
J Rheumatol (2013) 40: 761-7
IF: 3.258

Tejera E, Rocha-Perugini V, López-Martín S, Pérez-Hernández D, Bachir AI, Horwitz AR, Vázquez J, Sánchez-Madrid F and Yáñez-Mo M.
CD81 regulates cell migration through its association with Rac GTPase.
Mol Biol Cell (2013) 24: 261-73
IF: 4.604

Téllez-Plaza M, Gribble MO, Voruganti VS, Francesconi KA, Goessler W, Umans JG, Silbergeld EK, Guallar E, Franceschini N, North KE, Kao WH, Maccluer JW, Cole SA and Navas-Acien A.
Heritability and Preliminary Genome-Wide Linkage Analysis of Arsenic Metabolites in Urine.
Environ Health Perspect (2013) 121: 341-51
IF: 7.260

Téllez-Plaza M, Guallar E, Howard BV and Navas-Acien A.
Cadmium and Cardiovascular Risk.
Epidemiology (2013) 24: 784-5
IF: 5.738

Téllez-Plaza M, Guallar E, Howard BV, Umans JG, Francesconi KA, Goessler W, Silbergeld EK, Devereux RB and Navas-Acien A.
Cadmium Exposure and Incident Cardiovascular Disease.
Epidemiology (2013) 24: 421-9
IF: 5.738

Través PG, López-Fontal R, Cuadrado I, Luque A, Bosca L, de Las Heras B and Hortelano S.
Critical role of the death receptor pathway in the antitumoral effects induced by hispanolone derivatives.
Oncogene (2013) 32: 259-68
IF: 7.357

Trigueros-Motos L, González-Granado JM, Cheung C, Fernández P, Sánchez-Cabo F, Dopazo A, Sinha S and Andrés V.
Embryological-Origin-Dependent Differences in Hox Expression in Adult Aorta: Role in Regional Phenotypic Variability and Regulation of NF-kappaB Activity.
Arterioscler Thromb Vasc Biol (2013) 33: 1248-56
IF: 6.338

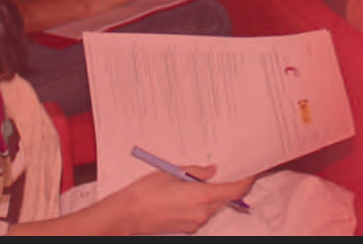
Trullo A, Corti V, Arza E, Caiolfa VR and Zamai M.
Application limits and data correction in number of molecules and brightness analysis.
Microsc Res Tech (2013) 76: 1135-46
IF: 1.593

Villa-Bellosta R, Rivera J, Osorio FG, Acín-Pérez R, Enríquez JA, López-Otín C and Andrés V.
Defective Extracellular Pyrophosphate Metabolism Promotes Vascular Calcification in a Mouse Model of Hutchinson-Gilford Progeria Syndrome that is Ameliorated upon Pyrophosphate Treatment.
Circulation (2013) 127: 2442-51
IF: 15.202

Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, Pérez-Hernández D, Vázquez J, Martín-Cofreces N, Martínez-Herrera DJ, Pascual-Montano A, Mittelbrunn M and Sánchez-Madrid F.
Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs.
Nat Commun (2013) 4: 2980
IF: 10.015

Zaidi M and Méndez-Ferrer S.
Cell biology: tumour stem cells in bone.
Nature (2013) 499: 414-6
IF: 38.597

Zhang Y, Post WS, Cheng A, Blasco-Colmenares E, Tomaselli GF and Guallar E.
Thyroid hormones and electrocardiographic parameters: findings from the third national health and nutrition examination survey.
PLoS One (2013) 8: e59489
IF: 3.730



APPENDIX

PUBLICATIONS 2013

Articles with a CNIC Main Author

Articles without an IF

Arranz L and Méndez-Ferrer S.
Network anatomy and in vivo physiology of mesenchymal stem cells.
Inflamm Regen (2013) 33: 38-47

Benedito R.
Werner Risau Prize.
DGZ Journal (2013) 2: 10-3

Burillo E, Vázquez J and Jorge I.
Quantitative proteomics analysis of high-density lipoproteins by stable (18)o-isotope labeling.
Methods Mol Biol (2013) 1000: 139-56

Calvo E, Martínez-Pinna R, Ramos-Mozo P, Pastor-Vargas C, Camafeita E, Egido J, Martin-Ventura JL and López JA.
Unraveling Biomarkers of Abdominal Aortic Aneurisms by iTRAQ Analysis of Depleted Plasma.
Methods Mol Biol (2013) 1000: 157-66

Castellano JM, Copeland-Halperin R and Fuster V.
Aiming at strategies for a complex problem of medical nonadherence.
Global Heart (2013) 8: 263-71

Franco M, Bilal U, Guallar E, Sanz G, Gómez AF, Fuster V and Cooper R.
Systematic review of three decades of Spanish cardiovascular epidemiology: improving translation for a future of prevention.
Eur J Prev Cardiol (2013) 20: 565-76

Isern J, Martín-Antonio B, Ghazanfari R, Martín AM, López JA, Del Toro R, Sánchez-Aguilera A, Arranz L, Martin-Pérez D, Suarez-Lledó M, Marin P, Van Pel M, Fibbe WE, Vázquez J, Scheding S, Urbano-Ispizua A and Méndez-Ferrer S.
Self-Renewing Human Bone Marrow Mesenspheres Promote Hematopoietic Stem Cell Expansion.
Cell Rep (2013) 3: 1714–24

Pello OM and Andrés V.
Role of c-MYC in tumor-associated macrophages and cancer progression.
Oncoimmunology (2013) 2: e22984

Penkov D, San Martín DM, Fernández-Díaz LC, Rosselló CA, Torroja C, Sánchez-Cabo F, Warnatz HJ, Sultan M, Yaspo ML, Gabrieli A, Tkachuk V, Brendolan A, Blasi F and Torres M.
Analysis of the DNA-Binding Profile and Function of TALE Homeoproteins Reveals Their Specialization and Specific Interactions with Hox Genes/Proteins.
Cell Rep (2013) 3: 1321-33

Pérez LM, Bernal A, San Martín N and Gálvez BG.
Obese-derived ASCs show impaired migration and angiogenesis properties.
Arch Physiol Biochem (2013) 119: 195-201

Téllez-Plaza M, Guallar E, Fabsitz RR, Howard BV, Umans JG, Francesconi KA, Goessler W, Devereux RB and Navas-Acien A.
Cadmium exposure and incident peripheral arterial disease.
Circ Cardiovasc Qual Outcomes (2013) 6: 626-33

Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Madrid F and Mittelbrunn M.
Analysis of MicroRNA and Protein Transfer by Exosomes During an Immune Synapse.
Methods Mol Biol (2013) 1024: 41-51

Articles with NON-CNIC Main Authors

Articles with an IF

Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayón T, Ors I, Grana O, Megías D, Domínguez O, Martínez D, Manzanares M, Ortega S and Serrano M.
Reprogramming in vivo produces teratomas and iPS cells with totipotency features.
Nature (2013) 502: 340-5
IF: 38.597

Abdulla T, Luna-Zurita L, de la Pompa JL, Schleich JM and Summers R.
Epithelial to mesenchymal transition-The roles of cell morphology, labile adhesion and junctional coupling.
Comput Methods Programs Biomed (2013) 111: 435-46
IF: 1.555

Aguilera-Montilla N, Chamorro S, Nieto C, Sánchez-Cabo F, Dopazo A, Fernández-Salguero PM, Rodríguez-Fernández JL, Pello OM, Andrés V, Cuenda A, Alonso B, Domínguez-Soto A, Sánchez-Ramon S and Corbí AL.
Aryl hydrocarbon receptor contributes to the MEK/ERK-dependent maintenance of the immature state of human dendritic cells.
Blood (2013) 121: e108-17
IF: 9.060

Álvarez-Llamas G, Martín-Rojas T, de la Cuesta F, Calvo E, Gil-Dones F, Darde VM, López-Almodovar LF, Padial LR, López JA, Vivanco F and Barderas MG.
Modification of the secretion pattern of proteases, inflammatory mediators and extracellular matrix proteins by human aortic valve is key in severe aortic stenosis.
Mol Cell Proteomics (2013) 12: 2426-39
IF: 7.251

Andrés E, Cordero A, León M, Alcalde V, Laclaustra M and Casasnovas JA.
[Score to predict hypertension in working male population].
Med Clin (Barc) (2013) 140: 487-92
IF: 1.399

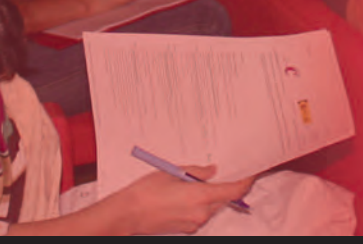
Annila T, Lihavainen E, Marqués I, Williams D, Yli-Harja O and Ribeiro A.
ZebIAT, an image analysis tool for registering zebrafish embryos and quantifying cancer metastasis.
BMC Bioinformatics (2013) 14: S5
IF: 3.024

Arias T, Chen J, Fayad ZA, Fuster V, Hajjar RJ and Chemaly ER.
Comparison of Echocardiographic Measurements of Left Ventricular Volumes to Full Volume Magnetic Resonance Imaging in Normal and Diseased Rats.
J Am Soc Echocardiogr (2013) 26: 910-8
IF: 4.277

Aslibekyan S, An P, Frazier-Wood AC, Kabagambe EK, Irvin MR, Straka RJ, Tiwari HK, Tsai MY, Hopkins PN, Borecki IB, Ordovás JM and Arnett DK.
Preliminary evidence of genetic determinants of adiponectin response to fenofibrate in the Genetics of Lipid Lowering Drugs and Diet Network.
Nutr Metab Cardiovasc Dis (2013) 23: 987-94
IF: 3.978

Bandín C, Martínez-Nicolás A, Ordovás JM, Ros Lucas JA, Castell P, Silvente T, Madrid JA and Garaulet M.
Differences in circadian rhythmicity in CLOCK 3111T/C genetic variants in moderate obese women as assessed by thermometry, actimetry and body position.
Int J Obes (Lond) (2013) 37: 1044-50
IF: 5.221

Banegas JR, López-García E, Dallongeville J, Guallar E, Halcox JP, Borghi C, Masso-González EL, Sazova O, Perk J, Steg PG, De Backer G and Rodríguez-Artalejo F.
Achievement of lipoprotein goals among patients with metabolic syndrome at high cardiovascular risk across Europe. The EURIKA study.
Int J Cardiol (2013) 166: 210-4
IF: 5.509



APPENDIX

PUBLICATIONS 2013

Belmar-López C, Mendoza G, Oberg D, Burnet J, Simon C, Cervello I, Iglesias M, Ramírez JC, López-Larrubia P, Quintanilla M and Martín-Duque P.
Tissue-derived mesenchymal stromal cells used as vehicles for anti-tumor therapy exert different in vivo effects on migration capacity and tumor growth.
BMC Med (2013) 11: 139
IF: 6.679

Bhardwaj D, Nager M, Camats J, David M, Benguría A, Dopazo A, Cantí C and Herreros J.
Chemokines induce axon outgrowth downstream of Hepatocyte Growth Factor and TCF/beta-catenin signaling.
Front Cell Neurosci (2013) 7: 52
IF: 4.466

Bini J, Izquierdo-García D, Mateo J, Machac J, Narula J, Fuster V and Fayad ZA.
Preclinical Evaluation of MR Attenuation Correction Versus CT Attenuation Correction on a Sequential Whole-Body MR/PET Scanner.
Invest Radiol (2013) 48: 313-22
IF: 5.460

Calcagno C, Ramachandran S, Izquierdo-García D, Mani V, Millon A, Rosenbaum D, Tawakol A, Woodward M, Bucerius J, Moshier E, Godbold J, Kallend D, Farkouh ME, Fuster V, Rudd JH and Fayad ZA.
The complementary roles of dynamic contrast-enhanced MRI and F-fluorodeoxyglucose PET/CT for imaging of carotid atherosclerosis.
Eur J Nucl Med Mol Imaging (2013) 40: 1884-93
IF: 5.114

Castell-Auví A, Cedó L, Movassat J, Portha B, Sánchez-Cabo F, Pallarès V, Blay M, Pinent M and Ardévol A.
Procyanidins modulate microRNA expression in pancreatic islets.
J Agric Food Chem (2013) 61: 355-63
IF: 2.906

Cavodeassi F, Bene FD, Furthauer M, Grabher C, Herzog W, Lehtonen S, Linker C, Mercader N, Mikut R, Norton W, Strahle U, Tiso N and Foulkes NS.
Report of the Second European Zebrafish Principal Investigator Meeting in Karlsruhe, Germany, March 21-24, 2012.
Zebrafish (2013) 10: 119-23
IF: 2.883

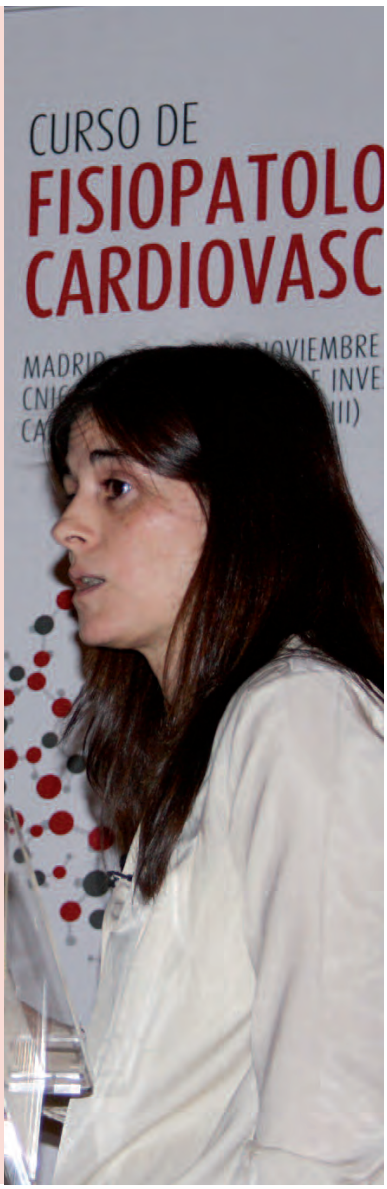
Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibáñez B, Bangalore S and Mukherjee D.
Early intravenous beta-blockers in patients with acute coronary syndrome-A meta-analysis of randomized trials.
Int J Cardiol (2013) 168: 915-21
IF: 5.509

Chen W, Cormode DP, Vengrenyuk Y, Herranz B, Feig JE, Klink A, Mulder WJ, Fisher EA and Fayad ZA.
Collagen-Specific Peptide Conjugated HDL Nanoparticles as MRI Contrast Agent to Evaluate Compositional Changes in Atherosclerotic Plaque Regression.
JACC Cardiovasc Imaging (2013) 6: 373-84
IF: 6.164

Daumit GL, Dickerson FB, Wang NY, Dalcin A, Jerome GJ, Anderson CA, Young DR, Frick KD, Yu A, Gennusa JV, 3rd, Oefinger M, Crum RM, Charleston J, Casagrande SS, Guallar E, Goldberg RW, Campbell LM and Appel LJ.
A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness.
N Engl J Med (2013) 368: 1594-602
IF: 51.658

de Juan-Sanz J, Nuñez E, Villarejo-López L, Pérez-Hernández D, Rodríguez-Fraticelli AE, López-Corcuera B, Vázquez J and Aragón C.
Na+/K+-ATPase Is a New Interacting Partner for the Neuronal Glycine Transporter GlyT2 That Downregulates Its Expression In Vitro and In Vivo.
J Neurosci (2013) 33: 14269-81
IF: 6.908

Del Fresno C, Soulat D, Roth S, Blazek K, Udalova I, Sancho D, Ruland J and Ardavín C.
Interferon-beta Production via Dectin-1-Syk-IRF5 Signaling in Dendritic Cells Is Crucial for Immunity to C. albicans.
Immunity (2013) 38: 1176-86
IF: 19.795

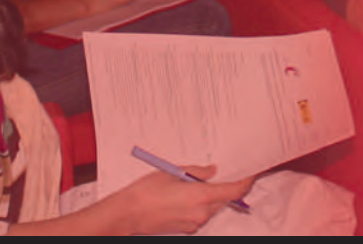


Devi S, Wang Y, Chew WK, Lima R, A-González N, Mattar CN, Chong SZ, Schlitzer A, Bakocevic N, Chew S, Keeble JL, Goh CC, Li JL, Evrard M, Malleret B, Larbi A, Renia L, Haniffa M, Tan SM, Chan JK, Balabanian K, Nagasawa T, Bachelerie F, Hidalgo A, Ginhoux F, Kubes P and Ng LG.
Neutrophil mobilization via plerixafor-mediated CXCR4 inhibition arises from lung demargination and blockade of neutrophil homing to the bone marrow.
J Exp Med (2013) 210: 2321-36
IF: 13.214

Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernández D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altshuler D, Ordovás JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM and Kathiresan S.
Common variants associated with plasma triglycerides and risk for coronary artery disease.
Nat Genet (2013) 45: 1345-52
IF: 35.209

Domínguez F, Cobo-Marcos M, Guzzo G, Cavero MA, Mirelis JG, Alonso-Pulpón L and García-Pavía P.
Erysipelas and Acute Myocarditis: An Unusual Combination.
Can J Cardiol (2013) 29: 1138.e3-5
IF: 3.122

Elmariah S, Budoff MJ, Delaney JA, Hamirani Y, Eng J, Fuster V, Kronmal RA, Halperin JL and O'Brien KD.
Risk factors associated with the incidence and progression of mitral annulus calcification: The multi-ethnic study of atherosclerosis.
Am Heart J (2013) 166: 904-12
IF: 4.497



APPENDIX

PUBLICATIONS 2013

Espín R, Roca FJ, Candel S, Sepulcre MP, González-Rosa JM, Alcaraz-Pérez F, Meseguer J, Cayuela ML, Mercader N and Mulero V.
TNF receptors regulate vascular homeostasis through a caspase-8, caspase-2 and P53 apoptotic program that bypasses caspase-3.
Dis Model Mech (2013) 6: 383-95
IF: 4.959

Fadrowski JJ, Abraham AG, Navas-Acien A, Guallar E, Weaver VM and Furth SL.
Blood Lead Level and Measured Glomerular Filtration Rate in Children with Chronic Kidney Disease.
Environ Health Perspect (2013) 121: 965-70
IF: 7.260

Ferrarini A, Rupérez FJ, Erazo M, Martínez MP, Villar-Álvarez F, Peces-Barba G, González-Mangado N, Troncoso MF, Ruiz-Cabello J and Barbas C.
Fingerprinting based metabolomic approach with lc-ms to sleep apnea and hypopnea sindrome: A pilot study.
Electrophoresis (2013) 34: 2873-81
IF: 3.261

Frazier-Wood AC, Kabagambe EK, Wojczynski MK, Borecki IB, Tiwari HK, Smith CE, Ordovás JM and Arnett DK.
The association between LRP-1 variants and chylomicron uptake after a high fat meal.
Nutr Metab Cardiovasc Dis (2013) 23: 1154-8
IF: 3.978

Frazier-Wood AC, Manichaikul A, Aslibekyan S, Borecki IB, Goff DC, Hopkins PN, Lai CQ, Ordovás JM, Post WS, Rich SS, Sale MM, Siscovick D, Straka RJ, Tiwari HK, Tsai MY, Rotter JI and Arnett DK.
Genetic variants associated with VLDL, LDL and HDL particle size differ with race/ethnicity.
Hum Genet (2013) 132: 405-13
IF: 4.633

Frazier-Wood AC, Ordovás JM, Straka RJ, Hixson JE, Borecki IB, Tiwari HK and Arnett DK.
The PPAR alpha gene is associated with triglyceride, low-density cholesterol and inflammation marker response to fenofibrate intervention: the GOLDN study.
Pharmacogenomics J (2013) 13: 312-7
IF: 5.134

Fuentes QE, Fuentes QF, Andrés V, Pello OM, de Mora JF and Palomo GI.
Role of platelets as mediators that link inflammation and thrombosis in atherosclerosis.
Platelets (2013) 24: 255-62
IF: 2.240

Garaulet M, Gómez-Abellán P, Alburquerque-Bejar JJ, Lee YC, Ordovás JM and Scheer FA.
Timing of food intake predicts weight loss effectiveness.
Int J Obes (Lond) (2013) 37: 604-11
IF: 5.221

García-Bernal D, Redondo-Muñoz J, Dios-Esponera A, Chèvre R, Bailón E, Garayoa M, Arellano-Sánchez N, Gutiérrez NC, Hidalgo A, García-Pardo A and Teixidó J.
Sphingosine-1-phosphate activates chemokine-promoted myeloma cell adhesion and migration involving alpha4beta1 integrin function.
J Pathol (2013) 229: 36-48
IF: 7.585

García-Corzo L, Luna-Sánchez M, Doerrier C, García JA, Guarás A, Acín-Pérez R, Bullejos-Peregrín J, López A, Escames G, Enríquez JA, Acuna-Castroviejo D and López LC.
Dysfunctional Coq9 Protein Causes Predominant Encephalomyopathy Associated to CoQ Deficiency.
Hum Mol Genet (2013) 22: 1233-48
IF: 7.692

García-Pavía P, Cobo-Marcos M, Guzzo-Merello G, Gómez-Bueno M, Bornstein B, Lara-Pezzi E, Segovia J and Alonso-Pulpón L.
Genetics in dilated cardiomyopathy.
Biomark Med (2013) 7: 517-33
IF: 3.217

Gómez-Garay A, López JA, Camafeita E, Bueno MA and Pintos B.
Proteomic perspective of Quercus suber somatic embryogenesis.
J Proteomics (2013) 93: 314-25
IF: 4.088

Hadri L, Kratlian RG, Benard L, Maron BA, Dorfmüller P, Ladage D, Guignabert C, Ishikawa K, Aguero J, Ibáñez B, Turnbull IC, Kohlbrenner E, Liang L, Zsebo K, Humbert M, Hulot JS, Kawase Y, Hajjar RJ and Leopold JA.
Therapeutic Efficacy of AAV1.SERCA2a in Monocrotaline-Induced Pulmonary Arterial Hypertension.
Circulation (2013) 128: 512-23
IF: 15.202

Hernansanz-Agustín P, Izquierdo-Álvarez A, García-Ortiz A, Ibiza S, Serrador JM and Martínez-Ruiz A.
Nitrosothiols in the immune system: signaling and protection.
Antioxid Redox Signal (2013) 18: 288-308
IF: 7.189

Howe K, Clark MD, Torroja CF, Torrance J, Berthelot C, Muffato M, Collins JE, Humphray S, McLaren K, Matthews L, McLaren S, Sealy I, Caccamo M, Churcher C, Scott C, Barrett JC, Koch R, Rauch GJ, White S, Chow W, Kilian B, Quintais LT, Guerra-Assuncao JA, Zhou Y, Gu Y, Yen J, Vogel JH, Eyre T, Redmond S, Banerjee R, Chi J, Fu B, Langley E, Maguire SF, Laird GK, Lloyd D, Kenyon E, Donaldson S, Sehra H, Almeida-King J, Loveland J, Trevanion S, Jones M, Quail M, Willey D, Hunt A, Burton J, Sims S, McLay K, Plumb B, Davis J, Clee C, Oliver K, Clark R, Riddle C, Eliott D, Threadgold G, Harden G, Ware D, Mortimer B, Kerry G, Heath P, Phillimore B, Tracey A, Corby N, Dunn M, Johnson C, Wood J, Clark S, Pelan S, Griffiths G, Smith M, Glithero R, Howden P, Barker N, Stevens C, Harley J, Holt K, Panagiotidis G, Lovell J, Beasley H, Henderson C, Gordon D, Auger K, Wright D, Collins J, Raisen C, Dyer L, Leung K, Robertson L, Ambridge K, Leongamornlert D, McGuire S, Gilderthorp R, Griffiths C, Manthravadi D, Nichol S, Barker G, Whitehead S, Kay M, Brown J, Murnane C, Gray E, Humphries M, Sycamore N, Barker D, Saunders D, Wallis J, Babbage A, Hammond S, Mashreghi-Mohammadi M, Barr L, Martin S, Wray P, Ellington A, Matthews N, Ellwood M, Woodmansey R, Clark G, Cooper J, Tromans A, Grafham D, Skuce C, Pandian R, Andrews R, Harrison E, Kimberley A, Garnett J, Fosker N, Hall R, Garner P, Kelly D, Bird C, Palmer S, Gehring I, Berger A, Dooley CM, Ersan-Urun Z, Eser C, Geiger H, Geisler M, Karotki L, Kirn A, Konantz J, Konantz M, Oberlander M, Rudolph-Geiger S, Teucke M, Osoegawa K, Zhu B, Rapp A, Widaa S, Langford C, Yang F, Carter NP, Harrow J, Ning Z, Herrero J, Searle SM, Enright A, Geisler R, Plasterk RH, Lee C, Westerfield M, de Jong PJ, Zon LI, Postlethwait JH, Nusslein-Volhard C, Hubbard TJ, Crollius HR, Rogers J and Stemple DL.
The zebrafish reference genome sequence and its relationship to the human genome.
Nature (2013) 469: 498-503
IF: 38.597

Imbernon M, Beiroa D, Vázquez MJ, Morgan DA, Veyrat-Durebex C, Porteiro B, Díaz-Arteaga A, Senra A, Busquets S, Velasquez DA, Al-Massadi O, Varela L, Gándara M, López-Soriano FJ, Gallego R, Seoane LM, Argiles JM, López M, Davis RJ, Sabio G, Rohner-Jeanrenaud F, Rahmouni K, Dieguez C and Nogueiras R.
Central Melanin-Concentrating Hormone Influences Liver and Adipose Metabolism Via Specific Hypothalamic Nuclei and Efferent Autonomic/JNK1 Pathways.
Gastroenterology (2013) 144: 636-49 e06
IF: 12.821

Islami F, Pourshams A, Vedanthan R, Poustchi H, Kamangar F, Golozar A, Etemadi A, Khademi H, Freedman ND, Merat S, Garg V, Fuster V, Wakefield J, Dawsey SM, Pharoah P, Brennan P, Abnet CC, Malekzadeh R and Boffetta P.
Smoking water-pipe, chewing nass and prevalence of heart disease: a cross-sectional analysis of baseline data from the Golestan Cohort Study, Iran.
Heart (2013) 99: 272-8
IF: 5.014

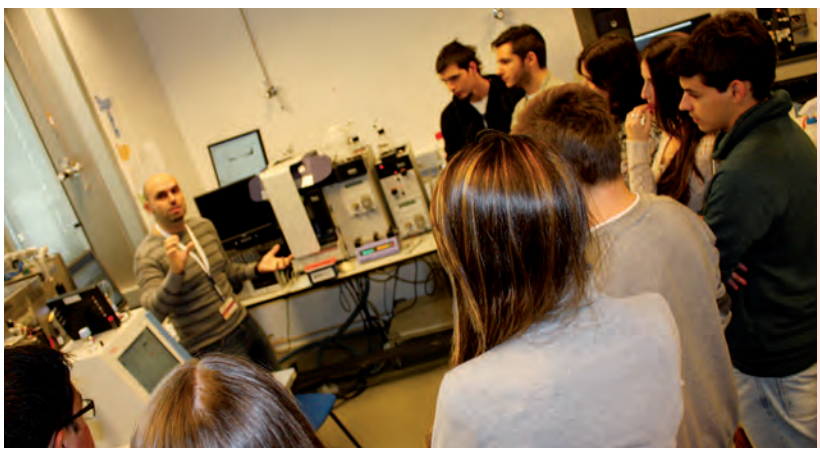
Johnen H, González-Silva L, Carramolino L, Flores JM, Torres M and Salvador JM.
Gadd45g is essential for primary sex determination, male fertility and testis development.
PLoS One (2013) 8: e58751
IF: 3.730

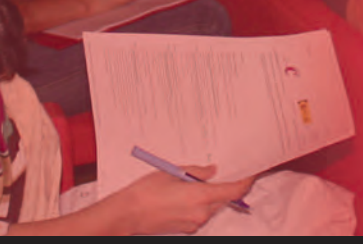
Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz GS, Fuster V, Narula J, Sharma SK and Moreno PR.
Changes in Plaque Lipid Content after Short-Term, Intensive versus Standard Statin Therapy: The YELLOW Trial.
J Am Coll Cardiol (2013) 62: 21-9
IF: 14.086

Kraja AT, Borecki IB, Tsai MY, Ordovás JM, Hopkins PN, Lai CQ, Frazier-Wood AC, Straka RJ, Hixson JE, Province MA and Arnett DK.
Genetic Analysis of 16 NMR-Lipoprotein Fractions in Humans, the GOLDN Study.
Lipids (2013) 48: 155-65
IF: 2.557

Leskela S, Rodríguez-Muñoz A, de la Fuente H, Figueroa-Vega N, Bonay P, Martín P, Serrano A, Sánchez-Madrid F, González-Amaro R and Marazuela M.
Plasmacytoid dendritic cells in patients with autoimmune thyroid disease.
J Clin Endocrinol Metab (2013) 98: 2822-33
IF: 6.430

Lin Y, Wolk A, Hakansson N, Peñalvo JL, Lagergren J, Adlercreutz H and Lu Y.
Validation of FFQ-based assessment of dietary lignans compared with serum enterolactone in Swedish women.
Br J Nutr (2013) 109: 1873-80
IF: 3.302





APPENDIX

PUBLICATIONS 2013

López-Bravo M, Minguito de la Escalera M, Domínguez PM, González-Cintado L, Del Fresno C, Martin P, Martínez Del Hoyo G and Ardavín C.
IL-4 blocks TH1-polarizing/inflammatory cytokine gene expression during monocyte-derived dendritic cell differentiation through histone hypoacetylation.
J Allergy Clin Immunol (2013) 132: 1409-19 e13
IF: 12.047

López-Huertas MR, Mateos E, Sánchez Del Cojo M, Gómez-Esquer F, Díaz-Gil G, Rodríguez-Mora S, López JA, Calvo E, López-Campos G, Alcamí J and Coiras M.
The Presence of HIV-1 Tat Second Exon Delays Fas-Mediated Apoptosis in CD4+ T lymphocytes: a Potential Mechanism for Persistent Viral Production.
J Biol Chem (2013) 288: 7626-44
IF: 4.651

López-Lera A, Sánchez Cabo F, Garrido S, Dopazo A and López-Trascasa M.
Disease-modifying factors in hereditary angioedema: an RNA expression-based screening.
Orphanet J Rare Dis (2013) 8: 77
IF: 4.315

Martínez-Pinna R, Madrigal-Matute J, Tarín C, Burillo E, Esteban-Salan M, Pastor-Vargas C, Lindholt JS, López JA, Calvo E, de Ceniga MV, Meilhac O, Egido J, Blanco-Colio LM, Michel JB and Martín-Ventura JL.
Proteomic Analysis of Intraluminal Thrombus Highlights Complement Activation in Human Abdominal Aortic Aneurysms.
Arterioscler Thromb Vasc Biol (2013) 33: 2013-20
IF: 6.338

Martínez-Revelles S, Avendano MS, García-Redondo AB, Álvarez Y, Aguado A, Pérez-Girón JV, García-Redondo L, Esteban V, Redondo JM, Alonso MJ, Briones AM and Salaices M.
Reciprocal relationship between reactive oxygen species and cyclooxygenase-2 and vascular dysfunction in hypertension.
Antioxid Redox Signal (2013) 18: 51-65
IF: 7.189

Mendes M, Pérez-Hernández D, Vázquez J, Coelho AV and Cunha C.
Proteomic changes in HEK-293 cells induced by hepatitis delta virus replication.
J Proteomics (2013) 89: 24-38
IF: 4.088

Menezes J, Makishima H, Gómez I, Acquadro F, Gómez-López G, Grana O, Dopazo A, Álvarez S, Trujillo M, Pisano DG, Maciejewski JP and Cigudosa JC.
CSF3R T618I co-occurs with mutations of splicing and epigenetic genes and with a new PIM3 truncated fusion gene in chronic neutrophilic leukemia.
Blood Cancer J (2013) 3: e158
IF: 1.400

Molina-Estévez FJ, Lozano ML, Navarro S, Torres Y, Grabundzija I, Ivics Z, Samper E, Bueren JA and Guenechea G.
Impaired Cell Reprogramming in Non-Homologous End Joining Deficient Cells.
Stem Cells (2013) 31: 1723-30
IF: 7.701

Moon KA, Guallar E, Umans JG, Devereux RB, Best LG, Francesconi KA, Goessler W, Pollak J, Silbergeld EK, Howard BV and Navas-Acien A.
Association Between Exposure to Low to Moderate Arsenic Levels and Incident Cardiovascular Disease: A Prospective Cohort Study.
Ann Intern Med (2013) 159: 649-59
IF: 13.976

Mourino-Álvarez L, Calvo E, Moreau J, Padial LR, López JA, Barderas MG and Gil-Dones F.
Proteomic Characterization of EPCs and CECs "in vivo" from Acute Coronary Syndrome patients and Control subjects.
Biochim Biophys Acta (2013) 1830: 3030-53
IF: 3.848

Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V and Finn AV.
Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques.
J Am Coll Cardiol (2013) 61: 1041-51
IF: 14.086

Neria F, Del Carmen Serrano-Pérez M, Velasco P, Urso K, Tranque P and Cano E.
NFATc3 promotes Ca(2+) -dependent MMP3 expression in astroglial cells.
Glia (2013) 61: 1052-66
IF: 5.066

Park C, Guallar E, Linton JA, Lee DC, Jang Y, Son DK, Han EJ, Baek SJ, Yun YD, Jee SH and Samet JM.
Fasting Glucose Level and the Risk of Incident Atherosclerotic Cardiovascular Diseases.
Diabetes Care (2013) 36: 1988-93
IF: 7.735

Petrini S, Minnone G, Coccetti M, Frank C, Aiello C, Cutarelli A, Ambrosini E, Lanciotti A, Brignone MS, D'Oria V, Strippoli R, De Benedetti F, Bertini E and Bracci-Laudiero L.
Monocytes and macrophages as biomarkers for the diagnosis of megalencephalic leukoencephalopathy with subcortical cysts.
Mol Cell Neurosci (2013) 56: 307-21
IF: 3.837

Pla D, Sanz L, Molina-Sánchez P, Zorita V, Madrigal M, Flores-Díaz M, Alape-Giron A, Núñez V, Andrés V, Gutiérrez JM and Calvete JJ.
Snake venomics of Lachesis muta rhombeata and genus-wide antivenomics assessment of the paraspecific immunoreactivity of two antivenoms evidence the high compositional and immunological conservation across Lachesis.
J Proteomics (2013) 89: 112-23
IF: 4.088

Prati F, Uemura S, Souteyrand G, Virmani R, Motreff P, Di Vito L, Biondi-Zoccai G, Halperin J, Fuster V, Ozaki Y and Narula J.
OCT-based diagnosis and management of STEMI associated with intact fibrous cap.
JACC Cardiovasc Imaging (2013) 6: 283-7
IF: 6.164

Quereda JJ, Pucciarelli MG, Botello-Morte L, Calvo E, Carvalho F, Bouchier C, Vieira A, Mariscotti JF, Chakraborty T, Cossart P, Hain T, Cabanes D and García-Del Portillo F.
Occurrence of mutations impairing sigma factor B (SigB) function upon inactivation of Listeria monocytogenes genes encoding surface proteins.
Microbiology (2013) 159: 1328-39
IF: 2.852

Rallon NI, López-Fernández LA, García MI, Benguría A, Fiorante S, Soriano V and Benito JM.
Interferon stimulated genes are associated with peginterferon plus ribavirin treatment response regardless IL28B alleles in HCV/HIV coinfected patients.
AIDS (2013) 27: 687-96
IF: 6.407

Redpath SA, van der Werf N, Cervera AM, Macdonald AS, Gray D, Maizels RM and Taylor MD.
ICOS controls Foxp3(+) regulatory T-cell expansion, maintenance and IL-10 production during helminth infection.
Eur J Immunol (2013) 43: 705-15
IF: 4.970

Richard C, Drevon C, Canto PY, Villain G, Bollerot K, Lempereur A, Teillet MA, Vincent C, Rosselló Castillo C, Torres M, Piwarzyk E, Speck NA, Souyri M and Jaffredo T.
Endothelio-mesenchymal interaction controls runx1 expression and modulates the notch pathway to initiate aortic hematopoiesis.
Dev Cell (2013) 24: 600-11
IF: 12.861

Ruiz A, Salas G, Calero M, Hernández Y, Villanueva A, Herranz F, Veintemillas-Verdaguer S, Martínez E, Barber DF and Morales MP.
Short-chain PEG molecules strongly bound to magnetic nanoparticle for MRI long circulating agents.
Acta Biomater (2013) 9: 6421-30
IF: 5.093

Samaniego R, Estecha A, Relloso M, Longo N, Escat JL, Longo-Imedio I, Avilés AJ, Del Pozo MA, Puig-Kroger A and Sánchez-Mateos P.
Mesenchymal contribution to recruitment, infiltration, and positioning of leukocytes in human melanoma tissues.
J Invest Dermatol (2013) 133: 2255-64
IF: 6.193

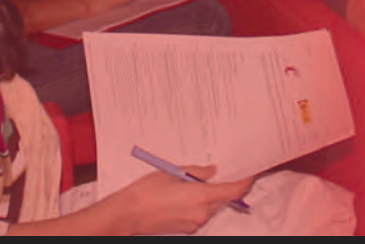
Schneider RP, Garrobo I, Foronda M, Palacios JA, Marion RM, Flores I, Ortega S and Blasco MA.
TRF1 is a stem cell marker and is essential for the generation of induced pluripotent stem cells.
Nat Commun (2013) 4: 1946
IF: 10.015

Segales J, Paz JC, Hernández-Álvarez MI, Sala D, Muñoz JP, Noguera E, Pich S, Palacín M, Enríquez JA and Zorzano A.
A form of Mitofusin 2 (Mfn2) lacking the transmembrane domains and the C-terminal end stimulates metabolism in muscle and liver cells.
Am J Physiol Endocrinol Metab (2013) 305: E1208-21
IF: 4.514

Serrano-Ruiz D, Laurenti M, Ruiz-Cabello J, López-Cabarcos E and Rubio-Retama J.
Hybrid microparticles for drug delivery and magnetic resonance imaging.
J Biomed Mater Res B Appl Biomater (2013) 101: 498-505
IF: 2.308

Smith CE, Ngwa J, Tanaka T, Qi Q, Wojczynski MK, Lemaitre RN, Anderson JS, Manichaikul A, Mikkila V, van Rooij FJ, Ye Z, Bandinelli S, Frazier-Wood AC, Houston DK, Hu F, Langenberg C, McKeown NM, Mozaffarian D, North KE, Viikari J, Zillikens MC, Djousse L, Hofman A, Kahonen M, Kabagambe EK, Loos RJ, Saylor GB, Forouhi NG, Liu Y, Mukamal KJ, Chen YD, Tsai MY, Uitterlinden AG, Raitakari O, van Duijn CM, Arnett DK, Borecki IB, Cupples LA, Ferrucci L, Kritchevsky SB, Lehtimaki T, Qi L, Rotter JI, Siscovick DS, Wareham NJ, Witteman JC, Ordovás JM and Nettleton JA.
Lipoprotein receptor-related protein 1 variants and dietary fatty acids: meta-analysis of European origin and African American studies.
Int J Obes (Lond) (2013) 37: 1211-20
IF: 5.221

Spector JT, Navas-Acien A, Fadrowski J, Guallar E, Jaar B and Weaver V.
Lead and CKD Reply.
Nephrol Dial Transplant (2013) 28: e8-9
IF: 3.371



APPENDIX

PUBLICATIONS 2013

Spinola-Amilibia M, Rivera J, Ortiz-Lombardía M, Romero A, Neira JL and Bravo J.
BRMS151-98 and BRMS151-84 are crystal oligomeric coiled coils with different oligomerization states, which behave as disordered protein fragments in solution.
J Mol Biol (2013) 452: 2147-63
IF: 3.905

Tanaka T, Ngwa JS, van Rooij FJ, Zillikens MC, Wojczynski MK, Frazier-Wood AC, Houston DK, Kanoni S, Lemaitre RN, Luan J, Mikkila V, Renstrom F, Sonestedt E, Zhao JH, Chu AY, Qi L, Chasman DI, de Oliveira Otto MC, Dhurandhar EJ, Feitosa MF, Johansson I, Khaw KT, Lohman KK, Manichaikul A, McKeown NM, Mozaffarian D, Singleton A, Stirrups K, Viikari J, Ye Z, Bandinelli S, Barroso I, Deloukas P, Forouhi NG, Hofman A, Liu Y, Lyytikainen LP, North KE, Dimitriou M, Hallmans G, Kahonen M, Langenberg C, Ordovás JM, Uitterlinden AG, Hu FB, Kalafati IP, Raitakari O, Franco OH, Johnson A, Emilsson V, Schrack JA, Semba RD, Siscovick DS, Arnett DK, Borecki IB, Franks PW, Kritchevsky SB, Lehtimaki T, Loos RJ, Orho-Melander M, Rotter JI, Wareham NJ, Witteman JC, Ferrucci L, Dedoussis G, Cupples LA and Nettleton JA.
Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake.
Am J Clin Nutr (2013) 97: 1395-402
IF: 6.307

Tarone G, Sbroggio M and Brancaccio M.
Key role of ERK1/2 molecular scaffolds in heart pathology.
Cell Mol Life Sci (2013) 70: 4047-54
IF: 5.615

Vacaru AM, Isern J, Fraser ST and Baron MH.
Analysis of primitive erythroid cell proliferation and enucleation using a cyan fluorescent reporter in transgenic mice.
Genesis (2013) 51: 751-62
IF: 2.584

Vidal-Pérez R, Otero-Ravina F, Franco M, Rodríguez García JM, Stolle RL, Álvarez RE, Díaz CI, López EO, Vázquez López MJ and González-Juanatey JR.
Determinants of cardiovascular mortality in a cohort of primary care patients with chronic ischemic heart disease. BARBANZA Ischemic Heart Disease (BARIHD) study.
Int J Cardiol (2013) 167: 442-50
IF: 5.509

Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernández D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Ordovás JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E and

Abecasis GR.
Discovery and refinement of loci associated with lipid levels.
Nat Genet (2013) 45: 1274-83
IF: 35.209

Zanon-Moreno V, Asensio-Márquez EM, Ciancotti-Oliver L, García-Medina JJ, Sanz P, Ortega-Azorín C, Pinazo-Duran MD, Ordovás JM and Corella D.
Effects of polymorphisms in vitamin E-, vitamin C-, and glutathione peroxidase-related genes on serum biomarkers and associations with glaucoma.
Mol Vis (2013) 19: 231-42
IF: 1.987

Zheng LY, Umans JG, Téllez-Plaza M, Yeh F, Francesconi KA, Goessler W, Silbergeld EK, Guallar E, Howard BV, Weaver VM and Navas-Acien A.
Urine arsenic and prevalent albuminuria: evidence from a population-based study.
Am J Kidney Dis (2013) 61: 385-94
IF: 5.294

Zotes TM, Arias CF, Fuster JJ, Spada R, Pérez-Yague S, Hirsch E, Wymann M, Carrera AC, Andrés V and Barber DF.
PI3K p110γ deletion attenuates murine atherosclerosis by reducing macrophage proliferation but not polarization or apoptosis in lesions.
PLoS One (2013) 8: e72674
IF: 3.730

Articles with NON-CNIC Main Authors

Articles without an IF

Alonso-Orgaz S, Martín-Rojas T, Calvo E, López JA, Vivanco F and Barderas MG.
Differential protein expression analysis of degenerative aortic stenosis by iTRAQ labeling.
Methods Mol Biol (2013) 1005: 109-17

Brea A, Laclaustra M, Martorell E and Pedragosa A.
[Epidemiology of cerebrovascular disease in Spain].
Clin Investig Arterioscler (2013) 25: 211-7

Cheng A, Dalal D, Butcher B, Norgard S, Zhang Y, Dickfeld T, Eldadah ZA, Ellenbogen KA, Guallar E and Tomaselli GF.
Prospective observational study of implantable cardioverter-defibrillators in primary prevention of sudden cardiac death: study design and cohort description.
J Am Heart Assoc (2013) 2: e000083

De la Cuesta F, Álvarez-Llamas G, Gil-Dones F, Darde VM, Calvo E, López JA, Vivanco F and Barderas MG.
Secretome of human aortic valves.
Methods Mol Biol (2013) 1005: 237-43

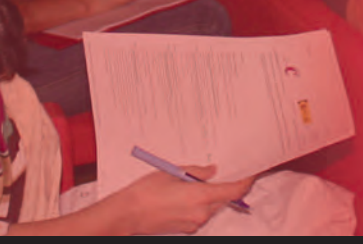
De la Cuesta F, Barderas MG, Calvo E, Zubiri I, Maroto AS, López JA, Vivanco F and Álvarez-Llamas G.
Characterization and analysis of human arterial tissue secretome by 2-DE and nLC-MS/MS.
Methods Mol Biol (2013) 1000: 81-90

Field JJ, Calvo E, Northcote PT, Miller JH, Altmann KH and Díaz JF.
Methods for studying microtubule binding site interactions: zampanolide as a covalent binding agent.
Methods Cell Biol (2013) 115: 303-25

Martínez-Pinna R, López JA, Ramos-Mozo P, Blanco-Colio LM, Camafeita E, Calvo E, Meilhac O, Michel JB, Egido J and Martin-Ventura JL.
Identification of novel biomarkers of abdominal aortic aneurysms by 2D-DIGE and MALDI-MS from AAA-thrombus-conditioned media.
Methods Mol Biol (2013) 1000: 91-101

Purushothaman KR, Krishnan P, Purushothaman M, Wiley J, Alviar CL, Ruiz FJ, Zubatov Y, Kini AS, Sharma SK, Fuster V and Moreno PR.
Expression of angiotensin-converting enzyme 2 and its end product angiotensin 1-7 is increased in diabetic atheroma: implications for inflammation and neovascularization.
Cardiac & Cardiovascular Systems (2013) 22: 42-8

Raimondi MT, Balconi G, Boschetti F, Di Metri A, Azmi Mohammed SA, Quaglini V, Araneo L, Gálvez BG, Lupi M, Latini R and Remuzzi A.
An opto-structural method to estimate the stress-strain field induced by cell contraction on substrates of controlled stiffness in vitro.
J Appl Biomater Funct Mater (2013) 11: e143-50



APPENDIX

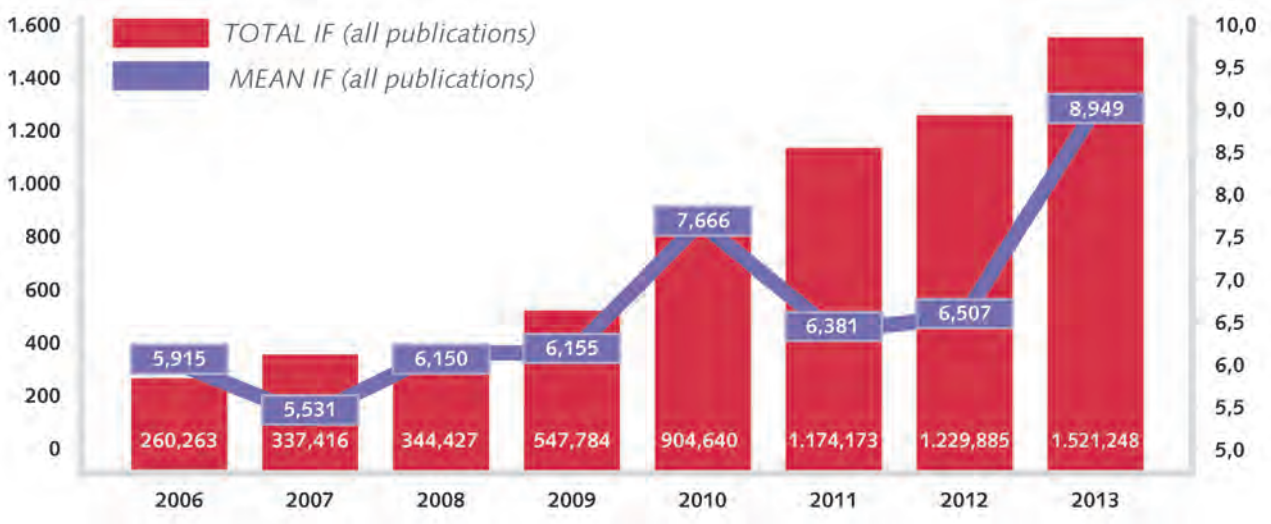
PUBLICATIONS 2013

Verma S, Farkouh ME, Yanagawa B, Fitchett DH, Ahsan MR, Ruel M, Sud S, Gupta M, Singh S, Gupta N, Cheema AN, Leiter LA, Fedak PWM, Teoh H, Latter DA, Fuster V and Friedrich JO.
Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: A meta-analysis of randomised controlled trials.
Lancet Diab Endocrin (2013) 1: 317-28

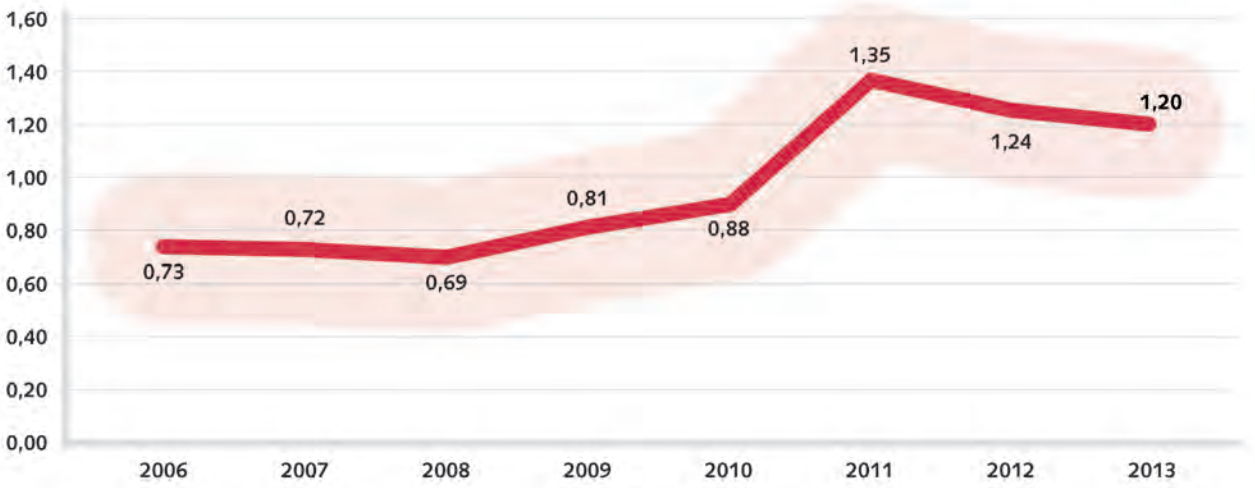
	TOTAL PUBLICATIONS	TOTAL IF PUBLICATIONS	CUMULATIVE IF	MEAN IF
TOTAL*	**192**	**170**	**1.521,248**	**8.949**
CARDIOVASCULAR DEVELOPMENT AND REPAIR	48	42	413.174	9.837
ATHEROTHROMBOSIS, IMAGING AND EPIDEMIOLOGY	94	86	808.180	9.397
VASCULAR BIOLOGY AND INFLAMMATION	33	30	247.598	8.253
TECHNICAL UNITS	35	27	232.079	8.596

** The sum of publications for all Departments and Units in these columns exceeds the total given in the first row because some publications are signed by members from more than one Department or Unit, and these duplicates have been eliminated from the total.*

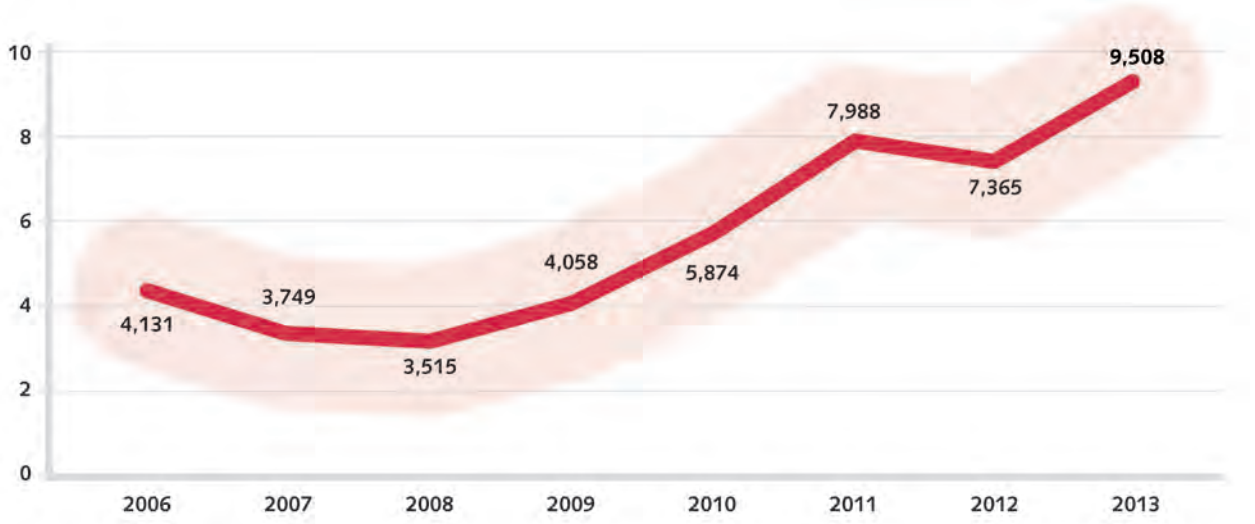
TOTAL AND MEAN IMPACT FACTOR PER YEAR

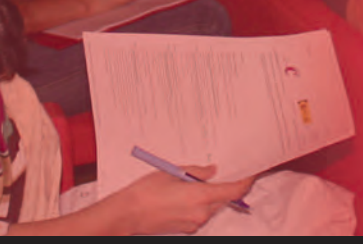


PUBLICATIONS/RESEARCHER



IF/RESEARCHER





APPENDIX

TRAINING PROGRAMS AND COURSES

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 2013

Name	Secondary School	Autonomous Region
Díaz García, Claudio	IES Viera y Clavijo	Canarias
Ferrús Salvadó, Cristina	Institut de Flix	Cataluña
Fortún Belenguer, Marta	IES Félix de Azara	Aragón
González Recio, Pablo	Colegio Sagrado Corazón PP Capuchinos	Madrid
Medina García, Elena	IES Luis Cobiella Cuevas	Canarias
Palací Bataller, Ana	Centro Educativo Palma	Valencia
Ruiz del Valle, Víctor	Juan XXIII Cartuja	Andalucía
Sánchez Ortiz, David	IES Carlos III	Castilla-La Mancha

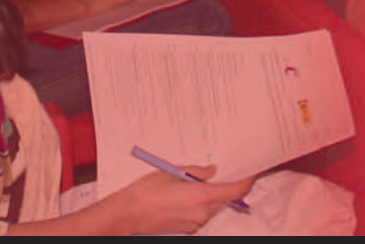
CICERONE Program

The CICERONE Program is open to advanced undergraduate students studying towards 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 university students first-hand knowledge of biomedical research so that they can make informed choices about the possibility of pursuing a scientific career.

Fellowships in 2013

Candidate	Degree	University
Aboy Pardal, Mª del Carmen	Biology	Santiago de Compostela
Alonso Herranz, Laura	Biology	Complutense de Madrid
Álvarez Varela, Adrián	Biochemistry	Autónoma de Madrid
Aparicio Sánchez, José Juan	Biotechnology	Pablo Olavide, Sevilla
Bernardez Noya, Sara	Biology	Santiago de Compostela
Cabrera Bañegil, Manuel	Chemistry	Extremadura
Candela Noguera, Vicente	Biotecnnology	Miguel Hernández, Elche
Cordani, Marco	Biotechnology	Parma, Italy
De Lucas Moreno, Beatriz	Health Biology	Alcalá de Henares
Díaz Marugán, Laura	Biology	Autónoma de Madrid
Fanjul Hevia, Victor	Biology	Oviedo
Fernández Alfara, Marcos	Biochemistry	Autónoma de Madrid
Fernández Cáceres, Eva	Biotecnnology	Pablo Olavide, Sevilla
Gómez Apiñániz, Paula	Biology	Autónoma de Madrid
González del Hoyo, Mª Isabel	Medicine	Complutense de Madrid
Gutierrez Gutierrez, Oscar	Biotecnnology	Autónoma de Madrid
Lechuga, Ana Victoria	Biotechnology	Autónoma de Madrid
Martín Peciña, María	Biology	Salamanca
Martos Folgado, Mª Inmaculada	Biology	Sevilla
Matí Gómez-Aldaraví, Carlos	Biotechnology	Politécnica de Valencia
Montalvo Romedal, Mª del Valle	Biology	Autónoma de Madrid
Mora Gallardo, Carmen	Biotecnology	Pablo Olavide, Sevilla
Muñoz Martín, Noelia	Biology	Salamanca
Nicolás Ávila, José Ángel	Biology	Santiago de Compostela
Ortiz Sánchez, Paula	Biotechnology	Pablo Olavide, Sevilla
Ortiz Simarro, Silvia	Pharmacy	Albacete (UCLM)
Pérez Howell, Oliver	Biotechnology	Miguel Hernández, Elche
Pérez López, María	Health Biology	Alcalá de Henares
Rouco García, Raquel	Biology	Complutense de Madrid
Saz Leal, Paula	Biochemistry	Zaragoza
Sebastián Martín, Alba	Biology	Autónoma de Madrid
Siguero Álvarez, Marcos	Biochemistry	Autónoma de Madrid
Torregrosa Carrión, Rebeca	Biology	Murcia
Vega Gordillo, Miriam Montserrat	Biotechnology	Autónoma de Querétaro, México
Verde Ortega, Ángel	Bioinformatics Engineering	Extremadura



APPENDIX

TRAINING PROGRAMS AND COURSES

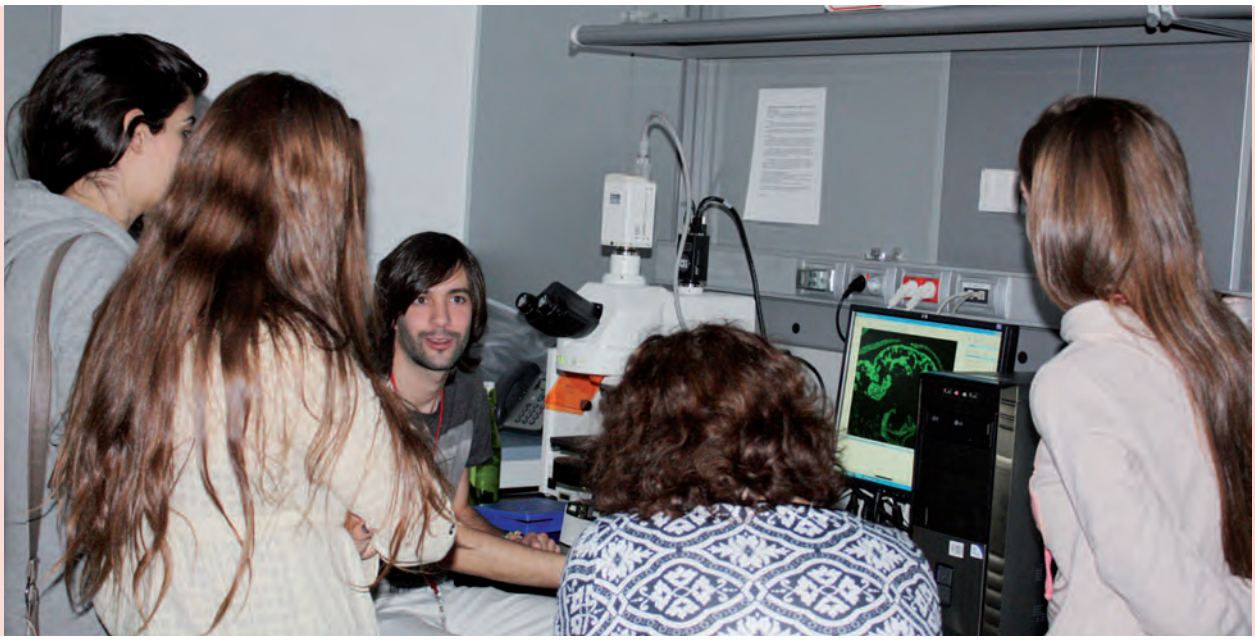
Recent Graduates

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 2013-2014, the CNIC collaborated 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: *13 January-19 February 2014*
Venue: *CNIC*
UAM MSc Students: *21*
CNIC PhD students: *18*



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 2013

Name	Degree - University	MSc	MSc - University
Alonso, Laura	Complutense de Madrid	Biomedicina Molecular	Autónoma de Madrid
Cueto, Francisco Javier	Granada	Biomedicina Molecular	Autónoma de Madrid
Fanjul, Víctor	Oviedo	Biomedicina y Oncología Molecular	Oviedo
Martos, Mª Inmaculada	Sevilla	Biomedicina Molecular	Autónoma de Madrid
Muñoz, Noelia	Salamanca	Biología Celular y Molecular	Autónoma de Madrid
Nicolás, Jose Ángel	Santiago de Compostela	Biología Celular y Molecular	Autónoma de Madrid
Rouco, Raquel	Complutense de Madrid	Biomedicina Molecular	Autónoma de Madrid
Sierra, Federico	Extremadura	Biomedicina Molecular	Autónoma de Madrid

PREDOCTORAL (PhD) Program

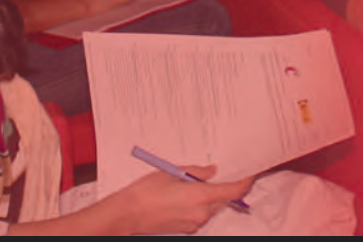
The PREDOCTORAL Program provides a unified framework for all researchers at the CNIC who are working towards a doctoral degree. All predoctoral researchers are signed up to this program, independently of their funding source.

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 2013

Name	Thesis Title	University	CNIC Department	Thesis Advisor(s)
De Luxan, Guillermo	Regulating NOTCH ligands. The role of Mind bomb1 during cardiac development and disease	Autónoma de Madrid	Cardiovascular Development and Repair	Jose Luis de la Pompa
González Rosa, Juan Manuel	Study of the epicardial contribution during heart regeneration in a model of ventricular cryoinjury in Zebrafish.	Autónoma de Madrid	Cardiovascular Development and Repair	Nadia Mercader
Koziol, A. Agnieska	Identification of the substrates of the protease MT1#MMP in TNFalpha stimulated endothelial cells by quantitative proteomics. Analysis of their potential use as biomarkers in inflammatory bowel disease.	Autónoma de Madrid	Vascular Biology and Inflammation	Alicia G Arroyo
Lavin Plaza, Begoña	Vascular Wall Remodelling by proteolitic enzymes and vasoactive factors in cardiovascular pathology models.	Universidad de Alcalá	Epidemiology, Atherothrombosis and Imaging	Carlos Zaragoza
Mateos San Martín, Daniel	The DNA binding profile of tale proteins in the embryo: contrast with in vitro studies and functional implications.	Autónoma de Madrid	Cardiovascular Development and Repair	Miguel Torres
Verdugo, Mª Ángeles	Role of p38MAPKs in the development of hepatic damage produced by obesity.	Autónoma de Madrid	Vascular Biology and Inflammation	Guadalupe Sabio



APPENDIX

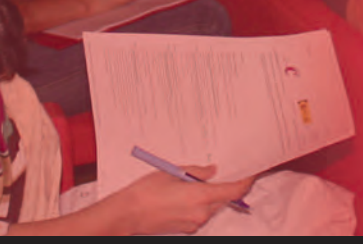
TRAINING PROGRAMS AND COURSES

Graduate students studying for their PhD theses at the CNIC during 2013

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Álvarez Prado, Ángel Francisco	CNIC contract	Autónoma de Madrid	Vascular Biology and Inflammation	No
Aix Sacido, Esther	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	BMM9 2009-2010 / MASTER Program 2009
Bartolomé Izquierdo, Nahikari	FPI (Spanish Ministry of Education)	Universidad del País Vasco	Vascular Biology and Inflammation	No
Bednareck, Dorota	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Bernal, Aurora	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2010 / MASTER Program 2010
Bernardo Vasco, Edgar	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Blanco Menéndez, Noelia	CNIC contract	Autónoma de Madrid	Vascular Biology and Inflammation	No
Bustos Morán, Eugenio	La Caixa Foundation Fellowship	Autónoma de Madrid	Vascular Biology and Inflammation	No
Casanova Acebes, María	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Epidemiology, Atherothrombosis and Imaging	No
Cedenilla Horcajuelo, Marta	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 /Cardiovascular Postgraduate Program 2008-2009 / MASTER Program 2008
Cruz Uréndez, Francisco Miguel	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2010 / MASTER Program 2010
D'Amato, Gaetano	Marie Curie Initial Training Network (NotchIT)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Díaz Díaz, Covadonga	FPU (Spanish Ministry of Education)	Universidad de Oviedo	Cardiovascular Development and Repair	No
Fernández Jiménez, Rodrigo	Río Hortega (ISCIII)	Universidad de Zaragoza	Epidemiology, Atherothrombosis and Imaging	No
Gatto, Alberto	Eurpean International Training Network (FP7)	Autónoma de Madrid	Cardiovascular Development and Repair	No
García-Prieto Cuesta,Jaime	CNIC contract	Autónoma de Madrid	Epidemiology, Atherothrombosis and Imaging	No
Gómez Salinero, Jesús Mª	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	PRACTICALS Program 2009-10 / MASTER Program 2010

Graduate students studying for their PhD theses at the CNIC during 2013

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Gómez Velázquez, Melisa	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	MASTER Program 2009/Cardiovascular Postgraduate Program 2009-2010
González Hernández, Sara	FPI (Spanish Ministry of Education)	Universidad de Sevilla	Cardiovascular Development and Repair	No
González Sainz de Aja, Julio	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
González Terán, Bárbara	European Research Council	Autónoma de Madrid	Vascular Biology and Inflammation	No
González Valdés, Ileana Beatriz	Reseach National Project (Spanish Ministry of Economy and Competitiveness)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Grivas, Dimitris	Research European Agency - Cardionet	Autónoma de Madrid	Cardiovascular Development and Repair	No
Guarás Rubio, Adela Mª	FPI (Spanish Ministry of Education)	Zaragoza	Cardiovascular Development and Repair	No
Gutiérrez Vázquez, Cristina	CAM (Madrid Autonomous Region)	Autónoma de Madrid	Vascular Biology and Inflammation	CICERONE Program 2007 /Cardiovascular Postgraduate Program 2008-2009
Hamczyk, Magda	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Epidemiology, Atherothrombosis and Imaging	CICERONE Program 2010
Herrera Merchán, Antonio	Human Frontier Science Foundation	Autónoma de Madrid	Cardiovascular Development and Repair	
Hidalgo Gavilán, Isabel	contrato CNIC	Autónoma de Madrid	Cardiovascular Development and Repair	No
Izquierdo Hernández, Helena	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	CICERONE Program 2008 and 2009 / PRACTICALS Program 2009-10
Lioux, Ghislaine	Research European Agency - Cardionet	Université Paris	Cardiovascular Development and Repair	No
Lozano Vidal, Noelia	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	Cardiovascular Postgraduate Program 2009-2010 / MASTER Program 2009
Manieri, Elisa	La Caixa Foundation Fellowship	Autónoma de Madrid	Vascular Biology and Inflammation	No



APPENDIX

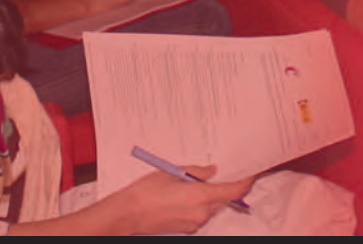
TRAINING PROGRAMS AND COURSES

Graduate students studying for their PhD theses at the CNIC during 2013

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Martín Alonso, Mara	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	CICERONE Program 2008 / Cardiovascular Postgraduate Program 2009-2010
Laura Martín Pérez	FPI (Spanish Ministry of Education)	Universidad de León	Cardiovascular Development and Repair	No
Méndez Barbero, Nerea	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	Cardiovascular Postgraduate Program 2008-2009 / MASTER Program 2008
Molina Sánchez, Pedro	FPU (Spanish Ministry of Education)	Universidad de Valencia	Epidemiology, Atherothrombosis and Imaging	No
Montes Menéndez, Iván	La Caixa Foundation Fellowship	Universidad de Oviedo	Cardiovascular Development and Repair	No
Moreno Vicente, Roberto	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	CICERONE Program 2011
Munch, Juliane	Notch IT, Marie Curie	Autónoma de Madrid	Cardiovascular Development and Repair	Cardiovascular Postgraduate Program 2009-2010
Nieto Arellano, Rocío	FPU (Spanish Ministry of Education)	Universidad de Valencia	Cardiovascular Development and Repair	CICERONE Program 2012
Núñez Andrade, Norman	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Oller Pedrosa, Jorge	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Peralta López, Marina	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2009 /PRACTICALS Program 2008-9 /Cardiovascular Postgraduate Program 2009-20010 / MASTER Program 2009
Pérez García, Atrantxa	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Rayón Alonso, Teresa	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Pun Hidalgo, Andrés	FPI (Spanish Ministry of Education)	Universidad Complutense de Madrid	Epidemiology, Atherothrombosis and Imaging	No
Roche Molina, Marta	FPI (Spanish Ministry of Education)	Universidad de Sevilla	Cardiovascular Development and Repair	No
Sánchez Ferrer, Carlota	FPI (Spanish Ministry of Education)	Universidad Complutense de Madrid	Cardiovascular Development and Repair	No

Graduate students studying for their PhD theses at the CNIC during 2013

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Sánchez Iranzo, Héctor	FPU (Spanish Ministry of Education)	Universidad de Valencia	Cardiovascular Development and Repair	MASTER Program 2011
Tomé Pizarro, María	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 / Cardiovascular Postgraduate Program 2008-2009
Travisano, Stanislaolgor	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Uribe Sokolov, Verónica	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2007 and 2008 / MASTER Program 2008
Valiente Alandí, Iñigo	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 /Cardiovascular Postgraduate Program 2008-2009 / MASTER Program 2008
Villa del Campo, Cristina	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2007-09 /Cardiovascular Postgraduate Program 2009-20010 / MASTER Program 2009
Villahoz Lázaro, Silvia	FPI (Spanish Ministry of Education)	Universidad de León	Cardiovascular Development and Repair	CICERONE Program 2011-2012



APPENDIX

TRAINING PROGRAMS AND COURSES

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 edition of the Severo Ochoa Award. In 2013 the *la Caixa* Foundation provided support for five 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, 2013

Name	CNIC Supervisor	CNIC Department
Bustos, Eugenio	Sánchez Madrid, Francisco	Vascular Biology and Inflammation
Enamorado, Neris Michel	Sancho Madrid, David	Vascular Biology and Inflammation
García García, Andrés	Méndez Ferrer, Simón	Cardiovascular Development and Repair
Menéndez Montes, Iván	Martín-Puig, Silvia	Cardiovascular Development and Repair
Pontes, Samuel	Benedito, Rui	Cardiovascular Development and Repair

CARDIO-IMAGE Program

The CARDIO-IMAGE Program (CNIC-MSSM) was launched within the collaboration agreement between the CNIC and the Mount Sinai School of Medicine (MSSM), the aim of which is to create a Joint Training and Research Unit in Cardiovascular Imaging. The goal of this Program is to offer blue-ribbon training in state-of-the-art cardiovascular imaging. This is achieved through laboratory-based training at the CNIC-MSSM Joint Unit, located on the MSSM campus in New York.

Fellowships in 2013

Name	Institution
Arís Sánchez, Ruth	BARCELONA SUPERCOMPUTING CENTER - Spain
Pérez Medina, Carlos	CIBERES - Spain
Pérez Sánchez, José Manuel	CIBERES - Spain

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 collaboration with the CNIC.

RES@CNIC was launched in 2012. Students selected for the second call will join the CNIC during January and February 2014.

Selected Candidates for the second call

Candidate	Hospital	CNIC Supervisor
Álvarez García-Rovés, Reyes	H.G.U. Gregorio Marañón (Madrid)	Jose Luis de la Pompa
Bazal Chacón, Pablo	Complejo Hospitalario de Navarra	Jesus Borreguero
Caravaca Pérez, Pedro Joaquín	H.U. "Virgen de la Macarena" (Sevilla)	Miguel Torres
Enríquez Rodríguez, Luis Eduardo	H. Clínico San Carlos (Madrid)	Borja Ibáñez
Espejo Paeres, Carolina	H. Clínico San Carlos (Madrid)	Jose Luis de la Pompa
Gómez Polo, Juan Carlos	H. Clínico San Carlos (Madrid)	Jesús Ruiz-Cabello
Jiménez-Blanco Bravo, Marta	H.U. Puerta de Hierro (Majadahonda)	Borja Ibáñez
Lorca Gutiérrez, Rebeca	H. U. Central de Asturias	Borja Ibáñez
Lozano Granero, Vanesa Cristina	H.U. Ramón y Cajal (Madrid)	Jesús Borreguero
Martínez de Bourio Uniarte, Rafael	H. U. de Basurto (Bilbao)	Borja Ibáñez
Pascual Izco, Marina	H.U. Ramón y Cajal (Madrid)	Jose Antonio Enríquez
Ruiz Pizarro, Virginia	H. Clínico San Carlos (Madrid)	Enrique Lara
Sanz Sánchez, Jorge	H.U. y Politècnic " La Fe" (Valencia)	Jesús Ruiz-Cabello
Ullate de la Torre, Alberto	H. U. de Basurto (Bilbao)	Jesús Ruiz-Cabello
Valverde Gómez, María	H.U. Ramón y Cajal (Madrid)	Enrique Lara

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 2013

Candidate	Hospital	CNIC Department
Gulillén Zabala, Hetmuth	Universitario Ramón y Cajal (Madrid)	Atherothrombosis, Imaging and Epidemiology
Gutierez Bejarano, Dayro Zamyr	Unidad Docente Medicina Familiar y Comunitaria (Segovia)	Atherothrombosis, Imaging and Epidemiology
Maseda Uriza, Ramón	Universitario de Ciudad Real	Atherothrombosis, Imaging and Epidemiology
Vilchez Tschischke, Jean Paul	Universitario Clínico San Carlos (Madrid)	Atherothrombosis, Imaging and Epidemiology

CICERONE Workshop: "What you need to know about cardiovascular research"

Fundación Interhospitalaria Investigación Cardiovascular

This group of lectures provides a general introduction to cardiovascular research in Spain, and also gives participants the chance to question key researchers and opinion leaders in the field. Since 2012 editions of the Jornada CICERONE have been run in collaboration with the Fundación Interhospitalaria para la Investigación Cardiovascular and takes place in the Hospital Clínico San Carlos, Madrid.

Dates: *September 13-14, 2013*
Attendees: *114*

CARDIOVASCULAR PATHOPHYSIOLOGY Course: "From symptoms to genes"

The course in CARDIOVASCULAR PATHOPHYSIOLOGY 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 22-23, 2013*
Venue: *CNIC Lecture Hall*
Attendees: *113*

VASCULAR BIOLOGY Course

Dr. Valentín Fuster delivers this lecture series, sponsored by FERRER, on "From Cardiovascular Disease to Health. A Journey from Molecules and Genetics to Society" as part of the summer program of the Universidad Internacional Menéndez Pelayo (UIMP).

Dates: *July 15-16, 2013*
Attendees: *104*

Research Professionals

CNIC International Incoming Fellowships for Young Group Leaders

The CNIC IFF program aims to increase the mobility within Europe of experienced researchers in the cardiovascular research area. The program has been designed to support transnational mobility of researchers and to broaden and deepen their individual competencies, particularly in terms of acquisition of complementary skills needed to attain or strengthen a senior independent position in biomedical research.

The CNIC IIF is supported by the CNIC and the European Commission through the COFUND Programme, within the Marie Curie Actions theme in FP7. The EC contributes 40% of the total cost of the program.

Fellowships in 2013

Name	CNIC Department
Alegre Cebollada, Jorge	Vascular Biology and Inflammation

APPENDIX

SEMINARS, EVENTS AND AWARDS

January

8 **Nuria Gago-López**
University of Washington Medical Center
Seattle, USA

17 **Stuart Pocock**
London School of Hygiene and Tropical Medicine
London, UK

21 **Klaus Rajewsky**
Max-Delbrück-Center for Molecular Medicine
Berlin, Germany

28 **Massimo Zeviani**
Fondazione IRCCS Istituto Neurologico "C. Besta"
Milan, Italy

30 **Salvador Aznar-Benitah**
Center for Genomic Regulation (CRG)
Barcelona, Spain

February

4 **Jeffery Molkentin**
Howard Hughes Medical Institute,
Children's Hospital Medical Center
Cincinnati, USA

18 **Jagat Narula**
Mount Sinai School of Medicine, Zena and
Michael A. Wiener Cardiovascular Institute
and Marie-Josée and Henry R. Kravis Center
for Cardiovascular Health, New York, USA

28 **John Welch**
Stem Cell Biology Section, Washington University
School of Medicine, St. Louis, USA

March

1 **CNIC Workshop**
Translational Aspects of Cardiovascular
and Pulmonary Imaging (TACPI2013)

1 **Manuel López Cabrera**
Centro de Biología Molecular-Severo Ochoa.
CSIC-UAM
Madrid, Spain

4 **Willem van Mechelen**
EMGO+ Institute, VU University Medical Center
Amsterdam, The Netherlands

7 **Alvar Agustí**
Instituto del Torax, Hospital Clinic,
Universidad de Barcelona
Barcelona, Spain

8 **Francisco Javier Cubero**
University Hospital Aachen
Aachen, Germany

11 **Catherine Shanahan**
James Black Centre, King's College London
London, UK

15 **William G. Kerr**
SUNY Upstate Medical University, Syracuse
New York, USA

22 **Thomas Graf**
Centre de Regulació Genómic
Barcelona, Spain

22 **Kannan M. Krishnan**
University of Washington
Seattle, USA

April

2 **Fernando Martín Belmonte**
CBMSO
Madrid, Spain

8 **Richard Cohen**
Whitaker Cardiovascular Institute,
Boston University School of Medicine
Boston, USA

10 **CNIC - First Course on Microscopy and Advanced Applications**

12 **Costanza Giampietro**
IFOM-IEO Campus
Milan, Italy

15 **Elly Tanaka**
Center for Regenerative Therapies Dresden
Dresden, Germany

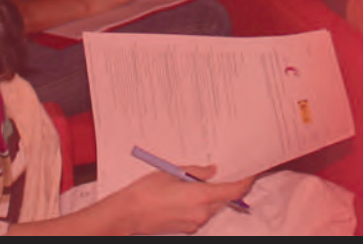
22 **Francois Spitz**
Developmental Unit – EMBL
Heidelberg, Germany

29 **Valerie Weaver**
University of California
San Francisco, USA

May

6 **Shahragim Tajbakhsh**
Pasteur Institute
Paris, France

13 **Donna Arnett**
University of Alabama at Birmingham
USA



APPENDIX

SEMINARS, EVENTS AND AWARDS

16 **Oliver Söhnlein**
Institute for Cardiovascular Prevention
Ludwig-Maximilians University
Munich, Germany

22 **Miguel Martín**
Hospital General Universitario Gregorio Marañón
Madrid, Spain

23 **Ingenuity Seminar**
Software "Ingenuity Pathway Analysis"
(IPA, Ingenuity systems)

27 **Jeroen Bakkers**
Hubrecht Institute,
Utrecht, The Netherlands

31 **Kai Simons**
Max-Planck-Institute of Molecular Cell Biology and Genetics
Dresden, Germany

June

13 **Eike Nagel**
King's College London
UK

17 **Roberto Bolli**
Institute of Molecular Cardiology
University of Louisville
USA

21 **César Nombela**
Children's Hospital
Boston, USA

25 **José Luis Martín Ventura**
IIS-Fundación Jiménez Díaz-UAM
Madrid, Spain

July

4 **Consolider COAT Annual Meeting**
Cell Compartmentation: integrating Membrane Trafficking, Mechanotransduction and the Cytoskeleton

5 **Paul Wiseman**
MacGill University
Montreal, Canada

15 **Curso Universidad Internacional Menéndez Pelayo 2013**
From Cardiovascular Disease to Health: A Journey from Molecules and Genetics to Society
Santander, Spain

16 **Martin Villalba González**
Institut de Recherche en Biothérapie
CHU Montpellier Hôpital Saint-Eloi
Montpellier, France

18 **Nathan Lawson**
University of Massachusetts Medical School
Worcester, USA

September

13 **Jornada Cicerone 2013**
What You Need to Know About Cardiovascular Research

16 **Dariush Mozaffarian**
Brigham and Women's Hospital and Harvard Medical School
Boston, USA

18 **Elisabeth Hinde**
Centre for Cardiovascular Research (CVR)
University of New South Wales
Sydney, Australia

20 **José Jalife**
Center for Arrhythmia Research
Michigan, USA

October

21 **Workshop: Current Trends in Biomedicine**
The Hemato-Vascular System: Development and Disease

21 **Mariano Vázquez**
Barcelona Supercomputing Center
Barcelona, Spain

28 **Akiyoshi Uemera**
Kobe University Graduate School of Medicine
Japan

31 **Ivan López**
Universidad Complutense de Madrid
Spain

November

4 **Hesham Sadek**
UT Southwestern Medical Center
Dallas, USA

5 **Semana de la Ciencia (Science Week)**
Ven a CNIC: Visita interactiva a sus departamentos para conocer la investigación cardiovascular

8-9 **CNIC Conference**
Cardiovascular Development, Disease and Repair

15 **Albert Pol**
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Barcelona, Spain

20 **Joaquín Dopazo**
Centro de Investigación Príncipe Felipe
Valencia

22 **Course in Cardiovascular Pathophysiology 2013**
From Symptoms to Genes

Awards

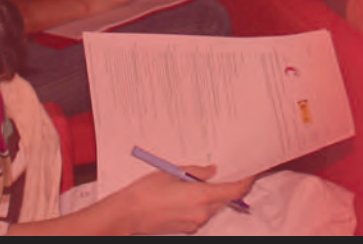
Cardiovascular Development and Repair Department

Award: 2013 Werner Risau Prize, for the article Benedito R, Rocha SF, Woeste M, Zamykal M, Radtke F, Casanovas C, Duarte A, Pytowski B, Adams RH. **Notch–dependent VEGFR3 upregulation allows angiogenesis without VEGF-VEGFR2 signalling.** Nature (2012) 484: 110-114
Awarded to: **Rui Benedito.**

Award: 2013 runner-up in the *Premio Juan Letona en Investigación en Medicina Traslacional (Fundación Hospital de Madrid)*; for the article Luxán G, Casanova JC, Martínez-Poveda B, Prados B, D'Amato G, MacGrogan D, Gonzalez-Rajal A, Dobarro D, Torroja C, Martinez F, Izquierdo-García JL, Fernández-Friera L, Sabater-Molina M, Kong YY, Pizarro G, Ibañez B, Medrano C, García-Pavía P, Gimeno JR, Monserrat L, Jiménez-Borreguero LJ, de la Pompa JL. **Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy.** Nat Med (2013) 19: 193-201
Awarded to: **Guillermo Luxán, José Luis de la Pompa group.**

Award: 2013 Achievement Award at the 55th Annual Meeting of the American Society of Hematology, New Orleans, USA, for the oral communication Arranz L, Sánchez-Aguilera A, Isern J, Martín-Pérez D, Tzankov A, Schwaller J, Skoda RC, Méndez-Ferrer S. **Sympathetic Neuropathy of the Hematopoietic Stem Cell Niche Is Essential for Myeloproliferative Neoplasms.** Blood, (2013) 122: 268
Awarded to: **Lorena Arranz, Simón Méndez group.**

Award: Arquímedes Award: runner-up prize for undergraduate final project in Biology
Awarded to: **Paula Gómez Apiñaniz, José Luis de la Pompa group.**



APPENDIX

SEMINARS, EVENTS AND AWARDS

Award: EMBO Poster Prize. EMBL Symposium on Cardiac Biology: From Development to Regenerative Medicine. June 07-10, 2013. Bednarek D, González-Rosa JM, Guzman G, Aguado T, de Diego I, Cortés A, Zapata A, Jiménez-Borreguero J, Mercader N, Flores I. **Telomerase supports zebrafish heart rejuvenation and regeneration.**
Awarded to: **Dorota Bednarek, Ignacio Flores group.**

Award: Best Poster. COST Action: Dealing with hypoxia: Regulatory aspects in cells, tissues and organisms. Oulu, Finland, June 8-12, 2013. Menéndez-Montes I, Escobar-Rodríguez B, Alonso-López AV, Jiménez-Borreguero LJ, Martín-Puig S. **Von Hippel-Lindau deletion in Wt1+ epicardial progenitors causes cardiac hypertrophy, fibrosis and abnormal coronary vessel development.**
Awarded to: **Iván Menéndez, Miguel Torres group.**

Vascular Biology and Inflammation Department

Award: *VIII Premio Banco Sabadell a la Investigación Biomédica.*
Awarded to: **Almudena R. Ramiro.**

Award: Named Academic Member of the *Real Academia Española de Farmacia.*
Awarded to: **Francisco Sánchez Madrid.**

Atherothrombosis, Imaging and Epidemiology Department

Award: Best presentation at the SEC (Spanish Society of Cardiology) conference, 2013.
Estimulación adrenérgica B3 como nueva alternativa terapéutica en hipertensión pulmonar aguda y crónica
Awarded to: **Ana García-Álvarez, Daniel Pereda, Mario Nuño-Ayala, Rodrigo Fernández-Jiménez, David Sanz-Rosa, José Manuel García-Ruiz, Valentin Fuster, Borja Ibáñez**

Award: 2013 Basic Research Poster Award at the Progeria Research Foundation Scientific Workshop, Bethesda, USA (presented by R. Villa-Bellosta)
Defective extracellular pyrophosphate metabolism promotes vascular calcification in a mouse model of Hutchinson-Gilford progeria syndrome
Awarded to: **Ricardo Villa-Bellosta, José Rivera, Fernando G. Osorio, Carlos López-Otín, Vicente Andrés.**

Award: 2013 Munster Heart Center Lecture Award, Munster, Germany
Awarded to: **Valentín Fuster**

Award: 2013 Honoris Causa, Universidad de VIC, Barcelona, Spain
Awarded to: **Valentín Fuster**

Award: 2013 Simon Dack Lecture Award, American College of Cardiology (ACC), San Francisco, USA
Awarded to: **Valentín Fuster**

Award: 2013 Honoris Causa, Universidad CEU Cardenal Herrera, Castellón, Spain
Awarded to: **Valentín Fuster**

Award: 2013 American Heart Association/American Stroke Association Ron Haddock International Impact Award. Houston, USA
Awarded to: **Valentín Fuster**

Award: 2013 Arthur S. Agatston Cardiovascular Disease Prevention Award, Society of Cardiovascular Computed Tomography (SCCT), Montreal, Canada
Awarded to: **Valentín Fuster**

Award: 2013 *Camino Real Award* (Alcalá de Henares, Spain) – July 18 2013
Awarded to: **Valentín Fuster**

Award: 2013 *Excelencia Sanitaria Award*, Instituto Europeo. Madrid, Spain
Awarded to: **Valentín Fuster**

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

The central aim of biomedical research is to translate knowledge generated in basic research laboratories into improved and innovative clinical practice, and reciprocally to stimulate research into questions raised in healthcare centers. Excellence in this area requires an integrated network based on close contacts with a wide range of institutions in different sectors.

In the last year, the CNIC has signed 57 inter-institutional agreements to create or consolidate partnerships.

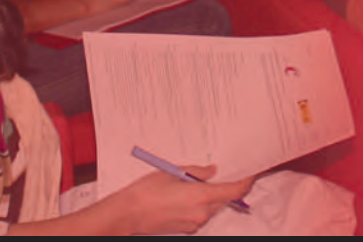
In the education sector, the CNIC has expanded its academic network by signing agreements with universities in Spain (Murcia, Valladolid, Oviedo) and abroad (Padua, Italy; Bristol, United Kingdom; Oxford, United Kingdom; Tufts, USA). These agreements mostly establish student exchange programs and short visits for practical work in the CNIC's laboratories.

The CNIC's international projection is greatly strengthened by finanacial support from the European Union, through the CardioNext and CardioNet Initial Training Networks and the International Postdoctoral Program (CNIC IPP). Direct support in this area also comes from the Spanish private sector, through the la Caixa Severo Ochoa International PhD Program.

The Center has also reinforced its relationships with the Sociedad Española de Cardiología and the Sociedad Española de Cirugía Torácica Cardiovascular.

Ongoing population research projects are being carried out through partnerships with the Gobierno de Aragón (Aragon's Workers Health Study; AWHS) and Philips Healthcare (Progression of Early Subclinical Atherosclerosis; PESA).

In 2013, support for the CNIC's activities was secured through a new partnership with Fundación Serra and a major injection of funding came with the incorporation of new Pro-CNIC member Fundación Mapfre.



Public-Private Partnership

In spite of the enormous advances in diagnosis and treatment witnessed over the last 20 years, cardiovascular diseases continue to be the main cause of death in the developed world. The costs generated in economic, social and human terms are immense. In response to this reality, the Spanish Government, through the Instituto de Salud Carlos III (Carlos III Health Institute), created the CNIC to bring together the best of Spanish cardiovascular research and provide it with a modern infrastructure and ample funding to carry out world-leading biomedical research.

To achieve the funding necessary for its ambitious plan, the Spanish government appealed to the sense of social obligation of some of the major players in Spanish civil society, inviting the largest businesses in the country to make an active and long-term commitment to this project. The outcome was an agreement, signed in December 2005, between the Spanish government and a group of some of the most important Spanish businesses. Through this agreement these companies pledged to fund the CNIC up to 2012. This commitment was recently extended until 2020.

Shortly after the agreement was signed, on January 24, 2006, the group of companies was formally constituted as the ProCNIC Foundation, signaling the most significant act of business sponsorship in recent years in terms of the amount of funding provided, its social significance, the group of companies involved, and the anticipated outcomes.

Since the signing of this agreement, the CNIC's funding has been based on a public-private partnership of a broad, socially-committed nature. In this innovative PPP, state funding is complemented by financing through the ProCNIC Foundation (**http://www.fundacionprocnic.es**).

On November 5 2013, **Fundación Mapfre**—the non profit organization set up by Spanish insurance giant MAPFRE—became the fourteenth partner in the Pro-CNIC Foundation, through an agreement signed by Pro-CNIC president Luis de Carlos and MAPFRE President Antonio Huertas, in the presence of Dr. Fuster. The other thirteen Pro-CNIC members are **Acciona**, **BBVA**, **Endesa**, **Fundación Abertis**, **Fundación Mutua Madrileña**, **Fundación Botín**, **Fundación Ramón Areces**, **Fundación Repsol**, **Gas Natural Fenosa**, **Grupo Prisa**, **Inditex**, **la Caixa**, and **Telefónica**. These full members are joined by ProCNIC International Collaborator Mitsubishi. This unique PPP allows the CNIC to fund special programs for the discovery and training of young investigators, to award extramural grants aimed at integrating basic and clinical research to answer specific questions, to acquire specialized research equipment that would otherwise be difficult to fund, and to run programs to incentivize and retain valuable investigators.

But the ProCNIC Foundation does more than provide the CNIC with money; it also contributes its accumulated managerial and business expertise. Representatives of the ProCNIC Foundation sit on the CNIC's Board of Trustees and actively participate in the management, planning and decision taking related to the Center. In this way, some of the most important organizations in the private sector in Spain have committed themselves to a direct involvement in biomedical research and the fight against cardiovascular diseases.

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.

Private Funding

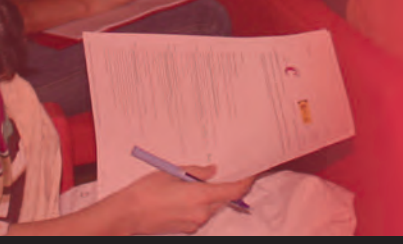
Fundación pro cnic

acciona · BBVA · endesa · fundación abertis · FUNDACIÓN MAPFRE · FUNDACIÓN MUTUAMADRILEÑA · FUNDACION RAMON ARECES · FUNDACIÓN BOTÍN · Fundación REPSOL · gasNatural fenosa · PRISA · INDITEX · "la Caixa" · Telefónica

ProCNIC
International Collaborator
Mitsubishi Corporation

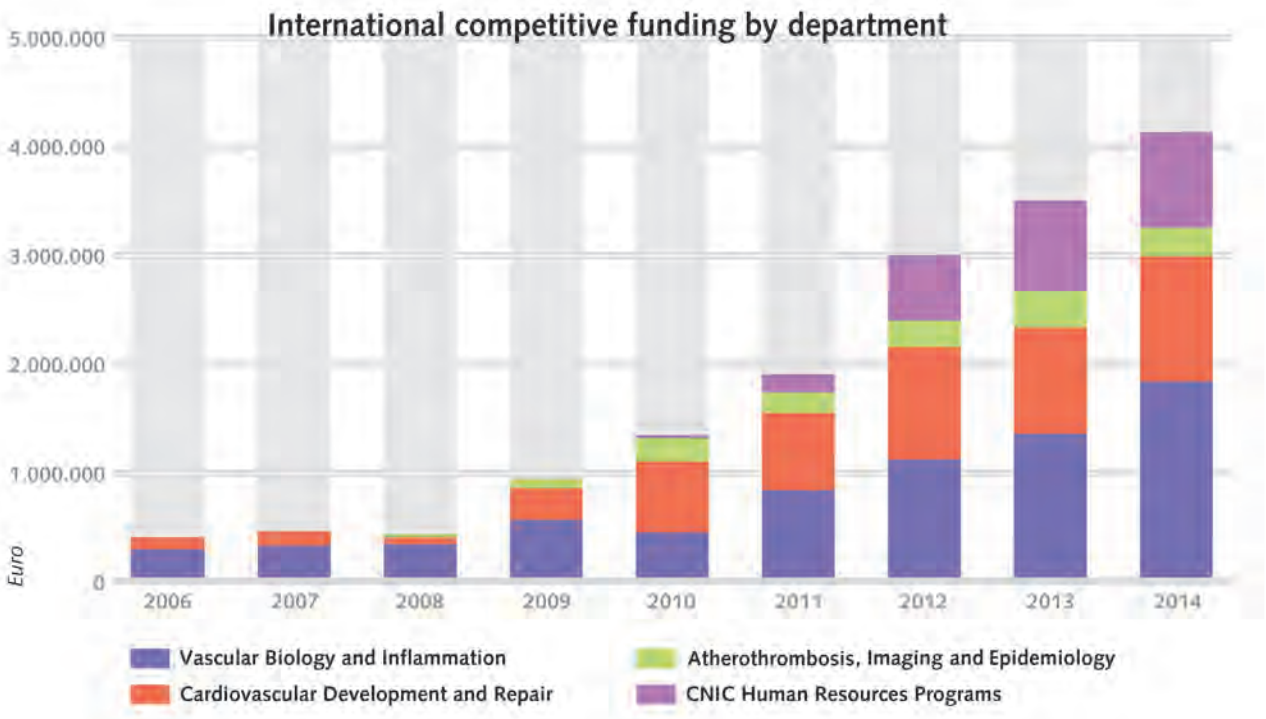
Competitive Funding

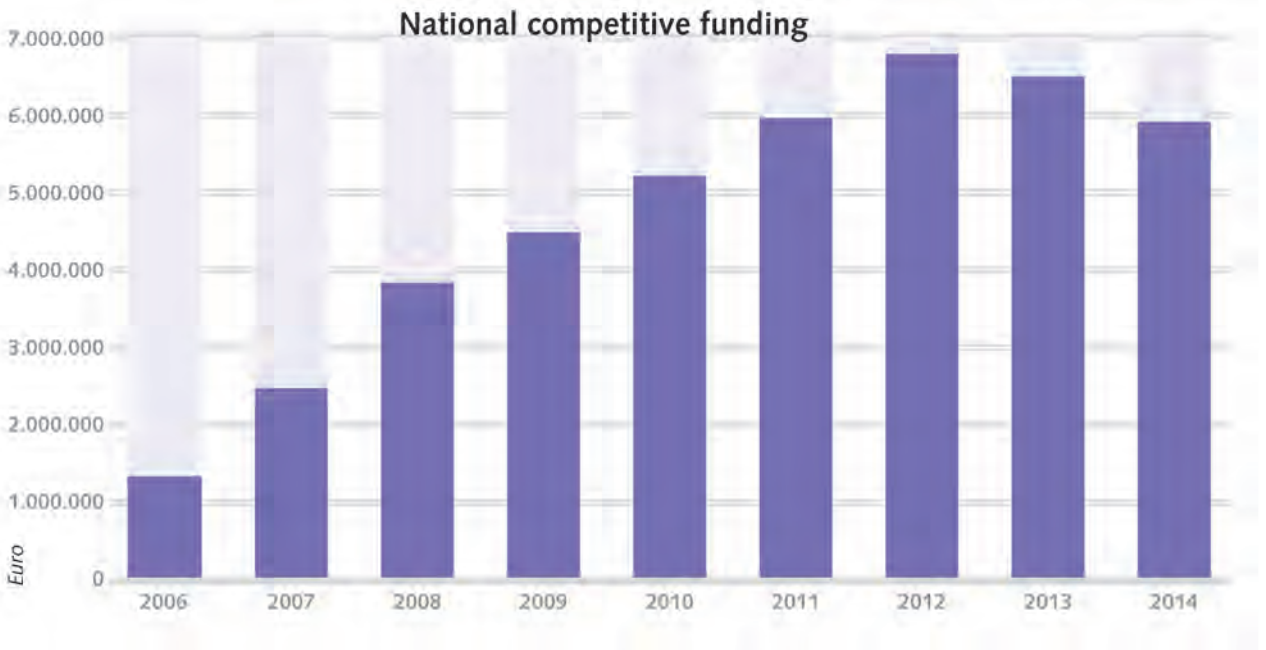
Since 2004 the CNIC has attracted more than €24m from international competitive sources to fund projects, contracts and awards. The figure for national funds is around €50m; however, in recent years the CNIC's attraction of international resources has almost matched new national funding (not counting the Severo Ochoa award).

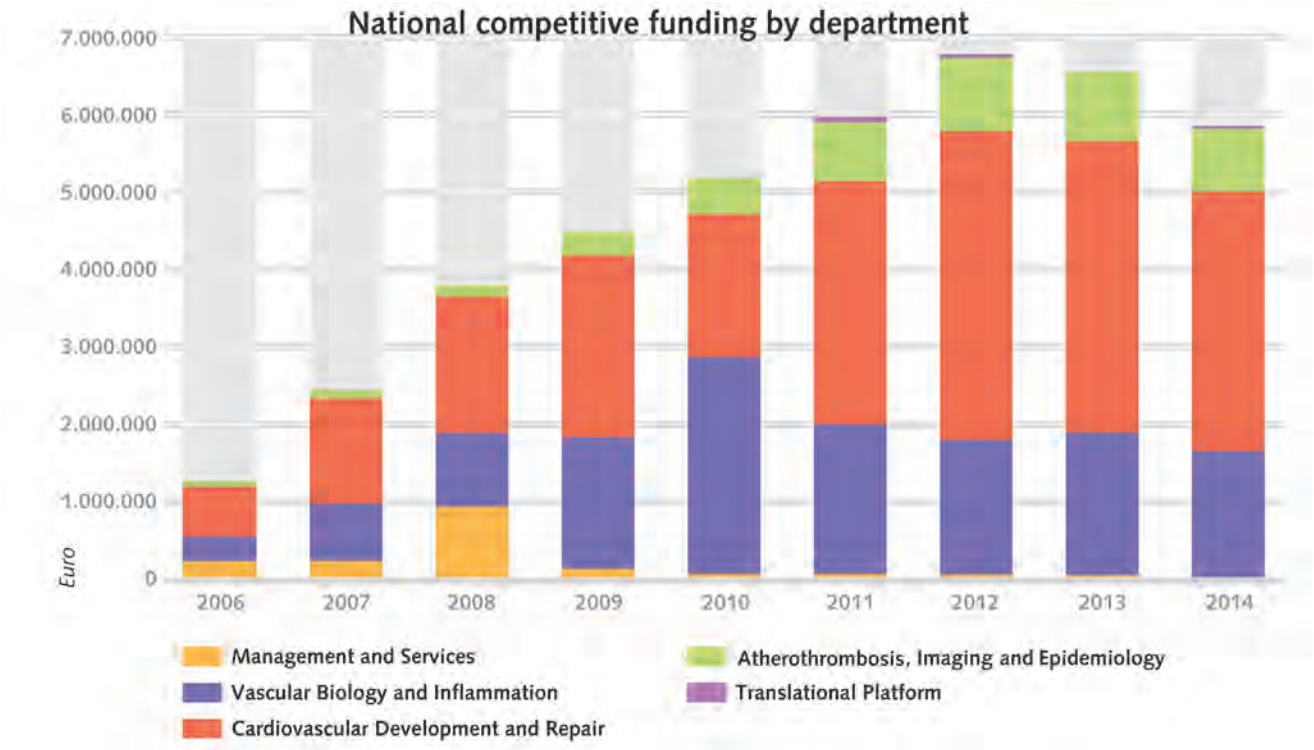


APPENDIX

F U N D I N G







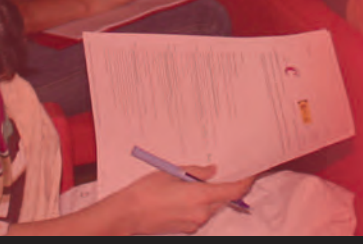
The CNIC is the third-ranking Spanish institution (after the CSIC and IkerBasque) in funds awarded under the PEOPLE Programme (Marie Curie) of The European Commission's Seventh Framework Programme (FP7). Highlights of 2013 include an ERC starting grant, an ITN-IDP PROJECT (CardioNext) and the CNIC International Postdoctoral Program (CNIC IPP), which is funded by a COFUND project.

Key FP7-funded CNIC projects:

- **ERC Advanced Grant:** Mechanisms of MTOC guidance and Genetic Transfer at the Immune Synapse: novel modes of Immuno-modulation (GENTRIS). PI: Francisco Sánchez Madrid.
- **ERC Starting Grant:** CLR Sensing Necrosis - Immune functions of myeloid Syk-coupled C-type lectin receptors sensing necrosis (CLR Sensing Necrosis). PI: David Sancho.
- **ERC Starting Grant:** Role of obesity in the development of hepatocellular carcinoma (OBECAN). PI: Guadalupe Sabio Buzo.
- **ERC Starting Grant:** Mechanisms of mature B cell lymphomagenesis (BCLYM). PI: Almudena R. Ramiro.
- **ERC Starting Grant:** Novel insights into cardiac regeneration through studies in the zebrafish (zebraHeart). PI: Nadia Mercader Huber.
- **CARE-MI** (CNIC-coordinated project. FP7-COOPERATION-HEALTH) http://www.caremiproject.eu/ PI: Antonio Bernad Miana.
- **FOCUS** (CNIC-coordinated project. FP7-COOPERATION-HEALTH) http://www.focus-fp7.eu/pages/homepage.php?lang=EN PIs: Ginés Sanz y V. Fuster.
- **CardioNet:** ITN (CNIC-coordinated FP7-Marie Curie action) http://www.cardionet-itn.eu/ PIs: Miguel Torres, José Luis de la Pompa, Enrique Lara.
- **CardioNext:** ITN-IDP (CNIC-coordinated FP7-Marie Curie action) PI: Alicia García Arroyo.

Other projects:

- **Stem cell niche physiopathology** (Howard Hughes Medical Institute). PI: Simón Méndez-Ferrer.
- **LiPhos: Monitoring light propagation through cells** (FP7-COOPERATION-ICT) – As partner. CNIC PIs: V. Andrés, B. Ibáñez & V Fuster.
- **MEET: Mitochondrial European Educational Training** (FP7-PEOPLE-ITN). – As partner. PI: JA Enríquez.
- **NotchIT: Notch signalling in development and pathology** (FP7-PEOPLE-ITN). – As partner. PI: JL de la Pompa.
- **HOX and TALE transcription factors in development and disease** (COST Action - European cooperation in the field of scientific and technical research). – As coordinator. PI: M. Torres.



APPENDIX

PATENT PORTFOLIO

CNIC Patent Portfolio 2013

TITTLE	INVENTORS	APPLICANTS	PATENT APPLICATIONS
Stable episomes based on non-integrative lentiviral vectors	Juan Carlos Ramírez Martínez, Raúl Torres Ruiz, Aida García Torralba	CNIC	EP
Modulador selectivo del receptor de estrógenos para el tratamiento de una enfermedad mieloproliferativa	Simón Méndez Ferrer, Lorena Arranz Salas, Abel Sánchez-Aguilera Peño	CNIC	ES
Terapia neuroregeneradora/neurocompensatoria para el tratamiento de las neoplasias mieloproliferativas	*Simón Méndez Ferrer, Lorena Arranz Salas,* Joan Isern Marín	*CNIC*	*ES*
Immune modulation by targeting the C-type lectin Mincle receptor	Salvador Iborra, Helena María Izquierdo Fernández, David Sancho Madrid	CNIC	EP
LxVP-mediated calcineurin inhibition in macrophages	Juan Miguel Redondo, Amelia Escolano	CNIC	EP, PCT
Secuencias nucleotídicas motivo que dirigen la localización de los ácidos nucleicos	Francisco Sánchez Madrid, María Mittelbrum Herrero, Cristina Gutiérrez Vázquez, Fátima Sánchez Cabo Carolina Villarroya Beltri	UAM, CNIC	ES, PCT
Uso de agonistas selectivos de receptores beta-3 adrenérgicos para el tratamiento de hipertensión pulmonar	Borja Ibañez Cabeza, Valentín Fuster Carulla Ana García-Álvarez	H. Clinic, CNIC	ES, PCT
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 y Jesús Gómez Salinero	EMBL, CNIC	EP, PCT
*Nanopartículas recubiertas de gelatin*a	Fernando Herranz Rabanal, Jesús Ruíz-Cabello Osuna, Beatriz Salinas Rodriguez	UCM, CNIC	ES, PCT
Caveolin-1 in tumor-associated fibroblasts as biomarker for tumor progression	Miguel Ángel del Pozo, Jacky Goetz	CNIC	EP
*Uso de células mesenquimales Nestina positivas para el mantenimiento de la hematopoyesis"/PCT: Célula*s *multipotenciales Nestina positivas*	Simón Méndez Ferrer, Álvaro Urbano Ispizua	H. Clinic, Fund. Progreso y Salud, CNIC	EP, US
Selective peptides that inhibit the biological activity of calcineurin	Juan Miguel Redondo, Antonio Rodriguez, Sara Martínez	CNIC	EP, US

Patent Applications

ES - Spanish patent

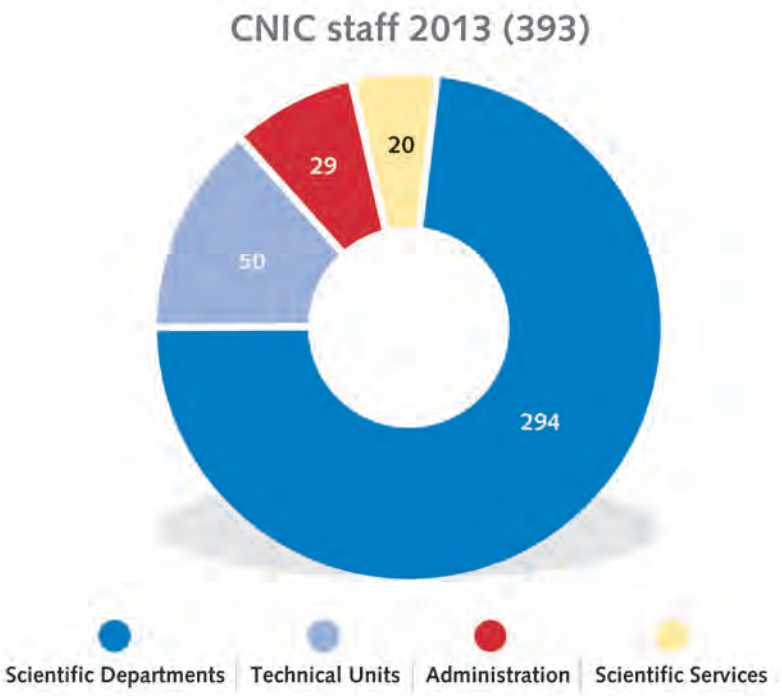
PCT (Patent Cooperation Treatry) - InternationalApplication

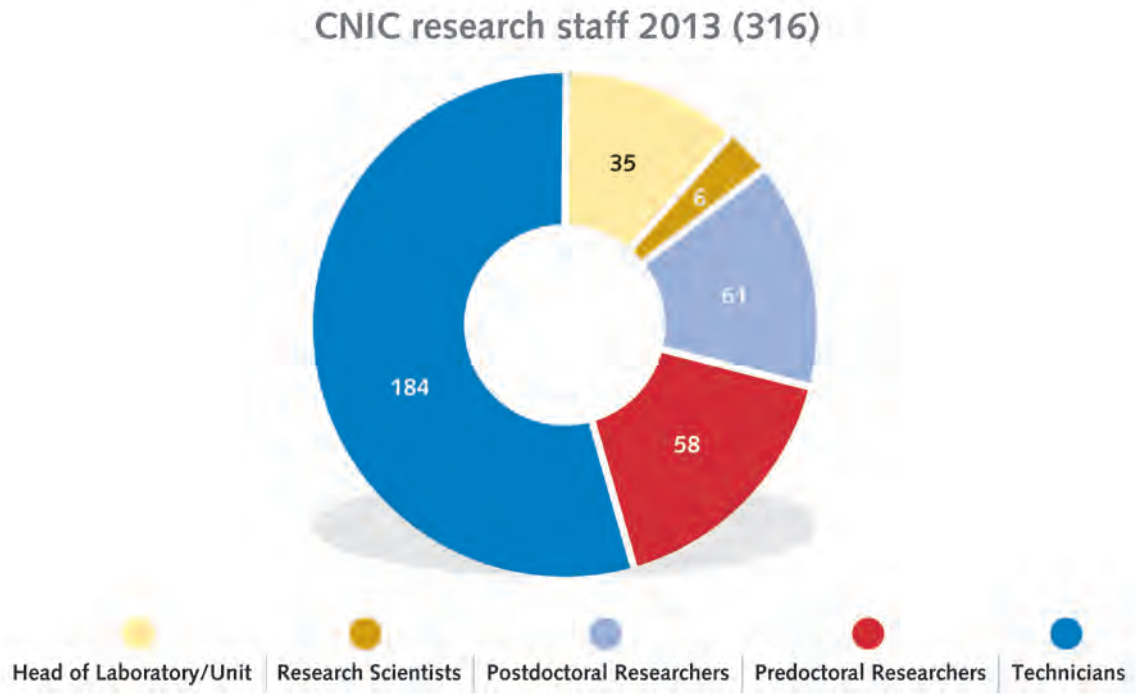
EP - European

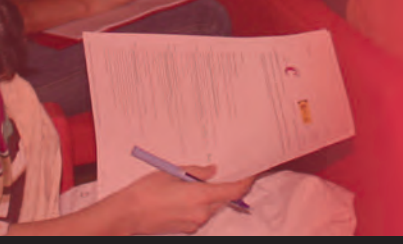
US - USA

APPENDIX

STAFF FIGURES



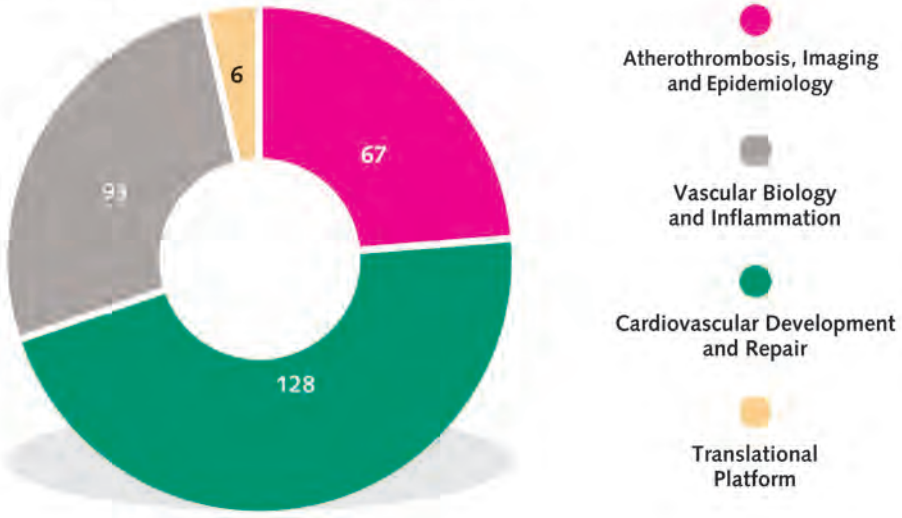




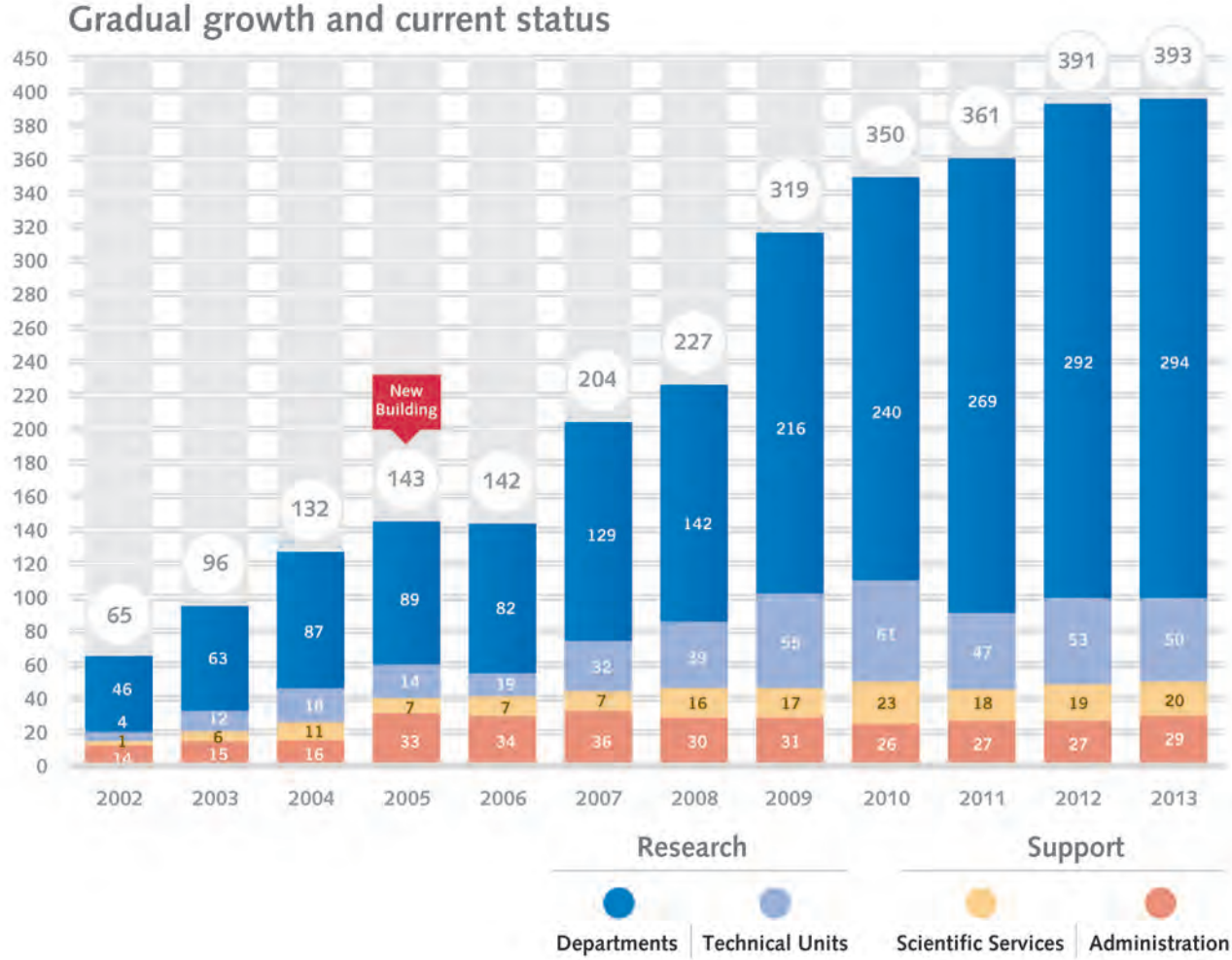
APPENDIX

STAFF FIGURES

Staff by department 2013 (294)

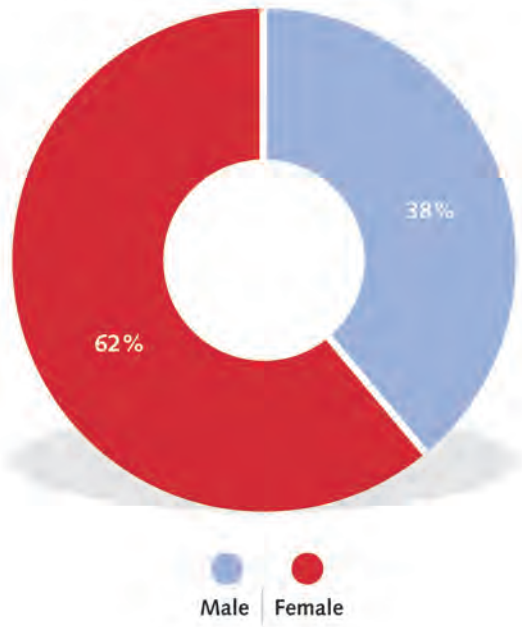


Gradual growth and current status

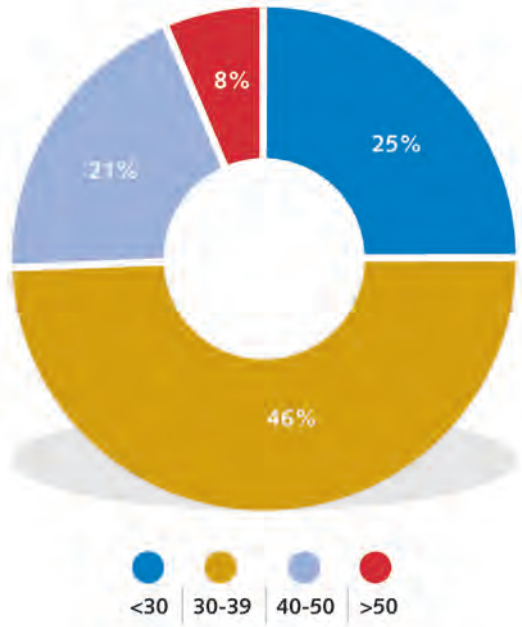


STAFF FIGURES

Gender distribution 2013



Age distribution 2013 in percentage



GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
Instituto de Salud Carlos III

Fundaciónprocnic

cnic

Melchor Fernández Almagro, 3 - 28029 Madrid. Spain T. (34) 91 453 12 00 - F. (34) 91 453 12 45 - www.cnic.es