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Carlos III

EXCELENCIA SEVERO OCHOA

SCIENTIFIC REPORT 2012

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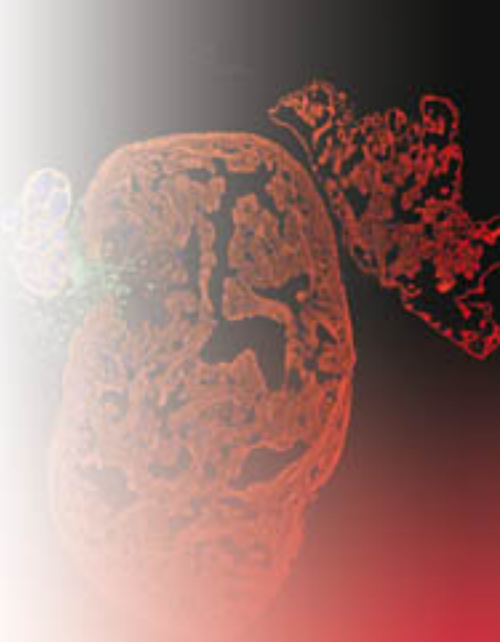

SCIENTIFIC REPORT 2012

SCIENTIFIC REPORT


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Valentín Fuster

One of the CNIC's most important goals in these times of recession is to secure and maintain long term financial support. In June 2012, the Ministry for Economic Affairs and the consortium of private companies in the Pro-CNIC Foundation renewed their commitment to the CNIC. This unique public-private joint initiative is allowing our center to maintain the pioneering drive that resulted in our accreditation as a Severo Ochoa's Center of Excellence in 2011, one of only eight institutes to receive this award in its inaugural year. During 2012 the CNIC has been intensively seeking competitive external research funding, presenting more than 34 applications to the 7th European Union Framework Programme and 17 applications to other international agencies (NIH, Leducq Foundation, etc.). The Center also secured financing from the Spanish Company Fina Biotech to study genetic risk markers of restenosis after coronary stent implantation.

The continuing support for the CNIC from the public and private sectors is based on the strength of our programs in basic and translational research and our innovative training programs aimed at identifying and supporting talent and cementing long term collaboration between basic researchers and clinicians.

In the arena of basic research 2012 was another year of increasing strength, with key publications on stem-cell aging and regulation, bioenergetics, immune regulation and tissue damage, signaling mechanisms central to heart development and disease, and ground-breaking work on the intercellular transfer of genetic information via extracellular vesicles. These discoveries were published in leading journals including Cell Stem Cell, Cell Metabolism, The Journal of Experimental Medicine, The Journal of Clinical Investigation, Developmental Cell, Nature Medicine and Nature Communications. Studies with a more direct clinical focus included the discovery of a new therapeutic target for the treatment of acute MI, and the identification of potential targets for the control of hypertension and atherosclerosis.

In April, our international Scientific Advisory Board gave a highly positive evaluation to the Department of Cardiovascular Development and Repair, and four group leaders were also evaluated positively. Assessments will continue in May 2013 with the evaluation of the Department of Epidemiology, Atherothrombosis and Imaging.

Our capacity for basic research was boosted last year with the inauguration of the Advanced Imaging Unit, led by Jesús Ruiz-Cabello. This was accompanied by the initial steps toward the future installation of new equipment for magnetic particle imaging, which will turn this facility in one of the most sophisticated units of its kind in the world. The Microscopy Unit's capacity for dynamic imaging was consolidated last year through the agreement with the "Fundazione Centro San Raffaele" (Milan) for continued collaboration with Valeria Caiolfa, and the Department of Development and Repair was strengthened with the recruitment in August of Rui Benedito as an Assistant Professor working on the molecular genetics of angiogenesis.

The translation of scientific knowledge into clinical practice is now a firmly established part of the CNIC brand. 2012 saw progress in important clinical studies, including PESA and the the Aragon Workers Health Study, which study aspects of the subclinical development of atherothrombosis and associated risk factors, as well as the European Union funded FOCUS trial of the CNIC-FERRER polypill (now commercialized in several countries), the IMJOVEN study into myocardial infarction (MI) in young women, and the METOCARD trial of early post-MI administration of beta-blockers. An opportunity for us to bring our translational message to a large sector of the population came last year with the invitation to Dr. Fuster from Minister of Health Ana Mato to head the projected national Obesity Observatory.

In 2012 we also strengthened strategic alliances with the Spanish health system—through an agreement with the *Fundación Interhospitalaria para la Investigación Cardiovascular* for collaboration in training and research—and with industrial partners. Alliances with industry are fundamental to our leadership in advanced imaging, and the core of this program is our partnership with Philips. During a visit to the CNIC's imaging facility in March, Philips world president Frans Van Houten reaffirmed the technological partnership with the CNIC.

Miguel Torres

Researchers at the Center received recognition in the form of awards in basic and translational research. Simón Mendez-Ferrer, whose group investigates the regulation of stem cell niches, received a highly prestigious career award from the Howard Hughes Medical Institute. Guadalupe Sabio, whose research centers on signaling cascades in obesity and diabetes, was awarded the *Impulsa* young-researcher prize from the *Fundación Principes de Girona*. And postdoctoral researcher Tomas Röszer, from Mercedes Ricote's group, received the Lilly/European Foundation for the Study of Diabetes prize for his work on retenoid X receptors in macrophages.

Prizes awarded to more senior CNIC researchers included the Premio Ciencias de la Salud to Miguel Ángel del Pozo (Vascular Biology and Inflammation Department) for the most relevant publication of 2011.This work on the biomechanical properties of tissue matrix, published in Cell, was also instrumental in his receipt in October of the prestigious Premio Carmen y Severo Ochoa. Valentín Fuster's awards in 2012 included the "Legend of Cardiovascular Medicine" award from the American College of Cardiology (ranking him as one of the five top cardiologists in the world in the last two decades) and the 2012 American Heart Association Research Achievement Award, the highest honor awarded by the AHA.

2012 also saw significant advances in intellectual property protection. Nine new patent applications were filed, five of them Spanish and four European patents (EP). In addition, four patent families were extended: two international applications (PCT), two US applications and two EP applications. Moreover, three patents were granted, the polypill has been approved for its prescription in patients with a previous history of acute myocardial infarction in Guatemala, Argentina, México and Nicaragua.

The CNIC's training activities were strengthened through new alliances with universities (*Universidad Autónoma de Madrid*, the Universities of *Alcalá* and *Lleida* and the *Universidad Politécnica de Madrid*) and the launch of programs to attract clinicians to research. A highlight in this area was the launch of the RES@CNIC program, offering young medical professionals first-hand experience of the latest techniques in cardiovascular research.

The CNIC also coordinates the ambitious European Union funded CardioNeT project. CardioNeT, launched last year, will train 17 researchers in the molecular and cellular biology underlying cardiac development, homeostasis and disease. Also last year, the €1.6m cofinancing of the CNIC's International Postdoctoral Program through the European Union's COFUND Programme entered the negotiation stages.

The second CNIC Conference, on "Vascular Inflammation, Aging and Imaging" was held 9-10 March 2012. The conference, chaired by Vicente Andrés and Francisco Sánchez-Madrid of the CNIC and Paul Frenette of the Albert Einstein College of Medicine (New York), was attended by 17 expert presenters from Europe and North America. This was in addition to the 46 center seminars held throughout the year, presented by leading invited national and international experts. The CNIC's commitment to the public understanding of biomedicine was cemented last year with the inclusion of two CNIC projects within the European Union funded CommHERE project (Communication of European Health Research).

The combination of basic and translational research excellence, partnerships with the health and industrial sectors, and an unbending commitment to training the researchers of tomorrow are the linchpins of the CNIC's mission. As these strands gain momentum and cohesion, we are already seeing the benefits in accumulated knowledge and expertise that will produce real improvements in public health.

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Cardiovascular Development and Repair

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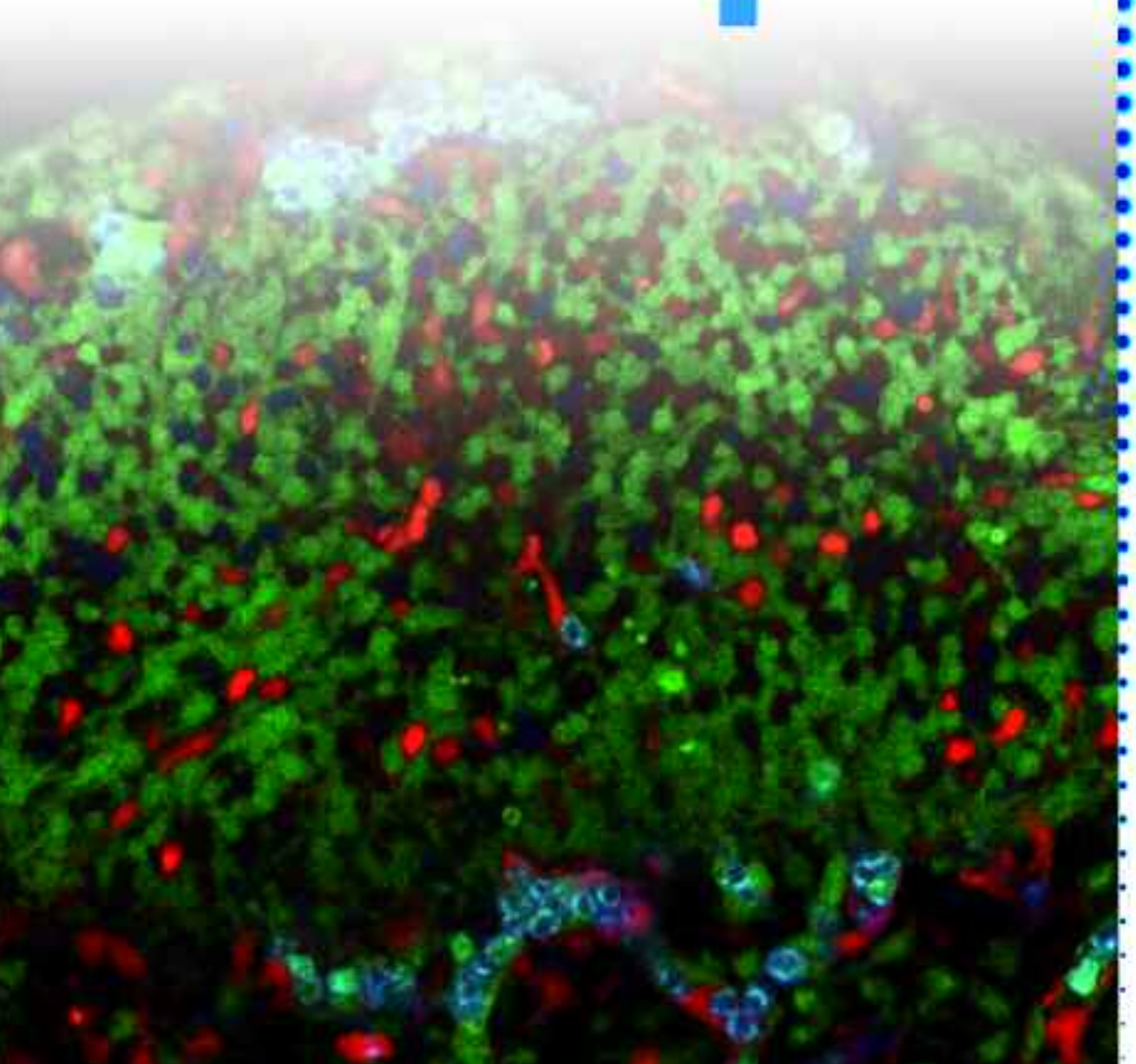


Research Departments

1 Cardiovascular Development and Repair

The Department of Cardiovascular Development and Repair seeks to understand how the cardiovascular system is built, maintained and 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 and José Antonio Enríquez*
Department Managers: *Beatriz Ferreiro (coordinator), Ángel Ciprés and Isabel Barthelemy*
Department Logistics: *Teresa Casaseca and Mª Ángeles Oliva*
Administrative Support: *Sandra Cillero and Marta Ramón*

A. Cardiovascular Developmental Biology

We study how cardiac lineage specification occurs and how proliferation and patterning of the different cardiac regions that will form the mature heart is regulated. We want to unravel how alterations to these mechanisms lead to cardiovascular disease and how they can be manipulated to repair a 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
Ricardo Costa
Daniel A. Felix
Mónica González Lázaro
Laura Padrón de Vaumas
Alberto Roselló-Díez

Predoctoral Researchers: Ghislaine Lioux
Daniel Mateos San Martín
Iván Menéndez Montes
Verónica Uribe (JJSE group)
Cristina Villa

Masters Student: Covadonga Díaz

Technicians: Vanessa C. Cadenas
Beatriz Escobar
Rocío Sierra
Susana Temiño
Paloma Vaquero (JJSE group)

Visiting Scientist: Juan José Sanz-Ezquerro

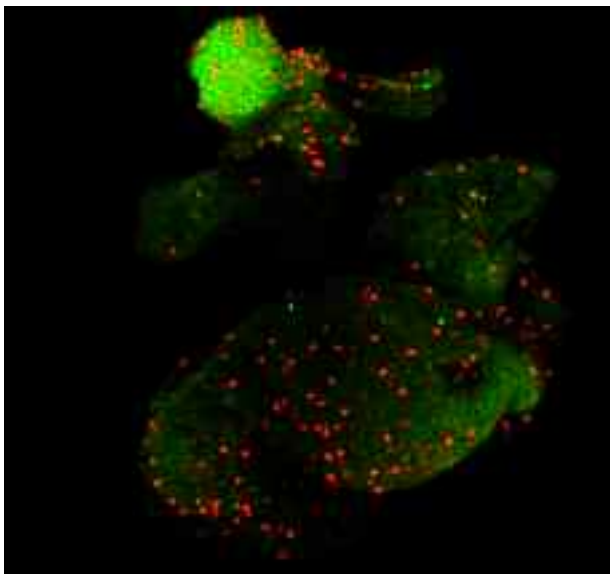
Research Interest

Our work focuses on three areas: the role of transcription factors and the environment in cardiovascular and limb pattern formation, the use of new genetic mosaic approaches to study the cellular basis of organ morphogenesis and homeostasis, and the role of hypoxia during cardiogenesis.

Our work on pattern formation has identified a novel mechanism (diffusible signals, not autonomous mechanisms) through which antagonistic signals control a network of transcription factors (Hox-TALE) to form the distinct structures of vertebrate limbs. This study has contributed to the understanding of how embryonic cells obtain and interpret instructions to produce body structures and organs in the correct spatio-temporal order. We are now studying the relevance of this mechanism to heart development and characterizing the role of TALE transcription factors in angiogenesis.

Our work with genetic mosaics has generated two new strategies to analyze the cellular basis of organ development and homeostasis. In one, an in vivo clonal analysis is used to define cell lineage and topological relationships among cardiovascular lineages during embryonic development and adult homeostasis. The second strategy allows the generation of random genetic mosaics and has allowed us to demonstrate that cell competition in the early mouse embryo is a driving force for the maintenance of cell quality in stem cell pools (submitted). We are currently analyzing the role of cell competition in cardiac development, homeostasis and regeneration.

For our work on hypoxia, we have generated conditional gain- and loss-of-function lines for the canonical hypoxia regulators HIF and VHL, in which we are analyzing the consequences of manipulating embryonic hypoxia on cardiovascular progenitors. We are also determining relative oxygen levels in different regions of the embryonic heart in order to understand the distribution of cardiac populations within hypoxic niches.



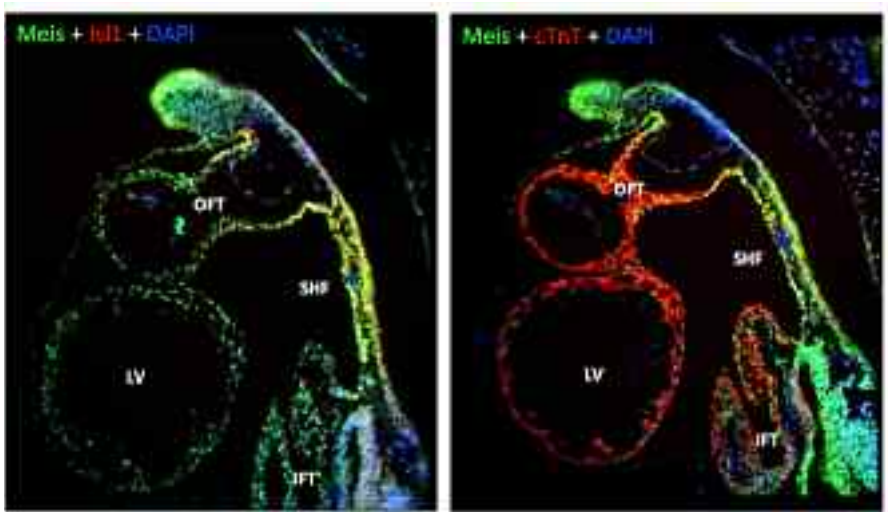
3D reconstruction of the developing heart. *Dorsolateral view of an embryonic heart from an E9.5 embryo. Dividing cells are PH3 labeled (red), and gamma tubulin is stained green, revealing the polarity of cell division.*

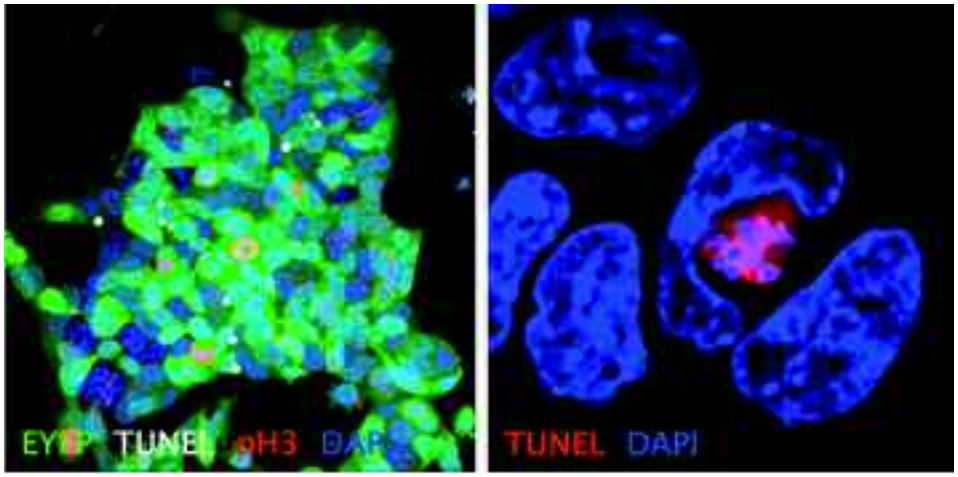
Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

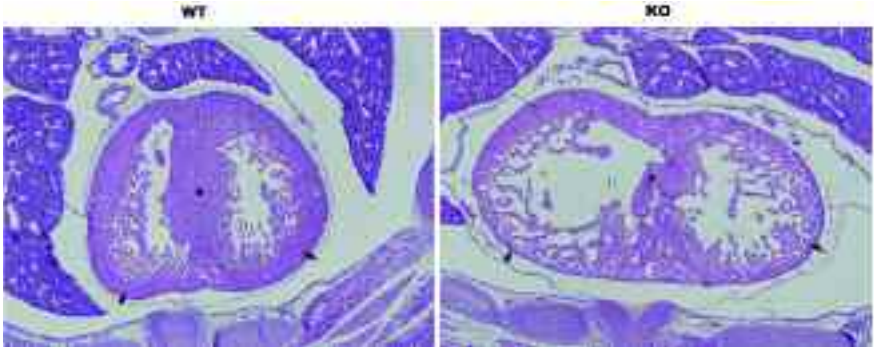
Meis expression during heart development in E9.5 mouse embryos. *Meis proteins are strongly expressed in the second heart field (SHF), as evidenced by their co-expression with Isl1, a SHF marker (left). In this region cells proliferate and provide progenitors that progressively move towards heart poles, the outflow (OFT) and the inflow (IFT) tracts. As these cells progress into the heart tube they switch on cardiomyocyte markers such as cardiac troponin-T (cTnT). Meis expression fades progressively as cells progress into the heart concomitantly with cTnT upregulation (right). In more mature regions of the heart such as the left ventricle (LV) Meis expression is diminished.*





Cell competition in ESCs. (Left) *Induced mosaic culture of iMOS$^{T1\text{-}c\text{-}myc}$ embryonic stem cells (ESCs) containing two, one or no extra c-myc copies (reported by EYFP levels). Cell competition drives progressive enrichment in cells with higher c-Myc levels as result of an increased incidence of apoptosis (shown in white) in cells expressing lower levels of c-Myc, while no differences in proliferation rates (shown in red) are observed.* ***(Right)*** *Outcompeted ESCs are phagocytosed by neighboring cells.*

Hematoxilin & Eosin staining of wild type (WT) and knockout (KO) mice in which Von Hippel Lindau (VHL) protein has been conditionally deleted in the myocardium and partially in the epicardium and endocardium by the Nkx2.5-Cre driver. VHL deletion stabilizes HIFs, and by E16.5 results in several cardiac abnormalities including ventricular chamber dilation, thin myocardium (arrows in LV, RV) and ventricular septal defects (asterisk).



Research Departments

1 Cardiovascular Development and Repair

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***
- ***Ministerio de Economía y Competitividad. FIS. RETICS (TERCEL: RD06/0010/0008)***
- ***Ministerio de Economía y Competitividad (BFU2009-08331)***
- ***Ministerio de Economía y Competitividad. FIS (CP09/00100). PI: S. Martín Puig***
- ***EU FP7. Marie Curie European Reintegration Grant (276891) PI: S. Martín Puig***
- ***EU FP7 Marie Curie (IEF-GA-2009-251226)***
- ***EU FP7. Initial Training Network (28600)***
- ***Comunidad de Madrid: (S2010/BMD-2315)***
- ***Comunidad de Madrid (S2010/BMD-2542) PI: S. Martín Puig***
- ***Ministerio de Economía y Competitividad (SAF2011-29830) PI: S. Martín Puig***

Selected Publications

Roselló-Díez A, Ros MA, Torres. M. **Diffusible signals, not autonomous mechanisms, determine the main proximodistal limb subdivision.** *Science* (2011) 332: 1086-8.

Casanova J, Uribe V, Badia Careaga C, Giovinazzo G, Torres M, Sanz Ezquerro JJ. **Apical ectodermal ridge morphogenesis in limb development is controlled by Arid3b-mediated regulation of cell movements.** *Development* (2011) 138: 1195-205.

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.

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 tissue homeostasis

Head of Laboratory: José Luis de la Pompa

Postdoctoral Researchers: Jesús Fernández Casanova
Luis Luna Zurita
Donal MacGrogan
Beatriz Martínez Poveda
Meritxell Nus
Belén Prados
Mauro Sbroggio

Predoctoral Researchers: Gaetano D'Amato
Álvaro González Rajal
Dimitrios Grivas
Guillermo Luxán
Juliane Münch
Stanislao I. Travisano

Technicians: Vanesa Bou
Ana Cabrero
Abel Galicia Martín
Patricia Martínez

Visiting Students: Paula Gómez Apiñariz
Marcos Siguero Álvarez

Research Interest

We are interested in the signaling mechanisms that regulate cardiac development, homeostasis and repair and how the alteration of these signals may cause cardiac disease. Last year we continued our study of the role of the Notch pathway, through which cells direct cell fate in adjacent tissues, in cardiac development and disease. We studied the function of Notch in cardiac valve morphogenesis and ventricular chamber development and cardiomyopathy, analyzed the influence of inflammatory stimuli on aortic valve disease and atherosclerosis, and explored the implication of Notch and other signaling mechanisms in zebrafish cardiac and fin regeneration. We address these questions using a combination of state-of-the-art mouse and zebrafish genetics, cell biology, biochemistry, next-generation sequencing (NGS) and image analysis in the embryo and in the adult.

3D-reconstruction and functional analysis of mouse ventricular chamber development indicate that during this process Notch is sequentially activated by the ligands Dll4 and Jag1, with Dll4 activating Notch in the early chamber, while Jag1 takes over as development proceeds. Both ligands are modified by the activity of the ubiquitin ligase Mind bomb1 (Mib1), which is essential for Notch signaling activation. Specific inactivation of *Mib1* in the myocardium affects ventricular chamber maturation and function, leading to a phenotype equivalent to that of a human cardiomyopathy termed left ventricular non-compaction (LVNC). In collaboration with our colleagues in and outside the CNIC we have demonstrated that autosomal dominant mutations in the human *MIB1* gene are causally involved in familial LVNC. We are currently generating new genetically modified mouse models to study the differentiation potential of induced pluripotent stem cells generated from LVNC patients and analyze the involvement of the NOTCH pathway in LVNC and in other cardiomyopathies. We have also generated new conditional mouse models to study the role of other signaling pathways such as Bmp2 in cardiac development and disease.

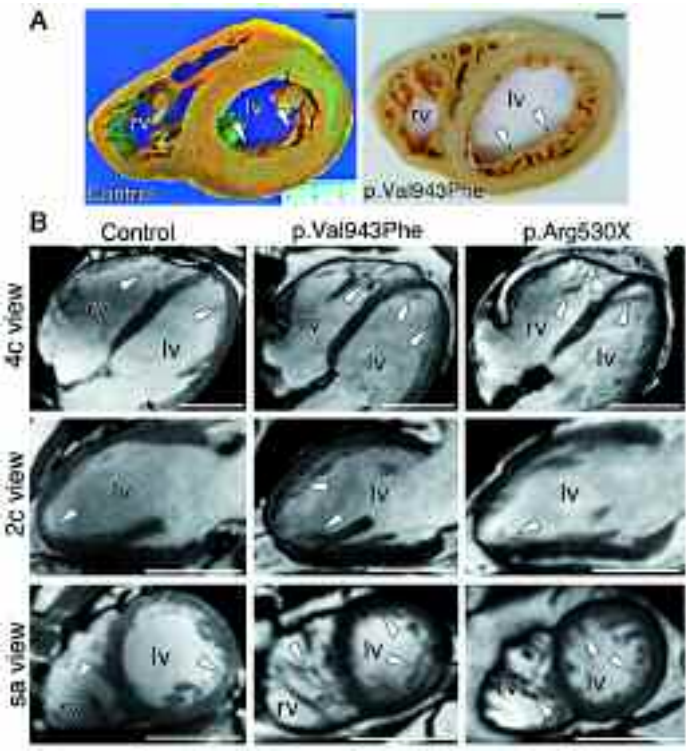
We also manipulate Notch (and other pathways) in the zebrafish heart and fin to determine their effect on cardiac and fin regeneration. These signals are reactivated after cardiac damage and their activities are required for repair. Loss- and gain-of-function studies with Notch indicate that it is essential for fin regeneration, maintaining blastema cells in an undifferentiated, progenitor-like state, and must be turned off to allow differentiation of the repaired tissue.

Through detailed dissection of the mechanism of action of these highly conserved and crucially important signaling mechanisms, our ultimate goal is to identify new diagnostic or potential therapeutic targets to treat the diseased heart.

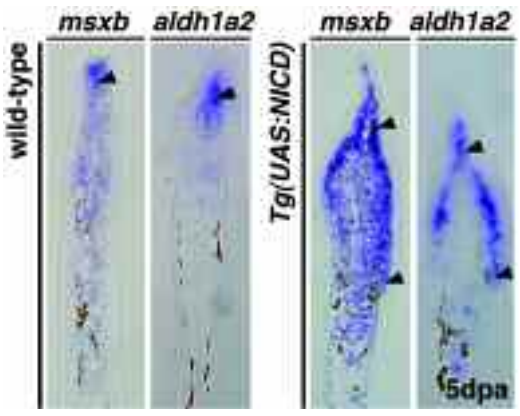
Research Departments

1 Cardiovascular Development and Repair

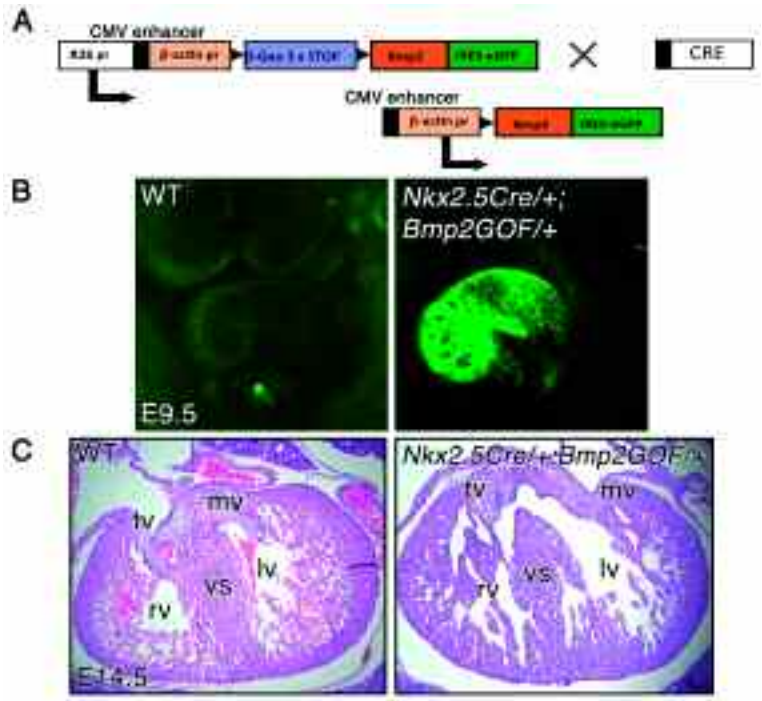
A. Cardiovascular Developmental Biology Program



Mutations in MIB1 cause LVNC. (A) *Section of a structurally normal heart and of the heart of an LVNC patient with an* MIB1 *mutation (p.Val943Phe). Arrowheads mark the compacted myocardium in the control and the non-compacted myocardium in the proband. Scale bar=10mm.* ***(b)*** *CMRI sections of hearts showing four-chamber (4c), two-chamber (2c) and short axis (sa) views of the hearts of a control (in a person without an* MIB1 *mutation) and of two LVNC patients, one with p.Val943Phe* MIB1 *mutation and the other with the p.Arg530X* MIB1 *mutation. Arrowheads mark the trabeculae, which are prominent in the ventricles of the individuals with* MIB1 *mutations. Scale bar=50mm.*



Notch signaling pathway overactivation in the regenerating fin leads to an increased number of undifferentiated blastema cells. *In situ hybridization on fin sections at 5 days post amputation (5dpa) reveals expanded expression (arrowheads) of the blastema marker msxb and the proliferation regulator* aldh1a2 *in transgenic fish* (Tg(hsp70:Gal4);Tg(UAS:myc-N1ICD)) *compared with wild-type fish.*



Overexpression of Bmp2 in the heart leads to cardiovascular defects and embryonic death. *(A) Construct which overexpresses Bmp2 under the control of a desired promoter. (B) GFP reporter signal, showing the expression of the transgene in the heart upon expression of Cre under the control of the* Nkx2.5 *promoter. (C) HE staining of transgenic mice overexpressing* Bmp2. *An obvious phenotype can be observed. tv, tricuspid valve; mv, mitral valve; rv, right ventricle; lv, left ventricle; vs, ventricular septum.*

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Major Grants

- ***European Commission FP7. Initial Training Network (215761 and 28600)***
- ***Ministerio de Economía y Competitividad. FIS RETICS (TERCEL: RD06/0010/1013 and RECAVA II: RD06/0014/0038)***
- ***Ministerio de Economía y Competitividad (SAF2010-17555)***
- ***Ministerio de Economía y Competitividad. FIS (CD08/00257). PI: B. Prados***
- ***Ministerio de Economía y Competitividad. FIS (CD09/00452). PI: M. Nus***
- ***Ministerio de Ciencia e Innovación (JCI-2010-06343) PI: B. Martínez Poveda***

Selected Publications

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 non-compaction cardiomyopathy.** *Nat Med* doi: 10.1038/nm.3046. [Epub ahead of print]

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

Casanova JC, Travisano S & de la Pompa JL. **Epithelial-to-mesenchymal transition in epicardium is independent of snail1.** *Genesis* doi: 10.1002/dvg.22353. Epub Nov 7 2012

de la Pompa JL and Epstein J. **Coordinating tissue interactions: Notch signaling in cardiac development and disease.** *Dev Cell* (2012) 22: 244-54.

Pérez-Pomares JM, de la Pompa JL. **Signaling during epicardium and coronary vessel development.** *Circ Res* (2011) 109: 1429-42.

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

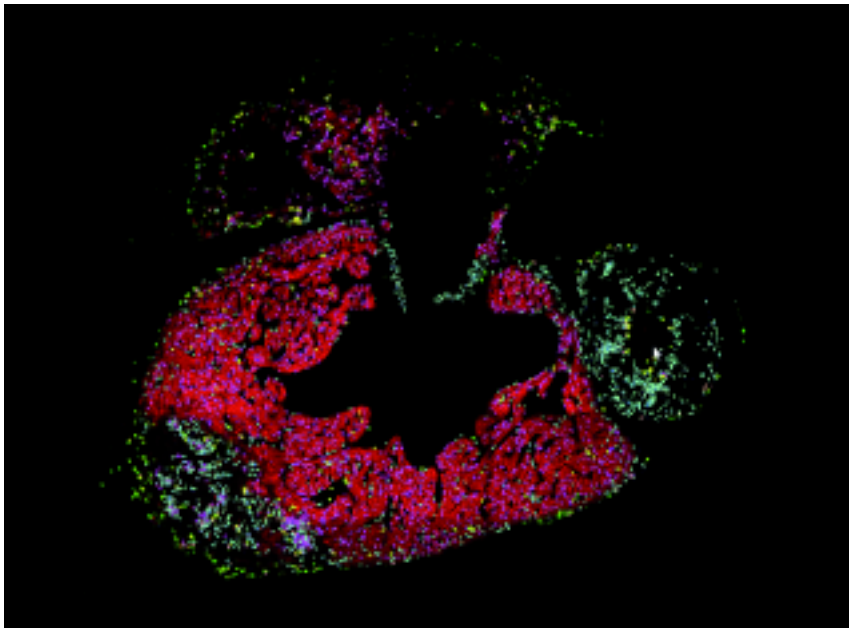
Stem cells in organ generation, regeneration and aging

Head of Laboratory: Ignacio Flores
Posdoctoral Researchers: Tania Aguado
Cristina González Estévez
Predoctoral Researchers: Esther Aix
Dorotha Bednarek
Technician: Irene de Diego
Visiting student: Óscar Gutiérrez Gutiérrez

Research Interest

The promise of regenerative medicine is now a reality. Successful cases of enhanced repair with stem cells have been achieved in tissues with high turnover rates, such as the skin or the hematopoietic system. However, for tissues with limited regeneration capacity, for example, the heart, progress to the clinic is more challenging. Nevertheless, the fact that a subpopulation of cardiomyocytes can divide after infarction or pressure overload suggests that the heart may contain an internal mechanism of self-healing. Stimulation of such an inbuilt repair mechanism could be used to partially replenish those cells that are lost after a heart attack or during normal aging. Achieving this goal requires deeper understanding of the nature of the replicating cells, their putative progenitors and the pathways that control their fate.

We are interested in the location, prevalence and status of different stem cell populations and their progeny during organogenesis and aging, focusing primarily on cardiac cells. Our experimental approach will exploit our recent finding that longer telomeres are a general feature of adult stem cell compartments. We are also interested in characterizing potential regulators of telomere length during the course of stem cell differentiation, with the aim of defining their contribution to cell fate determination. Another research line is aimed at understanding how cells sense different amounts of telomerase and telomeres during organogenesis and tissue maintenance. Through these efforts, we hope to achieve a more complete picture of the role of stem cells in organ formation and maintenance, which could lead to the development of improved regeneration therapies.

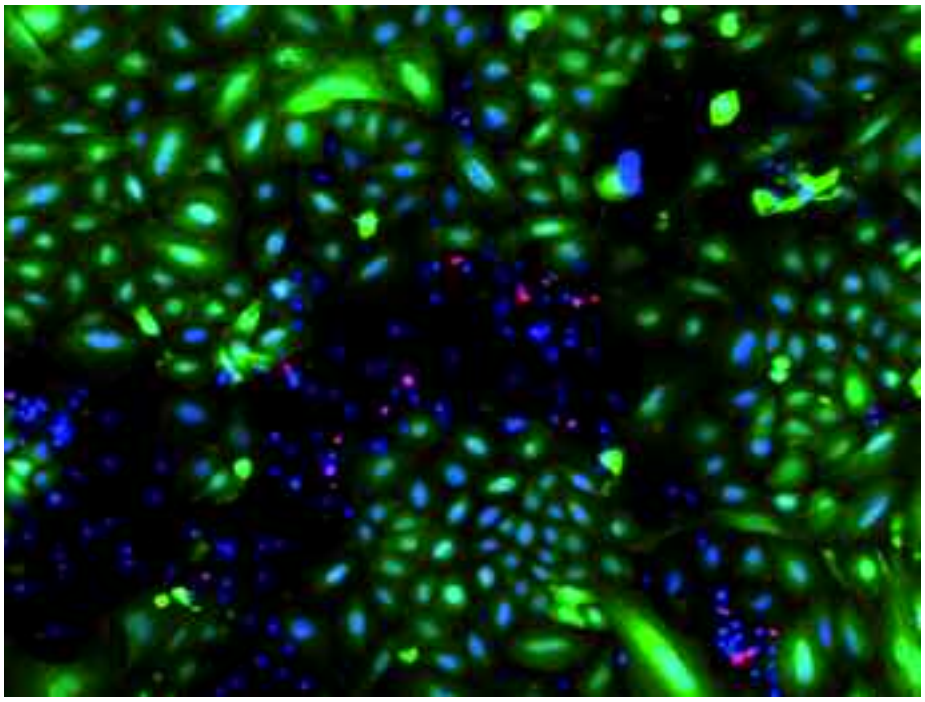


Quantitative analysis of cardiac proliferation in zebrafish heart after infarction. *A specifically tailored image analysis program was used to segment, classify and quantify proliferation of different subtypes of cardiac cells after infarction. This work was done in collaboration with Hind Azegrouz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

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program



Apoptotic cell death in co-cultures of cells of different genotypes. *One population expresses the marker act-GFP. Apoptotic cells of one genotype are detected when the cells are in close proximity to the other genotype, suggesting cell competition.*

Major Grants

- ***Ministerio de Economía y Competitividad (SAF2009-10480)***
- ***Ministerio de Economía y Competitividad (RYC-2006-3067)***
- ***Asociación Española contra el Cáncer PI: Tania Aguado***

Selected Publications

Blázquez C, Chiarlone A, Sagredo O, Aguado T, Pazos MR, Resel E, Palazuelos J, Julien B, Salazar M, Börner C, Benito C, Carrasco C, Diez-Zaera M, Paoletti P, Díaz-Hernández M, Ruiz C, Sendtner M, Lucas JJ, de Yébenes JG, Marsicano G, Monory K, Lutz B, Romero J, Alberch J, Ginés S, Kraus J, Fernández-Ruiz J, Galve-Roperh I, Guzmán M. **Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease.** *Brain* (2011) 134: 119-36.

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

Predoctoral Researchers: Juan Manuel González-Rosa
Marina Peralta

Master Student: Héctor Sánchez

Technician: Inês João Dos Santos Marques

Visiting Scientists: Yaniv Hinits, *Randall Division for Cell and Molecular Biophysics, King's College London, UK*

Research Interest

Our work is aimed at understanding the morphogenesis of the epicardium and its role as a source of cells and signals during development and regeneration. A second main goal is to elucidate the molecular mechanisms of fibrotic tissue degradation in zebrafish.

The epicardium is the mesothelial layer that envelops the myocardium. It derives from the proepicardium (PE), a group of cells that arises at the inflow tract of the forming heart. During development, epicardium-derived cells delaminate from the embryonic epicardium, undergo epithelial-mesenchymal transition (EMT), and contribute to cardiac development by promoting myocardial proliferation and contributing progenitor cells for the formation of the coronary vasculature and intracardiac fibroblasts. We are interested the mechanisms involved in the transfer of PE cells to the myocardium, which ultimately lead to the formation of the epicardial layer. For this purpose we use the zebrafish animal model, which allows in vivo visualization of cardiac development, and we have generated reporter lines that allow us to track PE cells and analyze epicardium morphogenesis in detail.

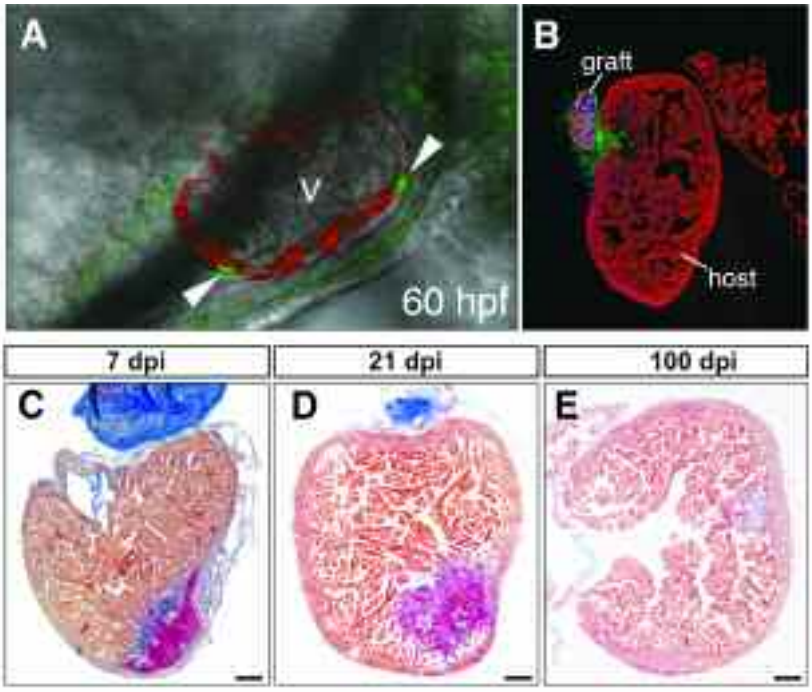
In mammals and fish, the epicardium contributes to the injury response of the adult heart by secreting paracrine factors and contributing to cardiac repair. Damage to the myocardium leads to the rapid reexpression of epicardial genes and the formation of a thickened epicardial cap over the injured area. These observations suggest a role for the epicardium as a source both of signals and of progenitor cells during cardiac regeneration. Recent findings suggest that the epicardium is composed of a hetergenous cell population. In order to study the fate of epicardial cells in a reporter-unbiased manner, we have set up a transplantation technique in the adult zebrafish, which allowed us to determine that epicardial cells contribute to fibrotic repair, an important intermediate step for proper regeneration.

Cardiac regeneration after cryoinjury is preceded by the deposition of fibrotic tissue, which is eliminated during regeneration. We are interested in understanding the mechanisms through which the zebrafish heart eliminates cellular and acellular components of the scar, which in other species, including humans, is irreversible.

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program



***Studying the development of the epicardium and its role during regeneration in the zebrafish. A. In vivo imaging of epicardium formation**. Confocal section of a zebrafish embryonic heart at 60 hours postfertilization. In this transgenic reporter line the myocardium is visualized in red and epicardium in green. Note the two epicardial cells attached to the myocardium. **B. Pan-epicardial cell tracing using a novel transplantation assay**. Section of an adult cryoinjuired zebrafish heart transplanted with a graft from a reporter line expressing GFP ubiquitously and permanently in all cells. Note that graft-derived cells invade the host heart and contribute to its repair. Myocardium is labeled red, transplanted cells green. **C. Complete regeneration and scar removal after cryoinjury of the adult zebrafish ventricle**. Histological staining on sagittal sections of adult zebrafish heart fixed at the indicated days after cryoinjury of 24% of the ventricle. Collagen is stained blue, damaged tissue red and myocardium brown. At 3 days postinjury (dpi) a massive collagen deposition can be observed, which subsequently regresses. At 100 dpi the heart has nearly completely regenerated.*

Major Grants

- ***Ministerio de Economía y Competitividad (RYC-2006-001694)***
- ***Ministerio de Economía y Competividad (BFU2011-25297)***
- ***Comunidad de Madrid (P2010/BMD-2321) (PI: E. Lara)***
- ***Ministerio de Economía y Competitividad. FIS. RETICS (TERCEL: RD06/0010/0008) (PI: M. Torres)***

Selected Publications

Gonzalez-Rosa JM, Mercader N. **Cryoinjury as a myocardial infarction model for the study of cardiac regeneration in the zebrafish.** *Nat Protoc* (2012) 7: 782-8.

Gonzalez-Rosa JM, Peralta M, Mercader N. **Pan-epicardial lineage tracing reveals that epicardium derived cells give rise to myofibroblasts and perivascular cells during zebrafish heart regeneration.** *Dev Biol* (2012) 370: 173-86.

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

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: 301-11.

Gonzalez-Rosa JM, Martin V, Peralta M, Torres M, Mercader N. **Extensive scar formation and regression during heart regeneration after cryoinjury in zebrafish.** *Development* (2011) 138: 1663-74.

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program

Molecular genetics of angiogenesis

Head of Laboratory: Rui Benedito

Technicians: Adrián Galiana
Susana Rocha
Iker Rodríguez Arabaolaza

Research Interest

Blood and lymphatic vessels are not simply conduits for the body's fluids; they also control essential biological responses and are an important therapeutic target in cancer and cardiovascular diseases. The vascular system is distributed throughout the organism, and the plastic and adaptable nature of its heterogenous microstructure enables it to change in response to diverse pathological stimuli. The progression of many diseases is dependent on this plasticity of the vascular system, and involves the genetic reprogramming of the different vascular cell types, in order to modify their quiescent state.

Different lines of evidence lead us to believe that the molecular mechanisms responsible for these changes are similar to those responsible for the normal process of vascular development, differentiation and patterning. Our research goal is to understand these molecular mechanisms, and how they orchestrate the different context-dependent behaviors of the diverse cell types that compose our vascular system.

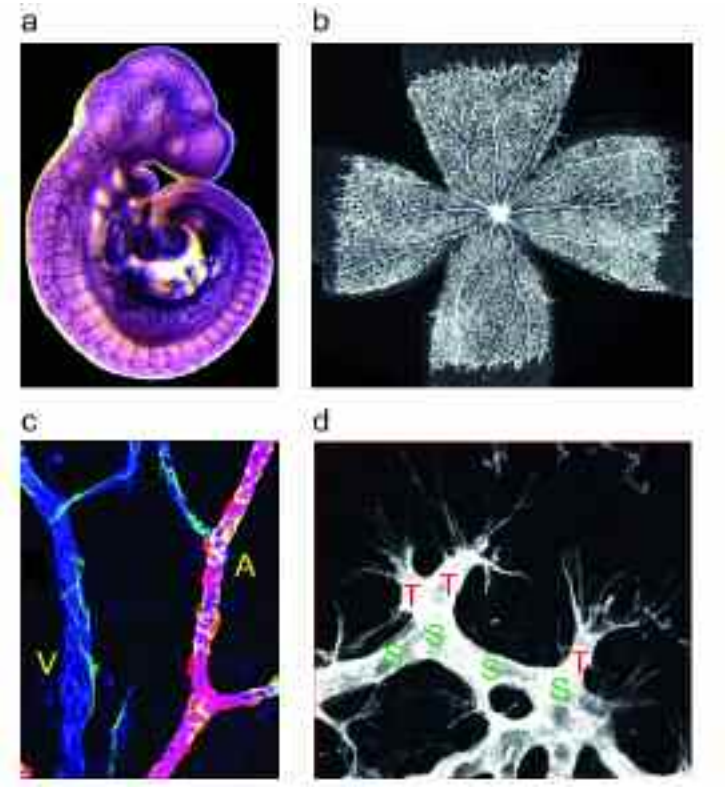
Several studies in the past have revealed the importance of cell-to-cell signaling for the differentiation and patterning of the vascular system. One of the most important and well-conserved mechanisms of cell-to-cell communication involves the Notch family of receptors and their transmembrane ligands Delta and Jagged. In recent years we have investigated the function of several components of the Notch signaling pathway and how they generate heterogeneity among endothelial cells during angiogenesis and arterial-venous differentiation. We found that differential expression and activity of the different Notch ligands and modulators is responsible for the diversity of cell behaviors necessary for normal and pathological vascular sprouting and growth. Our work also shows that inhibiting Notch induces excessive angiogenesis by non-conventional means, triggering molecular mechanisms that can promote vascular expansion even in the absence of the main vascular endothelial growth factor (VEGF).

We use a combination of advanced mouse models, several in vitro systems, quantitative gene expression analysis and the latest imaging technologies to further understand the biology of blood vessels and discover how some of their genes execute their diverse and context-dependent roles during development and disease.

Research Departments

1 Cardiovascular Development and Repair

A. Cardiovascular Developmental Biology Program



(a) Staining revealing the complete vasculature of a mouse embryo. (b) View of the vasculature of a flattened mouse retina. (c) A vein (V) and an artery (A) stained to highlight their constituent cells: endothelial cells (blue), pericytes (green) and smooth muscle cells (red). (d) Close-up of an angiogenic front, composed of endothelial-tip cells (T), which emit long filopodia to sense the gradients of angiogenic factors, and the adjacent stalk cells (S), which form the wall of the perfused vessels. An appropriate interplay between all these different cell types, each with their specific genetic signatures, is essential for shaping the vascular system during development and disease.

Selected Publications

Benedito R, Rocha SF, Woeste M, Zamykal M, Radtke F, Casanovas O, Duarte A, Pytowski B, Adams RH.**Notch-dependent VEGFR3 upregulation allows angiogenesis without VEGF-VEGFR2 signalling.** *Nature* (2012) 484: 110-4.

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* Nov 27 [Epub ahead of print]

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.

Pitulescu ME, Schmidt I, Benedito R, Adams RH. **Inducible gene targeting in the neonatal vasculature and analysis of retinal angiogenesis in mice.** *Nat Protoc* (2010) 5:1518-34.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program

Functional genomics of embryonic pluripotency and heart development

Head of Laboratory: Miguel Manzanares

Postdoctoral Researchers: M. Eva Alonso
Luis Augusto Aguirre
Cristina Arias Sánchez
Elena López
Beatriz Fernández-Tresguerres

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

Masters Student: Sergio Menchero

Technicians: Claudio Badía
Inmaculada Ors

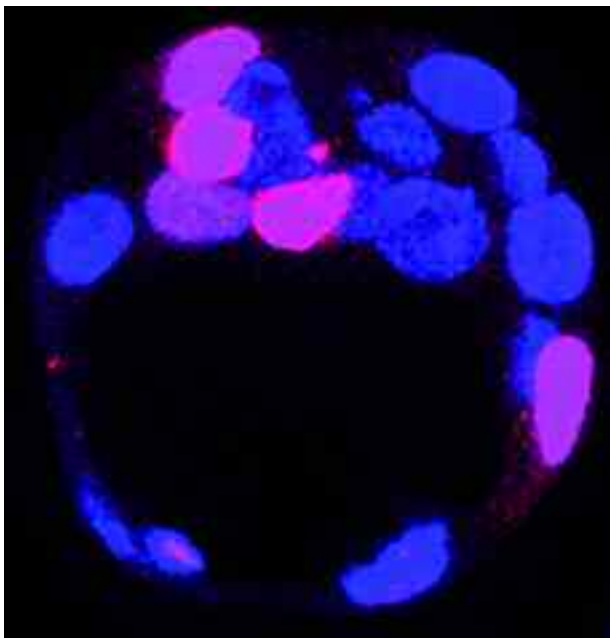
Visiting Scientists: Agustín Martín
Lidia Martínez

Research Interest

The central aim of our research is to understand how genome activity is regulated during development, and how this can contribute to human disease. For our approach, we identify regulatory sequences and study how they act on their target genes, organizing them into regulatory networks. This work is conducted through a combination of bioinformatics, comparative genomics, genome-wide analysis, and functional assays in transgenic mouse embryos, chick embryos, and stem cells.

We have shown that the pluripotency of embryonic cells is an evolutionary novelty in mammals. Using bioinformatics tools we found that the regulatory elements through which core factors control their downstream targets appeared de novo in the mammalian lineage. We have also analyzed the role of miRNAs in stem cells by deleting *Dicer*, finding that embryonic and extra-embryonic stem cells have different requirements for miRNAs. We also find that miRNAs do not have critical patterning or lineage-specification roles in the early embryo, but rather act as modulators of signaling pathways that ensure proper growth and proliferation.

In an effort to understand how regulatory elements interact with target genes, we have studied the genomic architecture of the *Irx* gene clusters, a family of homeobox transcription factors with crucial roles in heart development and function. We find that the chromatin factor CTCF acts to partition the regulatory landscape of the clusters, allowing differential expression of *Irx* genes in the heart. We have also participated in a genome-wide screen analyzing the evolutionary conservation of CTCF-bound regions among vertebrates, which has established the importance of these regions in maintaining proper regulation of adjacent genes. Future studies will address how general this role of CTCF and chromatin domains is in regulating cardiac gene expression, and how it is linked to disease.

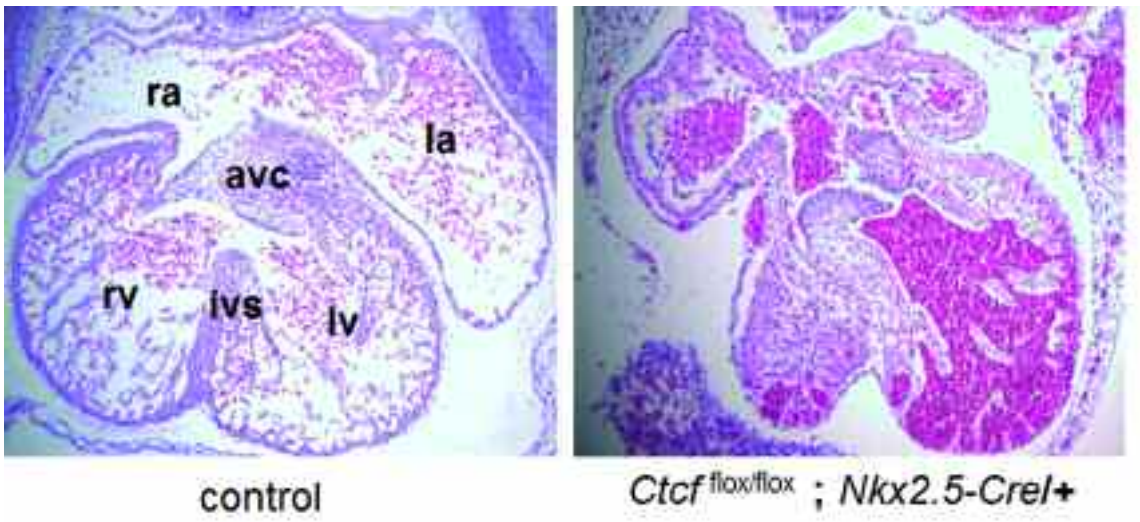


Transgenic mouse blastocyst showing activity of RFP (red fluorescent protein) driven by an Oct4 *regulatory element that predominantly functions in the inner cell mass.*

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program



Effect of the deletion of the chromatin-binding protein CTCF in the embryonic mouse heart. Embryos in which the Ctcf *gene is deleted using an* Nkx2.5-Cre *deleter line die at midgestation. At 12.5 dpc, a gross malformation of the intraventricular septum (ivs) is apparent, as well as dysmorphology of the cardiac chambers (left panel).*

Major Grants

- ***Ministerio de Economía y Competitividad (BFU2011-23083)***
- ***Ministerio de Economía y Competitividad, CONSOLIDER Project (CSD2007-00008)***
- ***CNIC Translational Grants (08-2009)***
- ***Comunidad de Madrid (S2010/BMD-2315)***

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.

Pernaute B, Spruce T, Rodriguez TA, Manzanares M. **MiRNA-mediated regulation of cell signaling and homeostasis in the early mouse embryo.** *Cell Cycle* (2011) 10: 584-91.

Cañon S, Fernandez-Tresguerres B, Manzanares M. **Pluripotency and lineages in the mammalian blastocyst: an evolutionary view.** *Cell Cycle* (2011) 10: 1731-8.

Tena JJ, Alonso ME, de la Calle-Mustienes E, Splinter E, de Laat W, Manzanares M, Gómez-Skarmeta JL. **An evolutionarily conserved three-dimensional structure in the vertebrate Irx clusters facilitates enhancer sharing and coregulation.** *Nat Commun* (2011) 2: 310.

Martin D, Pantoja C, Fernández Miñán A, Valdes-Quezada C, Moltó E, Matesanz F, Bogdanoviç O, de la Calle-Mustienes E, Domínguez O, Taher L, Furlan-Magaril M, Alcina A, Cañón S, Fedetz M, Blasco MA, Pereira PS, Ovcharenko I, Recillas-Targa F, Montoliu L, Manzanares M, Guigó R, Serrano M, Casares F, Gómez-Skarmeta JL. **Genome-wide CTCF distribution in vertebrates defines equivalent sites that aid the identification of disease-associated genes.** *Nat Struct Mol Biol* (2011) 18: 708-14.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program

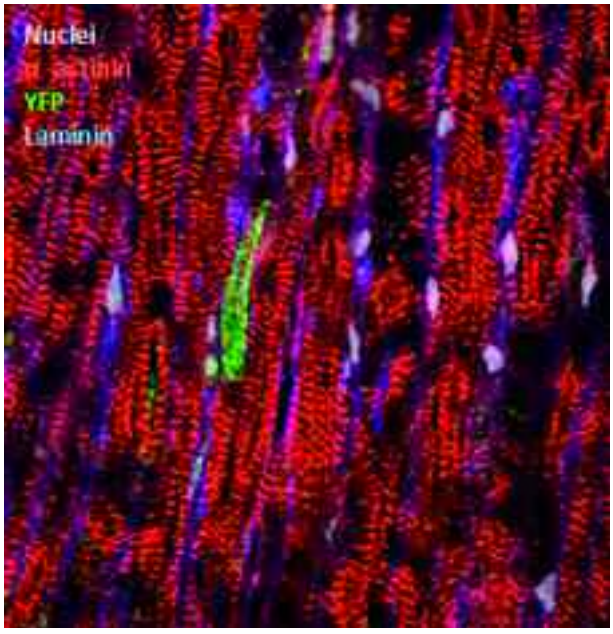
Gene expression and genetic stability in adult stem cells

Head of Laboratory:	Antonio Bernad
Research Scientists:	Manuel Ángel González
Postdoctoral Researchers:	Isabel Moscoso Galán Juan A Bernal Rodríguez José Luis Torán García Beatriz Escudero Susana Cañón Sánchez Alberto Izarra Pérez
Predoctoral Researchers:	Juan Camilo Estrada Rodríguez María Tomé Íñigo Valiente Alandi Francisco Miguel Cruz Urende
Masters Students:	Ánxela Louzao Boado Diego Herrero
Scientific Support:	Candelas Carreiro Quintana Carmen Albo Castellanos
Visiting Scientists:	Enrique Samper Guadalupe Gómez Mauricio
Technicians:	Juan Carlos Sepúlveda Muñoz Yaima Torres Rodríguez Rosa María Carmona Canorea Susana Aguilar García Juan A. Quintana Fernández

Research Interest

An organism's health and fitness depend on the preservation and functional maintenance of adult stem cells (aSCs). To investigate how stem cells balance the processes of self renewal and differentiation, we work with cardiac progenitor cells (CPCs) isolated from adult mammalian heart and with mouse and human mesenchymal stem cells (MSCs).

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 transcriptional factor Bmi-1 is an important marker of mouse CPCs (mCPCs). The Bmi-1+ CPC subpopulation contributes both to homeostatic cardiac turnover and to repair after acute injury. Furthermore, we have shown that two muscle-specific microRNAs, miRNA-1 and miRNA-133a, modulate the ability of several adult and embryonic stem-cell populations to respond to cardiomyogenic signals. Transplantation experiments revealed that mCPCs genetically manipulated to overexpress miRNA-133a protect against the deleterious effects of acute experimental infarction. We are now investigating the mechanism underlying this activity, which is most probably associated with an improved survival of transplanted CPCs and the derived paracrine effects on affected myocardium, including endogenous CSCs (eCSC). By differential analysis of miRNA expression, we have also established that a set of miRNAs associated with miR-335 and Bmi-1 activity in mCPCs is required to maintain hMSCs in the undifferentiated state, its downregulation being critical for the acquisition of reparative MSC phenotypes.

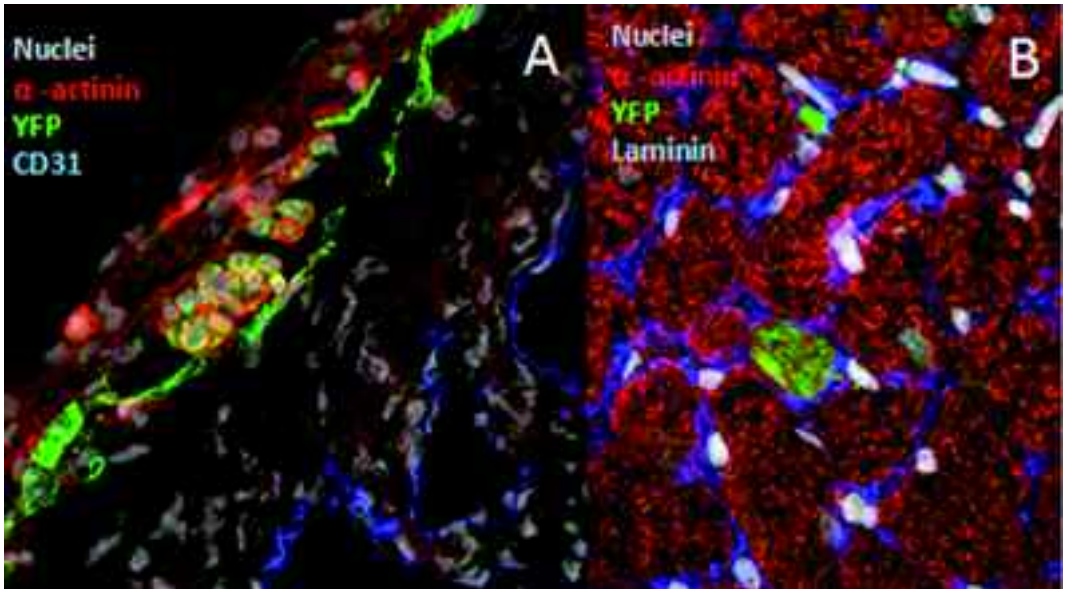


Role of Bmi1-CSCs in heart homeostasis. Bmi1-CSCs are able to contribute to the endogenous physiological turnover of the heart through the generation of the novo cadiomyocytes (YFP+; green).

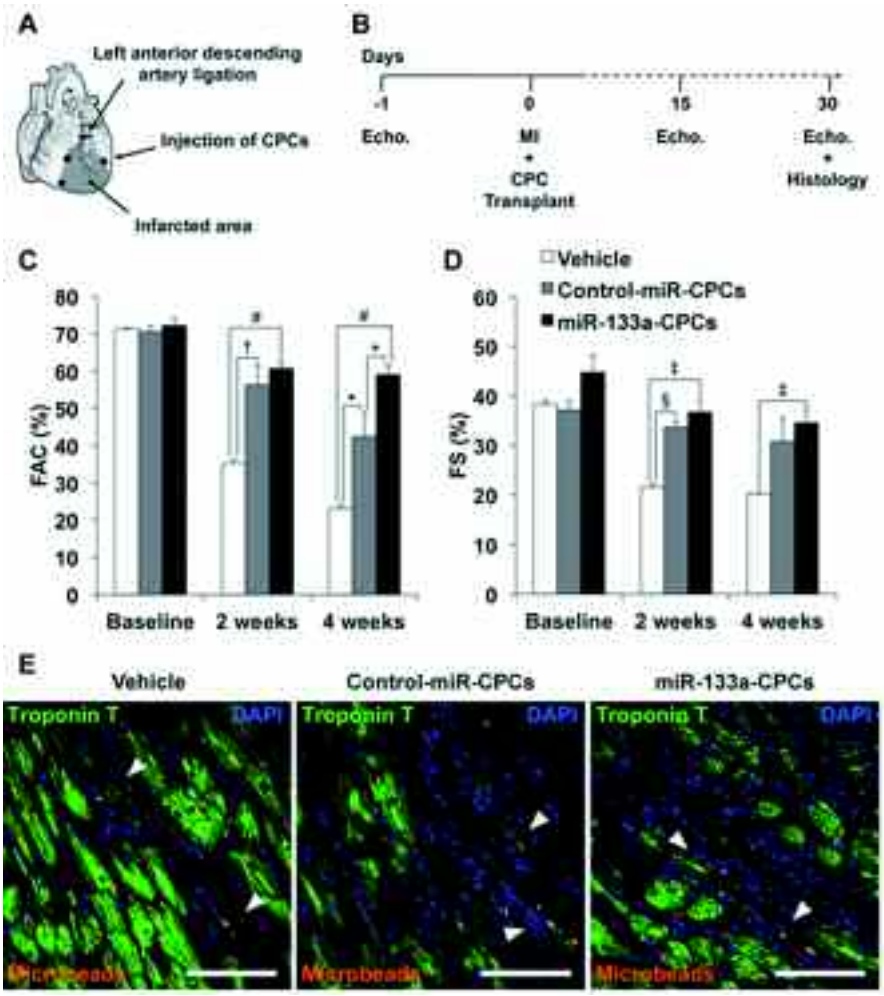
Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program



Response of Bmi1-CSCs to acute myocardial infarction (AMI). A. Activation of cardiac Bmi1-expressing cells (YFP; green) in the injured area. B. De novo YFP+ cardiomyocyte generation three months after infarction.



*Transplantation of CPCs into a rat model of AMI. **A**, After ligation of the left descending coronary artery, vehicle, control-miR–CPCs or miR-133a–CPCs were injected (x3) at the infarct border together with red fluorescent microbeads. **B**, Experimental timeline of echocardiography analysis. **C-D**, Echocardiography studies of fractional area change (FAC) and fractional shortening (FS) **E**, Detection of fluorescent microbeads (white arrowheads) in the infarct border zone (white bars: 100mm).*

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program

Major Grants

- ***Comunidad de Madrid (GRUPOSCAM10/ CELLCAM: S2011/BMD-2420). Sub-project coordinator: A. Bernad***
- ***European Commission FP7. European Multidisciplinary Initiative (FP7-HEALTH -2009 CAREMI). PI: A. Bernad (coordinator)***
- ***Ministerio de Economía y Competitividad (IPT-2011-1307-010000) Sub-project coordinator: A. Bernad***
- ***Ministerio de Economía y Competitividad (PLE2009-0147). Sub-project coordinator: A. Bernad***
- ***Ministerio de Economía y Competitividad (PLE2009-0100). Sub-project coordinator: A. Bernad***

Selected Publications

Tomé M, López-Romero P, Fernández-Gutiérrez B, Dopazo A, Bernad A*, González MA*. **miR-335 orchestrates cell proliferation, migration and differentiation in human mesenchymal stem cells.** (2011) *Cell Death Differ* 18: 985-95.
*Corresponding authors

Mittelbrunn M, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MA, Bernad A, Sánchez-Madrid F. **Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells.** (2011) *Nat Commun* 2: 282.

Fuster JJ, González-Navarro H, Vinué A, Molina-Sànchez P, Andrés-Manzano MJ, Nakayama KI, Nakayama K, Díez-Juan A, Bernad A, Rodríguez C, Martínez-González J, Andrés V. **Deficient p27 phosphorylation at serine 10 increases macrophage foam cell formation and aggravates atherosclerosis through a proliferation-independent mechanism** (2011). *Arterioscler Thromb Vasc Biol* 31: 2455-63.

Estrada JC, Albo C, Benguría A, Dopazo A, Carrera-Quintanar L, Morgado L, Roche E, Bernad A*, Samper E*. **Culture of human mesenchymal stem cells at low oxygen tension improves growth and genetic stability by activating glycolysis.** (2011) *Cell Death Differ* 19: 743-55.
*Corresponding authors

Casado J G, Gomez-Mauricio G, Alvarez V, Mijares J, Martinez-Caballero S, Bernad A, Sanchez-Margallo FM. **Comparative phenotypic and molecular characterization of porcine mesenchymal stem cells from different sources for translational studies in a large animal model.** (2012) *Vet Immunol Immunopathol* 147: 104-12.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program

Stem cell niche pathophysiology

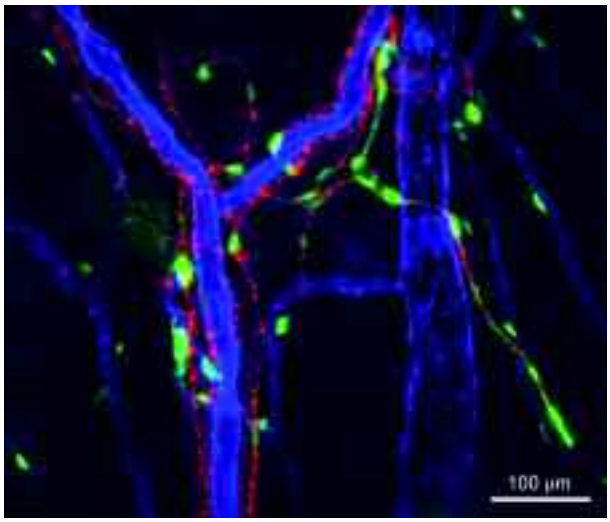
Head of Laboratory: Simón Méndez-Ferrer

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

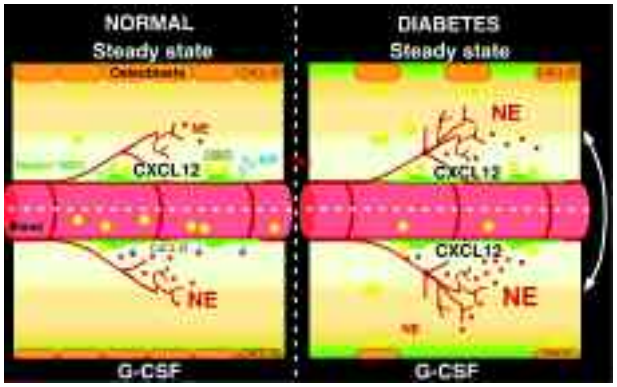
Masters Students: Andrés García
Siddhi Lama

Technicians: Ana M. Martín
Daniel Martín
Sandra Martín

Research Interest



Peri-vascular nestin⁺ mesenchymal stem cells are innervated by sympathetic fibers in the bone marrow. Projection stack (~100 µm) of fluorescent images showing the distribution of Nestin-*GFP⁺ cells (green), CD31/PECAM⁺ vascular endothelial cells (blue) and tyrosine hydroxylase⁺ sympathetic nerve fibers (red) after whole mount staining of the skull bone marrow (from Isern and Méndez-Ferrer, 2011).*



Stem cells reside in specialized niches that allow them to self-renew, proliferate, differentiate and migrate according to the organism's requirements. Our group studies the mechanisms by which the stem cell niche fulfils these complex functions and how its deregulation contributes to disease.

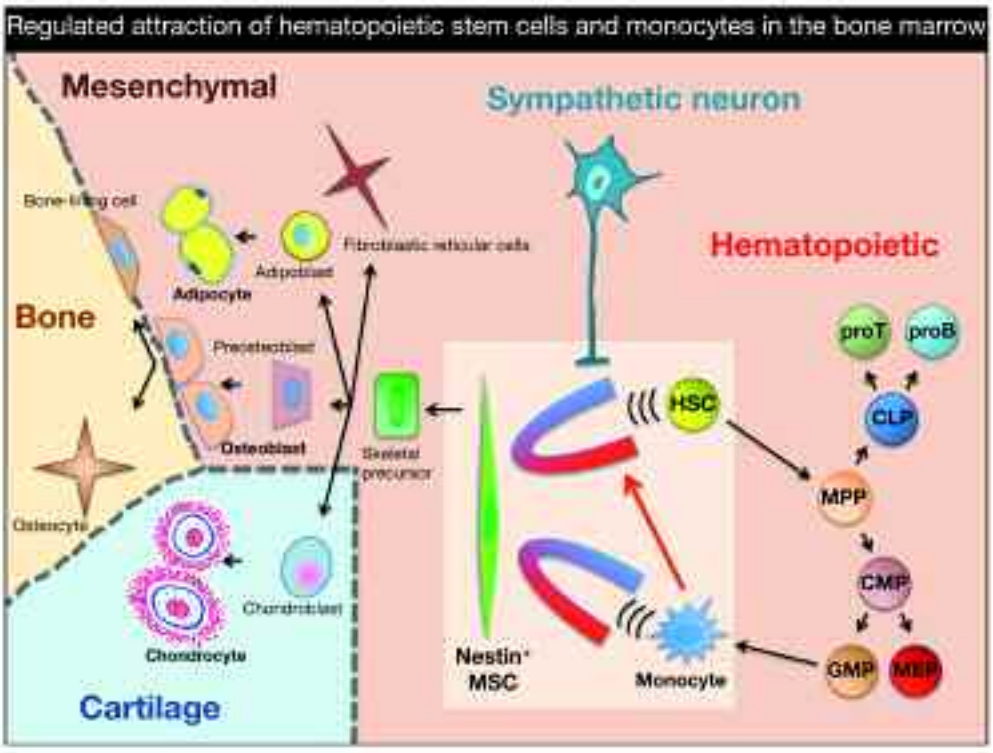
Our earlier work described a tight regulation of the bone marrow stem cell niche by circadian oscillations of sympathetic activity. Light onset induces noradrenaline release from nerve terminals in the bone marrow, leading to downregulation of CXCL12/SDF-1, the only chemokine known to direct hematopoietic stem cell (HSC) migration. The HSC mobilizing agent granulocyte colony-stimulating factor (G-CSF) increases sympathetic stimulation of nestin⁺ mesenchymal stem cells (MSCs), which we have identified as the stromal cells that critically regulate HSC traffic. Collaborative studies have recently shown that deregulation of this pathway contributes to poor HSC mobilization in diabetic subjects. An increased number of sympathetic fibers in the bone marrow of diabetic mice correlates with the inability of MSCs to down-modulate the production of CXCL12. HSC attraction to MSCs is also affected by other cells of the bone marrow microenvironment. A subset of monocytes promotes the retention of HSCs by MSCs in the bone marrow. MSCs regulate not only HSC traffic but also the egress of inflammatory monocytes from the bone marrow. MSCs respond to pro-inflammatory cytokines by producing the chemokine CCL2/MCP1, which directs the egress of these monocytes from the bone marrow compartment toward the peripheral circulation. These studies have dissected critical HSC-MSC interactions in the bone marrow stem-cell niche.

Deficient hematopoietic stem cell mobilization in diabetes. Diabetic bone marrow shows several alterations compared with the healthy state: the content of hematopoietic stem cells (HSCs) is increased, and these cells are more proliferative; there are fewer osteoblasts; and there are more sympathetic nerve terminals, leading to impaired responsiveness of β3-adrenergic receptors (β3-AR) expressed on nestin⁺ MSCs, the major source of CXCL12. In healthy bone marrow, granulocyte colony-stimulating factor (G-CSF) decreases osteoblast numbers, releases norepinephrine (NE), which binds to β3-AR, and reduces CXCL12 expression in nestin⁺ MSCs, resulting in transmigration of hematopoietic stem cells to the peripheral circulation. In diabetic bone marrow, G-CSF induces a similar reduction of osteoblasts and CXCL12 expression in osteoblasts but no reduction of CXCL12 expression in nestin⁺ MSCs, thereby impeding HSC mobilization toward the peripheral circulation.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program



Model of the regulation of HSC and monocyte traffic in the bone marrow. Nestin+ MSCs, which can generate mesenchymal lineages in the bone marrow, regulate the egress of monocytes in response to Toll-like receptor ligands and also the traffic of hematopoietic stem cells (HSC). Both the production of CXCL12 by nestin+ MSCs and these cells' attraction to HSCs are inhibited by sympathetic nerve fibers and stimulated by soluble factors produced by monocytes. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-macrophage progenitor; MEP, megakaryocyte-erythroid progenitor; MPP, multipotential progenitor. (From Arranz and Méndez-Ferrer, 2013).

Major Grants

- ***Howard Hughes Medical Institute. International Early Career Scientist.***
- ***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)***
- ***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

Lucas D, Bruns I, Battista M, Méndez-Ferrer S, Magnon C, Kunisaki Y, Frenette PS. **Norepinephrine reuptake inhibition promotes mobilization in mice: potential impact to rescue low stem cell yields.** *Blood.* (2012) 119: 3962-5.

Ferraro F, Lymperi S, Méndez-Ferrer S, Saez B, Spencer JA, Yeap BY, Masselli E, Graiani G, Prezioso L, Rizzini EL, Mangoni M, Rizzoli V, Sykes SM, Lin CP, Frenette PS, Quaini F, Scadden DT. **Diabetes impairs hematopoietic stem cell mobilization by altering niche function.** *Sci Translat Med* (2011) 3: 104ra101.

Isern J, Méndez-Ferrer S. **Stem cell interactions in a bone marrow niche.** *Curr Osteopor Rep* (2011) 9: 210-8.

Shi C, Jia T, Méndez-Ferrer S, Hohl TM, Serbina NV, Lipuma L, Leiner I, Li MO, Frenette PS, Pamer EG. **Bone marrow mesenchymal stem and progenitor cells induce monocyte emigration in response to circulating TLR-ligands.** *Immunity* (2011) 34: 590-601.

Chow A, Lucas D, Hidalgo A, Méndez-Ferrer S, Hashimoto D, Scheiermann C, Battista M, Leboeuf M, Prophete C, van Rooijen N, Tanaka M, Merad M, Frenette PS. **Bone marrow CD169+ macrophages promote the retention of hematopoiteic stem and progenitor cells in the mesenchymal stem cell niche.** *J Exp Med* (2011) 208: 261-71.

Research Departments

1 Cardiovascular Development and Repair

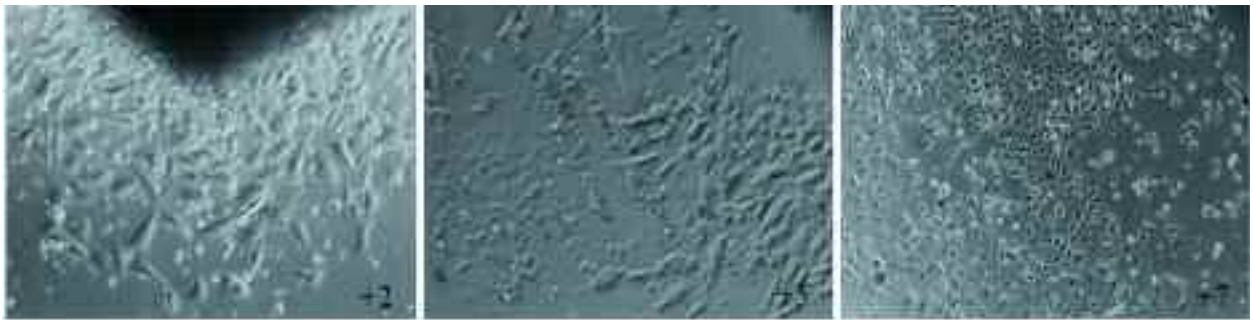
B. Stem Cell Biology Program

Cardiovascular related risks of obesity

Head of Laboratory: Beatriz González Gálvez
Predoctoral Researchers: Aurora Bernal Mera
Laura Martín Pérez
Technician: Nuria San Martín Fernández
Visiting Scientists: Andrea Enguita
Alexis Pernas

Research Interest

In the last year we have developed an easy and efficient method for obtaining adult committed precursors from different mouse tissues. This work demonstrates that it is possible to isolate and expand mesenchymal precursors from skin and lung by a non-enzymatic method. These skin and lung precursors have a defined morphology in vitro and characteristic gene-expression and surface-marker profiles, including stem-cell and mesenchymal surface markers, as well as epithelial markers. However, they were negative for markers of endothelium, cardiac and skeletal muscle and adipose tissue, indicating that they have initiated commitment to the tissues from which were isolated. The precursors can migrate without stimulus and also in response to SDF1, MCP1 and TNFα, and can be differentiated into epithelial lineages. The properties of these precursors from adult tissues indicate that they have potential as tools for regenerative biomedicine.

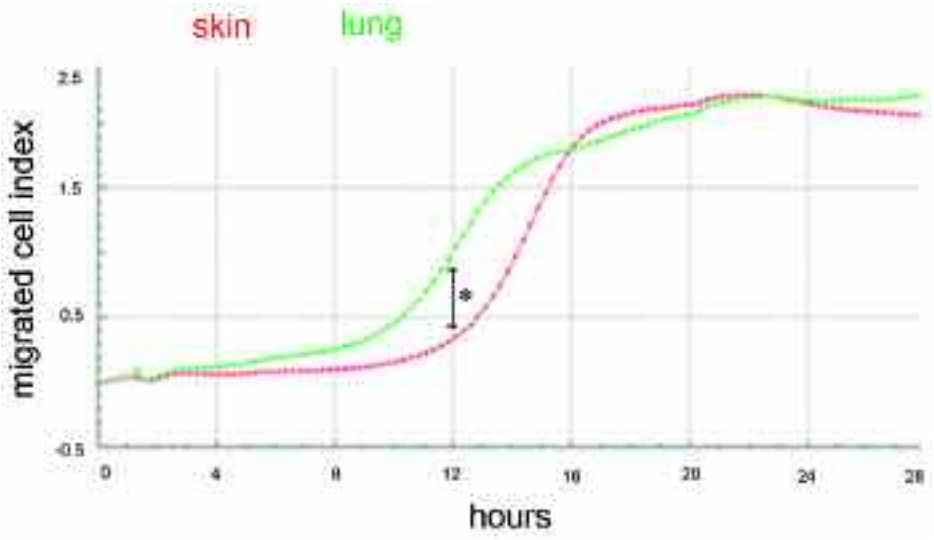


Explant method for isolating committed precursors.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program



Real time migration curve of skin and lung mesenchymal precursors.

Major Grants

- Ministerio de Economía y Competitividad (RYC2009-04669)

- Ministerio de Economía y Competitividad (SAF2010-15239)

Selected Publications

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

Vanelli A, Pennarossa G, Maffei S, Galvez BG, Cossu G, Rahaman M, Gandolfi F, Brevini TA. **Isolation, characterization and differentiation potential of cardiac progenitor cells in adult pigs.** *Stem Cell Rev* (2012) 8: 706-19.

Crippa S, Cassano M, Messina G, Galli D, Galvez BG, Curk T, Altomare C, Ronzoni F, Toelen J, Gijsbers R, Debyser Z, Janssens S, Zupan B, Zaza A, Cossu G, Sampaolesi M. **miR669a and miR669q prevent skeletal muscle differentiation in postnatal cardiac progenitors.** *J Cell Biol* (2011) 193: 1197-212.

San Martín N, Gálvez BG. **A new paradigm for the understanding of obesity: the role of stem cells.** *Arch Physiol Biochem* (2011) 117: 188-94.

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.

Research Departments

1 Cardiovascular Development and Repair

B. Stem Cell Biology Program

Cellular signaling

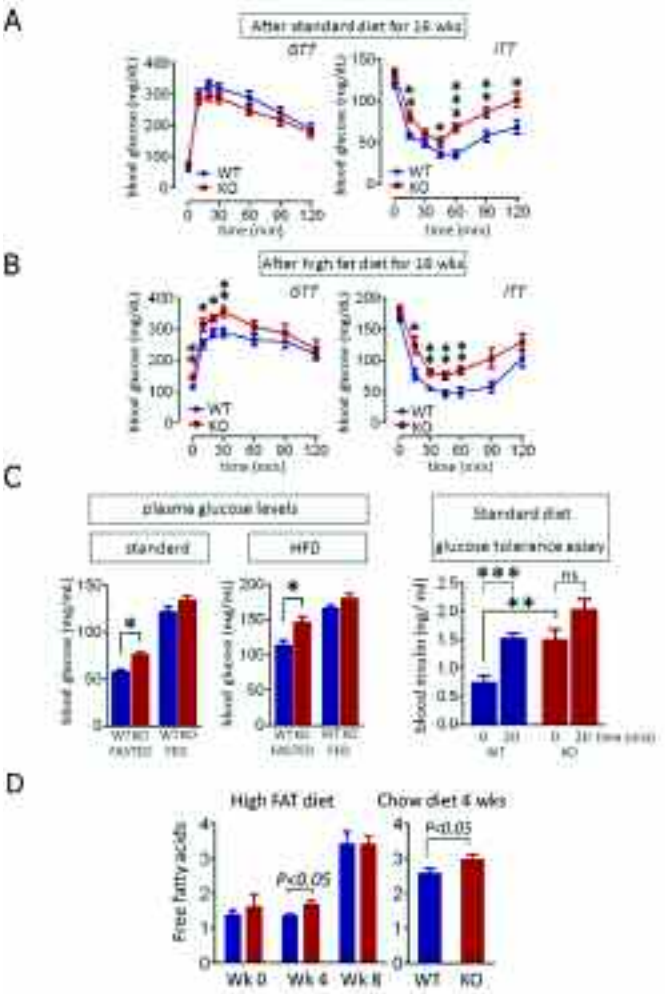
Head of Laboratory: Kenneth J. McCreath
Research Scientist: Ana Mª Cervera
Postdoctoral Researcher: Sandra Espada
Masters Student: Enrique Gallego

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.

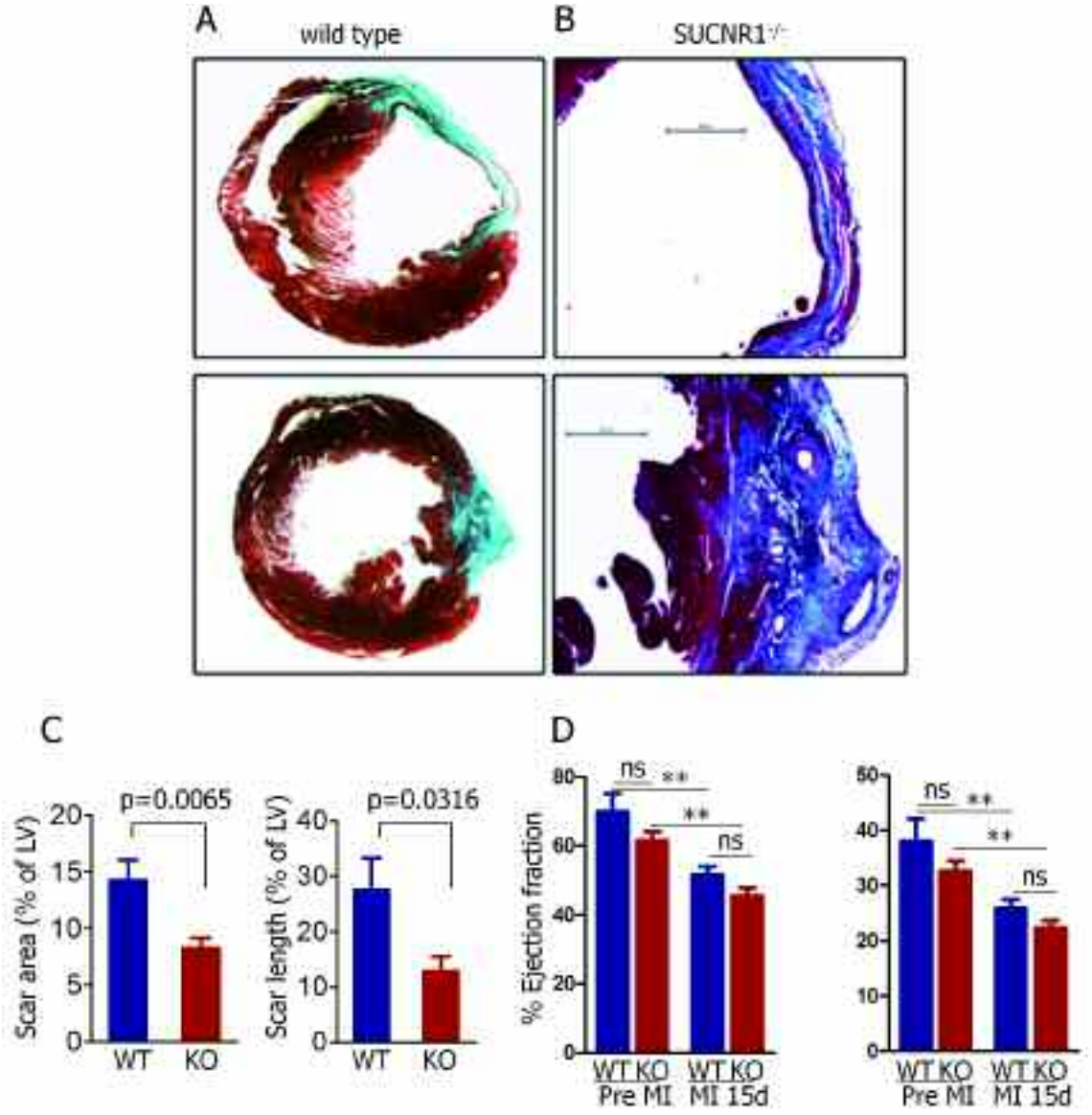


SUCNR1 *deletion alters metabolic homeostasis.* ***(A,B)*** *A glucose tolerance test (GTT) was carried out in animals (n=11) after an overnight fast, and an insulin tolerance test (ITT) was carried out in animals after a 2 h fast.* ***(C)*** *Basal plasma glucose levels were measured in fasted animals (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.*

Research Departments

1 Cardiovascular Development and Repair

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.*

Major Grants

- Ministerio de Economía y Competitividad (SAF2009-07965)

Selected Publications

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.

Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program

Functional genetics of the oxidative phosphorylation system

Head of Laboratory: Jose Antonio Enríquez

Research Scientists: Rebeca Acín-Pérez

Postdoctoral Researchers: Carmen Colás
Cristiane Benincá

Predoctoral Researchers: Ricardo Marco
Adela Guarás
Ana Latorre
Isabel Martínez

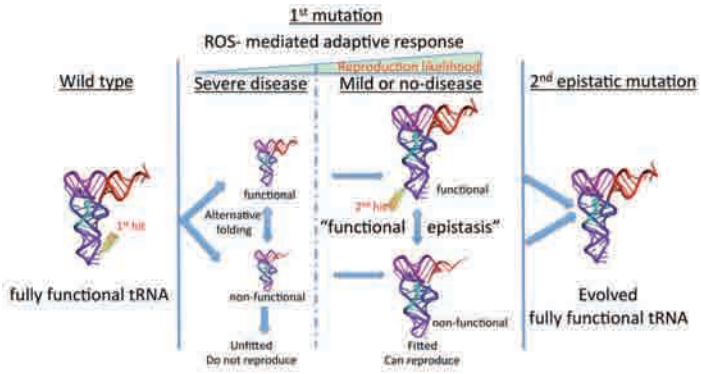
Technician: Andrés González Guerra

Support Scientists: Mª Concepción Jiménez
Marta Roche

Visiting Scientists: Patricio Fernández-Silva
Rocío Nieto
Pilar Bayona
Laura G. Corzo
Raquel Moreno Loshuertos
Ana Martínez
Eduardo Balsa
Sandra Chocrón
Sara Cogliati
Rosa Bretón
Ana Lechuga
Alberto Cecconi

Research Interest

Our group studies the biogenesis, structural organization and functional regulation of the OXPHOS system. Our main goal is to gain a molecular understanding of the role of the OXPHOS system in health and disease. We are especially interested in the role of mitochondria in the pathological consequences of ischemia/reperfusion and in how mitochondrial dysfunction impacts longevity and the progression of cardiovascular and neurodenerative diseases. A longer term aim is to identify potential therapies for these conditions. Our approach involves functional genetic studies of genes encoded by the mitochondrial genome (mtDNA) and others encoded by the nuclear genome (nDNA). We are currently conducting a series of high-throughput screens based on a genome-wide lentiviral siRNA library, genome trap technologies, and mitochondrial proteomics. The purpose of this program is to identify and characterize 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 the protection from or development of disease. For this project, the group works with human and mouse cell lines and mouse disease models, and studies the disease association of common human mtDNA haplotypes.

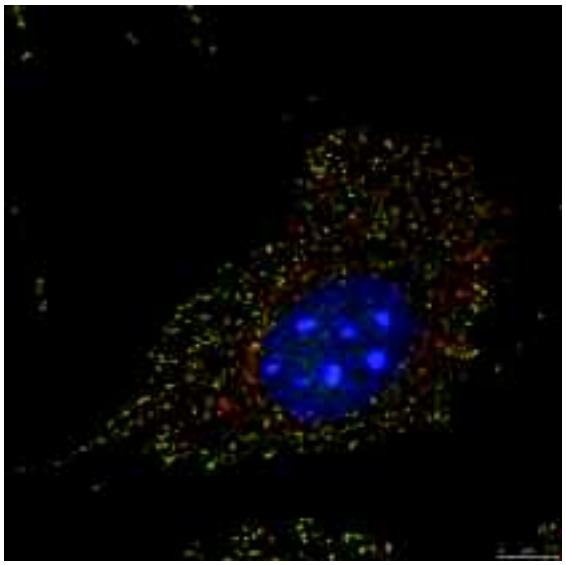


Model of the potential consequences of "functional epistasis" on disease penetrance and sequence evolution of mitochondrial tRNAs.

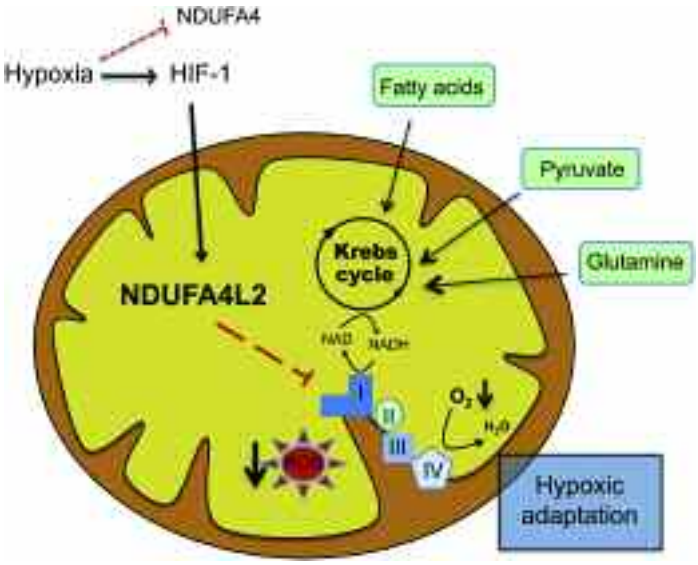
Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program



Confocal micrographs of NIH3T3 cells incubated with 100 nM mitotracker (Red), fixed with formaldehyde (3,7%) and immunostained with anti-DNA (green). Maximum projection of Z-stacks is shown, scale bar: 10 um.



Model showing the involvement of NDUFA4L2 induction by HIF-1α in hypoxic adaptation.

Major Grants

- ***Ministerio de Economía y Competitividad (SAF2009-08007)***
- ***Ministerio de Economía y Competitividad CONSOLIDER project (CSD2007-00020)***
- ***Comunidad de Madrid. GRUPOSCAM10 (P2010/BMD-2402)***
- ***Ministerio de Economía y Competitividad (RYC-2011-07826). PI: Rebeca Acín***

Selected Publications

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.

Diaz F, Enríquez JA, Moraes CT. **Cells lacking Rieske iron-sulfur protein have a reactive oxygen species-associated decrease in respiratory complexes I and IV.** *Mol Cell Biol* (2012) 32: 415-29.

Estrada JC, Albo C, Benguría A, Dopazo A, López-Romero P, Carrera-Quintanar L, Roche E, Clemente EP, Enríquez JA, Bernad A, Samper E: **Culture of human mesenchymal stem cells at low oxygen tension improves growth and genetic stability by activating glycolysis.** *Cell Death Differ* (2012) 19:743-55.

Quirós PM, Ramsay AJ, Sala D, Fernández-Vizarra E, Rodríguez F, Peinado JR, Fernández-García MS, Vega JA, Enríquez JA, Zorzano A, López-Otín C: **Loss of mitochondrial protease OMA1 alters processing of the GTPase OPA1 and causes obesity and defective thermogenesis in mice.** *EMBO J* (2012) 31:2117-33.

García-Corzo L, Luna-Sánchez M, Doerrier C, García JA, Guarás A, Acín-Pérez R, Bullejos-Peregrín J, López A, Escames G, Enríquez JA, Acuña-Castroviejo D, López LC: **Dysfunctional Coq9 protein causes predominant encephalomyopathy associated with CoQ deficiency.** *Hum Mol Genet* (2013) Jan 3. [Epub ahead of print]

Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program

Stem cell aging

Head of Laboratory: Susana González

Predoctoral Researchers: Antonio Herrera Merchán
Isabel Hidalgo
Ileana González

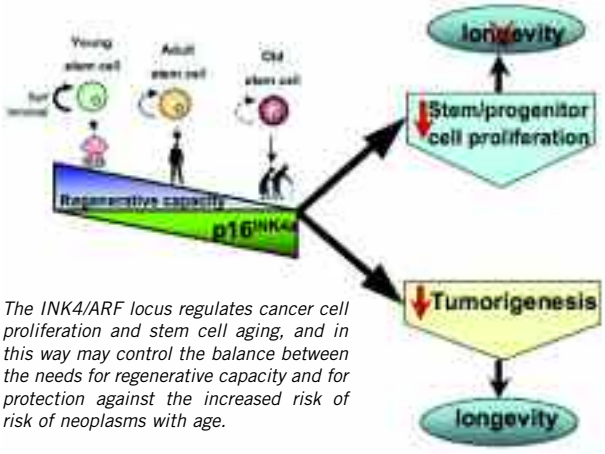
Technichians: Milagros Sonseca
Rebeca Diges

Visiting Scientist: José Manuel Garrido

Research Interest

The INK4b-ARF-INK4a locus encodes three tumor 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 tumor 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 tumor 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 Economía y Competitividad (SAF2010-15386)

Selected Publications

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: 22-9.

Mittelbrunn M, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MÁ, Bernad A, Sánchez-Madrid F. **Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells.** *Nat Commun* (2011) 2: 282.

Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program

Nuclear receptor signaling

Head of Laboratory: Mercedes Ricote

Postdoctoral Researchers: Piedad Menéndez, Tamas Röszer, Lucía Fuentes

Predoctoral Researchers: Daniel Alameda, Marta Cedenilla

Technician: Vanessa Núñez

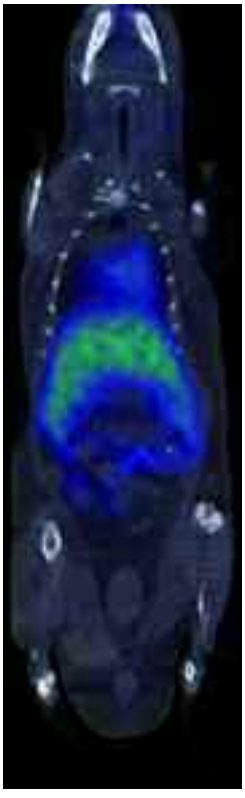
Research Interest

Nuclear hormone receptors constitute a superfamily of ligand activated transcription factors with diverse roles in development and homeostasis. Work by our group is contributing to the definition of a role for nuclear receptors in lipid metabolism and inflammatory responses in macrophages. We are interested in the roles of PPARs (peroxisome proliferator-activated receptors) and RXRs (retinoid X receptors) in two areas: chronic inflammatory disease and the homeostasis of adult stem cells.

Recent studies from our group have demonstrated that macrophage genes regulated by PPARs and RXRs are involved in apoptotic cell clearance and macrophage inflammatory phenotype shift. We have also embarked on an investigation of the *in vivo* role of macrophage RXRs in the development of chronic inflammation and consequent insulin resistance. Our objective is to identify RXR-controlled mechanisms in macrophage gene regulation which may be involved in inflammation and metabolic control. We are also exploring the role of PPARs and RXRs in the promotion and control of inflammation during cardiac repair and regeneration, with the aim of understanding how macrophage PPARs and RXRs might modulate these processes.

Our research into adult stem cells addresses the roles of PPARs and RXRs in the differentiation, proliferation and self-renewal of hematopoietic stem cells. We have found that nuclear receptors of the myeloid lineage are key determinants of osteoclast functional maturation and bone resorption, and are thus potential targets for the treatment of low bone mineral density.

Our studies identify macrophage PPARs and RXRs as key players in tissue and organ homeostasis, and open new perspectives on the use of RXR ligands as potential regulators of the immune response and metabolism.

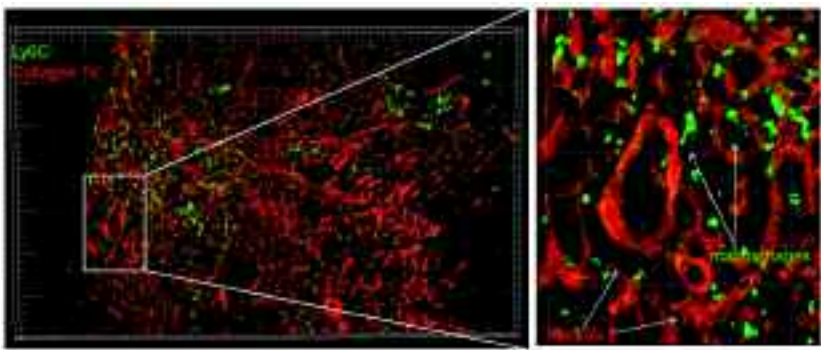


PET image showing fluorodeoxyglucose [^{18}F] distribution in a mouse liver and heart. *Whole-body PET scans allow us to detect alterations in glucose uptake by insulin target organs.*

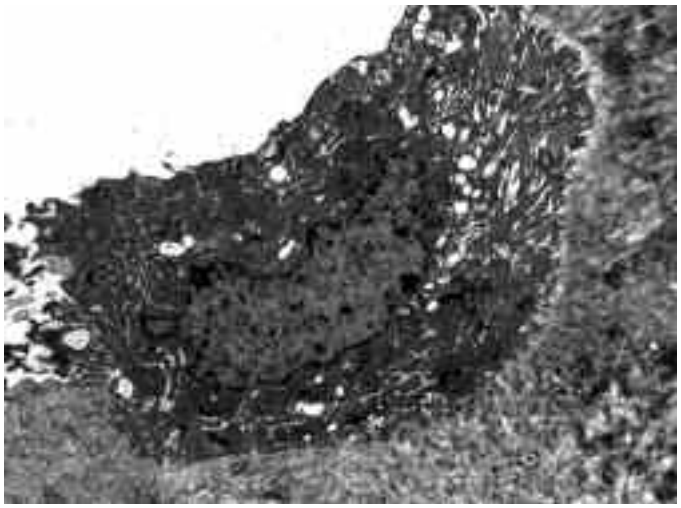
Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program



Macrophage infiltration analysis by 2D and 3D reconstruction of confocal fluorescence of whole mount cryoinfart. *3D rendering of the surface volume of whole mount heart 3 days after cryoinjury (using IMARIS 7.3.1 software; tile scan, 25x magnification, z stacks every micron). Heart pieces were stained with anti-collagen IV (red) and anti-Ly6C fitc (green). The cryolesion is characterized by extensive infiltration of macrophages (Ly6C+) and a vascular morphology (collagen IV+).*



Transmission electron micrograph of an actively resorbing mouse osteoclast. *The ventral cell surface forms a ruffled border and attaches to the mineralized bone matrix. Several secretory vesicles, filled with acidic phosphatases, are present in the ruffled border. Magnification 8000x, JEM Jeol 1010, 80 keV.*

Major Grants

- ***Fundación la Marató TV3·(MTV3012)***
- ***Ministerio de Economía y Competitividad (SAF2012-31483)***
- ***European Foundation for the Study of Diabetes/Lilly Research Fellowships (EFSDF2012). PI T. Röszer***
- ***Fundación la Mataró TV3 (MTV308)***
- ***Ministerio de Economía y Competitividad (SAF 2009-07466)***
- ***Fundación Genoma España. MEICA Project (PICPPFGE08)***
- ***European Commission FP7. Marie Curie European Reintegration Grant (FP7-PEOPLE-2009-RG -25321) PI L.Fuentes***

Selected Publications

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

Prieur X, Mok CY, Velagapudi VR, Nunez V, Fuentes L, Montaner D, Ishikawa K, Camacho A, Barbarroja N, O'Rahilly S, Sethi J, Dopazo J, Oresic M, Ricote M,* Vidal-Puig A*. **Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice.** *Diabetes* (2011) 60: 797-809.
*Corresponding authors

Roszer T, Menendez-Gutierrez MP, Lefterova MI, Alameda D, Nunez V, Lazar MA, Fischer T, Ricote M. **Autoimmune kidney disease and impaired engulfment of apoptotic cells in mice with macrophage peroxisome proliferator-activated receptor γ or retinoid X receptor α deficiency.** *J Immunol* (2011) 186: 621-31.

Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program

Molecular regulation of heart development and disease

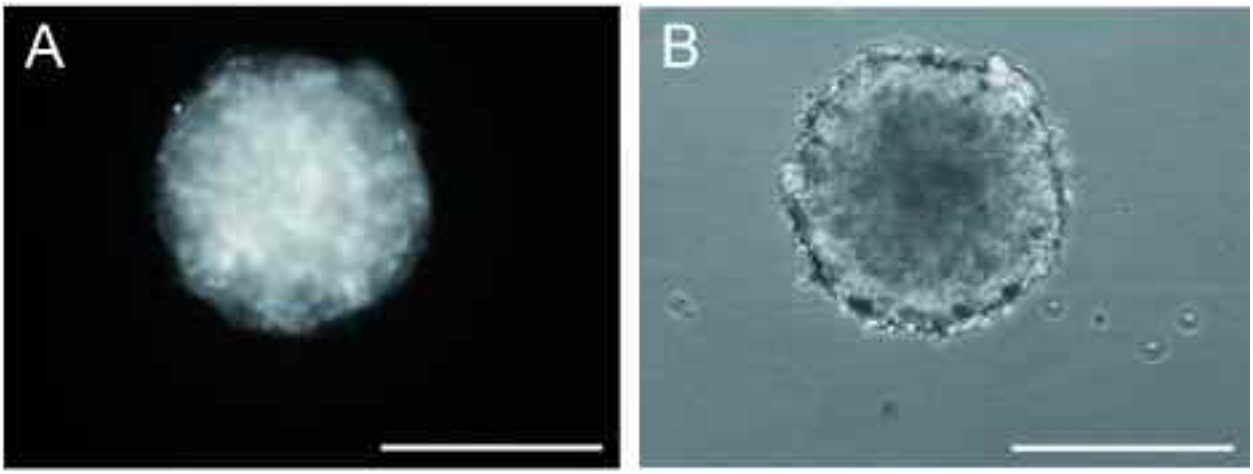
Head of Laboratory: Enrique Lara Pezzi
Predoctoral Researchers: Jesús M. Gómez Salinero
Alberto Gatto
Graduate technician: Maria Villalba
Technician: Marina M. López Olañeta
Visiting Scientist: José del Carmen González Santamaria

Research Interest

Our lab studies the molecular mechanisms that regulate cardiac development and heart disease. One of our major goals is to understand the role of alternative splicing (AS) in these processes. AS is the molecular process that removes introns from immature pre-mRNAs and links exons together in different combinations. AS affects 86% of all human genes and is in part responsible for the great diversity of proteins that are generated from the relatively small number of genes found in the human genome.

We have used RNA-Seq and exon microarrays to analyze the splicing pattern in heart failure. Using these data we have been able to identify cis-regulatory sequences and trans-regulatory splicing factors associated with AS. We are now analyzing the roles of these factors in the heart through gain- and loss-of-function strategies.

A prime example of how alternative splicing can dramatically change protein function is the calcineurin variant CnAβ1. Calcineurin regulates a wide variety of physiological and pathological processes, including cardiac development and hypertrophy. CnAβ1 is a naturally occurring splice variant of the calcineurin Aβ gene which contains a unique C-terminal region, different from the autoinhibitory domain present in all other CnA isoforms. Our recent results show that CnAβ1 promotes heart recovery after myocardial infarction by improving cardiac function and reducing inflammation and scar formation. This is achieved through the activation of the Akt signaling pathway. We are now exploring the role of CnAβ1 in stem cells and in the developing embryo, where it is strongly expressed.

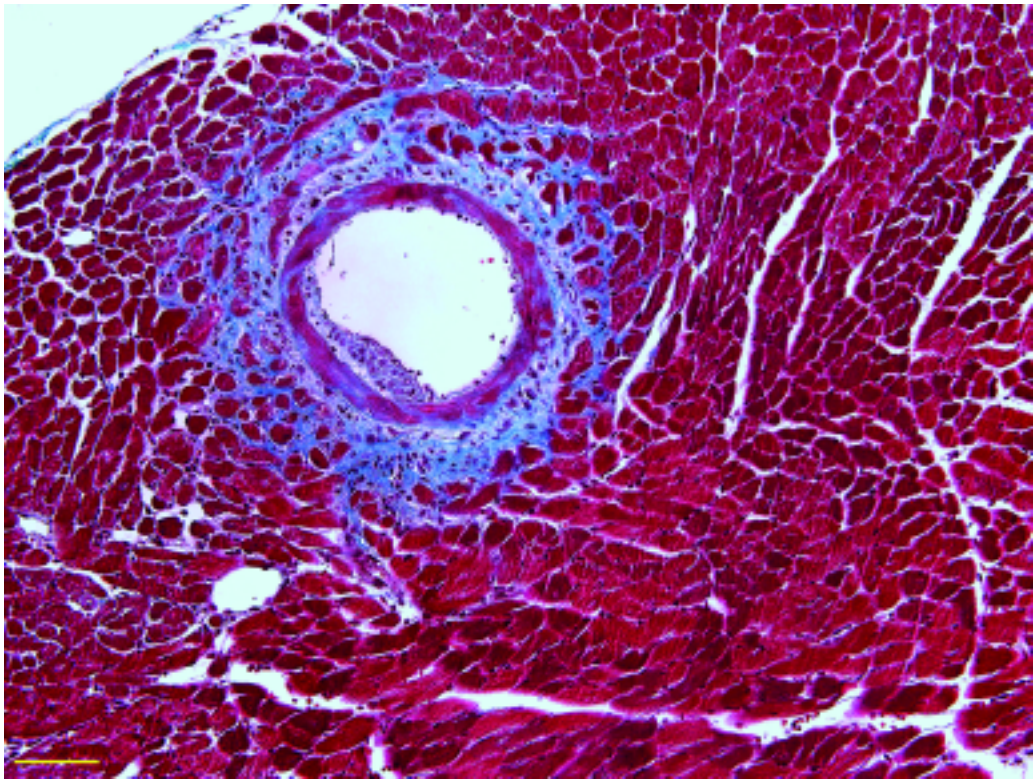


Highly efficient transfection of mouse embryonic stem cells (mESCs) with mRNA. *mESCs were transfected with mRNA coding for the enhanced green fluorescent protein (EGFP) and allowed to differentiate towards the mesodermal lineage using the hanging drop method. A and B show fluorescence and phase-contrast images two days after transfection. Bar, 250 µm.*

Research Departments

1 Cardiovascular Development and Repair

C. Tissue Homeostasis and Repair Program



Perivascular fibrosis in a hypertrophic heart following aortic stenosis. *Mice underwent transaortic constriction to induce pressure overload hypertrophy. They were sacrificed 28 days after surgery and hearts were fixed and analyzed using the Masson's Trichrome method. Cardiomyoctes and collagen fibers are stained in red and blue, respectively. Bar, 100 µm.*

Major Grants

- ***Marie Curie Action Initial Training Network (ITN) (FP7-PEOPLE-2011-ITN, "CardioNeT")***
- ***Comunidad de Madrid (GRUPOSCAM10, "Fibroteam")***
- ***Ministerio de Economía y Competitividad (BFU2009-10016)***
- ***Ministerio de Economía y Competitividad. FIS (CP08/00144)***

Selected Publications

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: 814-26.

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.

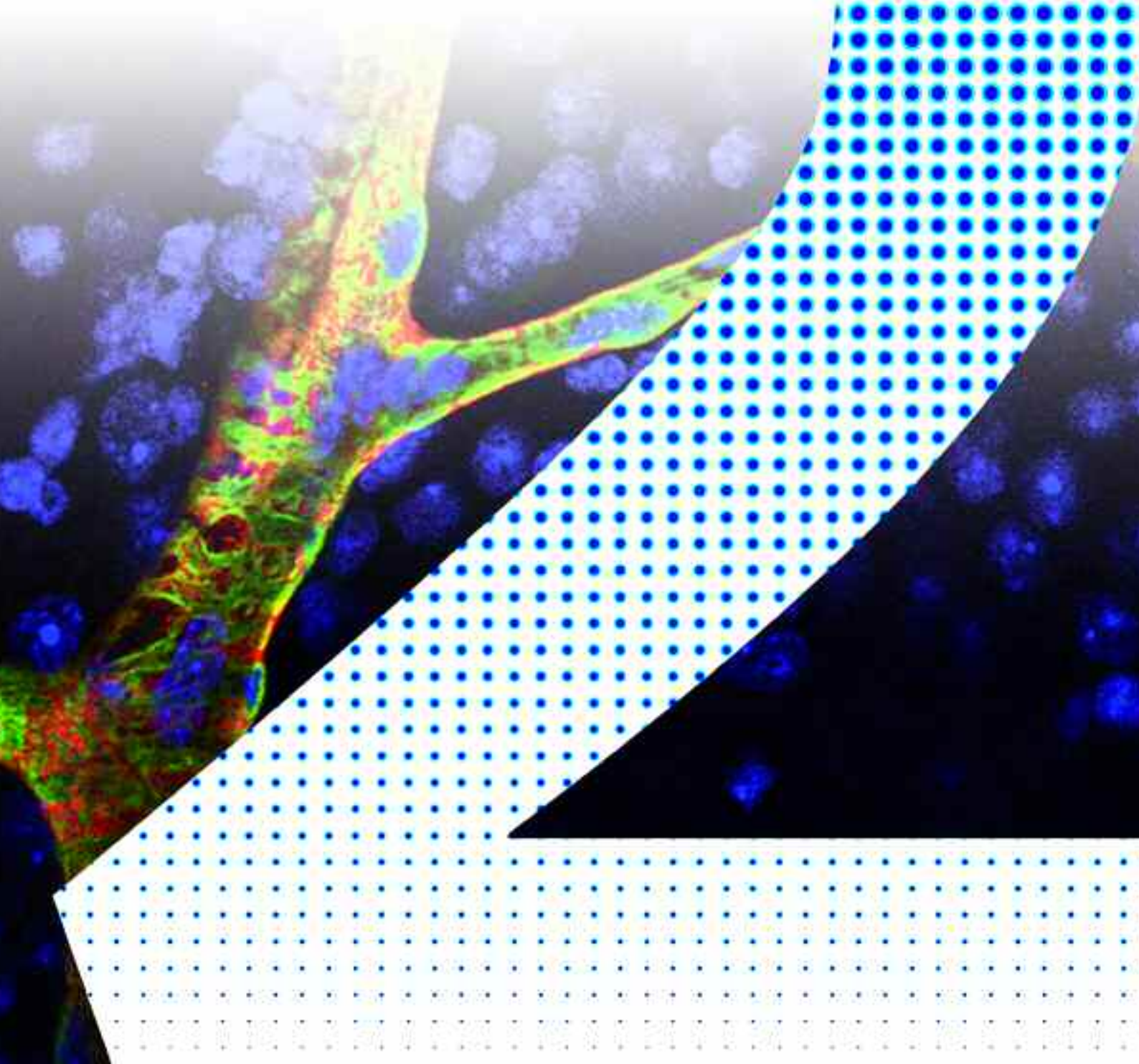
Gómez-Gaviro MV, Lovell-Badge R, Fernández-Avilés F, Lara-Pezzi E. **The vascular stem cell niche.** *J Cardiovasc Transl Res* (2012) 5: 618-30.

Felkin LE, Narita T, Germack R, Shintani Y, Takahashi K, Sarathchandra P, López-Olañeta MM, Gómez-Salinero JM, Suzuki K, Barton PJ, Rosenthal N and Lara-Pezzi E. **Calcineurin splicing variant calcineurin Aβ1 improves cardiac function after myocardial infarction without inducing hypertrophy.** *Circulation* (2011) 123: 2838-47.

Shimano M, Ouchi N, Nakamura K, Oshima Y, Higuchi A, Pimentel DR, Panse KD, Lara-Pezzi E, Lee SJ, Sam F and Walsh K. **Cardiac myocyte-specific ablation of follistatin-like 3 attenuates stress-induced myocardial hypertrophy.** *J Biol Chem* (2011) 286: 9840-8.

2

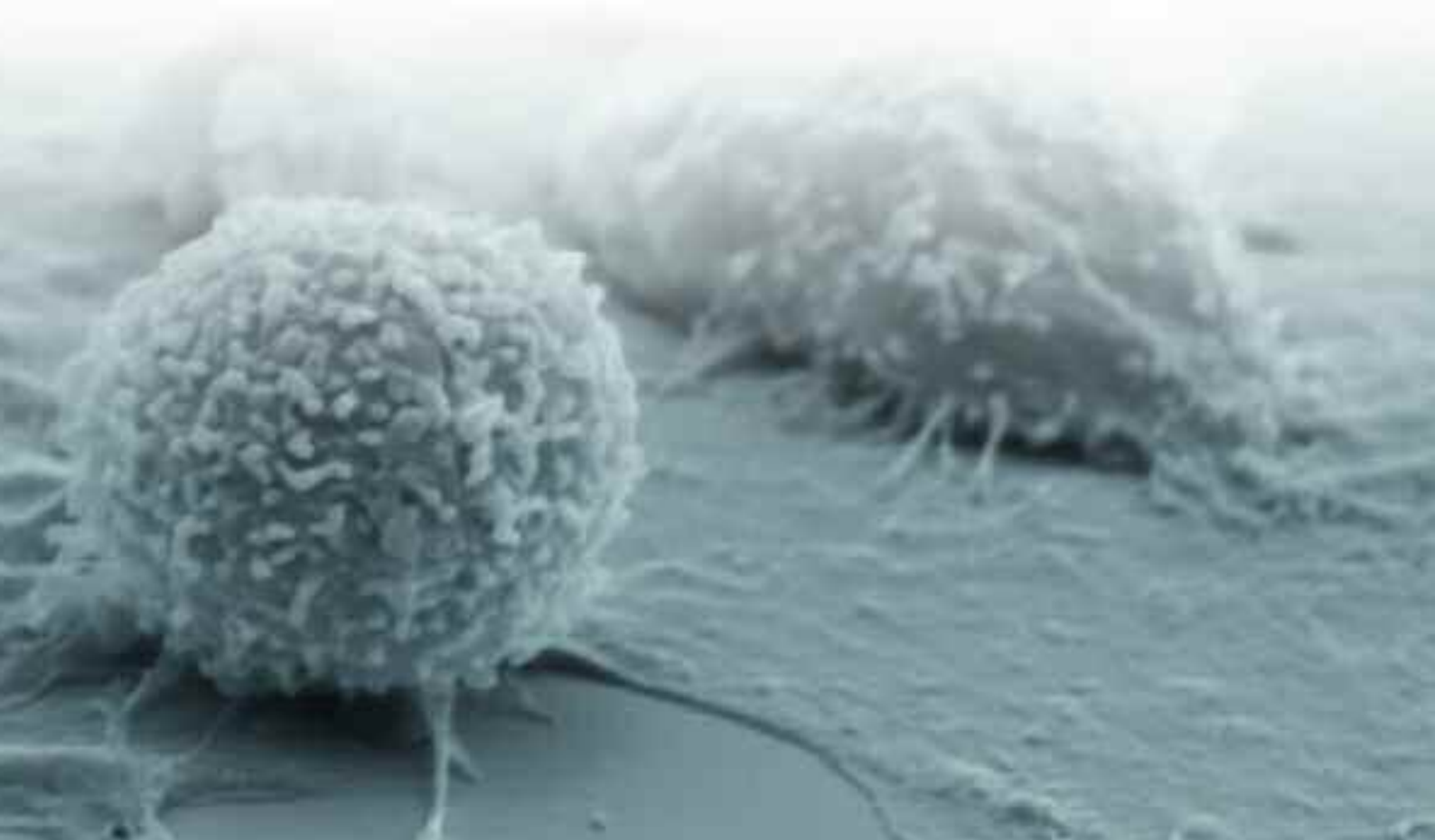
Vascular Biology and Inflammation



2 Vascular Biology and Inflammation

The Department of Vascular Biology and Inflammation (DVBI) investigates the complex interactions between the components of circulating blood and the vascular wall, with emphasis on vessel wall remodeling, physiological and pathological angiogenesis, inflammation and autoimmunity, and cell biology and signaling in metabolism and disease. Groups within the department use a range of 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*
Technicians:	*Andrea Quintana* *Juan José Lazcano* *María José Gómez* *Bahia El Maimouni (Charles River)* *Elisabeth Daniel (Charles River)*
Administrative Support:	*Almudena Fernández* *Eduardo Bieger*



Research Departments

2 Vascular Biology and Inflammation

Regulation of gene expression in vascular endothelium

Head of Laboratory: Juan Miguel Redondo

Research Scientists: Pablo Gómez-del Arco
Sara Martínez-Martínez

Postdoctoral Researchers: Katia Urso

Predoctoral Researchers: Amelia Escolano
Nerea Méndez
Noelia Lozano
Jorge Oller

Masters Student: Silvia Villahoz

Technicians: Dolores López Maderuelo
Beatriz Carolina Ornés
Raquel Sánchez
Ruth Alberca

Visiting Scientist: Ángel Luis Armesilla

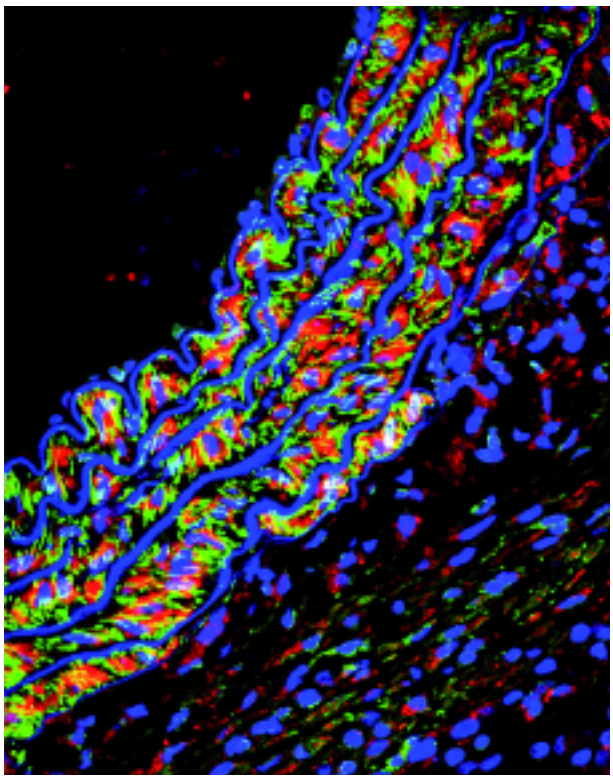
Research Interest

Many important biological processes, including the regulation and development of the immune and cardiovascular systems, are regulated by the calcineurin-NFAT (CN-NFAT) pathway. Much of our previous work relates to molecular interactions of CN with substrates. We are now studying the regulation and function of this pathway in inflammation and cardiovascular and inflammatory diseases. Our work on angiogenesis addresses the regulation of CN in endothelial cells by VEGF. We use retinopathy of prematurity as a model of the mechanisms of neovessel formation in ischemic retinopathies, and are using lentiviral vectors to identify potential therapeutic targets.

We are also analyzing gene expression triggered by angiotensin II (AngII) in cardiomyocytes and vascular smooth muscle (VSM). This work is aimed at identifying molecular mediators of cardiac hypertrophy. We have found several CN-regulated genes in two mouse models of cardiac hypertrophy, and plan to characterize their roles in this pathology.

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 the subsequent migration of these cells to inflammation sites.

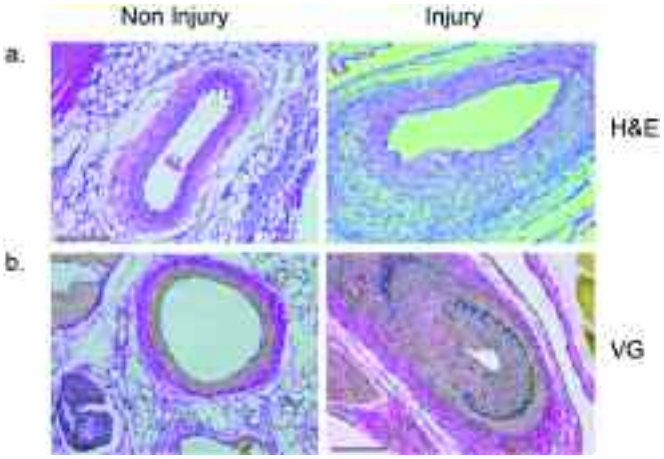
We are also dissecting signaling pathways involved in vascular wall remodeling, a major feature of vascular diseases such as atherosclerosis, aneurysm, and restenosis. We have set up animal models of these pathologies, and have generated mice deficient for AngII-target molecules that are regulated by CN. Some of these animals are totally resistant to these diseases and we are working to elucidate the molecular and cellular mechanisms underlying this protection.



confocal microscopy merged images of Rcan1 (red) and SMA (green) immunostaining and nuclear staining (blue) of abdominal aortic cross-sections from either saline (image 1) or AngII-treated (image 2) Apoe$^{-/-}$ mice. Images are maximal projections of a complete z-series.

Research Departments

2 Vascular Biology and Inflammation



Cross-sections of uninjured and injured mouse femoral arteries stained with hematoxilin-eosin (H&E) and Van Gieson's stain (VG).

Major Grants

- ***Ministerio de Economía y Competitividad (SAF2009-10708)***
- ***Ministerio de Economía y Competitividad. FIS RETICS (RECAVA II: RD06/0014/0005)***
- ***Fundación Genoma España MEICA Project***
- ***Fundació La Marató TV3 (081731)***

Selected Publications

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* doi: 10.1038/mt.2012.131. Epub July 3 2012

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

Esteban V, Méndez-Barbero N, Jiménez-Borreguero LJ, Roqué M, Novensá L, García-Redondo AB, Salaices M, Vila L, Arbonés ML, Campanero MR, Redondo JM. **Regulator of calcineurin 1 mediates pathological vascular wall remodeling.** *J Exp Med* (2011) 208: 2125-39.

Urso K, Alfranca A, Martínez-Martínez S, Escolano A, Ortega I, Rodríguez A, Redondo JM. **NFATc3 regulates the transcription of genes involved in T-cell activation and angiogenesis.** Blood (2011) 118: 795-803.

Bonzon-Kulichenko E, Pérez-Hernández D, Núñez E, Martínez-Acedo P, Navarro P, Trevisan-Herraz M, Ramos Mdel C, Sierra S, Martínez-Martínez S, Ruiz-Meana M, Miró-Casas E, García-Dorado D, Redondo JM, Burgos JS, Vázquez J. **A robust method for quantitative high-throughput analysis of proteomes by 18O labeling.** *Mol Cell Proteomics* (2011) Jan;10(1):M110.003335.

Research Departments

2 Vascular Biology and Inflammation

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
Predoctoral Researchers:	Francesc Baixauli Danay Cibrian Cristina Gutierrez Giulia Morlino Norman Núñez Mª Laura Saiz Carolina Villarroya
Masters Student:	Ángel Luis Jaso
Technicians:	Marta Esther Ramirez María José López

Research Interest

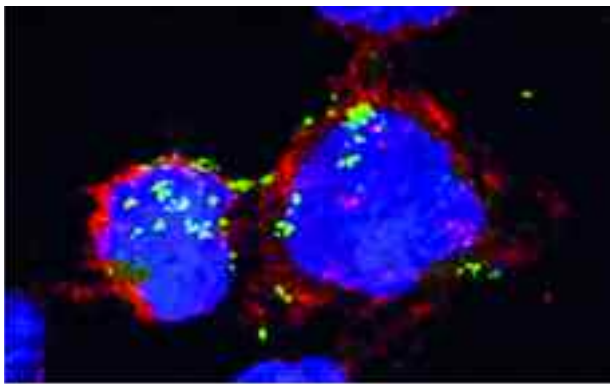
The group's present work focuses on key cell-to-cell communication events during cognate immune interactions. A key goal is to define how the microtubule organizing complex (MTOC), by controlling cytoskeletal rearrangements at the immune synapse (IS), provides a mechanism for macromolecular transport and the concentration of signaling molecules during synaptic contact. This research program has the potential to reveal how transfer of miRNA between the T cell and the cognate antigen presenting cell (APC) regulates the early initiation of immunity. We are also developing methodologies for the in vivo imaging of immune cell infiltration, the inflammatory response and the role of immunoregulatory molecules (galectins and tetraspanins) in animal models of inflammation and human diseases.

Our current specific objectives are the following:

1. To assess the role of MTOC polarization as a signaling and structural platform for the control of secretion during IS formation.

2. To investigate the mechanisms and functional consequences of intercellular transfer of miRNA via the IS.

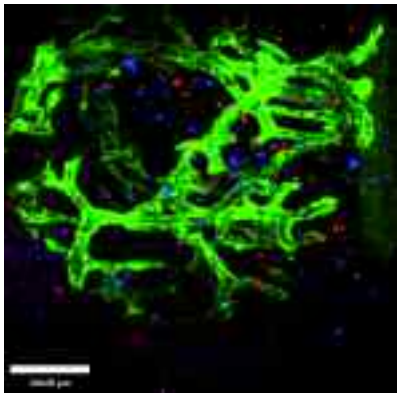
3. To image immune-inflammatory responses in vivo in order to define the role of immunoregulatory molecules in autoimmune inflammatory diseases



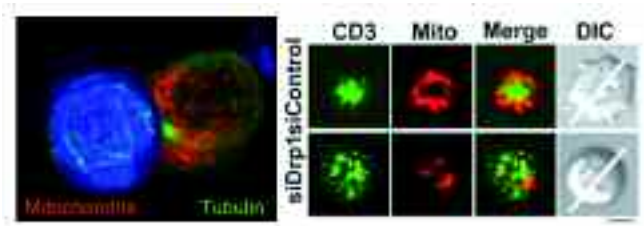
T cells transfer microRNA-loaded exosomes to antigen presenting cells. *The image shows confocal microscopy detection of the exosomal marker CD63-GFP (green) on the surface of recipient APCs (Raji) after incubation with J77-CD63-GFP exosomes. CD45 is stained red and nuclei are blue.*

Research Departments

2 Vascular Biology and Inflammation



Distribution of dendritic cells in peripheral lymph nodes. *Dendritic cells from wild-type (red) and CD69$^{-/-}$ (blue) mice were transferred into C57BL6 recipient mice together with a marker of high endothelial venules (green). Two-photon analysis of draining lymph nodes showed that DCs were mostly located near high endothelial venules and the outer T cell zone inside the lymph node.*



The mitochondrial fission factor Drp1 modulates T-cell receptor signaling, regulating mitochondria translocation toward the immune synapse. Left: *A T cell conjugated with an APC (blue cell). The intense tubulin staining reveals the localization of the T cell MTOC at the IS, at the center of the concentration of translocated mitochondria.* Right: *Detail of IS structures showing mitochondria (red) relocated toward the IS. Depletion of the mitochondrial fission protein Drp1 impairs this process and disrupts T cell receptor clustering (green) and T cell activation.*

Major Grants

- *European Commission. European Research Council. Advanced Grant (ERC-2011-AdG 20110310) (GENTRIS)*
- *Ministerio de Economía y Competitividad (SAF2011-25834)*
- *Ministerio de Economía y Competitividad. FIS RETICS (RECAVA: RD06/0014/0030)*
- *Fundación Genoma España. MEICA Project. Coordinator, F. Sanchez Madrid*

Selected Publications

Martín-Cófreces NB, Baixauli F, López MJ, Gil D, Monjas A, Alarcón B, Sánchez-Madrid F. **End-binding protein 1 controls signal propagation from the T cell receptor.** *EMBO J* (2012) 31: 4140-52.

Gordón-Alonso M, Rocha-Perugini V, Álvarez S, Moreno-Gonzalo O, Ursa A, López-Martín S, Izquierdo-Useros N, Martínez-Picado J, Muñoz-Fernández MÁ, Yáñez-Mó M, Sánchez-Madrid F. **The PDZ-adaptor protein syntenin-1 regulates HIV-1 entry.** *Mol Biol Cell* (2012) 12: 2253-63.

Mittelbrunn M, Sánchez-Madrid F. **Intercellular communication: diverse structures for exchange of genetic information.** *Nat Rev Mol Cell Biol* (2012) 13(5):328-35.

de la Fuente H, Perez-Gala S, Bonay P, Cruz-Adalia A, Cibrian D, Sanchez-Cuellar S, Dauden E, Fresno M, García-Diez A, Sanchez-Madrid F. **Psoriasis in humans is associated with down-regulation of galectins in dendritic cells.** *J Pathol.* 2012 2: 193-203.

Mittelbrunn M, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MÁ, Bernad A, Sánchez-Madrid F. **Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells.** *Nat Commun.* (2011) 2:282.

Research Departments

2 Vascular Biology and Inflammation

Integrin signaling

Head of Laboratory:	Miguel Angel Del Pozo
Research Scientist:	Asier Echarri Inés Martín 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 Dacil M. Pavón Teresa Osteso Ibañez Mauro Catalá
Visiting Scientist:	Marco Cordani

Research Interest

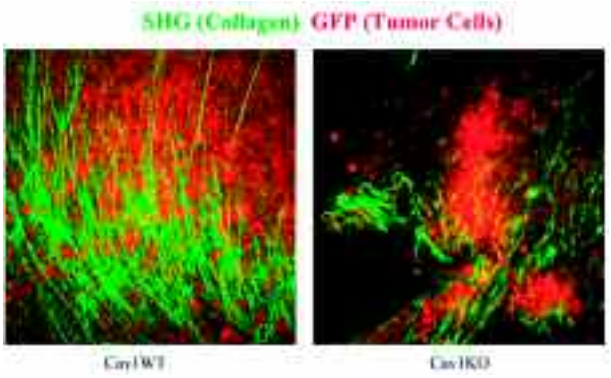
Our interest is in the mechanisms through which integrins, caveolae and Rho/Rac GTPases cooperate to regulate mechanotransduction, membrane organization and trafficking, cell migration, cell growth, and epithelial-mesenchymal transition (EMT), key processes in the pathogenesis of cancer and inflammatory and cardiovascular diseases.

A growing body of work supports a role for caveolae and Cav1 in mechanosensing and mechanotransduction. We have shown that Cav1 can modulate cell shape and responses via force-dependent remodeling of the 3D microenvironment. Stromal fibroblast cells surrounding many human cancers express high levels of Cav1, which activate the enzyme Rho, causing cells to stretch out. In three-dimensional gel matrices in vitro and in vivo, the elongated Cav1-fibroblasts form stiff, parallel-fiber networks through which cancer cells move rapidly, promoting local invasion and subsequently distant metastasis.

Loss of integrin-mediated adhesion triggers an inward traffic of Cav1-rich membranes, which regulates Rac1 plasma membrane (PM) targeting and hence directs cell migration and controls cell proliferation. We have now found that Rac1 can be palmitoylated, and identified palmitoylation as a mechanism of Rac1 function in actin cytoskeleton remodeling by controlling its membrane partitioning, which in turn regulates membrane organization.

Other recent work has delineated how filamin A regulates actin-linked caveolae dynamics at the PM, and shows that Cav1-membrane inward trafficking depends on the on an Abl-mDia1-actin polymerization machinery, microtubules (MT), dynamin2, and PKCα-mediated phosphorylation of filamin A. Upon loss of tension caused by loss of adhesion, Cav1-rich membranes internalize in the form of complex multilobed caveolar "rosettes" in an actin-dependent manner. Caveolar domains are then transferred to an MT-dependent system that targets them to a Rab11-recycling endosome. In response to cell adhesion, Cav1 recycles back to the PM via a mechanism involving actin polymerization. Cav1 forms caveolae as stress fibers are formed, but caveolae are flattened by high PM tension induced by excessive actin-mediated force. Caveolar domain plasticity and trafficking are thus tightly coupled to adhesive and stress fiber regulatory pathways.

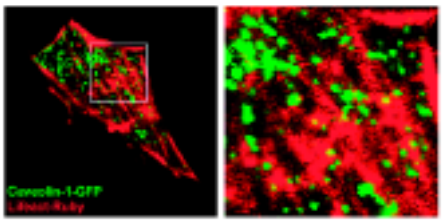
We also recently identified transforming growth factor-activated kinase 1 (TAK1) as a key biochemical mediator of EMT and fibrosis in mesothelial cells from human peritoneum. The study of signaling pathways induced by TAK1 activity might help in the design of new therapies for peritoneal fibrosis.



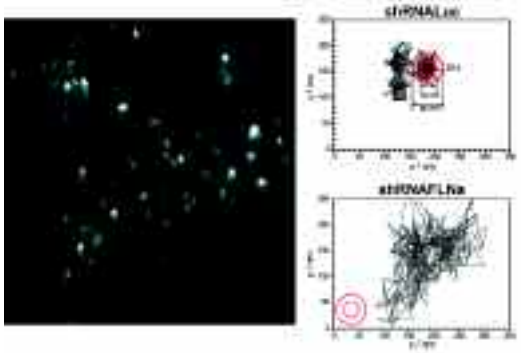
Orthotopic mammary gland allografts injected into wild-type (left) or Cav1-deficient mice (right) were imaged for SHG (second harmonic generation). In the wild-type background the collagen fibers are highly aligned and perpendicular to the tumor-stroma interface, which correlates with a highly invasive behaviour.

Research Departments

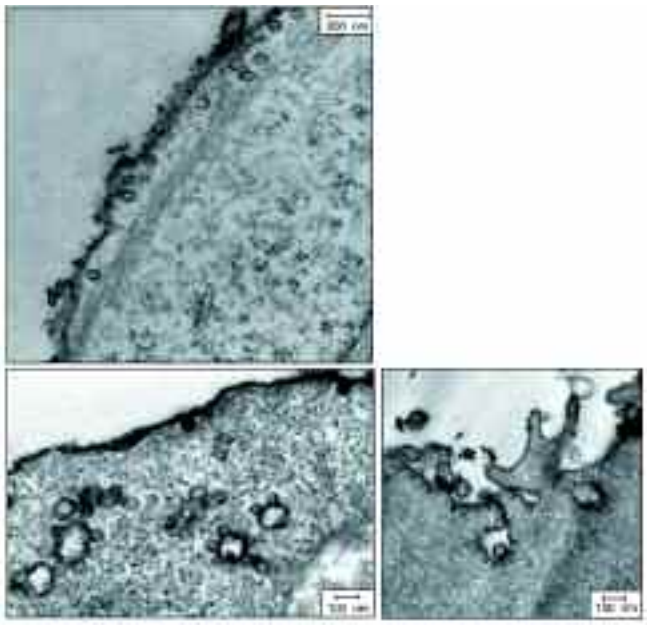
2 Vascular Biology and Inflammation



Total internal reflection fluorescence (TIRF) microscopy image at 90nm penetration showing caveolin vesicles and actin fibers (stained with RFP-Ruby-Lifeact) in HeLa cells.



High spatio-temporal resolution particle tracking of Cav1-GFP vesicles by TIRFm in control HeLa cells (shRNALuc) or filamin A depleted cells (shRNAFLNa). Sequential vesicle positions were recorded at 85 ms intervals and connected by straight lines. Outer circles show the threshold for an anchoring event (60 nm diameter); inner circles show the positioning accuracy (30 nm). Duration of anchoring events is indicated.



EM images of Ruthenium-red-labeled cells at various magnifications. Surface connected caveolae "rosettes" labeled with ruthenium red are shown in the bottom panels.

Major Grants

- ***Ministerio de Economía y Competitividad (SAF2011-25047)***
- ***Ministerio de Economía y Competitividad. Consolider COAT (CSD2009-00016)***

Selected Publications

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.

Strippoli R, Benedicto I, Perez Lozano ML, Pellinen T, Sandoval P, Lopez-Cabrera M, Del Pozo MA. **Inhibition of transforming growth factor-activated kinase 1 (TAK1) blocks and reverses epithelial to mesenchymal transition of mesothelial cells.** *PLoS One.* (2012) 7: e31492.

Echarri A, Del Pozo MA. **Caveolae.** *Current Biology* (2012) 22: R114-R116.

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.

Goetz JG, Minguet S, Navarro-Lérida I, Lazcano JJ, Samaniego R, Calvo E, Tello M, Osteso-Ibáñez T, Pellinen T, Echarri A, Cerezo A, Klein-Szanto AJ, Garcia R, Keely PJ, Sánchez-Mateos P, Cukierman E, Del Pozo MA. **Biomechanical remodeling of the microenvironment by stromal caveolin-1 favors tumor invasion and metastasis.** *Cell* (2011) 146: 148-63.

Research Departments

2 Vascular Biology and Inflammation

Cardiovascular Proteomics

Head of Laboratory: Jesús María Vázquez Cobos

Postdoctoral Researchers: Estefanía Núñez Sánchez
Elena Bonzón Kulichenko
Inmaculada Jorge Cerrudo

Predoctoral Researchers: Pilar Caro Chinchilla
Fernando García Marqués
Pablo Martínez Acedo
Daniel Pérez Hernández
Marco Trevisan Herraz

Masters Student: Marta Loureiro

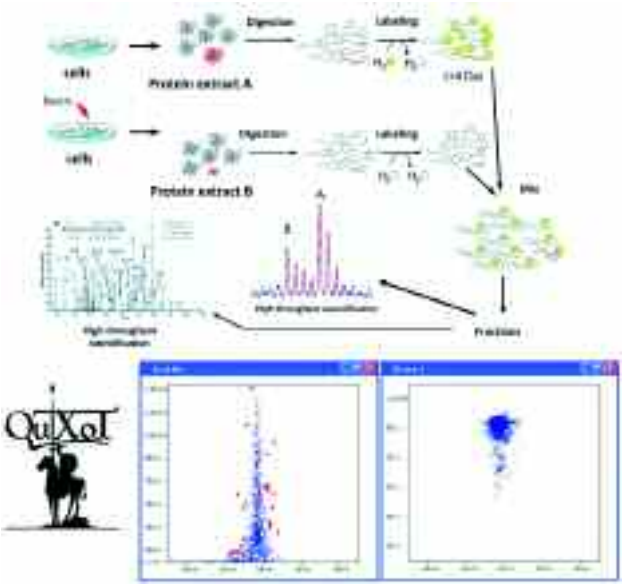
Technicians: Raquel Mesa Carrasco

Visiting Scientist: 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. We have developed a comprehensive technology that includes advanced peptide identification algorithms and a novel, multi-layered statistical model for the analysis of quantitative data. Our approach also includes a universally applicable method for stable-isotope labeling that allows full control of variance sources. We are working on the generalization of the statistical model and on the integration with systems biology algorithms to improve interpretation of results from a proteome-wide perspective. We have also developed a novel method for simultaneous analysis of relative protein abundance and dynamic alterations in the thiol redoxome.

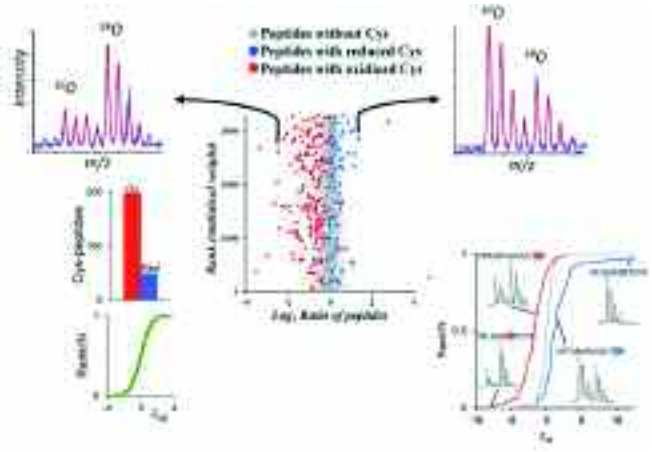
We are applying these developments to the study of key aspects of cardiovascular disease, with the aim of defining molecular mechanisms and identifying specific protein factors for use as pharmacological targets or biomarkers. One area of interest is the dynamic expression changes to the secretome and other subcellular fractions of vascular smooth muscle cells in models of hypertension and hypertrophy, including the role of the calcineurin-NFAT pathway. In addition, we are analyzing dynamic alterations to the mitochondrial proteome and the targets of oxidative damage that occur upon ischemia-reperfusion and the mechanisms of ischemic preconditioning in animal models of deletion or overexpression of several protein factors. We are also studying protein interactions during T-cell activation by APCs and during leukocyte recruitment to the activated endothelium. This work has recently characterized the interactome of tetraspanins in T-lymphocytes and derived exosomes from human patients, as well as from KO mouse models lacking specific tetraspanin components.



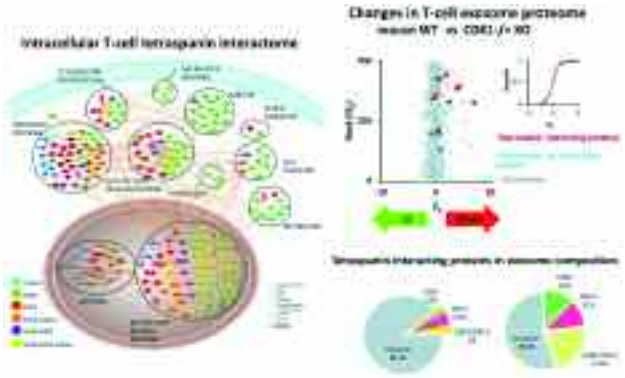
Top: *Workflow scheme for high-throughput quantification of proteomes by stable isotope labeling.* Bottom: *The "Quixot" bioinformatics platform developed in the laboratory for identification, quantification and statistical analysis of mass spectrometry data.*

Research Departments

2 Vascular Biology and Inflammation



Determination of changes in the redox state of cysteine-containing peptides in high-throughput proteomics experiments using GELSILOX technology. The figure shows the effect a thiol-specific oxidative agent on vascular endothelial cells. The abundance of peptides containing cysteines in the oxidized state (red points) tends to increase (toward the left), that of peptides containing reduced cysteines (blue points) tends to decrease (toward the right), while non-cysteine containing peptides remain unaltered (green curve). The effect is more evident when the standardized peptide log2-ratio distributions are analyzed separately (red and blue curves).



Left: *Characterization of the intracellular tetraspanin interactome in human T-cells.* Lower right: *The tetraspanin interactome encompasses a large proportion of the composition of T-cell exosomes.* Upper right: *Quantitative high-throughput proteomics demonstrates that elimination of tetraspanin CD81 in KO mice diminishes the abundance in exosomes of some of its specific interaction partners, suggesting a role in the sorting machinery.*

Major Grants

- ***Ministerio de Economía y Competitividad (BIO2009-07990)***
- ***Ministerio de Economía y Competitividad. FIS RETICS (RECAVA: RD06/0014/0030)***

Selected Publications

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.** *Journal of Immunology* (2012) 189: 689-700.

McDonagh B, Martínez-Acedo P, Vázquez J, Padilla CA, Sheehan D, Bárcena JA. **Application of iTRAQ Reagents to Relatively Quantify the Reversible Redox State of Cysteine Residues.** *Int J Proteomics* (2012) 2012: 514847.

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.

Bonzon-Kulichenko E, Martínez-Martínez S, Trevisan-Herraz M, Navarro P, Redondo JM, Vázquez J. **Quantitative in-depth analysis of the dynamic secretome of activated Jurkat T-cells.** *J Proteomics* (2011) 75: 561-71.

Bonzon-Kulichenko E, Pérez-Hernández D, Núñez E, Martínez-Acedo P, Navarro P, Trevisan-Herraz M, Ramos Mdel C, Sierra S, Martínez-Martínez S, Ruiz-Meana M, Miró-Casas E, García-Dorado D, Redondo JM, Burgos JS, Vázquez J. **A robust method for quantitative high-throughput analysis of proteomes by ^{18}O labeling.** *Mol Cell Proteomics* (2011) Jan;10(1):M110.003335.

Research Departments

2 Vascular Biology and Inflammation

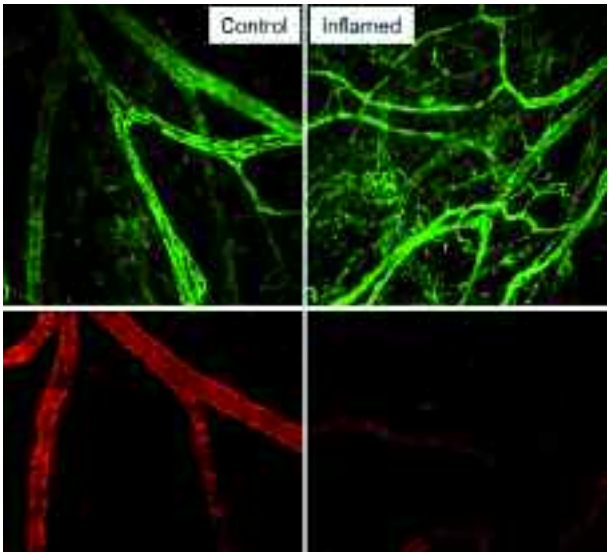
Matrix metalloproteinases in angiogenesis and inflammation

Head of Laboratory: Alicia G. Arroyo
Research Scientist: Pilar Gonzalo
Postdoctoral Researcher: Vanessa Moreno
Predoctoral Researchers: Cristina Clemente, Agnieszka Koziol, Mara Martín Alonso
Master Student: 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 contribute to the development and progression of chronic inflammatory disorders such as atherosclerosis, rheumatoid arthritis, inflammatory bowel disease or psoriasis. Our previous work showed the contribution of the matrix metalloproteinase MT1-MMP to inflammation and angiogenesis and the cell context-dependence of MT1-MMP functions in inflammation. To explore this in more depth we have conducted proteomic analyses (SILAC) to identify the collection of cellular substrates (degradome) processed by MT1-MMP in endothelial cells and leukocytes. We have also used a similar approach to identify the substrates of MT4-MMP, a poorly characterized GPI-anchored MMP, in macrophages. Our proteomics analysis points to specific and unexpected functions for these proteases in the interplay between inflammation and angiogenesis, in particular the induction of endothelial tip cells and the decision between stabilization and regression of the new vasculature, and how these processes are linked to the phenotype of macrophages and other components of the inflammatory infiltrate. We are currently exploring these functions in cell-based systems, genetically-modified mouse models of angiogenesis and inflammation, and samples from patients affected by inflammatory disease. We are also characterizing the role of recently identified MT-MMP substrates and other related molecules such as extracellular matrix metalloproteinase inducer (EMMPRIN) in the regulation of vascular integrity and stability.

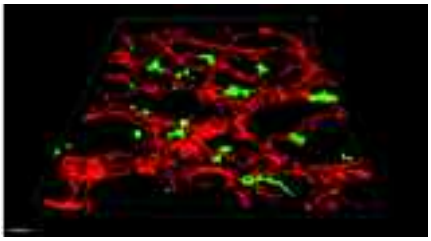
Through these efforts we aim to extend our knowledge of where, when and how MT-MMPs and their substrates modulate endothelial, smooth-muscle cell and leukocyte behavior during the establishment and progression of chronic inflammatory disorders.



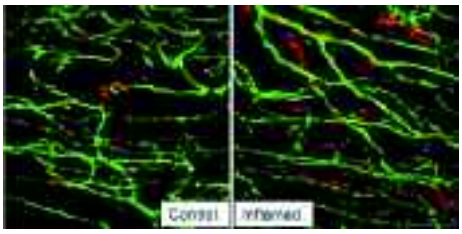
Analysis of inflammation-driven angiogenesis. *Whole-mount staining of the skin (endothelial cells in green and smooth muscle cells in red) shows the changes in numbers and structure of the vasculature upon acute inflammation (wound healing) compared with quiescent vessels (control).*

Research Departments

2 Vascular Biology and Inflammation



Imaging cellular crosstalk in angiogenesis. *3D-reconstruction with Imaris software of whole-mount staining shows the close association of vessels (red) and macrophages (green) in the developing vasculature of mouse retinas six days postpartum.*



Analysis of vascular integrity. *Intravascular injection of fluorescent-dextran (red) in mice allows the analysis of vascular integrity in basal and inflamed conditions. Vessels are stained green.*

Major Grants

- *Ministerio de Economía y Competitividad (SAF2011-25619)*
- *Ministerio de Economía y Competitividad. FIS RETICS (RECAVA; RD/06/0014/1016)*
- *Fundación Genoma España. MEICA Project*
- *Comunidad Autónoma de Madrid (S2010/BMD-2312)*
- *Fundación La Marató TV3 (165/C/2012)*

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.

Research Departments

2 Vascular Biology and Inflammation

B cell biology

Head of Laboratory: Almudena R Ramiro

Research Scientists: Virginia G de Yébenes
Maria Pilar Delgado

Postdoctoral Researchers: Laura Belver (until November 2012)
Pablo Pérez-Durán

Predoctoral Researchers: Nahikari Bartolomé
Arantxa Pérez-García

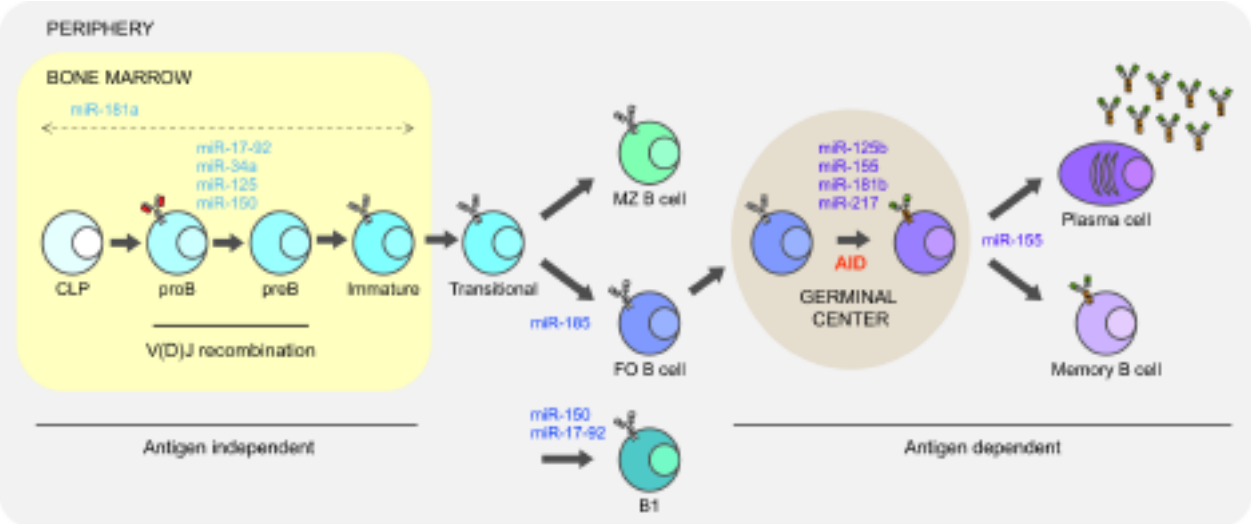
Master Students: Ángel F. Álvarez
Faiz Bilial

Technician: Sonia Mur

Research Interest

B lymphocytes are central players in the immune response, mostly through the generation of a hugely diverse repertoire of protective antibodies. However, misregulation of B-lymphocyte function is associated with 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 two mechanisms—called somatic hypermutation (SHM) and class-switch recombination (CSR)—that allow the generation of high-affinity, specialized antibodies. SHM and CSR are initiated by the same enzyme, activation-induced deaminase (AID), whose activity can also promote deliterious lesions in DNA, such as mutations and chromosome translocations.

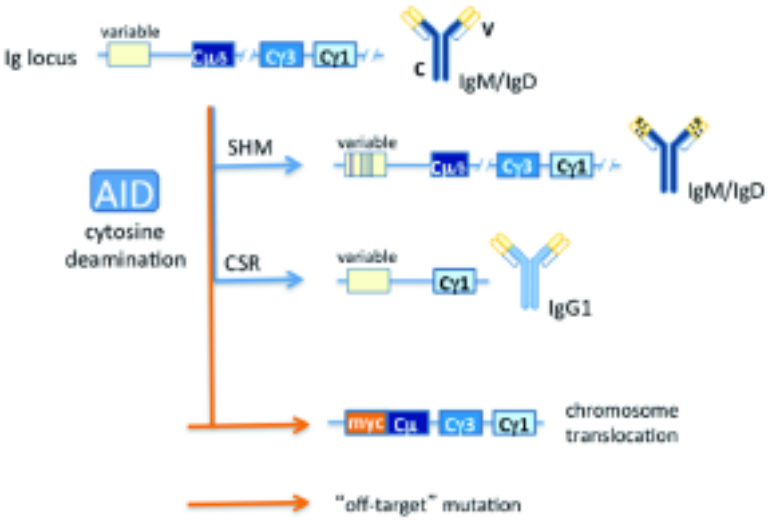
Over several years we have focused on understanding AID function and microRNA-regulatory mechanisms in germinal centers. We have found that microRNAs play a crucial role in the establishment of tolerance during late B-cell differentiation *(Belver et al. Immunity 2010, 33: 713)*. In addition, functional and expression screenings allowed the identification of miR-181b, a negative regulator of AID *(de Yébenes et al. J Exp Med 2008, 205, 2199)*, and miR-217, a positive regulator of the germinal center reaction that displays lymphomagenic potential. We are currently investigating various aspects of AID function, including sequence specificity and its contribution to autoimmune disease and cancer development.



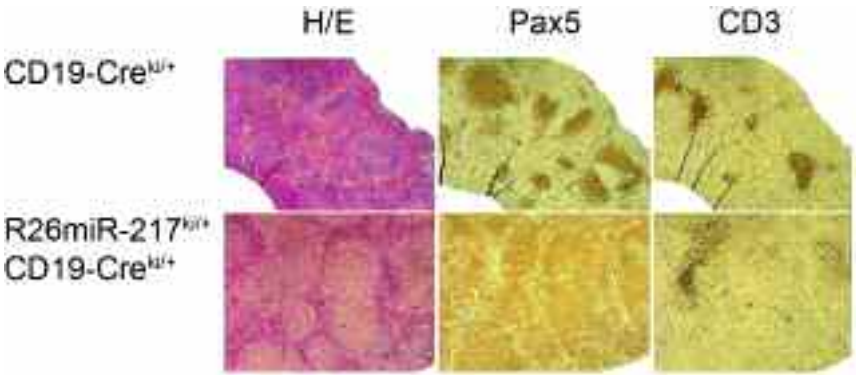
The generation of functional B cells involves their differentiation in the bone marrow, where the primary repertoire of antibodies is generated through the V(D)J recombination reaction. Upon antigen encounter in the periphery, B cells engage in the germinal center reaction, where AID triggers the secondary diversification of antibodies and allows the generation of plasma cells and long-lived memory cells that express high affinity antibodies. A number of microRNAs is involved at several of these developmental transitions.

Research Departments

2 Vascular Biology and Inflammation



AID activity in germinal center B lymphocytes. By deaminating cytosines in the DNA of the immunoglobulin locus, AID initiates both antibody diversification reactions that take place in germinal centers: somatic hypermutation (SHM) and class-switch recombination (CSR). SHM and CSR allow the generation of specialized antibody isotypes with high affinity for antigen, and are therefore critical for the immune response. However, AID activity can also promote chromosome translocations and mutations outside immunoglobulin genes, potentially leading to oncogenic transformation.



miR-217 promotes B cell lymphomagenesis. Mice were generated overexpressing miR-217 in the B-cell lineage (R26miR-217$^{ki/+}$ CD19-Cre$^{ki/+}$). Spleens from 85-week old R26miR-217$^{ki/+}$ CD19-Cre$^{ki/+}$ mice and controls (CD19-Cre$^{ki/+}$) were stained with hematoxilin eosin (H/E) and antibodies to Pax5 (B-cell marker) and CD3 (T-cell marker).

Major Grants

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

Selected Publications

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.

Belver L, Papavasiliou FN, Ramiro AR. **MicroRNA control of lymphocyte differentiation and function.** *Curr Opin Immunol* (2011) 23: 368-73.

Research Departments

2 Vascular Biology and Inflammation

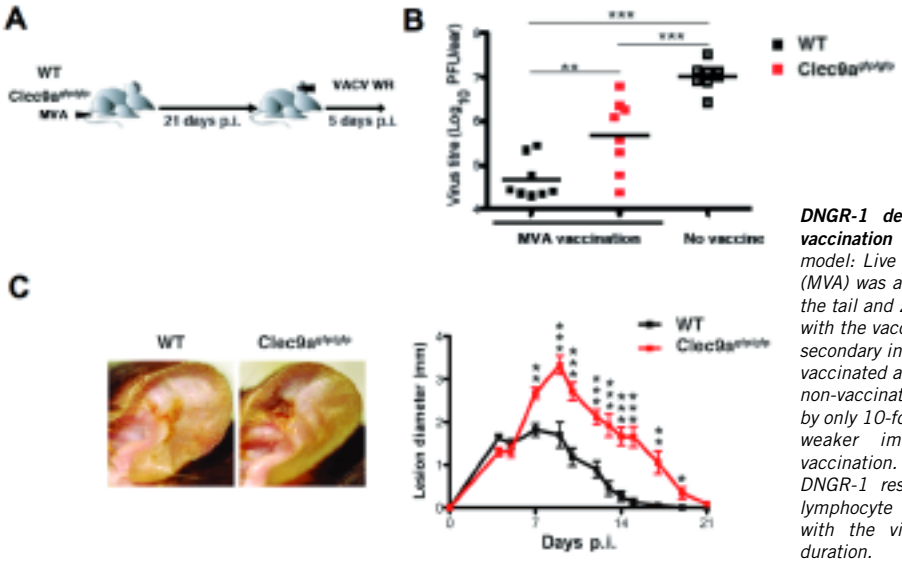
Immunobiology of inflammation

Head of Laboratory:	David Sancho Madrid
Postdoctoral Researchers:	Salvador Iborra Martín Johan J.B. Garaude
Predoctoral Researchers:	Noelia Blanco Menéndez Helena M. Izquierdo Fernández María Martínez López
Master Student:	Neris M. Enamorado Escalona
Technician:	Ruth Conde Garrosa

Research Interest

Necrosis occuring after tissue damage or inefficient efferocytosis provokes the macrophage inflammatory response, which normally triggers tissue repair but can also induce a state of chronic inflammation that is the basis of many diseases. Damaged cells also contribute to an adaptive immune response via presentation of antigens by dendritic cells (DCs). Some myeloid C-type lectin receptors (CLRs), such as Mincle (CLEC4E) in macrophages and DNGR-1 (CLEC9A) in DCs, are receptors for necrotic cells that couple to the tyrosine kinase Syk, which in turn can trigger innate and adaptive immune responses. We are investigating the existence of non-redundant mechanisms by which these CLRs translate tissue damage in models of sterile or infectious immunity or inflammation, including viral infection, lupus, atherosclerosis and obesity.

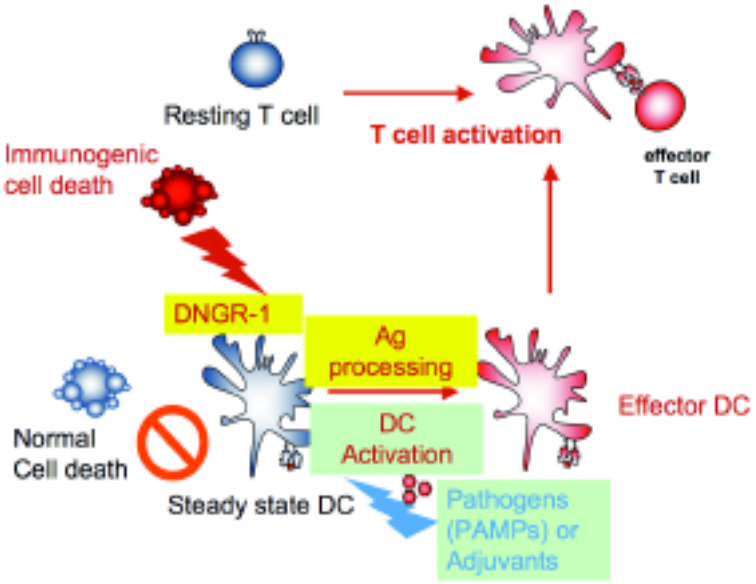
We investigated the possibility that sensing of tissue damage via DNGR-1 affects immunity to cytopathic viruses. Following injection of vaccinia virus (VACV) or VACV-infected cells into mice, DNGR-1 detected the ligand in dying infected cells and mediated crosspriming of anti-VACV CD8+ T cells. Loss of DNGR-1 impaired the CD8+ cytotoxic response to VACV, and this was associated with a strong increase in viral load and delayed resolution of the primary lesion. In addition, lack of DNGR-1 markedly diminished the protection against infection induced by vaccination with the modified vaccinia Ankara (MVA) strain. DNGR-1 thus contributes to anti-VACV immunity in response to both primary infection and vaccination. The non-redundant ability of DNGR-1 to regulate cross-presentation of viral antigens suggests that this form of regulation of antiviral immunity could be exploited for vaccination.



DNGR-1 deficiency blocks protection conferred by vaccination with live attenuated virus. *A) Vaccination model: Live attenuated modified vaccinia virus Ankara (MVA) was administered by scarification in the base of the tail and 21d later mice were infected i.d. in the ear with the vaccinia virus WR. B) Viral titers at day 5 after secondary infection with the WR virus. The viral titer in vaccinated animals is more than 100-fold lower than in non-vaccinated mice, whereas viral titers are reduced by only 10-fold in animals lacking DNGR-1, which show weaker immunity against the virus following vaccination. C) Deficient immunity in the absence of DNGR-1 results in a weaker secondary cytotoxic T lymphocyte (CTL) response after auricular inoculation with the virus, with lesions larger and of longer duration.*

Research Departments

2 Vascular Biology and Inflammation



Tissue damage signal detected via DNGR-1 collaborates with adjuvants from the pathogen in the generation of immunity. *Cell death generated by viral infection is detected by DNGR-1. Dendritic cells detect and coordinate two signals, one coming from the pathogen and another from the tissue damage associated with infection. The virus generates a potent adjuvant signal that leads to the activation of the dendritic cell. We have shown that the tissue damage detected through DNGR-1 affects antigen processing and is essential for the generation of an optimal CD8+ CTL response against the virus.*

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

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.

Ahrens S, Zelenay S, Sancho D, HančP, Kjær S, Feest C, Fletcher G, Durkin C, Postigo A, Skehel M, Batista F, Thompson B, Way M, Reis e Sousa C, Schulz O. **F-actin is an evolutionarily conserved damage-associated molecular pattern recognized by DNGR-1, a receptor for dead cells.** *Immunity* (2012) 36:635-45.

Poulin LF, Reyal Y, Uronen-Hansson H, Schraml BU, Sancho D, Murphy KM, Håkansson UK, Moita LF, Agace WW, Bonnet D, Reis e Sousa C. **DNGR-1 is a specific and universal marker of mouse and human Batf3-dependent dendritic cells in lymphoid and nonlymphoid tissues.** *Blood* (2012) 119:6052-62.

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

Research Departments

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

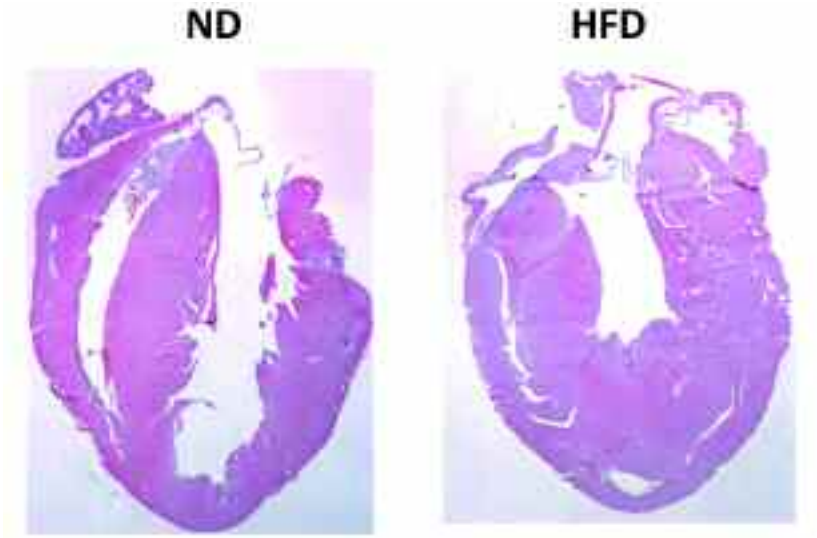
Technicians: Elena González
Luis Leiva

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 the major clinical outcomes are 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 disease parameters in both might be improved by agents acting on the same therapeutic targets. 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 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 shown that the SAPK JNK regulates fat metabolim, obesity, dyslipidemia and glucose intolerance through its actions in various tissues.

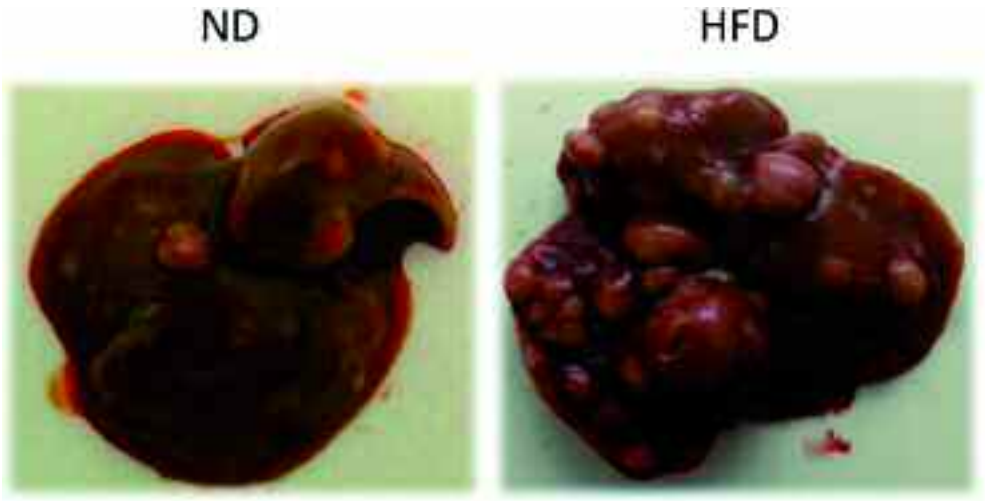


Hematoxylin and eosin (H&E)-stained section of heart from C57Bl6/J mice fed a normal diet (ND) or a high-fat diet (HFD) for 16 weeks.

Research Departments

2 Vascular Biology and Inflammation

C57Bl6/J mice fed a high-fat diet (left) or normal chow diet (right).



Hepatocellular carcinoma in liver from C57Bl6/J mice fed a normal diet (ND) or a high-fat diet (HFD).

Major Grants

- European Commission. European Research Council Starting Independent Researcher Grant (ERC-StG-260464)
- European Foundation for the Study of Diabetes (EFSD 0203)
- Comunidad Autónoma 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* doi:10.1172/JCI65124. Epub Dec 3 2012.

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.** *Gastroenterology* doi:10.1053/j.gastro.2012.10.051. Epub Nov 8 2012.

Noubade R, Krementsov DN, Del Rio R, Thornton T, Nagaleekar V, Saligrama N, Spitzack A, Spach K, Sabio G, Davis RJ, Rincon M, Teuscher C. **Activation of p38 MAPK in CD4 T cells controls IL-17 production and autoimmune encephalomyelitis.** *Blood* (2011) 118: 3290-300.

Cellurale C, Sabio G, Kennedy NJ, Das M, Barlow M, Sandy P, Jacks T, Davis RJ. **Requirement of c-Jun NH(2)-terminal kinase for Ras-initiated tumor formation.** *Mol Cell Biol* (2011) 31: 1565-76.

Research Departments

2 Vascular Biology and Inflammation

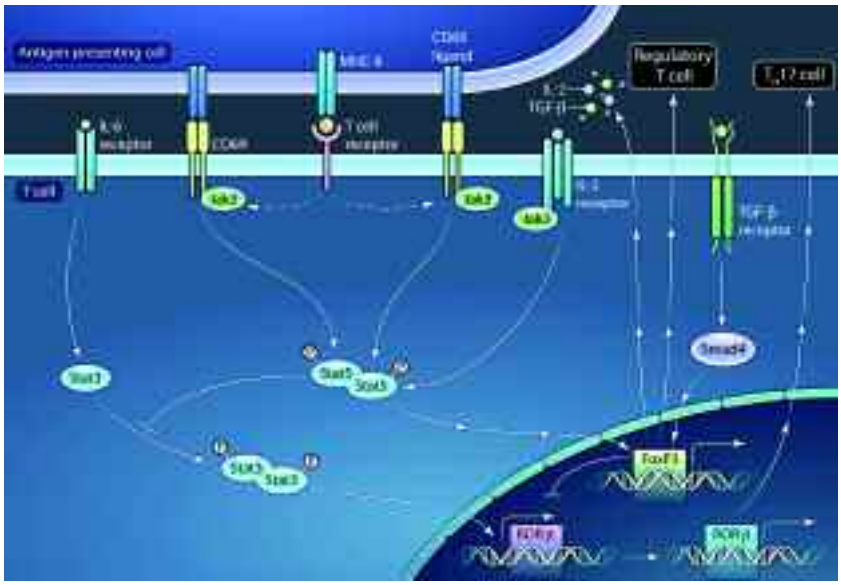
Regulatory molecules of inflammatory processes

Head of Laboratory: Pilar Martín
Postdoctoral Researcher: José Rodríguez Cortés
Predoctoral Researchers: Adela Matesanz Marín
Elena G. Rodríguez Bovolenta
Masters Student: Manuel Daza
Technician: Sara Salvanés
Visiting Scientist: Georgios Liappas

Research Interest

Understanding peripheral mechanisms operating in autoimmune and chronic inflammatory diseases is critical for the design and development of novel treatments. Autoimmune diseases, which include conditions such as arthritis, asthma, contact dermatitis and myocarditis, are characterized by a breakdown in the mechanisms of tolerance to self antigens, and there is no definitive treatment for their eradication. Our group seeks to identify new regulatory cells and molecules involved in the control of these diseases.

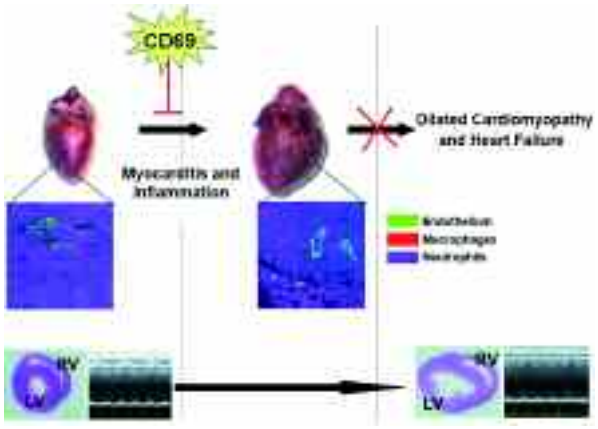
The early leukocyte activation antigen CD69 is a membrane receptor of the family of type II C-type lectins. CD69 is rapidly induced after cell activation in all bone marrow derived cells except erythrocytes. Expression in vivo is restricted to positively selected thymocytes and leukocytes undergoing activation, particularly at inflammation sites. Engagement of CD69 with monoclonal antibodies in the presence of phorbol esters induces Ca^{2+} influx that activates ERK, induces IL-2 and IFN-γ gene expression, and promotes T cell proliferation. Our recent work shows that the cytoplasmic tail of CD69 interacts with Jak3/Stat5 proteins, which regulate the transcription of RORγt in human and mouse Th17 cells, thus establishing a mechanistic link between CD69 and the regulation of Th17 differentiation. The balance between Th17 cells and regulatory T cells determines the net balance between pro- and anti-inflammatory cytokines at inflammatory foci, and is thus critical for the regulation of the immune response. CD69 might also regulate the function or differentiation of regulatory T cells, thus affecting the outcome of Th17 responses indirectly. This is supported by the finding that mice lacking CD69 develop exacerbated forms of contact dermatitis, allergic asthma and autoimmune myocarditis. Our data demonstrate that CD69, by regulating Th17 effector responses, limits myocardial inflammation and subsequent heart failure. A similar process is likely to occur in humans with myocarditis and related dilated cardiomyopathy.



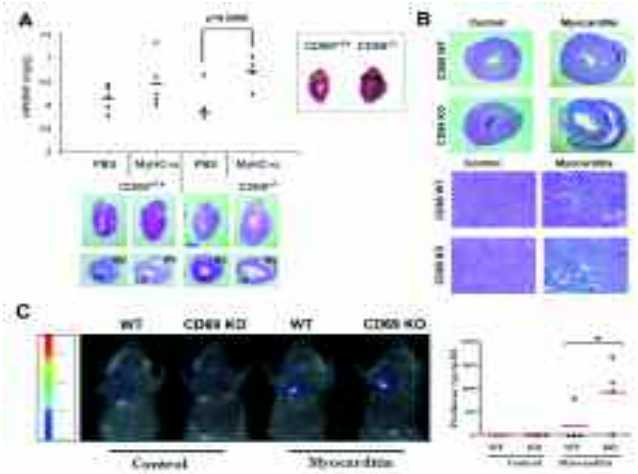
CD69 receptors are expressed on the membrane of T cells following activation. *The cytoplasmic tail of CD69 associates with Jak3 and Stat 5 proteins, triggering phosphorylation of Stat5 and its translocation to the nucleus where it can activate the transcription factor FoxP3, stimulating the differentiation of regulatory T cells. CD69 engagement can also induce expression of IL-2 and TGFβ. These cytokines may act in an autocrine manner to induce the differentiation of regulatory T cells. CD69 can inhibit the Th17 differentiation pathway through at least two mechanisms: CD69-activated Stat5 directly inhibits the translocation of Stat3 to the nucleus and indirectly, via FoxP3 activation, antagonizes Stat3-mediated RORγt activation.*

Research Departments

2 Vascular Biology and Inflammation



CD69 acts as a brake on the progression and severity of autoimmune myocarditis and the development of dilated cardiomyopathy (DCM). *Our study paves the way to research into whether defects in CD69 expression or function influence the development of DCM in humans. These findings increase our knowledge of the development of myocarditis, providing a cellular and molecular basis for the development of novel therapies.*



Analysis of heart inflammation and fibrosis in experimental autoimmune myocarditis (EAM). *(A) Mice lacking CD69 (CD69$^{-/-}$) show a larger increase in heart-weight/body-weight (HW/BW) ratio upon treatment with myosin heavy chain peptide α (MyHCα). Representative myocardial cross sections are shown, LV, left ventricle; RV, right ventricle. (B) Masson's trichrome stanining reveals enhanced fibrosis in heart tissue from CD69$^{-/-}$ mice in the chronic phase of EAM. (C) Fluorescence molecular tomography (FMT) imaging of control or MyHC-peptide injected mice. The graph shows quantitative analysis of heart inflammation after injection of the protease-activated fluorescence agent ProSense 750 (Perkin Elmer).*

Major Grants

- ***Ministerio de Economía y Competitividad (SAF2011-27330)***
- ***Ministerio de Economía y Competitividad. FIS RETICS (P2010/BMD-2332)***

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* doi:10.1172/JCI65124. Epub Dec 3 2012.

Sánchez-Madrid F, Martín P. I**mmune system sentinels, guardians of the body.** *An Real Acad Nac F* (2012) 78: 62-81.

Martín P, Moscat J. **Th1/Th2 differentiation and B cell function by the atypical PKCs and their regulators.** *Frontiers Immunol* (2012) 3: 241.

Martín P, Sanchez-Madrid F. **CD69: an unexpected regulator of Th17-driven inflammatory responses.** *Sci Signal* (2011) 4: pe14.

Lamana A, Martín P, de la Fuente H, Martinez-Muñoz L, Cruz-Adalia A, Ramirez-Huesca M, Escribano C, Gollmer K, Mellado M, Stein JV, Rodriguez-Fernandez JL, Sanchez-Madrid F and Martinez del Hoyo G. **CD69 modulates sphingosine-1-phosphate-induced migration of skin dendritic cells.** (2011) *J Invest Dermatol* 131:1503-12.

Epidemiology, Atherothrombosis and Imaging

3

3 Epidemiology, Atherothrombosis and Imaging

Our department integrates basic science, clinical data, and population-level studies to better understand the occurrence, natural history, and prognosis of cardiovascular disease. 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, and cardioprotection during myocardial infarction, including studies in animal models and humans using latest-generation advanced imaging techniques.

For this work, the department works closely with the recently established Advanced Imaging Unit, bringing in expertise in imaging, nanomedicine, radiochemistry and metabolomics. The department also coordinates epidemiological 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*
Technicians:	*Javier Mateos* *Inés Ortega* *Virginia Zorita* *Gonzalo Javier López* *Angel Macías* *Ana Vanesa Alonso*
Study Nurse:	*Maite Dubraska Rodríguez Cabrera*
Administrative Support:	*Eeva Inari Soininen* *Ana Gutiérrez*

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Cardiovascular imaging

Head of Laboratory: Valentín Fuster *(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)*
Ginés Sanz
Jesús Mateo *(CNIC)*
Oliver Michel Weber *(CNIC, Philips Healthcare)*
Javier Sánchez *(CNIC, Philips Healthcare)*
Leticia Fernández Friera *(CNIC)*
Beatriz López-Melgar

Project Managers: Laura García Leal
Luz Alvarez Vilela

CardioImage Fellow: Gabriela Guzmán *(CNIC, Hospital de La Paz, Madrid)*

Technicians: Carolina Rojas Murcia
Natalia Serrano Juzgado
Isabel Pérez García
Aurora Del Barrio Mantecas
Alberto Ávila Morales
Ricardo Ponce Sánchez
Sergio Cárdenas Melero
Rosa Villa Povo
Rosario Pérez Rubiño

Visiting Scientists: Vicente Martínez de Vega
Juan Carlos Alonso
Ana Álvarez Vázquez
Estefanía Fernández Delgado
Claudia Susana Linares González

Research Interest

Our group conducts research into the development and application of non-invasive, high-resolution imaging technologies. Sophisticated imaging technologies play an ever more important role in research into cardiovascular disease, yielding novel information about the origin and development of disease, and through this providing means for diagnosing asymptomatic disease and monitoring treatment outcomes.

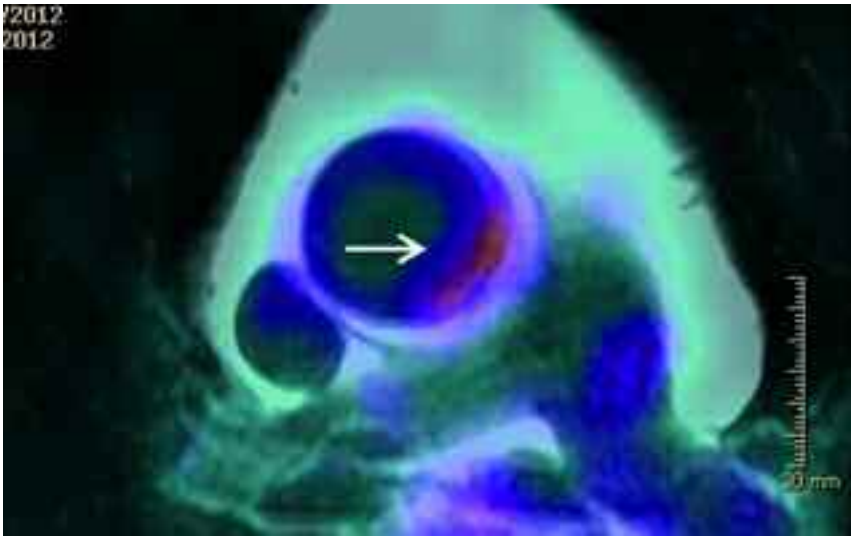
We are directly involved in the development of two large cohort studies (PESA and AWHS, see multidepartamental projects), where we are evaluating the use of non-invasive imaging for tracking atherosclerosis development and stratifying risk in asymptomatic populations. Through these projects we have established a strong international network of collaborators studying subclinical atherosclerosis in different countries by means of imaging technologies.

During 2012, the FOCUS trial, a multinational trial testing the efficacy of a novel polypill for secondary prevention, was actively recruiting patients. We plan to finish enrolment in Q1 during 2013. We also collaborate with other CNIC groups and centers throughout Spain in the METOCARD-CNIC trial, which compares the effect of early and delayed ,-blocker treatment on infarct size and clinical outcome in patients with acute myocardial infarction. Our group is performing the advanced imaging in these trials. Recruitment is already complete and data on the primary endpoint will be available in the first half of 2013.

2012 also saw the consolidation of the new imaging equipment in our human imaging facility, which is already in use for hybrid PET/MR evaluation of subclinical atherosclerosis within the PESA study. The equipment in our ambitious advanced imaging program includes a wide range of state of the art imaging modalities for small animals (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 has already started and we are developing novel agents and probes that are being tested in our preclinical models.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging



MRI-^{18}FDFG PET scan of human ascending aorta, from the PESA study. Arrow: ^{18}FDG uptake in an atherosclerotic plaque in the ascending aorta reveals plaque inflammation.

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 (R01 HL-092989)***
- ***NIH Grant (NHLBI-BAA-10-08)***

Selected Publications

Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S 3rd, Bertrand M, Fuster V. **Strategies for multivessel revascularization in patients with diabetes.** *N Engl J Med* (2012) 367: 2375-84.

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) 125:1795-808.

Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. **Acute coronary events.** *Circulation* (2012) 125:1147-56.

Fuster V, Bhatt DL, Califf RM, Michelson AD, Sabatine MS, Angiolillo DJ, Bates ER, Cohen DJ, Coller BS, Furie B, Hulot JS, Mann KG, Mega JL, Musunuru K, O'Donnell CJ, Price MJ, Schneider DJ, Simon DI, Weitz JI, Williams MS, Hoots WK, Rosenberg YD, Hasan AA. **Guided antithrombotic therapy: current status and future research direction: report on a National Heart, Lung and Blood Institute working group.** *Circulation* (2012) 126: 1645-62.

Fuster V, Chinitz JS. **The Net Clinical Benefit of Warfarin: Extending the Reach of Antithrombotic Therapy for Atrial Fibrillation.** *Circulation* (2012);125(19):2285-7.0

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Molecular and genetic cardiovascular pathophysiology

Head of Laboratory: Vicente Andrés García

Postdoctoral Researchers: Raphaël Chèvre
José María González Granado
Oscar Muñiz Pello
José Rivera Torres
Laia Trigueros Motos
Ricardo Villa Bellosta
Vanesa Esteban

Predoctoral Researchers: Pedro Molina Sánchez
Carlos Silvestre Roig
Magda Rita Hamczyk

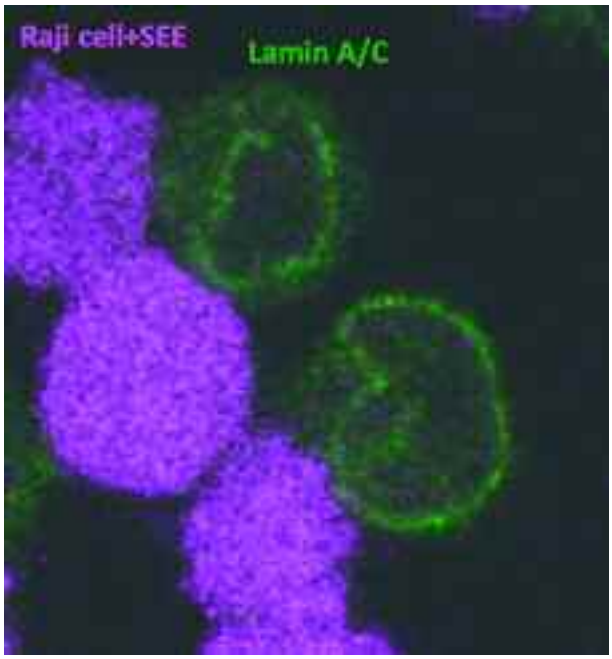
Technicians: María Jesús Andrés Manzano
Cristina González Gómez
Marta Blanco Berrocal

Undergraduate Student: Alba de Juan Guillén

Research Interest

Accumulation of blood-borne leukocytes and their proliferation within the atherosclerotic plaque is a hallmark of atherosclerosis. During disease progression, inflammatory mediators produced by activated neointimal macrophages and lymphocytes induce the proliferation of vascular smooth muscle cells (VSMCs) and their migration toward the growing lesion. An additional processes contributing to atheroma growth is the accumulation of non-cellular material, such as modified lipids and extracellular matrix components produced by activated VSMCs, which undergo de-differentiation from a 'contractile' to a 'synthetic' phenotype. Excessive cellular hyperplasia is also a feature of restenosis, the major limitation to the long-term success of revascularization via stent placement.

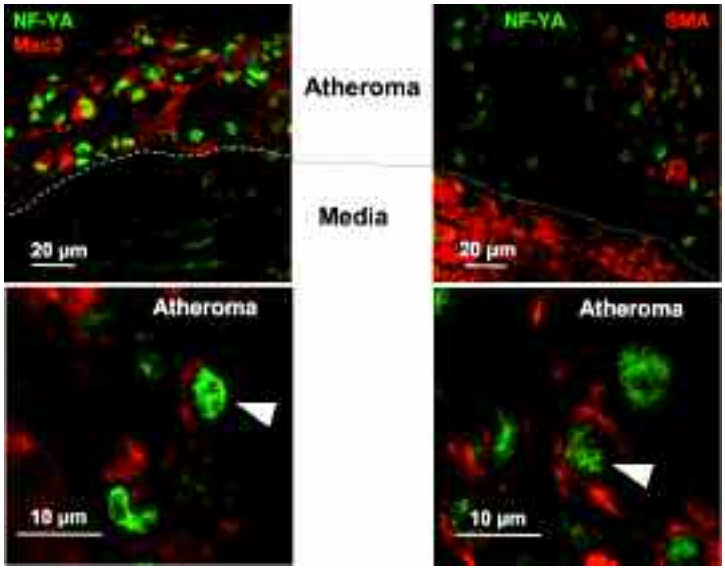
We investigate cellular, molecular and genetic mechanisms that underlie the development of atherosclerosis, restenosis and vascular calcification. Our main interest is in regulatory circuits that control gene transcription and cell proliferation, and our long-term goal is to identify novel therapeutic targets and provide the basis for the development of new tools for the early diagnosis of individuals at high risk of cardiovascular disease (CVD). We also investigate the role of telomeres and A-type lamins in the regulation of signal transduction, gene expression and cell-cycle activity in pathophysiological processes, including aging and CVD. Our multifaceted approach combines in vitro, cellular, animal and human studies and a variety of technologies, including mouse genetic engineering, proteomics, transcriptomics, FRET, confocal microscopy, and yeast 2-hybrid screens. We have a special interest in the use of cre/lox strategies combined with studies of VSMC and macrophage primary cultures to manipulate genes of interest and examine their role in CVD and in normal and premature aging.



Lamin A/C expression in T lymphoblasts upon activation by antigen presenting cells (Raji+SEE).

Research Departments

3 Epidemiology, Atherothrombosis and Imaging



NF-YA expression in Mac-3-immunoractive macrophages and SMA-immunoreactive smooth muscle cells in atheroma of apolipoprotein E-null mice.

Major Grants

- ***Ministerio de Economía y Competitividad. FIS RETICS (RECAVA, RD06/0014/0021)***
- ***Ministerio de Economía y Competitividad (SAF2010-16044)***
- ***Progeria Research Foundation – Call 2012***
- ***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

Fuster JJ, Molina P, Jovaní D, Vinué A, Serrano M, Andrés V. **Increased gene dosage of the Ink4/Arf locus does not attenuate atherosclerosis development in hypercholesterolaemic mice.** *Atherosclerosis* (2012) 221: 98-105.

Andrés V, Pello OM, Silvestre-Roig C. **Macrophage proliferation and apoptosis in atherosclerosis.** *Curr Opin Lipidol* (2012) 23: 429-38.

Pello OM, Chèvre R, Laoui D, De Juan A, Lolo F, Andrés-Manzano MJ, Serrano M, Van Ginderachter JA, Andrés V. **In vivo inhibition of c-MYC in myeloid cells impairs tumor-associated macrophage maturation and pro-tumoral activities.** *PLoS One* (2012) 7: e45399.

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* doi: 10.1111/acel.12023. Epub Dec 5 2012.

Andrés V, Fuster JJ, Silvestre C, Wessely R. **Modulating the proliferative response to treat restenosis after vascular injury.** *In* Homeister JW, Willis MS (Eds) *Molecular and Translational Vascular Medicine.* (2012) p 227-48. Humana Press – Springer.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Imaging in experimental cardiology

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

Postdoctoral Researchers: David Sanz-Rosa
Leticia Fernández Friera
Gonzalo Pizarro Sánchez *(CNIC, Hospital Quirón Madrid)*
Ana García-Alvarez *(CNIC, Hospital Clinic Barcelona)*
Rodrigo Fernández-Jiménez

Predoctoral Researcher: Jaime García-Prieto

CardioJoven Fellows: José Manuel García Ruiz

CardioImage Fellows: Jesús González Mirelis

Research Coordinator: Noemi Escalera

Technicians: Mario Nuño Ayala
Parvin Rupa Khaton

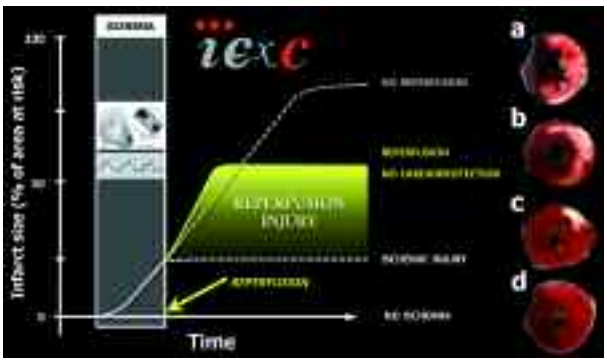
Visiting Scientists: Alonso Antonio Mateos Rodríguez
Lorena Montes Villalobos
Daniel Pereda Arnau
Jacobo Silva Guisasola

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 also investigate the relationship between circadian oscillations and spontaneous cardioprotection, and another program examines the potential of gene therapy for myocardial diseases in swine models of cardiomyopathy. We are also interested in the myocardial response to pulmonary hypertension, and have developed small and large animal models of pulmonary hypertension and use imaging technology to evaluate the response to different therapies.

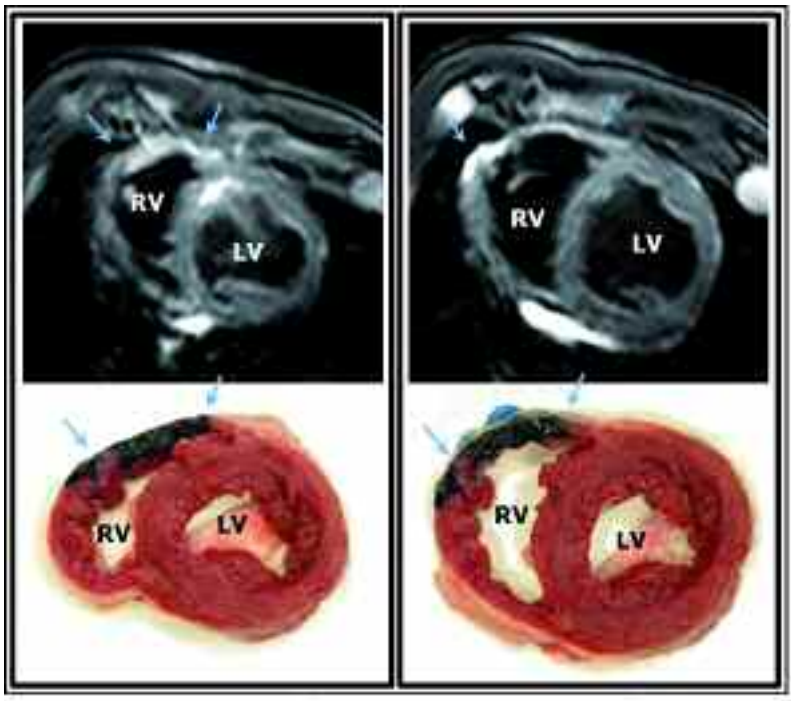
In the clinical setting, our team is a key participant in the METOCARD-CNIC trial, which uses magnetic resonance imaging to evaluate the effectiveness of a cardioprotective strategy based on beta adrenergic modulation in patients with a previous myocardial infarction. Enrolment of patients is complete and we will report the results during the first half of 2013. Recruitment continues of patients with infarction for the metocard-CLOCK study, which prospectively evaluates circadian oscillations of infarct size in humans with ST-segment elevation MI (STEMI). Finally, we are using novel magnetic resonance imaging sequences to evaluate diffuse fibrosis within the myocardium, and are recruiting patients with different cardiomyopathies for this endeavour.



Ischemia/reperfusion injury.
Death of myocardium during ischemia follows an exponential course. (a) If there is no reperfusion, the entire ischemic area becomes necrotic. (b) When reperfusion is limited to antegrade flow restoration, necrosis is significantly reduced (b); however the reperfusion itself induces additional damage to the myocardium (reperfusion injury). (c) Minimizing reperfusion injury further reduces infarct size. (d) Non infarcted myocardium. Panels a to d show representative axial slices of left ventricles of mice. Coronary occlusion was applied for 45 minutes, and reperfusion for 24 h. Red staining (TTC positive) represents live myocardium, and the pale area (TTC negative) indicates necrosis.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging



Local delivery of probes to swine myocardium. *Local delivery of different probes to the endocardium is achieved by in vivo percutaneous injection via the femoral artery. This technique allows the direct injection of selected probes in a chosen area of the swine heart. In this case, Evans blue was injected into the outflow tract of the right ventricle. Axial slices of swine heart (LV=left ventricle, RV=right ventricle). Top panels are axial slices obtained by in vivo magnetic resonance imaging (MRI) immediately after RV Evans blue injection. Arrows mark areas of edema on T2W sequences. Bottom panels show corresponding post-mortem axial slices. Arrows mark the blue/black areas of RV Evans blue staining, which were visualized in vivo as edemic areas by MRI.*

Major Grants

- *European Commision FP7-ICT-2011-8 (LIPHOS-317916).*
- *Fundacion Mutua Madrileña (AP8695-2011)*
- *CNIC Translational Grants (01-2009)*
- *Ministerio de Sanidad y Politica Social. FICI (EC10-042)*
- *Ministerio de Economía y Competitividad. FIS (PI10/02268).*

Selected Publications

Ibanez B, Fuster V, Macaya C, Sánchez-Brunete V, Pizarro G, López-Romero P, Mateos A, Jiménez-Borreguero J, Fernández-Ortiz A, Sanz G, Fernández-Friera L, Corral E, Barreiro MV, Ruiz-Mateos B, Goicolea J, Hernández-Antolín R, Acebal C, García-Rubira JC, Albarrán A, Zamorano JL, Casado I, Valenciano J, Fernández-Vázquez F, de la Torre JM, Pérez de Prado A, Iglesias-Vázquez JA, Martínez-Tenorio P, Iñiguez A. **Study design for the "effect of METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion" (METOCARD-CNIC): a randomized, controlled parallel-group, observer-blinded clinical trial of early pre-reperfusion metoprolol administration in ST-segment elevation myocardial infarction.** *Am Heart J* (2012) 164: 473-80.

Fernández-Friera L, García-Álvarez A, Ibáñez B. **Imagining the future of diagnostic imaging.** *Rev Esp Cardiol* doi: 10.1016/j.recesp.2012.10.012. Epub Dec 27 2012.

Bell R, Beeuwkes R, Bøtker HE, Davidson S, Downey J, Garcia-Dorado D, Hausenloy DJ, Heusch G, Ibanez B, Kitakaze M, Lecour S, Mentzer R, Miura T, Opie L, Ovize M, Ruiz-Meana M, Schulz R, Shannon R, Walker M, Vinten-Johansen J, Yellon D. **Trials, tribulations and speculation! Report from the 7th Biennial Hatter Cardiovascular Institute Workshop.** *Basic Res Cardiol* (2012) 107: 300.

Ibanez B, Giannarelli C, Cimmino G, Santos-Gallego CG, Alique M, Pinero A, Vilahur G, Fuster V, Badimon L, Badimon JJ. **Recombinant HDL(Milano) exerts greater anti-inflammatory and plaque stabilizing properties than HDL(wild-type).** *Atherosclerosis* (2012) 220: 72-7.

Fernández-Jiménez R, López-Romero P, Suárez-Barrientos A, García-Rubira JC, Fernández-Ortiz A, Fuster V, Macaya C, Ibanez B. **Troponin release overestimates infarct size in presence of left ventricular hypertrophy.** *J Am Coll Cardiol* (2012) 60: 640-1.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Imaging cardiovascular inflammation and the immune response

Head of Laboratory: Andres Hidalgo Alonso

Postdoctoral Researchers: Vinatha Sreeramkumar
Noelia Alonso
Magdalena Leiva

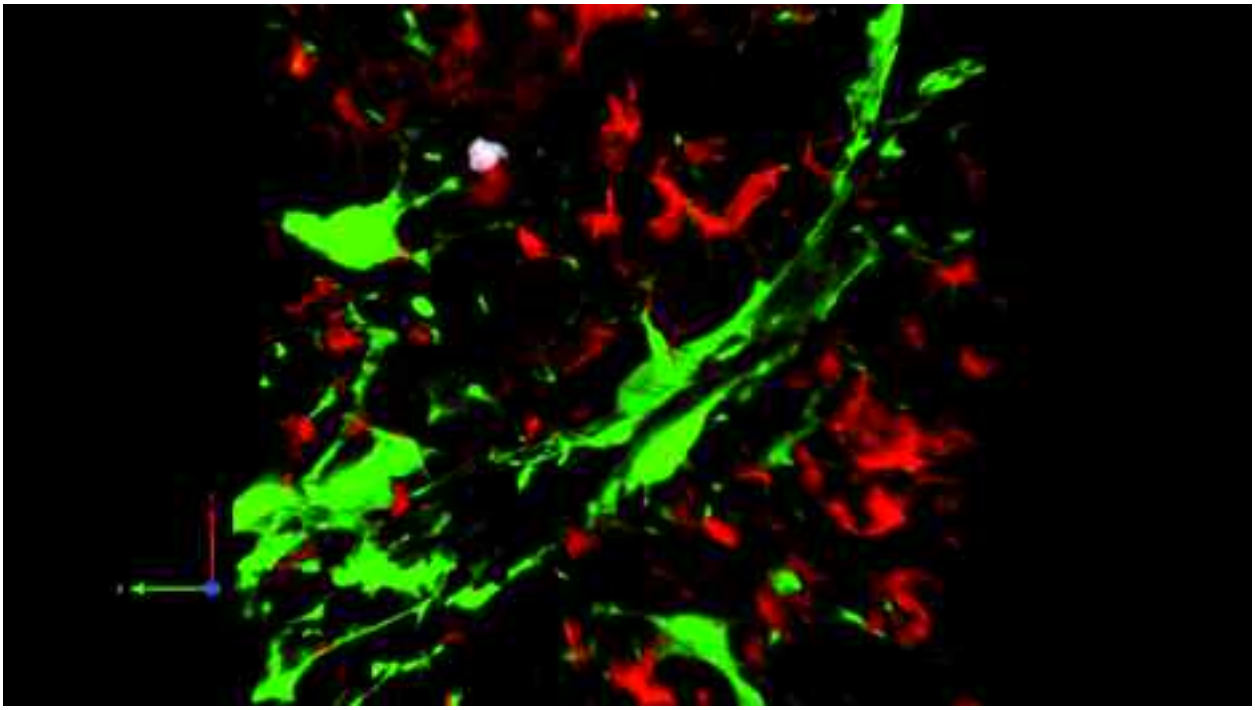
Predoctoral Researcher: María Casanova Acebes

Technician: Christophe Pitaval

Visiting Scientist: Linnea Weiss

Research Interest

Our group is interested in the roles that neutrophils and other leukocytes play in the body. Part of their functions relate to their well-known roles during inflammation as the first and critical cellular response to injury. Studies currently in progress examine the ability of neutrophils to interact with platelets and the consequences of these interactions on inflammatory injury, as well as the recruitment of neutrophils and other myeloid leukocytes to atherosclerotic plaques. We are also interested in the molecules involved in these interactions and in the infiltration of inflamed tissues by neutrophils and other inflammatory leukocytes. Other functions of neutrophils are less expected, and relate to their modulation of fundamental homeostatic processes in the body. One example of these processes is the modulation of hematopoietic stem-cell niches in the bone marrow by a population of *old* neutrophils, which we are currently characterizing. Our studies make use of gene-modified mice, inflammatory models of disease and subcellular-resolution in-vivo imaging. Our ultimate goal is to uncover processes at work during situations of health and disease in which myeloid cells are involved. In our work, we try to combine the excitement of discovering basic physiological phenomena with the mission of identifying therapeutic targets for the promotion of human health.



Whole-mount staining of a neutrophil (white) that has migrated to a bone-marrow niche composed of macrophages (red) and CXCL12-producing cells (green). The panel show a 3D reconstruction of confocal microscopy images.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Major Grants

- *BAYER HealthCare Grants 2012*
- *Comunidad de Madrid (P2010-BMD-2314)*
- *Ministerio de Ciencia e Innovación (SAF2009-11037)*
- *Ministerio de Ciencia e Innovación (RYC-2007-00697-11037)*
- *European Commission FP7 (246655 LEMPIT 2009)*

Selected Publications

Garcia-Bernal D, Redondo-Muñoz J, Dios-Esponera A, Chevre RI, Bailen E, Garayoa M, Arellano-Sanchez N, Gutierrez NC, Hidalgo A, García-Pardo A, Teixido J. **Sphingosine-1-phosphate activates chemokine-promoted myeloma cell adhesion and migrationinvolving alpha4beta1 integrin function.** *J Pathol* (2012) doi: 10.1002/path.4066. Epub Dec 17 2012.

Jang J-E, Hidalgo A, Frenette PS. **Intravenous immunoglobulins modulate neutrophil activation and vascular injury through FcγRIII and SHP-1.** *Circ Res* (2012) 110: 1057-66.

Research Departments

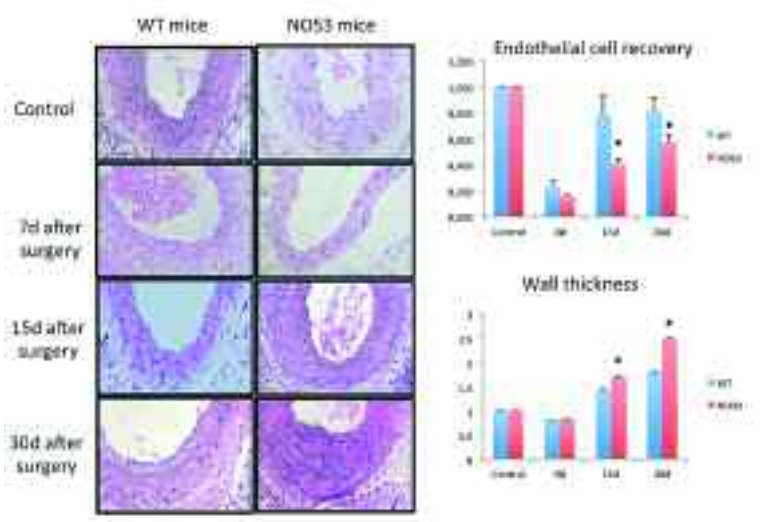
3 Epidemiology, Atherothrombosis and Imaging

Vascular wall remodeling and cardiovascular disease

Head of Laboratory: Carlos Zaragoza Sánchez
Postdoctoral Researcher: Beatriz Herranz Sánchez
Predoctoral Researchers: Begoña Lavin Plaza
Technician: Mónica Gómez Parrizas
Visiting Scientists: Borja Castejón
María José García Miguel

Research Interest

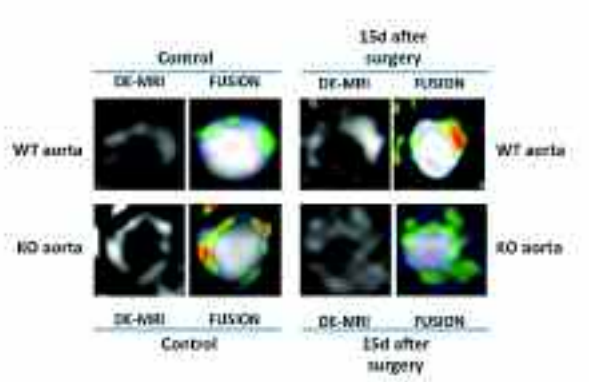
Our research focuses on the effect of vasoactive factors and proteolytic enzymes during the early steps of vascular wall remodeling, a process fundamental to the development and progression of atherosclerosis, aneurysm, myocardial infarction, and arterial hypertension, four of the most prevalent diseases worldwide. Our recent work has defined the important role of nitric oxide-mediated inhibition of proteolysis in the prevention of neointimal hyperplasia of denuded arteries, the contribution of eNOS partner molecules to the maintenance of vascular tone, and the cardioprotective efficiency of NO in mice subjected to ischemia/reperfusion. Our results open avenues of research toward the use of new strategies for early visualization and treatment of cardiovascular disease. Based on our previous findings, we are now proceeding with the synthesis of reagents for early and multimodal non-invasive detection of selected targets of myocardial infarction, with potential therarpeutical applications.



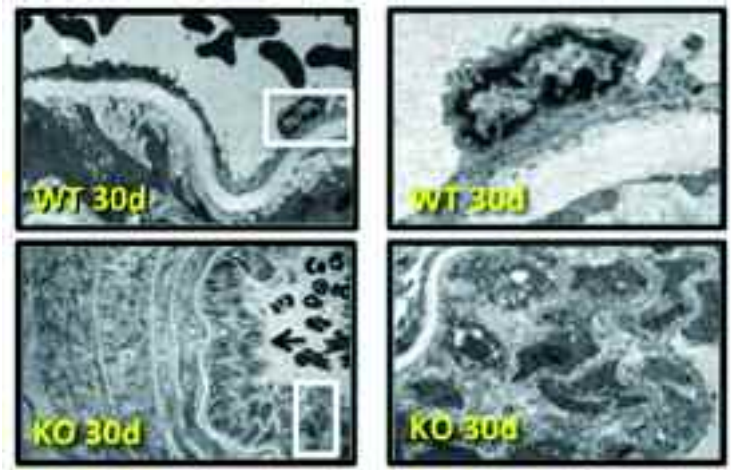
Neointimal hyperplasia in mice after abdominal aortic denudation. Left *HE staining of abdominal aortic sections isolated at different times after endothelial denudation. Right* Upper right *Time profile of aortic endothelial cell regeneration after surgical denudation.* Lower right. *Time profile of abdominal aorta wall thickness after surgical denudation.*

Research Departments

3 Epidemiology, Atherothrombosis and Imaging



Noninvasive magnetic resonance imaging of endothelial permeability in denuded mouse arteries using an albumin-binding contrast agent. Wild-type and NOS3 KO mice were imaged 48 hours after injection of Vasovist, a contrast agent which detects vascular permeability in mouse atherosclerotic lesions. In NOS3 null mice, delayed enhancement magnetic resonance imaging of the abdominal artery, 30 minutes after injection, showed increased vessel wall enhancement and relaxation rate (R(1)) with progression of permeability. In contrast, wild-type mice showed less enhancement 15 days after denudation.



Electron microscopy detection of abdominal aortic abnormalities in mice subjected to endothelial denudation over 30 days. Upper left *Wild-type aorta showing endothelial cell regeneration.* Lower left *NOS3 KO aorta showing extensive neointilmal hyperplasia. Boxed areas are shown at high magnification on the right.*

Major Grants

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

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.

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

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Cardiovascular Epidemiology and Population Genetics

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

Research Scientists: José Luis Peñalvo
Manuel Franco
Martín Laclaustra

Visiting Scientists: Eliseo Guallar *(CNIC, Johns Hopkins Bloomberg School of Public Health, Baltimore)*
José Mª Ordovás *(CNIC, Tufts University, Boston, IMDEA-FOOD, Madrid)*
Stuart Pocock *(CNIC, London School of Hygiene and Tropical Medicine, London)*

Post-residency Researcher: María Téllez

Predoctoral Researchers: Belén Moreno
Usama Bilal
Marta Ledesma

Biostatistician: Pedro López

Technicians: Raquel Langarita
Esther Rovira
Alicia Usón
Rosa Villa

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. The group works closely with the Translational Platform on the design and coordination of the CNIC's population studies, such as the Aragon Workers' Health Study (AWHS), PESA (Progression of Subclinical Atherosclerosis), and IMJOVEN.

The multidisciplinary group pursues highly innovative research that covers the major risk factors for cardiovascular disease, 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 cardiovascular diseases.

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.

Research Departments

3 Epidemiology, Atherothrombosis and Imaging

Major Grants

- *Instituto de Salud Carlos III (CP08/112). PI: M Laclaustra*
- *Instituto de Salud Carlos III (CM08/0037). PI: M Tellez*
- *Comunidad de Madrid (P2009/AGR-1469). PI: JL Peñalvo*
- *Ministerio de Ciencia e Innovación (RYC-2010-07554). PI: M Franco*
- *Instituto de Salud Carlos III (PI10/21). PI: M Laclaustra*
- *FP7 Marie Curie Reintegration Grant (GA-249302). PI: M Franco*
- *Instituto de Salud Carlos III (PI11/00403). PI: JL Peñalvo*

Selected Publications

Casasnovas JA, Alcalde V, Civeira F, Guallar E, Ibanez B, Jimenez-Borreguero J, Peñalvo JL, Laclaustra M, Leon M, Ordovas JM, Pocovi M, Sanz G, Fuster V. **Aragon workers' health study - design and cohort description.** *BMC Cardiovasc Disord* (2012) 12: 45.

Peñalvo JL, Moreno-Franco B, Ribas-Barba L, Serra-Majem L. **Determinants of dietary lignan intake in a representative sample of young Spaniards: association with lower obesity prevalence among boys but not girls.** *Eur J Clin Nutr* (2012) 66: 795-8.

Moore LV, Diez Roux AV, Franco M. **Measuring availability of healthy foods: agreement between directly measured and self-reported data.** *Am J Epidemiol* (2012) 175: 1037-44.

Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. **Cadmium exposure and all cause and cardiovascular mortality in the US general population.** *Environ Health Perspect* (2012) 120: 1017-22.

Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart AF, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. **Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study.** *Lancet* (2012) 380: 572-80.

4

Multi-departmental Clinical Projects

Multi-departmental 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 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.

Multi-departmental Projects

AWHS

The Aragon Workers Health Study (AWHS) is an ongoing project being 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 check-ups and biochemistry tests are collected at each annual health check-up.

In 2011, a screen was begun to detect subclinical atherosclerosis among 40-54-year-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.

Multi-departmental Projects

PESA CNIC- GRUPO SANTANDER AND FUNDACIÓN BOTÍN

(Progression of Early Subclinical Atherosclerosis)

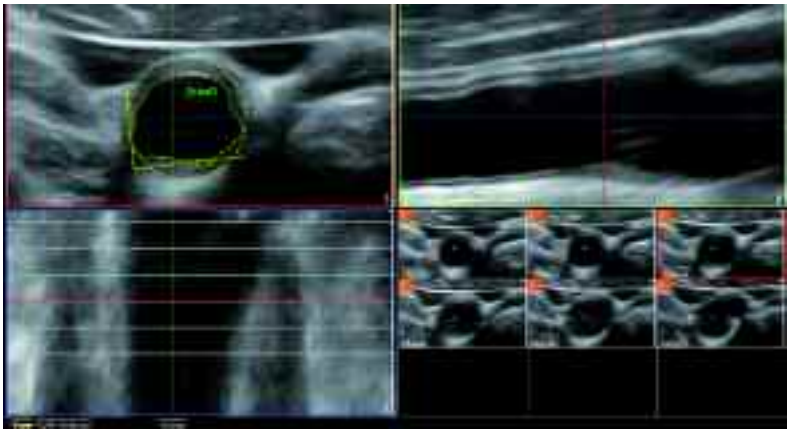
The ongoing PESA CNIC-Grupo Santander and Fundación Botín study will achieve early diagnosis of atherosclerosis before the appearance of symptoms and help to identify risk factors and daily habits that influence the onset and development of atherosclerosis. Future follow-up of this population may identify 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. However, most studies to date have examined populations composed of individuals above the age of 60. Atherosclerotic disease in this group has already several decades of evolution and may be too advanced for prevention of future events. To assess the early onset of atherosclerosis, longitudinal vascular imaging studies are needed to provide information on middle-aged asymptomatic populations.

The PESA study is an observational, prospective, cohort study in a target population of 4000 healthy middle-aged subjects (40-54 years old, 35% women) based in Madrid. Participant inclusion began in June 2010 and will be completed within 3 years. All participants will be followed for 6 years. Recruitment of study participants is based on volunteer participation after completion of the annual medical checkup performed 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 additionally assessed for coronary artery calcification by computed tomography (CT) and undergoes dedicated interviews to identify classical and new cardiovascular risk factors (including lifestyle and psychosocial factors). Plasma, serum, RNA, DNA and leucocyte 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 baseline measurements. In addition, advanced imaging by contrast-enhanced magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose–positron emission tomography (^{18}FDG PET) for carotid and ilio-femoral plaques will be offered at baseline and at 6 years to a selected group of 1500 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 duration will be 9 years, ending in 2019.

The study will also provide important information about the prevalence of unrecognized myocardial infarction in this population, and will assess the prevalence and progression of subclinical atherosclerosis in women during perimenopause and its relation to cardiovascular risk factors and hormonal changes.

As of the end of 2012, the PESA study has received more than 2800 applications for participation, from 1800 men and 1000 women. PESA technical staff and Santander Group Medical Service staff are coordinated, trained and certified in accordance with the study procedures, and quality control procedures have been established. All participants have been assessed for subclinical atherosclerosis by vascular 2D and 3D ultrasound. As planned, advanced RMN-PET imaging studies have commenced in those participants having atheroma plaques. Anonymized data are recorded in the PESA study database, and samples of serum, plasma, whole blood, urine and DNA from all study participants are stored in a biobank for further analysis. All participants receive a report with their test results, together with healthy lifestyle recommendations.



3D carotid ultrasound assessment of atherosclerosis burden. Upper-left: reconstruction in an axial plane of the carotid artery to assess the edges of the atherosclerotic plaques: Upper-right and lower-left: reconstruction of orthogonal planes of carotid artery in longitudinal axis. Inferior-right: reconstruction in several parallel slices of an axial plane of the carotid artery.

Multi-departmental Projects

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 a fixed dose polypill for secondary prevention, comprising aspirin, simvastatin and ramipril. The CNIC-Ferrer polypill project is led by Valentín Fuster and is coordinated by the CNIC Translational Platform.

During 2012 we conducted several clinical trials to ensure the quality and safety of the polypill. Early last year the results came in from the Spanish pharmacodynamic interactions study with simvastatin in 100 patients. These results showed that our polypill significantly reduced 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.

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 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 made possible 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 effect 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 4000 patients across 80 centers and five countries. The Consortium 2012 Annual General Assembly of the FOCUS project was held in La Plata, Argentina last October.

The CNIC-FERRER polypill (Trinomia^{R}/Sincronium^{R}) has been approved for prescription in patients with a previous history of acute myocardial infarction in Guatemala, Argentina, México and Nicaragua. We are also working on new fixed-dose combinations to provide physicians and patients with more effective therapeutic tools.

Multi-departmental Projects

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. What remains unclear is what timing and route of β-blocker administration gives the maximum cardioprotective effect. In particular, whether early β-blocker administration is able to reduce infarct size is a subject of debate. Our experimental data suggest that the β1 selective blocker metoprolol is able to limit the area of necrosis only when administered before reperfusion.

METOCARD-CNIC is a multicenter randomized clinical trial comparing the effect of early and delayed metoprolol initiation on infarct size and clinical events. Recruitment is already closed, 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. At the time of writing, 175 patients have undergone a second MRI study 6 months after the initial scan. The remaining patients will undergo MRI over the coming months. Studies of patients recruited in Madrid were performed at the CNIC's human imaging facility, where the advanced imaging protocol is performed with a novel cutting-edge MRI system. MRI scan data are being analyzed in a core laboratory at the CNIC.

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. Hospitals participating in the METOCARD-CNIC trial are Hospital Clínico San Carlos, Puerta de Hierro, Hospital de la Princesa, Hospital 12 de Octubre and Hospital Quirón in Madrid, Hospital Meixoeiro in Vigo, Hospital Marqués de Valdecilla in Santander, and 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. This initiative is a pilot endeavor that will be followed by larger clinical trials in which more centers will participate in close collaboration with the CNIC.

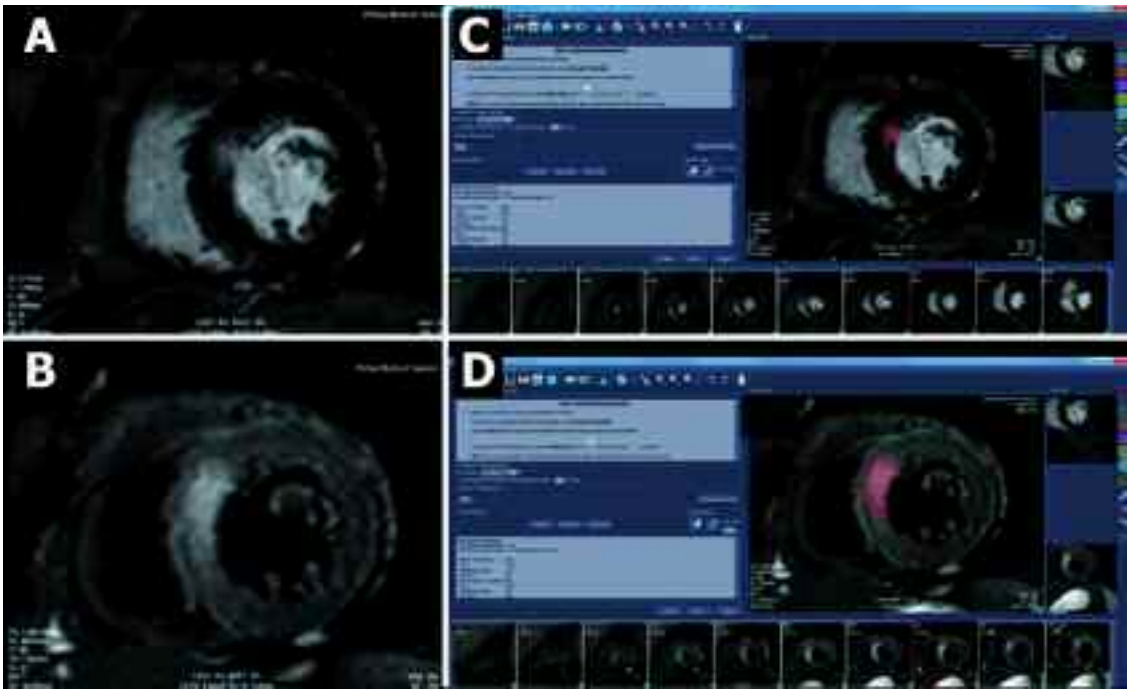


FIGURE: Magnetic resonance imaging analysis of area at risk and size of necrosis in the METOCARD-CNIC trial.

MRI short-axis images obtained at the same LV level in a patient recruited to the METOCARD-CNIC trial. The MRI scan was performed 7 days post-infarction. Panel A shows the area of delayed enhancement (infarcted area, bright area in the anterior interventricular septum), and B shows the area at risk at the same level of the LV (hyperintense area in the interventricular septum). Panels C and D show automatic quantification of infarcted area (C) and area at risk (D) for the hearts imaged in A and B, respectively. Note that the area of necrosis is significantly smaller than that of area at risk. (Picture taken from Am Heart J 2012;164:473-480: METOCARD-CNIC design publication).

Multi-departmental Projects

METOCARD-CNIC trial

Dr. Fuster (CNIC General Director), Frans van Houten (CEO Philips Electronics), and Borja Ibáñez (METOCARD-CNIC PI) welcome a recruited patient to the magnetic resonance imaging suite in the CNIC human cardiovascular imaging laboratory,

5 Translational Platform

Translational Platform

Technology Transfer & Translational Research 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 Epidemiology, Atherothrombosis and Imaging 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.

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 will be 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 will be subject to a feasibility analysis and approval by the [T]^{3}RP Scientific Advisory Committee. The Unit's activity is scheduled to begin in 2013, after design refinement.

Translational Platform

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.

Patent Filing & Technology Transfer

Last year saw a significant increase in the number of new invention disclosures assessed, with 15 new inventions evaluated compared with five in 2011. Moreover, nine of these were filed as new priority applications (Figure 1). Also, some of the Center's active patent families were extended to patent cooperation treaty (PCT) status or entered regional or national phases (European and US patent offices only). The CNIC portfolio currently includes 19 active patent families at different stages. Of these, 15 are new applications filed in 2012, and 11 are shared with other institutions (Figure 2).

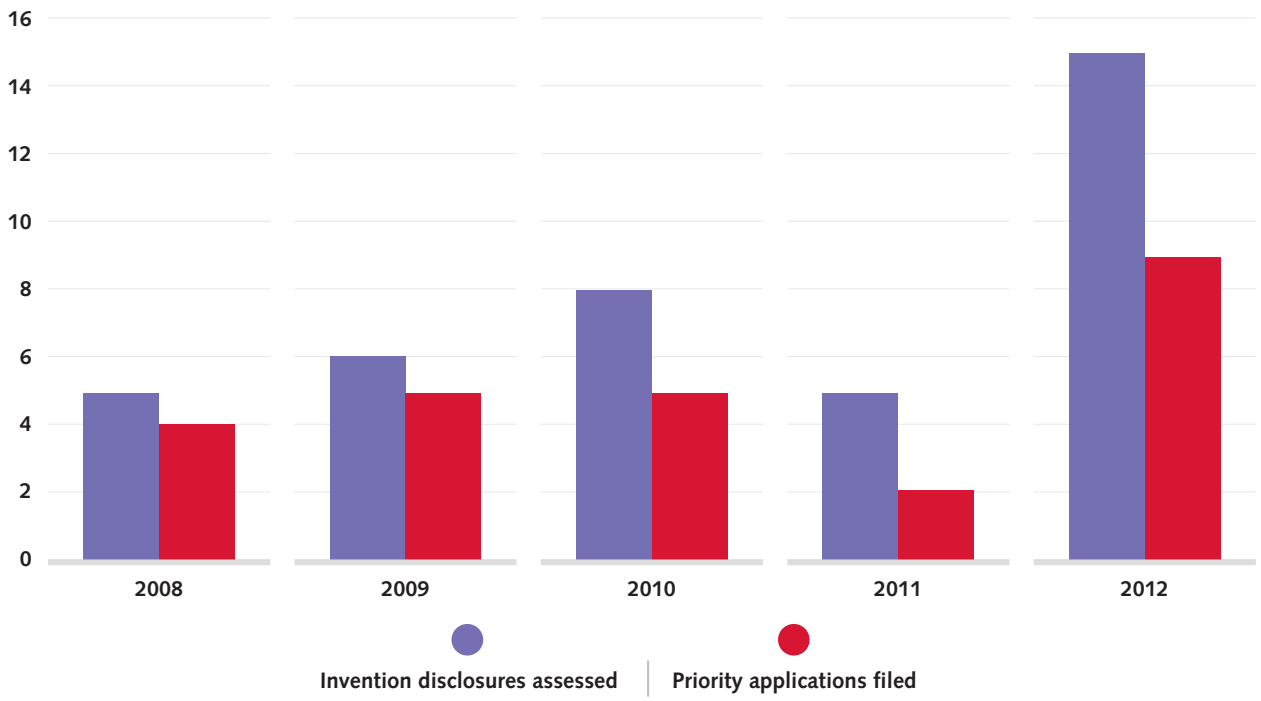


Figure 1. Number of new invention disclosures assessed & filed

Translational Platform

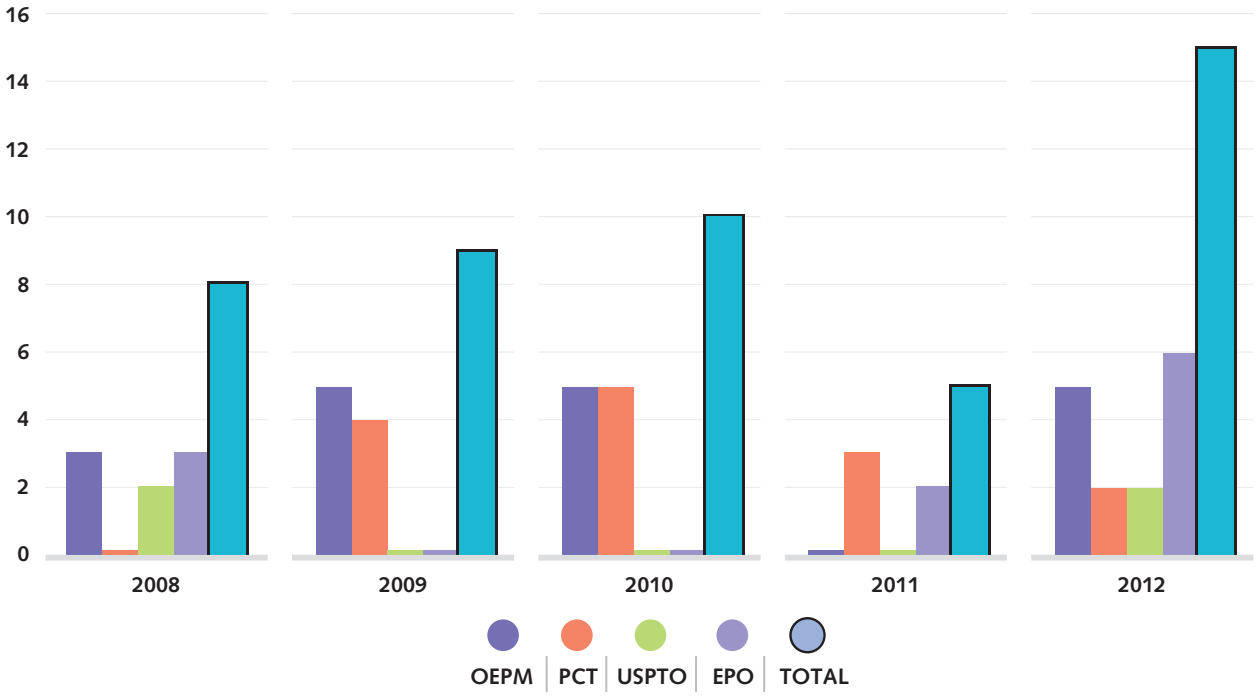


Figure 2. Number and type of applications filed in the last five years. OEPM: Oficina Española de Patentes y Marcas. PCT: Patent Cooperation Treaty: Under a PCT, an "international application" can be filed in several offices; we normally use the EPO or OEPM. USPTO: United States Patents and Trademarks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

In 2012 we also carried out due diligence checks for three inventions. A letter of commitment has already been signed for one of them, and we are negotiating a license contract for another; the third is still active. In the first months of 2013 we will initiate negotiations with a company interested in another of our inventions. Active invention disclosures protected by the Center are listed in the appendix.

Research Cooperation:

Research Cooperation Agreements (RCAs)

A new RCA, which also covers terms and conditions for royalties, has been signed with a Spanish biotechnology company, and another, with an American biotechnology company, is under negotiation (terms letter already signed).

Translational Platform

Material Transfer Agreements (MTAs) and Confidential Disclosure Agreements (CDAs)

In 2012, 64 MTAs were managed, 57 of which have already been signed (Figure 3).

In 2012, the CNIC signed 28 new CDAs (also called non-disclosure agreements, or NDAs). Of these, 17 were with international agents, and 11 with Spanish stakeholders.

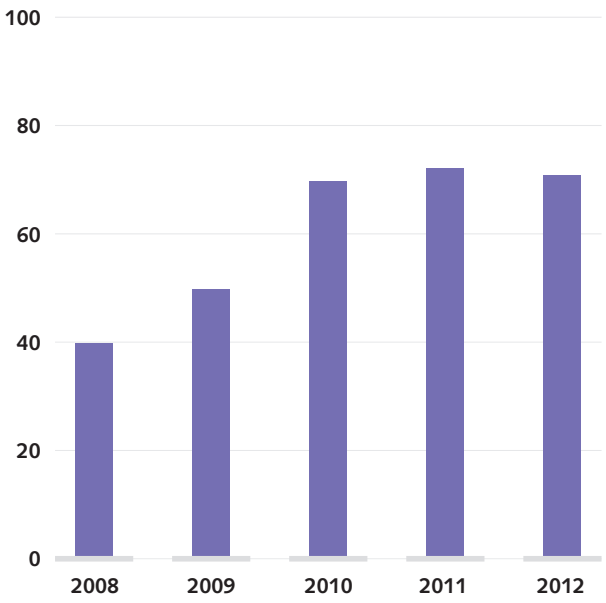


Figure 3.
Number of Material Transfer Agreements (MTAS) signed.

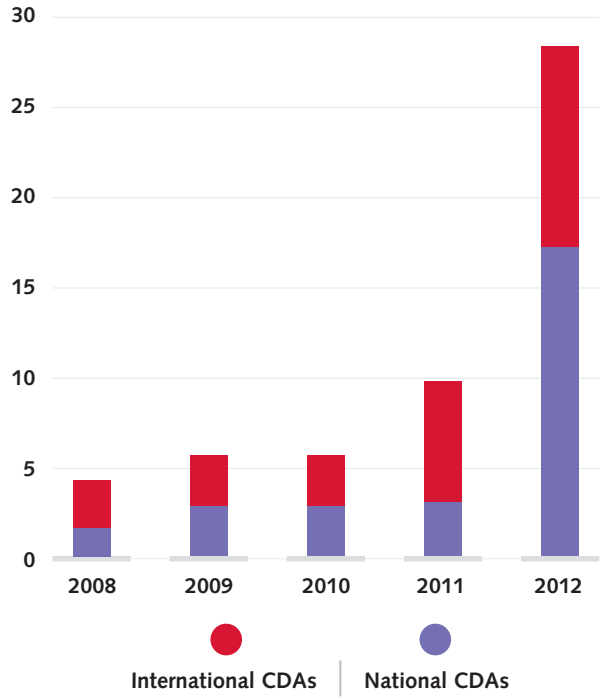


Figure 4.
Number of Confidential Disclosure Agreements (CDAs) signed.

Translational Platform

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.

Biobank

The CNIC Biobank (CB^b) was created and began to collect samples last year. The CB^b 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 CB^b currently holds 25,922 samples, including whole blood, serum, plasma, buffy coats, DNA, RNA (PAXgene tubes), and urine.

The CB^b is undergoing procedures for certification as an official biobank under current national regulations *(Ley 14/2007 de Investigación biomedical y Real Decreto 1716/2011 de Biobancos)*.

Translational Research & Epidemiology

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

Departamental Staff

PLATFORM COORDINATOR:

Antonio Bernad

HEAD OF PROJECT OFFICE AND TECHNOLOGY TRANSFER AREA:

Luzma García

PROJECT OFFICE AND TECHNOLOGY TRANSFER AREA:

Magdalena Blanco (TTO – Commercialization Affairs Manager),
Noelia López (TTO – IPR & TT Manager),
Cristina Giménez (TTO – National Projects Manager),
Marta Abelleira (TTO – International Projects Manager),
Benito Domínguez (TTO – International Projects Manager)

TECHNOLOGY DEVELOPMENT GROUP:

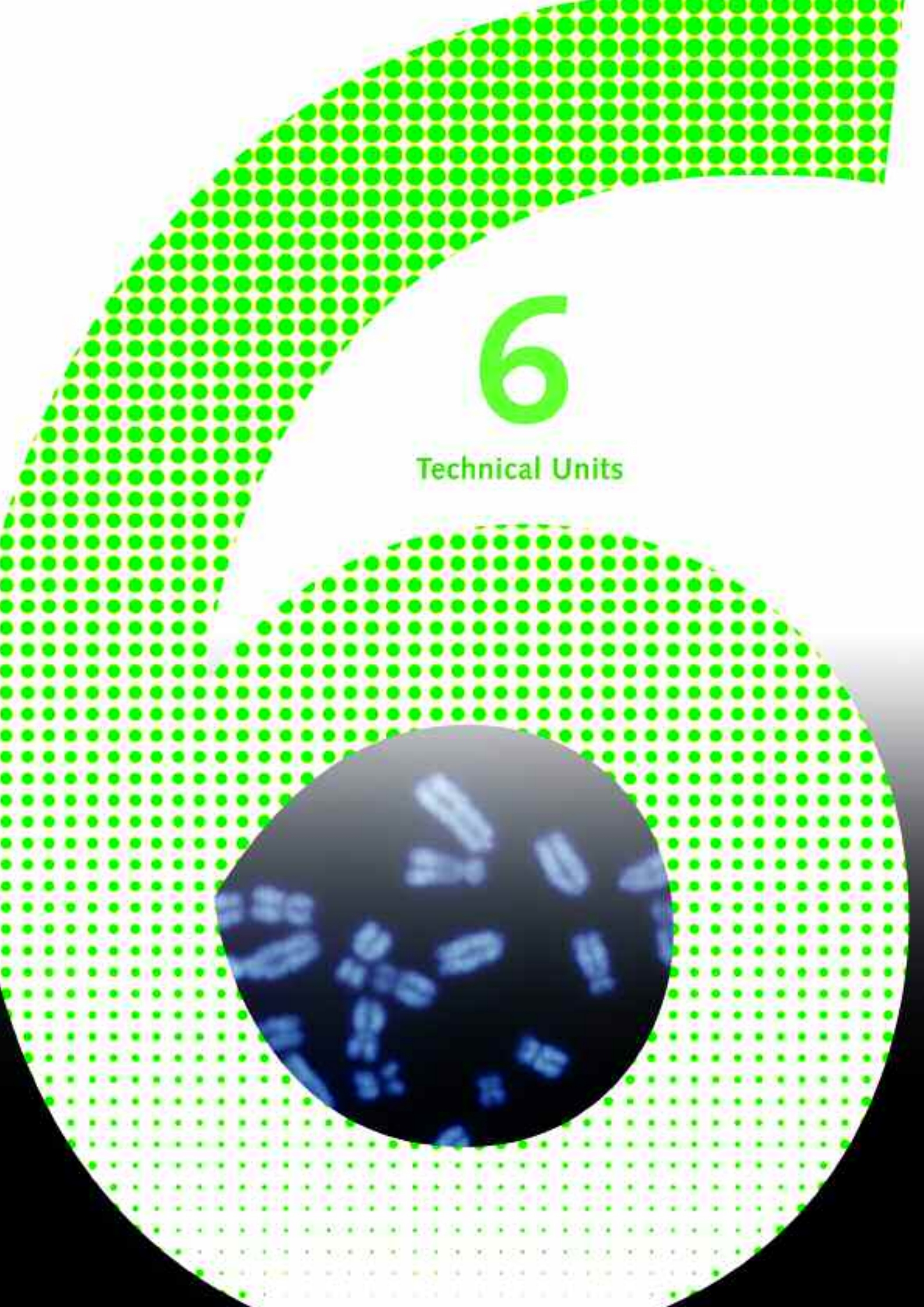
Ricardo Ponce (CBb. Senior Technician)
Laura García (PESA-CBb. Management Technician)

ADMINISTRATIVE SUPPORT:

Ana Gutiérrez

6

Technical Units



Technical Units

Advanced Imaging

Head of Unit: Jesús Ruiz-Cabello

Postdoctoral Researchers: Fernando Herranz
José Manuel Pérez
Carlos Pérez

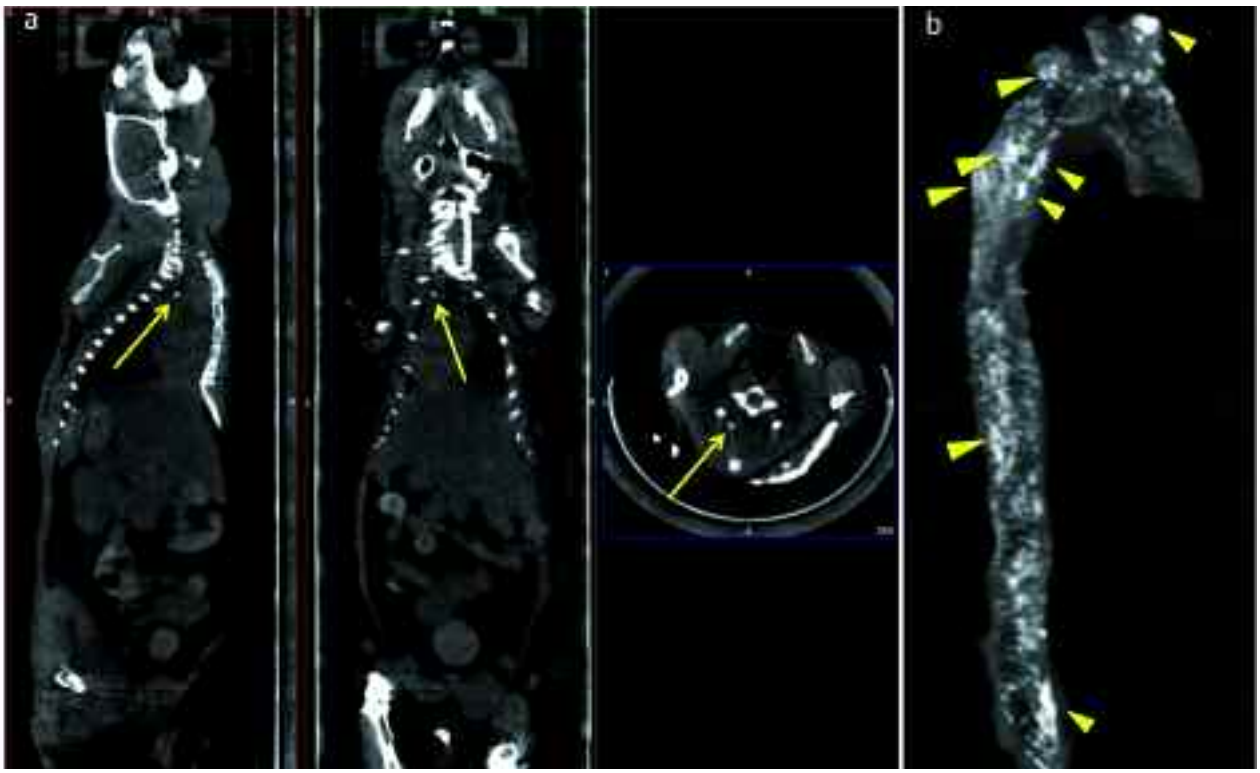
Support Scientists: Ignacio Rodriguez *(Professor UCM)*
Juan Manuel García Segura *(Professor UCM)*

Predoctoral Researchers: Beatriz Salinas
Hugo Groult
Juan Pellico

Technicians: Marina Benito
Izaskun Bilbao

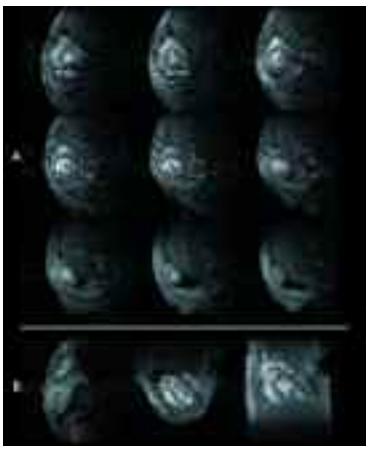
Research Interest

The Advanced Imaging Unit (AIU), established at the CNIC early in 2012, is a multidisciplinary group focused on the development of new imaging applications that will expand molecular and cellular knowledge of cardiovascular diseases. The AIU's work falls into three areas: 1) cardiovascular imaging, 2) nanomedicine and radiochemistry, and 3) metabolomics. The AIU offers the CNIC and the scientific community state-of-the-art technologies for cardiovascular imaging in five modalities: MRI, X-ray CT, nuclear imaging (PET), ultrasound (echocardiography) and optical (bi and tri-dimensional luminescence and fluorescence). The nanomedicine program, run from a dedicated nanotechnology and organic chemistry laboratory, develops 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, such as iron oxide, up-converting nanophosphors and gold nanoparticles, all of them functionalized with different cardiovascular biomarkers. Additionally, the new ^{68}Ga radiochemistry laboratory will be fully operative at the beginning of 2013 to provide the Center with specific PET radiotracers for cardiovascular nuclear imaging. The members of the Unit also have a long experience in the application of metabolic analysis to the study of various pathologies through 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. An example of this last approach is PINET, the FP7 Initial Training Network in Pulmonary Imaging that has been coordinated by members of the new unit since 2008.

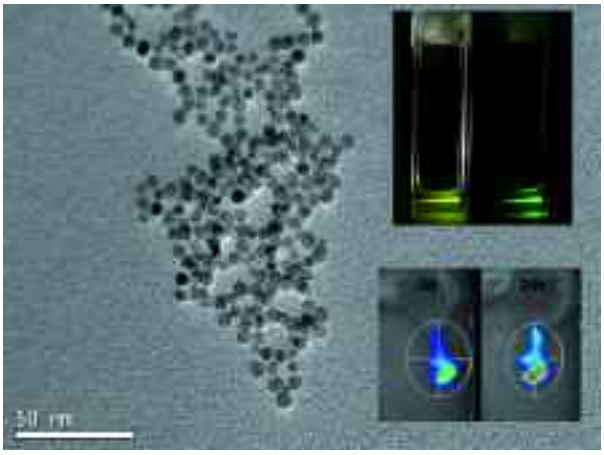


Detection by CT of atherosclerotic plaques in aorta (a) a mouse (wholebody in vivo) and (b) a rabbit (ex vivo).

Technical Units



(A) Short and (B) long axis magnetic resonance images of mouse heart



Nanoparticles for multimodal cardiovascular imaging

Selected Publications

Izquierdo-García JL, Peces-Barba G, Ruiz-Cabello J. **Influence of ambient air on NMR-based metabolomics of exhaled breath condensates.** *Eur Respir J* (2012) 40: 1294-6.

Herranz F, Schmidt-Weber CB, Shamji MH, Narkus A, Ruiz-Cabello J, Vilar R. **Superparamagnetic iron oxide nanoparticles conjugated to a grass pollen allergen and an optical probe.** *Contrast Media Mol Imaging* (2012) 7: 435-9.

Salinas B, Ruiz-Cabello J, Morales MP, Herranz F. **Olefin metathesis for the functionalization of superparamagnetic nanoparticles.** *Bioinsp. Biomim. Nanobiomat.* (2012) 1: 166-72.

Ruiz-Cabello J, Barnett BP, Bottomley PA, Bulte JWM. **Fluorine (19F) MRS and MRI in biomedicine.** *NMR Biomed* (2011) 24: 114–29

Izquierdo-García JL, Peces-Barba G, Heili S, Diaz R, Want E, Ruiz-Cabello J. **Is NMR-based metabolomic analysis of exhaled breath condensate accurate?** *Eur Respir J* (2011) 37: 468–70.

Barnett BP, Ruiz-Cabello J, Hota P, Liddell R, Walczak P, Howland V, Chacko VP, Kraitchman DL, Arepally A, Bulte JWM. **Fluorocapsules for improved function, immunoprotection, and visualization of cellular therapeutics with MR, US, and CT imaging.** *Radiology* (2011) 258: 182–91.

Technical Units

Microscopy and dynamic imaging

Head of Unit: Valeria R. Caiolfa

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

Postdoctoral Researchers: Giulia Ossato
Valeria Corti
Antonio Trullo

Research Interest

The Unit houses a large number of state-of-art bright- and 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.

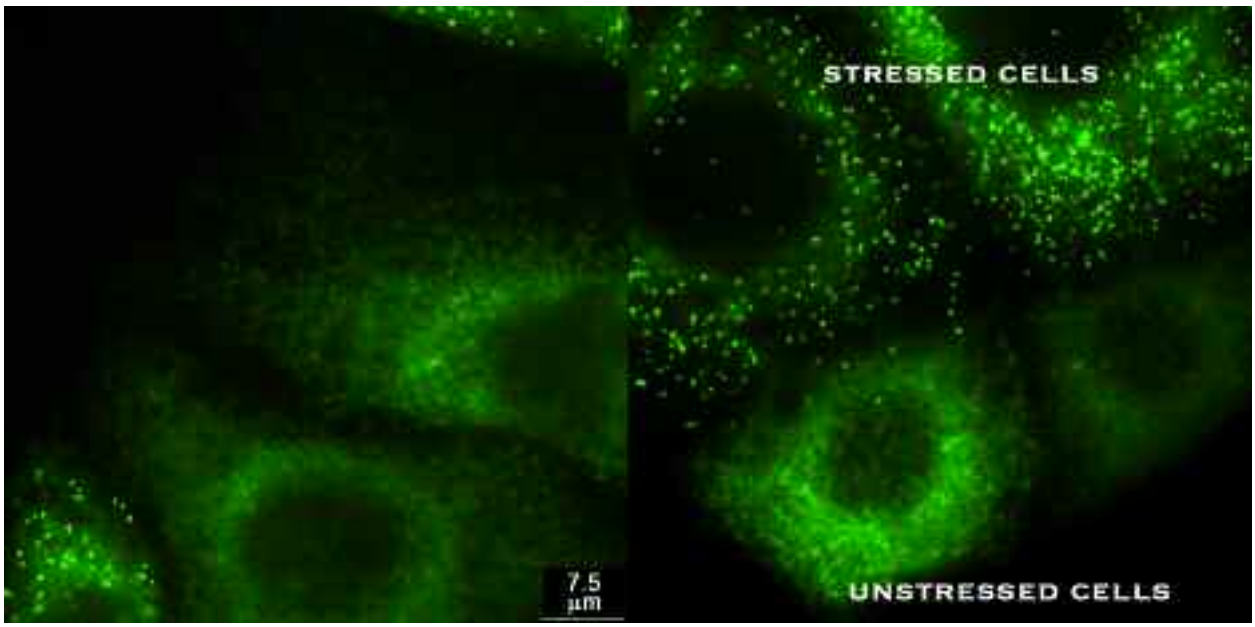
The Unit is also strongly committed to technological innovation and development of new applications of interest to scientists at the CNIC and beyond.

Ongoing research collaborations with all CNIC Departments and a number of external groups has led to the submission of several joint grant applications in 2012.

Our research collaborations involve membrane fluidity analysis by multiphoton laurdan and confocal di-4-ANEPPS imaging, and methods for measuring atheromic burden in tissues from 3D images. In collaboration with the Advanced Imaging Unit, we have established multiphoton approaches for tracking novel nanoscale carriers, which are under development for combined magnetic resonance and fluorescence imaging and therapy.

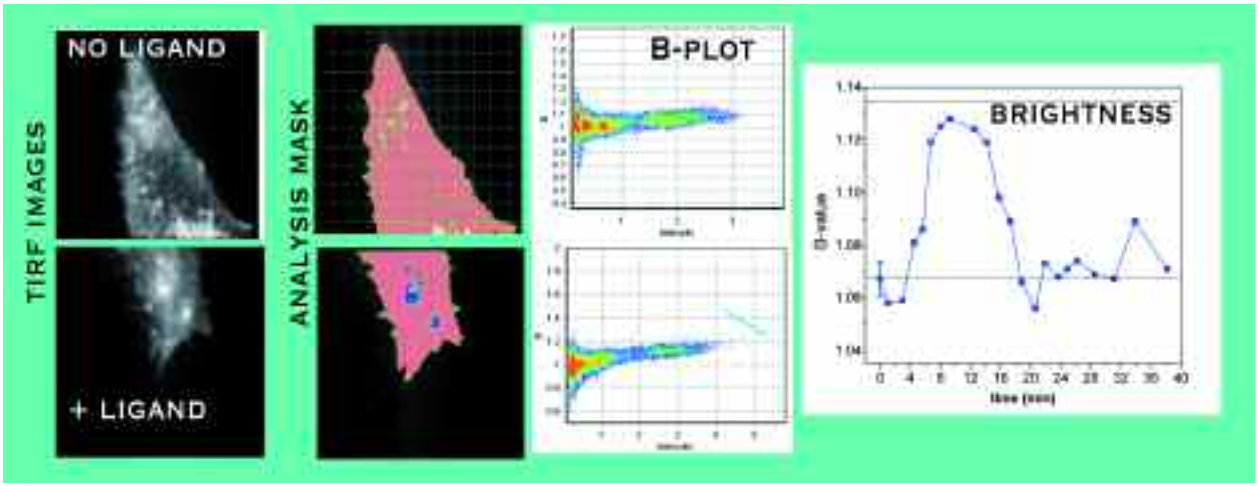
Internal Unit activities have focused on the full development of TIRF microscopy for combined multi-color and Number & Brightness imaging. This unique approach is suitable for the analysis of protein clusters and molecular binding kinetics in live cells, at the single molecule level, and without the need for super-resolution equipment.

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 Master Program) through the provision of theoretical and practical sessions.



Cell stress kinetics tracked by the clustering of a stress response protein in the endoplasmic reticulum. TIRF images at 150 nm depth.

Technical Units



Kinetics of the dimerization of FGFR1 receptor after FGF2 stimulation followed by TIRF-Number of Molecules and Brightness analysis at a depth of 150 nm.

Selected Publications

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, Sánchez S, Sotomayor CP. **Differential dynamic and structural behavior of lipid-cholesterol domains in model membranes.** *PLoS One* (2012) 7: e40254.

Sánchez SA, Tricerri MA, Gratton E. **Laurdan generalized polarization fluctuations measures membrane packing micro-heterogeneity in vivo.** *Proc Natl Acad Sci USA* (2012) 109: 7314-9.

Montecinos-Franjola F, Ross JA, Sánchez SA, Brunet JE, Lagos R, Jameson DM, Monasterio O. **Studies on the dissociation and urea-induced unfolding of FtsZ support the dimer nucleus polymerization mechanism.** *Biophys J* (2012) 102: 2176-85.

Hellriegel C, Caiolfa VR, Corti V, Sidenius N, Zamai M. **Number and brightness image analysis reveals ATF-induced dimerization kinetics of uPAR in the cell membrane.** *FASEB J* (2011) 25: 2883-97.

Technical Units

Transgenesis

Head of Unit: Luis-Miguel Criado Rodríguez
Support Scientist: José Mª Fernández
Technician: David Esteban Martínez

Research Interest

The Transgenesis Unit provides a range of services for the production of genetically-modified mice—known as transgenic mice—to serve the needs of the CNIC research groups. The interest is twofold: to understand how genomic activity translates into the complexity of a whole organism, and to generate mouse models of human cardiovascular disease.

Transgenic mice are produced in the Unit by the established methodologies of microinjection of DNA in solution into zygote pronuclei (pronuclear microinjection) or of recombinant lentiviruses beneath the zygote zona pellucida (subzonal or perivitelline microinjection). Chimeric mice for the generation of knockout and knockin mice are produced by a variety of techniques, but mainly by microinjection of genetically-modified mouse embryonic stem cells into eight-cell embryos or blastocysts. Other key services and techniques include rederivation of mouse and rat strains by embryo transfer, cryopreservation of mouse strains (frozen embryos or sperm), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI).

In addition to its routine work, the Unit collaborates with several CNIC groups on specific aspects of their research programs.

As in previous years, an important activity of the Unit in 2012 was the rederivation of mouse strains, and a total of 118 new mouse strains were rederived to the specific pathogen free area of the Comparative Medicine Unit, bringing the total number of rederived mouse strains at the Center to 349.

Zeiss AxioObserver-D1optical inverted microscope and motorized micromanipulators used for the production of genetically-modified mice.

Microinjection plate used for injection of mouse embryonic stem cells (mESC) into 8-cell and blastocyst mouse embryos.

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.

Technical Units

Genomics

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

Research Interest

The Genomics Unit provides cutting-edge genomic technologies to the scientific community at the CNIC and beyond, as well as expert assistance with experimental design.

With the advent of high throughput sequencing (next-generation sequencing, NGS) as an important technology in modern biomedicine, the Unit now provides massively parallel NGS on the Illumina Genome Analyzer IIx. The Genomics Unit's NGS services include gene expression and alternative splicing (RNA-Seq), low input RNA Seq (RNA Seq starting from minute amounts of RNA), protein-nucleic acid association profiling (ChIP-Seq), small RNA discovery (small RNA-Seq) and PCR Seq. For each sequencing project the Unit's tasks include project consultation, sample quality check, sample library preparation and data generation.

The team has recently developed AG-NGS, an informatics application that allows the automation of Illumina-NGS library preparation using an open liquid handling platform. By automating this time-consuming process, the Unit has considerably increased the throughput of NGS library preparation, avoiding the bottleneck created by the increasing number of samples that can be included in a single sequencing run and, additionally, reducing the risk of human error during this step. The Unit continues to offer microarray analysis services using Agilent and Affymetrix microarray platforms, the world's leading DNA chip technologies. Microarray applications include whole-genome differential gene expression analysis (including at the exon level using Exon arrays), microRNA expression analysis, and CGH arrays. 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.

Technical Units

NGS reads distribution within the genome

Major Grants

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

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.

Estrada JC, Albo C, Benguría A, Dopazo A, López-Romero P, Carrera-Quintanar L, Roche E, Clemente EP, Enríquez Domínguez JA, Bernad A, Samper E. **Culture of human mesenchymal stem cells at low oxygen tension improves growth and genetic stability by activating glycolysis.** *Cell Death Differ* (2012) 19: 743-55.

Vivas Y, Martínez-García C, Izquierdo A, Garcia-Garcia F, Callejas S, Velasco I, Campbell M, Ros M, Dopazo A, Dopazo J, Vidal-Puig A, Medina-Gomez G. E**arly peroxisome proliferator-activated receptor gamma regulated genes involved in expansion of pancreatic beta cell mass.** *BMC Med Genom* (2011) 4: 86.

Martin Y, Dopazo A, Hernandez-Chico C. **Progress and challenges in developing a molecular diagnostic test for neurofibromatosis type 1.** *Expert Rev Mol Diagn* (2011) 11: 671-3.

Technical Units

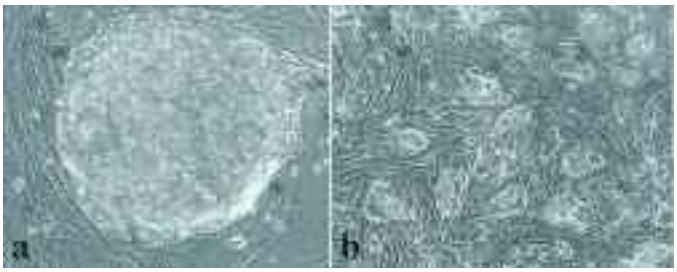
Pluripotent cell technology

Head of Service: Giovanna Giovinazzo
Support Scientist: Francisco Gutierrez
Technicians: Maria Angeles Sanguino
Elisa Santos

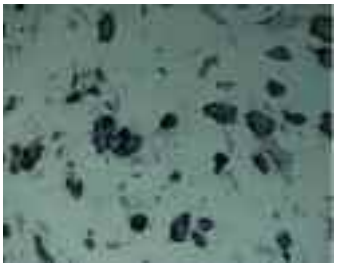
Research Interest

The Pluripotent Cell Technology Service (PCTS) provides centralized support in the culture and manipulation of mouse and human pluripotent stem cells. In order to provide CNIC researchers with a suitable work area, the facility personnel supervise two culture rooms, each devoted entirely either to human or to mouse stem cells (mESCs). The broad range of support services offered includes expert advice and training in the maintenance and differentiation of stem cells and the provision of validated reagents. One of the core functions of the Service is to facilitate the generation of genetically-modified mice through homologous recombination in mouse embryonic stem cells (mESCs). Our staff takes charge of all the key steps of the gene targeting protocol: electroporation of the targeting vector, selection, karyotyping, culture, and the preparation of cells for appropriate targeting and screening strategies. The systems developed in the unit achieve efficient transmission of targeted mESCs to the germline, and more than 20 new mutant mice are already available at the Center.

In 2012, we continued our program of protocol development for the derivation of mESCs from mutant mice and we provided support in differentiation to the cardiac lineage. We have also applied our specialist expertise in pluripotent stem-cell manipulation to the fine-tuning of protocols for inducing pig pluripotent stem cells.

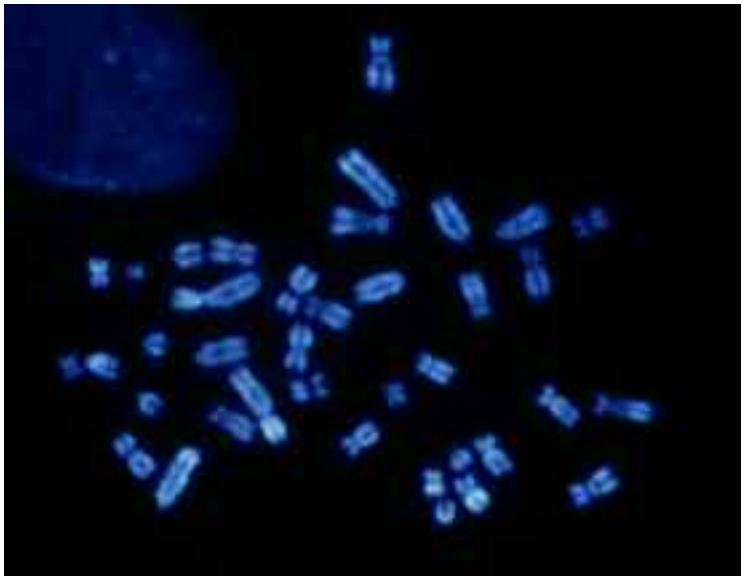


Pig induced pluripotent cells derived from primary fibroblasts. a) Colony ready for picking. b) A colony during its expansion.



Alkaline phosphatase staining of pig reprogrammed somatic cells.

Technical Units



Metaphase spread of pig induced pluripotent stem cells. Chromosomes are DAPI counterstained

Major Grants

- Ministerio de Economía y Competitividad. FIS (CTA0801)

Selected Publications

Casanova JC, Uribe V, Badia-Careaga C, Giovinazzo G, Torres M, Sanz-Ezquerro JJ. **Apical ectodermal ridge morphogenesis in limb development is controlled by Arid3b-mediated regulation of cell movements.** *Development* (2011) 138: 1195-205.

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.

Technical Units

Proteomics

Head of Unit: Juan Antonio López
Support Scientists: Enrique Calvo, Emilio Camafeita
Technician: Juan Carlos Silla

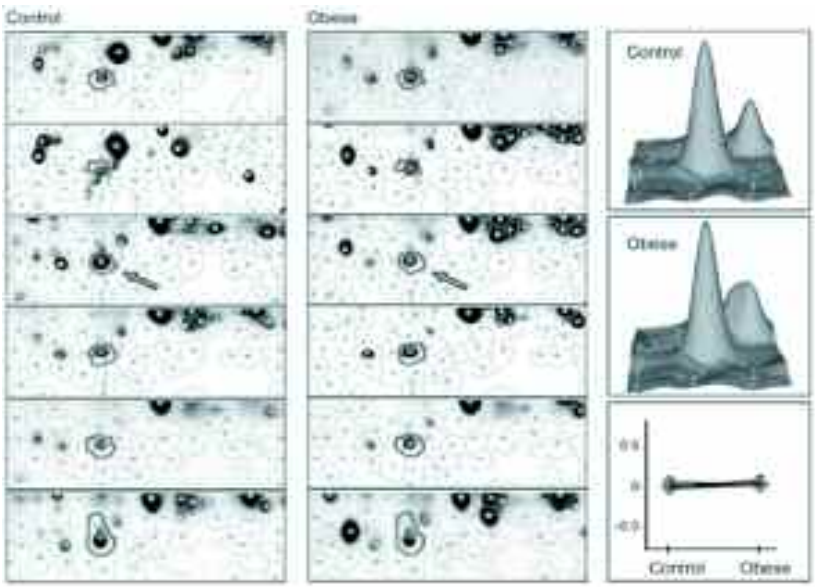
Research Interest

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 2012 substantial progress was made in sample fractionation and enrichment, together with the deployment of the latest state-of-the-art mass spectrometers.

Continuous improvements are being made in the separation and quantitative analysis of protein expression 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.

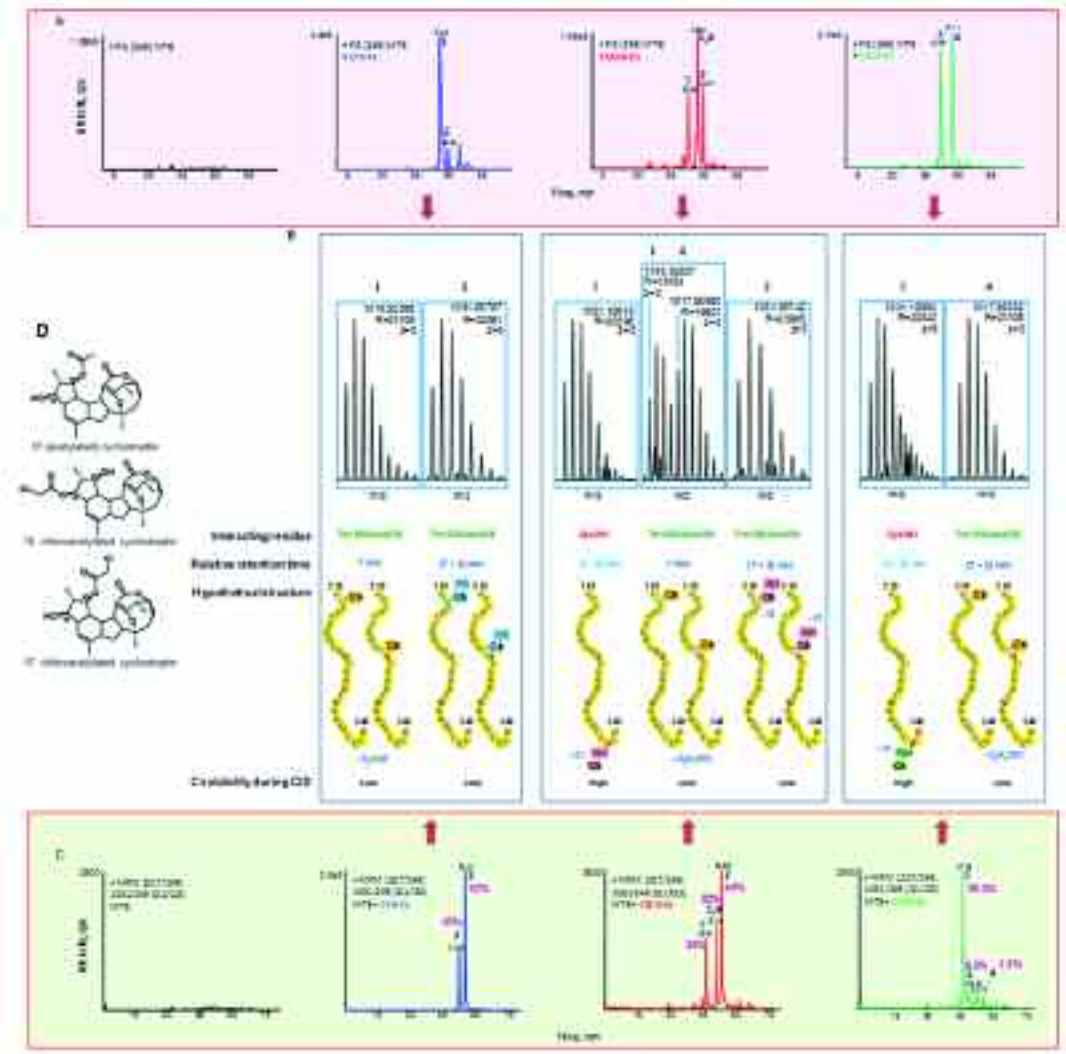
These approaches make use of shotgun and targeted proteomic analyses. By using high-throughput tandem mass spectrometry methods for global proteome profiling, we are increasing the analytical sensitivity to the level where it can reliably quantify and detect low-abundance proteins in complex biological specimens, for example a biopsy or cell extract. For validation purposes and targeted analysis, we use directed approaches in which specific precursor/product ion transitions are selectively monitored (selected reaction monitoring; SRM) to improve overall detection sensitivity, reliability, and quantification of specific proteins. Protein quantitation using mass spectrometry-based techniques, including label-free, stable isotope labeling (^{18}O and iTRAQ), and SRM approaches, allows us to analyze hundreds of proteins in a single experiment. This year we have set up the latest Thermo Orbitrap Elite and Thermo QExactive mass spectrometers for ultra-deep proteome analysis. Together with the fine tuning of these spectrometers, new acquisition modes are under development to increase the coverage and number of identified/quantified peptides and proteins in proteomic analysis.

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.



Proteins identified by 2D-DIGE and MS showing sustained expression in omental adipose tissue from non-obese and obese human subjects. *Protein extracts from omental fat of obese and non-obese subjects were analyzed by 2D-DIGE. Panels show zoomed images of 2D-DIGE gels centered on a selected protein (circled) in all subjects; 3D-views of selected spots are shown (arrow), together with graphical presentation of their standardized abundance (log). Modified from Perez-Perez et al.,* J Proteomics *(2012) 75: 783-95.*

Technical Units



MS analysis of cyclostreptin-derivatives (Cs) binding to microtubules (MTB). *(A) Total ion chromatogram (TIC) of a precursor ion scanning (PIS) experiment using the diagnostic fragment at m/z 249 Da from control or Cs-derivatives-treated MTB, digested with trypsin. Numbers 1-4 correspond to the identified sequences of MTB-derived peptides. (B) High-resolution analysis of the corresponding peptides. (C) To increase the sensitivity and the quantifiability of these data, we performed selected reaction monitoring (SRM) experiments by setting Q1 at the two masses of interest, and the diagnostic mass at m/z 249 in Q3. Results from these experiments show the percentage of each species in the sample, confirming the results previously obtained by PIS. Modified from Calvo et al.,* Biochemistry *(2012) 51: 329-41*

Selected Publications

Field JJ, Pera B, Calvo E, Canales A, Zurwerra D, Trigili C, Rodriguez-Salarichs J, Matesanz R, Kanakkanthara A, Wakefield SJ, Singh AJ, Jimenez-Barbero J, Northcote P, Miller JH, Lopez JA, Hamel E, Barasoain I, Altmann KH, Diaz JF. **Zampanolide, a potent new microtubule-stabilizing agent, covalently reacts with the taxane luminal site in tubulin alpha,beta-heterodimers and microtubules.** *Chem Biol* (2012) 19: 686-98.

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

de la Cuesta F, Barderas MG, Calvo E, Zubiri I, Maroto AS, Darde VM, Martin-Rojas T, Gil-Dones F, Posada M, Tejerina T, Lopez JA, Vivanco F, Alvarez-Llamas G. **Secretome analysis of atherosclerotic and non-atherosclerotic arteries reveals dynamic extracellular remodeling during pathogenesis.** *J Proteomics* (2012) 17: 2960-71.

Perez-Perez R, Garcia-Santos E, Ortega-Delgado FJ, Lopez JA, Camafeita E, Ricart W, Fernandez-Real JM, Peral B. **Attenuated metabolism is a hallmark of obesity as revealed by comparative proteomic analysis of human omental adipose tissue.** *J Proteomics* (2012) 75: 783-95.

Calvo E, Barasoain I, Matesanz R, Pera B, Camafeita E, Pineda O, Hamel E, Vanderwal CD, Andreu JM, Lopez JA, Diaz JF. **Cyclostreptin derivatives specifically target cellular tubulin and further map the Paclitaxel site.** *Biochemistry* (2012) 51: 329-41.

Technical Units

Bioinformatics

Head of Laboratory: Fernando Martínez
Support Scientists: Fátima Sánchez Cabo
Carlos Torroja

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 enhance their research.

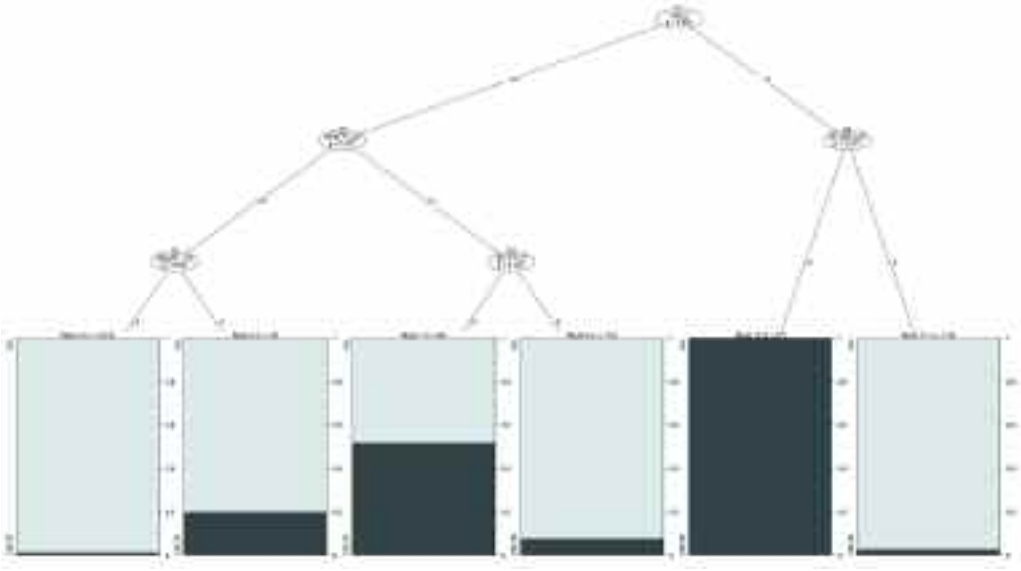
The Unit focuses on the analysis and interpretation of high-throughput biological data from CNIC research projects, with special emphasis on next-generation sequencing data. One of the Unit's main aims is to develop and implement analysis pipelines using state-of-the-art algorithms specific for each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

Other aims are to locally implement genome-related software (for example, genomics browsers such as GBrowse) and the most widely-used bioinformatics tools (Galaxy, Alexa-SEQ, etc.) and to generate local mirrors of public genomic databases (Ensembl, UCSC, NCBI, BioMart) for selected genomes (human, mouse and zebrafish).

The Unit also provides customized advice and training to CNIC researchers in the analysis and interpretation of their experimental data.

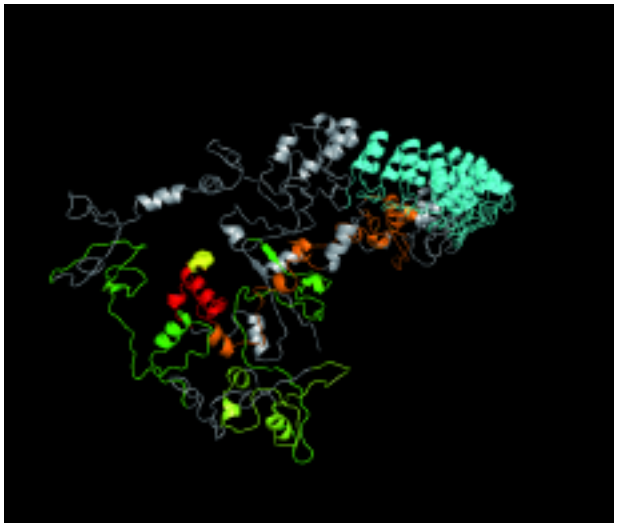
Services

- Help in experimental design for high-throughput experiments
- Quality control, preprocessing, data management and statistical analysis for microarray/next-generation sequencing (NGS) and other high-throughput technologies.
- Ad-hoc mathematical models for high-throughput data to enable systems biology
- Functional analysis using Ingenuity Pathway Analysis and Open Source Software
- Sequence analysis
- Genome data-mining using genome browsers (ENSEMBL, UCSC)
- Support in writing bioinformatics and biostatistics texts.

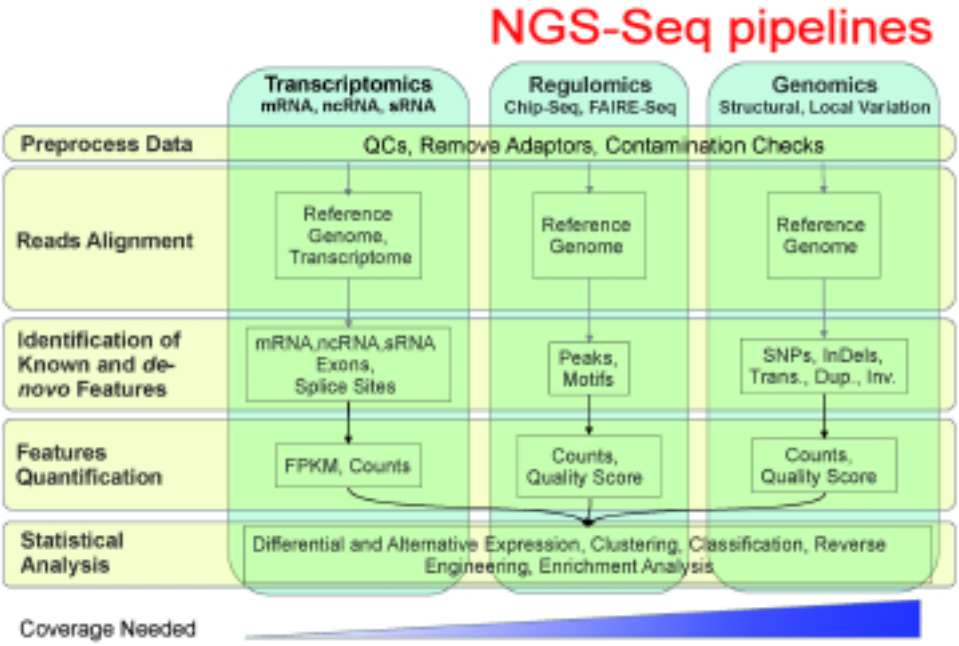


Decision tree to classify alternative splicing events based on the sequence motifs found in the exons and in the upstream and downstream adjacent intronic regions.

Technical Units



In silico *model of the Val943Phe Mutation in human* MIB1 *monomer. Color-coding of MIB1 domains: light green, Mib-Herc2 domains; olive green, ZZ zinc finger; dark green Mib repeats; blue, ankyrin repeats; orange, ring fingers; red, coiled-coil domain (with the surface of the aromatic ring of the F943 residue in yellow).*



Next-generation sequencing analysis pipelines implemented by the Bioinformatics Unit. All pipelines have essentially the same structure: preprocess data and quality checks; alignment of reads to the corresponding reference; detection of known and new features; quantification of features and statistical analysis

Selected Publications

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.

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.

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 Y, Pizarro G, Ibañez 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* (accepted).

Castell-Auví A, Cedó L, Movassat J, Portha B, Sánchez-Cabo F, Pallarès V, Blay M, Pinent M, Ardevol A. **Procyanidins modulate microRNA expression in pancreatic islets.** *J Agric Food Chem* (accepted).

Villar D, Ortiz-Barahona A, Gómez-Maldonado L, Pescador N, Sánchez-Cabo F, Hackl H, Rodriguez BA, Trajanoski Z, Dopazo A, Huang TH, Yan PS, Del Peso L. **Cooperativity of stress-responsive transcription factors in core hypoxia-inducible factor binding regions.** *PLoS One* (2012) 7: e45708.

Technical Units

Cellomics

Head of Unit: María Montoya

Support Scientists: Jose Manuel Ligos
Hind Azegrouz
Gopal Karemore

Technicians: Raquel Nieto
Mariano Vitón
Mª Montserrat Arroyo
Ignacio Cotillo

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.

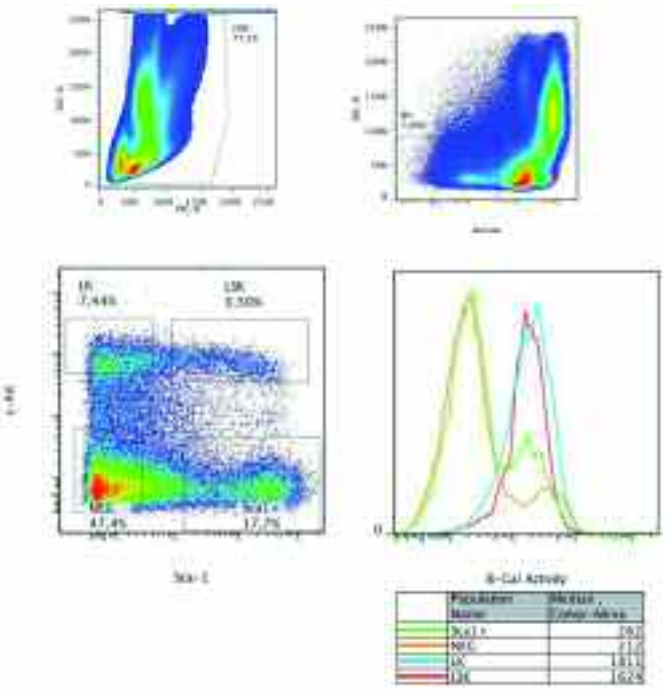
The Unit assists researchers in experimental design and data interpretation for flow cytometry experiments, and provides the necessary technical expertise in the manipulation of equipment and software, which include

- Three latest generation digital analytical flow cytometers: two FACSCanto II machines and one LSR Fortessa (Becton Dickinson).
- Two high-speed flow sorters: A MoFlo (Beckman Coulter) and a custom-made FACSAria II (Becton Dickinson).
- Cytometry software (Modfit and FlowJo).

HCS services include the design, development (miniaturization, automation, analysis) and performance of siRNA library screening. HCS resources include

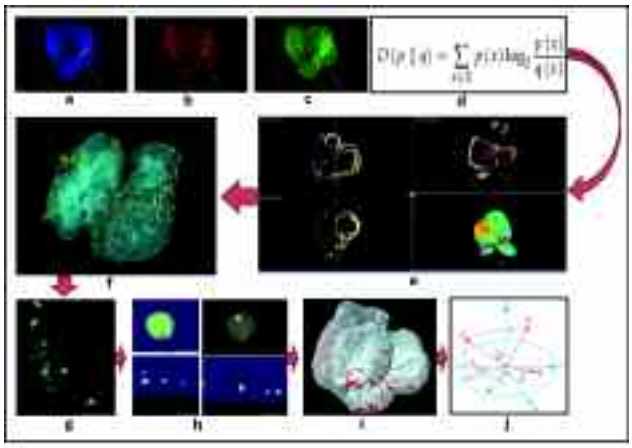
- A liquid handling workstation connected to a cell culture incubator with 110 plate throughput and a carousel handling 220 microplates (Freedom EVO, Tecan).
- An automated confocal microscope for microplate reading equipped with an automated plate feeder with a 14-position plate shelf (Opera, Perkin Elmer).
- Whole genome human and mouse siRNA libraries (4 individual siRNA-oligos per gene; Thermo Scientific).

The Image Analysis Unit (IAU) provides analysis solutions for image-based scientific applications by developing computational techiniques that extract information from biological images. The Unit is equipped with dedicated image analysis software packages (Acapella, Definiens, MatLab). The training activity includes the organization of the image cytometry workshop: microscopy image-based cell and subcellular structure identification and quantitation. The Unit also conducts research into the regulation of membrane trafficking during cell migration using HCS and quantitative image analysis tools.

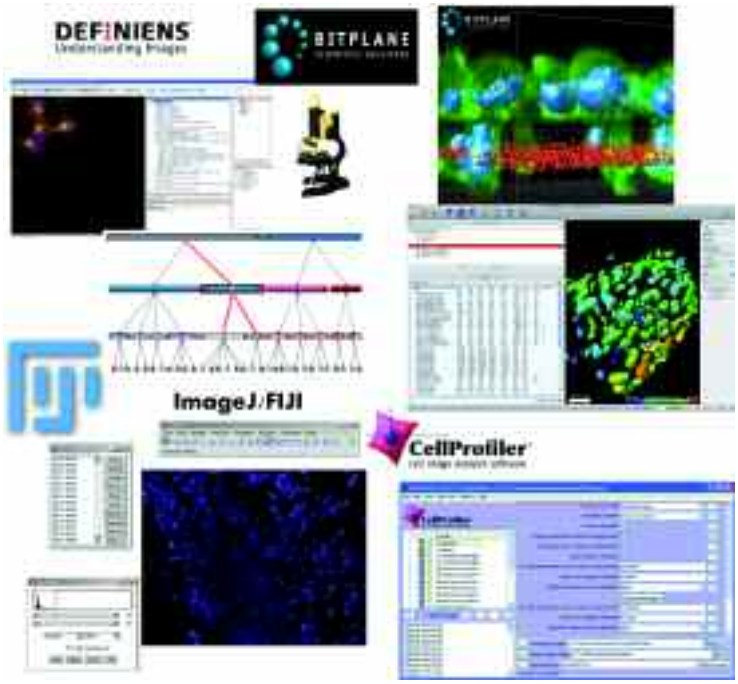


Detection of β-Gal activity in bone marrow cell subpopulations by multicolor flow cytometry. *Bone marrow cells were labeled with the β-galactosidase substrate C12-FDG (Life Technologies) and stained with antibodies to detect hematopoietc stem cells (Lineage-/Sca-1+/c-Kit+).*

Technical Units



3D visualization of heart morphogenesis to quantify the mitotic spindle orientation using computational geometry and shape modeling in image analysis. *Mouse embryonic heart stained for (a) nuclei (DAPI), (b) phospho histone, and (c) gamma-tubulin. (d) Kullback–Leibler divergence metric used for registering (a), (b), and (c) onto a reference heart. (e) Snap shot registration of hearts by both Landmark-based and Intensity-based registration using AMIRA software. (f) Iso-surface visualization of a registered volume. (g-h) Gamma-tubulin segmentation confined by the phospho-histone channel using Definiens software. (i) Vector field computing (red arrows) representing the orientation of the mitosis axis. (j) Vector field quantification in Euler's angle domain using the MATLAB programming environment.*



Images from the cytometry course organized by the image analysis group on microscopy image-based cell and subcellular structure identification and quantification.

Major Grants

- Ministerio de Economía y Competitividad. FIS (PS09/01028)

Selected Publications

Echarri A, Muriel O, Pavon DM, Azegrouz H, Escolar F, Terron MC, Sanchez-Cabo F, Mart›nez 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.

Karemore G, Keller B, Huan O, Tchou J, Nielsen M, Conant E, Kontos D. **Mammographic parenchymal texture analysis for estrogen-receptor subtype specific breast cancer risk estimation.** *In* Maidment ADA, Bakic PR, Gavenonis S (Eds) *IWDM 2012. LNCS* vol 7361: 596-603. Springer.

Technical Units

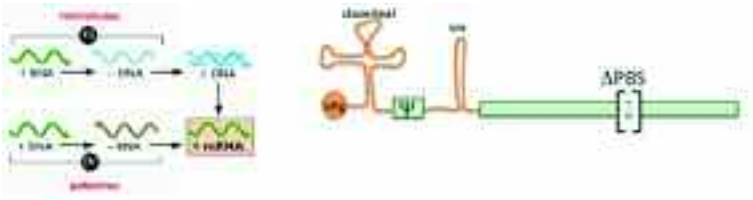
Viral vectors

Head of Service: Juan Carlos Ramírez
Support Scientist: Raúl Torres
Technician: Aída García
Visiting Scientist: Catarina Reis (CNIO)

Research Interest

The Viral Vector facility is dedicated to providing high-quality recombinant viruses (lentivirus, adenovirus and adeno-associated virus) for preclinical studies at the CNIC and beyond. The facility's capabilities expanded in 2012 to complete a collection of more than 80 HIV-derived lentiviral backbones containing promoter, polycistronic and selectable/fluorescent markers. Adeno-associated virus (AAV) derived vectors are currently produced and titrated in accordance with widely accepted gold-standard qPCR procedures. Of particular interest is the availability of backbones containing polycistronic expression cassettes that use the CHYSEL Picornaviridae 2A strategy and are driven by a cardiac-specific promoter (minimal TnT), and that can be serotyped with preferentially tropic capsids (AAV2, AAV8 or AAV9). This allows specific and efficient cardiac transcriptional and transductional targeting both in vivo and in vitro. Large-scale production using Hyperflask™ (Corning) simplifies the method for producing iodixanol gradient-purified stocks at the high-titer (10^{12} -10^{14} v.g./ml) required for use in research with AAVs in large animal models.

Our own research program is aimed at developing novel strategies for gene transfer using replicative viral vectors based on mRNA viruses with minimal interference in the genome.



Left: *The genome replication strategies of Picornaviridae (poliovirus) and Retroviridae (retroviruses). Note that poliovirus does not require any DNA intermediate, and that both genomes are based on RNA+.* Right: *The artificial genome that we have generated to assess packaging capabilities in retroviral capsids and further replication under poliovirus signals. Structured-RNA regions from poliovirus are indicated as cre and cloverleaf and VPg represents the primase. Retroviral packaging sequence (psi) and deleted primer binding site (PBS) are also marked.*

Major Grants

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

Selected Publications

Lonardo E, Hermann PC, Mueller MT, Huber S, Balic A, Miranda-Lorenzo I, Zagorac S, Alcala S, Rodriguez-Arabaolaza I, Ramirez JC, Torres R, Garcia E, Hidalgo M, Cebrián DA, Heuchel R, Löhr M, Berger F, Bartenstein P, Aicher A, Heeschen C. **Nodal/Activin signaling drives self-renewal and tumorigenicity of pancreatic cancer stem cells and provides a target for combined drug therapy.** *Cell Stem Cell* (2011) 9: 433-46.

Torres R, García A, Ramirez JC. **Non-integrative lentivirus drives high-frequency cre-mediated cassette exchange in human cells.** *PLoS ONE* (2011) 6: e19794.

Alonso-Ferrero ME, Valeri A, Yañez R, Navarro S, Garin MI, Ramirez JC, Bueren JA, Segovia JC. **Immunoresponse against the transgene limits hematopoietic engraftment of mice transplanted in utero with virally transduced fetal liver.** *Gene Therapy* (2011) 18: 469-78.

Leandro-García LJ, Leskelä S, Inglada-Pérez L, Landa I, de Cubas AA, Maliszewska A, Comino-Méndez I, Letón R, Gómez-Graña A, Torres R, Ramírez JC, Alvarez S, Rivera J, Martínez C, Lozano ML, Cascón A, Robledo M, Rodríguez-Antona C. **Hematologic β-Tubulin VI Isoform Exhibits Genetic Variability That Influences Paclitaxel Toxicity.** *Cancer Res* (2012) 72: 4744-52.

Technical Units

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 ani mals. Housing and husbandry conditions conform to European and national regulations for the use of animals for experimental and other scientific purposes, including the provision of mandatory training to resear chers involved in animal experiments.

- The Pathology Core (PC), run by an on-site laboratory animal pathologist. The PC has established collaborations with the Comparative Pathology Laboratory of the Weill Cornell Medical College and the Memorial Sloan-Kettering Center in New York, and with the Phenotyping Core at the Department of Molecular and Comparative Pathobiology, Johns Hopkins Hospital in Baltimore.

- The Phenotyping Core (PhC), which provides a comprehensive cardiovascular phenotype evaluation service, includes a clinical pathology service, which provides expertise in hematology and clinical bioche mistry in a variety of species.

- 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 the head of the Comparative Medicine Unit, a diplomate of the European College of Laboratory Animal Medicine, and provides training for resident veterinarians through a program in Laboratory Animal Medicine.

- The Quality Control Core (QCC) is run by a senior micro biologist and monitors the health and the genetic status of the animals on site. The QCC produces a FELASA report every quarter.

The PC and PhC services combine in vivo evaluation, imaging strategies, and clinical and anatomic pathology to characterize complex phenotypes—including multisystemic phenotypes or syndromes—for the development and validation of genetically engineered mouse models.

The Comparative Medicine Unit has gained ISO 9001 accreditation for all the five core work areas.

7

Appendix

Publications
Training Programs and Courses
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Publications 2012

During 2012 CNIC scientists published 168 articles, 86.31% of them in journals belonging to the first quartile of their category (according to the most recent JCR listing, for 2011). Of the 168 published articles, 70% related to studies done in collaboration with foreign institutions, 24% were collaborations with national institutions, and 6% were entirely by CNIC researchers.

Eighty-five of the published articles were signed by a CNIC scientist as a main author, and the average impact factor (IF) for these articles was 8.017. These publications are listed below, alphabetically by first author.

Aguirre E, Lopez-Bernardo E, Cadenas S.
Functional evidence for nitric oxide production by skeletal-muscle mitochondria from lipopolysaccharide-treated mice.
Mitochondrion. (2012) 12: 126-31.
IF: 3.615

Andres V, Pello OM, Silvestre-Roig C.
Macrophage proliferation and apoptosis in atherosclerosis.
Curr Opin Lipidol. (2012) 23: 429-38.
IF: 6.086

Arbab-Zadeh A, Nakano M, Virmani R, Fuster V.
Acute coronary events.
Circulation. (2012) 125: 1147-56.
IF: 14.739

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.
IF: 5.359

Balsa E, Marco R, Perales-Clemente E, Szklarczyk R, Calvo E, Landazuri MO, Enriquez JA.
NDUFA4 is a subunit of complex IV of the mammalian electron transport chain.
Cell Metab. (2012) 16: 378-86.
IF: 13.668

Bansilal S, Farkouh ME, Hueb W, Ogdie M, Dangas G, Lansky AJ, Cohen DJ, Magnuson EA, Ramanathan K, Tanguay JF, Muratov V, Sleeper LA, Domanski M, Bertrand ME, Fuster V.
The Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial: Clinical and angiographic profile at study entry.
Am Heart J. (2012) 164: 591-9.
IF: 4.651

Bernal A, Fernandez M, Perez LM, San Martin N, Galvez BG.
Method for obtaining committed adult mesenchymal precursors from skin and lung tissue.
PLoS One. (2012) 7: e53215.
IF: 4.092

Bernal A, San Martin N, Fernandez M, Covarello D, Molla F, Soldo A, Latini R, Cossu G, Galvez BG.
L-selectin and SDF-1 enhance the migration of mouse and human cardiac mesoangioblasts.
Cell Death Differ. (2012) 19: 345-55.
IF: 8.849

Calvo E, Barasoain I, Matesanz R, Pera B, Camafeita E, Pineda O, Hamel E, Vanderwal CD, Andreu JM, Lopez JA, Diaz JF.
Cyclostreptin derivatives specifically target cellular tubulin and further map the Paclitaxel site.
Biochemistry. (2012) 51: 329-41.
IF: 3.422

Calvo E, Dediego ML, Garcia P, Lopez JA, Perez-Brena P, Falcon A.
Severe acute respiratory syndrome coronavirus accessory proteins 6 and 9b interact in vivo.
Virus Res. (2012) 169: 282-8.
IF: 2.941

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Publications 2012

Carrero-Gonzalez L, Kaulisch T, Ruiz-Cabello J, Perez-Sanchez JM, Peces-Barba G, Stiller D, Rodriguez I.
Apparent diffusion coefficient of hyperpolarized (3)He with minimal influence of the residual gas in small animals.
NMR Biomed. (2012) 25: 1026-32.
IF: 3.214

Casanova JC, Badia-Careaga C, Uribe V, Sanz-Ezquerro JJ.
Bambi and sp8 expression mark digit tips and their absence shows that chick wing digits 2 and 3 are truncated.
PLoS One. (2012) 7: e52781.
IF: 4.092

Castellano JM, Kovacic JC, Sanz J, Fuster V.
Are we ignoring the dilated thoracic aorta?
Ann N Y Acad Sci. (2012) 1254: 164-74.
IF: 3.155

Chang Y, Ryu S, Zhang Y, Son HJ, Kim JY, Cho J, Guallar E.
A cohort study of serum bilirubin levels and incident non-alcoholic Fatty liver disease in middle aged korean workers.
PLoS One. (2012) 7: e37241.
IF: 4.092

Chinitz JS, Castellano JM, Kovacic JC, Fuster V.
Atrial fibrillation, stroke, and quality of life.
Ann N Y Acad Sci. (2012) 1254: 140-50.
IF: 3.155

Chinitz JS, Halperin JL, Reddy VY, Fuster V.
Rate or rhythm control for atrial fibrillation: update and controversies.
Am J Med. (2012) 125: 1049-56.
IF: 5.430

Corella D, Carrasco P, Sorli JV, Coltell O, Ortega-Azorin C, Guillen M, Gonzalez JI, Saiz C, Estruch R, Ordovas JM.
Education modulates the association of the FTO rs9939609 polymorphism with body mass index and obesity risk in the Mediterranean population.
Nutr Metab Cardiovasc Dis. (2012) 22: 651-8.
IF: 3.731

Corella D, Ordovas JM.
Interactions between dietary n-3 fatty acids and genetic variants and risk of disease.
Br J Nutr. (2012) 107 Suppl 2: S271-83.
IF: 3.013

de la Fuente H, Cibrian D, Sanchez-Madrid F.
Immunoregulatory molecules are master regulators of inflammation during the immune response.
FEBS Lett. (2012) 586: 2897-905.
IF: 3.538

de la Pompa JL, Epstein JA.
Coordinating tissue interactions: notch signaling in cardiac development and disease.
Dev Cell. (2012) 22: 244-54.
IF: 14.030

Echarri A, Del Pozo MA.
Caveolae.
Curr Biol. (2012) 22: R114-6.
IF: 9.647

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.
IF: 6.111

Estrada JC, Albo C, Benguria A, Dopazo A, Lopez-Romero P, Carrera-Quintanar L, Roche E, Clemente EP, Enriquez JA, Bernad A, Samper E.
Culture of human mesenchymal stem cells at low oxygen tension improves growth and genetic stability by activating glycolysis.
Cell Death Differ. (2012) 19: 743-55.
IF: 8.849

Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, 3rd, Bertrand M, Fuster V.
Strategies for multivessel revascularization in patients with diabetes.
N Engl J Med. (2012) 367: 2375-84.
IF: 53.298

Fayad ZA, Mani V, Fuster V.
The time has come for clinical cardiovascular trials with plaque characterization as an endpoint.
Eur Heart J. (2012) 33: 160-1
IF: 10.478

Fernandez-Friera L, Fuster V, Sanz J.
Characterization of a mediastinal thymic seminoma using cardiac magnetic resonance.
Rev Esp Cardiol. (2012) 65: 97.
IF: 2.530

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Publications 2012

Fernandez-Jimenez R, Lopez-Romero P, Suarez-Barrientos A, Garcia-Rubira JC, Fernandez-Ortiz A, Fuster V, Macaya C, Ibanez B.
Troponin release overestimates infarct size in presence of left ventricular hypertrophy.
J Am Coll Cardiol. (2012) 60: 640-1.
IF: 14.156

Field JJ, Pera B, Calvo E, Canales A, Zurwerra D, Trigili C, Rodriguez-Salarichs J, Matesanz R, Kanakkanthara A, Wakefield SJ, Singh AJ, Jimenez-Barbero J, Northcote P, Miller JH, Lopez JA, Hamel E, Barasoain I, Altmann KH, Diaz JF.
Zampanolide, a potent new microtubule-stabilizing agent, covalently reacts with the taxane luminal site in tubulin alpha, beta-heterodimers and microtubules.
Chem Biol. (2012) 19: 686-98.
IF: 5.829

Fuente HD, Perez-Gala S, Bonay P, Cruz-Adalia A, Cibrian D, Sanchez-Cuellar S, Dauden E, Fresno M, Garcia-Diez A, Sanchez-Madrid F.
Psoriasis in humans is associated with downregulation of galectins in dendritic cells.
J Pathol. (2012) 228: 193-203.
IF: 6.318

Fuster JJ, Molina-Sanchez P, Jovani D, Vinue A, Serrano M, Andres V.
Increased gene dosage of the Ink4/Arf locus does not attenuate atherosclerosis development in hypercholesterolaemic mice.
Atherosclerosis. (2012) 221: 98-105.
IF: 3.794

Fuster V.
An alarming threat to secondary prevention: low compliance (lifestyle) and poor adherence (drugs).
Rev Esp Cardiol. (2012) 65S2: 10-16.
IF: 2.530

Fuster V, Bhatt DL, Califf RM, Michelson AD, Sabatine MS, Angiolillo DJ, Bates ER, Cohen DJ, Coller BS, Furie B, Hulot JS, Mann KG, Mega JL, Musunuru K, O'Donnell CJ, Price MJ, Schneider DJ, Simon DI, Weitz JI, Williams MS, Hoots WK, Rosenberg YD, Hasan AA.
Guided antithrombotic therapy: current status and future research direction: report on a national heart, lung and blood institute working group.
Circulation. (2012) 126: 1645-62.
IF: 14.739

Fuster V, Chinitz JS.
Net clinical benefit of warfarin: extending the reach of antithrombotic therapy for atrial fibrillation.
Circulation. (2012) 125: 2285-7.
IF: 14.739

Fuster V, Torres M.
CNIC: achieving research excellence through collaboration.
Rev Esp Cardiol. (2012) 65: 511-6.
IF: 2.530

Garaulet M, Esteban Tardido A, Lee YC, Smith CE, Parnell LD, Ordovas JM.
SIRT1 and CLOCK 3111T>C combined genotype is associated with evening preference and weight loss resistance in a behavioral therapy treatment for obesity.
Int J Obes (Lond). (2012) 36: 1436-41.
IF: 4.691

Gomez-Gaviro MV, Lovell-Badge R, Fernandez-Aviles F, Lara-Pezzi E.
The vascular stem cell niche.
J Cardiovasc Transl Res. (2012) 5: 618-30.
IF: 2.611

Gonzalez-Rosa JM, Mercader N.
Cryoinjury as a myocardial infarction model for the study of cardiac regeneration in the zebrafish.
Nat Protoc. (2012) 7: 782-8.
IF: 9.924

Gonzalez-Rosa JM, Peralta M, Mercader N.
Pan-epicardial lineage tracing reveals that epicardium derived cells give rise to myofibroblasts and perivascular cells during zebrafish heart regeneration.
Dev Biol. (2012) 370: 173-86.
IF: 4.069

Gordon-Alonso M, Rocha-Perugini V, Alvarez S, Moreno-Gonzalo O, Ursa A, Lopez S, Izquierdo-Useros N, Martinez-Picado J, Munoz-Fernandez MA, Yanez-Mo M, Sanchez-Madrid F.
The PDZ-adaptor protein syntenin-1 regulates HIV-1 entry.
Mol Biol Cell. (2012) 23: 2253-63.
IF: 4.942

Gordon-Alonso M, Sala-Valdes M, Rocha-Perugini V, Perez-Hernandez D, Lopez-Martin S, Ursa A, Alvarez S, Kolesnikova TV, Vazquez J, Sanchez-Madrid F, Yanez-Mo M.
EWI-2 association with alpha-actinin regulates T cell immune synapses and HIV viral infection.
J Immunol. (2012) 189: 689-700.
IF: 5.788

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Publications 2012

Herranz B, Marquez S, Guijarro B, Aracil E, Aicart-Ramos C, Rodriguez-Crespo I, Rodriguez-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.
IF: 9.489

Herranz F, Schmidt-Weber CB, Shamji MH, Narkus A, Ruiz-Cabello J, Vilar R.
Superparamagnetic iron oxide nanoparticles conjugated to a grass pollen allergen and an optical probe.
Contrast Media Mol Imaging. (2012) 7: 435-9.
IF: 3.328

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.
IF: 7.396

Hidalgo I, Herrera-Merchan A, Ligos JM, Carramolino L, Nunez 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.
IF: 25.421

Ibanez B, Fuster V, Macaya C, Sanchez-Brunete V, Pizarro G, Lopez-Romero P, Mateos A, Jimenez-Borreguero J, Fernandez-Ortiz A, Sanz G, Fernandez-Friera L, Corral E, Barreiro MV, Ruiz-Mateos B, Goicolea J, Hernandez-Antolin R, Acebal C, Garcia-Rubira JC, Albarran A, Zamorano JL, Casado I, Valenciano J, Fernandez-Vazquez F, de la Torre JM, Perez de Prado A, Iglesias-Vazquez JA, Martinez-Tenorio P, Iniguez A.
Study design for the "effect of METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion" (METOCARD-CNIC): A randomized, controlled parallel-group, observer-blinded clinical trial of early pre-reperfusion metoprolol administration in ST-segment elevation myocardial infarction.
Am Heart J. (2012) 164: 473-480 e5.
IF: 4.651

Ibanez B, Giannarelli C, Cimmino G, Santos-Gallego CG, Alique M, Pinero A, Vilahur G, Fuster V, Badimon L, Badimon JJ.
Recombinant HDL(Milano) exerts greater anti-inflammatory and plaque stabilizing properties than HDL (wild-type).
Atherosclerosis. (2012) 220: 72-7.
IF: 3.794

Ibanez B, Suarez-Barrientos A, Lopez-Romero P.
Circadian variations of infarct size in STEM1.
Circ Res. (2012) 110: e22.
IF: 9.489

Iborra S, Izquierdo HM, Martinez-Lopez M, Blanco-Menendez N, Reis ESC, 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.
IF: 13.069

Izquierdo-Garcia JL, Peces-Barba G, Ruiz-Cabello J.
Influence of ambient air on NMR-based metabolomics of exhaled breath condensates.
Eur Respir J. (2012) 40: 1294-6.
IF: 5.895

Kovacic JC, Castellano JM, Fuster V.
The links between complex coronary disease, cerebrovascular disease, and degenerative brain disease.
Ann N Y Acad Sci. (2012) 1254: 99-105.
IF: 3.155

Kovacic JC, Castellano JM, Fuster V.
Cardiovascular defense challenges at the basic, clinical, and population levels.
Ann N Y Acad Sci. (2012) 1254: 1-6.
IF: 3.155

Kovacic JC, Fuster V.
Vascular calcification, diabetes, and cardiovascular disease: connecting the dots.
JACC Cardiovasc Imaging. (2012) 5: 367-9.
IF: 5.431

Kovacic JC, Fuster V.
Smoking gun theory: angiographically "normal" or "mild" coronary plaque as a cause of myocardial infarction.
Circulation. (2012) 126: 2918-20.
IF: 14.739

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: 1795-808.
IF: 14.739

Koziol A, Gonzalo P, Mota A, Pollan A, Lorenzo C, Colome 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.
IF: 5.712

Koziol A, Martin-Alonso M, Clemente C, Gonzalo P, Arroyo AG.
Site-specific cellular functions of MT1-MMP.
Eur J Cell Biol. (2012) 91: 889-95.
IF: 2.806

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Publications 2012

Laclaustra M, Ordonez B, Leon M, Andres EM, Cordero A, Pascual-Calleja I, Grima A, Luengo E, Alegria E, Pocovi M, Civeira F, Casasnovas-Lenguas JA.
Metabolic syndrome and coronary heart disease among spanish male workers: a case-control study of MESYAS.
Nutr Metab Cardiovasc Dis. (2012) 22: 510-6.
IF: 3.731

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.
IF: 4.937

Martin-Cofreces NB, Baixauli F, Lopez MJ, Gil D, Monjas A, Alarcon B, Sanchez-Madrid F.
End-binding protein 1 controls signal propagation from the T cell receptor.
EMBO J. (2012) 31: 4140-52.
IF: 9.205

Martinez-Acedo P, Nunez E, Sanchez-Gomez FJ, Moreno M, Ramos E, Izquierdo-Alvarez A, Miro-Casas E, Mesa R, Rodriguez P, Martinez-Ruiz A, Garcia-Dorado D, Lamas S, Vazquez J.
GELSILOX: a novel strategy for global analysis of the dynamic thiol redox proteome.
Mol Cell Proteomics. (2012) 11: 800-13.
IF: 7.398

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.
IF: 3.155

Menendez-Gutierrez MP, Roszer T, Ricote M.
Biology and therapeutic applications of peroxisome proliferator-activated receptors.
Curr Top Med Chem. (2012) 12: 548-84.
IF: 4.174

Menke A, Muntner P, Fernandez-Real JM, Guallar E.
The association of biomarkers of iron status with mortality in US adults.
Nutr Metab Cardiovasc Dis. (2012) 22: 734-40.
IF: 3.731

Mittelbrunn M, Sanchez-Madrid F.
Intercellular communication: diverse structures for exchange of genetic information.
Nat Rev Mol Cell Biol. (2012) 13: 328-35.
IF: 39.123

Moore LV, Diez Roux AV, Franco M.
Measuring availability of healthy foods: agreement between directly measured and self-reported data.
Am J Epidemiol. (2012) 175: 1037-44.
IF: 5.216

Narayan RL, Vaishnava P, Castellano JM, Fuster V.
Quantitative assessment of right ventricular function in pectus excavatum.
J Thorac Cardiovasc Surg. (2012) 143: e41-2.
IF: 3.406

Navarro-Lerida I, Sanchez-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.
IF: 9.205

Panse KD, Felkin LE, Lopez-Olaneta MM, Gomez-Salinero J, Villalba M, Munoz 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: 814-26.
IF: 2.611

Pello OM, Chevre R, Laoui D, De Juan A, Lolo F, Andres-Manzano MJ, Serrano M, Van Ginderachter JA, Andres V.
In vivo inhibition of c-MYC in myeloid cells impairs tumor-associated macrophage maturation and pro-tumoral activities.
PLoS One. (2012) 7: e45399.
IF: 4.092

Penalvo JL, Lopez-Romero P.
Urinary enterolignan concentrations are positively associated with serum HDL cholesterol and negatively associated with serum triglycerides in US adults.
J Nutr. (2012) 142: 751-6.
IF: 3.916

Perez-Duran P, Belver L, de Yebenes VG, Delgado P, Pisano DG, Ramiro AR.
UNG shapes the specificity of AID-induced somatic hypermutation.
J Exp Med. (2012) 209: 1379-89.
IF: 13.853

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Publications 2012

Ryu S, Chang Y, Zhang Y, Kim SG, Cho J, Son HJ, Shin H, Guallar E.
A cohort study of hyperuricemia in middle-aged South Korean men.
Am J Epidemiol. (2012) 175: 133-43.
IF: 5.216

Sala-Valdes M, Gordon-Alonso M, Tejera E, Ibanez A, Cabrero JR, Ursa A, Mittelbrunn M, Lozano F, Sanchez-Madrid F, Yanez-Mo M.
Association of syntenin-1 with M-RIP polarizes Rac-1 activation during chemotaxis and immune interactions.
J Cell Sci. (2012) 125: 1235-46.
IF: 6.111

Salvado MD, Alfranca A, Haeggstrom JZ, Redondo JM.
Prostanoids in tumor angiogenesis: therapeutic intervention beyond COX-2.
Trends Mol Med. (2012) 18: 233-43.
IF: 10.355

Sanchez SA, Tricerri MA, Gratton E.
Laurdan generalized polarization fluctuations measures membrane packing micro-heterogeneity in vivo.
Proc Natl Acad Sci U S A. (2012) 109: 7314-9.
IF: 9.681

Sancho D, Reis ESC.
Signaling by myeloid c-type lectin receptors in immunity and homeostasis.
Annu Rev Immunol. (2012) 30: 491-529.
IF: 52.761

Sanz J, Garcia-Alvarez A, Fernandez-Friera L, Nair A, Mirelis JG, Sawit ST, Pinney S, Fuster V.
Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study.
Heart. (2012) 98: 238-43.
IF: 4.223

Sanz-Rosa D, Garcia-Prieto J, Ibanez B.
The future: therapy of myocardial protection.
Ann N Y Acad Sci. (2012) 1254: 90-8.
IF: 3.155

Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, Fuster V.
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. (2012) 5: 681-9.
IF: 5.431

Stranges S, Guallar E.
Cardiovascular disease prevention in women: A rapidly evolving scenario.
Nutr Metab Cardiovasc Dis. (2012) 22: 1013-8.
IF: 3.731

Strippoli R, Benedicto I, Perez Lozano ML, Pellinen T, Sandoval P, Lopez-Cabrera M, Del Pozo MA.
Inhibition of transforming growth factor-activated kinase 1 (TAK1) blocks and reverses epithelial to mesenchymal transition of mesothelial cells.
PLoS One. (2012) 7: e31492.
IF: 4.092

Tellez-Plaza M, Navas-Acien A, Caldwell KL, Menke A, Muntner P, Guallar E.
Reduction in cadmium exposure in the United States population, 1988-2008: the contribution of declining smoking rates.
Environ Health Perspect. (2012) 120: 204-9.
IF: 7.036

Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E.
Cadmium exposure and all cause and cardiovascular mortality in the US general population.
Environ Health Perspect. (2012) 120: 1017-22.
IF: 7.036

Villa-Bellosta R.
On the role of the type III phosphate transporters in vascular calcification.
Bone. (2012) 51: 828.
IF: 4.023

Zaragoza C, Marquez S, Saura M.
Endothelial mechanosensors of shear stress as regulators of atherogenesis.
Curr Opin Lipidol. (2012) 23: 446-52.
IF: 6.086

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Publications 2012

The remaining 83 CNIC-affiliated articles for 2012 were produced through collaborative work carried out with other institutions, where the main or corresponding author was not from the CNIC. The average IF of these articles was 6.024.

Abhyankar LN, Jones MR, Guallar E, Navas-Acien A.
Arsenic exposure and hypertension: a systematic review.
Environ Health Perspect. (2012) 120: 494-500.
IF: 7.036

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.
IF: 4.092

Ahrens S, Zelenay S, Sancho D, Hanc P, Kjaer S, Feest C, Fletcher G, Durkin C, Postigo A, Skehel M, Batista F, Thompson B, Way M, Reis ESC, Schulz O.
F-Actin is an evolutionarily conserved damage-associated molecular pattern recognized by DNGR-1, a receptor for dead cells.
Immunity. (2012) 36: 635-45.
IF: 21.637

Alcolea S, Anton R, Camacho M, Soler M, Alfranca A, Aviles-Jurado FX, Redondo JM, Quer M, Leon X, Vila L.
Interaction between head and neck squamous cell carcinoma (HNSCC) cells and fibroblasts in the biosynthesis of PGE2.
J Lipid Res. (2012) 53: 630-42.
IF: 5.559

Ares-Carrasco S, Picatoste B, Camafeita E, Carrasco-Navarro S, Zubiri I, Ortiz A, Egido J, Lopez JA, Tunon J, Lorenzo O.
Proteome changes in the myocardium of experimental chronic diabetes and hypertension Role of PPARalpha in the associated hypertrophy.
J Proteomics. (2012) 75: 1816-29.
IF: 4.878

Arrebola-Moreno AL, Laclaustra M, Kaski JC.
Noninvasive assessment of endothelial function in clinical practice.
Rev Esp Cardiol. (2012) 65: 80-90.
IF: 2.530

Aslibekyan S, Goodarzi MO, Frazier-Wood AC, Yan X, Irvin MR, Kim E, Tiwari HK, Guo X, Straka RJ, Taylor KD, Tsai MY, Hopkins PN, Korenman SG, Borecki IB, Chen YD, Ordovas JM, Rotter JI, Arnett DK.
Variants identified in a GWAS meta-analysis for blood lipids are associated with the lipid response to fenofibrate.
PLoS One. (2012) 7: e48663.
IF: 4.092

Aslibekyan S, Kabagambe EK, Irvin MR, Straka RJ, Borecki IB, Tiwari HK, Tsai MY, Hopkins PN, Shen J, Lai CQ, Ordovas JM, Arnett DK.
A genome-wide association study of inflammatory biomarker changes in response to fenofibrate treatment in the genetics of lipid lowering drug and diet network.
Pharmacogenet Genomics. (2012) 22: 191-7.
IF: 3.485

Barquilla A, Saldivia M, Diaz R, Bart JM, Vidal I, Calvo E, Hall MN, Navarro M.
Third target of rapamycin complex negatively regulates development of quiescence in trypanosoma brucei.
Proc Natl Acad Sci U S A. (2012) 109: 14399-404.
IF: 9.681

Bucerius J, Mani V, Moncrieff C, Rudd JH, Machac J, Fuster V, Farkouh ME, Fayad ZA.
Impact of noninsulin-dependent type 2 diabetes on carotid wall (18)f-fluorodeoxyglucose positron emission tomography uptake.
J Am Coll Cardiol. (2012) 59: 2080-8.
IF: 14.156

Caballero P, Alonso R, Rosado P, Mata N, Fernandez-Friera L, Jimenez-Borreguero LJ, Badimon L, Mata P.
Detection of subclinical atherosclerosis in familial hypercholesterolemia using non-invasive imaging modalities.
Atherosclerosis. (2012) 222: 468-72.
IF: 3.794

Campbell KA, Lipinski MJ, Doran AC, Skaflen MD, Fuster V, McNamara CA.
Lymphocytes and the adventitial immune response in atherosclerosis.
Circ Res. (2012) 110: 889-900.
IF: 9.489

Citterio C, Menacho-Marquez M, Garcia-Escudero R, Larive RM, Barreiro O, Sanchez-Madrid F, Paramio JM, Bustelo XR.
The rho exchange factors vav2 and vav3 control a lung metastasis-specific transcriptional program in breast cancer cells.
Sci Signal. (2012) 5: ra71.
IF: 7.499

Corella D, Ortega-Azorin C, Sorli JV, Covas MI, Carrasco P, Salas-Salvado J, Martinez-Gonzalez MA, Aros F, Lapetra J, Serra-Majem L, Lamuela-Raventos R, Gomez-Gracia E, Fiol M, Pinto X, Ros E, Marti A, Coltell O, Ordovas JM, Estruch R.
Statistical and biological gene-lifestyle interactions of MC4R and FTO with diet and physical activity on obesity: new effects on alcohol consumption.
PLoS One. (2012) 7: e52344.
IF: 4.092

Cowley AW, Jr., Nadeau JH, Baccarelli A, Berecek K, Fornage M, Gibbons GH, Harrison DG, Liang M, Nathanielsz PW, O'Connor DT, Ordovas J, Peng W, Soares MB, Szyf M, Tolunay HE, Wood KC, Zhao K, Galis ZS.
Report of the national heart, lung, and blood institute working group on epigenetics and hypertension.
Hypertension. (2012) 59: 899-905.
IF: 6.207

Index

Publications 2012

Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA, Henneman P, Heid IM, Kizer JR, Lyytikainen LP, Fuchsberger C, Tanaka T, Morris AP, Small K, Isaacs A, Beekman M, Coassin S, Lohman K, Qi L, Kanoni S, Pankow JS, Uh HW, Wu Y, Bidulescu A, Rasmussen-Torvik LJ, Greenwood CM, Ladouceur M, Grimsby J, Manning AK, Liu CT, Kooner J, Mooser VE, Vollenweider P, Kapur KA, Chambers J, Wareham NJ, Langenberg C, Frants R, Willems-Vandijk K, Oostra BA, Willems SM, Lamina C, Winkler TW, Psaty BM, Tracy RP, Brody J, Chen I, Viikari J, Kahonen M, Pramstaller PP, Evans DM, St Pourcain B, Sattar N, Wood AR, Bandinelli S, Carlson OD, Egan JM, Bohringer S, van Heemst D, Kedenko L, Kristiansson K, Nuotio ML, Loo BM, Harris T, Garcia M, Kanaya A, Haun M, Klopp N, Wichmann HE, Deloukas P, Katsareli E, Couper DJ, Duncan BB, Kloppenburg M, Adair LS, Borja JB, Wilson JG, Musani S, Guo X, Johnson T, Semple R, Teslovich TM, Allison MA, Redline S, Buxbaum SG, Mohlke KL, Meulenbelt I, Ballantyne CM, Dedoussis GV, Hu FB, Liu Y, Paulweber B, Spector TD, Slagboom PE, Ferrucci L, Jula A, Perola M, Raitakari O, Florez JC, Salomaa V, Eriksson JG, Frayling TM, Hicks AA, Lehtimaki T, Smith GD, Siscovick DS, Kronenberg F, van Duijn C, Loos RJ, Waterworth DM, Meigs JB, Dupuis J, Richards JB, Voight BF, Scott LJ, Steinthorsdottir V, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Hofmann OM, Segre AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bostrom KB, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jorgensen T, Kao WH, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Petersen AK, Platou C, Proenca C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparso T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllensten U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Morris AD, Palmer CN, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Pedersen O, Barroso I, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI, Soranzo N, Wheeler E, Glazer NL, Bouatia-Naji N, Magi R, Randall J, Elliott P, Rybin D, Dehghan A, Hottenga JJ, Song K, Goel A, Lajunen T, Doney A, Cavalcanti-Proenca C, Kumari M, Timpson NJ, Zabena C, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, Roccasecca RM, Pattou F, Sethupathy P, Ariyurek Y, Barter P, Beilby JP, Ben-Shlomo Y, Bergmann S, Bochud M, Bonnefond A, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Crisponi L, Day IN, de Geus EJ, Delplanque J, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Grundy S, Gwilliam R, Hallmans G, Hammond N, Han X, Hartikainen AL, Hayward C, Heath SC, Hercberg S, Hillman DR, Hingorani AD, Hui J, Hung J, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Mahley R, Mangino M, Martinez-Larrad MT, McAteer JB, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Mukherjee S, Naitza S, Neville MJ, Orru M, Pakyz R, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Rice K, Ripatti S, Rivadeneira F, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Seedorf U, Sharp SJ, Shields B, Sigurethsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tonjes A, Uitterlinden AG, van Dijk KW, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Ward KL, Watkins H, Wild SH, Willemsen G, Witteman JC, Yarnell JW, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Meneton P, Magnusson PK, Nathan DM, Williams GH, Silander K, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Serrano-Rios M, Lind L, Palmer LJ, Hu FBs, Franks PW, Ebrahim S, Marmot M, Wright AF, Stumvoll M, Hamsten A, Buchanan TA, Valle TT, Rotter JI, Penninx BW, Boomsma DI, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin MR, Peltonen L, Mooser V, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Chasman DI, Johansen CT, Fouchier SW, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Feitosa MF, Orho-Melander M, Melander O, Li X, Cho YS, Go MJ, Kim YJ, Lee JY, Park T, Kim K, Sim X, Ong RT, Croteau-Chonka DC, Lange LA, Smith JD, Ziegler A, Zhang W, Zee RY, Whitfield JB, Thompson JR, Surakka I, Smit JH, Sinisalo J, Scott J, Saharinen J, Sabatti C, Rose LM, Roberts R, Rieder M, Parker AN, Pare G, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, McArdle W, Masson D, Martin NG, Marroni F, Lucas G, Luben R, Lokki ML, Lettre G, Launer LJ, Lakatta EG, Laaksonen R, Konig IR, Khaw KT, Kaplan LM, Johansson A, Janssens AC, Igl W, Hovingh GK, Hengstenberg C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Groop LC, Gonzalez E, Freimer NB, Erdmann J, Ejebe KG, Doring A, Dominiczak AF, Demissie S, de Faire U, Caulfield MJ, Boekholdt SM, Assimes TL, Quertermous T, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Taylor HA, Jr., Gabriel SB, Holm H, Gudnason V, Krauss RM, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Strachan DP, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, Kathiresan S.

Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals.

PLoS Genet. (2012) 8: e1002607.

IF: 8.694

Index

Publications 2012

de Haas HJ, van den Borne SW, Boersma HH, Slart RH, Fuster V, Narula J.
Evolving role of molecular imaging for new understanding: targeting myofibroblasts to predict remodeling.
Ann N Y Acad Sci. (2012) 1254: 33-41.
IF: 3.155

de la Cuesta F, Barderas MG, Calvo E, Zubiri I, Maroto AS, Darde VM, Martin-Rojas T, Gil-Dones F, Posada M, Tejerina T, Lopez JA, Vivanco F, Alvarez-Llamas G.
Secretome analysis of atherosclerotic and non-atherosclerotic arteries reveals dynamic extracellular remodeling during pathogenesis.
J Proteomics. (2012) 17: 2960-71.
IF: 4.878

de la Hera JM, Delgado E, Martinez-Camblor P, Vegas JM, Garcia-Ruiz JM, Rodriguez-Lambert JL.
Oral glucose tolerance test as a tool for patient improvement after percutaneous coronary intervention.
Rev Esp Cardiol. (2012) 65: 1054-6.
IF: 2.530

Dellegrottaglie S, Perrone-Filardi P, Garcia-Alvarez A, Moral S, Stevens GR, Fuster V, Sanz J.
Serial phase-contrast MRI for prediction of pulmonary hemodynamic changes in patients with pulmonary arterial hypertension.
Int J Cardiol. (2012) 157: 140-2.
IF: 7.078

Derbre F, Gomez-Cabrera MC, Nascimento AL, Sanchis-Gomar F, Martinez-Bello VE, Tresguerres JA, Fuentes T, Gratas-Delamarche A, Monsalve M, Vina J.
Age associated low mitochondrial biogenesis may be explained by lack of response of PGC-1alpha to exercise training.
Age (Dordr). (2012) 34: 669-79.
IF: 3.948

Diaz F, Enriquez JA, Moraes CT.
Cells lacking rieske iron sulfur protein have a ROS-associated decrease in respiratory complexes I and IV.
Mol Cell Biol. (2012) 32: 415-29.
IF: 5.527

Elmariah S, Delaney JA, Bluemke DA, Budoff MJ, O'Brien KD, Fuster V, Kronmal RA, Halperin JL.
Associations of LV hypertrophy with prevalent and incident valve calcification: multi-ethnic study of atherosclerosis.
JACC Cardiovasc Imaging. (2012) 5: 781-8.
IF: 5.431

Fernandez-Pisonero I, Duenas AI, Barreiro O, Montero O, Sanchez-Madrid F, Garcia-Rodriguez C.
Lipopolysaccharide and sphingosine-1-phosphate cooperate to induce inflammatory molecules and leukocyte adhesion in endothelial cells.
J Immunol. (2012) 189: 5402-10.
IF: 5.788

Fernandez-Velasco M, Prieto P, Terron V, Benito G, Flores JM, Delgado C, Zaragoza C, Lavin B, Gomez-Parrizas M, Lopez-Collazo E, Martin-Sanz P, Bosca L.
NOD1 activation induces cardiac dysfunction and modulates cardiac fibrosis and cardiomyocyte apoptosis.
PLoS One. (2012) 7: e45260.
IF: 4.092

Frazier-Wood AC, Aslibekyan S, Borecki IB, Hopkins PN, Lai CQ, Ordovas JM, Straka RJ, Tiwari HK, Arnett DK.
Genome-wide association study indicates variants associated with insulin signaling and inflammation mediate lipoprotein responses to fenofibrate.
Pharmacogenet Genomics. (2012) 22: 750-7.
IF: 3.485

Frazier-Wood AC, Kabagambe EK, Borecki IB, Tiwari HK, Ordovas JM, Arnett DK.
Preliminary evidence for an association between LRP-1 genotype and body mass index in humans.
PLoS One. (2012) 7: e30732.
IF: 4.092

Futterer A, Raya A, Llorente M, Izpisua-Belmonte JC, de la Pompa JL, Klatt P, Martinez AC.
Ablation of Dido3 compromises lineage commitment of stem cells in vitro and during early embryonic development.
Cell Death Differ. (2012) 19: 132-43.
IF: 8.849

Galper MW, Saung MT, Fuster V, Roessl E, Thran A, Proksa R, Fayad ZA, Cormode DP.
Effect of computed tomography scanning parameters on gold nanoparticle and iodine contrast.
Invest Radiol. (2012) 47: 475-81.
IF: 4.593

Index

Publications 2012

Gamez-Pozo A, Sanchez-Navarro I, Calvo E, Agullo-Ortuno MT, Lopez-Vacas R, Diaz E, Camafeita E, Nistal M, Madero R, Espinosa E, Lopez JA, Vara JA.
PTRF/Cavin-1 and MIF proteins are identified as non-small cell lung cancer biomarkers by label-free proteomics.
PLoS One. (2012) 7: e33752.
IF: 4.092

Gangireddy SR, Halperin JL, Fuster V, Reddy VY.
Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: an assessment of net clinical benefit.
Eur Heart J. (2012) 33: 2700-8.
IF: 10.478

Gasull M, Pumarega J, Tellez-Plaza M, Castell C, Tresserras R, Lee DH, Porta M.
Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia.
Environ Sci Technol. (2012) 46: 7799-810.
IF: 5.228

Giannarelli C, Cimmino G, Ibanez B, Chiesa G, Garcia-Prieto J, Santos-Gallego CG, Alique-Aguilar M, Fuster V, Sirtori C, Badimon JJ.
Acute ApoA-I Milano administration induces plaque regression and stabilisation in the long term.
Thromb Haemost. (2012) 108: 1246-8.
IF: 5.731

Gil-Izquierdo A, Penalvo JL, Gil JI, Medina S, Horcajada MN, Lafay S, Silberberg M, Llorach R, Zafrilla P, Garcia-Mora P, Ferreres F.
Soy isoflavones and cardiovascular disease epidemiological, clinical and -omics perspectives.
Curr Pharm Biotechnol. (2012) 13: 624-31.
IF: 2.805

Gomez-Abellan P, Diez-Noguera A, Madrid JA, Lujan JA, Ordovas JM, Garaulet M.
Glucocorticoids affect 24 h clock genes expression in human adipose tissue explant cultures.
PLoS One. (2012) 7: e50435.
IF: 4.092

Gomez-Abellan P, Madrid JA, Lujan JA, Frutos MD, Gonzalez R, Martinez-Augustin O, de Medina FS, Ordovas JM, Garaulet M.
Sexual dimorphism in clock genes expression in human adipose tissue.
Obes Surg. (2012) 22: 105-12.
IF: 3.286

Hernandez-Morante JJ, Gomez-Santos C, Margareto J, Formiguera X, Martinez CM, Gonzalez R, Martinez-Augustin O, Madrid JA, Ordovas JM, Garaulet M.
Influence of menopause on adipose tissue clock gene genotype and its relationship with metabolic syndrome in morbidly obese women.
Age (Dordr). (2012) 34: 1369-80.
IF: 3.948

Iglesias-Gutierrez E, Egan B, Diaz-Martinez AE, Penalvo JL, Gonzalez-Medina A, Martinez-Camblor P, O'Gorman DJ, Ubeda N.
Transient increase in homocysteine but not hyperhomocysteinemia during acute exercise at different intensities in sedentary individuals.
PLoS One. (2012) 7: e51185.
IF: 4.092

Irimia M, Denuc A, Ferran JL, Pernaute B, Puelles L, Roy SW, Garcia-Fernandez J, Marfany G.
Evolutionarily conserved A-to-I editing increases protein stability of the alternative splicing factor Nova1.
RNA Biol. (2012) 9: 12-21.
IF: 4.933

Jang JE, Hidalgo A, Frenette PS.
Intravenous immunoglobulins modulate neutrophil activation and vascular injury through FcgammaRIII and SHP-1.
Circ Res. (2012) 110: 1057-66.
IF: 9.489

Juraschek SP, Guallar E, Appel LJ, Miller ER, 3rd.
Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials.
Am J Clin Nutr. (2012) 95: 1079-88.
IF: 6.669

Kalra H, Simpson RJ, Ji H, Aikawa E, Altevogt P, Askenase P, Bond VC, Borras FE, Breakefield X, Budnik V, Buzas E, Camussi G, Clayton A, Cocucci E, Falcon-Perez JM, Gabrielsson S, Gho YS, Gupta D, Harsha HC, Hendrix A, Hill AF, Inal JM, Jenster G, Kramer-Albers EM, Lim SK, Llorente A, Lotvall J, Marcilla A, Mincheva-Nilsson L, Nazarenko I, Nieuwland R, Nolte-'t Hoen EN, Pandey A, Patel T, Piper MG, Pluchino S, Prasad TS, Rajendran L, Raposo G, Record M, Reid GE, Sanchez-Madrid F, Schiffelers RM, Siljander P, Stensballe A, Stoorvogel W, Taylor D, Thery C, Valadi H, van Balkom BW, Vazquez J, Vidal M, Wauben MH, Yanez-Mo M, Zoeller M, Mathivanan S.
Vesiclepedia: a compendium for extracellular vesicles with continuous community annotation.
PLoS Biol. (2012) 10: e1001450.
IF: 11.452

Index

Publications 2012

Kauselmann G, Dopazo A, Link W.
Identification of disease-relevant genes for molecularly-targeted drug discovery.
Curr Cancer Drug Targets. (2012) 12: 1-13.
IF: 4.327

Kovacic JC, Lee P, Baber U, Karajgikar R, Evrard SM, Moreno P, Mehran R, Fuster V, Dangas G, Sharma SK, Kini AS.
Inverse relationship between body mass index and coronary artery calcification in patients with clinically significant coronary lesions.
Atherosclerosis. (2012) 221: 176-82.
IF: 3.794

Leandro-Garcia LJ, Leskela S, Inglada-Perez L, Landa I, de Cubas AA, Maliszewska A, Comino-Mendez I, Leton R, Gomez-Grana A, Torres R, Ramirez JC, Alvarez S, Rivera J, Martinez C, Lozano ML, Cascon A, Robledo M, Rodriguez-Antona C.
Hematological beta-tubulin VI isoform exhibits genetic variability that influences paclitaxel toxicity.
Cancer Res. (2012) 72: 4744-52.
IF: 7.856

Lin B, Kim J, Li Y, Pan H, Carvajal-Vergara X, Salama G, Cheng T, Lo CW, Yang L.
High-purity enrichment of functional cardiovascular cells from human iPS cells.
Cardiovasc Res. (2012) 95: 327-35.
IF: 6.064

Lluis-Ganella C, Subirana I, Lucas G, Tomas M, Munoz D, Senti M, Salas E, Sala J, Ramos R, Ordovas JM, Marrugat J, Elosua R.
Assessment of the value of a genetic risk score in improving the estimation of coronary risk.
Atherosclerosis. (2012) 222: 456-63.
IF: 3.794

Madeira A, da Silva CL, Dos Santos F, Camafeita E, Cabral JM, Sa-Correia I.
Human mesenchymal stem cell expression program upon extended ex-vivo cultivation, as revealed by 2-DE-based quantitative proteomics.
PLoS One. (2012) 7: e43523.
IF: 4.092

Mendes-Jorge L, Llombart C, Ramos D, Lopez-Luppo M, Valenca A, Nacher V, Navarro M, Carretero A, Mendez-Ferrer S, Rodriguez-Baeza A, Ruberte J.
Intercapillary bridging cells: Immunocytochemical characteristics of cells that connect blood vessels in the retina.
Exp Eye Res. (2012) 98: 79-87.
IF: 3.580

Milagro FI, Gomez-Abellan P, Campion J, Martinez JA, Ordovas JM, Garaulet M.
CLOCK, PER2 and BMAL1 DNA Methylation: association with obesity and metabolic syndrome characteristics and monounsaturated fat intake.
Chronobiol Int. (2012) 29: 1180-94.
IF: 4.028

Moon K, Guallar E, Navas-Acien A.
Arsenic exposure and cardiovascular disease: an updated systematic review.
Curr Atheroscler Rep. (2012) 14: 542-55.
IF: 2.664

Moral S, Fernandez-Friera L, Stevens G, Guzman G, Garcia-Alvarez A, Nair A, Evangelista A, Fuster V, Garcia MJ, Sanz J.
New index alpha improves detection of pulmonary hypertension in comparison with other cardiac magnetic resonance indices.
Int J Cardiol. (2012) 161: 25-30.
IF: 7.078

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: 301-11.
IF: 6.596

Nunez-Gil IJ, Molina M, Bernardo E, Ibanez B, Ruiz-Mateos B, Garcia-Rubira JC, Vivas D, Feltes G, Luaces M, Alonso J, Zamorano J, Macaya C, Fernandez-Ortiz A.
Tako-tsubo syndrome and heart failure: long-term follow-up.
Rev Esp Cardiol. (2012) 65: 996-1002.
IF: 2.530

Ortega-Azorin C, Sorli JV, Asensio EM, Coltell O, Martinez-Gonzalez MA, Salas-Salvado J, Covas MI, Aros F, Lapetra J, Serra-Majem L, Gomez-Gracia E, Fiol M, Saez-Tormo G, Pinto X, Munoz MA, Ros E, Ordovas JM, Estruch R, Corella D.
Associations of the FTO rs9939609 and the MC4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the mediterranean diet pattern is low.
Cardiovasc Diabetol. (2012) 11: 137.
IF: 3.346

Mourino-Alvarez L, Calvo E, Moreu J, Padial LR, Lopez JA, Barderas MG, Gil-Dones F.
Proteomic characterization of EPCs and CECs "in vivo" from acute coronary syndrome patients and control subjects.
Biochim Biophys Acta. (2012) 1830: 3030-53.
IF: 5.000

Perez-Perez R, Garcia-Santos E, Ortega-Delgado FJ, Lopez JA, Camafeita E, Ricart W, Fernandez-Real JM, Peral B.
Attenuated metabolism is a hallmark of obesity as revealed by comparative proteomic analysis of human omental adipose tissue.
J Proteomics. (2012) 75: 783-95.
IF: 4.878

Index

Publications 2012

Perez-Perez R, Lopez JA, Garcia-Santos E, Camafeita E, Gomez-Serrano M, Ortega-Delgado FJ, Ricart W, Fernandez-Real JM, Peral B.
Uncovering suitable reference proteins for expression studies in human adipose tissue with relevance to obesity.
PLoS One. (2012) 7: e30326.
IF: 4.092

Poulin LF, Reyal Y, Uronen-Hansson H, Schraml B, Sancho D, Murphy KM, Hakansson UK, Ferreira Moita L, Agace WW, Bonnet D, Reis E, C. S.
DNGR-1 is a specific and universal marker of mouse and human Batf3-dependent dendritic cells in lymphoid and non-lymphoid tissues.
Blood. (2012) 119: 6052-62.
IF: 9.898

Purushothaman KR, Purushothaman M, Levy AP, Lento PA, Evrard S, Kovacic JC, Briley-Saebo KC, Tsimikas S, Witztum JL, Krishnan P, Kini A, Fayad ZA, Fuster V, Sharma SK, Moreno PR.
Increased expression of oxidation-specific epitopes and apoptosis are associated with haptoglobin genotype: possible implications for plaque progression in human atherosclerosis.
J Am Coll Cardiol. (2012) 60: 112-9.
IF: 14.156

Purushothaman M, Krishnan P, P KR, Baber U, Tarricone A, Perez JS, Wiley J, Kini A, Sharma SK, Fuster V, Moreno PR.
Genotype-dependent impairment of hemoglobin clearance increases oxidative and inflammatory response in human diabetic atherosclerosis.
Arterioscler Thromb Vasc Biol. (2012) 32: 2769-75.
IF: 6.368

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.
IF: 4.092

Quiros PM, Ramsay AJ, Sala D, Fernandez-Vizarra E, Rodriguez F, Peinado JR, Fernandez-Garcia MS, Vega JA, Enriquez JA, Zorzano A, Lopez-Otin C.
Loss of mitochondrial protease OMA1 alters processing of the GTPase OPA1 and causes obesity and defective thermogenesis in mice.
EMBO J. (2012) 31: 2117-33.
IF: 9.205

Ramos-Cejudo J, Gutierrez-Fernandez M, Rodriguez-Frutos B, Exposito Alcaide M, Sanchez-Cabo F, Dopazo A, Diez-Tejedor E.
Spatial and temporal gene expression differences in core and periinfarct areas in experimental stroke: a microarray analysis.
PLoS One. (2012) 7: e52121.
IF: 4.092

Rampal S, Mahadeva S, Guallar E, Bulgiba A, Mohamed R, Rahmat R, Arif MT, Rampal L.
Ethnic differences in the prevalence of metabolic syndrome: results from a multi-ethnic population-based survey in malaysia.
PLoS One. (2012) 7: e46365.
IF: 4.092

Rayman MP, Blundell-Pound G, Pastor-Barriuso R, Guallar E, Steinbrenner H, Stranges S.
A randomized trial of selenium supplementation and risk of type-2 diabetes, as assessed by plasma adiponectin.
PLoS One. (2012) 7: e45269.
IF: 4.092

Rodriguez P, Higueras MA, Gonzalez-Rajal A, Alfranca A, Fierro-Fernandez M, Garcia-Fernandez RA, Ruiz-Hidalgo MJ, Monsalve M, Rodriguez-Pascual F, Redondo JM, de la Pompa JL, Laborda J, Lamas S.
The non-canonical NOTCH ligand DLK1 exhibits a novel vascular role as a strong inhibitor of angiogenesis.
Cardiovasc Res. (2012) 93: 232-41.
IF: 6.064

Rodriguez-Mahillo AI, Gonzalez-Munoz M, Vega JM, Lopez JA, Yart A, Kerdelhue C, Camafeita E, Garcia Ortiz JC, Vogel H, Petrucco Toffolo E, Zovi D, Battisti A, Roques A, Moneo I.
Setae from the pine processionary moth (Thaumetopoea pityocampa) contain several relevant allergens.
Contact Dermatitis. (2012) 67: 367-74.
IF: 3.509

Rosell M, Hondares E, Iwamoto S, Gonzalez FJ, Wabitsch M, Staels B, Olmos Y, Monsalve M, Giralt M, Iglesias R, Villarroya F.
Peroxisome proliferator-activated receptors-alpha and -gamma, and cAMP-mediated pathways, control retinol-binding protein-4 gene expression in brown adipose tissue.
Endocrinology. (2012) 153: 1162-73.
IF: 4.459

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Publications 2012

Ruperez FJ, Ramos-Mozo P, Teul J, Martinez-Pinna R, Garcia A, Malet-Martino M, Camafeita E, Lopez JA, Pastor-Vargas C, Egido J, Balayssac S, Gilard V, Barbas C, Martin-Ventura JL.
Metabolomic study of plasma of patients with abdominal aortic aneurysm.
Anal Bioanal Chem. (2012) 403: 1651-60.
IF: 3.778

Sanchez-Cuellar S, de la Fuente H, Cruz-Adalia A, Lamana A, Cibrian D, Giron RM, Vara A, Sanchez-Madrid F, Ancochea J.
Reduced expression of galectin-1 and galectin-9 by leucocytes in asthma patients.
Clin Exp Immunol. (2012) 170: 365-74.
IF: 3.360

Sawit ST, Garcia-Alvarez A, Suri B, Gaztanaga J, Fernandez-Friera L, Mirelis JG, D'Anca M, Fuster V, Sanz J, Garcia MJ.
Usefulness of cardiac computed tomographic delayed contrast enhancement of the left atrial appendage before pulmonary vein ablation.
Am J Cardiol. (2012) 109: 677-84.
IF: 3.368

Seija M, Baccino C, Nin N, Sanchez-Rodriguez C, Granados R, Ferruelo A, Martinez-Caro L, Ruiz-Cabello J, de Paula M, Noboa O, Esteban A, Lorente JA.
Role of peroxynitrite in sepsis-induced acute kidney injury in an experimental model of sepsis in rats.
Shock. (2012) 38: 403-10.
IF: 2.848

Sobrado M, Ramirez BG, Neria F, Lizasoain I, Arbones ML, Minami T, Redondo JM, Moro MA, Cano E.
Regulator of calcineurin 1 (Rcan1) has a protective role in brain ischemia/reperfusion injury.
J Neuroinflammation. (2012) 9: 48.
IF: 3.827

Sorianello E, Soriano FX, Fernandez-Pascual S, Sancho A, Naon D, Vila-Caballer M, Gonzalez-Navarro H, Portugal J, Andres V, Palacin M, Zorzano A.
The promoter activity of human Mfn2 depends on Sp1 in vascular smooth muscle cells.
Cardiovasc Res. (2012) 91: 38-47.
IF: 6.064

Stevens GR, Garcia-Alvarez A, Sahni S, Garcia MJ, Fuster V, Sanz J.
RV dysfunction in pulmonary hypertension Is independently related to pulmonary artery stiffness.
JACC Cardiovasc Imaging. (2012) 5: 378-87.
IF: 5.431

Vanelli A, Pennarossa G, Maffei S, Galvez GB, Cossu G, Rahaman M, Gandolfi F, Brevini TA.
Isolation, characterization and differentiation potential of cardiac progenitor cells in adult pigs.
Stem Cell Rev. (2012) 8: 706-19.
IF: 3.739

Vegas-Valle JM, Garcia-Ruiz JM, Hernandez-Martin E, de la Hera JM.
Metabolic syndrome, diabetes, and coronary artery disease: a very common association.
Rev Esp Cardiol. (2012) 65: 108-109.
IF: 2.530

Villar D, Ortiz-Barahona A, Gomez-Maldonado L, Pescador N, Sanchez-Cabo F, Hackl H, Rodriguez BA, Trajanoski Z, Dopazo A, Huang TH, Yan PS, Del Peso L.
Cooperativity of stress-responsive transcription factors in core hypoxia-inducible factor binding regions.
PLoS One. (2012) 7: e45708.
IF: 4.092

Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart AF, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler

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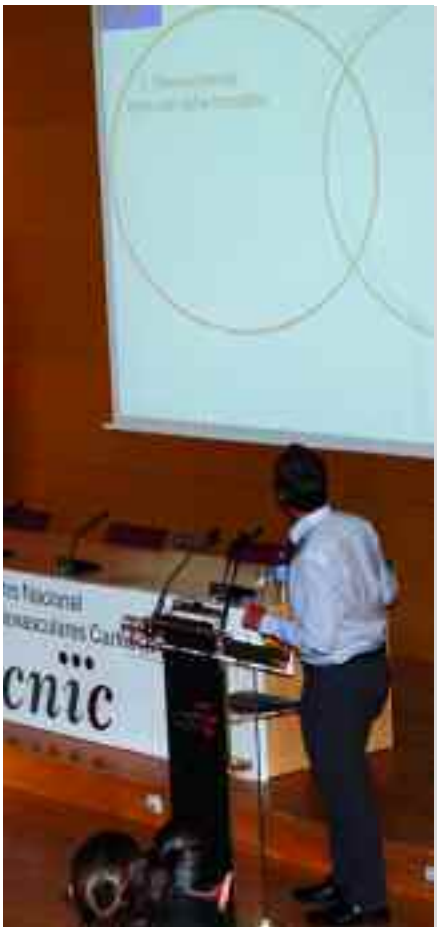
Publications 2012

A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S.
Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study.
Lancet. (2012) 380: 572-80.
IF: 38.278

Vucic E, Calcagno C, Dickson SD, Rudd JH, Hayashi K, Bucerius J, Moshier E, Mounessa JS, Roytman M, Moon MJ, Lin J, Ramachandran S, Tanimoto T, Brown K, Kotsuma M, Tsimikas S, Fisher EA, Nicolay K, Fuster V, Fayad ZA.
Regression of inflammation in atherosclerosis by the LXR agonist R211945: a noninvasive assessment and comparison with atorvastatin.
JACC Cardiovasc Imaging. (2012) 5: 819-28.
IF: 5.431

Yiannakouris N, Katsoulis M, Dilis V, Parnell LD, Trichopoulos D, Ordovas JM, Trichopoulou A.
Genetic predisposition to coronary heart disease and stroke using an additive genetic risk score: a population-based study in Greece.
Atherosclerosis. (2012) 222: 175-9.
IF: 3.794

Zelenay S, Keller AM, Whitney PG, Schraml BU, Deddouche S, Rogers NC, Schulz O, Sancho D, Reis ESC.
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.
IF: 13.069



	TOTAL(*)	CUMULATIVE IF	AVERAGE IF
TOTAL	**168**	**1181.421**	**7.032**
CARDIOVASCULAR DEVELOPMENT AND REPAIR	30	207.085	6.903
EPIDEMIOLOGY, ATHEROTHROMBOSIS AND IMAGING	95	612.185	6.444
VASCULAR BIOLOGY AND INFLAMMATION	28	298.187	10.650
TECHNICAL UNITS	27	171.043	6.335

(*) 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.

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Training Programs and Courses

Training is one of the CNIC's core activities, and the Center has devised a comprehensive training plan, called **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 2012

Name	Secondary School	Autonomous Region
Aguilar Romero, Isabel María	IES Ingeniero Juan de la Cierva	Andalucía
Cabañero Navalón, Marta Dafne	Iale School	Valencia
Castillo Martínez, Alba	IES Montserrat Roig	Valencia
Castillo Martínez, María	IES Montserrat Roig	Valencia
Fernández Besoy, Blanca	IES Dionisio Aguado	Madrid
García Escolano, Alba	IES Antonio Serna Serna	Valencia
Nieto Ibáñez, Daniel	IES Inventor Cosme García	La Rioja
Salazar Moya, Alba Pastora	IES Fernando de Herrera	Andalucía

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 more informed choices about the possibility of pursuing a scientific career in the future.

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Training Programs and Courses

Fellowships in 2012

Candidate	Degree	University
Alonso Herranz, Laura	Biology	Complutense de Madrid
Bilal Espejo, Faiz	Biochemistry	Córdoba
Bleye González, Ainoa Cristina	Human Nutrition	Valladolid
Buena Atienza, Elena	Biotechnology	León
Bujarrabal Dueso, Arturo	Biology	Autónoma de Madrid
Cid Carbajales, Sandra	Biology	Complutense de Madrid
Cueto Rodríguez, Francisco Javier	Biochemistry	Granada
Enguita Marruedo, Andrea	Biology	Autónoma de Madrid
Esteban Iglesias, Sergio	Biology	Autónoma de Madrid
Fanjul Hevia, Victor	Biology	Oviedo
Fernández Cáceres, Eva	Biotechnology	Pablo Olavide
García Campos, Francisco Javier	Chemistry	Complutense de Madrid
García García, Andrés	Biology	Málaga
Jaso Tamame, Angel Luís	Biología	Sevilla
Lechuga Vieco, Ana Victoria	Biotecnology	Pablo Olavide
Lioux, Ghislaine	Science of Genetics	Paris Diderot Paris 7, France
López Martínez, David	Biochemistry	Autónoma de Madrid
Loureiro López, Marta	Biotechnology	Francisco de Vitoria
Louzao Boado, Ánxela	Biology	Santiago de Compostela
Martí Gómez-Aldaraví, Carlos	Biotechnology	Valencia
Martos Folgado, Mª Inmaculada	Biology	Sevilla
Menéndez Montes, Iván	Chemistry	Oviedo
Morán Luengo, Tania	Chemistry	Oviedo
Muñóz López, Álvaro	Biotechnology	Pablo Olavide
Nevado Serrano, Pedro	Physics	Complutense de Madrid
Nieto Arellano, Rocío	Biology	Valencia
Ortíz Sánchez, Paula	Biotechnology	Pablo Olavide
Pascual Gamarra, José Miguel	Biochemistry	Granada
Ramirez Martínez, Andrés	Biochemistry and Molecular Biology /Biotechnology	Rovira i Virgili
Rodríguez Martín, Daniel	Biology	Complutense de Madrid
Rouco García, Raquel	Biology	Complutense de Madrid
Sierra Rodríguez de la Rubia, Federico	Veteriny	Extremadura
Siguero Álvarez, Marcos	Biochemistry	Autónoma de Madrid
Torralba Garjales, Daniel	Biochemistry	Autónoma de Madrid
Villahoz Lázaro, Silvia	Biotechnology	León
Zygmunt, Magdalena Agatha	Biotechnology	Jagiellonian, Poland

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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 2011-2012, 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: 16 January-20 February 2012
Venue: CNIC
UAM MSc Students: 5
CNIC PhD students: 4

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.

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Training Programs and Courses

Fellowships in 2012

Name	Degree - University	Master	Master - University
Bilal Espejo, Faiz	Córdoba	Molecular Biomedicine	Autónoma de Madrid
Díez Sánchez, Alberto	Francisco de Vitoria	Molecular Biomedicine	Autónoma de Madrid
Enamorado Escalona, Neris Michel	La Habana	Molecular Biomedicine	Autónoma de Madrid
Esteban Iglesias, Sergio	Autónoma de Madrid	Molecular Biomedicine	Autónoma de Madrid
Jaso Tamame, José Luis	Sevilla	Molecular and Cellular Biology	Autónoma de Madrid
Lama, Shiddi Blanca Camila	Colorado State USA	Organ Tissue and cell transplantation	Universidad de Barcelona
Loureiro López, Marta	Francisco de Vitoria	Research in Immunology	Autónoma de Madrid
Menchero Fernández, Sergio	Autónoma de Madrid	Molecular Biomedicine	Autónoma de Madrid

PREDOCTORAL (PhD) Program

The PREDOCTORAL Program provides a common 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
- To work in accordance with the rights and obligations laid out in Real Decreto 63/2006, which relates to the training of research personnel

Graduate students at the CNIC who obtained their PhD degrees in 2012

Name	Title of thesis	University	CNIC Department	Thesis Advisor(s)
Estrada Rodríguez, Juan Camilo	Role of oxidative stress in the genetic stability and biosafety of adult human mesenchymal stem cells	Autónoma de Madrid	Cardiovascular Development and Repair	Bernad, Antonio / Samper, Enrique
González Rajal, Álvaro	Identification and functional validation of novel genes involved in zebrafish heart and fin regeneration	Autónoma de Madrid	Cardiovascular Development and Repair	de La Pompa, Jose Luís

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Training Programs and Courses

Graduate students at the CNIC who obtained their PhD degrees in 2012

Name	Title of thesis	University	CNIC Department	Thesis Advisor(s)
Guadamillas Mora, Marta C.	Role of calveolin-1 in signal transduction: cell cycle integrin dependent regulation, and generation of a new mouse model of non-phosphorylable caveolin-1	Complutense de Madrid	Vascular Biology and Inflammation	del Pozo, Miguel Ángel/ Cerezo, Ana
Hernández de Riquer, Mª Victoria	Search and characterization of new molecular associations of MT-MMP cytosolic tails	Complutense de Madrid	Vascular Biology and Inflammation	Arroyo, Alicia G.
Herrera Merchan Antonio	Epigenetic regulation by EZH2 and BMI1 in hematopoietic stem cells	Autónoma de Madrid	Cardiovascular Development Repair	González, Susana
Moreno Rodríguez, Vanessa	Characterization of the membrane protein EMMPRIN in endothelial cell-cell adhesion and vascular integrity	Autónoma de Madrid	Vascular Biology and Inflammation	Arroyo, Alicia G.
Sánchez Ramos, Cristina	Regulation of the antioxidant system in the liver: molecular mechanism and physiopathology	Autónoma de Madrid	Cardiovascular Development and Repair	Monsalve, Martía
Urso, Katia	Differential role of NFATc1 and NFATc3 in T cell activation and angiogenesis	Autónoma de Madrid	Vascular Biology and Inflammation	Redondo, Juan Miguel/ Rodríguez, Antonio

Graduate students carrying out their PhD theses at the CNIC during 2012

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Aix Sacido, Esther	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	BMM9 2009-2010 / MASTER Program 2009
Alameda Serrano, Daniel	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Regenerative Cardiology	CICERONE Program 2007
Bednareck, Dorota	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Bergacín Liberman, Gabriel	CNIC contract	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)	UAM	Vascular Biology and Inflammation	No
Blanco Menéndez, Noelia	CNIC contract	Autónoma de Madrid	Vascular Biology and Inflammation	No
Casanova Acebes, María	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Epidemiology, Atherothrombosis and Imaging	No

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Training Programs and Courses

Graduate students carrying out their PhD theses at the CNIC during 2012

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
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
Díez Cabezas, Begoña	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Escolano Artigas, Amelia	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	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
Gómez Velázquez, Melisa	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	MASTER Program 2009 / Cardiovascular Postgraduate Program 2009-2010
González Rajal, Álvaro	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	No
González Rosa, Juan Manuel	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 / MASTER Program 2008
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

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Training Programs and Courses

Graduate students carrying out their PhD theses at the CNIC during 2012

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
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
Hidalgo Gavilán, Isabel	contrato CNIC	Autónoma de Madrid	Cardiovascular Development and Repair	No
Izarra Pérez, Alberto	FPI (Spanish Ministry of Education)	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
Koziol, Agnieszka	FPU (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Latorre Pellicer, Ana	Diputación General de Aragón	Universidad de Zaragoza	Cardiovascular Development and Repair	No
Lavín Plaza, Begoña	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Epidemiology, Atherothrombosis and Imaging	No
López Fontal, Raquel	FIS (Carlos III National Institute of Health)	Autónoma de Madrid	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
Luna Zurita, Luis	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	No
Luxán García, Guillermo	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Manieri, Elisa	La Caixa Foundation Fellowship	Autónoma de Madrid	Vascular Biology and Inflammation	No
Marco Lázaro, Ricardo	CNIC contract	Universidad de Zaragoza	Cardiovascular Development and Repair	No
Martín Alonso, Mara	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	CICERONE Program 2008 / Cardiovascular Postgraduate Program 2009-2010

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Training Programs and Courses

Graduate students carrying out their PhD theses at the CNIC during 2012

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Martín Pérez, Lara	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 / Cardiovascular Postgraduate Program 2009-2010
Mateos San Martín, Daniel	CAM (Madrid Autonomous Region)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Matesanz Marín, Adela	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	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
Munch, Juliane	Notch IT, Marie Curie	Autónoma de Madrid	Cardiovascular Development and Repair	Cardiovascular Postgraduate Program 2009-2010
Muñoz Agudo, Carmen	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Núñez Andrade, Norman	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Olmos Buchelt, Yolanda	SAF (Spanish Ministry of Economy and Competitiveness)	Complutense de Madrid	Cardiovascular Development and Repair	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
Rodríguez, Juan Camilo Estrada	Red TERCEL (La Paz Hospital)	Autónoma de Madrid	Cardiovascular Development and Repair	No
Roselló Díez, Alberto	FPI (Spanish Ministry of Education)	Autónoma de Madrid	Cardiovascular Development and Repair	No

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Training Programs and Courses

Graduate students carrying out their PhD theses at the CNIC during 2012

Name	Funding Agency	University	CNIC Department	Joined previously through another Training Program
Sala Valdés, Mónica	FIS (Carlos III National Institute of Health)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Silvestre Roig, Carlos	Mariano Losantos del Campo Foundation	Universidad de Valencia	Epidemiology, Atherothrombosis and Imaging	No
Tarín Cerezo, Carlos A.	FPI (Spanish Ministry of Education)	Universidad de Alcalá	Epidemiology, Atherothrombosis and Imaging	No
Tejera Puente, Emilio	FIS (Carlos III National Institute of Health)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Tomé Pizarro, María	CNIC contract	Autónoma de Madrid	Cardiovascular Development and Repair	CICERONE Program 2008 / Cardiovascular Postgraduate Program 2008-2009
Travisano, Stanislao Igor	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
Verdugo Becerra, Mª de los Ángeles	CAM (Madrid Autonomous Region)	Autónoma de Madrid	Vascular Biology and Inflammation	No
Wild, Brigitte	Spanish Ministry of Economy and Competitiveness contract	Autónoma de Madrid	Cardiovascular Development and Repair	No

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Training Programs and Courses

CARDIO-IMAGE Program

The CARDIO-IMAGE Program (CNIC-MSSM) has been launched against the backdrop of the Collaboration Agreement signed 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 2012

Name	Institution
Arias Guedón, Teresa	Centro de Investigación Médica Aplicada - Navarra
Mateo de Castro, Jesús	Centro Nacional de Investigaciones Cardiovasculares - Madrid
Pérez Medina, Carlos	CIBERES - España
Pérez Sánchez, José Manuel	CIBERES - España

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 make contact with cardiovascular research, learning about and becoming familiar with the latest techniques in biomedical research that are being developed in the CNIC's laboratories, under the guidance of a scientist of the Center. Additionally, residents participating in the Res@CNIC program will receive training in theoretical aspects of cardiovascular research via a module of classes taken by experts in the area. 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 their research projects in their respective National Health System centers in collaboration with the CNIC.

The first call for this program was launched in 2012. Selected students will attend the CNIC during January and February 2013.

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Training Programs and Courses

Selected Candidates

Candidate	Hospital	Researcher-Supervisor
Alonso Salinas, Gonzalo Luis	Universitario Ramón y Cajal (Madrid)	Hidalgo, Andrés
Asmarats Serra , Luis	Universitario Son Espases (Palma de Mallorca)	Lara, Enrique
Chacón Hernández, Gina Natalia	General Universitario de Valencia	Sabio, Guadalupe
Cordero Pereda, David	Universitario de Basurto (País Vasco)	Ruiz Cabello, Jesús
De la Chica Sánchez, José Antonio	Regional Universitario Carlos Haya (Málaga)	Borreguero, Jesús
Del Val Martín, David	Universitario Ramón y Cajal (Madrid)	Ibañez, Borja
García Piney, Eva	Universitario de Salamanca	Borreguero, Jesús
Lobo González, Manuel	Universitario Virgen Macarena (Sevilla)	Borreguero, Jesús
Macaya Ten, Fernando	Universitario Son Espases (Baleares)	Ibañez, Borja
Martínez Losas, Pedro	Clínico San Carlos (Madrid)	Enríquez, José Antonio
Moreno Ortiz, Alicia	Regional Universitario Carlos Haya (Málaga)	Ramiro, Almudena
Pastor Puello, Pablo	Universitario Ramón y Cajal (Madrid)	de la Pompa, José Luis
Rufián Andújar, Sebastián	Universitario de Valme (Sevilla)	Redondo, Juan Miguel
Rozado Castaño, José	Universitario Central de Asturias	de la Pompa, José Luis
Vázquez López-Ibor, Jorge	Puerta de Hierro (Madrid)	Andrés, Vicente

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 2012

Name	Hospital	CNIC Department
Beltrán Correas, Paula	Hospital Universitario Puerta de Hierro (Madrid)	Cardiovascular Development and Repair
García Salvador, José Juan	Hospital Universitario de Gran Canaria Dr. Negrin	Cardiovascular Development and Repair
González Torres, Luís	Hospital Universitario Virgen Macarena de Sevilla	Epidemiology, Atherothrombosis and Imaging
Roselló Lozano, Francisco Javier	Hospital de la Santa Creu i Sant Pau (Barcelona)	Epidemiology, Atherothrombosis and Imaging
Saravia, Gabriela	Hospital Universitario 12 de Octubre (Madrid)	Epidemiology, Atherothrombosis and Imaging

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Training Programs and Courses

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

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. The 2012 edition of the Jornada CICERONE was run in collaboration with the Fundación Interhospitalaria para la Investigación Cardiovascular and took place in the Hospital Clínico San Carlos, Madrid.

Dates: 14 - 15 September 2012
Attendees: 139

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: 16 - 17 November 2012
Venue: CNIC Lecture Hall
Attendees: 100

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Training Programs and Courses

VASCULAR BIOLOGY Course

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

Dates: 16-17 July 2012
Attendees: 88

Research Professionals

CNIC International Incoming Fellowships for Young Group Leaders

The CNIC IFF 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 competence, 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 under the FP7 Marie Curie Actions- PEOPLE- COFUND Programme. The EC contributes 40% of the total cost of the program.

Fellowships in 2012

Name	CNIC Department
Benedito, Rui	Cardiovascular Development and Repair

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Seminars, Events and Awards

January

23 **Duncan Odom**
Cambridge Research Institute
Cambridge, UK

27 **Rubén Nogueiras**
Faculty of Medicine
University of Santiago de Compostela
Santiago de Compostela, Spain

27 **Patricia Barral**
Cancer Research UK
London Research Institute
London, UK

30 **Jürgen Ruland**
Technical University of Munich
Klinikum rechts der Isar
Munich, Germany

February

3 **Pere Roca- Cusachs**
University of Barcelona
Institute for Bioengineering of Catalonia
Barcelona, Spain

13 **Olivier Pourquie**
I.G.B.M.C., Université de Strasbourg
Illrich Cedex, France

16 **María Luaces**
Hospital Universitario de Fuenlabrada
Universidad Rey Juan Carlos
Madrid, Spain

20 **Charles Murry**
Center for Cardiovascular Biology
Institute for Stem Cell and Regenerative Medicine
University of Washington
Washington, USA

27 **Peter Libby,**
Brigham and Women's Hospital
Harvard Medical School
Boston, USA

March

8 **Rene Botnar**
King´s College
London, UK

9-10 **CNIC Conference**
"Vascular Inflammation, Aging and Imaging"

12 **Roger J. Davis**
Howard Hughes Medical Institute
UMASS Medical School
Massachusetts, USA

26 **Sebastian Amigorena**
Institut Curie
Paris Cedex, France

April

8 **Thomas Morgan**
Vanderbilt University
Children's Hospital at Vanderbilt
Nashville, USA

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Seminars, Events and Awards

9 **Jeff Robbins**
Molecular Cardiovascular Biology
Children's Hospital Research Foundation
Cincinnati, USA

23 **Walter Koch**
Center for Translational Medicine,
Temple University
Philadelphia, USA

May

4 **María Navarro**
College of Life Sciences, University of Dundee
Dundee, Scotland

14 **Dietmar Vestweber**
Max-Planck-Institute of Molecular Biomedicine
Muenster, Germany

18 **CNIC Workshop**
"Mock Editorial Meeting"

21 **Cliff Tabin**
Harvard Medical School
Boston, USA

24 **Shankar Srinivas**
Oxford University
Oxford, UK

June

4 **Stephan Beck**
UCL Cancer Institute, University College London
London, UK

5 **Susana Gonzalo**
Saint Louis University School of Medicine
St. Louis, USA

8 **AD Hoc Cardiovascular Development and Repair Department Meeting**
"Life sciences, EMBL alumni and funding in Spain"

11 **Mone Zaidi**
Mount Sinai School of Medicine
New York, USA

14 **Sigolene Meilhac**
Institut Pasteur
Paris CEDEX, France

18 **Alan Paau**
Cornell University
Ithaca, New York, USA

20 **Carlos Fernández-Hernando**
New York University School of Medicine
New York, USA

21 **Jacky Goetz**
Institute of Genetics and Molecular
and Cellular Biology – IGBMC
Illkirch, France

25 **Martin R Bennett**
Addenbrooke's Centre for Clinical Investigation
Addenbrooke's Hospital
Cambridge, UK

July

9 **Holger Gerhardt**
Cancer Research UK, London Research Institute
London, UK

12 **Giorgio Lenaz**
University of Bologna
Bologna, Italy

18 **Joaquín López Herraiz**
Massachusetts Institute of Technology (MIT)
Cambridge, USA

25 **John Ryals**
Metabolon Inc.
Durham, USA

September

13 **First Meeting of the Madrid Zebrafish Club**
"Live imaging in the zebrafish"

14 **Jornada Cicerone**
"What you need to know about Cardiovascular Research"

17 **Ángel González Ureña**
Instituto Pluridisicplinar
Universidad Complutense de Madrid
Madrid, Spain

17 **Juan Pablo Couso**
School of Life Sciences, University of Sussex
Brighton, UK

20 **Yosuke Mukoyama**
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, USA

24 **Michele De Palma**
The Swiss Institute for Experimental Cancer
Research (ISREC), School of Life Sciences -
Swiss Federal Institute of Technology Lausanne
(EPFL)
Lausanne, Switzerland

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Seminars, Events and Awards

October

November

December

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Seminars, Events and Awards

Awards

Cardiovascular Development and Repair

Award: First award for no master students in the Biological and Biomedical Sciences category of the *'Certamen Arquímedes'* from the *Ministerio de Educación, Cultura y Deportes*
Awarded to: **Sergio Menchero**

Award: Special prize Astra Zeneca of the *'Certamen Arquímedes'* from the *Ministerio de Educación, Cultura y Deportes*
Awarded to: **Enrique Gallego**

Award: Poster prize, 12th International Conference on Limb Development and Regeneration, 3-7 June, 2012, Mont-Tremblant Canada
Awarded to: **Alberto Roselló-Díez**

Award: 2nd prize for a lecture at The Amsterdam Cardiovascular Development Meeting (Interuniversity Cardiology Institute of the Netherlands and the European Society of Cardiology), 7-9 November 2012
Awarded to: **Guillermo Luxán**

Award: EFSD Lilly Research Fellowship
Awarded to: **Tamas Roszer**

Award: International Early Career Scientist Award from the Howard Huges Medical Institute
Awarded to: **Simón Méndez-Ferrer**

Award: EHA Research Fellowship from European Hematology Association
Awarded to: **Abel Sánchez-Aguilera**

Award: Travel Award from the Society for Hematology and Stem Cells
Awarded to: **Joan Isern Marí**n

Vascular Biology and Inflammation

Award: VII Edition of *Premios Ciencias de la Salud* from *Fundación Caja Rural de Granada*
Awarded to: **Miguel Angel del Pozo**

Award: *Premio Carmen y Severo Ochoa* 2012 from the *Fundación Carmen y Severo Ochoa*
Awarded to: **Miguel Angel del Pozo**

Award: *Premio Impulsa* 2012 from the *Fundación Príncipe de Girona*
Awarded to: **Guadalupe Sabio**

Epidemiology, Atherothrombosis and Imaging

Award: Legend of Cardiovascular Medicine from the American College of Cardiology (ACC)
Awarded to: **Valentín Fuster**

Award: Honoris Causa from the *Universidad de Cádiz*
Awarded to: **Valentín Fuster**

Award: John F. Kenney Award from the Institute of North American Studies
Awarded to: **Valentín Fuster**

Award: Honoris Causa from *Universidad de La Plata*
Awarded to: **Valentín Fuster**
Award: Research Achievement Award from the American Heart Association (AHA)
Awarded to: **Valentín Fuster**

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Seminars, Events and Awards

Award: Honoris Causa from the *Universidad de Zaragoza*
Awarded to: **Valentín Fuster**

Award: *Premio Grande Covián* 2012 from the *Fundación Dieta Mediterránea* (FDM)
Awarded to: **José Mª Ordovás**

Award: *Grand Prix de la Science de l'Alimentation* from the AIG
Awarded to: **José Mª Ordovás**

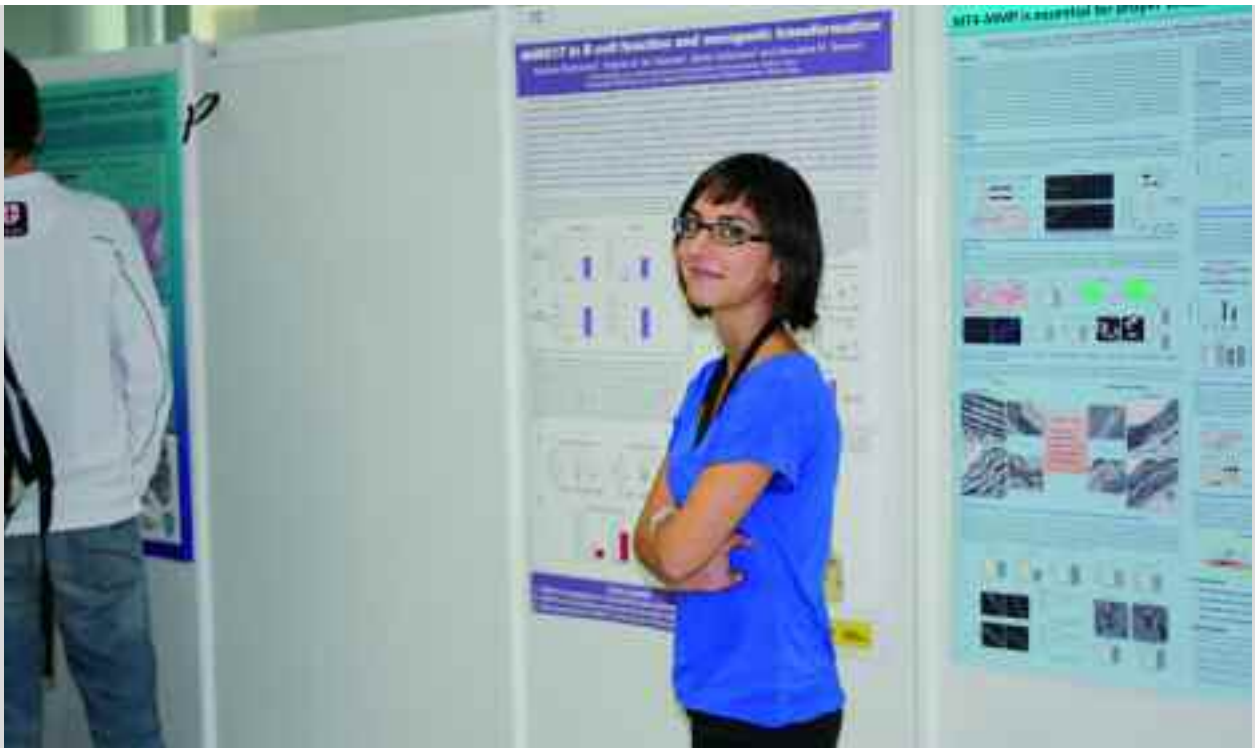
Award: *XXXI Lección Memorial Fernández-Cruz* from the *Fundación Fernández-Cruz*
Awarded to: **José Mª Ordovás**

Award: *Premio FENIL a la Divulgacion de la Ciencia de la Nutricion* from FENIL
Awarded to: **José Mª Ordovás**

Award: *Académico de Honor* from the *Real Academia de Medicina de Murcia*
Awarded to: **José Mª Ordovás**

Award: *Premio Sanitas MIR* 2012 from the *Fundación Sanitas, Ministerios de Sanidad y de Educación*
Awarded to: **Rodrigo Fernández Jiménez**

Award: First prize to best poster in the *Congreso de las Enfermedades Cardiovasculares* 2012: *Receptorβ3-adrenérgico: nueva diana terapéutica para reducir el tamaño del infarto. Estudio traslacional con resonancia magnética*, from the *Sociedad Española de Cardiología.*
Awarded to: **José Manuel García-Ruiz, David Sanz-Rosa, Jaime García-Prieto, Ana García-Alvarez, Leticia Fernandez-Friera, Mario Nuño-Ayala, Valentín Fuster and Borja Ibáñez**



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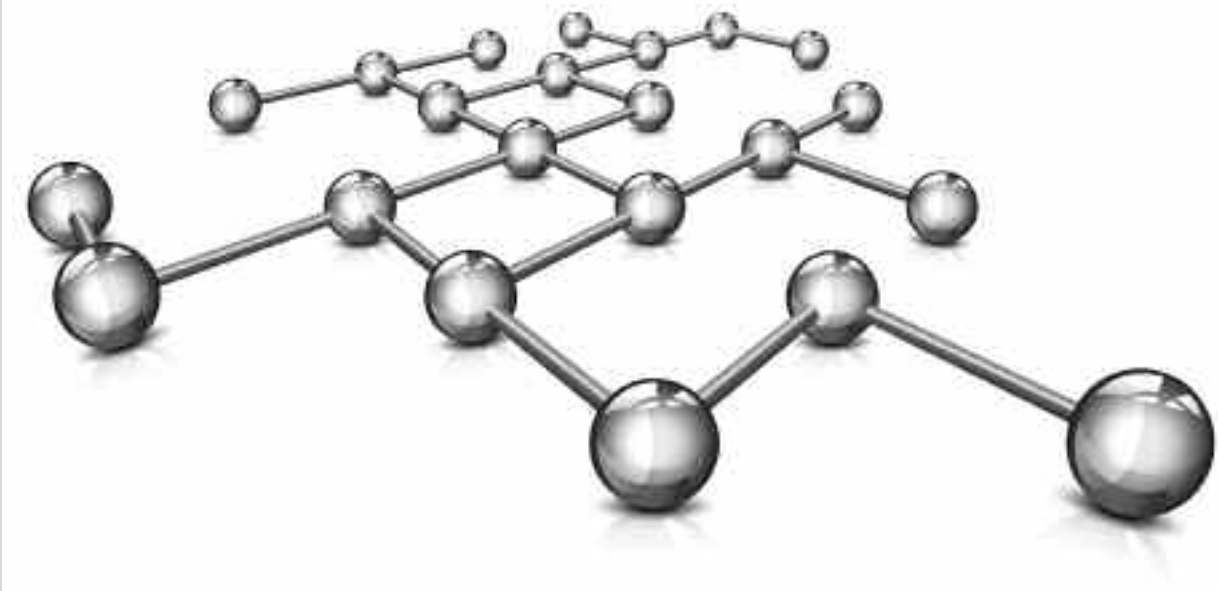
Strategic Alliances

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 a complex network based on close contacts with a wide range of institutions from different sectors.



In the last five years, the CNIC has established a strategic network with **institutions within the Spanish National Health System** to develop translational research projects and to identify and train the best investigators for these types of projects. During 2012 seven new collaboration agreements were signed with Spanish hospitals and their biomedical foundations.

At the level of **innovation**, the development of new therapies and drugs and the application of advanced technologies in the field of biomedical research require close collaboration with the **industrial sector**. The CNIC has established partnerships with companies from different sectors (pharmaceutical, biotechnology, medical technology and imaging, etc.) to take on cutting-edge research projects in these fields. Some of the main CNIC research projects are based on this type of collaboration. During 2012 the CNIC signed a research collaboration agreement with **Fina Biotech (Madrid)** and **the Academisch Medisch Centrum (Amsterdam)** for a validation study of genetic markers of the risk of restenosis after coronary stent implantation. The Center also had a strong presence at the **BioSpain** (Bilbao) and **BioEurope** (Hamburg, Germany) congresses, in order to offer its technological portfolio to some of the main international companies in the Pharma and Biotech sectors.

At the level of **training**, the CNIC-JOVEN Plan is being carried out thanks to collaborations that the Center has established with prestigious Spanish universities, research centers, foundations and scientific societies, as well as foreign biomedical research institutions such as the **Mount Sinai School of Medicine (New York, USA)** and **Johns Hopkins University (Baltimore, USA)**. During 2012, the Center also consolidated its collaboration with the **Universidad Autónoma de Madrid** and the **Spanish Society of Cardiology**, and new agreements have forged strong links with academia (**University of Oxford, Universidad de Alcalá, Universidad de Lleida, Universidad Politécnica de Madrid**) and the clinical sector (**Fundación Interhospitalaria para la Investigación Cardiovascular,** FIC). Intense efforts have also been made to expand the CNIC's educational Plan through the creation of new training programs with funds from the private sector (**Fundación La Caixa**) and the European Commission through **COFUND Programmes** for young group leaders (CNIC-IIF) and postdoctoral researchers (CNIC-IPP).

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Funding

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, by 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. Under the terms of this agreement these companies pledged their commitment to funding the CNIC up until 2012. This commitment has been extended until 2020.

Shortly after the agreement was signed, on January 24, 2006, this group of companies was formally constituted as the ProCNIC Foundation. Through its creation, the participating companies have made a long-term commitment to biomedical research that represents the most significant act of business sponsorship in recent years in terms of the amount of funding it provides, 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).

New companies have joined the ProCNIC Foundation since its creation, and there are now 13 members: Acciona, Banco Santander, BBVA, Endesa, Fundación Abertis, Fundación Ramón Areces, Gas Natural, Grupo Prisa, Inditex, La Caixa, Repsol YPF, Fundación de Investigación Mutua Madrileña, and Telefónica. This funding scheme 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 support 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.

Public Funding

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Funding

Private Funding

Fundación pro cnic

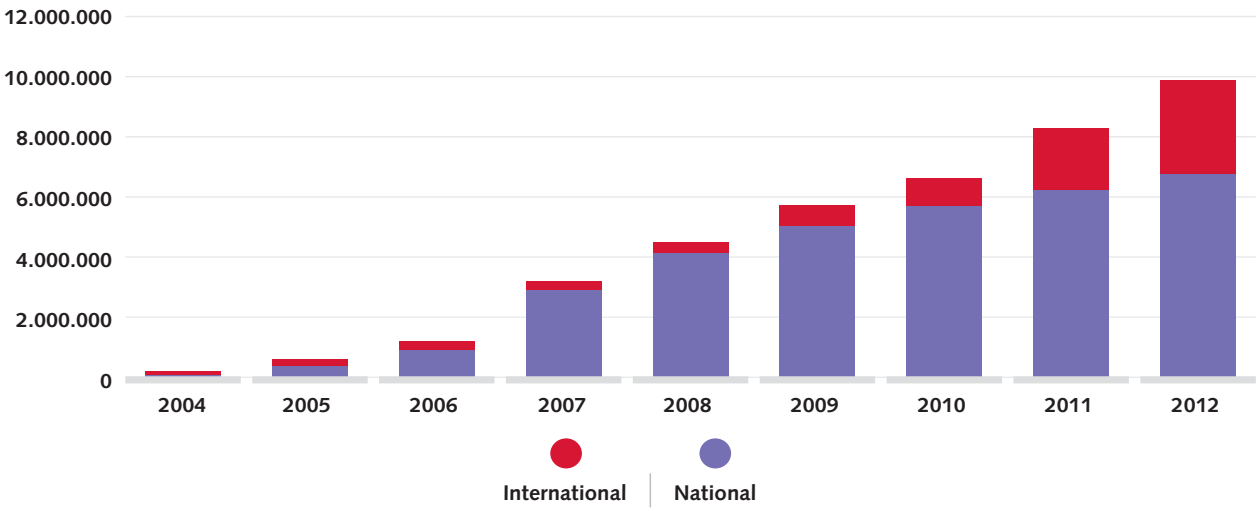
acciona · BBVA · fundación abertis · endesa · gasNatural fenosa · INDITEX · "la Caixa" · PRISA · Fundación REPSOL · Telefónica

International Collaboration

Mitsubishi Corporation

Competitive funding

Since 2004, the CNIC has attracted more than €18m from international competitive sources to fund projects, contracts and awards. The figure for national funds is around €43m; however, in recent years the CNIC's attraction of international resources has almost matched new national funding (not counting the Severo Ochoa award). Highlights of 2012 include an advanced ERC grant, an award from the Progeria Research Foundation, and the successful negotiation of a second COFUND project for the recruitment of postdoctoral researchers, which will become active in the first half of 2013.



Funds awarded to the CNIC up to 2012. Funds for individual projects are distributed evenly over the years of activity to illustrate the even growth of stable funding.

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Patent Portfolio

CNIC PATENT PORTFOLIO 2012

Nineteen inventions are currently being filed, eleven of them in cooperation with other institutions. Of these inventions, one is licensed, and another three are the cores of active due-diligence procedures.

TITTLE	INVENTORS	APPLICANTS	PATENT APPLICATIONS
Selective peptides that inhibit the biological activity of calcineurin	Juan Miguel Redondo, Antonio Rodriguez, Sara Martínez	CSIC, CNIC	ES, PCT, EP, US
Método de identificación de células madre mesenquimales senescentes	Enrique Samper, Juan Camilo Estrada, Antonio Bernad	CNIC	ES, PCT, EP, US
Capsule for the prevention of cardiovascular diseases	Marta Guerrero, Anna Orriols, Pablo Martín, Manuel Raga	CNIC, FERRER	EP, PCT,
Superficie bioactiva capaz de modificar genéticamente células o tejidos biológicos y su uso	Manuel Ángel González, Juan Carlos Ramírez, Antonio Bernad Miana, David Horna Tomás, Salvador Borrós Gómez, Anna Cifuentes	CNIC, IQS, URL	ES, PCT
Uso de compuestos anticalcineurina para el tratamiento de patologías que cursan con neovascularización ocular	Juan Miguel Redondo, Arántzazu Alfranca González	CNIC	ES, PCT
Uso de inhibidores de la TAK-1 en la protección y en el fracaso de la membrana peritoneal	Miguel Ángel del Pozo, Raffaele Strippoli, Manuel López Cabrera, Ignacio Benedicto	CIBERehd, CNIC, CSIC	ES, PCT
Compuestos para el tratamiento de daños cardiacos tras isquemia/reperfusión	Carlos Zaragoza Sánchez, Carlos Antonio Tarín, Mónica Gómez Parrizas, Begoña Lavín Plaza	CNIC	ES, PCT
Uso de células mesenquimales Nestina positivas para el mantenimiento de la hematopoyesis/PCT: Células multipotenciales Nestina positivas	Simón Méndez Ferrer, Álvaro Urbano Ispizua	CNIC , Hospital CLINIC, SAS	ES, PCT, EP
CAVEOLIN-1 in tumor-associated fibroblasts as biomarker for tumor progression	Miguel Ángel del Pozo, Jacky Goetz	CNIC	EP, PCT
MT1-MMP Substrates as biomarkers of inflammatory angiogenesis	Alicia García Arroyo, Agnieszka Koziol, Francesc Canals, Núria Colomé Calls, Joaquín Arribas	CNIC , ICREA, VHIO, VHIR	EP, PCT
p38 MAPK gamma and delta for use as biomarkers of NAFLD	Guadalupe Sabio Buzo, Bárbara González Terán, Edgar Bernardo Vasco, Nuria Matesanz Parellada, María de los ángeles Verdugo Becerra, Miguel Marcos Martín, Lourdes Hernández Cosido, Luis E. Ortega Martín-Corral	CNIC, CNB, Universidad de Salamanca	EP
Marcador molecular de potencia terapéutica de células madre mesenquimales humanas y sus usos	Manuel Ángel González, Antonio Bernad Miana, María Tomé	CNIC	ES

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Patent Portfolio

TITTLE	INVENTORS	APPLICANTS	PATENT APPLICATIONS
Nanopartículas recubiertas de gelatina	Fernando Herranz Rabanal, Jesús Ruíz-Cabello Osuna, Beatriz Salinas Rodriguez	CNIC, UCM	ES
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	CNIC , EMBL	EP
Uso de agonistas selectivos de resceptores beta-3 adrenérgicos para el tratameinto de hipertensión pulmonar	Borja Ibañez Cabeza, Valentín Fuster Carulla y Ana García-Álvarez	CNIC , CLINIC	ES
Secuencias nucleotídicas motivo que dirigen la localización de los ácidos nucleicos	Francisco Sánchez Madrid, María Mittelbrum Herrero, Cristina Gutiérrez Vázquez, Fátima Sánchez Cabo y Carolina Villarroya Beltri	CNIC, UAM	ES
Método de aislamiento de precursores mesenquimales	Beatriz González Gálvez, Aurora Bernal Mera, Nuria San Martín	CNIC	ES
LxVP-mediated calcineurin inhibition in macrophages	Juan Miguel Redondo, Amelia Escolano	CNIC	EP
eEF2/eEF2K as therapeutic target for treating TNF-alpha-related diseases	Guadalupe Sabio Buzo, Bárbara González Terán	CNIC	EP

ES - Spanish patent

PCT - International patent

EP - European patent

US - US patent

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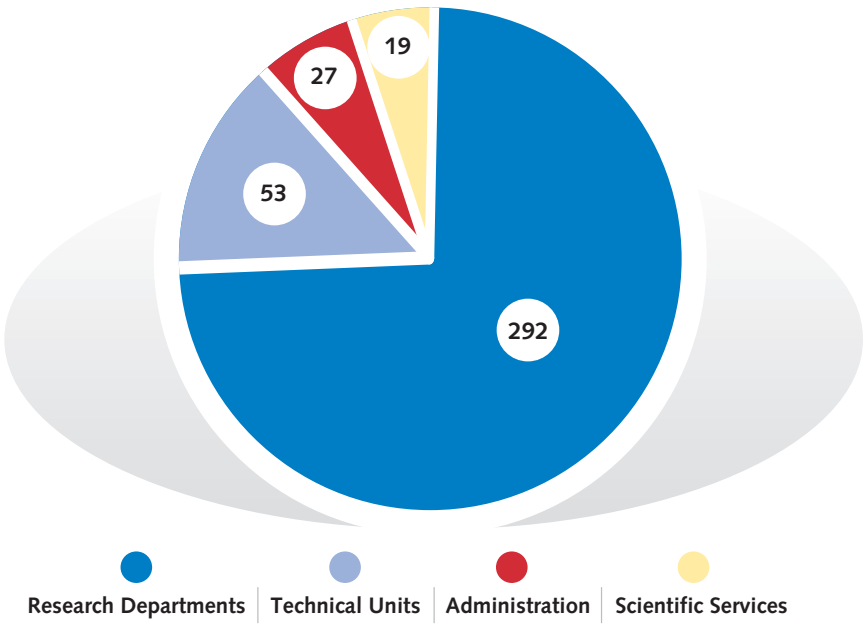
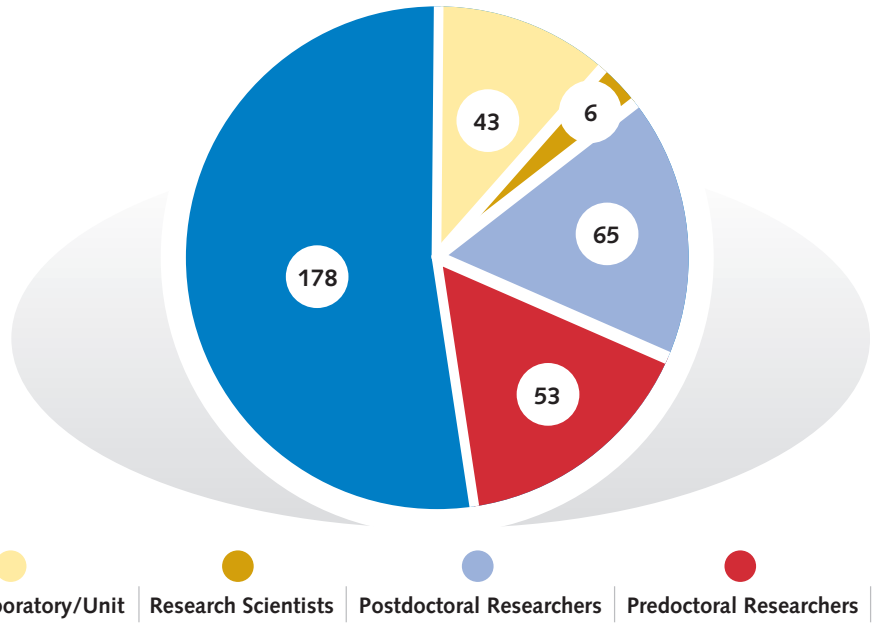
Staff Figures

CNIC staff 2012 (391)



CNIC research staff 2012 (345)



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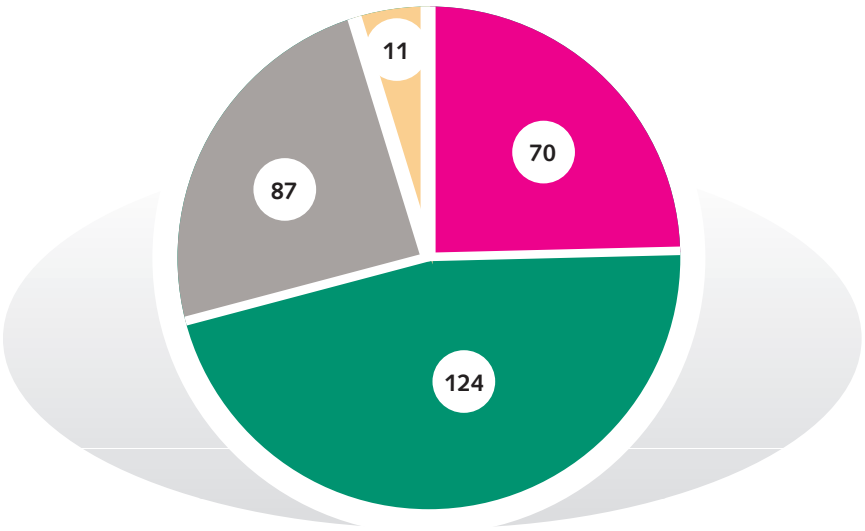
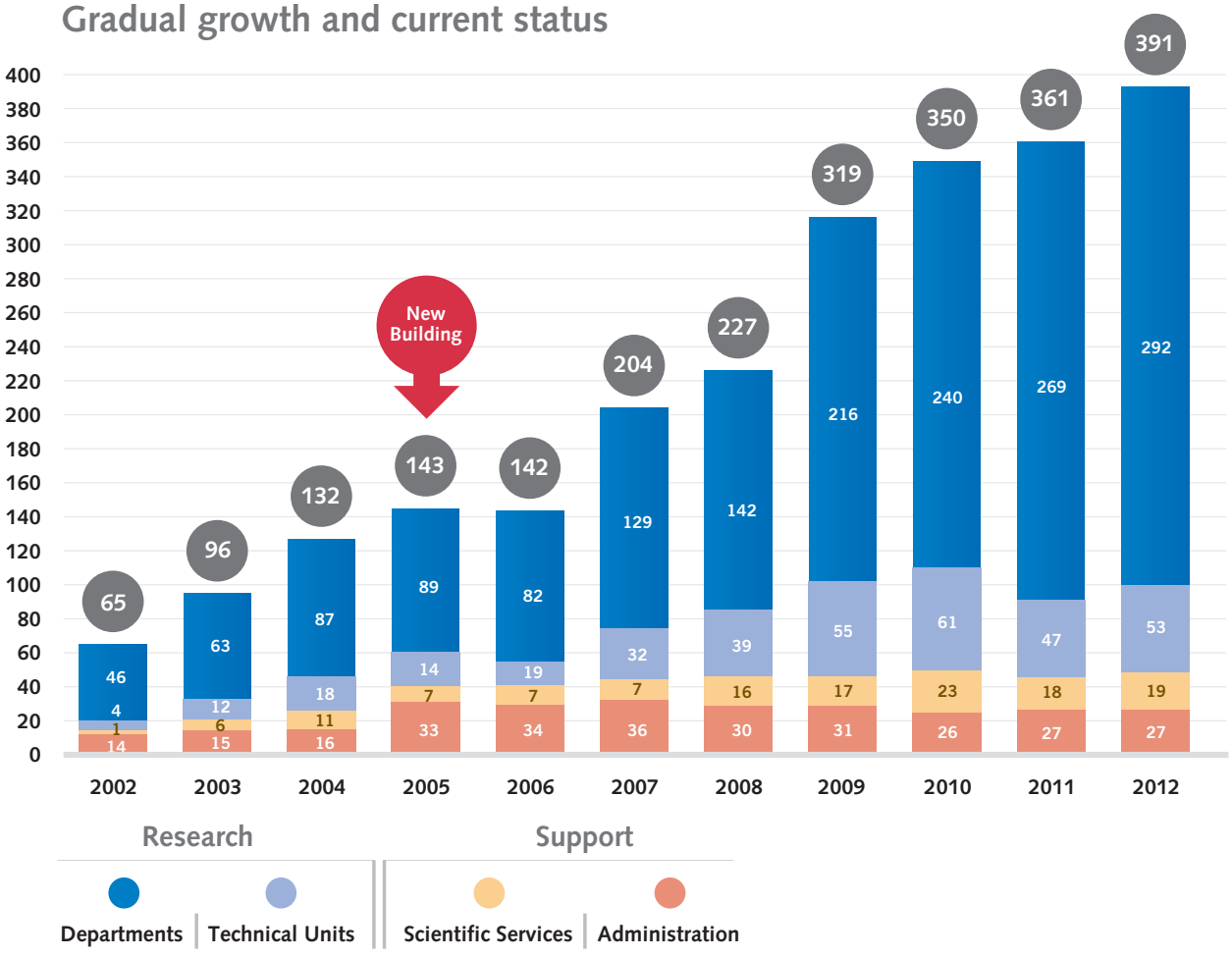
Staff Figures

Staff by department 2012 (292)



Gradual growth and current status



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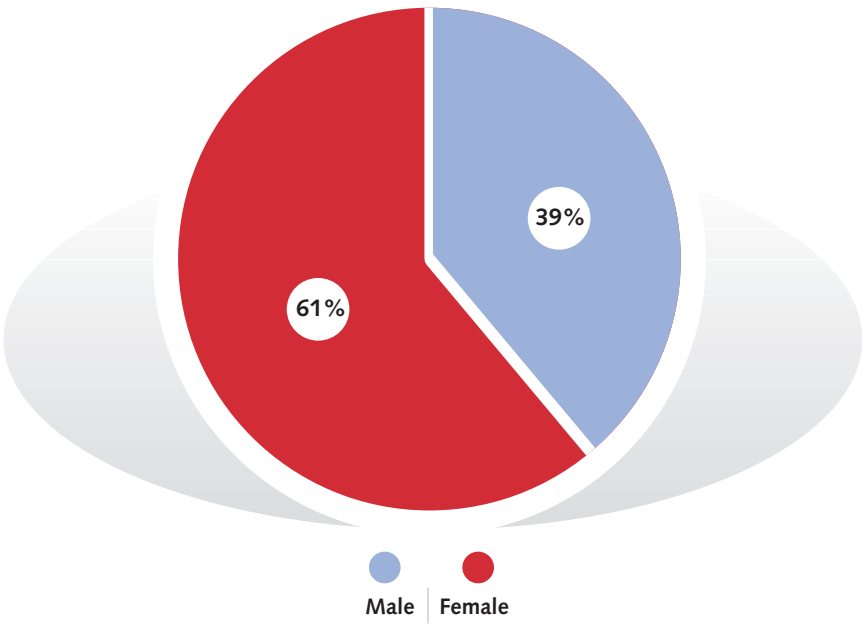
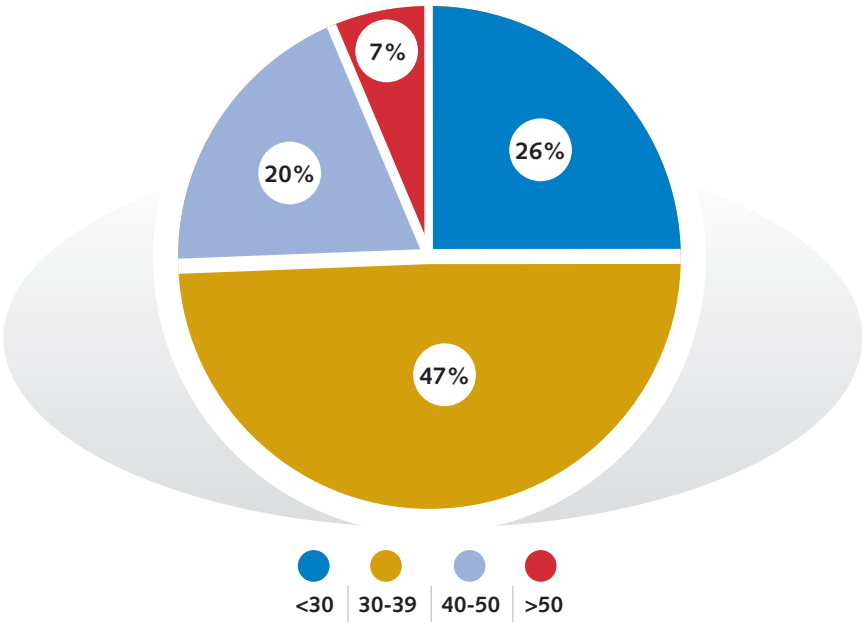
Staff Figures

Gender distribution 2012



Age distribution 2012 in percentage



Fundaciónprocnic

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