cnïc

Fundación
Centro Nacional de
Investigaciones
Cardiovasculares
Carlos III

SCIENTIFIC REPORT ´09

SCIENTIFIC REPORT ´09

cnïc

SCIENTIFIC REPORT ´09

cnïc

SCIENTIFIC

REPORT ´09

www.cnic.es

SCIENTIFIC

Dear friends,

The last year has been a crucial and exciting period in the growth of the CNIC. Almost 100 new staff joined the Center in 2009, bringing the total personnel from 227 to 319. This growth included the establishment of leading research groups in the departments of Epidemiology (José María Ordovás), Developmental Biology (José Luis de la Pompa and Ignacio Flores), Regenerative Cardiology (José Antonio Enríquez) and Atherothrombosis & Imaging (Vicente Andrés, Borja Ibañez and Luis Jesús Jiménez-Borreguero). In addition to these senior groups, three talented young researchers joined the Center as junior group leaders: Enrique Lara-Pezzi (Developmental Biology), David Sancho Madrid (Vascular Biology and Inflammation) and Beatriz González Gálvez (Regenerative Cardiology).

Last year also saw rapid growth in the CNIC's scientific production, with a significant increase in the volume and quality of published articles, including several in the leading journals in basic and clinical cardiovascular research. It gives us great pleasure to witness this rapid growth in the CNIC's scientific muscle, which has generated a tangible sense of dynamism that bodes very well for the future.

Our goal for the CNIC is for it to establish itself as an international reference center for cardiovascular research and translational medicine. Such high ambition requires financial stability in the long term, and the solid support of the ProCNIC Foundation is an essential ingredient in this. On June 29 last year, the agreement with the ProCNIC Foundation was extended until 2020, ensuring that despite the current delicate financial climate, the CNIC continues to march forward with confidence.

The CNIC's translational research program moved into a new phase in 2009 with the financing of the FOCUS project by the European Commission. This study, led by the CNIC, aims to test the fixed-dose-combination (polypill) concept for the prevention of cardiovascular disease in populations with diverse socio-economic characteristics. FOCUS will test a fixed-dose-combination pill, jointly developed by the CNIC and Grupo Ferrer, in a clinical trial involving two countries in Europe—Spain and Italy—and three in South America—Argentina, Brazil and Paraguay. Apart from the CNIC and Ferrer, the study includes eight other partners in centers throughout the world.

REPORT ´09

Another important CNIC translational study, PESA (Progression of Early Atherosclerosis in Santander), was approved at the end of 2009. The study will use advanced imaging techniques to detect the prevalence and progression of subclinical atherosclerosis in a population of 5000 workers aged between 40 and 54 years at the Banco Santander, and will evaluate the association of these clinical parameters with the presence of genetic, molecular-genetic, environmental and life-style risk factors.

The essential underpinning for these clinical studies is the development of pioneering imaging technologies. Preparations for the new imaging lab are at an advanced stage, and in December the CNIC signed a contract with Philips for the installation of new imaging equipment. This equipment will be used to establish innovative non-invasive imaging protocols for animal research and diagnosis in human patients, and will thus work at the interface between basic and translational research.

The CNIC's commitment to training the leading investigators of tomorrow was advanced by participation last year in the Campus de Excelencia run by the Universidad Autónoma de Madrid and the Spanish Research Council (CSIC). The CNIC also has a strong interest in international training. For this reason we encourage students to enroll on international PhD programs, and the Center, through its Cardiojoven and Cardio-imagen programs, has sent ten researchers to obtain expert training in cardiovascular imaging research at the Mount Sinai Medical School.

The coming months will see further developments, including the installation of infrastructure for large animal work and imaging. Looking back, the team of talented scientists, technicians and support personnel at the CNIC can feel justly satisfied with the progress made over the last year; and we share their keen enthusiasm for the challenges ahead.

Valentín Fuster. *General Director*

Miguel Torres. *Associate Director*

Index

Basic Research Departments

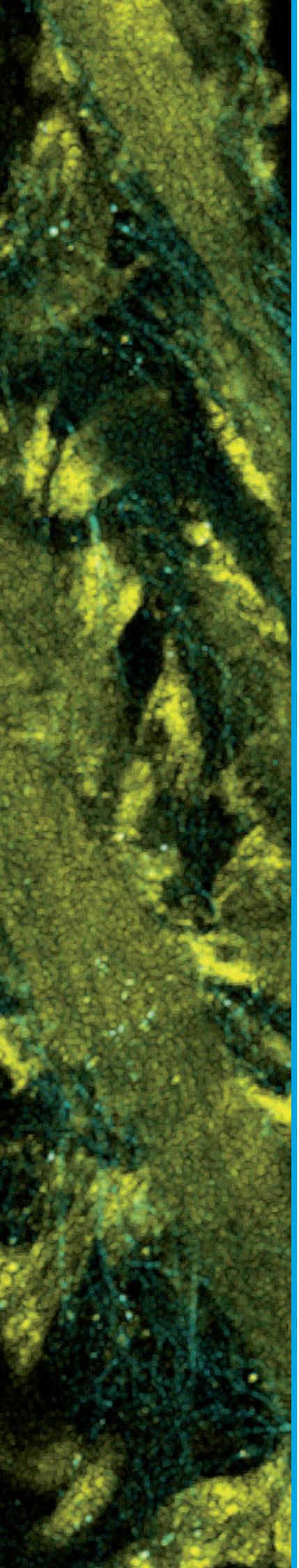
Applied Research Departments

Technical Units

Appendix

Basic Research Departments

1 *Cardiovascular Developmental Biology*



Basic Research Departments

Cardiovascular Developmental Biology

The CDB department investigates the origin, differentiation and integration of cardiovascular cell lineages in chick, mouse and zebrafish models, using complementary experimental embryology, genetic and mass screening approaches.

This focus is complemented by studies in classical models such as the limb primordium and mammalian blastocyst.

Department Director:	*Miguel Torres*
Department Manager:	*Beatriz Ferreiro*
Logistics:	*Teresa Casaseca*
Administrative support:	*Sandra Cillero*

Genetic control of organ development and regeneration

Head of Laboratory: *Miguel Torres*

Research Scientists: *Nadia Mercader*
Laura Carramolino

Postdoctoral Researchers: *Cristina Clavería*
Adrian Grimes
Laura Padrón

Predoctoral Researchers: *Catalina Ana Rosselló*
Clara García-Andrés
Juan Manuel González-Rosa
Daniel Mateos
Marina Peralta
Alberto Roselló
Cristina Villa

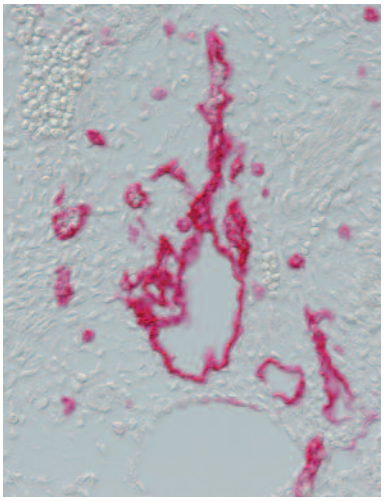
Technicians: *Joana Fuentes*
Víctor Martín
Rocío Sierra
Silvia Vela

> RESEARCH INTEREST

Our work focuses on two areas: the role of transcription factors in cardiovascular development and regeneration, and the development of new genetic models to study the cellular basis of organ morphogenesis and regeneration.

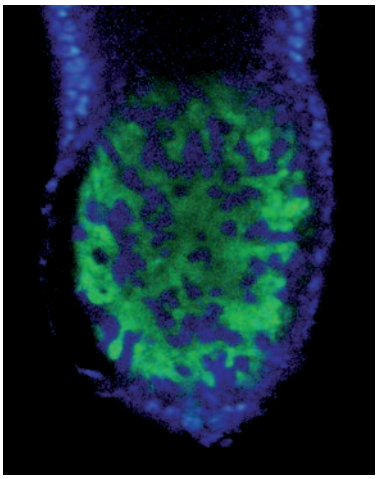
In the first area, we have generated gain- and loss-of-function mouse models of the homeodomain trancription factors Meis and Pbx, revealing new roles for these factors in cardiovascular development. These studies have identified a new morphogenetic role for platelets during lymphangiogenesis, and further suggest a general role for platelets in vascular morphogenesis and remodeling that might be relevant to vascular disease. Our work on heart regeneration focuses on the epicardium, the outermost layer of the vertebrate heart, which plays an important role during cardiac development as a source of progenitor cells and signals controlling myocardial proliferation. A role for the epicardium in regeneration has also been suggested, but its exact function here is still unkown. Using the zebrafish model system we are analyzing the formation of the epicardium in vivo and generating tools to study the fate of epicardium derived cells and their role during cardiac regeneration.

We have developed two new strategies for analyzing morphogenesis. In one, an in vivo clonal analysis is being 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 the role of cell competition in the early mouse embryo as a driving force for the maintenance of cell quality in stem cell pools; this work has been submitted for publication.

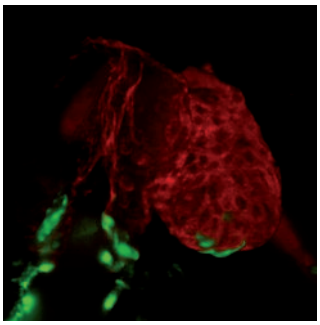


Lyve-1 immunohistochemistry (red) identifies nascent lymphatic vessels in the mouse embryo

1 Cardiovascular Developmental Biology



Green and cyan fluorescent proteins report induced genetic mosaicism in the mouse epiblast



Whole mount immunohistochemistry of a Tg(wt1b:GFP) zebrafish heart at three days post fertilization, revealing myocardium in red and epicardial cells and the sinus venosus in green

> MAJOR GRANTS

- **COST – European Cooperation in the field of Scientific and Technical Research (BM0805). PI and Action Chair, M. Torres**
- **Ministerio de Ciencia e Innovación. FIS RETICS (TERCEL; RD06/0010/0008). PI, M. Torres**
- **Ministerio de Ciencia e Innovación (BFU2006-10978). PI, M.Torres**
- **Ministerio de Ciencia e Innovación (BFU2008-00212/BMC). PI, N. Mercader**
- **Comunidad de Madrid (CM S-SAL0190-2006). PI, M. Torres**

SELECTED PUBLICATIONS

Carramolino L, Fuentes J, Garcia-Andres C, Azcoitia V, Riethmacher D, Torres M. **Platelets play an essential role in separating the blood and lymphatic vasculatures during embryonic angiogenesis**. *Circ Res* (accepted)

Mercader N, Selleri L, Criado LM, Pallares P, Parras C, Cleary ML, Torres M. **Ectopic Meis1 expression in the mouse limb bud alters P-D patterning in a Pbx1-independent manner.** *Int J Dev Biol* (2009) 53: 1483-94

Boot MJ, Westerberg CH, Sanz-Ezquerro JJ, Coterell J, Schweitzer R, Torres M, Sharpe J. **In vitro whole-organ imaging: Quantitative 4D analysis of growth and dynamic gene expression in mouse limb buds**. *Nat Methods* (2008) 5: 609-612

Burn SF, Boot MJ, de Angelis C, Doohan R, Arques CG, Torres M, Hill RE. **The Dynamics of Spleen Morphogenesis**. *Dev Biol* (2008) 318: 303-11

Duran AC, Fernandez B, Grimes AC, Rodriguez C, Arque JM, Sans-Coma V. **Chondrichthyans have a bulbus arteriosus at the arterial pole of the heart: morphological and evolutionary implications**. *J Anatom* (2008) 213: 597-606

Intercellular signaling in cardiovascular development and disease

Head of Laboratory: *José Luis de la Pompa*

Postdoctoral Researchers: *Jesús Chamorro*
Marta B. Evangelista
Donal MacGrogan
Meritxell Nus Cimeno
Belén Prados Pinto

Predoctoral Researchers: *Gonzalo del Monte*
Gaetano D'Amato
Alvaro González Rajal
Luis Luna-Zurita
Guillermo Luxán
Julianne Münch

Technicians: *Vanessa Bou*
Ana Cabrero
Eva García
Patricia Martinez

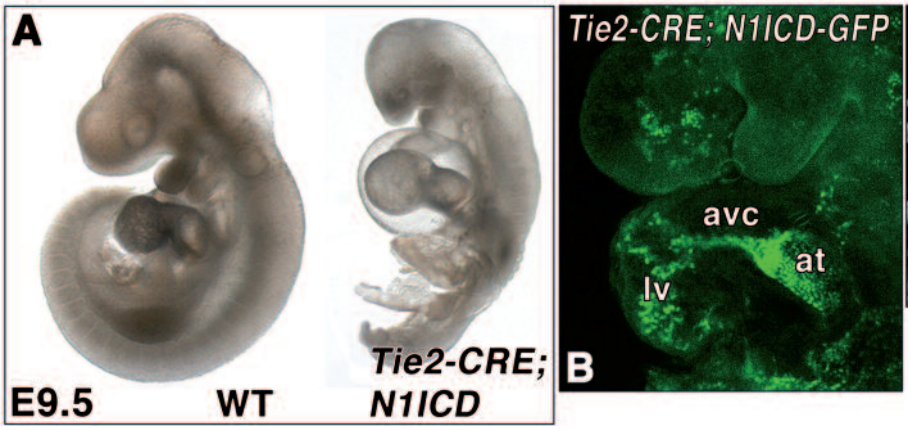
> RESEARCH INTEREST

We are interested in the molecular mechanisms that regulate cardiovascular development, homeostasis and disease. Most of our effort centers on the study of the Notch pathway, which is involved in many processes during vertebrate cardiac development and disease.

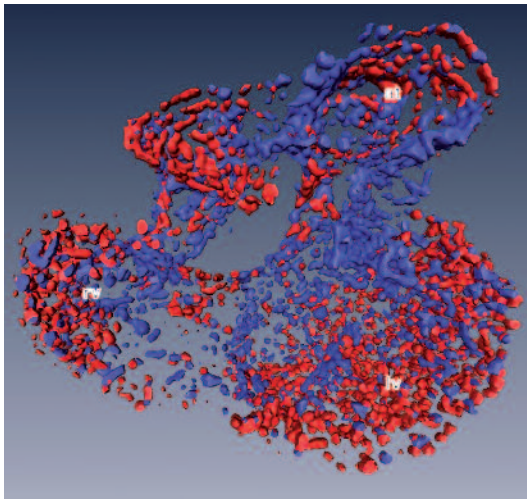
Our work over the last year focused on the role of Notch as a promoter of cardiac valve formation. We found that Notch activity in the endocardium—the inner endothelial lining of the heart—intersects with a myocardial signal, Bmp2, to activate a mesenchymal gene program that results in the formation of the valve primordia. Our work in this area has characterized the interplay between endocardium and myodcardium that underlies the role of Notch in this process.

We are currently conducting imaging and functional studies to define the expression and function of Notch in epicardium and coronary vessel development and to explore how the interplay between different Notch ligands and receptors generates signal specificity during chamber development. These studies are complemented by genetic manipulation of zebrafish to examine the role in heart and fin regeneration of Notch and other molecules identified in genomic screens.

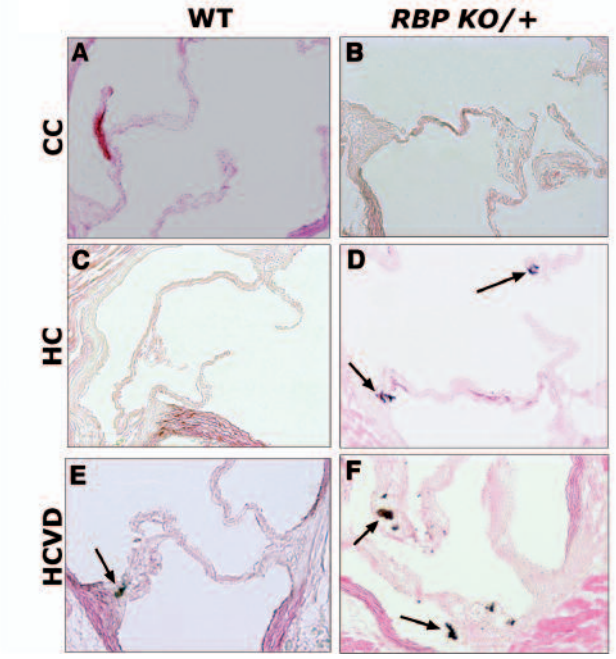
For our work on the adult heart we have established a pioneering mouse model of aortic valve stenosis, which we are using to study the role of Notch in this disease in combination with mouse genetics, cell culture and analysis of human pathological samples. In the future we plan to conduct similar studies with other carefully engineered mouse models, and to incorporate genetic and epidemiologic studies in patients. These studies will provide a clearer understanding of the molecular mechanisms underlying of the contribution of altered Notch signaling to neonatal and adult cardiac disease.



Mouse embryos engineered to constitutively express Notch 1 in endocardium (Tie2-Cre;N1ICD) ectopically express mesenchyme genes in chamber endocardium. *A) wild-type (WT) and Tie2-Cre;N1ICD E9.5 embryos. (B) Endocardial expression of Notch 1 (indicated by green fluorescence) in a Tie2-Cre;N1ICD embryo. at, atrium; avc, atrioventricular canal; lv, left ventricle.*



Computer reconstruction (Amira 3D) of the spatial distribution of the activated Notch1 receptor (N1ICD) in a WT E9.5 mouse heart. *N1ICD is labeled red and cell nuclei are blue. Note the predominant N1ICD expression in the ventricles (lv, rv) and atria (at).*



Mice deficient for the Notch effector RBPJK develop aortic valve stenosis. *(A, B) WT and RBPJK heterozygous (RBP KO/+) mice fed a normal diet (CC) have normal aortic valves. (C, D) RBP KO/+ mice fed a hypercholesterolemic diet (HC) show signs of valve calcifiaction (arrows). (E, F) RBP KO/+ mice fed a hypercholesterolemic diet plus vitamin D show signs of severe calcification (arrows in F).*

> MAJOR GRANTS

- **European Commission FP6 (LSHM-CT-2005-018630)**
- **European Commission FP7, Initial Training Network (215761)**
- **Ministerio de Ciencia e Innovación (SAF 2007-62445)**
- **Ministerio de Ciencia e Innovación. FIS RETICS (TERCEL; RD06/0010/1013)**
- **Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA II; RD06/0014/0038)**
- **Comunidad de Madrid (P-2006/ BIO-194). Coordinator and PI, JL de la Pompa**
- **Centro Nacional de Investigaciones Cardiovasculares (FPIT CNIC-09)**
- **Fundació La Marató TV3 (081731)**

SELECTED PUBLICATIONS

Ferjentsik Z, Hayashi S, Dale JK, Bessho Y, Herreman A, De Strooper B, del Monte G, de la Pompa JL, Maroto M. **Notch is a critical component of the mouse somitogenesis oscillator and is essential for the formation of the somites.** *PLoS Genet* (2009) 5: e1000662

Gonzalez-Garcia S, Garcia-Peydro M, Martin-Gayo E, Ballestar E, Esteller M, Bornstein R, de la Pompa JL, Ferrando AA, Toribio ML. **CSL-MAML-dependent Notch1 signaling controls T lineage-specific IL-7R{α} gene expression in early human thymopoiesis and leukemia.** *J Exp Med* (2009) 206: 779-91

Perez-Pomares JM, de la Pompa JL. **Tissue-patterned embryonic interactions in heart development: cell versus non-cell-autonomous molecular signalling and the origin of CHD.** *Nat Rev Cardiol (CNIC Edition)* (2009) 6: 73-8

de la Pompa JL. **Notch signaling in cardiac development and disease.** *Pediatr Cardiol.* (2009) 30: 643-50

Functional genomics of embryonic pluripotency and heart development

Head of Laboratory: *Miguel Manzanares*

Postdoctoral Researchers: *Susana Cañón*
Mª. Eva Alonso
Cristina Arias

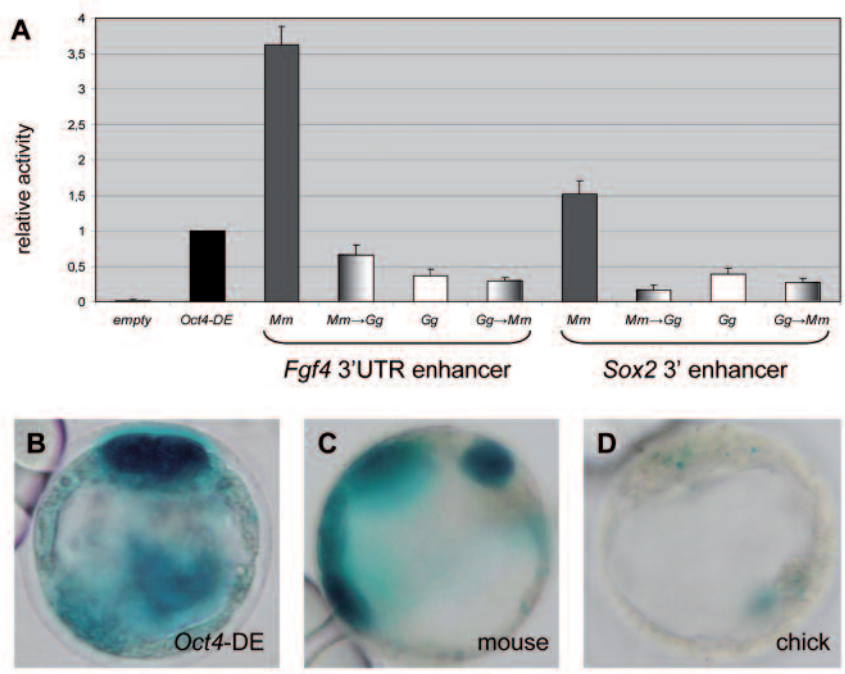
Predoctoral Researchers: *Bárbara Pernaute*
Beatriz Fernández-Tresguerres
Teresa Rayón
Melisa Gómez-Velázquez

> RESEARCH INTEREST

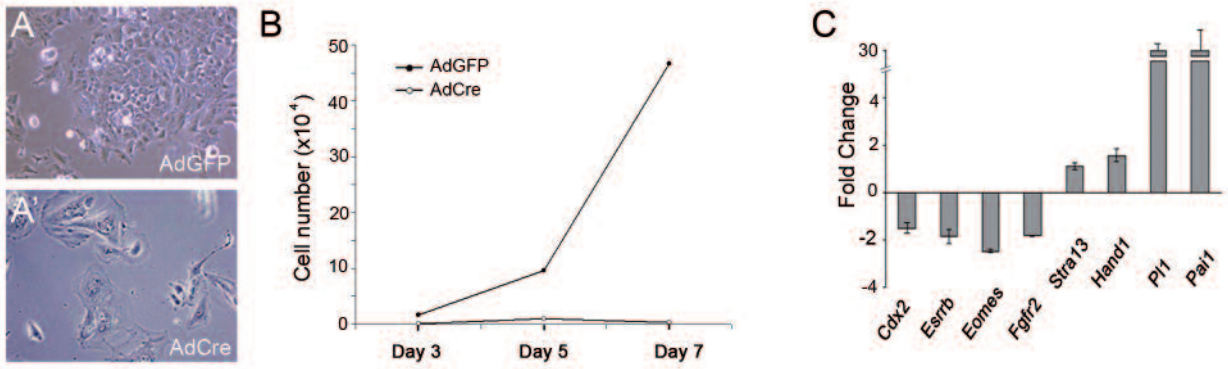
How the genome is co-ordinately regulated during development is one of the major unanswered questions in modern biology. We are exploring this issue by means of comparative and functional approaches, with the aim of understanding how gene regulatory networks were assembled during evolution and how this determines their function.

We are particularly interested in understanding the function of the gene regulatory network that controls embryonic pluripotency in the mouse embryo. Comparison with other vertebrates to determine the degree of conservation of these genes and their interactions shows that the core pluripotency factors (Oct4-Sox2-Nanog) were newly assembled into a network in the mammalian lineage and that downstream target genes of this core set were recruited through the appearance of novel enhancer elements. We are also exploring the role of miRNAs as a second layer of regulation in the establishment of extraembryonic stem cell populations.

Another area of interest is the potential regulatory function during development of intergenic genomic regions that have been identified with human diseases through genome-wide studies. These studies include analysis of the genomic regions associated with increased risk of type II diabetes and obesity as well as investigation into the role of p63 and its downstream regulatory network in human disease.



***A**, The mouse Fgf4 and Sox2 loci are associated with high enhancer activity. ES cells were transfected with genomic fragments containing the Fgf4 or Sox2 enhancers from mouse (Mm) or chick (Gg) or with versions in which the minimal mouse functional site was substituted by the equivalent chick sequence (Mm→Gg) or vice versa (Gg→Mm). **B-D**, Enhancer activity in transgenic blastocysts of the mouse Fgf4 3'UTR enhancer (C) and the equivalent chick genomic region (D). The activity of the mouse Oct4 distal enhancer in the inner cell mass is shown as a positive control (B).*



*Mouse trophoblast stem (TS) cells stop proliferating and differentiate upon loss of miRNAs. Cre-induced deletion of a conditional Dicer allele caused TS cells to change morphology (**A**, **A'**), stop proliferating (**B**) and to downregulate trophoblast stemness markers such as Cdx2 and upregulate genes involved in terminal differentiation such as Hand1 and Pl1 (**C**).*

Transgenic mouse embryo carrying a lacZ-linked genomic region from the Dlx5-Dlx6 intergenic region, which is a target of the regulator factor p63 and is deleted in cases of human Split Hand Foot Malformation. Expression of the lacZ reporter is observed in the eye, branchial region, tail and limb primordia.

> MAJOR GRANTS

- **European Commission FP7. EuroSyStems (200720)**
- **Ministerio de Ciencia e Innovación (BFU2008-00838)**
- **Ministerio de Ciencia e Innovación. CONSOLIDER Project (CSD2007-0008)**

SELECTED PUBLICATIONS

Ragvin A, Moro E, Fredman D, Navratilova P, Drivenes O, Engström PG, Alonso ME, de la Calle Mustienes E, Gomez-Skarmeta JL, J Tavares MJ, Casares F, Manzanares M, van Heyningen V, Molven A, Njølstad PR, Argenton F, Lenhard B, Becker TS. **Long-range gene regulation links genomic type 2 diabetes and obesity risk regions to *HHEX*, *SOX4* and *IRX3*.** *PNAS* (accepted)

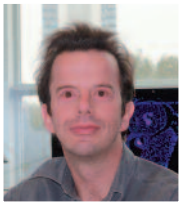
Pernaute B, Canon S, Crespo M, Fernandez-Tresguerres B, Rayon T, Manzanares M. **Comparison of extraembryonic expression of *Eomes* and *Cdx2* in pre-gastrulation chick and mouse embryo unveil regulatory changes along evolution.** *Dev Dyn* (accepted)

Alonso ME, Manzanares M. **The regulatory basis of common disease: how can genome-wide association studies help us understand cardiovascular disorders?** *Nat Rev Cardiol (CNIC edition)* (2009) 6: 55-60

Alonso ME, Pernaute B, Crespo M, Gomez-Skarmeta JL, Manzanares M. **Understanding the regulatory genome.** *Int J Dev Biol* (2009) 53: 1367-78.

Quijano C, Tomancak P, Lopez-Marti J, Suyama M, Bork P, Milan M, Torrents D and Manzanares M. **Selective maintenance of *Drosophila* tandemly-arranged duplicated genes during evolution.** *Genome Biol* (2008) 16: R176.

Stem cells in organ generation, regeneration and aging



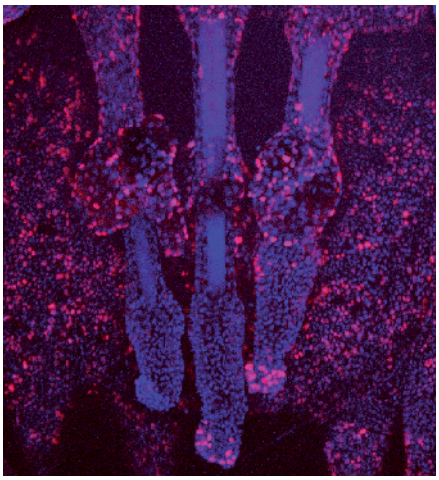
Head of Laboratory: *Ignacio Flores*

Predoctoral Researchers: *Dorota Bednarek*
Esther Aix

Technician: *Irene de Diego*

> RESEARCH INTEREST

Recent evidence acquired through radiocarbon dating of DNA unequivocally establishes that human hearts renew their own cells in adult life. This finding opens up the possibility of developing treatment strategies to stimulate heart regeneration as required, for example, after a heart attack or in degenerative syndromes. Achievement of this goal requires a deep understanding of the nature of the replicating cells, their putative progenitors and the pathways that control their fate. In the coming years, we plan to characterize the location, frequency and status of different stem cell populations and their progeny during organogenesis and aging, focusing primarily on cardiac stem cells. Our experimental approach will build on our recent finding that longer telomeres are a characteristic feature of adult stem cells. We also plan to assess whether cell competition takes place during organogenesis and tissue maintenance, by combining populations of cells with distinct contents of molecules related to cancer or aging. Through these efforts, we hope to achieve a more complete knowledge of the role of stem cells in organ formation, maintenance and aging, which could lead to the development of improved regenerative therapies.



Quiescence in a stem cell niche. *The hair follicle stem cell niche in the skin shows a reduction in proliferation rate under resting conditions. Three follicles are shown: Ki-67-positive cells in red, nuclei in blue.*

> MAJOR GRANTS

- Ministerio de Ciencia e Innovación (SAF2009-10480)

SELECTED PUBLICATIONS

Ferron SR, Marques-Torrejon MA, Mira H, Flores I, Taylor K, Blasco MA, Farinas I. **Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis.** J Neurosci (2009) 29: 14394-407

Flores I, Blasco MA **A p53-dependent response limits epidermal stem cell functionality and organismal size in mice with short telomeres.** PLoS One (2009) 4: e4934

Garcia-Lavandeira M, Quereda V, Flores I, Saez C, Diaz-Rodriguez E, Japon MA, Ryan AK, Blasco MA, Dieguez C, Malumbres M, Alvarez CV. **A GRFa2/Prop1/stem (GPS) cell niche in the pituitary.** PLoS One (2009) 4: e4815

Flores I, Canela A, Vera E, Tejera A, Cotsarelis G, Blasco MA. **The longest telomeres: a general signature of adult stem cell compartments.** Genes Dev (2008) 22: 654-67

Tomas-Loba A*, Flores I*, Fernandez-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borras C, Matheu A, Klatt P, Flores JM, Vina J, Serrano M, Blasco MA. **Telomerase reverse transcriptase delays aging in cancer-resistant mice.** Cell (2008) 135: 609-22.
* Joint 1st authors

Molecular regulation of heart development and disease

Head of Laboratory: *Enrique Lara-Pezzi*

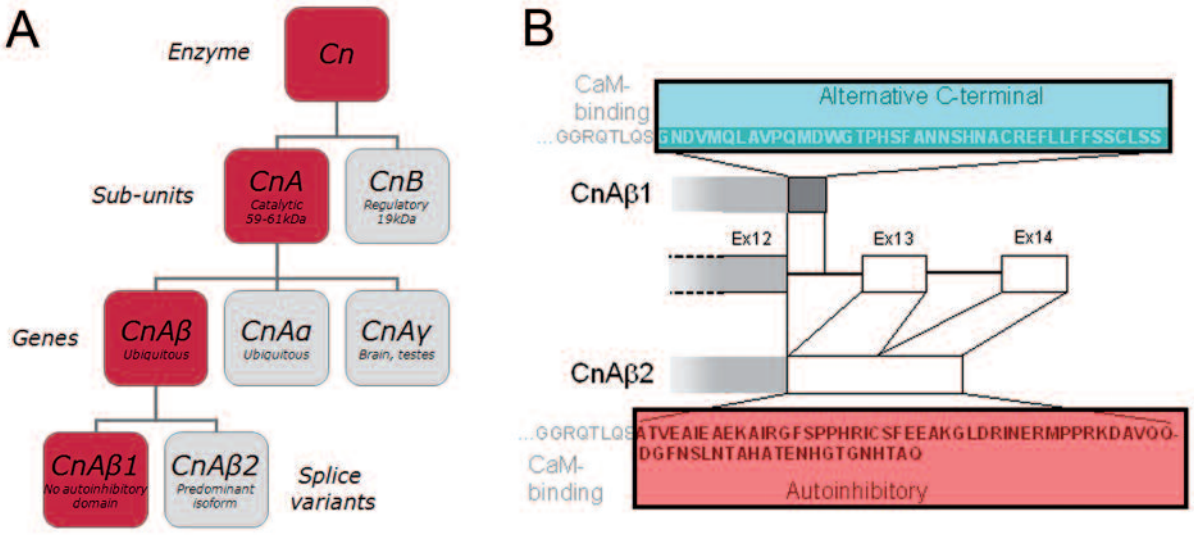
Technician: *Marina Mercedes López Oñaleta*

> RESEARCH INTEREST

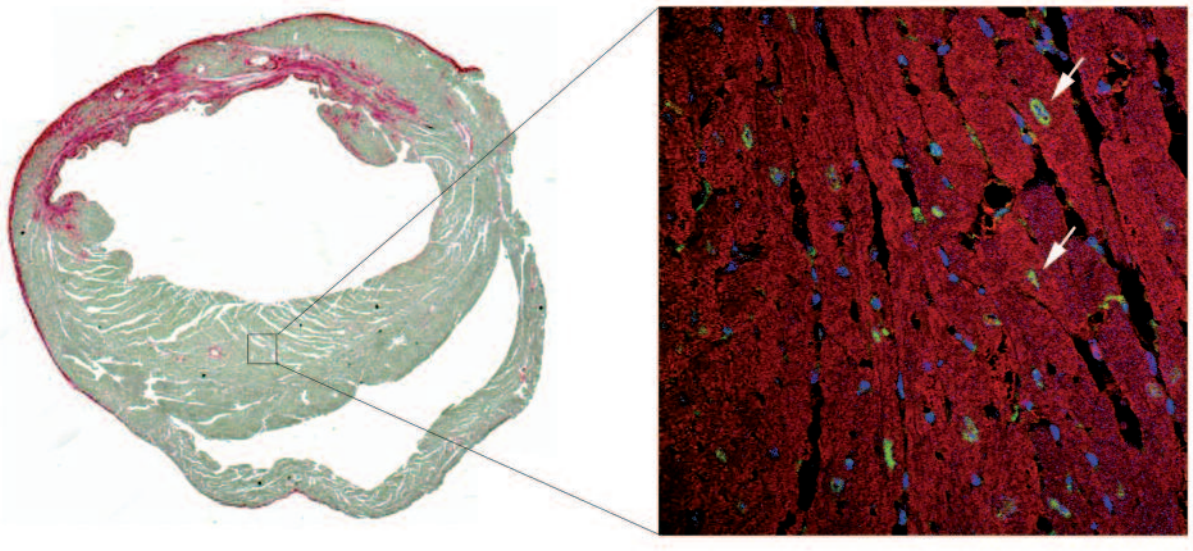
Our lab studies the molecular mechanisms that regulate cardiac development and heart disease. One of our main interests is the role of alternative splicing (AS) in these processes. AS is the molecular process that removes introns from immature pre-mRNAs and links exons together in different combinations. This mechanism 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.

Together with the Genomics Unit at the CNIC, we are using high density exon microarrays and deep sequencing to create a global map of AS isoforms expressed during heart failure. We are also studying cis-regulatory sequences and trans-regulatory splicing factors associated with AS and analyzing their role in the heart by using knockdown and knockout strategies.

A good 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 A gene which contains a unique C-terminal region, different from the autoinhibitory domain present in other CnA isoforms. We recently showed that CnAβ1 regulates cell proliferation and enhances skeletal muscle regeneration. Our results further suggest that CnAβ1 protects the heart from the effects of myocardial infarction by improving cardiac function and reducing inflammation and scar formation.



***Diversity of calcineurin A isoforms. A**, The calcium-regulated phosphatase calcineurin (Cn) consists of two subunits: a catalytic subunit (CnA) and a regulatory subunit (CnB). There are three distinct CnA isoforms, encoded by three genes (CnAα, CnAβ and CnAγ). Two variants of CnAβ, the main CnA isoform expressed in the heart, are generated by alternative splicing (CnAβ1 and CnAβ2). **B**, Like other CnA isoforms, CnAβ2 includes a C-terminal autoinhibitory domain that keeps the enzyme inactive in the absence of calcium. Uniquely, CnAβ1 has a C-terminal domain with no similarity to any known protein, as a result of the insertion of intron 12-13 before exon 13.*



***Expression of cyclin D2 in cardiomyocytes after an infarct. A**, Sirius red staining of a mouse heart section four weeks after ligation of the left coronary artery. Red staining denotes the presence of collagen in the infarcted area. **B**, Confocal immunofluorescence analysis of cyclin D2 in an area of myocardium remote from the infarct: Cyclin D2, green; a-sarcomeric actin, red; Dapi, blue. Arrows indicate cyclin D2-positive cardiomyocytes.*

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (BFU2009-20016)**
- **Ministerio de Ciencia e Innovación. FIS (CP08/00144)**

SELECTED PUBLICATIONS

Felkin LE, Lara-Pezzi E, George R, Yacoub MH, Birks EJ, Barton PJ. **Expression of extracellular matrix genes during myocardial recovery from heart failure after left ventricular assist device support.** *J Heart Lung Transplant* (2009) 28: 117-22

Lara-Pezzi E, Cesare M, Terracciano N, Soppa GKR, Smolenski RT, Felkin LE, Yacoub MH, Barton PJ. **A Gene Expression Profile of the Myocardial Response to Clenbuterol.** *J Cardiovasc Transl Res* (2009) 2: 191-7

Oshima Y, Ouchi N, Shimano M, Pimentel DR, Papanicolaou KN, Panse KD, Tsuchida K, Lara-Pezzi E, Lee SJ, Walsh K. **Activin A and follistatin-like 3 determine the susceptibility of heart to ischemic injury.** *Circulation* (2009) 120: 1606-15

Lara-Pezzi E, Felkin LE, Birks EJ, Sarathchandra P, Panse KD, George R, Hall JL, Yacoub MH, Rosenthal N, Barton PJ. **Expression of follistatin-related genes is altered in heart failure.** *Endocrinology* (2008) 149: 5822-7

Martin-Vilchez S, Sanz-Cameno P, Rodriguez-Munoz Y, Majano PL, Molina-Jimenez F, Lopez-Cabrera M, Moreno-Otero R, Lara-Pezzi E. **The hepatitis B virus X protein induces paracrine activation of human hepatic stellate cells.** *Hepatology* (2008) 47: 1872-83

Role of new genes in cardiovacular development

Head of Laboratory: *Juan José Sanz Ezquerro*

Predoctoral Researchers: *Jesús Chamorro Casanova*
Verónica Uribe Sokolov

Technician: *Claudio Badía Careaga*

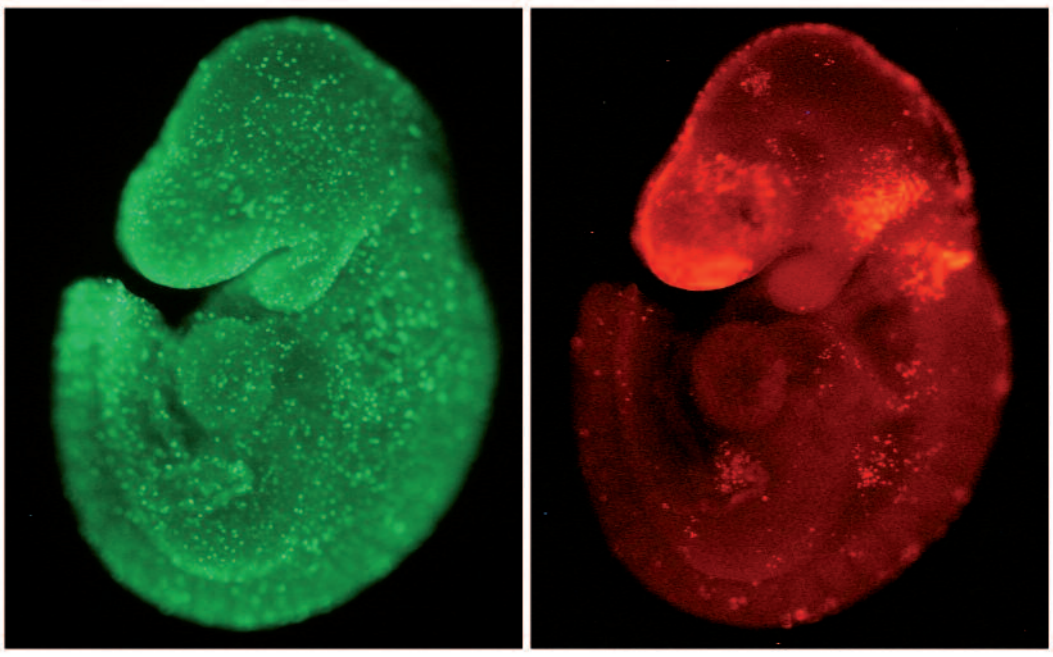
Masters student: *Laura González Calero*

> RESEARCH INTEREST

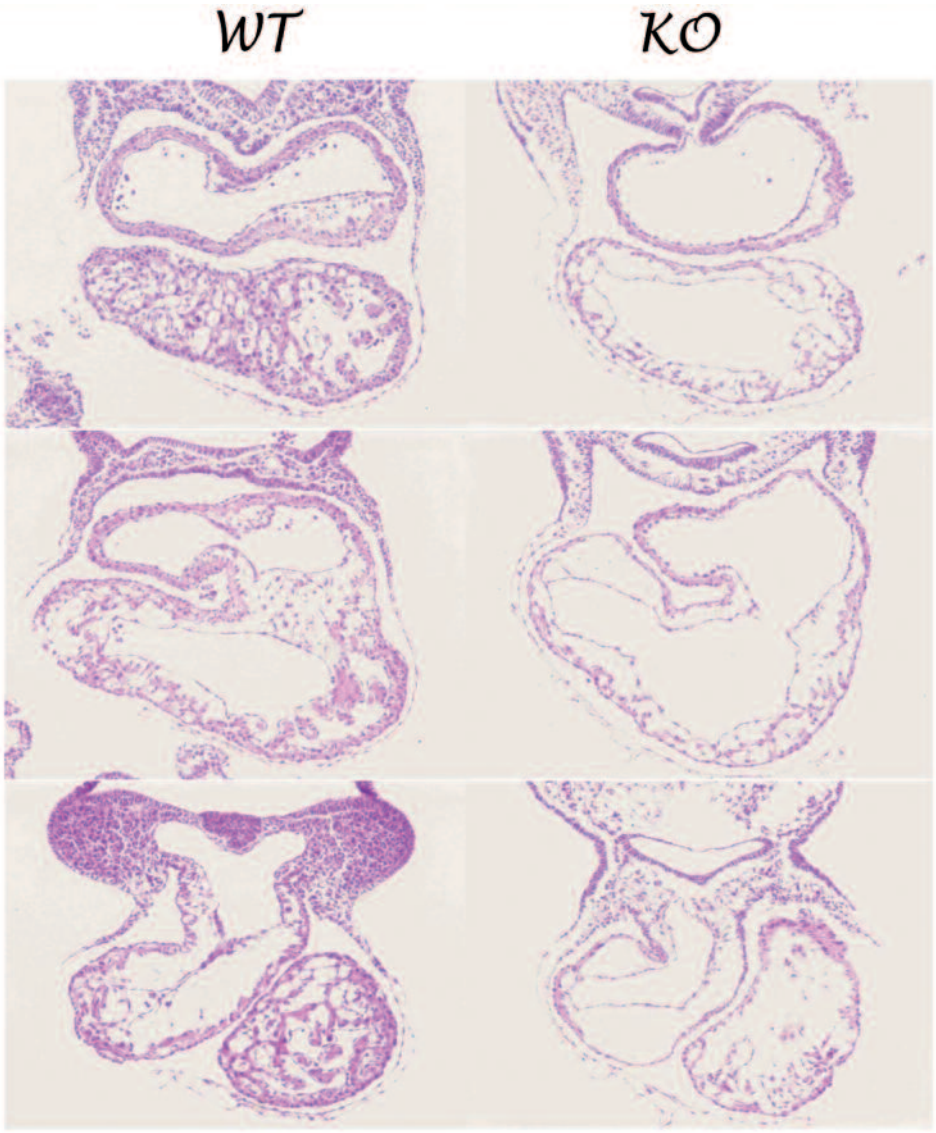
Our laboratory combines studies in chick and mouse embryos with in vitro cell culture strategies to address the role of new genes in the development of the cardiovascular system and in particular the morphogenesis of the heart. Our recent work has examined the role of AT-rich interactive domain-containing protein 3B (Arid3b) during heart formation. Arid3b is a transcription factor of the highly conserved ARID family, whose members share a common DNA-binding domain. Arid3b null-mice die early in embryonic development and their phenotype includes severe defects in many structures, especially the heart. However, the exact roles of Arid3b in development remain unclear.

Examination of the pattern of Arid3b expression shows that it is expressed at early stages of development in the heart tube and is later restricted to the myocardium of the outflow tract, right ventricle, atria and sinus venosus. We are currently carrying out anatomical, histological, cellular and molecular analyses to characterize the cardiac defects produced by the absence of the Arid3b gene. Our results so far identify a major defect in outflow tract formation in Arid3b knockout mice.

Our data also indicate that Arid3b regulates the contribution to the heart of cells from the secondary heart field. We plan to analyze the cellular basis of these Arid3b functions—for example its possible involvement in cell migration—and to identify its molecular targets by microarray analyses.



Proliferation (green labeling by anti-PH3) and apoptosis (red labeling by TUNEL) in Arid3b knockout embryos at E9. At this stage, embryos show no apparent heart defects, but there is a clear increase in the number of dead cells in cranial mesenchyme.



H&E stained heart sections at E9.5. Left, wild-type; right Arid3b knockout. Note the thinning and lack of trabeculae in the KO myocardium and the shortened outflow tract.

> MAJOR GRANTS

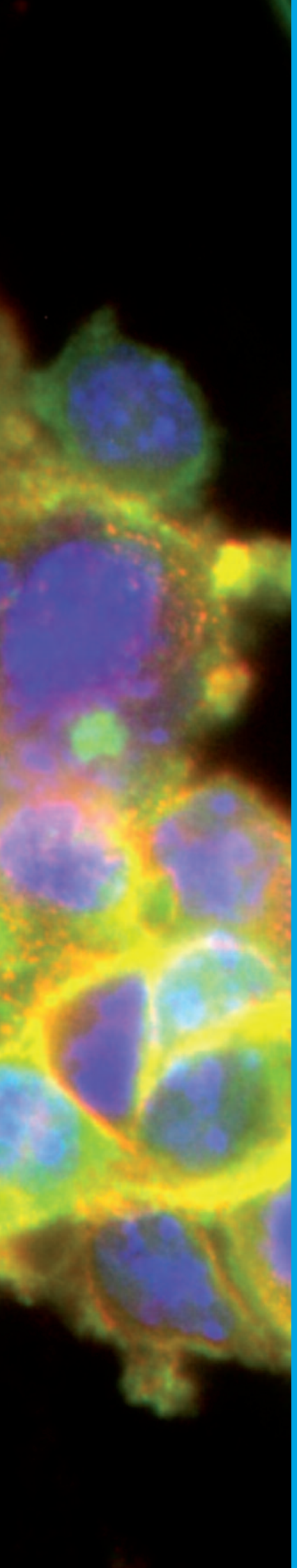
- **Fundació La Marató TV3 (082031)**
- **Ministerio de Ciencia e Innovación (BFU2006-12859)**
- **Ministerio de Ciencia e Innovación. FIS (CP07/251)**

SELECTED PUBLICATIONS

Boot M, Westerberg CH, Sanz-Ezquerro JJ, Schweitzer R, Torres M, Sharpe J. **In vitro whole-organ imaging: Quantitative 4D analysis of growth and dynamic gene expression in mouse limb buds.** *Nat Methods* (2008) 5: 609-12

Basic Research Departments

2 *Regenerative Cardiology*



Basic Research Departments

Regenerative Cardiology

The RC department's activities center on the characterization of stem cell populations associated with cardiovascular system homeostasis, the interdependence of the cardiovascular and immune-inflammatory systems, and the roles of stem cells, oxidative stress, and cell cycle alterations in tissue aging.

Department Director:	*Antonio Bernad*
Department Manager:	*Isabel Barthelemy*
Support Scientist:	*Carmen Albo*
Administrative support:	*Marta Ramón*

Gene expression and genetic stability in adult stem cells

Head of Laboratory: *Antonio Bernad Miana*

Research Scientists: *Enrique Samper*
Manuel A. González
Antonio Díez-Juan

Postdoctoral Researchers: *Kausalia Vijayaragavan*
Mª Paz Moreno
Isabel Moscoso
Suveera Dhup

Predoctoral Researchers: *Silvia García*
Beatriz Escudero
Alberto Izarra
Juan Camilo Estrada
Íñigo Valiente
María Tomé
David Lara
David Horna

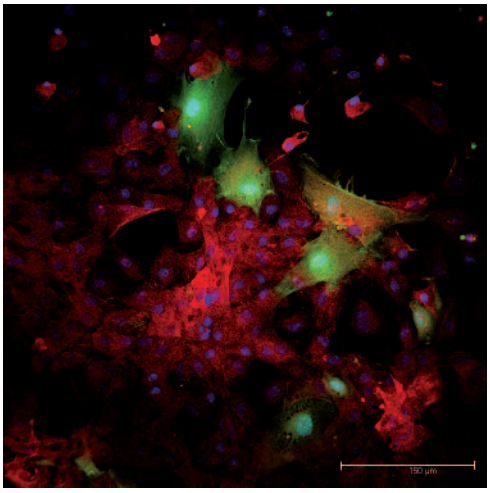
Support Scientist: *Candelas Carreiro*

Technicians: *Vanessa Blanca*
Virginia Zorita

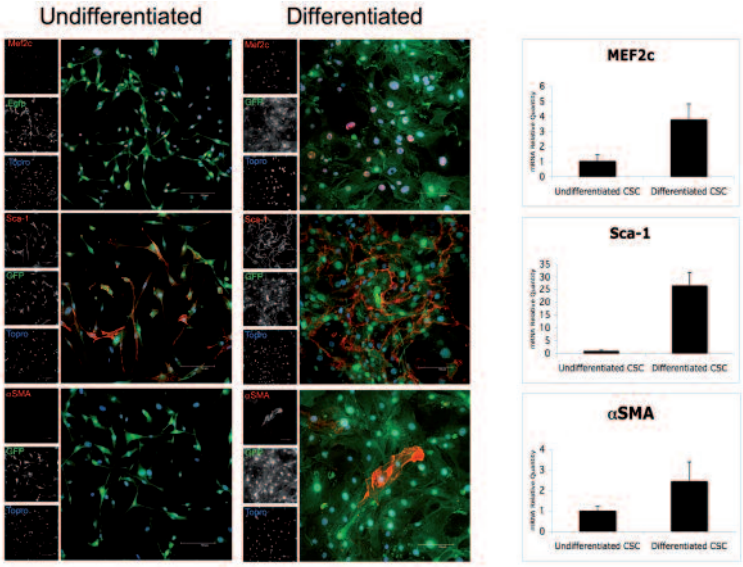
> RESEARCH INTEREST

Adult stem cells (aSC) are crucial for the maintenance of organ homeostasis throughout life. To understand how stem cells control the processes of self-renewal and differentiation, we focus on several related areas, working mainly with murine and human mesenchymal stem cells (MSC) and cardiac progenitor cells (CPC). In relation to the regulation of stem cell gene expression programs, we are studying several microRNAs (miRNAs) and some coding genes (cDNAs) as potential regulators of self-renewal, senescence and differentiation. We are currently carrying out in vitro studies to evaluate the putative roles of these miRNAs and identify their target genes, and we have started a program to generate specific mouse models for in vivo analyses. In a related project, we are investigating the putative role in cardiac wound healing played by the complement factors C3a and C5a expressed by different cell types (macrophages, multipotent cells and cardiomyocytes).

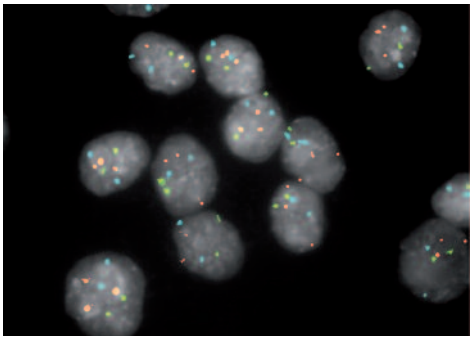
We are also interested in the mechanism of genome repair in relation to organism aging. As they accumulate damage, impaired aSC function can lead to ill health, and the genetic health of aSC is therefore essential to prevent disease, delay aging and counteract tissue damage. Our studies in this area currently center on the role of polymerase μ in DNA repair, aging, tumor suppression, and the maintenance of hematopoietic stem cells. We are also investigating the role of cell culture associated oxidative stress in the promotion of genetic instability and senescence in aSC, a critical concern for the further development of cell therapy.



Co-culture of neonatal rat cardiomyocytes with GFP-tagged murine cardiac progenitor cells (mCPC). *Cardiomyocytes were stained red (α-actinin) and nuclei are shown in blue (DAPI). mCPC were stably transfected with a GFP expression plasmid.*



Evaluation of the differentiation potential of GFP-tagged mCPC. *mCPC cultures stably transfected with an EGFP expression plasmid were treated with several differentiation stimuli. Markers of preferential lineage differentiation were analyzed by immunofluorescence and qPCR.*



Evaluation of the genomic instability associated with extended in vitro culture of aSC. *Interphase in situ fluorescence hybridization with centromere probes for human chromosomes 8 (red), 11 (green) and 17 (blue). Nuclei are counterstained with DAPI (gray). This image shows primary mesenchymal stem cells that are triploid for chromosome 8.*

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación. Programa Nacional de Internacionalización de la I+D (PLE 2009/0147). Sub-project coordinator, A. Bernad**
- **Ministerio de Ciencia e Innovación. Programa Nacional de Internacionalización de la I+D (PLE2009 2009/0112). PI, M. A. González de la Peña**
- **Ministerio de Ciencia e Innovación. Proyecto Singular Estratégico (PSE-01000-2009-3). Sub-project coordinator, A. Bernad**
- **Ministerio de Ciencia e Innovación (SAF2008-02099). PI, A. Bernad**
- **Ministerio de Ciencia e Innovación. Programa Nacional de Internacionalización de la I+D (PLE 2009/0100). Sub-project coordinator, A. Bernad**
- **Ministerio de Ciencia e Innovación. FIS (PI071073). PI, E. Samper**
- **Ministerio de Ciencia e Innovación (SAF 200802099). PI, A. Díez-Juan**

SELECTED PUBLICATIONS

Bailey B, Izarra A, Alvarez R, Fischer KM, Cottage CT, Quijada P, Diez-Juan A, Sussman MA. **Cardiac stem cell genetic engineering using the alphaMHC promoter.** *Regen Med* (2009) 4: 823-33

Gozalbo-Lopez B, Andrade P, Terrados G, de Andres B, Serrano N, Cortegano I, Palacios B, Bernad A, Blanco L, Marcos MA, Gaspar ML. **A role for DNA polymerase mu in the emerging DJH rearrangements of the postgastrulation mouse embryo.** *Mol Cell Biol* (2009) 29: 1266-75

Gonzalez MA, Gonzalez-Rey E, Rico L, Büscher D & Delgado M. **Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses.** *Gastroenterology* (2009) 136: 978-89

Lucas D, Escudero B, Ligos JM, Segovia JC, Estrada JC, Terrados G, Blanco L, Samper E, Bernad A. **Altered hematopoiesis in mice lacking DNA polymerase micro is due to inefficient double-strand break repair.** *PLoS Genet* (2009) 5: e1000389

Samper E, Morgado L, Estrada JC, Bernad A, Hubbard A, Cadenas S, Melov S. **Increase in mitochondrial biogenesis, oxidative stress, and glycolysis in murine lymphomas.** *Free Radic Biol Med* (2009) 46: 387-96

Functional genetics of the oxidative phosphorylation system

Head of Laboratory: *José Antonio Enríquez*

Research Scientists: *Acisclo Pérez Martos*
Patricio Fernández Silva

Postdoctoral Researchers: *Pilar Bayona Bafaluy*
Erika Fernández -Vizarra
Nuria Garrido Pérez
Patricia Meade Huerta
Raquel Moreno Loshuertos
Carmen Colás
Ester Perales Clemente

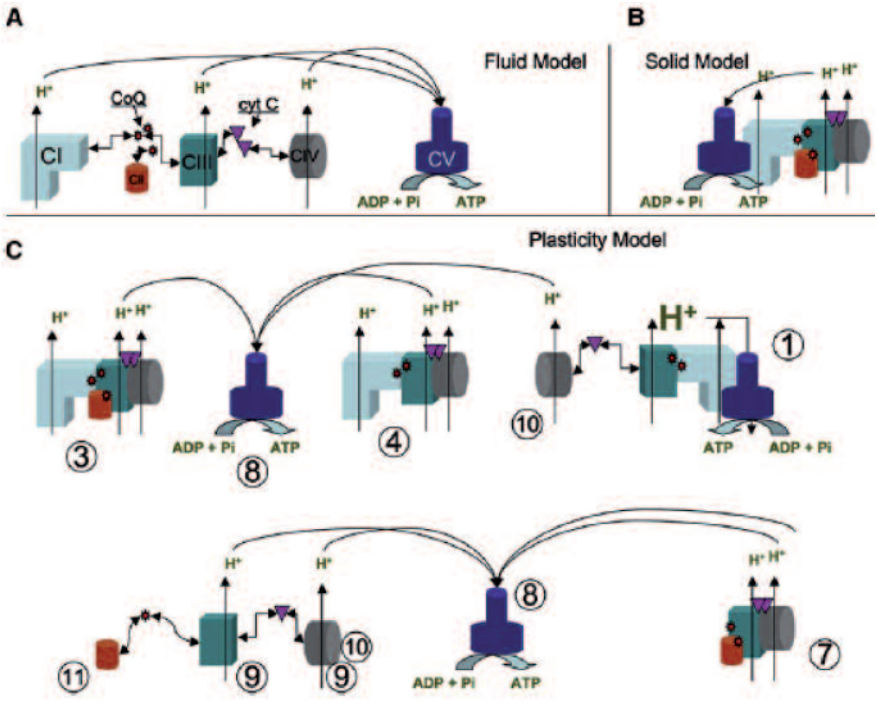
Predoctoral Researchers: *Ricardo Marco Lázaro*
Ana Latorre Pellicer
Esther Lapuente Brun
Elena de Tomás Mateo

Support Scientists: *Nieves Movilla Meno*
Mª Concepción Jiménez

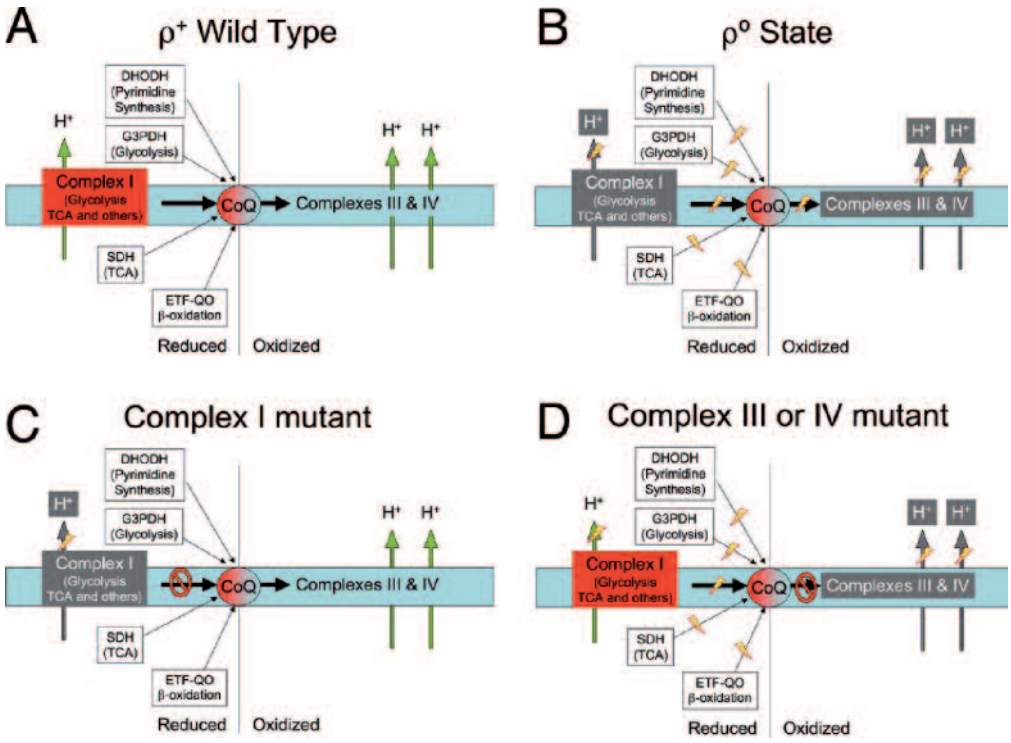
RESEARCH INTEREST

Our laboratory researches the mammalian mitochondrial electron transport chain (MtETC) and H+-ATP synthase, which together constitute the oxidative phosphorylation (OXPHOS) system. We view this system as a functional entity, and use a range of approaches aimed at determining its role in health and disease. We are particularly interested in the role of the OXPHOS system in the development of the cardiovascular system, its relevance to ischemia-reperfusion, and its influence on microvascular blood flow.

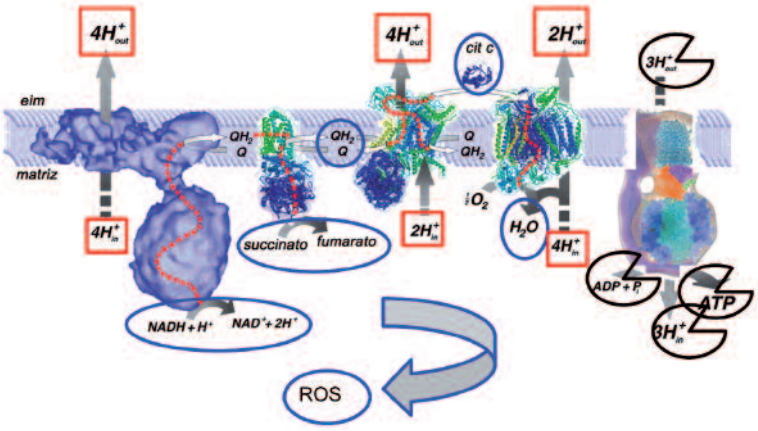
Currently very little is known about why, where and how impaired function of the OXPHOS system manifests in disease. One reason for this is that there are major deficiencies in the established models of the organization of the electron transport chain. Thus the main lesson from research to date into human OXPHOS diseases is that our basic understanding is far from complete. In order to fill this gap, we are implementing high-throughput strategies to catalogue the set of the genes whose products participate in the biogenesis and regulation of the OXPHOS system (which we call the OXPHOME). We are also determining the factors that regulate the structural organization of the electron transport chain and the role that this superstructural organization plays in the production of reactive oxygen species (ROS). This area is linked to our interest in the role of ROS as mitochondrial second messengers and to our aim to deconstruct, in cellular models, the mammalian OXPHOS system into its functional components (electron transport, proton pumping and ATP synthesis).



Fluid, solid and plasticity models of the mitochondrial OXPHOS system organization.



Role of CoQ in the mtETC. The schemes depict the status of the respiratory chain (electron flow and proton pumping activities) in wild-type (ρ+) cells (A), mtDNA-less (ρ°) cells (B), and in cells with knockout mutations in either complex I (C) or in complexes III or IV (D). The pivotal role of CoQ as the acceptor for electrons from different sources and as the electron donor to complexes III and IV is highlighted. DHODH, dihydroorotate dehydrogenase; G3PDH, glycerol-3-phosphate dehydrogenase (glycerol-phosphate shuttle); SDH, succinate dehydrogenase; ETF-QO, electron-transfer flavoprotein-ubiquinone oxidoreductase; TCA, tricarboxylic acid cycle.



The three functional processes of the mitochondrial OXPHOS system: electron transport (blue); proton pumping (red) and ATP synthesis.

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2006-00428)**
- **Ministerio de Ciencia e Innovación. CONSOLIDER Project (CSD2007-00020)**

SELECTED PUBLICATIONS

Fernandez-Vizarra E, Ferrin G, Perez-Martos A, Fernandez-Silva P, Zeviani M, Enriquez JA. **Isolation of mitochondria for biogenetical studies: An update.** *Mitochondrion*. (accepted)

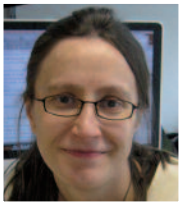
Kirby DM, Rennie KJ, Smulders-Srinivasan TK, Acin-Perez R, Whittington M, Enriquez JA, Trevelyan AJ, Turnbull DM, Lightowlers RN. **Transmitochondrial embryonic stem cells containing pathogenic mtDNA mutations are compromised in neuronal differentiation.** *Cell Prolif* (2009) 42: 413-24.

Acin-Perez R, Fernandez-Silva P, Peleato ML, Perez-Martos A, Enriquez JA. **Respiratory active mitochondrial supercomplexes.** *Mol Cell* (2008) 32: 529-39

Garrido N, Perez-Martos A, Faro M, Lou-Bonafonte JM, Fernandez-Silva P, Lopez-Perez MJ, Montoya J, Enriquez JA. **Cisplatin-mediated impairment of mitochondrial DNA metabolism inversely correlates with glutathione levels.** *Biochem J* (2008) 414: 93-102

Perales-Clemente E, Bayona-Bafaluy MP, Perez-Martos A, Barrientos A, Fernandez-Silva P, Enriquez JA. **Restoration of electron transport without proton pumping in mammalian mitochondria.** *Proc Natl Acad Sci USA* (2008) 105: 18735-9

Stem cell aging



Head of Laboratory: *Susana Gonzalez*

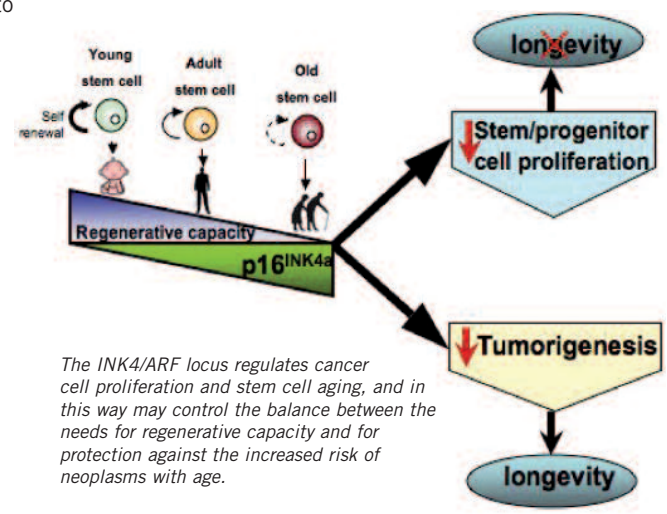
Postdoctoral Researchers: *Celia Cerrato Rivera*

Technicians: *Pilar Mendoza Doroca*
Christian Torrenteras Ruano
Cristiana de Jesús Oliveira Leite
Antonio Herrara Merchán
Ma Eugenia Alonso Ferrero
Antonio José Montes Ruiz

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 tumor 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 neoplasms with age.

MAJOR GRANTS

- **Human Frontier Science Program Organization (HFSPO). Career Development Award**
- **Ministerio de Ciencia e Innovación. FIS (PI060627)**

SELECTED PUBLICATIONS

Gonzalez S, Pisano D, Serrano M. **Mechanistic principles of chromatin remodeling guided by siRNAs and miRNAs.** *Cell Cycle* (2008) 7: 2601-8

Benetti R, Gonzalo S, Jaco I, Munoz P, Gonzalez S, Schoeftner S, Murchison E, Andl T, Chen T, Klatt P, Li E, Serrano M, Millar S, Hannon G, Blasco MA. **A mammalian microRNA cluster controls DNA methylation and telomere recombination via Rbl2-dependent regulation of DNA methyltransferases.** *Nat Struct Mol Biol.* (2008) 15: 268-79

de Yebenes VG, Belver L, Pisano DG, Gonzalez S, Villasante A, Croce C, He L , Ramiro AR. **miR-181b negatively regulates activation-induced cytidine deaminase in B cells.** *J Exp Med* (2008) 205: 2199-206

Toll-like receptors and innate immunity in cardiovascular disease and generation

Head of Laboratory: *Sonsoles Hortelano*

Scientific Collaborator: *Alfonso Luque*

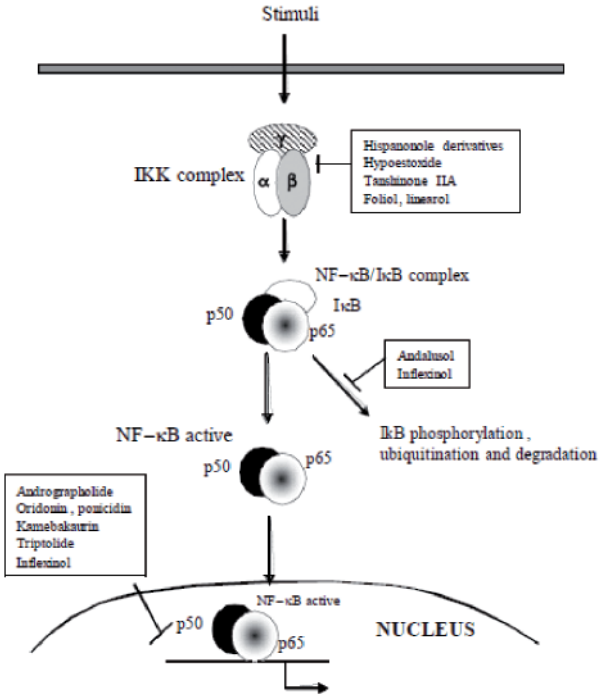
Predoctoral Researcher: *Raquel López Fontal*

Technician: *Gabriel Bergazyn Liberman*

RESEARCH INTEREST

Our group is interested in the molecular basis of the inflammatory response and in the search of new therapeutic agents with anti-inflammatory properties. Many natural products are used for the prevention and treatment of inflammatory conditions. The largest and most widespread class of these compounds is the terpenoids (also referred to as terpenes). As part of a program of research into the biological activities of terpenoids, we are evaluating the antiatherogenic and antiinflammatory potential of several natural product derivatives. To investigate the mechanism of action of this class of compounds, we are studying targets relevant to the regulation of the inflammatory response. We have recently shown that several labdane derivatives inhibit inflammatory processes in vitro and in vivo through a mechanism involving inhibition of NF-κB activity. This effect seems to be related to the ability of these compounds to reduce IκBα degradation and phosphorylation, leading to inhibition of NF-κB translocation. These findings establish the potential of labdane diterpenoids as alternatives to current treatments for the treatment of inflammatory diseases.

We are also investigating the role of the tumor suppressor ARF in immune responses. We recently identified a decreased inflammatory response in ARF-deficient animals associated with impaired activation of toll-like receptors, particularly TLR4. We are currently investigating the impact of ARF deficiency and TLR signaling in models of cardiovascular disease.



Main signaling pathways inhibited by diterpenoids.

MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS (P1080070)

SELECTED PUBLICATIONS

de las Heras B, Hortelano S. **Molecular basis of the anti-inflammatory effects of terpenoids**. *Inflamm Allergy Drug Targets* (2009) 8: 28-39

Giron N, Traves PG, Rodriguez B, Lopez-Fontal R, Bosca L, Hortelano S*, de las Heras B. **Supression of inflammatory responses by labdane-type diterpenoids.** *Toxicol Appl Pharmacol* (2008) 228: 179-89
** Corresponding author*

Diaz-Viciedo R, Hortelano S, Giron N, Masso JM, Rodriguez B, Villar A, de las Heras B. **Modulation of inflammatory responses by diterpene acids from Helianthus annuus L.** *Biochem Biophys Res Commun.* (2008) 369: 761-6

Stem cell signaling

Head of Laboratory: *Kenneth J. McCreath*

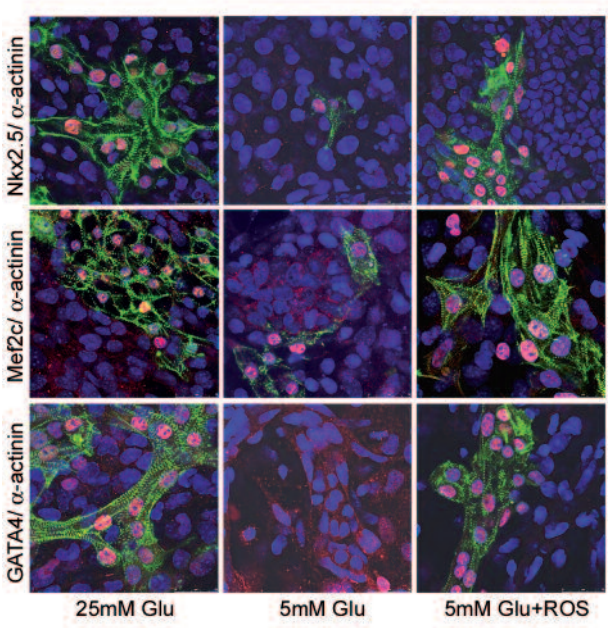
Research Scientist: *Ana M. Cervera*

Postdoctoral Researcher: *Veronica. R. Sobrado*

Predoctoral Researcher: *Laura Gomez*

RESEARCH INTEREST

The prevailing view of mitochondria as bioenergetic facilitators has been recently extended by the observation that these organelles play critical roles in many cellular events. Using embryonic stem (ES) and induced pluripotential stem (iPS) cells as in vitro models, we are investigating the participation of mitochondria in the maintenance of stem cell pluripotency and the capacity for differentiation. In particular we are examining the role of mitochondrial-generated reactive oxygen species (ROS) during differentiation to the cardiovascular lineage. We are exploring the possibility that ROS have the capacity to regulate microRNA (miRNA) expression during this progression, and we have recently identified several miRNAs that are differentially expressed upon ROS depletion. In addition, we are devising protocols for the directed differentiation of human iPS cells to cardiac progenitor populations, in the hope that these cells might have therapeutic potential. We are also examining the possibility that stem cells derived from patients with congenital defects might provide valuable models of cardiovascular disease. Our long-term interest in the citric acid cycle has led us to examine the role of mitochondrial dysfunction during heart failure and we are currently creating a knockout mouse model to test our hypothesis that mitochondrial metabolites play important roles during angiogenesis and remodeling after myocardial infarction. We expect that together these approaches will contribute to the understanding of mitochondrial participation during cardiovascular development and disease.



Role of ROS during cardiomyocyte differentiation from ES cells at different glucose concentrations. *Cardiac transcription factors (Nkx2.5, Mef2c and Gata4) are shown in red, α-actinin is shown in green, and nuclei are stained with DAPI. Note that exogenous addition of ROS re-initiates cardiac differentiation under low glucose.*

MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS (PI06/0299)

SELECTED PUBLICATIONS

Cervera AM, Bayley J-P, Devilee P, McCreath KJ. **Inhibition of succinate dehydrogenase dysregulates histone modification in mammalian cells.** *Mol Cancer* (2009) 8: 89 (Evaluated by Faculty of 1000 Biology)

Hernandez C, Santamatilde E, McCreath KJ, Cervera AM, Diez I, Ortiz-Masia D, Martinez N, Calatayud S, Esplugues JV, Barrachina MD. **Induction of trefoil factor (TFF) 1, TFF2 and TFF3 by hypoxia is mediated by hypoxia inducible factor-1: implications for gastric mucosal heaing.** *Br J Pharmacol* (2009) 156: 262-72

Cervera AM, Apostolova N, Luna Crespo F, Mata M, McCreath KJ. **Cells silenced for SDHB expression display characteristic features of the tumor phenotype.** *Cancer Res* (2008) 68: 4058-67 (Evaluated by Faculty of 1000 Biology)

Transcriptional regulation of oxidative stress protection systems

Head of Laboratory: *María Monsalve*

Postdoctoral Researchers: *Alberto Tierrez*
Nieves García

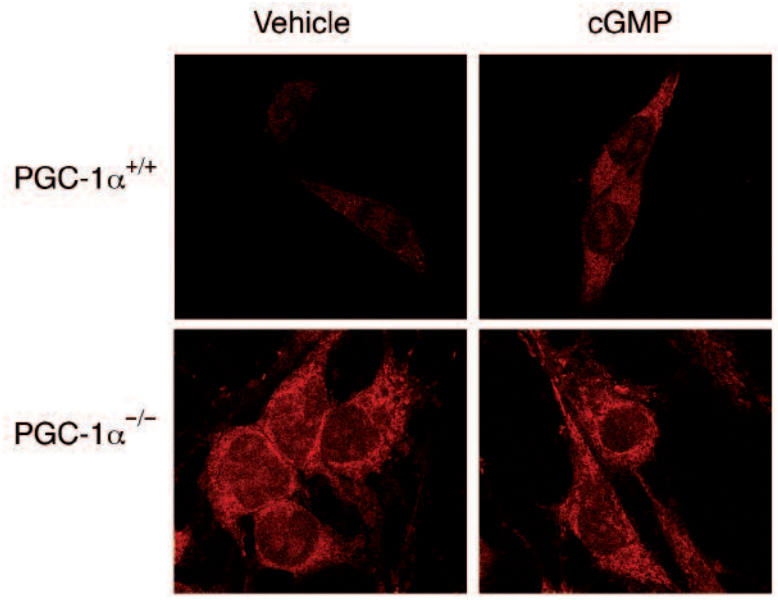
Predoctoral Researchers: *Yolanda Olmos*
Cristina Sanchez

Technician: *Brigitte Wild*

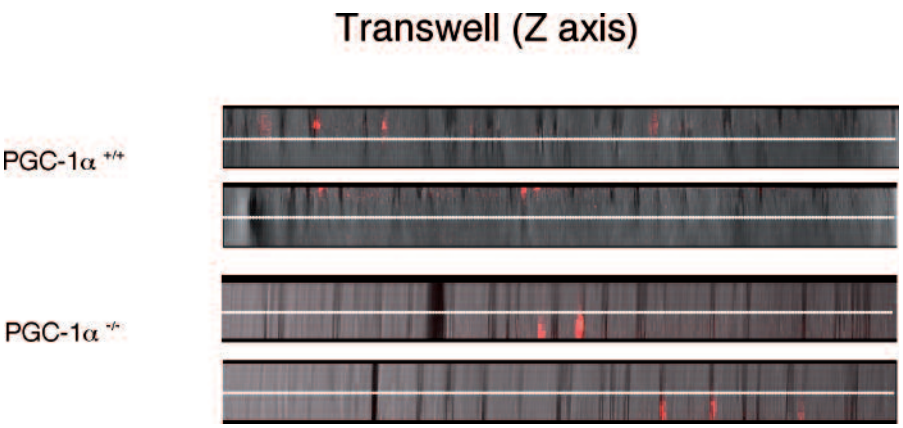
> RESEARCH INTEREST

Metabolic dysfunction and associated mitochondrial oxidative stress are emerging as primary risk factors for several major diseases, and a precise understanding of the mechanisms that control ROS detoxification will therefore be crucial for the development of new treatment strategies. We research the transcription factors involved the regulation of the ROS detoxification system and the impact this regulation has on human diseases, with particular emphasis on those affecting the cardiovascular system. An important aim of our work is to identify molecules that modulate the activity of these factors and that would serve as the starting point for the development of new therapeutic interventions.

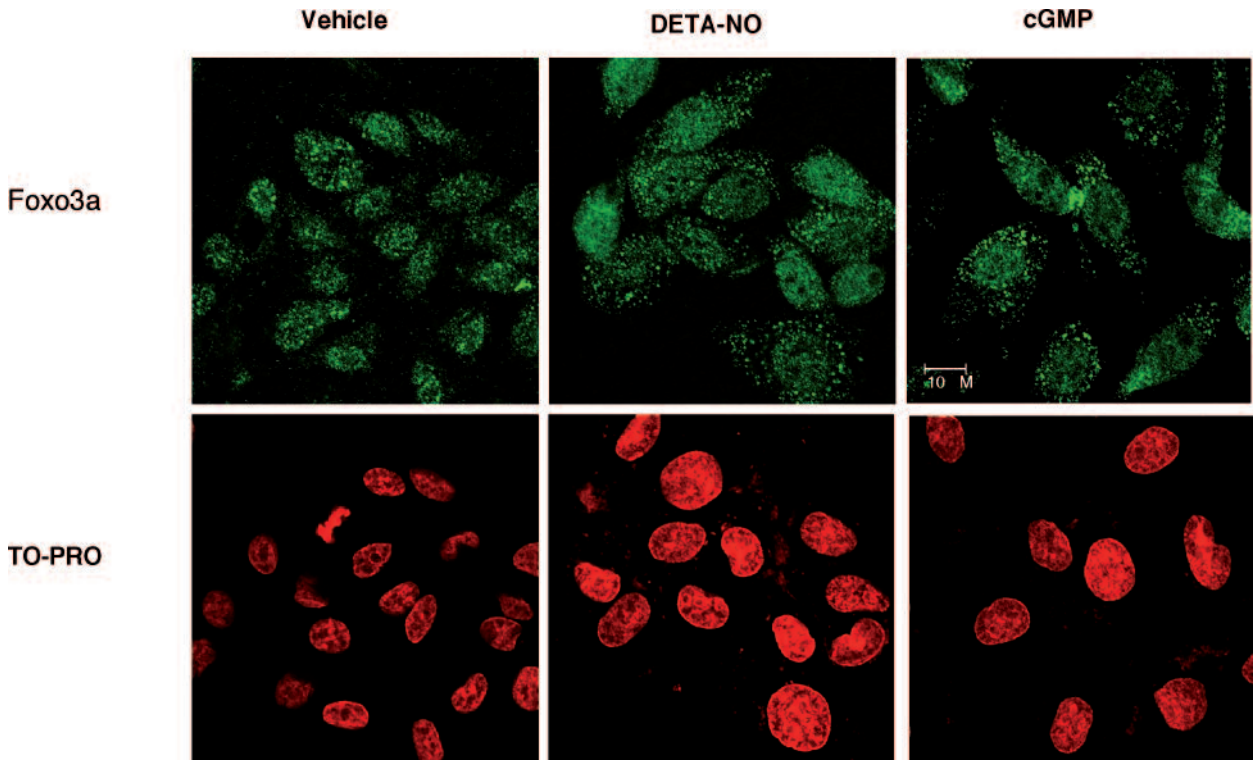
Our hypothesis is that common metabolic dysfunctions that impair mitochondrial activity, such as metabolic syndrome, diabetes and NASH, inactivate a key set of transcription factors that control the protection against oxidative stress. This inactivation leads to increased cellular accumulation of ROS and associated cellular damage. Based on our findings, we think that pharmacological activation of at least two of these transcription factors is feasible, and would counter the metabolic and oxidative stress dysfunctions of patients with these diseases.



The nitric oxide/cGMP pathway cannot regulate mitochondrial ROS production in the absence of peroxisome proliferator activated receptor γ-coactivator 1α (PGC-1α). MitoSOX Red labeling reveals mitochondrial superoxide levels in wild-type (PGC-1α$^{+/+}$) and PGC-1α knockout (PGC-1α$^{-/-}$) mouse lung endothelial cells treated with 8-Br-cGMP.



PGC-1α inhibits endothelial cell migration. PGC-1α$^{+/+}$ and PGC-1α$^{-/-}$ endothelial cells were seeded in the upper chambers of transwells and allowed to migrate. The figure shows transwells in cross section (Z-axis), illustrating the distance migrated by the cells (stained red).



The nitric oxide/cGMP pathway inactivates the transcription factor FoxO3a. Serum-starved bovine endothelial cells were incubated with the NO donor DETA-NO or cGMP. Immunostaining of Foxo3a (green) shows the nuclear export of this factor in NO and cGMP stimulated cells. Nuclei are labeled with TO-PRO-3.

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2006-01619)**
- **Ministerio de Ciencia e Innovación. CONSOLIDER Project (CSD2007-00020)**

SELECTED PUBLICATIONS

Olmos Y, Valle I, Borniquel S, Tierrez A, Soria E, Lamas S, Monsalve M. **Mutual dependence of Foxo3a and PGC-1α in the induction of oxidative stress genes.** *J Biol Chem* (2009) 284:14476-84

Nuclear receptor signaling

Head of Laboratory: *Mercedes Ricote*

Postdoctoral Researchers: *Piedad Menéndez*
Tamás Röszer
Lucía Fuentes

Technician: *Vanessa Núñez*

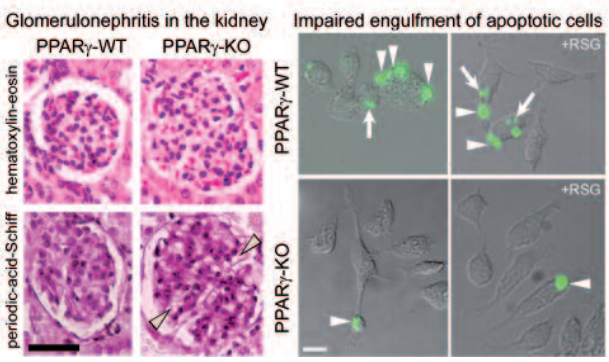
Predoctoral Researchers: *Daniel Alameda*
Marta Cedenilla

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 diseases and the homeostasis of adult stem cells.

We have found that myeloid-specific PPARγ or RXRα knockout (KO) mice develop chronic renal inflammation and autoantibodies to nuclear antigens, a phenotype that resembles the nephritis seen in human systemic lupus erythematosus. This phenotype is caused by the impaired clearance of apoptotic cells by the knockout macrophages. These defects eventually lead to the development of cardiac hypertrophy, and we are currently trying to understand how the lack of PPARs and RXRs leads to this condition.

Our research into adult stem cells addresses the roles of RXRs and PPARs in the differentiation, proliferation and self-renewal of hematopoietic stem cells in vitro and in vivo. Emerging evidence suggests that nuclear receptors regulate the decision between maintenance of stemness or differentiation in embryonic stem cells and tissue-specific adult stem cells. We have generated hematopoietic-specific PPARγ and RXRα,β-knockout mice, and have embarked on a research program to define the role of these nuclear receptors in the differentiation of bone marrow stem cells into diverse cell populations, including cardiomyocytes, adipocytes and osteoclasts.



Left: Glomerular inflammation in myeloid-specific PPARγ-KO mice. Arrowheads mark thickened capillary walls. Right: Impaired uptake of apoptotic cells by PPARγ-KO macrophages. Arrowheads mark fluorescently labeled apoptotic cells and arrows label ingested cells. Images were obtained 60 minutes after exposure of macrophages to labeled apoptotic cells. Scale bar: 30 μm.

MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF 2009-07466)**
- **Fundació La Marató TV3**
- **Fundación Genoma España. MEICA Project**

SELECTED PUBLICATIONS

Prieur X, Roszer T, Ricote M. **Lipotoxicity in macrophages: evidence from diseases associated with the metabolic syndrome.** *Biochim Biophys Acta* (accepted)

Cardiovascular related risks of obesity

Head of Laboratory: *Beatriz González Gálvez*

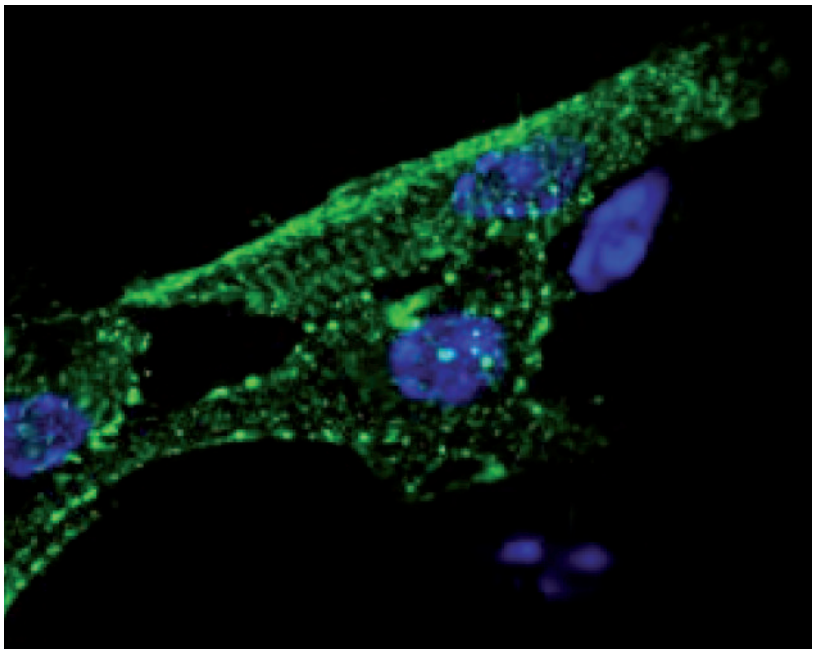
Technician: *Nuria San Martín*

> RESEARCH INTEREST

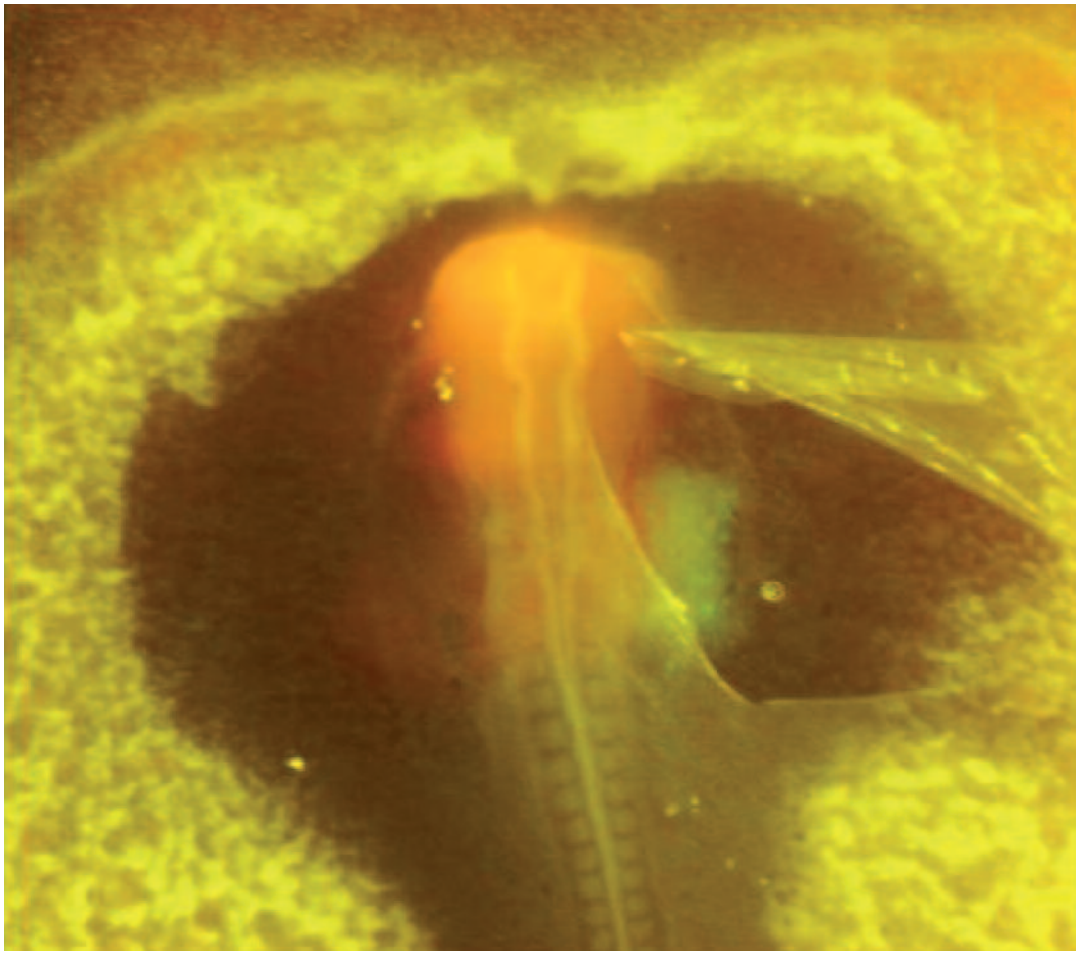
The adult heart contains resident mesenchymal stem cells capable of regenerating damaged cardiac tissue. Our group is interested in the clinical use of isolated stem-cell populations to treat heart disease and in the contribution of aberrant mesenchymal precursor migration to the cardiovascular complications associated with obesity.

The bulk of the experimental work in our lab is conducted with mesenchymal precursor lines isolated from the heart tissue of adult mice, pigs and human patients. These cells can differentiate into cardiomyocytes and have demonstrated ability to regenerate cardiac tissue in animal models of myocardial infarction and coronary artery disease.

Evidence from ob/ob mice (which become obese due to the inactivity of the leptin gene) indicates that obesity diverts mesenchymal precursor migration to adipose tissue, a phenomenon called adipotaxis. This misdirected migration contributes to the obesity-associated risk of heart disease, stroke, arterial hypertension, type II diabetes and some forms of cancer. Our work in this area has led to the development of protocols for screening anti-obesity compounds, and we are studying the migratory properties of these cells in order to improve cardiac stem cell therapy.



Human cardiomyocytes differentiated in culture from cardiac mesoangioblasts. Cells are stained with anti α-actin antibody (green), and nuclei are stained with Hoescht (blue).



At an earlier stage of its development, this chick embryo was injected in the area of heart development with GFP-labeled human cardiac mesoangioblasts, which have gone on to populate the heart tissue.

SELECTED PUBLICATIONS

Galvez BG, Covarello D, Tolorenzi R, Brunelli S, Dellavalle A, Crippa S, Mohammed SA, Scialla L, Cuccovillo I, Molla F, Staszewsky L, Maisano F, Sampaolesi M, Latini R, Cossu G. **Human cardiac mesoangioblasts isolated from hypertrophic cardiomyopathies are greatly reduced in proliferation and differentiation potency.** *Cardiovasc Res* (2009) 83: 707-16

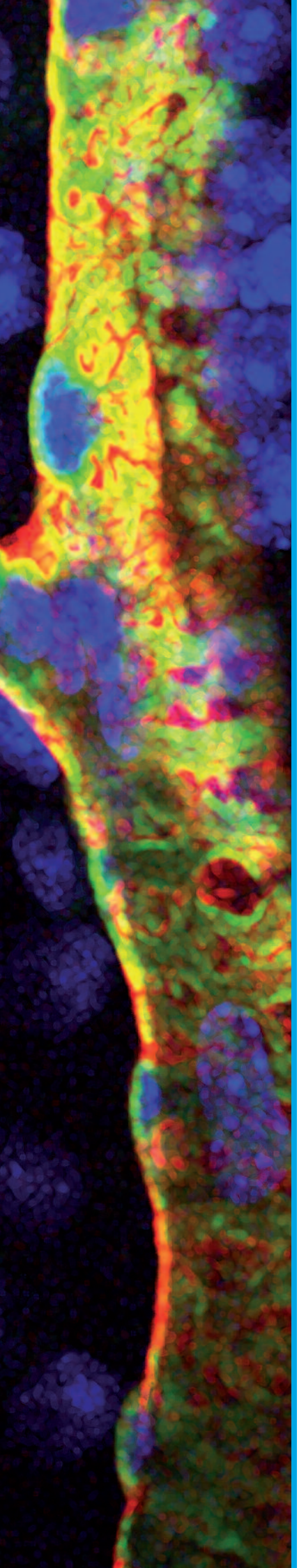
Galvez BG, San Martin N, Rodriguez C. **TNF-α is required for the attraction of mesenchymal precursors to white adipose tissue in Ob/ob mice.** *PLoS One* (2009) 4: e4444

Messina G, Sirabella D, Monteverde S, Galvez BG, Tonlorenzi R, Schnapp E, De Angelis L, Brunelli S, Relaix F, Buckingham M, Cossu G. **Skeletal muscle differentiation of embryonic mesoangioblasts requires pax3 activity.** *Stem Cells* (2009) 27: 157-64

Galvez BG, Sampaolesi M, Barbuti A, Crespi A, Covarello D, Brunelli S, Dellavalle A, Crippa S, Balconi G, Cuccovillo I, Molla F, Staszewsky L, Latini R, Difrancesco D, Cossu G. **Cardiac mesoangioblasts are committed, self-renewable progenitors, associated with small vessels of juvenile mouse ventricle.** *Cell Death Differ* (2008) 15: 1417-28

Basic Research Departments

3 *Vascular Biology and Inflammation*



Basic Research Departments

Vascular Biology and Inflammation

The groups in the VBI department use a variety of molecular, cellular, tissue and animal models to investigate the functioning of the vascular system in physiological settings and in the pathological inflammatory situations that lie at the root of atherothrombotic disease.

Department Director:	*Juan Miguel Redondo*
Department Manager:	*Antonio Jesús Quesada*
Technician:	*Andrea Quintana*
Administrative support:	*Mª Jesús De La Calle* *Almudena Fernández*

CNIC-UAM COLLABORATIVE PROGRAM: Intercellular communication in the inflammatory response

Program Director: *Francisco Sánchez-Madrid*

Research Scientists:
Pilar Martín
Juan Manuel Serrador
David Sancho
María Yáñez-Mó

Postdoctoral Researchers:
Olga Barreiro
Hortensia de la Fuente
Noa B. Martín Cofreces
Gloria Martínez del Hoyo
María Mittelbrunn
José María González
Vera Rocha

Predoctoral Researchers:
Aránzazu Cruz
Cristina Gutiérrez
Adela Matesanz
Mónica Sala-Valdés
María Sales Ibiza
Emilio Tejera
Almudena García
Norman Núñez
Noelia Blanco

Technicians:
Marta Ramírez
María José López

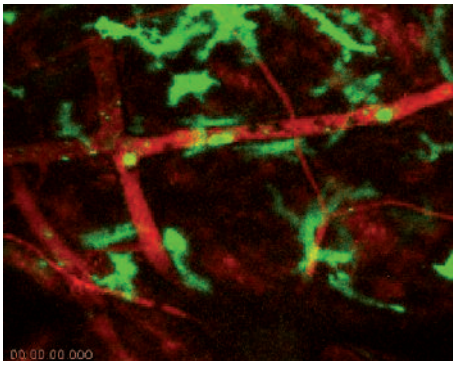
> RESEARCH INTEREST

Intercellular communication is fundamental to the innate and adaptive immune responses. Our group is interested in the molecular basis of key communication processes involving immune cells, such as the formation of the immune synapse between antigen presenting cells (APC) and T cells and the migration of leukocytes across the endothelium.

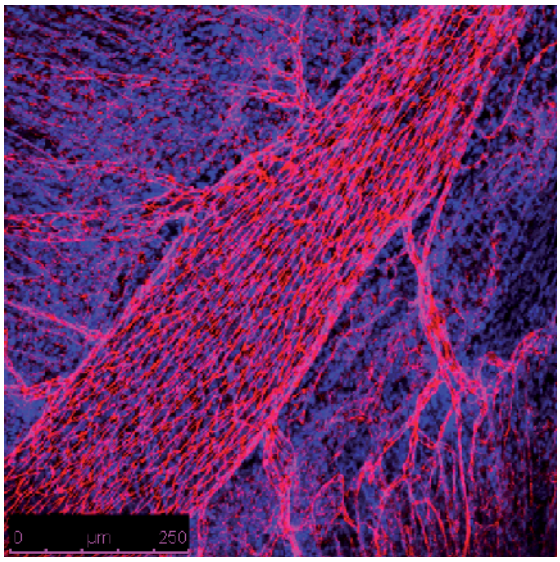
The immune synapse (IS) is a highly segregated structure formed at the contact site between the T cell and APC by the polarized reorganization of transmembrane and membrane-associated molecules. We are currently investigating the possibility that this structure permits the directional transfer of miRNA-loaded exosomes from T cell to APC, providing a specific means of cell-cell communication with important functional consequences for APC biology.

The interaction of leukocytes with the vascular endothelium is a highly regulated step-wise process that allows the selective recruitment of inflammatory leukocyte subsets to inflammatory foci, where they exert their effector functions. Understanding the supra-molecular organization of the receptors involved in this process is another of our main goals, with the ultimate aim of identifying new molecular targets for therapy. A related area of interest is the crucial roles played in inflammation by specific receptors: CD69, galectins, PSGL-1 and the tetraspanins CD9 and CD81. The biology of these molecules is being investigated using gene-deficient mouse strains in models of diverse inflammatory diseases, including allergic asthma, experimental autoimmune myocarditis, delayed-contact hypersensitivity and DSS-induced ulcerative colitis.

We are also interested in T lymphocyte synthesis of nitric oxide (NO) and other soluble mediators that regulate the production of pro-inflammatory cytokines. Our interest here centers on the molecular mechanisms regulating polarized secretion during antigen-dependent T cell-APC interactions and the regulatory role of T-cell derived NO in vascular lesions.



Intravital microscopy image showing leukocyte-endothelium interactions in an inflamed area (mouse ear). To view these events, we adoptively transferred GFP+ hematopoietic cells from a donor mouse to a recipient, and revealed the vasculature by injecting the tracer TRITC-dextran.



Wholemount staining of the diaphragm vasculature in a CD81-deficient mouse. Endothelial junctions are revealed by staining with anti-CD31 antibody, and nuclei are stained with DAPI.

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2008-02635). PI, F. Sánchez-Madrid**
- **Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA; RD06/0014/0030). PI, F. Sánchez-Madrid**
- **Fundación Genoma España. MEICA Project. Coordinator and PI, F. Sánchez-Madrid**
- **Ministerio de Ciencia e Innovación (SAF2008-02719). PI, P. Martín**
- **Ministerio de Ciencia e Innovación. FIS (PI07/0356). PI, JM Serrador**

SELECTED PUBLICATIONS

Barreiro O, Aguilar RJ, Tejera E, Megias D, Torres Alba F, Evangelista A, Sanchez-Madrid F. **Specific Targeting of Human Inflamed Endothelium and in situ Vascular Tissue Transfection by the use of Ultrasound Contrast Agents.** *JACC: Cardiovasc Imaging* (2009) 2: 997-1005

Mittelbrunn M, Martinez del Hoyo G, Lopez-Bravo M, Martin-Cofreces NB, Holer A, Hugues S, Fetler L, Amigorena S, Ardavin C, Sanchez-Madrid F. **Imaging of plasmacytoid dendritic cell interactions with T cells.** *Blood* (2009) 113: 75-84

Sanchez-Madrid F, Serrador JM. **Bringing up the rear: defining the roles of the uropod.** *Nat Rev Mol Cell Biol* (2009) 10: 353-9

Sancho D, Joffre OP, Keller AM, Rogers NC, Martinez D, Hernanz-Falcon P, Rosewell I, Reis e Sousa C. **Identification of a dendritic cell receptor that couples sensing of necrosis to immunity.** *Nature* (2009) 458: 899-903

Yanez-Mo M, Barreiro O, Gordon-Alonso M, Sala-Valdes M, Sanchez-Madrid F. **Tetraspanin-enriched microdomains: a functional unit in cell plasma membranes.** *Trends Cell Biol* (2009) 19: 434-46

Regulation of gene expression in vascular endothelium

Head of Laboratory: *Juan Miguel Redondo Moya*

Research Scientist: *Eva Cano*

Postdoctoral Researchers: *Pablo Gómez del Arco*
Sara Martínez
Aránzazu Alfranca
Vanesa Esteban

Predoctoral Researchers: *Katia Urso*
Amelia Escolano
Nerea Méndez
Noelia Lozano

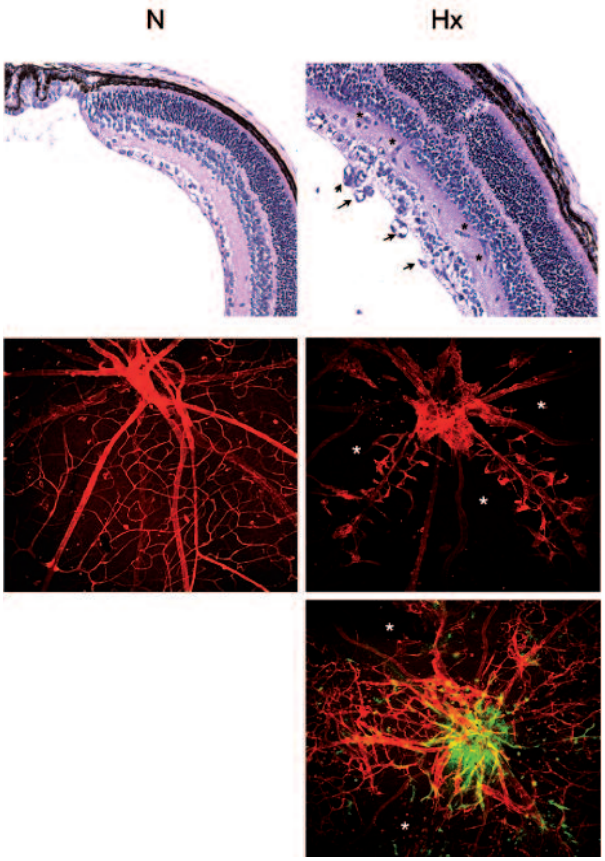
Technicians: *Dolores López*
Felipe Were
Isabel Mirones
Ana Guio
Gema Benito
Raquel Sánchez
Belén Ramírez

> RESEARCH INTEREST

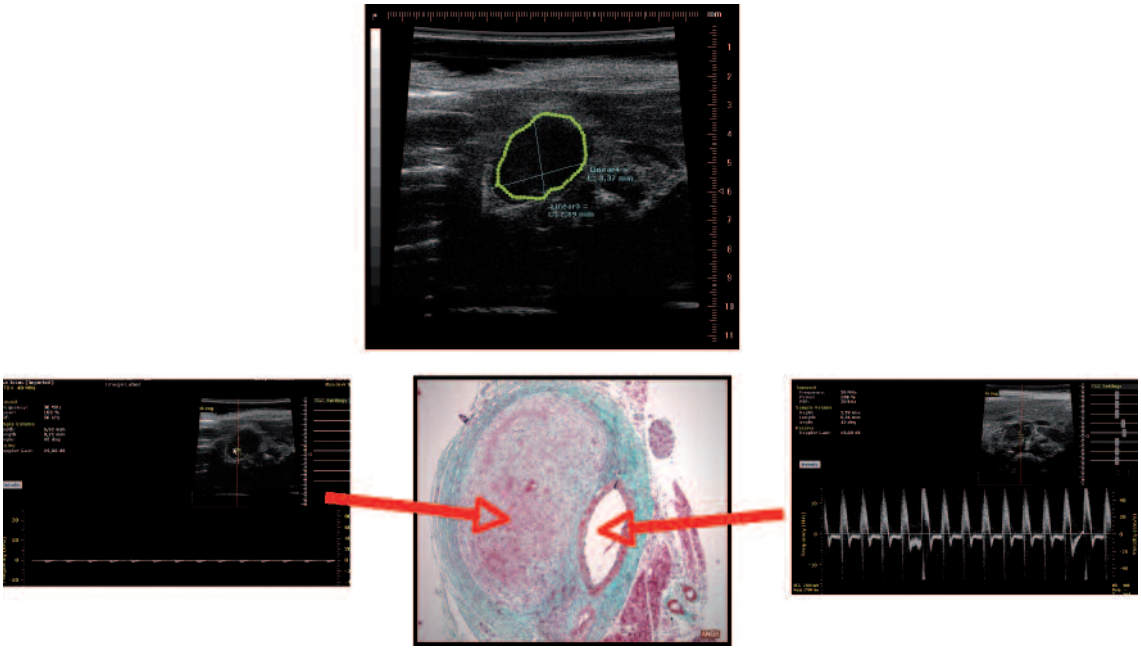
The calcium-calcineurin-NFAT (CN-NFAT) pathway regulates development of the immune, vascular and nervous systems, heart valve morphogenesis, and pancreatic beta-cell function, and is implicated in many related pathological processes. We study the regulation and function of CN-NFAT signaling in lymphocyte activation, angiogenesis and cardiac hypertrophy. Much of our work relates to molecular interactions of the phosphatase calcineurin with NFAT transcription factors and other substrates and regulators. This work has identified sequence motifs important for these interactions and sheds light on the mechanism of immunosuppressive drugs.

Our work on angiogenesis addresses the regulation of NFAT in endothelial cells by VEGF and the profile and actions of prostanoids released by activated endothelium. We use retinopathy of prematurity (ROP) 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 the gene expression program triggered by angiotensin II (Ang-II) in cardiomyocytes and vascular smooth muscle and the role of CN-NFAT signaling in these processes. Likewise we are dissecting signaling pathways involved in abdominal aortic aneurysim (AAA) triggered by infusion of Ang-II in ApoE-/- mice.

A separate area of interest, directed by Dr. E. Cano, relates to the inflammatory reaction initiated by stroke. Cerebral ischemia triggers local production of inflammatory mediators, of which glial cells are an efficient source. This production sustains immune-inflammatory signaling if not halted by endogenous or exogenous anti-inflammatory agents. We are interested in the signaling pathways that contribute to lesion expansion, or conversely have a role in lesion containment and repair of the injured brain. In this context, we have been studying the role of calcium-dependent pathways in astroglial cells.



Histological images of retinas from mice with oxygen-induced retinopathy (OIR). A, Hematoxylin-eosin stained sections from control (N) and OIR (Hx) mice; note the increase in the number of vessels in the inner plexiform layer (asterisks) and the presence of pre-retinal neovascularization (vascular tufts; arrows) in OIR retinas. B, Whole mount retinas from control (N) and OIR (Hx) mice. Vessels are stained with Isolectin B4 (red). Upper panels, non-infected retinas; Lower panel, retinas infected with GFP-encoding-lentiviruses. Note the avascular central areas (asterisks) in OIR retinas.



Restricted blood flow in AAA. The top image shows a transverse ultrasound scan of a mouse abdominal aortic aneurysm; note the enlarged dark area, marked by the dotted line. The thrombus is clearly visible in the Masson Trichome stained section below. Doppler measurements detect pulsed flow in the lumen (right) and its absence in the thrombus (right).

MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF 2006-08348)**
- **Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA; RD06/0014/0005)**
- **Comunidad de Madrid (S-BIO-0194-2006)**
- **European Commission FP6 (LSHM-CT-2004-05033, EICOSANOX). Funds held at the Universidad Autónoma de Madrid**
- **Fundació La Marató TV3 (081731)**
- **Fundación Genoma España. MEICA Project**

SELECTED PUBLICATIONS

Martinez-Martinez S, Genesca L, Rodriguez A, Salichs E, Raya A, Were F, Lopez-Maderuelo MD, Redondo JM*, de la Luna S*. **The RCAN carboxyl-end mediates calcineurin docking-dependent inhibition via a site that dictates binding to substrates and regulators.** *Proc Natl Acad Sci USA* (2009) 14: 6117-22
** Corresponding authors*

Rodriguez A, Roy J, Martinez-Martinez S, Lopez-Maderuelo MD, Nino-Moreno P, Orti L, Pantoja D, Pineda-Lucena A, Cyert M, Redondo JM. **A conserved docking surface on calcineurin mediates interaction with substrates and immunosuppressants.** *Molecular Cell* (2009) 13: 616-26

Salvado MD, Alfranca A, Escolano A, Haeggström J, Redondo JM. **COX-2 limits prostanoid production in activated endotelial cells and is a source of PGH_2 for transcellular metabolism to PGE_2 by tumor cells.** *Arterioscler Thromb Vasc Biol* (2009) 29: 1131-7

Alfranca A, Lopez-Oliva JM, Genis L, Lopez-Maderuelo D, Salvado D, Quesada J, Garcia-Arroyo A and Redondo JM. **PGE_2 Induces angiogenesis via MT1-MMP-mediated activation of the TGFβ/Alk5 signalling pathway.** *Blood* (2008) 15: 1120-8

Canellada A, Ramirez BG, Minami T, Redondo JM* and Cano E*. **Calcium/calcineurin signaling in primary cortical astrocyte cultures Rcan1-4 and cyclooxygenase-2 as NFAT target genes.** *Glia* (2008) 56: 709-22
** Corresponding authors*

Integrin signaling

Head of Laboratory: *Miguel Ángel del Pozo*

Postdoctoral Researchers: *Asier Echarri*
Ana Cerezo
Raffaele Strippoli
Inmaculada Navarro
Susana Minguet
Jacky Goetz
Teijo Pellinen

Predoctoral Researchers: *Marta C. Guadamillas*
Olivia Muriel
Miguel Foronda

Technicians: *Sara Sánchez*
Dácil M. Pavón
Teresa Osteso

> RESEARCH INTEREST

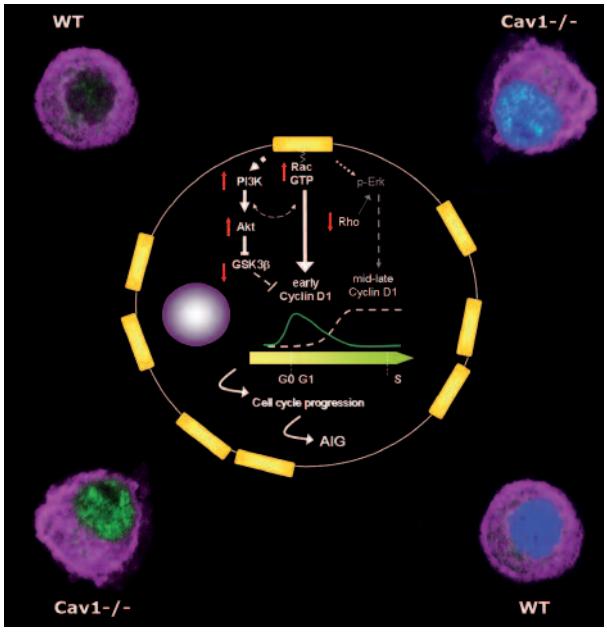
Signals are the language of life, mediating the communication essential for cells' proper behavior. Within cells, intricate networks of proteins transduce signals into the appropriate physiological response, and many diseases are caused by malfunctioning of these signal transduction networks. Our interest is in the mechanisms through which integrins, Rho/Rac GTPases and caveolin cooperate to regulate gene expression, cell cycle progression, migration, polarization, vesicle trafficking and epithelial-mesenchymal transition (EMT), key processes in the pathogenesis of cancer and inflammatory and cardiovascular diseases.

Integrins (the main ECM receptors) regulate caveolin-mediated endocytosis of Rac binding sites within cholesterol-enriched membrane microdomains (CEMM). Our recent work shows that cells lacking caveolin exit quiescence and progress through the cell cycle faster than wild-type cells, and are able to proliferate without anchorage to substrate and do not show the normal downregulation of cyclin D1 upon serum deprivation or detachment. Surprisingly, this proliferative advantage is independent of Erk–MAPK, being instead driven by increased membrane order and Rac membrane targeting. We are currently assessing the contribution of this mechanism to atherogenesis.

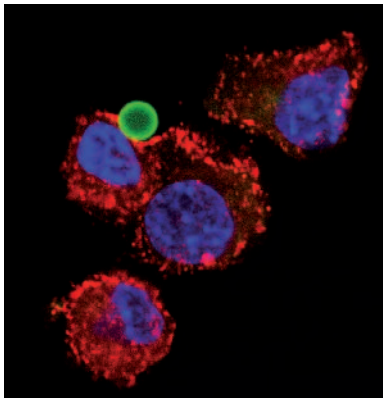
A related interest is the influence of caveolin on cell polarity and directional migration. Caveolin regulates these processes in 2D, through coordination of Src kinase and Rho GTPase signaling. We are investigating how this regulation operates in 3D, focusing on the contribution of caveolin to 3D microenvironment remodeling.

To understand the molecular mechanisms by which integrins regulate caveolin trafficking, we are studying actin polymerization pathways that control caveolae dynamics, and we are also conducting an RNAi-based genome-wide high-content image analysis screen in collaboration with the Cellomics Unit.

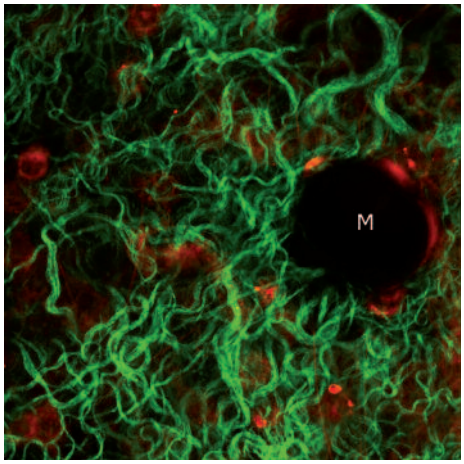
Our work on EMT has identified a role for ERK/NF-kB/Snail1 signaling, and we are currently studying signaling pathways underlying EMT and fibrosis during chronic peritoneal inflammation.



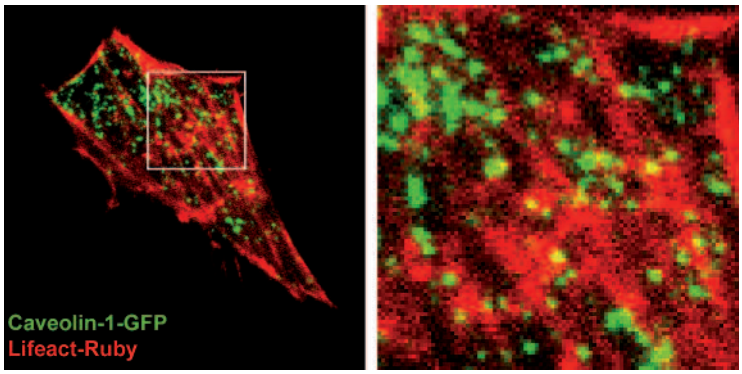
Cav1$^{-/-}$ cells show anchorage-independent proliferation and expression of cyclin D1. Cav1$^{-/-}$ cells placed in suspension show nuclear accumulation of cyclin D1 (left panels, green). The right panels show the same cells with nuclei labeled blue with Hoechst. Magenta shows phalloidin-labeled actin. In the absence of Cav1, CEMM (yellow boxes in the central scheme) cannot be internalized. This allows activation of Rac, PI3K/Akt and Erk pathways, resulting in an altered timing of cyclin D1 expression that permits cell cycle progression in the absence of substrate anchorage.



CEMM are recruited to the site of interaction between the plasma membrane and cholera toxin B-coated latex beads. The image shows WT cells that have been incubated with CTxB-647 beads (green) and later labeled with CTxB-594 to reveal GM1ganglioside (red). Nuclei are stained blue with Hoescht.



Multiphoton excitation microscopy image showing second harmonic generation (SHG, green) signal and autofluorescence (red) in intact mammary tissue from WT mice. The green staining reflects the degree of parallelism in collagen fibers. M=Mammary gland.



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

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2008-02100)**
- **Instituto de Salud Carlos III. Red RTICC (RD06/0020/1033).**
- **EURYI Award and EMBO Young Investigator Programme.**

SELECTED PUBLICATIONS

Gonzalo P, Guadamillas MC, Hernandez-Riquer MV, Pollan A, Grande-Garcia A, Bartolome RA, Vasanji A, Ambrogio C, Chiarle R, Teixido J, Ristel J, Apte SS, del Pozo MA, and Arroyo AG. **MT1-MMP is required for myeloid cell fusion via regulation of Rac1 signaling.** *Dev Cell* (accepted)

Cerezo A, Guadamillas MC, Goetz J, Sanchez-Perales S, Klein E, Assoian R, del Pozo MA. **Absence of Caveolin-1 Increases Proliferation and Anchorage-Independent Growth by a Rac-Dependent, Erk-Independent Mechanism.** *Mol Cell Biol* (2009) 29: 5046-59

Strippoli R, Foronda M, Lopez-Cabrera M and del Pozo MA. **Targeting the ERK/NF-κB/Snail1 pathway as a potential therapeutic strategy to prevent the failure of peritoneal dialysis.** *Nat Rev Cardiol* (CNIC Edition) (2009) 6: 43-8

Strippoli R, Benedicto I, Perez Lozano ML, Cerezo A, Lopez-Cabrera M, del Pozo MA. **Epithelial to Mesenchymal Transition of Peritoneal Mesothelial Cells is Regulated by an ERK/NF-κB/Snail1 pathway.** *Dis Model Mech* (2008) 1: 264-74

Santibanez JF, Blanco FJ, Garrido-Martin EM, Sanz-Rodriguez F, del Pozo MA, Bernabeu C. **Caveolin-1 interacts and cooperates with the TGF-b type I receptor ALK1 in endothelial cell caveolae.** *Cardiovasc Res* (2008) 77: 791-9

Matrix metalloproteinases in angiogenesis and inflammation

Head of Laboratory: *Alicia G. Arroyo*

Postdoctoral Researchers: *Pilar Gonzalo*
Rubén A. Mota
Fernando Neria

Technician: *Ángela Pollán*

Predoctoral Researchers: *María Victoria Hernández de Riquer*
Agnieszka Koziol
Mara Martín
Vanessa Moreno

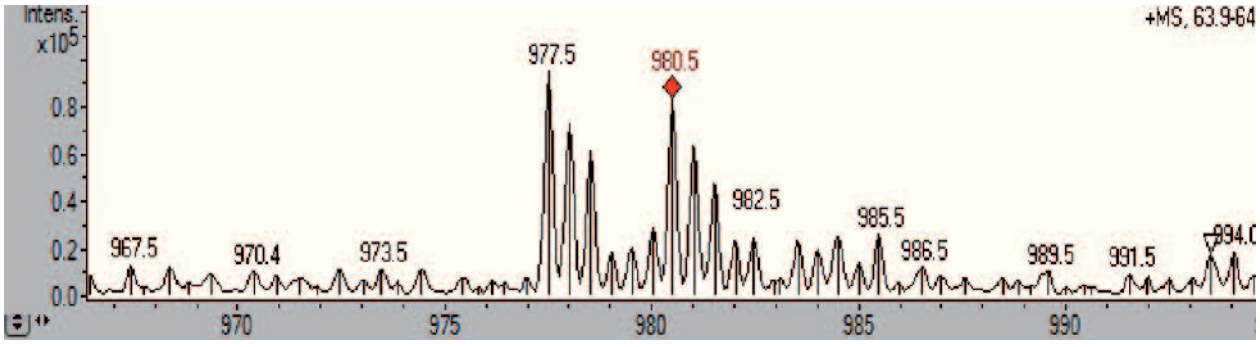
> RESEARCH INTEREST

Angiogenesis, the formation of new capillaries, is closely linked to inflammation. We are interested in the molecular and cellular processes that initiate angiogenesis and control the decision between stabilization or regression of new vasculature, and how these are linked to the inflammatory infiltrate. Our work focuses on proteases and related molecules involved in matrix remodeling, and has characterized the contribution of membrane-type matrix metalloproteinase 1 (MT1-MMP) to chemokine and nitric oxide-induced angiogenesis and monocyte migration. We are also interested in MT4-MMP, a GPI-anchored MMP of unknown function.

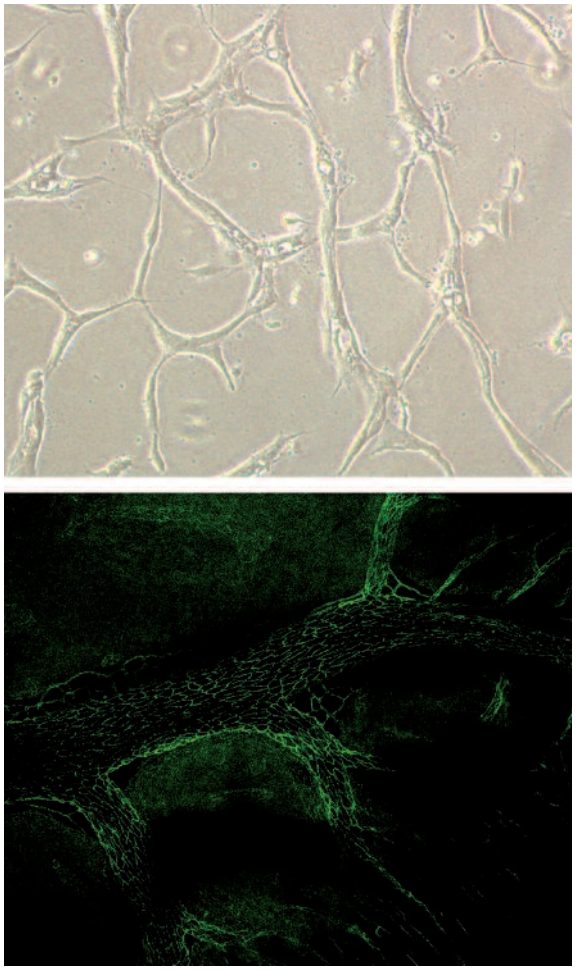
We have recently identified a novel, catalysis-independent function for MT1-MMP in macrophage fusion during osteoclast and giant cell formation. The mechanism involves binding of the MT1-MMP cytosolic tail to the adaptor p130Cas, resulting in increased Rac1 membrane targeting and activity. This finding suggests that MT1-MMP regulation and functions are cell-context dependent, and we are currently testing this hypothesis in endothelial cells in the context of angiogenesis.

We are also conducting proteomic studies to identify the collection of cellular substrates (degradome) processed by MT1-MMP and MT4-MMP in endothelial cells and leukocytes, and further efforts are directed at defining the molecular networks in which these proteases participate in these cells. We are exploring the functional impact of MT1-MMP and MT4-MMP through studies in cell-based systems and genetically-modified mouse models of angiogenesis, leukocyte recruitment and inflammatory disorders such as atherosclerosis. We are also interested in characterizing new molecules of potential relevance to vascular integrity and angiogenesis, such as extracellular matrix metalloproteinase inducer (EMMPRIN).

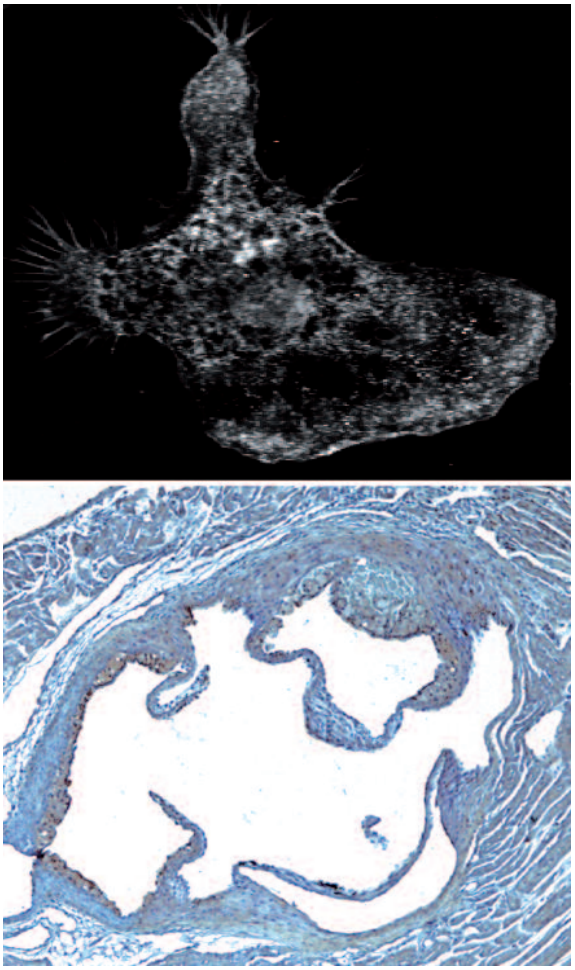
Through these projects, we aim to extend our knowledge of where, when and how MT-MMPs and their regulators modulate endothelial and leukocyte behavior during the establishment and progression of chronic inflammatory disorders.



SILAC (stable isotype labeling of aminoacids in culture) is a quantitative proteomic approach that we are using to identify the degradome of specific proteases in cell types involved in inflammation and angiogenesis. The figure shows a mass spectrum obtained from an actin peptide labeled with heavy or light amino acids.



Analysis of angiogenesis and vascular integrity. *Top: Human endothelial cells grown in vitro in 3D collagen I gels form capillary-like tubes. Bottom: PECAM-1 staining of endothelial junctions reveals the integrity of the blood vessels in the mouse diaphragm vasculature.*



Macrophages and inflammation. *Top: Mouse peritoneal macrophages display a polarized morphology in culture. Bottom: Mac-3 staining reveals the presence of macrophages in atherosclerotic plaques of LDLR$^{-/-}$ mice fed a high fat diet.*

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2008-0214)**
- **Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA; RD/06/0014/1016)**
- **Fundación Genoma España. MEICA Project**

SELECTED PUBLICATIONS

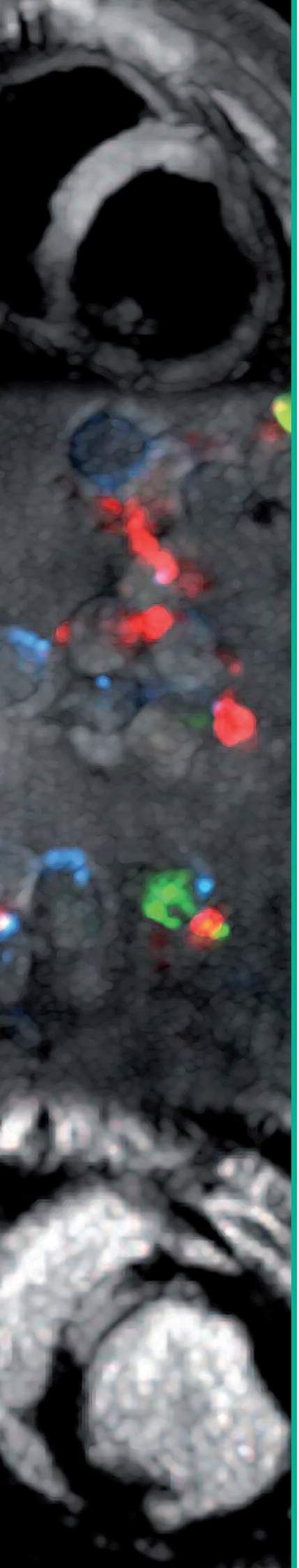
Gonzalo P, Guadamillas MC, Hernandez-Riquer MV, Pollan A, Grande-Garcia A, Bartolome RA, Vasanji A, Ambrogio C, Chiarle R, Teixido J, Risteli J, Apte SS, del Pozo MA, Arroyo AG. **MT1-MMP is required for myeloid cell fusion via regulation of Rac1 signaling.** *Dev Cell* (accepted)

Yanez-Mo M, Barreiro O, Gonzalo P, Batista A, Megias D, Genis L, Sachs N, Sala-Valdes M, Alonso MA, Montoya MC, Sonnenberg A, Arroyo AG, Sanchez-Madrid F. **MT1-MMP proteolytic activity is regulated through association with tetraspanin CD151 in primary endothelial cells.** *Blood* (2008) 112: 3217-26

Alfranca A, Lopez JM, Genis L, Lopez-Maderuelo D, Salvado D, Quesada AJ, Arroyo AG, Redondo JM. **PGE_2 induces angiogenesis via the MT1-MMP-mediated activation of the TGFβ/ALK5 signaling pathway.** *Blood* (2008) 112: 1120-8

Applied Research Departments

Multi-departamental Clinical Projects



Applied Research Departments

Multi-departamental Clinical Projects

Atherosclerosis, the underlying cause of most cardiovascular diseases, progressively damages vital organs and vascular areas, leading to clinical conditions such as peripheral vascular disease, myocardial infarction and stroke. Aside from the human cost, these clinical manifestations of atherosclerotic disease also incur a high economic cost. The prevention of cardiovascular disease is hampered by the limited predictive power of screening procedures to detect people at high risk. The CNIC's multi-departmental clinical projects apply the latest imaging technologies to improve diagnosis and to test the efficacy of new treatments.

IMJOVEN

Although heart disease causes many deaths in young women, 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 aim of VIRGO and IMJOVEN is to identify key demographic, clinical, metabolic, psychosocial, healthcare delivery, and biological determinants of prognosis. Our aim with IMJOVEN is to study 300 women with a previous history of AMI, using the same protocol as the VIRGO study. IMJOVEN is coordinated by the Department of Translational Research 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.

AWHS

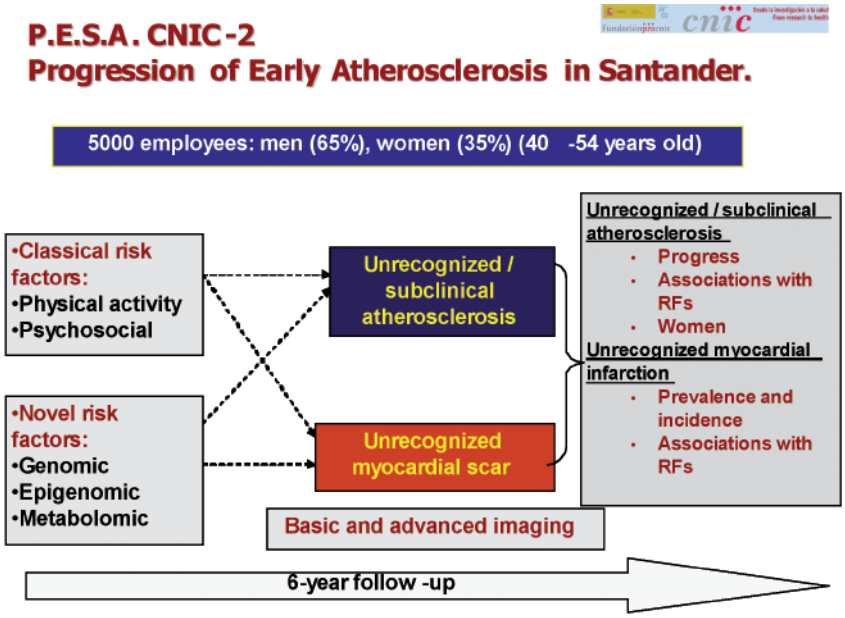
The Aragon Workers Health Study is being carried out in collaboration with the Instituto Aragonés de Ciencias de la Salud (IACS) and the General Motors Spain factory in Zaragoza. The study examines the development of cardiovascular disease and its risk factors by monitoring factory workers at their annual medical checkups. Enrollment has been completed, and we have recruited 5589 workers to the study, a participation of greater than 95%. Even though the population in the study is relatively young, 35% of study participants were hypertensive at baseline, 5% had diabetes, 22.5% were obese, and 53.7% were overweight. The project is now in its clinical phase, consisting of measurements of subclinical atherosclerosis in study participants and follow-up over at least five years. The study is financed by the Departamento de Salud y Consumo of the Aragonese regional government, General Motors Spain, and the CNIC.

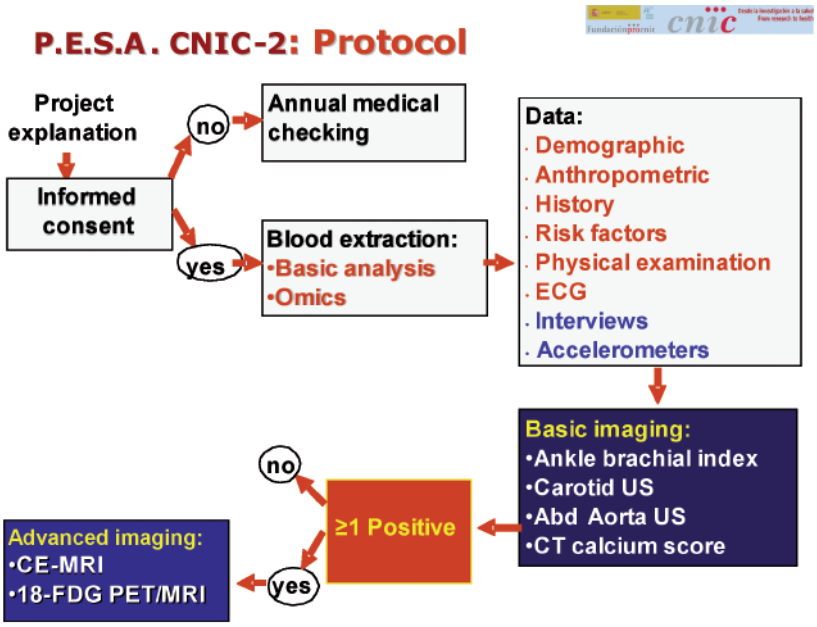
PESA, CNIC2-Santander

PROGRESSION OF EARLY SUBCLINICAL ATHEROSCLEROSIS, CNIC2-SANTANDER

Strategies to identify individuals with subclinical alterations indicating increased risk of cardiovascular disease have been boosted by the recent development of 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 of men over the age of 60; atherosclerotic disease in this group has already had several decades of evolution and may not be fully reversible. To assess the early onset of atherosclerosis, longitudinal vascular imaging studies are needed to provide information about middle-aged populations.

PESA is a longitudinal study into the use of imaging techniques to detect the prevalence and rate of progression of subclinical vascular lesions in a population of 5000 male and female workers aged between 40 and 54 years. The study examines the association of these clinical parameters with the presence of genetic, epigenetic, metabolomic, proteomic and environmental factors, including dietary habits, physical activity, biorhythms, psychosocial characteristics and exposure to environmental pollutants. Participants are first assessed with basic techniques, including CT imaging to estimate coronary calcium, 3D ultrasound of carotid artery, and 2D ultrasound measurement of abdominal aorta and the rate of ankle-brachial pressure. These techniques are used for the early diagnosis of individuals with subclinical atherosclerosis, and participants are then studied with advanced imaging techniques in order to determine the atherosclerotic burden and the presence and progression of inflammation in atherosclerotic plaques. The study will also provide important data on the prevalence of unrecognized myocardial infarction in this population, and will assess the prevalence and progression of subclinical atherosclerosis in women during peri-menopause and its relation to cardiovascular risk factors and hormonal changes.





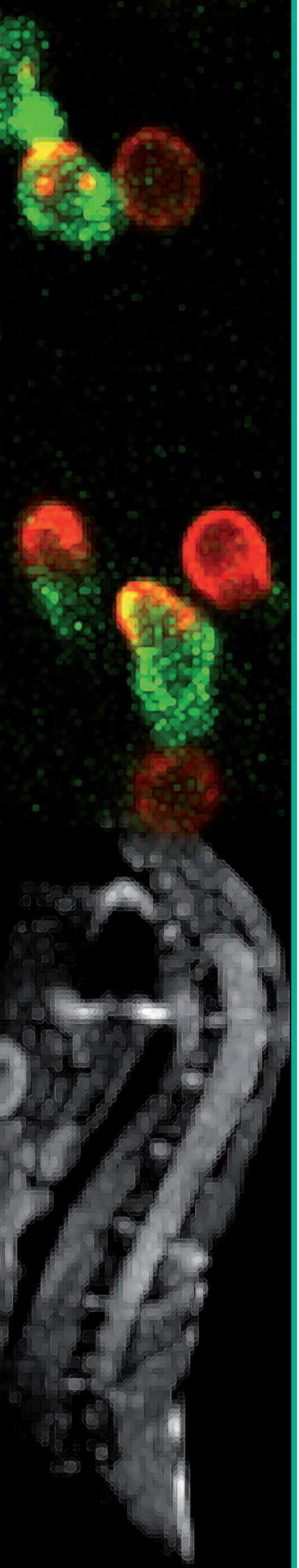
Polypill/FOCUS

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 fixed dose drug combinations (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 combination for secondary prevention. The CNIC-Ferrer polypill project is led by Valentín Fuster and is coordinated by the Translational Research Department. The project is now in its clinical testing phase.

We have also launched the FOCUS project, which tests the fixed-dose combination concept for cardiovascular prevention in populations with different socio-economic characteristics. An important aim of FOCUS is to understand the factors that determine poor treatment adherence and inappropriate prescribing for secondary cardiovascular prevention. This will allow FOCUS to establish recommendations for better use of medication in patients with ischemic heart disease. After the successful completion of FOCUS, secondary prevention medication will be available and affordable for large numbers of patients in developed and developing countries. The CNIC's partners in the FOCUS consortium are the Mario Negri Institute (Milan), the Fundación Ruscalleda (Buenos Aires), the Fundació Clinic (Barcelona), Ferrer Internacional (Barcelona), the Agencia Española de Evaluación de Tecnologías Sanitarias, the Instituto de Salud Carlos III (Madrid), the World Heart Federation (Geneva) and the Federación Argentina de Cardiología (Buenos Aires).

Applied Research Departments

4 *Atherothrombosis and Cardiovascular Imaging*



Applied Research Departments

Atherothrombosis and Cardiovascular Imaging

The ACI department is dedicated to developing non-invasive technologies for molecular-resolution imaging. Through these technologies, vulnerable plaques can be identified and characterized, providing invaluable information on the underlying molecular mechanisms of disease and leading to tools for accurate diagnosis and targeted drug delivery.

Department Director:	*Valentín Fuster*
Department Manager:	*Ana Isabel Castillo Varón*
Technicians:	*Javier Mateos Villa* *Inés Ortega Rodríguez*
Administrative support:	*Eeva Inari Soininen*

Cardiovascular imaging

The Cardiovascular Imaging Lab is a multi-center group formed through national and international collaborations

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)*
Zahi Fayad (Mt. Sinai Medical Center)
Juan José Badimón (Mt. Sinai Medical Center)
Jesús Mateo (CNIC)

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

Predoctoral Researcher: *Patricia García (CNIC)*

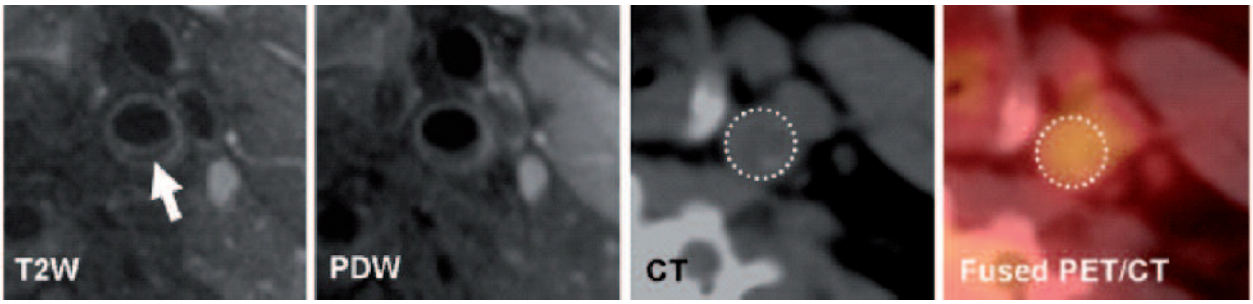
> RESEARCH INTEREST

Our laboratory develops advanced non-invasive, molecular-resolution technologies for precise diagnosis and treatment of cardiovascular disease.

Our recent work related to clinical studies has concentrated on the development of protocols connected to the High Risk Population study of middle aged populations. We have added protocols for the detection of unrecognized myocardial infarction and for the substitution of PET/CT technology with PET/MR, a hybrid system being developed through the European Union financed HYPERImage Project. These studies will enable detection of previous subclinical cardiovascular disease and may provide new prognostic markers for identifying patients at higher risk of severe clinical events.

Other projects ongoing during 2009 include the PESA study (Progression of Early Subclinical Atherosclerosis), run in collaboration with the Departments of Translational Research and Epidemiology. Subject recruitment for PESA is due to start in 2010. Last year also saw the planning of studies to use enhanced CE-MRI to quantify infarct size and post-infarction left ventricular remodeling. These data will be of great clinical value as they will allow accurate imaging and quantification of cardioprotection. The combination of MRI and clinical end points will permit a new stratification of patients at high risk of heart failure and future clinical events.

Animal studies in our laboratory address four key areas: the aortic territory (especially in relation to aneurysm), the brain and aging, vascular regeneration ("vasa vasorum"), and atherothrombosis as an inflammatory disease. Over the last year we have collaborated with groups in the Vascular Biology and Inflammation department to develop new immune models of mouse myocarditis and aortic aneurysm. In addition, a new mouse model of ventricular hypertrophy has been developed in collaboration with groups from the Universidad Autónoma, Madrid.



Characterization of carotid atherosclerosis. Complementary value of non-invasive FDG-PET/CT and MR imaging for the evaluation of atherosclerotic plaque composition and activity. Lipid-rich plaques are more inflamed than either calcified or collagen-rich plaques. Figures in transverse MR images and corresponding FDG-PET/CT images indicate a carotid artery lipid-necrotic core plaque, hypointense on T2W (white arrow) and on PDW images. CT image demonstrates the absence of calcification. The white dashed circle demonstrates FDG uptake into the entire artery section on the PET/CT image.

With permission from:
Silvera SS, Aidi HE, Rudd JH, Mani V, Yang L, Farkouh M, Fuster V, Fayad ZA. Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries. Atherosclerosis. 2009 Nov;207(1):139-43.

> MAJOR GRANTS

- **European Commission FP7 (201651 HYPERImage).**
- **European Commission FP7 (241559 FOCUS).**

SELECTED PUBLICATIONS

Fuster V. **Prime time for a polypill after myocardial infarction?** *Nat Clin Pract Cardiovasc Med* (2009) 6: 83

Fuster V, van der Zee S, Elmariah S, Bonow RO. **Academic careers in cardiovascular medicine.** *Circulation* (2009) 119: 754-60

Moreno PR, Sanz J, Fuster V. **Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport.** *J Am Coll Cardiol* (2009) 53: 2315-23

Sanz J, Moreno PR, Fuster V. **The year in atherothrombosis.** *J Am Coll Cardiol* (2009) 53: 1326-37

Silvera SS, Aidi HE, Rudd JH, Mani V, Yang L, Farkouh M, Fuster V, Fayad ZA. **Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries.** *Atherosclerosis* (2009) 207: 139-43

Imaging cardiovascular inflammation and the immune response

Head of Laboratory: *Andrés Hidalgo Alonso*

Predoctoral Researcher: *Maria Casanova Acebes*

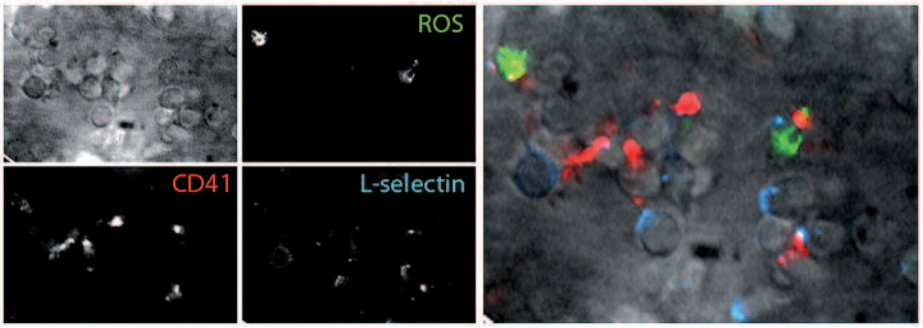
Technician: *Christophe Pitaval*

> RESEARCH INTEREST

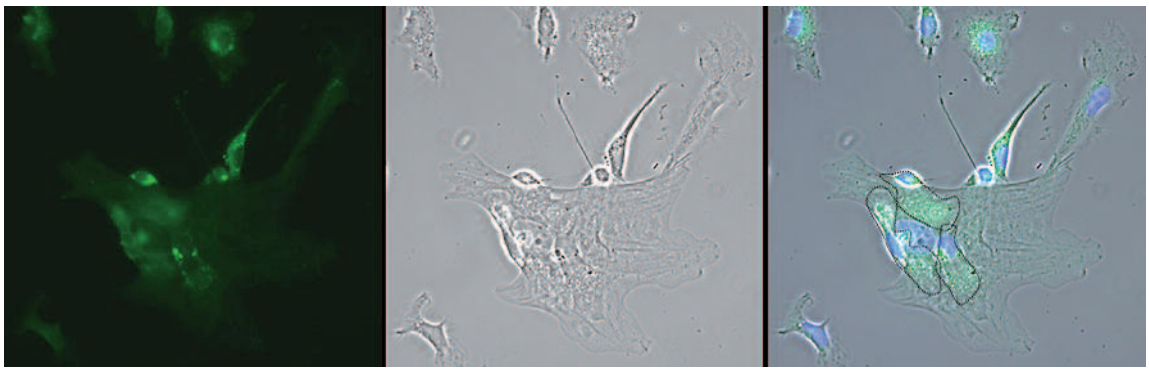
Our laboratory is interested in various aspects of the inflammatory response. We are developing techniques based on multichannel fluorescence intravital microscopy to visualize the molecular and cellular phenomena that occur within the inflamed vasculature. We are also interested in understanding the mechanisms by which leukocyte production and release during inflammation modulates homeostatic processes.

Imaging inflammation: Leukocytes and platelets are recruited to inflamed vessels via adhesion receptors, chemokines and cytokines. During this process, leukocytes redistribute surface receptors to discrete domains, each of which can mediate interactions with circulating platelets and erythrocytes. These interactions can lead to an excessive activation of the leukocyte, which in turn releases toxic mediators that damage the surrounding endothelium. We want to understand the biology of these interactions, including how they lead to the formation of polarized leukocyte domains, the identity of the receptors that mediate them and their consequences in inflammatory processes. We are particularly interested in understanding the potential contribution of these interactions to vascular injury under atherogenic conditions.

Control of leukocyte production and release: We aim to dissect the links between inflammation and alterations in the bone marrow niches, the home of hematopoietic stem cells and their differentiated progeny. We are addressing this through the use of gene-targeted mouse models with alterations in the immune and hematopoietic systems. Our goal is to define the signals that these biological systems use to communicate with each other and to understand how this is regulated and altered during disease.



Imaging thrombo-inflammatory events in the circulation of live mice. *Multichannel fluorescence intravital microscopy allows leukocytes to be identified in inflamed venules (labeled with anti-L-selectin antibody, blue). Leukocyte interactions with circulating platelets (labeled with anti-CD41 antibody, red) induces the production of reactive oxygen species (ROS; green intracellular spots), which can alter the integrity of the vasculature during acute inflammation.*



Modulation of bone marrow mesenchymal cells by macrophages. *Bone marrow macrophages and mesenchymal cells derived from MAFIA (mcsfr-gfp) mice. The epifluorescence and phase contrast images show the interaction of a mesenchymal cell with several macrophages expressing GFP (green). Strong associations are established between these cell types in culture, with macrophages frequently found underneath mesenchymal cells. We are investigating the significance of these interactions and the mechanisms by which they are established.*

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2009-11037)**
- **European Commission FP7 (246655 LEMPIT)**

SELECTED PUBLICATIONS

Hidalgo A, Chang J, Jang J, Peired AJ, Chiang EY, Frenette PS. **Heterotypic interactions enabled by polarized neutrophil microdomains mediate thrombo-inflammatory injury.** *Nat Med* (2009) 15: 384-91

Hidalgo A, Frenette PS. **When integrins fail to integrate.** *Nat Med* (2009) 15: 249-50

Hidalgo A. **Hematopoietic stem cell homing: The long, winding and adhesive road to the bone marrow.** *Inmunologia* (2008) 27: 22-35

Vascular wall remodeling and cardiovascular disease

Head of Laboratory: *Carlos Zaragoza*

Postdoctoral Researchers: *Beatriz Herranz*

Predoctoral Researchers: *Carlos Tarín*
Begoña Lavín

Technician: *Mónica Gómez*

> RESEARCH INTEREST

Our research is focused on the actions of vasoactive factors and proteolytic enzymes during the early steps of vascular wall remodeling, a fundamental process which plays a key role in the development and progression of atherosclerosis, aneurysm, myocardial infarction, and arterial hypertension, four of the most prevalent diseases worldwide. We study animal models of these diseases generated in the laboratory, and our ultimate goal is to translate the results of our research into validated clinical tools for diagnosis and treatment.

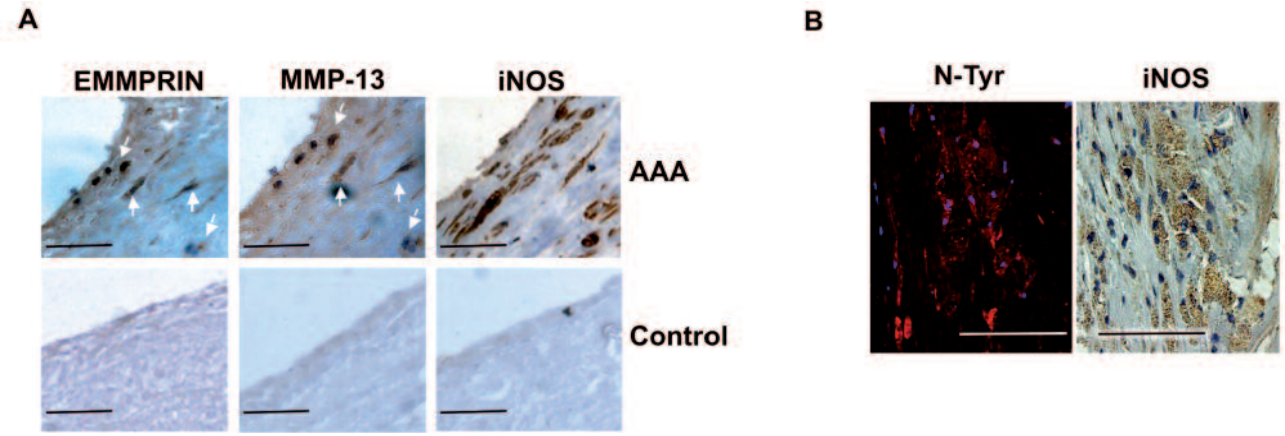
The following projects are currently running in our laboratory.

1) Identification of molecular determinants involved in the development, progression, and rupture of abdominal aortic aneurysms (AAA) and the development of new tools for non-invasive detection.

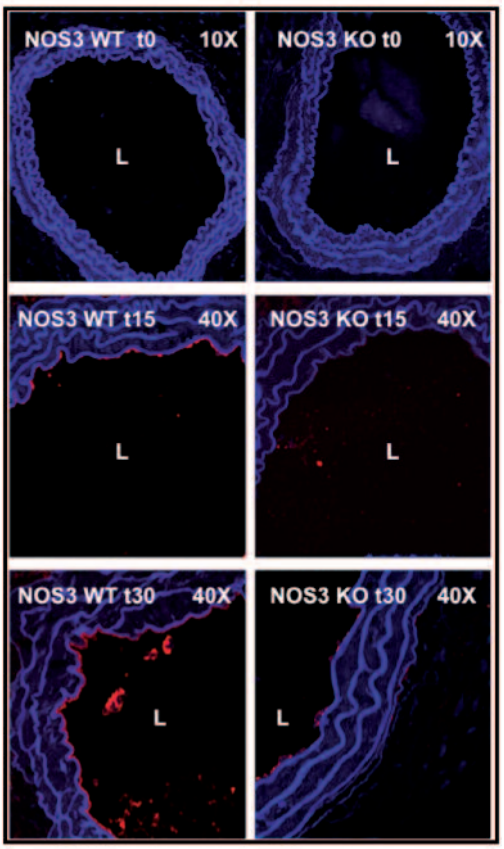
2) Determination of the contribution of proteolytic enzymes to the migration and homing of endothelial progenitor cells (EPCs) during vascular wall repair, and the development of new non-invasive tools for molecular tracking by high-frequency molecular ultrasound.

3) Identification of molecular determinants responsible for cardioprotection during late ischemic pre-conditioning, with the aim of finding new targets of potential benefit in the diagnosis or treatment of cardiac ischemia.

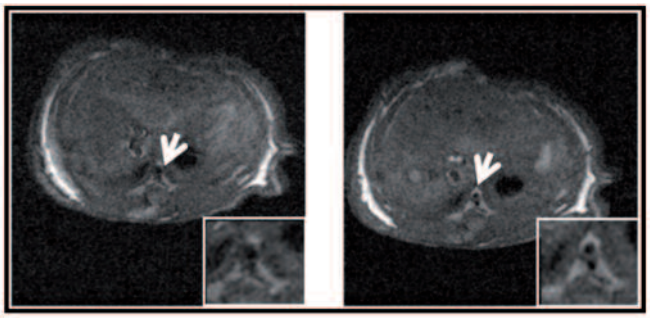
4). Participation in the European Comission funded FP7 HYPERImage project. Generation of a hybrid PET/MR system for concurrent clinical and pre-clinical detection: WP4, pre-clinical validation of the system towards cardiology: atherosclerosis and myocardial infarction; WP6, management of knowledge.



***Detection of EMMPRIN, MMP-13, iNOS, and nitro-tyrosine in human AAA. A**, Immunohistochemical detection of the expression of EMMPRIN, MMP-13, and iNOS in samples of AAA (upper panels) or healthy aorta (lower panels). Arrows indicate co-localization of EMMPRIN and MMP-13 in the serial sections. **B**, Serial sections of aortic tissue showing confocal immunofluorescence detection of nitrotyrosine (left; Red-Cy3. DAPI-stained nuclei in blue) and immunohistochemical detection of iNOS (right). Co-localization of nitrotyrosine and iNOS is evident.*



Confocal microscopy detection of ICAM-1 in aorta sections of WT and NOS3-null mice. ICAM-1 is shown in red at 0, 15 and 30 days after aortic endothelial denudation. L = lumen.



Non invasive detection of EMMPRIN in live mice by molecular MRI. *Gadolinium-containing micro-micelles conjugated to anti-EMMPRIN antibodies were injected into mice 15 days after surgical intervention to induce AAA. Magnetic resonance images were acquired at regular intervals after injection. Left. (t=0). Right (t=4h). Insets show magnified views of the region containing the abdominal aorta, marked with arrows.*

> MAJOR GRANTS

- Ministerio de Ciencia e Innovación (SAF2008-04629).

SELECTED PUBLICATIONS

Lizarbe TR, Tarin C, Gomez M, Lavin B, Aracil E, Orte LM, Zaragoza C. **Nitric oxide induces the progression of abdominal aortic aneurysms through the matrix metalloproteinase inducer EMMPRIN.** *Am J Pathol* (2009) 175: 1421-30

Martinez-Miguel P, Raoch V, Zaragoza C, Valdivieso JM, Rodriguez-Puyol M, Rodriguez-Puyol D , Lopez-Ongil S. **Endothelin-converting enzyme-1 increases in atherosclerotic mice: potential role of oxidized low density lipoproteins.** *J Lipid Res* (2009) 50: 364-75

Tarin C, Gomez M, Calvo E, Lopez JA, Zaragoza C. **Endothelial nitric oxide deficiency reduces MMP-13-mediated cleavage of ICAM-1 in vascular endothelium: a role in atherosclerosis.** *Arterioscler Thromb Vasc Biol* (2009) 29: 27-32

Lizarbe TR, Garcia-Rama C, Tarin C, Saura M, Calvo E, Lopez JA, Lopez-Otin C, Folgueras AR, Lamas S, Zaragoza C. **Nitric oxide elicits functional MMP-13 protein-tyrosine nitration during wound repair.** *FASEB J* (2008) 22: 3207-15

Molecular and genetic cardiovascular pathophysiology

Head of Laboratory: *Vicente Andrés García*

Postdoctoral Researchers: *José María González Granado*
José Rivera Torres
Laia Trigueros Motos

Predoctoral Researchers: *Pedro Molina Sánchez*
Carlos Silvestre Roig

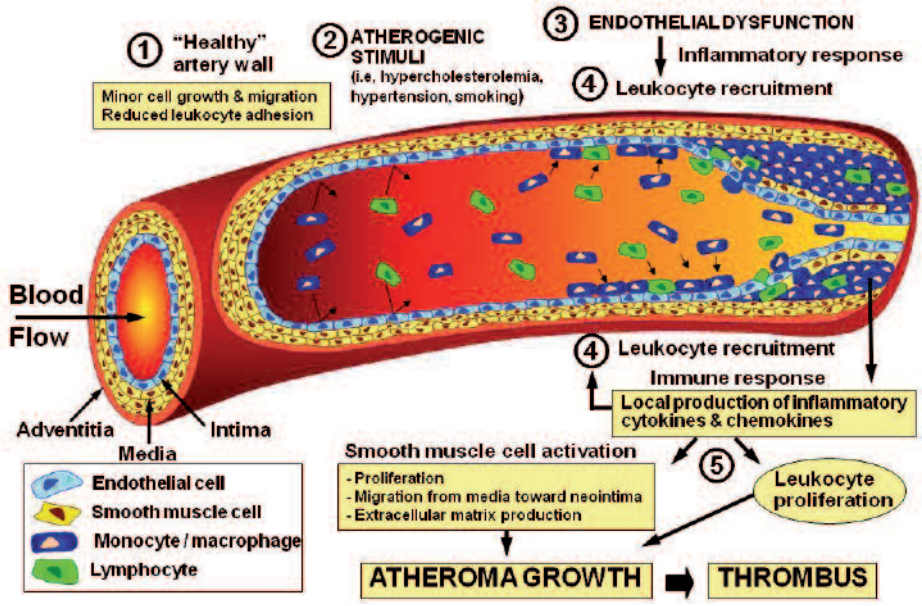
Technician: *María Jesús Andrés Manzano*

> RESEARCH INTEREST

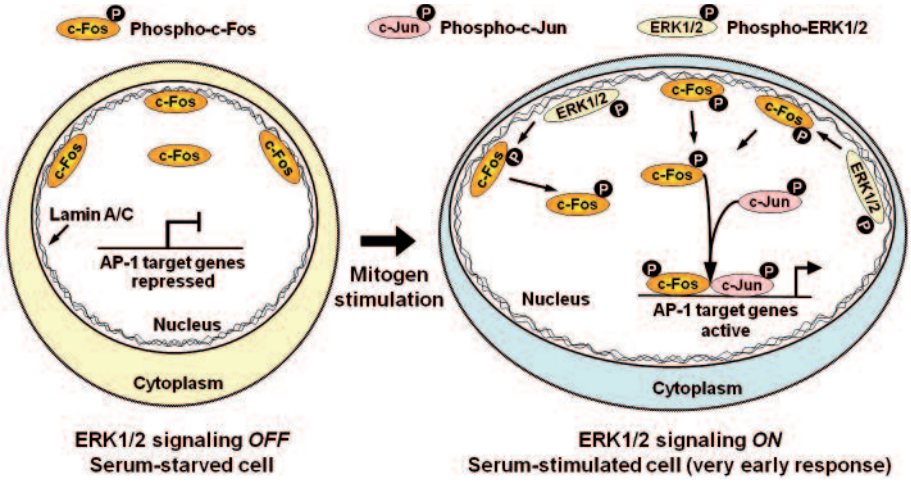
Accumulation of blood-borne leukocytes and their proliferation within the atherosclerotic plaque is a hallmark of atherosclerosis. During disease progression, inflammatory mediators produced by activated neointimal macrophages and lymphocytes induce the proliferation of vascular smooth muscle cells (VSMCs)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

Our research addresses the cellular, molecular and genetic mechanisms that underlie the development of atherosclerosis and restenosis, with particular emphasis on the role of cell-cycle regulatory factors, as well as the identification of biomarkers of these diseases. Our experimental strategy involves a multifaceted approach that 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 screening.

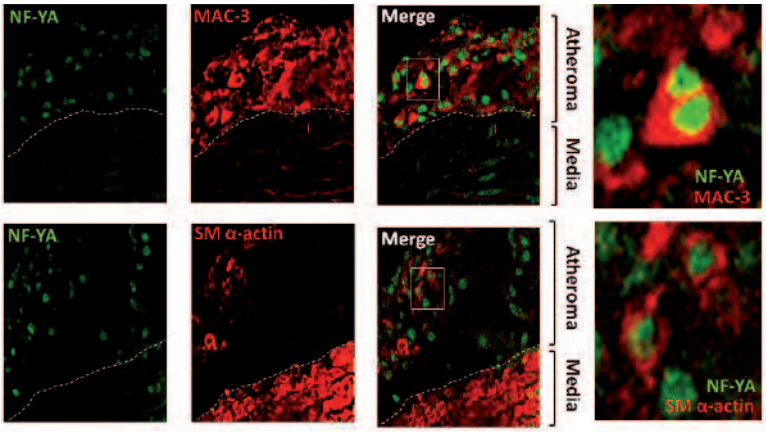
Specific projects in the lab include: 1) Generation and characterization of genetically-modified mice to investigate the role of candidate genes in atherosclerosis, including Cre/lox strategies to ablate genes specifically in cell types involved in atherosclerosis (VSMCs, endothelial cells and macrophages); 2) Studies of the consequences of single nucleotide polymorphisms in cell-cycle regulatory genes on human susceptibility to in-stent restenosis; and 3) Research into the role of the nuclear envelope in the regulation of signal transduction, gene expression and cell-cycle activity in cardiovascular disease and aging.



Mechanisms of atherosclerosis



Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2 and c-Fos at the nuclear envelope (NE). *Left: Quiescent cells contain low levels of the proto-oncogene c-Fos, which is predominantly hypophosphorylated and sequestered at the NE through its interaction with A-type lamins. Right: Upon mitogen stimulation, phosphorylated (active) ERKs 1 and 2 interact with A-type lamins and phosphorylate c-Fos, releasing it from the NE. The released c-Fos can heterodimerize in the nucleoplasm with other AP-1 family members (e.g. c-Jun), allowing the activation of AP-1 target genes prior to de novo c-Fos synthesis.*



Expression of the transcription factor NF-Y in atherosclerotic lesions. *Double immunofluorescence demonstrating expression of NF-Y in VSMCs (immunoreactive to smooth muscle α-actin) and macrophages (Mac3-immunoreactive) within aortic atheromas of fat-fed apolipoprotein E-null mice.*

> MAJOR GRANTS

- **Ministerio de Ciencia e Innovación (SAF2007-62110). Funds held at the CSIC**
- **Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA; RD06/0014/0021)**

SELECTED PUBLICATIONS

Fuster JJ, Gonzalez JM, Edo MD, Viana R, Boya P, Cervera J, Verges M, Rivera J, Andres V. **The tumor suppressor $p27^{Kip1}$ undergoes endo-lysosomal proteolysis through its interaction with sorting nexin 6.** *FASEB J* (accepted)

Gonzalez-Navarro H, Naim Abu Nabah Y, Vinue A, Andres-Manzano MJ, Collado M, Serrano M, Andres V. **$p19^{Arf}$ deficiency reduces macrophage and vascular smooth muscle cell apoptosis and aggravates atherosclerosis.** *J Am Coll Cardiol* (accepted)

Andres V, Gonzalez JM. **Role of A-type lamins in signaling, transcription and chromatin organization.** *J Cell Biol* (2009) 187: 945-57

Gomez M, Sanz-Gonzalez SM, Naim Abu Nabah Y, Lamana A, Sanchez-Madrid F, Andres V. **Atherosclerosis development in apolipoprotein E-null mice deficient for CD69.** *Cardiovasc Res* (2009) 81: 197-205

Gonzalez JM, Navarro-Puche A, Casar B, Crespo P, Andres V. **Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2 and c-Fos at the nuclear envelope.** *J. Cell Biol* (2008) 183: 653-66

Imaging in experimental cardiology

Head of Laboratory: *Borja Ibáñez Cabeza*

Postdoctoral Researcher: *David Sanz-Rosa*

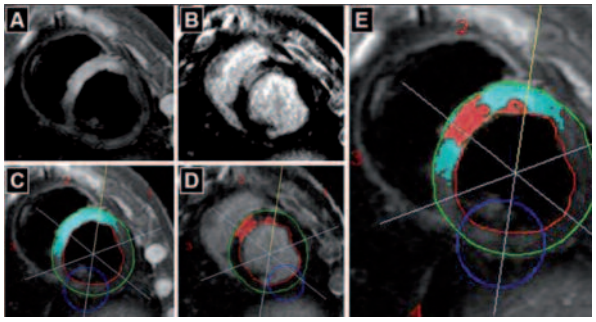
Predoctoral Researcher: *Jaime García-Prieto*

RESEARCH INTEREST

Our recently formed laboratory focuses on the development of experimental models of cardiovascular disease in order to obtain knowledge on the mechanisms underlying the origin and progression of these diseases and to test the efficacy of novel interventions. Our studies span the molecular origins of disease and their manifestations at the macro anatomical and physiological levels. 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 multi-disciplinary programs in close collaboration with hospitals and clinical researchers.

One of our major interests is cardioprotection during myocardial infarction (MI). In the initial phase of this project we are establishing different models of MI in rodents and large animals. These models will first be used to study the mechanisms underlying the beneficial effects of various cardioprotective strategies (mainly those related to the modulation of the adrenergic system). Once the advanced imaging equipment is fully installed at the CNIC, it will serve as a translational tool to confirm the mechanistic findings of the bench studies.

In our first year, we have already established collaborations with several hospitals and emergency medical services to carry out the imaging examinations for proof-of-principle clinical trials; and we are also participating in the European Commission funded HYPERImage project for the development of imaging technologies.



Analysis of MI size by magnetic resonance imaging. *With sequences potentiated in T2 (A, C) and T1 (B, D after administration of gadolinium) it is possible to quantify the at-risk and infarcted areas. The ability to use non-invasive in vivo imaging techniques to determine the extension of necrosis into the at-risk area makes it possible to reduce the number of experimental animals.*

SELECTED PUBLICATIONS

Ibanez B, Cimmino G, Prat-Gonzalez S, Vilahur G, Hutter R, Garcia MJ, Fuster V, Sanz J, Badimon L, Badimon J J. **The Cardioprotection Granted by Metoprolol is Restricted to its Administration Prior to Coronary reperfusion.** *Int J Cardiol* (accepted)

Cimmino G, Chen W, Speidl WS, Giannarelli C, Ibanez B, Fuster V, Hajjar R, Walsh CE, Badimon JJ. **Safe and sustained overexpression of functional apolipoprotein A-I/high-density lipoprotein in apolipoprotein A-I-null mice by muscular adeno-associated viral serotype 8 vector gene transfer.** *J Cardiovasc Pharmacol* (2009) 54: 405-11

Ibanez B, Cimmino G, Benezet-Mazuecos J, Santos-Gallego CG, Pinero A, Prat-Gonzalez S, Speidl WS, Fuster V, Garcia MJ, Sanz J, Badimon JJ. **Quantification of Serial Changes in Plaque Burden Using Multi-Detector Computed Tomography in Experimental Atherosclerosis.** *Atherosclerosis* (2009) 202: 185-91

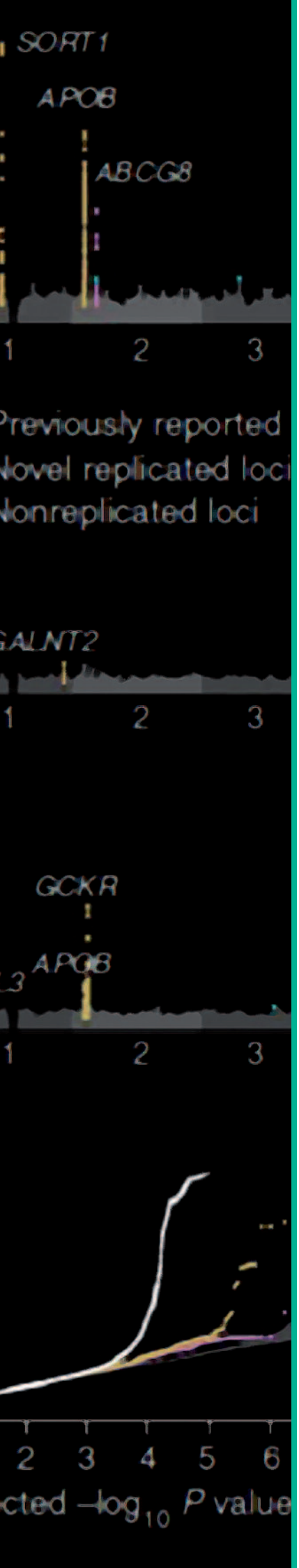
Ibanez B, Badimon JJ. **Cyclosporine in acute myocardial infarction.** *N Engl J Med* (2008) 359: 2287, author reply 2288-9

Ibanez B, Cimmino G, Vilahur G, Speidl WS, Fuster V, Badimon L and Badimon JJ. **Up-regulation of reverse cholesterol transport key players and rescue from global inflammation by ApoA-I(Milano).** *J Cell Mol Med* (2008) 13: 3226-35

Applied Research Departments

5

Cardiovascular Epidemiology and Population Genetics



Applied Research Departments

Cardiovascular Epidemiology and Population Genetics

This multidisciplinary department integrates population studies with the latest advances in basic and clinical research to identify environmental and genetic risk factors underlying the incidence, development and prognosis of cardiovascular disease.

The aim is to devise effective strategies for disease prevention and improved healthcare delivery.

Cardiovascular Epidemiology and Population Genetics

Department Director: *Eliseo Guallar*

Administrative Support: *Ana Gutiérrez*

Senior Researcher: *José Mª Ordovás*

Research Scientists: *Manuel Franco*
Martín Laclaustra
José Luis Peñalvo

Post-residency Researcher: *María Téllez*

Biostatistician: *Pedro López*

Support Scientists: *Marta Ledesma*

Technicians: *Piedad Antonia Fernández*
Alicia Usón
Belén Moreno
Raquel Langarita
Esther Rovira
Damaris Tamayo

RESEARCH INTEREST

The Department of Cardiovascular Epidemiology and Population Genetics achieved several major landmarks in 2009. One of the highlights was the incorporation as a Senior Researcher of José María Ordovás, a world leader in the field of Nutrigenomics. In addition, Manuel Franco, Martín Laclaustra and José Luis Peñalvo were promoted to the post of Research Scientist. Together with Eliseo Guallar and María Téllez, these scientists constitute the core group of researchers in the Department.

The Department conducts high-quality and high-impact population research projects into the environmental, individual and genetic risk factors that are causally related to cardiovascular disease. In coordination with the Departments of Atherothrombosis and Cardiovasuclar Imaging and Translational Cardiovascular Research, we launched the Aragon Workers Health Study (AWHS). Enrollment was completed in 2009, with 5589 workers recruited, a response rate of 95%. Follow-up is continuing as scheduled, and in 2010 we will commence measurement of subclinical atherosclerosis in the cohort. The Department also plays a major role in the planning of the PESA (Progression of Subclinical Atheroslclerosis) study, scheduled to start recruitment in 2010, and in the IMJOVEN study, which has recruited over 100 young women who have suffered a myocardial infarction. The members of the Department also continue to make significant contributions to leading international studies such as the Framingham Heart Study, the Multiethnic Study of Atheroslcerosis (MESA), the Strong Heart Study, the US National Health and Nutrition Examination Survey, and the UK National Diet and Nutrition Survey.

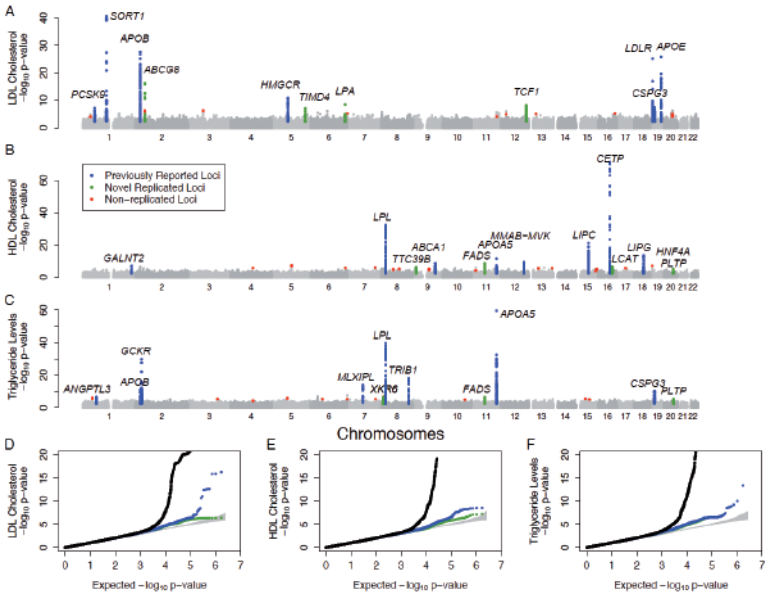
Members of the Department pursue highly innovative research lines that cover the major risk factors for cardiovascular disease, including diet (Ordovás, Guallar, Franco, Laclaustra, Peñalvo), genetics and epigenetics (Ordovás, Téllez), metabolic factors (Ordovás, Laclaustra, Peñalvo), the environment (Guallar, Téllez), and psychosocial factors (Franco). 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 Department is making significant contributions to the understanding and control of the current epidemic of cardiovascular diseases.

Adjusted differences in the low-quality dietary pattern (fats and processed meats) per 3 different food availability assessments ($n = 759$)[1]

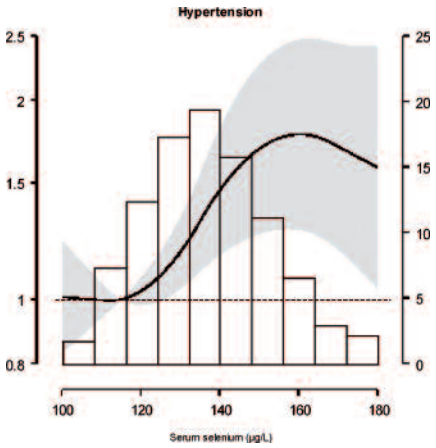
	Difference in fats and processed meats dietary pattern scores			
Availability of healthy foods assessment	Crude	Age + sex	Income + education	Race-ethnicity
Census tract of healthy food availability				
Low	0.19 ± 0.12[2,3]	0.25 ± 0.11[3]	0.23 ± 0.11[3]	0.12 ± 0.12
Medium	0.01 ± 0.10	0.04 ± 0.10	0.02 ± 0.10	−0.02 ± 0.10
High	Ref	Ref	Ref	Ref
P for trend[4]	0.14	0.05	0.08	0.50
No stores	0.11 ± 0.09	0.14 ± 0.09	0.11 ± 0.09	0.07 ± 0.09
Continuous measure of healthy food availability (per 1-SD increase)	−0.04 ± 0.04	−0.05 ± 0.04	−0.04 ± 0.04	−0.002 ± 0.04
Closest store food availability				
Low	0.23 ± 0.10[3]	0.25 ± 0.09[3]	0.22 ± 0.09[3]	0.12 ± 0.10
Medium	0.09 ± 0.09	0.12 ± 0.09	0.10 ± 0.09	0.09 ± 0.09
High	Ref	Ref	Ref	Ref
P for trend[4]	0.02	0.008	0.02	0.19
Continuous measure of healthy food availability (per 1-SD increase)	−0.08 ± 0.04[3]	−0.10 ± 0.04[3]	−0.08 ± 0.04[3]	−0.05 ± 0.04
All stores within 1 mile				
Low	0.14 ± 0.10	0.17 ± 0.10	0.15 ± 0.10	0.03 ± 0.10
Medium	−0.02 ± 0.10	−0.02 ± 0.10	−0.01 ± 0.10	−0.03 ± 0.10
High	Ref	Ref	Ref	Ref
P for trend[4]	0.25	0.13	0.17	0.73
No stores	−0.12 ± 0.12	−0.17 ± 0.12	−0.15 ± 0.12	−0.15 ± 0.12
Continuous measure of healthy food availability (per 1-SD increase)	−0.03 ± 0.04	−0.04 ± 0.04	−0.04 ± 0.04	−0.01 ± 0.04

[1] Ref, reference.
[2] Mean ± SD (all such values).
[3] $P < 0.05$ for the comparison of the lowest with the highest tertile of healthy food availability.
[4] Refers to the linear trend across the low, medium, and high categories of healthy food availability.

After adjustment for age, sex, income, and education, a lower availability of health foods in the tract of residence or in the closest store was associated with higher scores on the low-quality dietary pattern.



Genome-wide association study of cholesterol levels. *Summary of genome-wide association results for LDL cholesterol, HDL cholesterol and triglycerides from stage 1. (a-c) Chromosome number versus –log₁₀ P values for LDL cholesterol (a), HDL cholesterol (b) and triglycerides (c). Green, 11 newly identified loci; blue, previously reported loci; gray, loci not subjected to follow-up; red, loci that did not replicate. (d-f) Quantile-quantile plot for test statistics, with observed association P values plotted as a function of expected P values. Black line, all test statistics; blue line, 19 previously reported loci excluded; green line, 11 loci confirmed in this study also excluded; gray area, 90% confidence region from a null distribution of P values (generated from 100 simulations). Blue and green lines are superimposed for triglycerides.*



Adjusted odds ratios (95% confidence intervals) for hypertension by serum selenium concentrations in the US population (NHANES 2003-2004). The histogram shows the distribution of selenium concentrations in the study population.

MAJOR GRANTS

- ALIBIRD (P2009/AGR-1469). PI, E. Guallar

- Centro Nacional de Investigaciones Cardiovasculares (FPIT CNIC-08). PI, E. Guallar

- Ministerio de Ciencia e Innovación SAF2008-01995). PI, J. L. Peñalvo

SELECTED PUBLICATIONS

Franco M, Diez-Roux AV, Nettleton JA, Lazo M, Brancati F, Caballero B, Glass T, Moore LV. **Availability of Healthy Foods and Dietary Patterns, the MESA study.** *Am J Clin Nutr* (2009) 89: 897-904.

Laclaustra M, Navas-Acien A, Stranges S, Ordovas JM, Guallar E. **Serum selenium concentrations and hypertension in the US Population.** *Circ Cardiovasc Qual Outcomes* (2009) 2: 369-76.

Miller ER 3rd, Juraschek SP, Appel LJ, Madala M, Anderson CA, Bleys J, Guallar E. **The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials.** *Am J Clin Nutr* (2009) 89: 1937-45.

Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, Weaver V. **Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis.** *Am J Epidemiol* (2009) 170: 1156-64.

Vasan RS, Pencina MJ, Robins SJ, Zachariah JP, Kaur G, D'Agostino RB, Ordovas JM. **Association of Circulating Cholesteryl Ester Transfer Protein Activity With Incidence of Cardiovascular Disease in the Community.** *Circulation* (2009) 120: 2414-20.

José Mª Ordovás – Nutrigenomics

Coordinator of the CNIC - Tufts University Research Agreement

J. M. Ordovas's major research interest is in the genetic predisposition to cardiovascular disease and obesity, and how genetic risk factors interact with environmental and behavioral factors, especially diet and socioeconomic changes. His work has pioneered the field of Nutrigenomics, in which he is a world renowned expert. His success and productivity in this area has been primarily due to his establishing worldwide collaborative networks. In this he has been facilitated by his work with numerous international trainees over two decades; he has hosted over 60 visiting scientists from all continents to train in the application of systems biology approaches to nutrition, genetics, metabolism, behavior and their interactions. This network is fundamental to the creation of the large consortia needed to carry out modern cutting-edge science. Moreover, such networks provide the multidisciplinary expertise, sample size and variety of genetic and nutritional backgrounds needed to unravel the complexity of gene-diet interactions, and to translate this knowledge into personalized dietary and behavioral recommendations to prevent chronic diseases.

Manuel Franco – Psychosocial factors and cardiovascular disease

M. Franco's work focuses on the epidemiology and prevention of cardiovascular diseases (CVD) and its major risk factors. His European Commission funded research examines the influence of various psychosocial characteristics on CVD. In addition, as part of his contribution to the MESA study (NHLBI) he is examining how the neighborhood food environment determines the individual risk of CVD. At the CNIC he is currently developing CVD prevention programs for Spanish children.

Dr. Franco is a reviewer for several high impact journals in the fields of cardiology, epidemiology and public health. He also teaches courses on clinical epidemiology, cardiovascular epidemiology, cardiovascular prevention and social epidemiology.

Martín Laclaustra – Metabolic cardiovascular risk factors

M. Laclaustra's research focuses on the use of modern epidemiological and statistical methods to identify determinants of early progression of atherosclerosis that might be amenable to preventive intervention. His specific interests include the use of epidemiological data on metabolic cardiovascular risk factors to develop coherent pathophysiological and epidemiological models, and the development of clinical and molecular tests to reliably assess endothelial status and early atherosclerosis in large population studies.

Dr. Laclaustra maintains active collaborations with the Nutrition and Genomics Laboratory in Boston and with investigators of the Framingham cohort from Boston University. Through these collaborations, he is currently evaluating the association of adiposity and weight changes with the susceptibility to atherosclerosis, as well how fat distribution changes during the natural history of obesity. Other areas of interest include the differences in energy metabolism between men and women and how this is linked to the development of lipid, vascular and atherosclerotic disorders.

*José Luis Peñalvo – **Nutritional epidemiology***

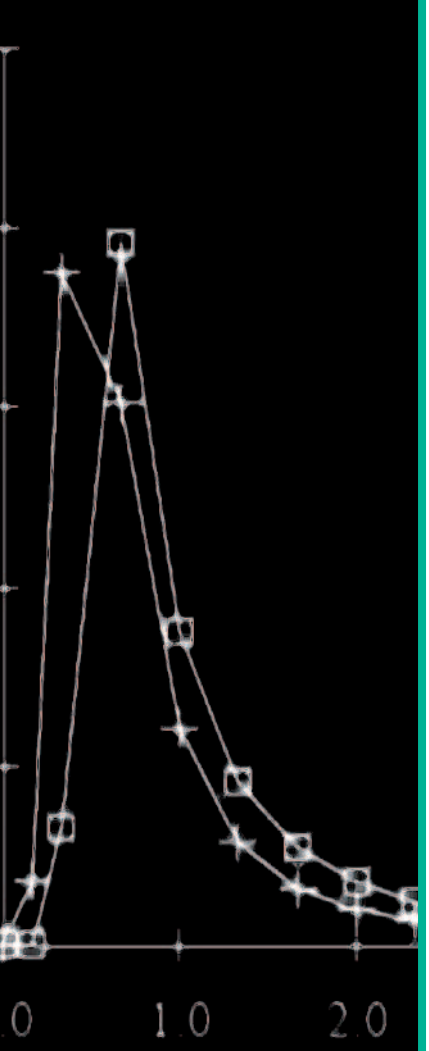
J. L. Peñalvo's research interest is in the mechanisms by which dietary components alter risk factors for cardiovascular disease. This interest is pursued through controlled dietary studies in humans that examine gene-diet interactions and biological responses to diet, with the aim of identifying biomarkers of dietary exposure. A specific interest is the use of cross-sectional and prospective analyses of human data to examine the metabolism and activities of dietary estrogens, with the aim of identifying factors that contribute to metabolic differences and of evaluating the biological implications of these differences for cardiovascular disease.

*María Téllez – **Epigenetic epidemiology***

M. Maria Tellez-Plaza's research interest is in the health consequences of widespread exposure to environmental toxicants. In recent years, her research has built expertise in population-based studies of the chronic cardiovascular effects of cadmium, lead and other toxic metals. Her current focus is on the use of DNA-methylation alterations as a tool for studying gene-environment interaction. The epigenetic epidemiology field is moving towards high-throughput platforms that allow genome-wide arrays and next-generation sequencing, and an important area of work involves the development of data analysis methods that can be applied to genome-wide DNA-methylation data. The simultaneous assessment of environmental exposures, genetic and epigenetic profiles and cardiovascular end-points can have important clinical and public health implications for cardiovascular disease prevention and control, while also developing novel research areas.

Applied Research Departments

6 *Cardiovascular Translational Research*



Applied Research Departments

Cardiovascular Translational Research

The TCR department is the nexus between the CNIC and the hospital system, facilitating collaboration between clinical research groups and the CNIC's scientists, encouraging the application and clinical testing of new technologies, and training clinical researchers.

Translational Cardiovascular Research

Department Director: *Ginés Sanz*

Administrative Support: *Laura González Betlinski*

Fixed-Dose Combination Therapy for Cardiovascular Prevention: The CNIC Polypill Project

During 2009 we completed the galaenic development of the CNIC polypill in cooperation with the research and development department at FERRER. Stability studies at 18 months have also been successfully completed.

Following the recommendations of the FDA and AEMPS, we have started the clinical phase of the project, including the following studies:

- Pharmacokinetic interaction (90 healthy volunteers)
- Bioequivalence (140 healthy volunteers)
- Ramipril and Simvastatin pharmacodynamic interactions (120 patients)
- Simvastatin pharmacodynamic interaction (350 patients)
- ASA pharmacodymic interactions (33 healthy volunteers)

Some of these studies have already been concluded and the rest will be completed during 2010. These studies will constitute the basis of the various regulatory dossiers.

Last year also saw the completion of the protocol for the FOCUS study. This is a European Union (FP7) funded project which will test the efficacy of the polypill in a population of more than 1300 patients in five countries: Argentina, Brazil, Italy, Paraguay and Spain. The Department of Translational Cardiovascular Research will coordinate this project, which will start in June 2010.

IMJOVEN Project

IMJOVEN is part of a large, multicenter case-controlled study aimed at identifying the clinical, genetic and demographic characteristics that determine the occurrence of myocardial infarction in young women.

The first patient was recruited on 1 January 2009, and by the end of the year we had recruited 169 participants, almost 70% more than expected. We are also supporting a subproject, led by Magda Heras (Hospital Clinic, Barcelona), which analyzes the burden of coronary disease in young women with acute myocardial infarction.

Early detection of cardiac involvement in Chagas disease

This project is funded by a three-year FIS grant (2008-10). The aim of the study is to analyze the predictive value of echocardiography, magnetic resonance imaging and biomarkers for the early detection of cardiac involvement. Patient recruitment was completed in June 2009, and a total of 98 patients and controls are included. All patients were assessed by conventional 2D-echocardiography with diastolic function analysis and image acquisition for applying DTI. Several biomarkers, including brain natriuretic peptide, were determined. The results were presented at the 2008 annual meeting of the American Heart Association meeting in Orlando (Florida) and at the 2009 European Congress of Cardiology (Barcelona). The final results have recently been submitted for publication.

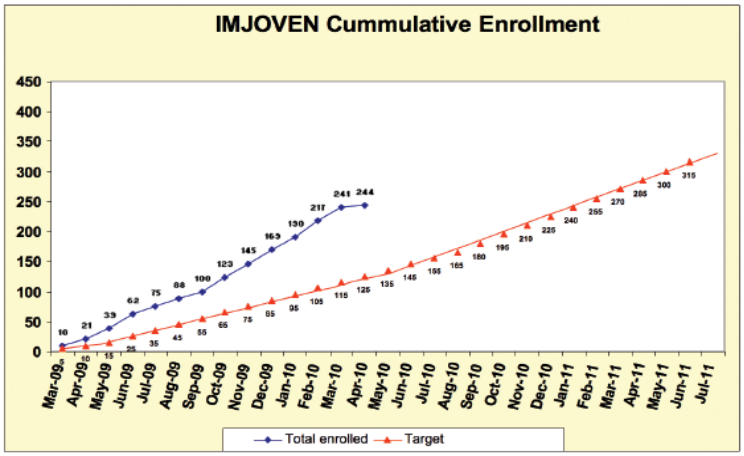
Translational Research Projects

Translational research is major priority at the CNIC, and the Center therefore has three departments focused on applied research. These departments cover Atherothrombosis and Cardiovascular Imaging, Cardiovascular Epidemiology and Population Genetics and Translational Cardiovascular Research of Novel Technologies and Therapeutics. Multidpartmental clinical projects involving teams from these departments are coordinated by the Translational Research department.

Last year we launched the second call for translational cardiovascular research projects led by hospital-based researchers. Two projects were selected for funding:

Ischemia-Reperfusion Injury: Novel Insights into β-blockade. Salvage Mechanisms in Acute Myocardial Infarction. Translating pre-clinical research into human care. Principal investigator: Borja Ibáñez (CNIC)

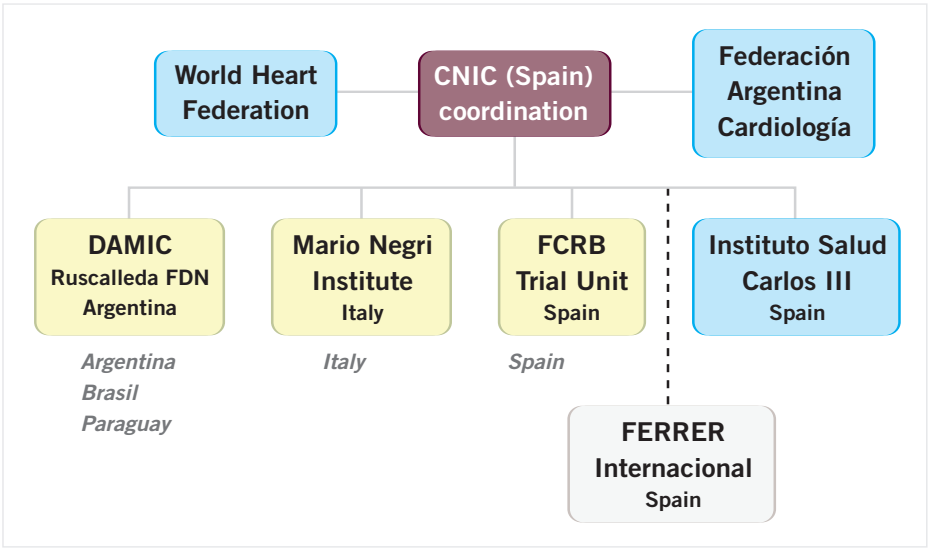
Genetic and functional bases of PITX2 involvement in human atrial fibrillation. Principal investigator: Miguel Manzanares (CNIC)



Recruitment of patients to the IMJOVEN study

The FOCUS Project: organization

Organization of the FOCUS project



MAJOR GRANTS

- **Ministerio de Ciencia e Innovación. FIS (PI07/0773)**
- **European Commission FP7 (241559 FOCUS)**

SELECTED PUBLICATIONS

Franco M, Sanz G, Guallar E. **Clinical and epidemiological research at CNIC: psychosocial factors and cardiovascular disease.** *Nat Rev Cardiol (CNIC Edition)* (2009) 6: 35-41

Gomez M, Valle V, Aros F, Sanz G, Sala J, Fiol M, Bruguera J, Elosua R, Molina L, Marti H, Covas MI, Rodriguez-Llorian A, Fito M, Suarez-Pinilla MA, Amezaga R and Marrugat J; FORTIAM group of researchers. **Oxidized LDL, lipoprotein (a) and other emergent risk factors in acute myocardial infarction (FORTIAM study).** *Rev Esp Cardiol* (2009) 62: 373-82

Ibanez B, Fuster V, Jimenez-Borreguero J, Sanz G, Macaya C, Badimon JJ. **Future perspectives for myocardial salvage. Role of β-blockers in cardioprotection: a new look at an old drug.** *Nat Rev Cardiol (CNIC Edition)* (2009) 6: 61-6

Munoz J, Gomez i Prat J, Gallego M, Gimeno F, Trevino B, Lopez-Chejade P, Ribera O, Molina L, Sanz S, Pinazo MJ, Riera C, Posada EJ, Sanz G, Portus M, Gascon J. **Clinical profile of Trypanosoma cruzi infection in a non-endemic setting: immigration and Chagas disease in Barcelona (Spain).** *Acta Trop* (2009) 111: 51-5

Sanz G, Fuster V. **Fixed-dose combination therapy and secondary cardiovascular prevention: rationale, selection of drugs and target population.** *Nat Clin Pract Cardiovasc Med* (2009) 6: 101-10

7 Technical Units

Cellomics

Head of Unit: *María Montoya*

Support Scientists: *José Manuel Ligos*
Hind Azegrouz

Technicians: *Raquel Nieto*
Mariano Vitón
Mª Montserrat Arroyo

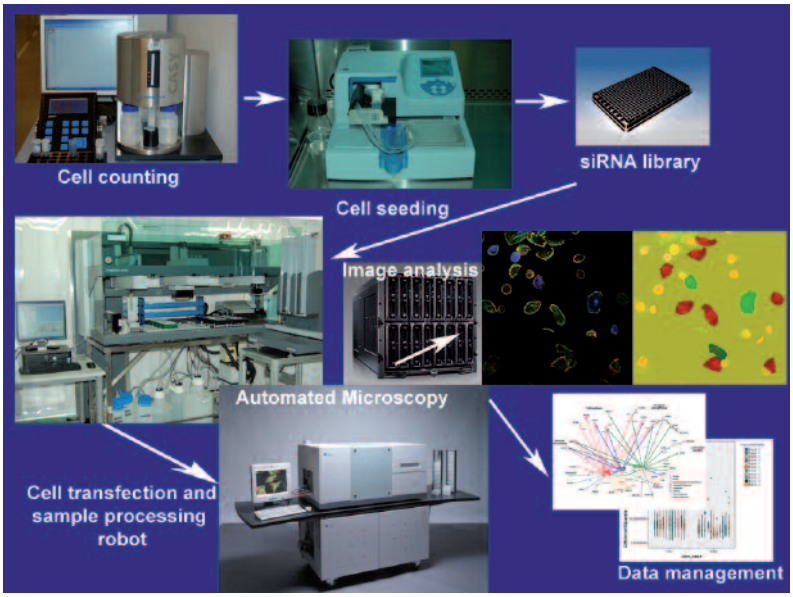
> RESEARCH INTEREST

The Cellomics Unit is committed to providing the CNIC with the latest technology in cell analysis. The Unit was established in December 2008 as a combined facility providing services in cytometry and high content screening (HCS). HCS is an emerging technology that originated in the drug discovery field, and consists of running automated cell biological assays in parallel in order to extract multiparametric data. The procedure involves a combination of liquid handling robotics, automated microscopy and image analysis in a high throughput format. The application of HCS to RNA interference (RNAi) loss-of-function studies will give CNIC research groups the capacity to perform genetic screens for cell-based systems-biology studies.

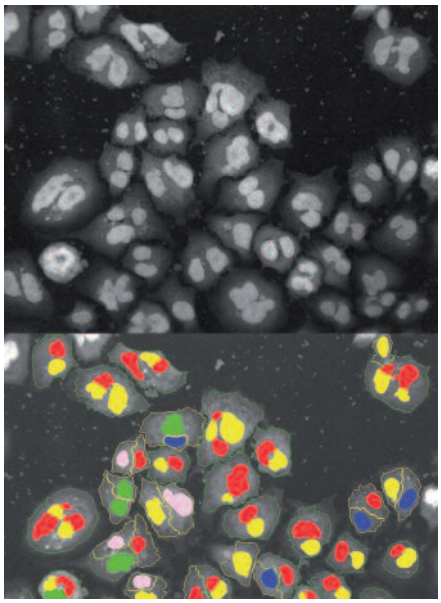
The Unit is equipped with

- Three latest generation digital analytical flow cytometers: two Becton Dickinson FACSCanto II machines and one Cyan (Beckman Coulter).
- Two high speed flow sorters: A MoFlo (Beckman Coulter) and a custom made FACSAria II (Becton Dickinson).
- A liquid handling workstation connected to a cell culture incubator with 110 plate throughput (Freedom EVO, Tecan).
- An automated confocal microscope for microplate reading (Opera, Perkin Elmer).
- A full range of dedicated cytometry and image analysis software packages (Modfit, FlowJo, Acapella, Definiens, MatLab).

The Unit is involved in a research program into the regulation of membrane trafficking during cell migration. We are interested in the role of Rab8, a GTPase that regulates cytoskeletal rearrangements and intracellular membrane trafficking to the plasma membrane.



Workflow scheme of high content screening. *The dedicated equipment housed in the Cellomics Unit enables automated sample processing and data handling to generate multiparametric data from individual samples.*



Example of high content analysis. *The cells in the image were transfected with siRNA targeting inner centromere protein (INCENP) by an automated process. Note the multi-lobed nuclei. The cells were stained with Hoechst and imaged with the Opera HCS platform. The image analysis (lower panel) was performed with Acapella software, and shows cell outlines and nuclear segmentation for determination of cells with multinucleated phenotype.*

SELECTED PUBLICATIONS

Aslam T, Fleck B, Patton N, Trucco M, Azegrouz H. **Digital image analysis of plus disease in retinopathy of prematurity.** *Acta Ophthalmol* (2009) 87: 368-77.

Lucas D, Escudero B, Ligos JM, Segovia JC, Estrada JC, Terrados G, Blanco L, Samper E, Bernad A. **Altered hematopoiesis in mice lacking DNA polymerase mu is due to inefficient double-strand break repair.** *PLoS Genet* (2009) 5: e1000389.

Marrero-Diaz R, Bravo-Cordero JJ, Megias D, Garcia MA, Bartolome RA, Teixido J, Montoya MC. **Polarized MT1-MMP-CD44 interaction and CD44 cleavage during cell retraction reveal an essential role for MT1-MMP in CD44 mediated invasion.** *Cell Motil Cytoskeleton* (2009) 66: 48-61

Megias D, Marrero-Diaz R, Del Peso BM, Garcia MA, Bravo-Cordero JJ, Garcia-Grande A, Santos A, Montoya MC. **Novel lambda FRET spectral confocal microscopy imaging method.** *Microsc Res Tech* (2009) 72: 1-11

Montoya MC, Piera A. **Microscopía Confocal.** *In* Técnicas en Histología y Biología Celular. Capítulo 7, p 181-208. Elsevier Masson 2009

Microscopy and dynamic imaging

Head of Unit: *Valeria R. Caiolfa*

Support Scientists: *Moreno Zamai*
Christian Hellriegel
Elvira Arza
Antonio Manuel Santoz Beneit

> RESEARCH INTEREST

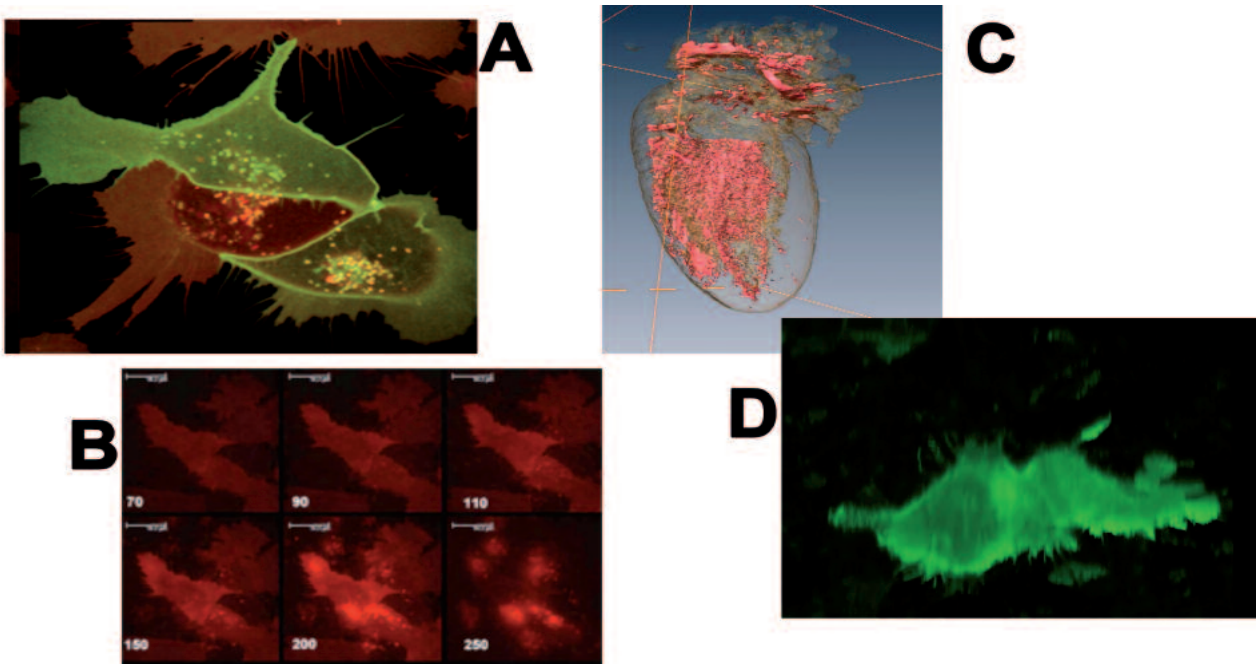
The Microscopy and Dynamic Imaging Unit provides state-of-the-art expertise and training in optical microscopy to scientists at the CNIC and beyond.

"Dynamic Imaging" refers to an array of technologies that employ the properties of light (particularly fluorescence and bioluminescence) to probe molecular and cellular behaviour and interactions. To multi-dimensional (multi-D) imaging, we add cutting-edge molecular spectro-microscopy imaging, which allows quantification of biological events through time and space. Imaging methodologies include immuno-labeling, time-lapse, multi-color TIRFM, FRET-FLIM, and 3D cross sectioning. We also provide capabilities in the tracking of single molecules, intracellular vesicles and cells, and in fluctuation analysis techniques such as FCS (fluorescence correlation spectroscopy), RICS and N&B—to quantify diffusion of single proteins, monomer-dimer-oligomer equilibrium, stoichiometry of protein and ligand binding, etc.

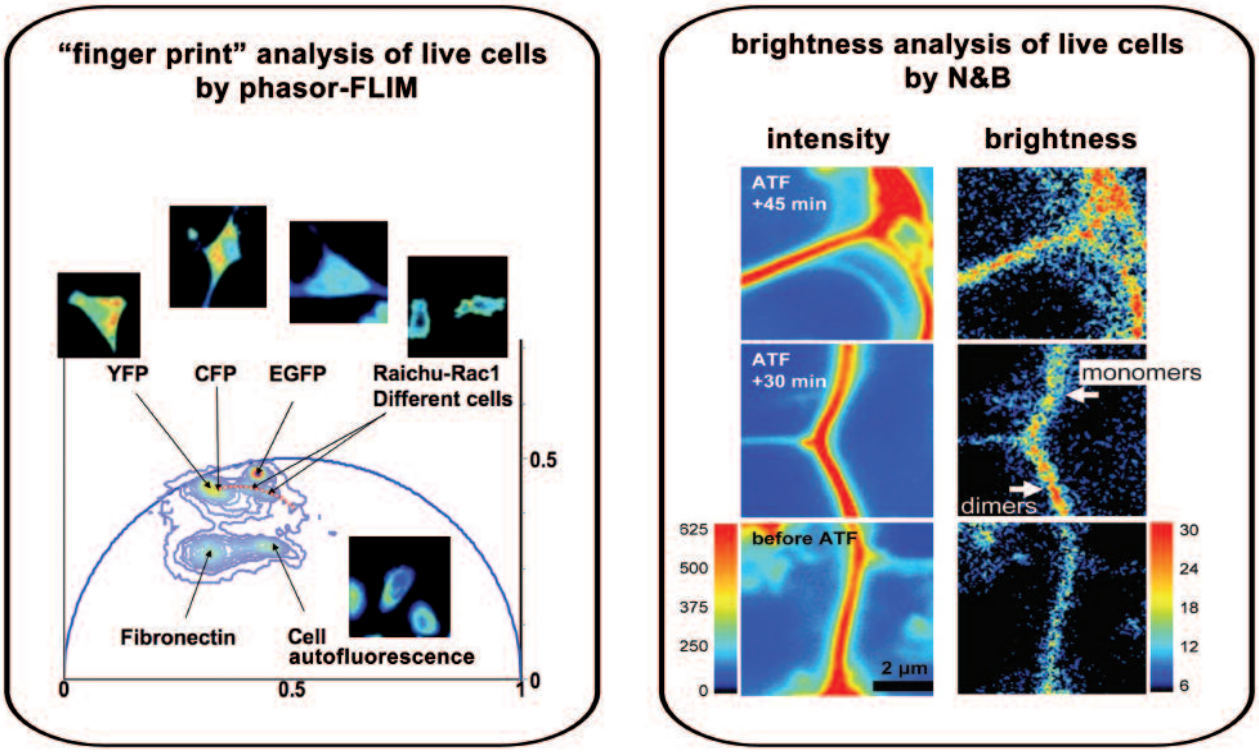
Resources are maintained for spectroscopy, microscopy, biochemistry, cell culture and data analysis.

In 2009, the Unit organized four internal courses for beginners and an advanced international workshop, with more than 40 participants from the CNIC and other institutes. During the year, the number of CNIC users that routinely access the facility increased from about 20 to more than 80. All microscopes can be booked online and users are given individual practical training.

The Unit pursues its own cell biophysical research program, and is involved in the development of new approaches in optical spectro-microscopy of live cells. The main interest is in the spatial targeting and assembly of receptors to cell membrane domains, molecular associations, translocations and intracellular trafficking, as they vary dynamically in living cells.



Gallery of images from (A) multicolor confocal live imaging; (B) multi-angle TIRF live imaging; (C) OPT 3D-rendering, and (D) 3D-confocal live imaging.



*Left: **F**luorescence **L**ifetime **Im**aging (FLIM) is one of our methods for distinguishing endogenous autofluorescent components (for example fibronectin) from multiple fluorophores in live cells. We can distinguish fluorescent proteins such as YFP, EGFP and CFP and measure FRET between them. Right: FRET pairs often cannot be inserted in the proteins of interest. In these cases the N&B approach can measure the brightness of the GFP-labeled proteins and detect their interaction, as in this example that shows ligand (ATF) induced dimerization of a GPI-anchored receptor.*

SELECTED PUBLICATIONS

Hellriegel C, Gratton E. **Real-time multi-parameter spectroscopy and localization in three-dimensional single-particle tracking.** *R Soc Interface* (2009) 6: S3-S14

Genomics

Head of Unit: *Ana Dopazo*

Support Scientists: *Sergio Callejas*
Alberto Benguría
Fátima Sánchez Cabo

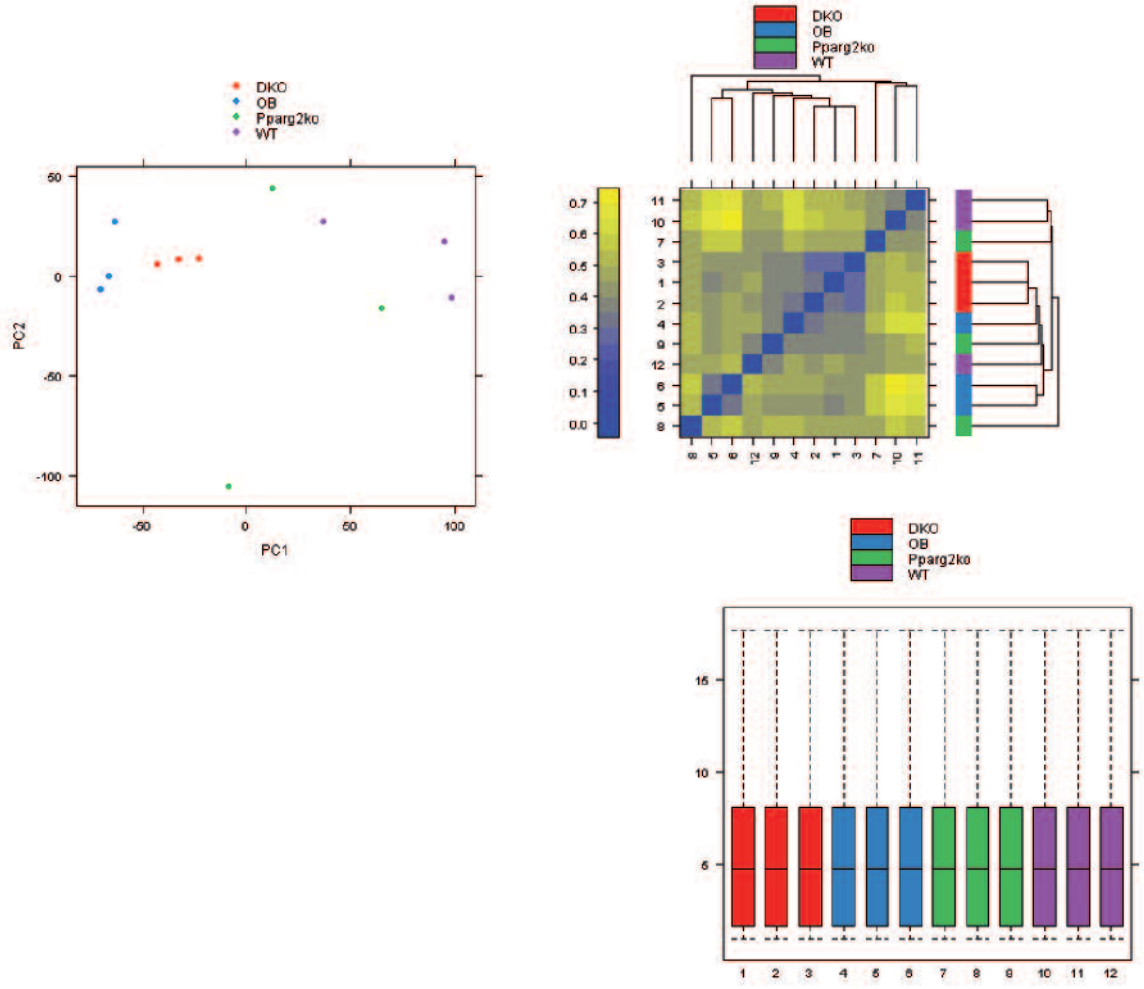
Technician: *Rebeca Álvarez*

> RESEARCH INTEREST

The Genomics Unit is dedicated to providing high-quality genomic technology to the scientific community at the CNIC and beyond. The Unit is equipped with Agilent and Affymetrix microarray platforms, the world's leading DNA chip technologies, and has extensive experience in the use of array-based technologies for genome studies. The Unit's expertise encompasses all the steps required for these high-throughput approaches, including experimental design, sample preparation and processing, and statistical data analysis.

Major services and array-based applications include whole-genome differential gene expression analysis (including at the exon level) and microRNA expression analysis. The Unit's service portfolio has recently been expanded to incorporate comparative genomic hybridization (CGH) arrays, a powerful tool for the genome-wide detection of copy number variations. 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. The Unit also provides user advice and training on topics related to the Unit's activity, particularly experimental design and statistical data analysis for qPCR and microarray experiments.

The Genomics Unit actively participates in one of the ongoing CNIC clinical projects, the IM-JOVEN study. IM-JOVEN is part of a large, multicenter case-controlled study aimed at identifying the clinical, genetic and demographic characteristics that determine the occurrence of myocardial infarction in young women.



QC plots for Agilent expression arrays

SELECTED PUBLICATIONS

Mlecnik B, Sanchez-Cabo F, Charoentong P, Bindea G, Pages F, Berger A, Galon J, Trajanoski Z. **Data integration and exploration for the identification of molecular mechanisms in tumor-immune cells interaction.** *BMC Genomics* (accepted)

Dopazo A. **Integrative approaches to genotype-phenotype association discovery.** *In* Bioinformatics and Biomarker Discovery: "Omic" Data Analysis for Personalized Medicine. F. Azuaje. John Wiley & Sons, Ltd., UK. (accepted)

Fernandez-Gonzalez R, Hourcade JD, Lopez-Vidriero I, Benguria A, Rodriguez De Fonseca F, Gutierrez-Adan A. **Analysis of gene transcription alterations at the blastocyst stage related to the long term consequences of in vitro culture in mice.** *Reproduction* (2009) 137: 271-83

Konstantinidou O, Khymenets O, Fito M, De La Torre R, Anglada R, Dopazo A, Covas MI. **Characterization of human gene expression changes after olive oil ingestion: an exploratory approach.** *Folia Biol (Praha)* (2009) 55: 85-91

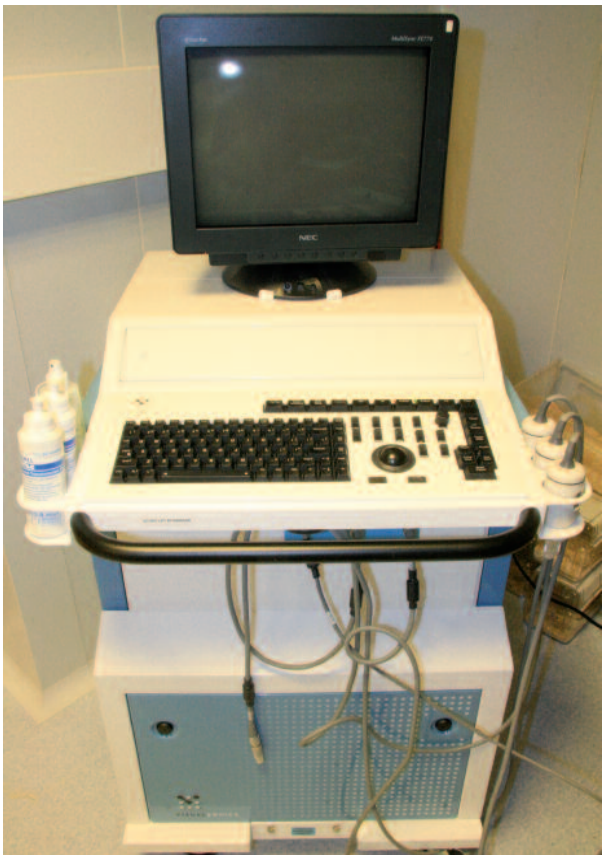
Varea O, Garrido JJ, Dopazo A, Mendez P, Garcia-Segura LM, Wandosell F. **Estradiol activates beta-catenin dependent transcription in neurons.** *PLoS ONE* (2009) 4: e5153

Comparative medicine

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

- Animal Husbandry and Veterinary Medicine. This area is staffed by dedicated animal technicians, managers and veterinarians who take charge of the daily husbandry and welfare of animals. 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 researchers involved in animals 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.
- The Experimental Surgery Core (ESC) provides highly specialized expertise in surgical procedures, minimally invasive intervention, and life support.
- The Quality Control Core (QCC) is run by a senior microbiologist and monitors the health and the genetic status of the animals on site.

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.



Ultrasound equipment

SELECTED PUBLICATIONS

Kent ML, Feist SW, Harper C, Hoogstraten-Miller S, Law JM, Sanchez-Morgado JM, Tanguay RL, Sanders GE, Spitsbergen JM, Whipps CM. **Recommendations for control of pathogens and infectious diseases in fish research facilities.** *Comp Biochem Physiol C Toxicol Pharmacol* (2009) 149: 240-8

Poynter S, Phipps JD, Naranjo-Pino A, Sanchez-Morgado JM. **Difficulties in the molecular diagnosis of helicobacter rodent infections.** *Vet Microbiol* (2009) 134: 272-8

Sanchez-Morgado JM, Gallagher A, Johnson LK. **Mycobacterium gordonae Infection in a Colony of African Tropical Clawed Frogs (Xenopus tropicalis).** *Lab Anim* (2009) 43: 300-3

Proteomics

Head of Unit: *Juan Antonio López*

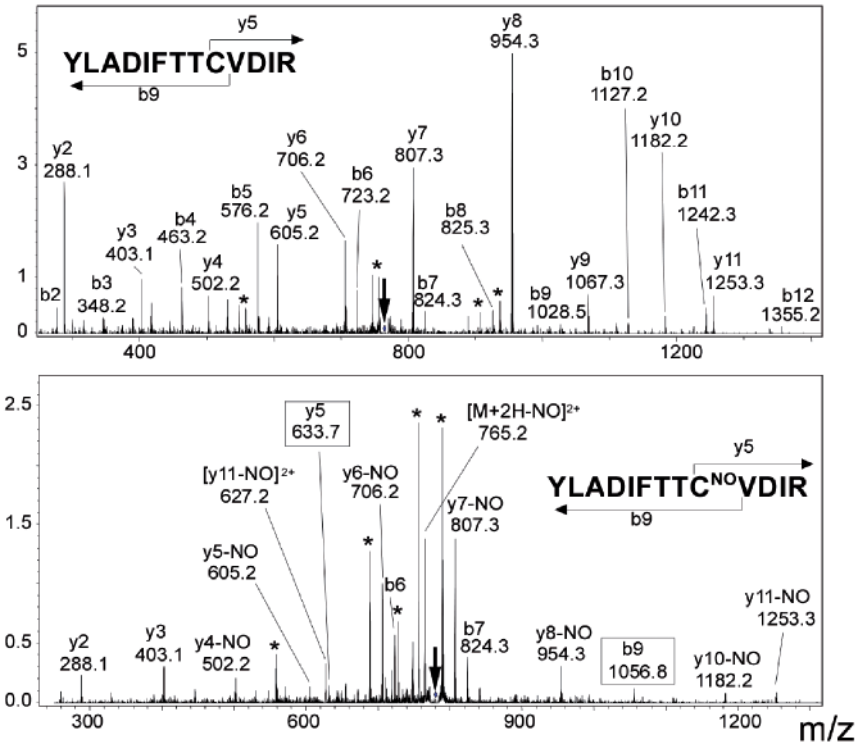
Research Scientists: *Enrique Calvo*
Emilio Camafeita

> RESEARCH INTEREST

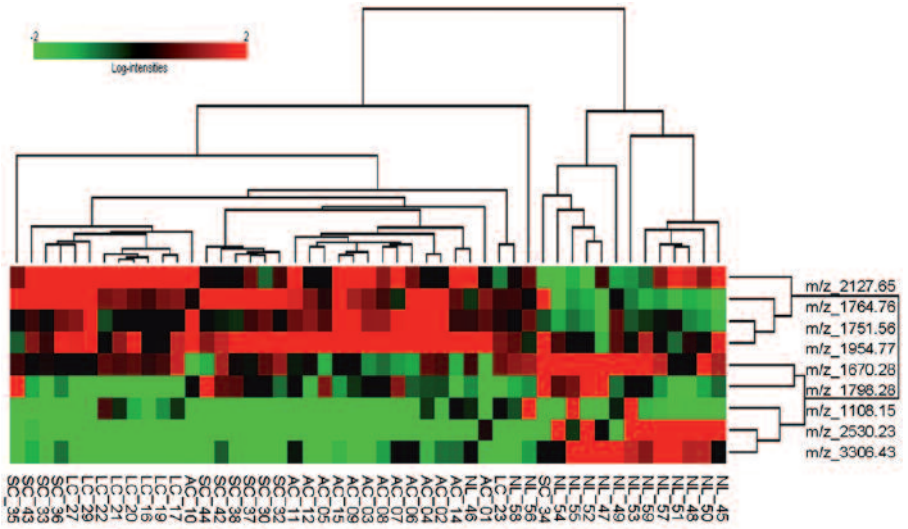
The Proteomics Unit provides technical expertise in several proteomics approaches for the separation, quantification, identification and characterization of proteins in biological systems, and maintains programs to develop and improve technologies and protocols to meet the demands of the research community. The Unit has a complete system for the separation and quantitative analysis of differential protein expression by 2D-DIGE as well as systems for gel-free separation based on multidimensional nanoHPLC. Proteins are identified using MALDI-TOF/TOF and ESI mass spectrometers, the latter comprising a hybrid triple quadrupole (TQ) and a linear ion trap coupled to an Orbitrap high resolution mass analyzer. The high resolution and scanning speed of the Orbitrap mass spectrometer enables optimal characterization of proteomes and subproteomes, while the specific scanning modes of the TQ allow sensitive targeted analysis of proteins and posttranslational modifications.

This robust and comprehensive analytical platform enables us to take on large and technically demanding research projects that require both qualitative and quantitative proteomic approaches for the detection of differential protein expression, chemical and posttranslational modifications, and protein-protein interactions in diverse biological systems. The Unit maintains close collaborations with other laboratories to investigate new approaches for the selective analysis of specific subproteomes and interactomes.

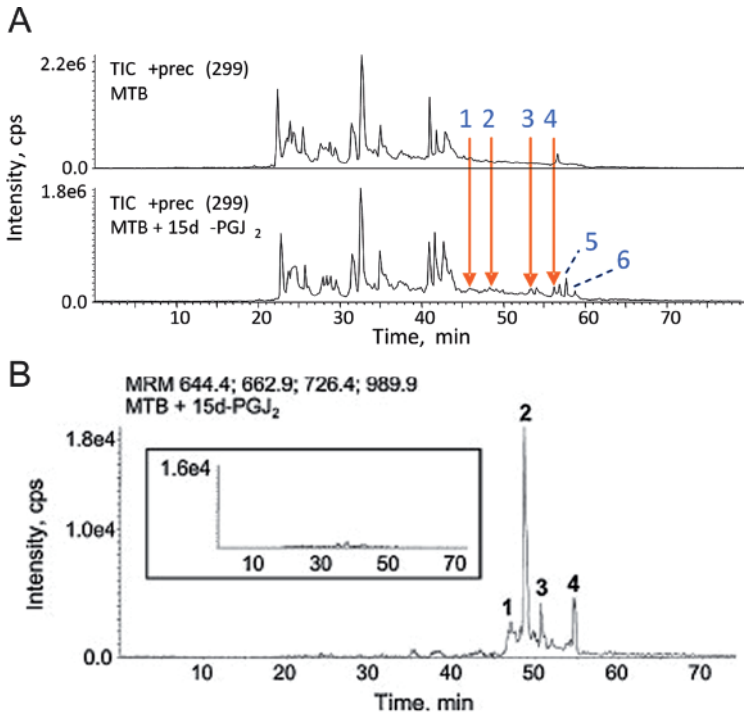
Last year, the Unit's recognized expertise in the field was reflected in the award to a member of the Unit (E. Calvo) of the *Sociedad Española de Proteómica* prize for the best proteomics paper of 2007-2008. This paper was published in Nature Chemical Biology (3, 117-125; 2007) and was featured on the journal cover.



Identification of nitrosylated Cys residues in peptides. *Fragmentation spectra from Cys76-unmodified (top) and Cys76-nitrosylated (bottom) Kir2.1 tryptic peptide. From Gómez et al.*



MALDI profiling of lung cancer subtypes. *Heat map of the supervised hierarchical centroid linkage clustering of normalized m/z peak areas, in two dimensions, for the 49 samples and the 9 m/z peaks included in the global discriminant model. From Gámez-Pozo et al.*



Identification of 15d-PGJ$_2$-modified Cys residues in microtubules by precursor ion scanning with the hybrid triple quadrupole mass spectrometer. *Total ion chromatogram (TIC) of the precursor ion scanning of a fragment at m/z 299.4 from control (A, upper panel) or 15d-PGJ$_2$-treated (A, lower panel) microtubule samples digested with trypsin. Arrows 1–5 indicate differences in peptide mass composition between control and 15d-PGJ$_2$-treated samples. Peak 6 corresponds to the 15d-PGJ$_2$ dimer. (B) Targeted analysis by multiple reaction monitoring (MRM) of control and 15d-PGJ$_2$-treated microtubule samples. The main panels shows MRM of trypsin digested 15d-PGJ$_2$-modified peptides 1–4. The inset shows the results for the corresponding control microtubule sample.*

SELECTED PUBLICATIONS

Cocca C, Dorado J, Calvo E, Lopez JA, Santos A, Perez-Castillo A. **15-deoxi-Δ12,14-prostaglandin J2 is a tubulin-binding agent that destabilizes microtubules and induces mitotic arrest.** *Biochem Pharmacol* (2009) 78: 1330-39

Gamez-Pozo A, Sanchez-Navarro I, Nistal M, Calvo E, Madero R, Diaz E, Camafeita E, de Castro J, Lopez JA, Gonzalez-Baron M, Espinosa E, Fresno-Vara JA. **MALDI Profiling of Human Lung Cancer Subtypes.** *PLoS ONE* (2009) 4: e7731

Gomez R, Caballero R, Barana A, Amoros I, Calvo E, Lopez JA, Klein H, Vaquero M, Osuna L, Atienza F, Almendral J, Pinto A, Tamargo J, Delpon E. **Nitric oxide increases cardiac IK1 by nitrosylation of cysteine 76 of Kir2.1 channels.** *Circ Res* (2009) 105: 383-92

Perez-Perez R, Ortega-Delgado FJ, Garcia-Santos E, Lopez JA, Camafeita E, Ricart W, Fernandez-Real JM, Peral B. **Differential proteomics of omental and subcutaneous adipose tissue reflects their unalike biochemical and metabolic properties.** *J Proteome Res* (2009) 8: 1682-93

Tarin C, Gomez M, Calvo E, Lopez JA, Zaragoza C. **Endothelial Nitric Oxide Deficiency Reduces MMP-13 Mediated Cleavage of ICAM-1 in Vascular Endothelium: A Role in Atherosclerosis.** *Arterioscler Thromb Vasc Biol* (2009) 29: 27-32

Transgenesis

Head of Unit: *Luís-Miguel Criado*

Support Scientist: *José Mª Fernández Toro*

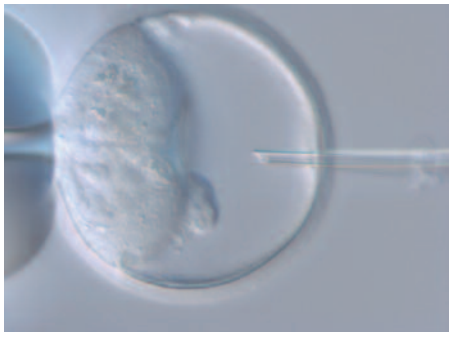
Technician: *David Esteban Martínez*

RESEARCH INTEREST

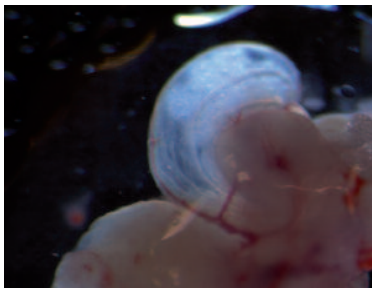
The Transgenesis Unit provides a range of services for the production of genetically-modified mice—so-called transgenic mice—to serve the needs of the CNIC research groups. The interest is twofold: to understand how genomic activity translates into the complexity of a whole organism, and to generate 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 pelicida (subzonal 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 strains by embryo transfer, cryopreservation of mouse strains (frozen embryos or sperm), in vitro fertilization, and intracytoplasmic sperm injection.

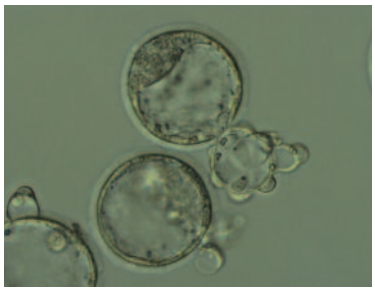
The main activity of the Unit in 2009 was the rederivation of mouse strains, and a total of 99 new mouse strains were rederived to the specific pathogen free area of the Comparative Medicine Unit, bringing the total number of rederived mouse strains at the Center to 162.



Subzonal microinjection of lentiviruses into a mouse zygote for the production of transgenic mice.



View of an oviduct in the mouse female reproductive tract. *The swollen and transluscent structure in the upper part of the picture is the ampulla. Mouse zygotes can be seen inside the ampulla as small spheres surrounded by tightly packed layers of cumulus cells.*



Mouse blastocysts at the hatching stage.

SELECTED PUBLICATIONS

Mercader N, Selleri L, Criado LM, Pallares P, Parras C, Cleary ML, Torres M. **Ectopic Meis1 expression in the mouse limb bud alters P-D patterning in a Pbx1-independent manner.** *Int J Dev Biol* (2009) 53: 1483-94

Pallares P, Garcia-Fernandez RA, Criado LM, Letelier CA, Esteban D, Fernandez-Toro JM, Flores JM, Gonzalez-Bulnes A. **Disruption of the endothelial nitric oxide synthase gene affects ovulation, fertilization and early embryo survival in a knockout mouse model.** *Reproduction* (2008) 136: 573-9

Pluripotent cell technology

Head of Unit: *Giovanna Giovinazzo*

Support Scientist: *Francisco Gutiérrez*

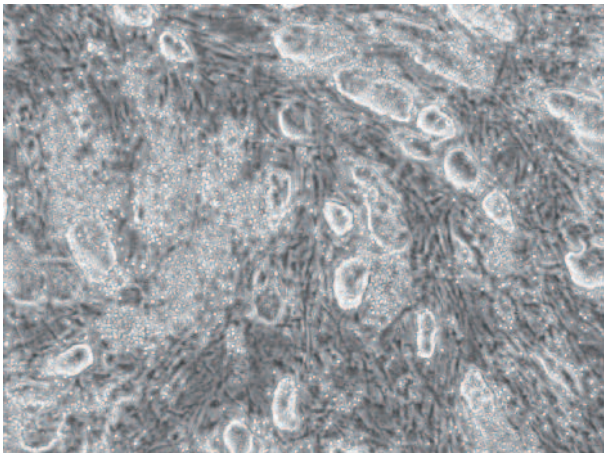
Technician: *María Ángeles Sanguino*

> RESEARCH INTEREST

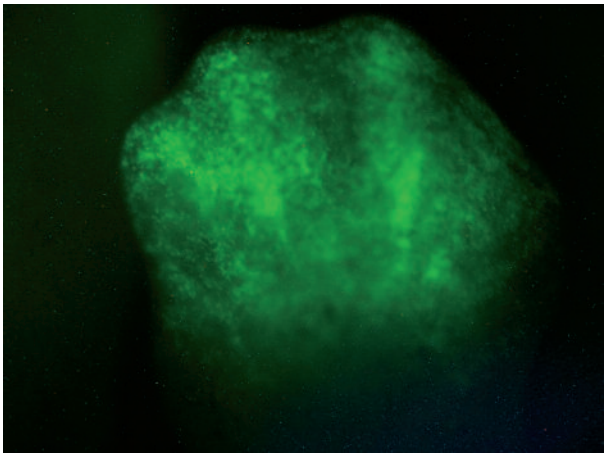
The Pluripotent Cell Technology Service (PCTService) provides technological innovation and support in the design and production of genetically modified mice through homologous recombination in mouse embryonic stem cells (mESCs) and in the culture and manipulation of human pluripotent stem cells. The PCTService was formed recently through the fusion of the gene targeting and stem cell technology facilities.

Our gene targeting services include the definition of appropriate targeting and screening strategies, electroporation of the targeting vector, selection, karyotyping, culture, and the preparation of cells for blastocyst injection. The technology developed in our laboratory has achieved efficient transmission of targeted mESCs to the germline, allowing us to generate, in collaboration with the Transgenesis Unit, several conditional knockout, conditional knockin and inducible mutant mouse models that are currently in use in research projects at the CNIC.

The PCTService also provides training and technical support in stem cell culture and pursues its own innovation program, an important aim of which is to apply its wide expertise to the manipulation of human stem cells.



Electroprated mESCs during the selection process



Tamoxifen induced clones (green) in the forelimb of Hoxa13CreERT2/+; Rosa26R-EYFP/+; x Hoxa13CreERT2/+; Rosa26R-EYFP/+ mutant mice (photo by Alberto Roselló).

> MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS (CA08/00357)

Viral vectors

Head of Unit: *Juan Carlos Ramirez*

Research Scientist: *Raúl Torres*

Predoctoral Researcher: *Zita Garate*

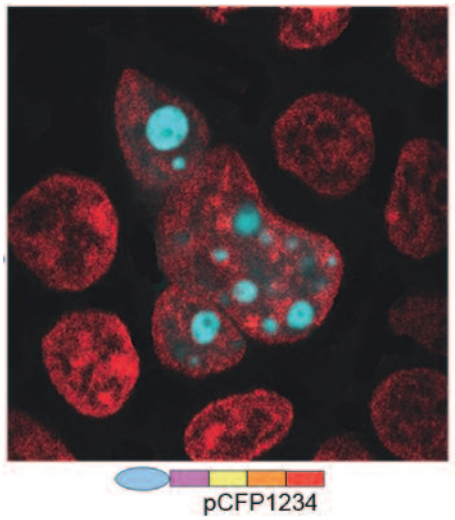
Technician: *Aida Garcia*

> RESEARCH INTEREST

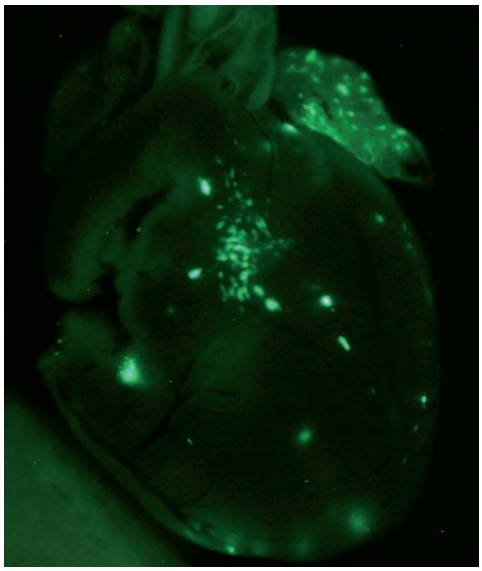
The Viral Vectors facility develops efficient recombinant viruses and strategies for gene transfer, using cloning strategies based both on restriction enzymes and on recombinases (cre, clonase™). The viral stocks currently produced, purified and titrated at the facility are second and third generation lentiviruses; eco-, ampho- and xenotropic pseudotyped retroviruses, and Ad5ΔE1a–derived adenoviruses. Our quality control procedures include replication competent particle assays. In addition to cDNA-encoding gain-of-function vectors, we design vectors for loss-of-function studies encoding Pol II/Pol III-driven miRNAs or shRNAs. Lentivectors designed to drive cre-mediated expression of shRNAs for in vitro and in vivo studies are also available. We are currently developing capacity for the production of Ad-gutless and Adeno-associated viruses (AAV) pseudotyped with 2, 8 and 9 capsids to enable targeted delivery in vivo.

We also conduct our own technical and basic research programs. Technical research projects include 1) the development of novel tools based on non-integrative lentivirus for efficient homologous recombination at specific loci in mouse or human embryonic stem cells; 2) development of strategies for the safe production of induced pluripotent stem cells; and 3) the establishment of miRNA-based positive sensor systems that will allow identification and selection of subsets of native and induced stem cells with specific pluripotencies and differentiation potentials. In collaboration with the Comparative Medicine Unit (Experimental Surgery Core) we are also implementing methods for efficient in vivo delivery of lenti- and adeno-vectors to the heart.

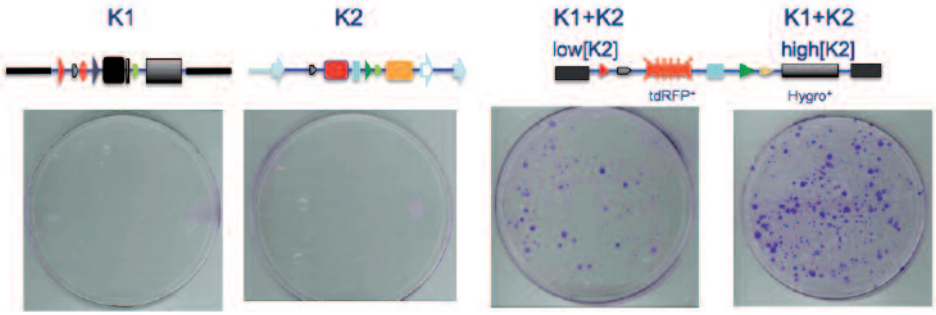
Our basic research is currently focused on how the gene for the chemokine SDF-1γ is specifically transcribed in heart cells to drive nucleolar localization of the protein. To characterize the role of this unprecedented feature and to define the expression profile of cardiac SDF-1γ during development, we are developing in vivo RNAi strategies using tetraploid embryos and conditional knockout mice.



The carboxy terminus of SDF-1γ contains a nucleolar localization signal that targets the protein (fused to cerulean fluorescent protein) to the nucleoli of transfected human cells, labeling them blue.



Heart cells of newborn mice expressing green fluorescent protein after transduction by direct intra-thoracic injection with lentivirus.



Lentiviral-delivered cre mediates recombination in human cells containing a floxed hygromicin resistance gene. HygroR colonies are induced in a dose dependent manner by lox-recombination between flox-stopped copies of the resistance gene and the floxed-promoter contained in the lentivector.

> MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS (PI06/0911)

SELECTED PUBLICATIONS

Torres R, Ramirez JC. **A chemokine targets the nucleus: Cxcl12-gamma isoform localizes to the nucleolus in adult mouse heart.** *PLoS One* (2009) 4: e7570

Appendix

Publications 2009

Publications by CNIC staff are listed by Department, followed by the Technical Units. In each section publications are listed alphabetically by first author. The table at the end summarizes the cumulative and average impact factors in each area, calculated according to the the ISI Journal Citation Reports (JCR), 2008. Publications with no IF, for example chapters from book series or articles published in journals not currently listed by the JCR, are not included in the table.

ATHEROTHROMBOSIS AND CARDIOVASCULAR IMAGING

El Aidi H, Mani V, Weinshelbaum KB, Aguiar SH, Taniguchi H, Postley JE, Samber DD, Cohen EI, Stern J, van der Geest RJ, Reiber JH, Woodward M, Fuster V, Gidding SS, Fayad ZA.
Cross-sectional, prospective study of MRI reproducibility in the assessment of plaque burden of the carotid arteries and aorta.
Nat Clin Pract Cardiovasc Med (2009)
6: 219-28
IF: 5.970

Andres V, Gonzalez JM.
Role of A-type lamins in signaling, transcription, and chromatin organization.
J Cell Biol (2009)
187: 945-57
IF: 9.120

Badimon JJ, Ibanez B, Cimmino G.
Genesis and dynamics of atherosclerotic lesions: implications for early detection.
Cerebrovasc Dis (2009)
27: 38-47
IF: 3.041

Farkouh ME, Fuster V.
Diabetes and aspirin: beware of underpowered negative trials.
Nat Clin Pract Cardiovasc Med (2009)
6: 1
IF: 5.970

Floris-Moore M, Fayad ZA, Berman JW, Mani V, Schoenbaum EE, Klein RS, Weinshelbaum KB, Fuster V, Howard AA, Lo Y, Schecter AD.
Association of HIV viral load with monocyte chemoattractant protein-1 and atherosclerosis burden measured by magnetic resonance imaging.
AIDS (2009)
23: 941-9
IF: 5.460

Fuster V.
Prime time for a polypill after myocardial infarction?
Nat Clin Pract Cardiovasc Med (2009)
6: 83
IF: 5.970

Fuster V, Bansilal S.
JUPITER strikes earth.
Nat Clin Pract Cardiovasc Med (2009)
6: 159
IF: 5.970

Fuster V, Sanz J.
[Visualizing arterial macrophage warfare with nuclear magnetic resonance, positron-emission tomography and computerized tomography].
Rev Esp Cardiol (2009)
62: 40392
IF: 2.880

Fuster V, van der Zee S, Elmariah S, Bonow RO.
Academic careers in cardiovascular medicine.
Circulation (2009)
119: 754-60
IF: 14.595

Garcia-Maceira P, Mateo J.
Silibinin inhibits hypoxia-inducible factor-1alpha and mTOR/p70S6K/4E-BP1 signalling pathway in human cervical and hepatoma cancer cells: implications for anticancer therapy.
Oncogene (2009)
28: 313-24
IF: 7.216

Gomez M, Sanz-Gonzalez SM, Nabah YN, Lamana A, Sanchez-Madrid F, Andres V.
Atherosclerosis development in apolipoprotein E-null mice deficient for CD69.
Cardiovasc Res (2009)
89: 197-205
IF: 5.947

Hidalgo A, Chang J, Jang JE, Peired AJ, Chiang EY, Frenette PS.
Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury.
Nat Med (2009)
15: 384-91
IF: 27.550

Hidalgo A, Frenette PS.
When integrins fail to integrate.
Nat Med (2009)
15: 249-50
IF: 27.550

Ibanez B, Cimmino G, Benezet-Mazuecos J, Santos-Gallego CG, Pinero A, Prat-Gonzalez S, Speidl WS, Fuster V, Garcia MJ, Sanz J, Badimon JJ.
Quantification of serial changes in plaque burden using multi-detector computed tomography in experimental atherosclerosis.
Atherosclerosis (2009)
202: 185-91
IF: 4.601

Publications 2009

Ibanez B, Fuster V, Jimenez-Borreguero J, Sanz G, Macaya C, Badimon JJ.
Future perspectives for myocardial salvage. Role of beta-blockers in cardioprotection: a new look at an old drug.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 61-6
IF: n/a

Ibanez B, Badimon JJ, Garcia MJ.
Diagnosis of atherosclerosis by imaging.
Am J Med (2009)
122: S15-25
IF: 5.105

Lizarbe TR, Tarin C, Gomez M, Lavin B, Aracil E, Orte LM, Zaragoza C.
Nitric oxide induces the progression of abdominal aortic aneurysms through the matrix metalloproteinase inducer EMMPRIN.
Am J Pathol (2009)
175: 1421-30
IF: 5.697

Martin AL, Aguilar L, Fuster V.
Cardiovascular disease, renal disease and other chronic diseases. Earlier intervention is needed in chronic renal disease.
Atencion Primaria (2009)
41: 511-4
IF: n/a

Martinez-Miguel P, Raoch V, Zaragoza C, Valdivielso JM, Rodriguez-Puyol M, Rodriguez-Puyol D, Lopez-Ongil S.
Endothelin-converting enzyme-1 increases in atherosclerotic mice: potential role of oxidized low density lipoproteins.
J Lipid Res (2009)
50: 364-75
IF: 4.409

Moreno PR, Sanz J, Fuster V.
Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport.
J Am Coll Cardiol (2009)
53: 2315-23
IF: 11.438

Murciano JC, Higazi AA, Cines DB, Muzykantov VR.
Soluble urokinase receptor conjugated to carrier red blood cells binds latent pro-urokinase and alters its functional profile.
J Control Release (2009)
139: 190-6
IF: 5.690

Sanz G, Fuster V.
Fixed-dose combination therapy and secondary cardiovascular prevention: rationale, selection of drugs and target population.
Nat Clin Pract Cardiovasc Med (2009)
6: 101-10
IF: 5.970

Sanz J, Moreno PR, Fuster V.
The year in atherothrombosis.
J Am Coll Cardiol (2009)
53: 1326-37
IF: 11.438

Silvera SS, Aidi HE, Rudd JH, Mani V, Yang L, Farkouh M, Fuster V, Fayad ZA.
Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries.
Atherosclerosis (2009)
207: 139-43
IF: 4.601

Sipido KR, Tedgui A, Kristensen SD, Pasterkamp G, Schunkert H, Wehling M, Steg PG, Eisert W, Rademakers F, Casadei B, Fuster V, Cerbai E, Hasenfuss G, Fernandez-Aviles F, Garcia-Dorado D, Vidal M, Hallen M, Dambrauskaite V.
Identifying needs and opportunities for advancing translational research in cardiovascular disease.
Cardiovasc Res (2009)
83: 425-35
IF: 5.947

Tarin C, Gomez M, Calvo E, Lopez JA, Zaragoza C.
Endothelial nitric oxide deficiency reduces MMP-13-mediated cleavage of ICAM-1 in vascular endothelium: a role in atherosclerosis.
Arterioscler Thromb Vasc Biol (2009)
29: 27-32
IF: 6.858

Tello D, Tarin C, Ahicart P, Breton-Romero R, Lamas S, Martinez-Ruiz A.
A "fluorescence switch" technique increases the sensitivity of proteomic detection and identification of S-nitrosylated proteins.
Proteomics (2009)
9: 5359-70
IF: 4.586

Thomas JD, Zoghbi WA, Beller GA, Bonow RO, Budoff MJ, Cerqueira MD, Creager MA, Douglas PS, Fuster V, Garcia MJ, Holmes DR Jr, Manning WJ, Pohost GM, Ryan TJ, Van Decker WA, Wiegers SE; American College of CArdiology Foundation (ACCF); American Heart Association (AHA); American College of Physicians (ACP) Task Force on Clinical Competence and Training.
ACCF 2008 Training Statement on Multimodality Noninvasive Cardiovascular Imaging A Report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training Developed in Collaboration With the American Society of Echocardiography, the American Society of Nuclear Cardiology, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society for Vascular Medicine.
J Am Coll Cardiol (2009)
53:125-46
IF: 11.438

Publications 2009

CARDIOVASCULAR DEVELOPMENTAL BIOLOGY

Alonso ME, Manzanares M.
The regulatory basis of common disease: how can genome-wide association studies help us understand cardiovascular disorders?
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 55-60
IF: n/a

Alonso ME, Pernaute B, Crespo M, Gomez-Skarmeta JL, Manzanares M.
Understanding the regulatory genome.
Int J Dev Biol (2009)
53: 1367-78
IF: 2.359

Aroeira LS, Lara-Pezzi E, Loureiro J, Aguilera A, Ramirez-Huesca M, Gonzalez-Mateo G, Perez-Lozano ML, Albar-Vizcaino P, Bajo MA, del Peso G, Sanchez-Tomero JA, Jimenez-Heffernan JA, Selgas R, Lopez-Cabrera M.
Cyclooxygenase-2 mediates dialysate-induced alterations of the peritoneal membrane.
J Am Soc Nephrol (2009)
20: 582-92
IF: 7.505

Arques CG, Torres M.
From lineage to shape: modeling dorsal-ventral specification in the developing mouse limb.
Contemporary Mathemathics (2009)
492: 13-25
[CL] IF: n/a

Felkin LE, Lara-Pezzi E, George R, Yacoub MH, Birks EJ, Barton PJ.
Expression of extracellular matrix genes during myocardial recovery from heart failure after left ventricular assist device support.
J Heart Lung Transplant (2009)
28: 117-22
IF: 3.323

Ferjentsik Z, Hayashi S, Dale JK, Bessho Y, Herreman A, De Strooper B, del Monte G, de la Pompa JL, Maroto M.
Notch is a critical component of the mouse somitogenesis oscillator and is essential for the formation of the somites.
PLoS Genet (2009)
5: e1000662
IF: 8.883

Ferron SR, Marques-Torrejon MA, Mira H, Flores I, Taylor K, Blasco MA, Farinas I.
Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis.
J Neurosci (2009)
29: 14394-407
IF: 7.452

Flores I, Blasco MA.
A p53-dependent response limits epidermal stem cell functionality and organismal size in mice with short telomeres.
PLoS One (2009)
4: e4934
IF: n/a

Garcia-Lavandeira M, Quereda V, Flores I, Saez C, Diaz-Rodriguez E, Japon MA, Ryan AK, Blasco MA, Dieguez C, Malumbres M, Alvarez CV.
A GRFa2/Prop1/stem (GPS) cell niche in the pituitary.
PLoS One (2009)
4: e4815
IF: n/a

Gonzalez-Garcia S, Garcia-Peydro M, Martin-Gayo E, Ballestar E, Esteller M, Bornstein R, de la Pompa JL, Ferrando AA, Toribio ML.
CSL-MAML-dependent Notch1 signaling controls T lineage-specific IL-7R{α} gene expression in early human thymopoiesis and leukemia.
J Exp Med (2009)
206: 779-9
IF: 15.219

Gonzalez-Rosa JM, Mercader N.
The epicardium: development, differentiation and its role during heart regeneration.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 67-72
IF: n/a

Grimes AC, Kirby ML.
The outflow tract of the heart in fishes: anatomy, genes and evolution.
J Fish Biol (2009)
74: 983-1036
IF: 1.246

Mercader N, Selleri L, Criado LM, Pallares P, Parras C, Cleary ML, Torres M.
Ectopic Meis1 expression in the mouse limb bud alters P-D patterning in a Pbx1-independent manner.
Int J Dev Biol (2009)
53: 1483-94
IF: 2.359

Oshima Y, Ouchi N, Shimano M, Pimentel DR, Papanicolaou KN, Panse KD, Tsuchida K, Lara-Pezzi E, Lee SJ, Walsh K.
Activin A and follistatin-like 3 determine the susceptibility of heart to ischemic injury.
Circulation (2009)
120: 1606-15
IF: 14.595

Perez-Pomares JM, de la Pompa JL.
Tissue-patterned embryonic interactions in heart development: cell versus non-cell-autonomous molecular signalling and the origin of CHD.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 73-8
IF: n/a

de la Pompa JL.
Notch signaling in cardiac development and disease.
Pediatr Cardiol (2009)
30: 643-50
IF: 1.030

Publications 2009

CARDIOVASCULAR EPIDEMIOLOGY AND POPULATION GENETICS

Blasco-Colmenares E, Perl TM, Guallar E, Baumgartner WA, Conte JV, Alejo D, Pastor-Barriuso R, Sharrett AR, Faraday N.
Aspirin plus clopidogrel and risk of infection after coronary artery bypass surgery.
Arch Intern Med (2009)
169: 788-96
IF: 9.110

Bleys J, Navas-Acien A, Laclaustra M, Pastor-Barriuso R, Menke A, Ordovas JM, Stranges S, Guallar E.
Serum Selenium and Peripheral Arterial Disease: Results From the National Health and Nutrition Examination Survey, 2003-2004.
Am J Epidemiol (2009)
169: 996-1003
IF: 5.454

Brugada R, Brugada J, Guallar E.
Sudden cardiac death: translating basic science into clinical care.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 29-34
IF: n/a

Cordero A, Andres E, Ordonez B, Leon M, Laclaustra M, Grima A, Luengo E, Moreno J, Bes M, Pascual I, Civeira F, Pocovi M, Alegria E, Casasnovas JA.
Metabolic Syndrome Active Subjects Study Investigators Usefulness of triglycerides-to-high-density lipoprotein cholesterol ratio for predicting the first coronary event in men.
Am J Cardiol (2009)
104: 1393-7
IF: 3.905

Cordero A, Leon M, Andres E, Ordonez B, Laclaustra M, Grima A, Pascual I, Luengo E, Civeira F, Pocovi M, Alegria E, Casasnovas JA, MESYAS Registry investigators.
Gender differences in obesity related cardiovascular risk factors in Spain.
Prev Med (2009)
48: 134-9
IF: 2.760

Corella D, Ordovas JM.
Nutrigenomics in cardiovascular medicine.
Circ Cardiovasc Genet (2009)
2: 367-51
IF: n/a

Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, Tucker K, Lai CQ, Parnell LD, Coltell O, Lee YC, Ordovas JM.
APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations.
Arch Intern Med (2009)
169: 1897-906
IF: 9.110

Flores-Mateo G, Carrillo-Santisteve P, Elosua R, Guallar E, Marrugat J, Bleys J, Covas MI.
Antioxidant Enzyme Activity and Coronary Heart Disease: Meta-analyses of Observational Studies.
Am J Epidemiol (2009)
170: 135-47
IF: 5.454

Franco M, Diez-Roux AV, Nettleton JA, Lazo M, Brancati F, Caballero B, Glass T, Moore LV.
Availability of healthy foods and dietary patterns: the Multi-Ethnic Study of Atherosclerosis.
Am J Clin Nutr (2009)
89: 897-904
IF: 6.740

Franco M, Sanz G, Guallar E.
Clinical and epidemiological research at CNIC: psychosocial factors and cardiovascular disease.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 35-41
IF: n/a

Gonzalez-Lazaro M, Dinglasan RR, Hernandez-Hernandez Fde L, Rodriguez MH, Laclaustra M, Jacobs-Lorena M, Flores-Romo L.
Anopheles gambiae Croquemort SCRBQ2, expression profile in the mosquito and its potential interaction with the malaria parasite Plasmodium berghei.
Insect Biochem Mol Biol (2009)
39: 392-402
IF: 2.626

Kalyani RR, Franco M, Dobs AS, Ouyang P, Vaidya D, Bertoni A, Gapstur SM, Golden SH.
The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women.
J Clin Endocrinol Metab (2009)
94: 4127-35
IF: 6.325

Laclaustra M, Navas-Acien A, Stranges S, Ordovas JM, Guallar E.
Serum Selenium Concentrations and Hypertension in the US Population.
Circ Cardiovasc Qual Outcomes (2009)
2: 369-76
IF: n/a

Laclaustra M, Navas-Acien A, Stranges S, Ordovas JM, Guallar E.
Serum Selenium Concentrations and Diabetes in US Adults: National Health and Nutrition Examination Survey (NHANES) 2003-2004.
Environ Health Perspect (2009)
117: 1409-13
IF: 6.123

Laerke HN, Mortensen MA, Hedemann MS, Bach Knudsen KE, Penalvo JL, Adlercreutz H.
Quantitative aspects of the metabolism of lignans in pigs fed fibre-enriched rye and wheat bread.
Br J Nutr (2009)
102: 985-94
IF: 2.764

Publications 2009

Leon Latre M, Andes EM, Cordero A, Pascual I, Vispe C, Laclaustra M, Luengo E, Casasnovas JA.
Relationship Between Metabolic Syndrome and Ischemic Heart Disease Mortality in Spain.
Rev Esp Cardiol (2009)
62: 1469-72
IF: 2.880

Menke A, Fernandez-Real JM, Muntner P, Guallar E.
The association of biomarkers of iron status with peripheral arterial disease in US adults.
BMC Cardiovasc Disord (2009)
9: 34
IF: n/a

Menke A, Muntner P, Silbergeld EK, Platz EA, Guallar E.
Cadmium levels in urine and mortality among U.S. adults.
Environ Health Perspect (2009)
117: 190-6
IF: 6.123

Miller ER 3rd, Guallar E.
Vitamin E supplementation: what's the harm in that?
Clin Trials (2009)
6: 47-9
IF: 1.694

Miller ER 3rd, Juraschek SP, Appel LJ, Madala M, Anderson CA, Bleys J, Guallar E.
The effect of n-3 long-chain polyunsaturated fatty acid supplementation on urine protein excretion and kidney function: meta-analysis of clinical trials.
Am J Clin Nutr (2009)
89: 1937-45
IF: 6.740

Moore LV, Diez Roux AV, Nettleton JA, Jacobs DR, Franco M.
Fast-Food Consumption, Diet Quality, and Neighborhood Exposure to Fast Food: The Multi-Ethnic Study of Atherosclerosis.
Am J Epidemiol (2009)
170: 29-36
IF: 5.454

Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E.
Rejoinder: Arsenic Exposure and Prevalence of Type 2 Diabetes: Updated Findings From the National Health Nutrition and Examination Survey, 2003-2006.
Epidemiology (2009)
20: 816-20
IF: 5.406

Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, Weaver V.
Blood Cadmium and Lead and Chronic Kidney Disease in US Adults: A Joint Analysis.
Am J Epidemiol (2009)
170: 1156-64
IF: 5.454

Navas-Acien A, Umans JG, Howard BV, Goessler W, Francesconi KA, Crainiceanu CM, Silbergeld EK, Guallar E.
Urine arsenic concentrations and species excretion patterns in American Indian communities over a 10-year period: the Strong Heart Study.
Environ Health Perspect (2009)
117: 1428-33
IF: 6.123

Ordovas JM.
Cardiovascular diseases: integrating genetics and the environment.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 49-53
IF: n/a

Smith CE, Arnett DK, Tsai MY, Lai CQ, Parnell LD, Shen J, Laclaustra M, Junyent M, Ordovas JM.
Physical inactivity interacts with an endothelial lipase polymorphism to modulate high density lipoprotein cholesterol in the GOLDN study.
Atherosclerosis (2009)
206: 500-4
IF: 4.601

Vasan RS, Pencina MJ, Robins SJ, Zachariah JP, Kaur G, D'Agostino RB, Ordovas JM.
Association of circulating cholesteryl ester transfer protein activity with incidence of cardiovascular disease in the community.
Circulation (2009)
120: 2414-20
IF: 14.595

REGENERATIVE CARDIOLOGY

Bailey B, Izarra A, Alvarez R, Fischer KM, Cottage CT, Quijada P, Diez-Juan A, Sussman MA.
Cardiac stem cell genetic engineering using the alpha MHC promoter.
Regen Med (2009)
4: 823-33
IF: 2.786

Cervera AM, Bayley JP, Devilee P, McCreath KJ.
Inhibition of succinate dehydrogenase dysregulates histone modifications in mammalian cells.
Mol Cancer (2009)
8: 89
IF: 5.362

Gago N, Perez-Lopez V, Sanz-Jaka JP, Cormenzana P, Eizaguirre I, Bernad A, Izeta A.
Age-dependent depletion of human skin-derived progenitor cells.
Stem Cells (2009)
27:1164-72
IF: 7.740

Galvez BG, Covarello D, Tolorenzi R, Brunelli S, Dellavalle A, Crippa S, Mohammed SA, Scialla L, Cuccovillo I, Molla F, Staszewsky L, Maisano F, Sampaolesi M, Latini R, Cossu G.
Human cardiac mesoangioblasts isolated from hypertrophic cardiomyopathies are greatly reduced in proliferation and differentiation potency.
Cardiovasc Res (2009)
83: 707-16
IF: 5.947

Publications 2009

Galvez BG, San Martin N, Rodriguez C.
TNF-alpha is required for the attraction of mesenchymal precursors to white adipose tissue in Ob/ob mice.
PLoS One (2009)
4: e4444
IF: n/a

Gonzalez MA, Gonzalez-Rey E, Rico L, Büscher D, Delgado M.
Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells.
Arthritis Rheum (2009)
60: 1006-19
IF: 6.787

Gonzalez MA, Gonzalez-Rey E, Rico L, Büscher D, Delgado M.
Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses.
Gastroenterology (2009)
136: 978-89
IF: 12.591

Gonzalez-Rey E, Anderson P, Gonzalez MA, Rico L, Büscher D, Delgado M.
Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis.
Gut (2009)
58: 929-39
IF: 9.766

Gozalbo-Lopez B, Andrade P, Terrados G, de Andres B, Serrano N, Cortegano I, Palacios B, Bernad A, Blanco L, Marcos MA, Gaspar ML.
A role for DNA polymerase mu in the emerging DJH rearrangements of the postgastrulation mouse embryo.
Mol Cell Biol (2009)
29: 1266-75
IF: 5.940

de las Heras B, Hortelano S.
Molecular basis of the anti-inflammatory effects of terpenoids.
Inflamm Allergy Drug Targets (2009)
8: 28-39
IF: n/a

Hernandez C, Santamatilde E, McCreath KJ, Cervera AM, Diez I, Ortiz-Masia D, Martinez N, Calatayud S, Esplugues JV, Barrachina MD.
Induction of trefoil factor (TFF)1, TFF2 and TFF3 by hypoxia is mediated by hypoxia inducible factor-1: implications for gastric mucosal healing.
Br J Pharmacol (2009)
156: 262-72
IF: 4.902

Jalife J, Atienza F, Lopez-Salazar B, Delpon E, Sanchez-Quintana D, Bernad A, Almendral J.
Molecular, cellular and pathophysiological mechanisms of human atrial fibrillation.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 15-21
IF: n/a

Kirby DM, Rennie KJ, Smulders-Srinivasan TK, Acin-Perez R, Whittington M, Enriquez JA, Trevelyan AJ, Turnbull DM, Lightowlers RN.
Transmitochondrial embryonic stem cells containing pathogenic mtDNA mutations are compromised in neuronal differentiation.
Cell Prolif (2009)
42: 413-24
IF: 2.423

Lucas D, Escudero B, Ligos JM, Segovia JC, Estrada JC, Terrados G, Blanco L, Samper E, Bernad A.
Altered hematopoiesis in mice lacking DNA polymerase mu is due to inefficient double-strand break repair.
PLoS Genet (2009)
5: e1000389
IF: 8.880

Messina G, Sirabella D, Monteverde S, Galvez BG, Tonlorenzi R, Schnapp E, De Angelis L, Brunelli S, Relaix F, Buckingham M, Cossu G.
Skeletal muscle differentiation of embryonic mesoangioblasts requires pax3 activity.
Stem Cells (2009)
27: 157-64
IF: 7.740

Olmos Y, Valle I, Borniquel S, Tierrez A, Soria E, Lamas S, Monsalve M.
Mutual dependence of Foxo3a and PGC-1alpha in the induction of oxidative stress genes.
J Biol Chem (2009)
284:14476-84
IF: 5.520

Orgaz JL, Ladhani O, Hoek KS, Fernandez-Barral A, Mihic D, Aguilera O, Seftor EA, Bernad A, Rodriguez-Peralto JL, Hendrix MJ, Volpert OV, Jimenez B.
Loss of pigment epithelium-derived factor enables migration, invasion and metastatic spread of human melanoma.
Oncogene (2009)
28: 4147-61
IF: 7.216

Samper E, Morgado L, Estrada JC, Bernad A, Hubbard A, Cadenas S, Melov S.
Increase in mitochondrial biogenesis, oxidative stress, and glycolysis in murine lymphomas.
Free Radic Biol Med (2009)
46: 387-96
IF: 5.399

Roszer T, Jozsa T, Szentmiklosi AJ, Banfalvi G.
Acetylcholine inhibits nitric oxide (NO) synthesis in the gastropod nervous system.
Cell Tissue Res (2009)
336: 325-35
IF: 2.740

Publications 2009

TRANSLATIONAL CARDIOVASCULAR RESEARCH

Franco M, Sanz G, Guallar E.
Clinical and epidemiological research at CNIC: psychosocial factors and cardiovascular disease.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 35-41
IF: n/a

Gomez M, Valle V, Aros F, Sanz G, Sala J, Fiol M, Bruguera J, Elosua R, Molina L, Marti H, Covas MI, Rodriguez-Llorian A, Fito M, Suarez-Pinilla MA, Amezaga R, Marrugat J; FORTIAM group of researchers.
Oxidized LDL, lipoprotein (a) and other emergent risk factors in acute myocardial infarction (FORTIAM study).
Rev Esp Cardiol (2009)
62: 373-82
IF: 2.880

Ibanez B, Fuster V, Jimenez-Borreguero J, Sanz G, Macaya C, Badimon JJ.
Future perspectives for myocardial salvage. Role of beta-blockers in cardioprotection: a new look at an old drug.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 61-6
IF: n/a

Munoz J, Gomez i Prat J, Gallego M, Gimeno F, Trevino B, Lopez-Chejade P, Ribera O, Molina L, Sanz S, Pinazo MJ, Riera C, Posada EJ, Sanz G, Portus M, Gascon J.
Clinical profile of Trypanosoma cruzi infection in a non-endemic setting: immigration and Chagas disease in Barcelona (Spain).
Acta Trop (2009)
111: 51-5
IF: 1.707

Sanz G, Fuster V.
Fixed-dose combination therapy and secondary cardiovascular prevention: rationale, selection of drugs and target population.
Nat Clin Pract Cardiovasc Med (2009)
6: 101-10
IF: 5.970

VASCULAR BIOLOGY AND INFLAMMATION

Acosta-Iborra B, Elorza A, Olazabal IM, Martin-Cofreces NB, Martin-Puig S, Miro M, Calzada MJ, Aragones J, Sanchez-Madrid F, Landazuri MO.
Macrophage oxygen sensing modulates antigen presentation and phagocytic functions involving IFN-gamma production through the HIF-1 alpha transcription factor.
J Immunol (2009)
182: 3155-64
IF: 6.000

Alfranca A.
VEGF therapy: a timely retreat.
Cardiovasc Res (2009)
83: 611-2
IF: 5.947

Alvaro-Blanco J, Martinez-Gac L, Calonge E, Rodriguez-Martinez M, Molina-Privado I, Redondo JM, Alcami J, Flemington EK, Campanero MR.
A novel factor distinct from E2 mediates C-MYC promoter activation through its E2F element during exit from quiescence.
Carcinogenesis (2009)
30: 440-8
IF: 4,930

Barreiro O.
Endothelial Adhesive Platforms Organize Receptors to Promote Leukocyte Extravasation.
Current Topics in Membranes (2009)
64: 277-96
IF: n/a

Barreiro O, Aguilar RJ, Tejera E, Megias D, de Torres-Alba F, Evangelista A, Sanchez-Madrid F.
Specific targeting of human inflamed endothelium and in situ vascular tissue transfection by the use of ultrasound contrast agents.
JACC Cardiovasc Imaging (2009)
2: 997-1005
IF: n/a

Barreiro O, Sanchez-Madrid F.
Molecular basis of leukocyte-endothelium interactions during the inflammatory response.
Rev Esp Cardiol (2009)
62: 552-62
IF: 2.880

Cerezo A, Guadamillas MC, Goetz JG, Sanchez-Perales S, Klein E, Assoian RK, del Pozo MA.
The absence of caveolin-1 increases proliferation and anchorage-independent growth by a Rac-dependent, Erk-independent mechanism.
Mol Cell Biol (2009)
29: 5046-59
IF: 5.942

Publications 2009

Esteban V, Heringer-Walther S, Sterner-Kock A, de Bruin R, van den Engel S, Wang Y, Mezzano S, Egido J, Schultheiss HP, Ruiz-Ortega M, Walther T.
Angiotensin-(1-7) and the g protein-coupled receptor MAS are key players in renal inflammation.
PLoS One (2009)
4: e5406
IF: n/a

de la Fuente H, Lamana A, Mittelbrunn M, Perez-Gala S, Gonzalez S, Garcia-Diez A, Vega M, Sanchez-Madrid F.
Identification of genes responsive to solar simulated UV radiation in human monocyte-derived dendritic cells.
PLoS One (2009)
4: E6735
IF: n/a

Gomez M, Sanz-Gonzalez SM, Nabah YN, Lamana A, Sanchez-Madrid F, Andres V.
Atherosclerosis development in apolipoprotein E-null mice deficient for CD69.
Cardiovasc Res (2009)
89: 197-205
IF: 5.947

Hernandez-Espinosa D, Minano A, Ordonez A, Mota R, Martinez-Martinez I, Vicente V, Corral J.
Dexamethasone induces a heat-stress response that ameliorates the conformational consequences on antithrombin of l-asparaginase treatment.
J Thromb Haemost (2009)
7: 1128-33
IF: 6.291

Jorge I, Navarro P, Martinez-Acedo P, Nunez E, Serrano H, Alfranca A, Redondo JM, Vazquez J.
Statistical model to analyze quantitative proteomics data obtained by 18O/16O labeling and linear ion trap mass spectrometry: Application to the study of VEGF-induced angiogenesis in endothelial cells.
Mol Cell Proteomics (2009)
8: 1130-49
IF: 8.830

Krunic D, Moshir S, Greulich-Bode KM, Figueroa R, Cerezo A, Stammer H, Stark HJ, Gray SG, Nielsen KV, Hartschuh W, Boukamp P.
Tissue context-activated telomerase in human epidermis correlates with little age-dependent telomere loss.
Biochim Biophys Acta (2009)
1792: 297-308
IF: 4.579

Lajoie P, Goetz JG, Dennis JW, Nabi IR.
Lattices, rafts, and scaffolds: domain regulation of receptor signaling at the plasma membrane.
J Cell Biol (2009)
185: 381-5
IF: 9.120

Martinez-Martinez S, Genescà L, Rodriguez A, Raya A, Salichs E, Were F, Lopez-Maderuelo MD, Redondo JM, de la Luna S.
The RCAN carboxyl end mediates calcineurin docking-dependent inhibition via a site that dictates binding to substrates and regulators.
Proc Natl Acad Sci U S A (2009)
14: 6117-22
IF: 9.380

Mittelbrunn M, Martinez del Hoyo G, Lopez-Bravo M, Martin-Cofreces NB, Scholer A, Hugues S, Fetler L, Amigorena S, Ardavin C, Sanchez-Madrid F.
Imaging of plasmacytoid dendritic cell interactions with T cells.
Blood (2009)
113: 75-84
IF: 10.432

Perez M, Santa-Maria I, de Barreda EG, Zhu X, Cuadros R, Cabrero JR, Sanchez-Madrid F, Dawson HN, Vitek MP, Perry G, Smith MA, Avila J.
Tau--an inhibitor of deacetylase HDAC6 function.
J Neurochem (2009)
109: 1756-66
IF: 4.500

Riol-Blanco L, Delgado-Martin C, Sanchez-Sanchez N, Alonso-C LM, Gutierrez-Lopez MD, Del Hoyo GM, Navarro J, Sanchez-Madrid F, Cabanas C, Sanchez-Mateos P, Rodriguez-Fernandez JL.
Immunological synapse formation inhibits, via NF-kappaB and FOXO1, the apoptosis of dendritic cells.
Nat Immunol (2009)
10: 753-60
IF: 25.110

Rodriguez A, Roy J, Martinez-Martinez S, Lopez-Maderuelo MD, Nino-Moreno P, Orti L, Pantoja-Uceda D, Pineda-Lucena A, Cyert MS, Redondo JM.
A conserved docking surface on calcineurin mediates interaction with substrates and immunosuppressants.
Mol Cell (2009)
33: 616-26
IF: 12.900

Publications 2009

Ryu JR, Echarri A, Li R, Pendergast AM.
Regulation of cell-cell adhesion by Abi/Diaphanous complexes.
Mol Cell Biol (2009)
29: 1735-48
IF: 5,940

Salvado MD, Alfranca A, Escolano A, Haeggström JZ, Redondo JM.
COX-2 Limits Prostanoid Production in Activated HUVECs and Is a Source of PGH2 for Transcellular Metabolism to PGE2 by Tumor Cells.
Arterioscler Thromb Vasc Biol (2009)
29: 1131-7
IF: 6.858

Sanchez-Madrid F, Barreiro O.
Leukocytes whisper to endothelial guards.
Blood (2009)
113: 6048-9
IF: 10.432

Sanchez-Madrid F, Serrador JM.
Bringing up the rear: defining the roles of the uropod.
Nat Rev mol Cell Biol (2009)
10: 353-9
IF: 35.420

Sancho D, Joffre OP, Keller AM, Rogers NC, Martinez D, Hernanz-Falcon P, Rosewell I, Reis e Sousa C.
Identification of a dendritic cell receptor that couples sensing of necrosis to immunity.
Nature (2009)
458: 899-903
IF: 31.434

Strippoli R, Foronda M, Lopez-Cabrera M, del Pozo MA.
Targeting the ERK/NF-κB/Snail1 pathway as a potential therapeutic strategy to prevent the failure of peritoneal dialysis.
Nat Rev Cardiol (CNIC EDITION) (2009)
6: 43-8
IF: n/a

Vera J, Fenutria R, Canadas O, Figueras M, Mota R, Sarrias MR, Williams DL, Casals C, Yelamos J, Lozano F.
The CD5 ectodomain interacts with conserved fungal cell wall components and protects from zymosan-induced septic shock-like syndrome.
Proc Natl Acad Sci U S A. (2009)
106: 1506-11
IF: 9.380

Yanez-Mo M, Barreiro O, Gordon-Alonso M, Sala-Valdes M, Sanchez-Madrid F.
Tetraspanin-enriched microdomains: a functional unit in cell plasma membranes.
Trends Cell Biol (2009)
19: 434-46
IF: 13.385

TECHNICAL UNITS

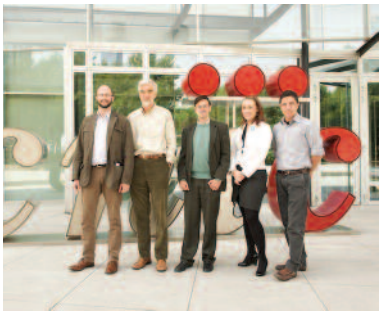
Aslam T, Fleck B, Patton N, Trucco M, Azegrouz H.
Digital image analysis of plus disease in retinopathy of prematurity.
Acta Ophthalmol (2009)
87: 368-77
IF: 2.138

Bhide MR, Escudero R, Camafeita E, Gil H, Jado I, Anda P.
Complement factor H binding by different Lyme disease and relapsing fever Borrelia in animals and human.
BMC Res Notes (2009)
2: 134
IF: n/a

Blanco-Colio LM, Lopez JA, Martinez-Pinna Albar R, Egido J, Martin-Ventura JL. **Vascular proteomics, a translational approach: from traditional to novel proteomic techniques.**
Expert Rev Proteomics (2009)
6: 461-4
IF: 3.848

Camafeita E, Lamas JR, Calvo E, Lopez JA, Fernandez-Gutierrez B.
Proteomics: New insights into rheumatic diseases.
Proteomics Clin Appl (2009)
3: 226-41
IF: 1.510

Cocca C, Dorado J, Calvo E, Lopez JA, Santos A, Perez-Castillo A.
15-Deoxi-Delta(12,14)-prostaglandin J(2) is a tubulin-binding agent that destabilizes microtubules and induces mitotic arrest.
Biochem Pharmacol (2009)
78: 1330-9
IF: 4.371



Publications 2009

Dominguez F, Garrido-Gomez T, Lopez JA, Camafeita E, Quinonero A, Pellicer A, Simon C.
Proteomic analysis of the human receptive versus non-receptive endometrium using differential in-gel electrophoresis and MALDI-MS unveils stathmin 1 and annexin A2 as differentially regulated.
Hum Reprod (2009)
24: 2607-17
IF: 3.773

Fernandez-Gonzalez R, Hourcade JD, Lopez-Vidriero I, Benguria A, Rodriguez De Fonseca F, Gutierrez-Adan A.
Analysis of gene transcription alterations at the blastocyst stage related to the long term consequences of in vitro culture in mice.
Reproduction (2009)
137: 271-83
IF: 3.070

Gamez-Pozo A, Sanchez-Navarro I, Nistal M, Calvo E, Madero R, Diaz E, Camafeita E, de Castro J, Lopez JA, Gonzalez-Baron M, Espinosa E, Fresno Vara JA.
MALDI Profiling of Human Lung Cancer Subtypes.
Plos One (2009)
4: e7731
IF: n/a

Gomez A, Lopez JA, Pintos B, Camafeita E, Bueno MA.
Proteomic analysis from haploid and diploid embryos of Quercus suber L. identifies qualitative and quantitative differential expression patterns.
Proteomics (2009)
9: 4355-67
IF: 4.590

Gomez R, Caballero R, Barana A, Amoros I, Calvo E, Lopez JA, Klein H, Vaquero M, Osuna L, Atienza F, Almendral J, Pinto A, Tamargo J, Delpon E.
Nitric oxide increases cardiac IK1 by nitrosylation of cysteine 76 of Kir2.1 channels.
Circ Res (2009)
105: 383-92
IF: 9,989

Kent ML, Feist SW, Harper C, Hoogstraten-Miller S, Law JM, Sanchez-Morgado JM, Tanguay RL, Sanders GE, Spitsbergen JM, Whipps CM.
Recommendations for control of pathogens and infectious diseases in fish research facilities.
Comp Biochem Physiol C Toxicol Pharmacol (2009)
149: 240-8
IF: 2.530

Konstantinidou O, Khymenets O, Fito M, De La Torre R, Anglada R, Dopazo A, Covas MI.
Characterization of human gene expression changes after olive oil ingestion: an exploratory approach.
Folia Biol (Praha) (2009)
55: 85-91
IF: 1.140

Lucas D, Escudero B, Ligos JM, Segovia JC, Estrada JC, Terrados G, Blanco L, Samper E, Bernad A.
Altered hematopoiesis in mice lacking DNA polymerase mu is due to inefficient double-strand break repair.
PLoS Genet (2009)
5: e1000389
IF: 8.880

Marrero-Diaz R, Bravo-Cordero JJ, Megias D, Garcia MA, Bartolome RA, Teixido J, Montoya MC.
Polarized MT1-MMP-CD44 interaction and CD44 cleavage during cell retraction reveal an essential role for MT1-MMP in CD44-mediated invasion.
Cell Motil Cytoskeleton (2009)
66: 48-61
IF: 2.625

Megias D, Marrero R, Martinez Del Peso B, Garcia MA, Bravo-Cordero JJ, Garcia-Grande A, Santos A, Montoya MC.
Novel lambda FRET spectral confocal microscopy imaging method.
Microsc Res Tech (2009)
72: 1-11
IF: 1.883

Publications 2009

Mercader N, Selleri L, Criado LM, Pallares P, Parras C, Cleary ML, Torres M.
Ectopic Meis1 expression in the mouse limb bud alters P-D patterning in a Pbx1-independent manner.
Int J Dev Biol (2009)
53: 1483-94
IF: 2.359

Merino N, Toledo-Arana A, Vergara-Irigaray M, Valle J, Solano C, Calvo E, Lopez JA, Foster TJ, Penades JR, Lasa I.
Protein A-mediated multicellular behavior in Staphylococcus aureus.
J Bacteriol (2009)
191: 832-43
IF: 3.636

Pallares P, Gonzalez-Bulnes A.
A new method for induction and synchronization of oestrus and fertile ovulations in mice by using exogenous hormones.
Lab Anim (2009)
43: 295-9
IF: 0.385

Pallares P, Gonzalez-Bulnes A.
Use of ultrasound imaging for early diagnosis of pregnancy and determination of litter size in the mouse.
Lab Anim (2009)
43: 91-5
IF: 0.385

Pallares P, Letelier C, Gonzalez-Bulnes A.
Progress toward "in vivo virtual histology" of ovarian follicles and corpora lutea by ultrasound biomicroscopy.
Fertil Steril (2009)
91: 624-6
IF: 4.167

Peral B, Camafeita E, Fernandez-Real JM, Lopez JA.
Tackling the human adipose tissue proteome to gain insight into obesity and related pathologies.
Expert Rev Proteomics (2009)
6: 353-61
IF: 3.848

Perez-Perez R, Ortega-Delgado FJ, Garcia-Santos E, Lopez JA, Camafeita E, Ricart W, Fernandez-Real JM, Peral B.
Differential Proteomics of Omental and Subcutaneous Adipose Tissue Reflects Their Unalike Biochemical and Metabolic Properties.
J Proteome Res (2009)
8: 1682-93
IF: 5.684

Poynter S, Phipps JD, Naranjo-Pino A, Sanchez-Morgado JM.
Difficulties in the molecular diagnosis of Helicobacter rodent infections.
Vet Microbiol (2009)
134: 272-8
IF: 6.660

Sanchez-Morgado JM, Gallagher A. Johnson L
Mycobacterium gordonae infection in a colony of African clawed frogs (Xenopus tropicalis).
Lab Anim (2009)
43: 300-3
IF: 0.385

Tarin C, Gomez M, Calvo E, Lopez JA, Zaragoza C.
Endothelial nitric oxide deficiency reduces MMP-13-mediated cleavage of ICAM-1 in vascular endothelium: a role in atherosclerosis.
Arterioscler Thromb Vasc Biol (2009)
29: 27-32
IF: 6.858

Tomas-Gallardo L, Canosa I, Santero E, Camafeita E, Calvo E, Schlömann M, Floriano B.
Molecular and biochemical characterization of the tetralin degradation pathway in Rhodococcus sp. strain TFB.
Microb Biotechnol (2009)
2: 262-73
IF: n/a

Torres R, Ramirez JC.
A chemokine targets the nucleus: Cxcl12-gamma isoform localizes to the nucleolus in adult mouse heart.
PLoS ONE (2009)
4: e7570
IF: n/a

Varea O, Garrido JJ, Dopazo A, Mendez P, Garcia-Segura LM, Wandosell F.
Estradiol activates beta-catenin dependent transcription in neurons.
PLoS ONE (2009)
4: e5153
IF: n/a

Publications 2009

	TOTAL (*)	TOTAL IF Publications (*)	CUMULATIVE IF	AVERAGE IF
TOTAL	143	116	801.062	6.905
ATHEROTHROMBOSIS AND CARDIOVASCULAR IMAGING	28	26	215.017	8.269
CARDIOVASCULAR DEVELOPMENTAL BIOLOGY	16	10	63.971	6.397
CARDIOVASCULAR EPIDEMIOLOGY AND POPULATION GENETICS	27	21	119.441	5.687
REGENERATIVE CARDIOLOGY	19	16	101.739	6.358
TRANSLATIONAL CARDIOVASCULAR RESEARCH	5	3	10.557	3.519
VASCULAR BIOLOGY AND INFLAMMATION	27	22	235.637	10.710
TECHNICAL UNITS	28	23	84.714	3.683

(*) 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 amount.

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 2009

Name	Secondary School	Comunidad Autónoma
Barbón Fernández, Omar	Santo Tomás de Aquino	Asturias
Fernández García, Isabel	IES Ángel San Briz- Casetas	Aragón
González de la Postilla-Concha, Carmen María	Sagrada Familia Urgel	Andalucía
Guerrero Ramos, José Juan	Sagrado Corazón Esclavas	Andalucía
Herrera Rodríguez, Silvia	IES Villa de Firga	Canarias
Martí Gómez-Adaraví, Carlos	San Pedro Pacual	Valencia
Martínez Núñez, Sara	IES Duques de Nájera	La Rioja
Vale Varela, Cristian	IES María Sarmiento	Galicia

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.

Training Programs and Courses

Fellowships in 2009

Name	Degree	University
Bilal Álvarez, Usama	Medicine	Oviedo
Blanco Suárez, Elena María	Biology	Oviedo
Calvo Rodríguez, María	Chemistry	Valladolid
Castejón Navarro, Borja	Medicine	Miguel Hernández
Castellano Castillo, Daniel	Biology	Málaga
Castillo Pérez, Carlos	Biochemistry	Granada
Clemente Toribio, Cristina	Biology	Autónoma de Madrid
de Miguel Sánchez Puerta, Fernando	Biochemistry	Navarra
Dudek, Aleksandra Maria	Biotechnology	Warsaw
García Cano, Jesús	Biology	Autónoma de Madrid
Hamczyk, Magda Rita	Biotechnology	Jagielloniana University
Izquierdo Fernández, Helena María	Biochemistry	Autónoma de Madrid
Jiménez García, Lidia	Pharmacy	Granada
Kolodziejski, Jakub Kamil	Biotechnology	Jagielloniana University
López Beas, Emilio Javier	Biochemistry	Granada
Mojsa, Bárbara	Biotechnology	Jagielloniana University
Olivas González, Francisco Javier	Biology	Granada
Peralta López, Marina	Biology	Granada
Pimentel Santillana, María	Biotechnology	Francisco de Vitoria
Ramudo Cela, Luis	Pharmacy	Santiago de Compostela
Ruz Maldonado, Inmaculada	Biology	Málaga
Villa del Campo, Cristina	Biology	Complutense de Madrid
Villarroya Beltri ,Carolina	Biochemistry	Autónoma de Madrid

PRACTICALS Program

Through agreements with Spanish universities, this program offers students the chance to carry out their undergraduate laboratory project at the CNIC.

The aim is to equip university students with in-depth knowledge of biomedical science so that they can make informed choices about a possible career in research.

Training Programs and Courses

Fellowships in 2009

Name	Degree	University
Cidre Aranaz, Florencia	Biotechnology	Francisco de Vitoria
Clemente Toribio, Cristina	Biology	Autónoma de Madrid
Gómez Salinero, Jesús María	Biotechnology	Francisco de Vitoria
Izquierdo Fernández, Helena María	Biochemistry	Autónoma de Madrid
Martín López, Javier	Medicine	Alcalá
Navarro Fernández-Hidalgo, Miguel	Medicine	Complutense de Madrid
Pazo Fernández, Alejandra	Biotechnology	Francisco de Vitoria
Tejeda Velarde, Amalia	Biochemistry	Autónoma de Madrid
Villaroya Beltri, Carolina	Biochemistry	Autónoma de Madrid

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 ask questions to key researchers and opinion leaders in the field. The 2009 edition of the **CICERONE workshop** took place in Barcelona as part of the Cardiovascular Diseases Meeting of the Sociedad Española de Cardiología.

Date: 22 October 2009
Attendees: 60

VASCULAR BIOLOGY Course

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

Dates: 27-28 July 2009
Attendees: 144

Training Programs and Courses

Recent Graduates

CARDIOVASCULAR POSTGRADUATE 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 2009 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: 12 January-10 February 2008
Venue: CNIC
Students: 8

MASTER Program

This grants program provides individual funding for study towards a Masters degree at a Spanish university. The program is aimed at students who are going to study for a PhD in one of the CNIC's labs: 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 throughout Europe.

Fellowships in 2009

Name	Master	University
Aix Sacido, Esther	Molecular Biomedicine	Autónoma de Madrid
Gómez Velázquez, Melisa	Celular and Molecular Biology	Autónoma de Madrid
González Calero, Laura	Molecular Biomedicine	Autónoma de Madrid
Lozano Vidal, Noelia	Celular and Molecular Biology	Autónoma de Madrid
Peralta López, Marina	Celular and Molecular Biology	Autónoma de Madrid
Villa del Campo, Cristina	Celular and Molecular Biology	Autónoma de Madrid

Training Programs and Courses

PREDOCTORAL (PhD) Program

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

The aims of the program are as follows:

- To ensure uniform quality of predoctoral training at the CNIC
- To ensure fair and equal access of predoctoral researchers to training opportunities
- 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 2009

Name	Title of thesis	University	CNIC Department	Thesis Advisor(s)
Chamorro Casanova, Jesús	Avances en el estudio de la extremidad en vertebrados: papel de Arid3b en la morfogénesis del AER y análisis de la formación de la punta de los dedos	Autónoma de Madrid	Cardiovascular Developmental Biology	Juan José Sanz
Ibiza Martínez, Sales	Óxido nítrico y respuesta inmune adaptativa: papel del NO en la activación de los linfocitos T	Valencia	Vascular Biology and Inflammation	Juan Manuel Serrador/ Juan Vicente Esplugués Mota
Melgar Rojas, Pedro	Función de la vía de señalización Notch en el desarrollo hematopoyético	Autónoma de Madrid	Cardiovascular Developmental Biology	José Luis de la Pompa
Pernaute Lomba, Bárbara	MicroRNAs en el desarrollo temprano de ratón: análisis de la falta de función de dicer en el linaje del trofoblasto	Autónoma de Madrid	Cardiovascular Developmental Biology	Miguel Manzanares
Rodríguez Juárez, Félix	Efecto del óxido nítrico endógeno sobre la guanilato ciclasa soluble, la respiración y la conducta de la membrana mitocondrial interna a los protones en células intactas	Autónoma de Madrid	Regenerative Cardiology	Susana Cadenas

Training Programs and Courses

Graduate students carrying out their PhD theses at the CNIC during 2009

Name	Funding Agency	CNIC Department	University	Joined CNIC previously through another Training Program
Alameda Serrano, Daniel	FPI (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	Yes
Cedenilla Horcajuelo, Marta	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	Yes
Cruz Adalia, Aránzazu	FPU (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Díez Cabezas, Begoña	FIS (Spanish Ministry of Health)	Vascular Biology and Inflammation	Autónoma de Madrid	
Escolano Artigas, Amelia	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Escudero González, Beatriz	FIS (Spanish Ministry of Health)	Regenerative Cardiology	Autónoma de Madrid	
Estrada, Juan Camilo	Red TERCEL (Spanish Ministry of Science and Innovation)	Regenerative Cardiology	Autónoma de Madrid	
Fernández-Tresguerres Torrecillas, Beatriz	FPI (Spanish Ministry of Education and Science)	Cardiovascular Developmental Biology	Autónoma de Madrid	
Foronda Álvaro, Miguel	FPU (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	Yes
García Andrés, Clara	CNIC contract	Cardiovascular Developmental Biology	Autónoma de Madrid	
García López, Silvia	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	
García-Prieto, Jaime	CNIC contract	Atherothrombosis and Cardiovascular Imaging	Autónoma de Madrid	
Gómez Cabañas, Laura	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	Yes
González Rosa, Juan Manuel	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	Yes
Guadamillas Mora, Marta C.	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Complutense de Madrid	
Gutiérrez Vázquez, Cristina	CAM (Madrid Autonomic Region)	Vascular Biology and Inflammation	Autónoma de Madrid	Yes
Hernández de Riquer, Mª Victoria	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Complutense de Madrid	
Herrera Merchán, Antonio	Human Frontier Science Foundation	Regenerative Cardiology	Autónoma de Madrid	

Training Programs and Courses

Izarra Perez, Alberto	FPI (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	
Koziol, Agnieszka	FPU (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Lara Astiaso, David	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	
Latorre Pellicer, Ana	Diputación General de Aragón	Cardiovascular Developmental Biology	Zaragoza	
Lavín Plaza, Begoña	FPI (Spanish Ministry of Education and Science)	Atherothrombosis and Cardiovascular Imaging	Autónoma de Madrid	
López Fontal, Raquel	FIS (Spanish Ministry of Health)	Regenerative Cardiology	Autónoma de Madrid	
Marco, Ricardo	CNIC contract	Cardiovascular Developmental Biology	Zaragoza	
Marcos Contreras, Óscar A.	FPU/MEC Grant (Spanish Ministry of Education and Science)	Atherothrombosis and Cardiovascular Imaging	Alcalá de Henares	
Martín Alonso, Mara	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	Yes
Mateos San Martín, Daniel	CAM (Madrid Autonomic Region)	Cardiovascular Developmental Biology	Autónoma de Madrid	
Matesanz Marín, Adela	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Méndez Barbero, Nerea	FPU (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Mendoza Daroca, Pilar	Human Frontier Science Foundation	Regenerative Cardiology	Autónoma de Madrid	
Molina Sánchez, Pedro	CNIC contract	Atherothrombosis and Cardiovascular Imaging	Valencia	
Montes Ruiz, Antonio José	Human Frontier Science Foundation	Regenerative Cardiology	Autónoma de Madrid	Yes
Moreno Rodríguez, Vanessa	CAM (Madrid Autonomic Region)	Vascular Biology and Inflammation	Autónoma de Madrid	
Muñoz Agudo, Carmen	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Muriel López, Olivia	FIS (Spanish Ministry of Health)	Vascular Biology and Inflammation	Autónoma de Madrid	Yes
Núñez Andrade, Norman	FPI (Spanish Ministry of Education and Science)	Vascular Biology and Inflammation	Autónoma de Madrid	
Olmos Buchelt, Yolanda	SAF (Spanish Ministry of Science and Innovation)	Regenerative Cardiology	Complutense de Madrid	
Rayón Alonso, Teresa	FPU (Spanish Ministry of Education and Science)	Cardiovascular Developmental Biology	Autónoma de Madrid	

Training Programs and Courses

Roselló Díez, Alberto	FPI (Spanish Ministry of Education and Science)	Cardiovascular Developmental Biology	Autónoma de Madrid	
Sánchez Ramos, Crístina	FPI (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	
Sala Valdes, Mónica	FIS (Spanish Ministry of Health)	Vascular Biology and Inflammation	Autónoma de Madrid	
Silvestre Roig, Carlos	Mariano Losantos del Campo Foundation	Atherothrombosis and Cardiovascular Imaging	Valencia	
Tarín Cerezo, Carlos A.	FPI (Spanish Ministry of Education and Science)	Atherothrombosis and Cardiovascular Imaging	Alcalá de Henares	
Tejera Puente, Emilio	FIS (Spanish Ministry of Health)	Vascular Biology and Infalmmation	Autónoma de Madrid	
Tomé Pizarro, María	CNIC contract	Regenerative Cardiology	Autónoma de Madrid	Yes
Uribe, Verónica	La Marató, TV3 Foundation	Cardiovascular Developmental Biology	Autónoma de Madrid	Yes
Urso, Katia	FIS (Spanish Ministry of Health)	Vascular Biology and Inflammation	Autónoma de Madrid	
Valiente Alandí, Iñigo	FPU (Spanish Ministry of Education and Science)	Regenerative Cardiology	Autónoma de Madrid	Yes

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 will be achieved through laboratory-based training at the CNIC-MSSM Joint Unit, located on the MSSM campus in New York.

Fellowships in 2009 (Provisional Award Decision)

Name	Instution
Arias Guedón, Teresa	Centro de Investigación Aplicada - Navarra
González Mirelis, Jesús	Hospital Puerta de Hierro - Madrid
Herranz Sánchez, Beatriz	Universidad de Alcalá - Madrid
Mateo de Castro, Jesús	Centro Nacional de Investigaciones Cardiovasculares - Madrid
Torrente Regidor, María	Universidad Autónoma - Madrid

Training Programs and Courses

Postgraduate Students & Medical Professionals

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 2009

Name	Hospital	CNIC Department
Núñez Gil, Iván Javier	Hospital Clínico San Carlos	Regenerative Cardiology
Vivas Balcones, David	Hospital Clínico San Carlos	Atherothrombosis and Cardiovascular Imaging

CARDIOJOVEN Program

The CARDIOJOVEN Program provides theoretical and practical training for medical practitioners in the cardiovascular area who are interested in research. The aim is to promote high-quality translational research at centers within the Spanish National Health System.

The program offers quality training in clinical research methodology-including statistical analysis, training in the newest basic research techniques used in cardiovascular medicine, and the possibility of further specialization in any clinical area of cardiology for up to three years.

The program includes a fellowship at the Johns Hopkins University and the possibility of fellowships at Mount Sinai Medical School or other international centers.

Fellowship in 2009 (Provisional Award Decision)

Name	Instution
García Ruiz, José Manuel	Hospital Universitario Central de Asturias

Training Programs and Courses

CARDIOVASCULAR PATHOPHYSIOLOGY Course: "From symptoms to genes"

The course in CARDIOVASCULAR PATHOPHYSIOLOGY 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 a modern vision of cardiac physiology.

Dates: 20 and 21 November 2009
Venue: CNIC Lecture Hall
Attendees: 101

Physicians & Researchers

POSTDOCTORAL Program

The POSTDOCTORAL Program is designed to attract young researchers (both Spanish and citizens of other countries) to receive top level training in one of the areas of cardiovascular research covered by the laboratories at our center. Research projects can also be carried out in collaboration with international centers with which the CNIC has established training agreements. With this program the CNIC aims to make a significant contribution to the creation of a strong base of internationally-trained scientists specialized in areas of relevance to cardiovascular research.

Fellowships in 2009

Candidate	Scientist (Supervisor)	Research line
Barros, Marta F.	José Luis de la Pompa	Osteoprogenitors Differentiation is Regulated by Cell-Cell and Cell-Extracellular Matrix Interactions: Implications for Bone Tissue Regeneration
Pellinen, Teijo	Miguel Ángel del Pozo	Mechanisms of prostate cancer extravasation
Rodríguez Cortés, José	Pilar Martín	Development of STAT6 Inhibiting Compounds: Therapeutic Application in Murine Model of Asthma
Sanz Rosa, David	Borja Ibañez	Role of beta-adrenergic system in acute myocardial infarction

TRANSLATIONAL RESEARCH Forum

This forum on Translational Research provides a shared space where basic and clinical researchers in the cardiovascular area can exchange ideas and scientific interests. The aim is to stimulate the development of translational projects that will permit rapid transfer of research findings to the clinic, to the benefit of patients.

Dates: 27 November 2009
Venue: CNIC Lecture Hall
Attendees: 107

Seminars, Events and Awards

January

19 **Jan Hoeijmakers,**
Institute of Genetics, Erasmus MC, Rotterdam, The Netherlands

20 **Félix Recillas–Targas,**
Universidad Nacional Autónoma de México

27 **Cristina Sánchez–Camacho,**
Instituto Cajal (CSIC), Madrid, Spain

February

02 **Elisabetta Dejana,**
IFOM Foundation FIRC Institute of Molecular Oncology, Milan, Italy

09 **Manuel Serrano,**
Centro Nacional de Investigaciones Oncológicas, Madrid, Spain

23 **Harlan Krumholz,**
Yale University, New Haven, USA

24 **Thomas Tuschl,**
Rockefeller University, USA

24 **Cristina Grande,**
Centro de Biología Molecular, Madrid, Spain

March

02 **Pilar Tornos i Mas,**
Hospital General Universitari Vall D'Hebrón, Barcelona

06 **Ginés Morata,**
Centro de Biología Molecular, Madrid, Spain

09 **Robert Parton,**
University of Queensland, Australia

16 **José López Barneo,**
Universidad de Sevilla, Spain

24 **Janet Rossant,**
Sick Kids Hospital, Toronto, Canada

27 **Lawrence J. Appel,**
Epidemiology and International Health (Human Nutrition), Johns Hopkins Medical Institutions, Baltimore, USA

27 **Miguel Maroto,**
College of Life Sciences, University of Dundee

April

06 **Josep Vidal,**
Hospital Clinic Barcelona, Spain

13 **Paola Bovolenta,**
Instituto Cajal, Madrid, Spain

20 **Angel Raya,**
Center for Regenerative Medicine in Barcelona, Spain

21 **Fernando Casares,**
Centro Andaluz de Biología del Desarrollo (CSIC-UPO), Sevilla, Spain

27 **Juan Lafaille,**
The Kimmel Center for Biology and Medicine of the Skirball Institute, New York, USA

28 **Carlos Torroja,** Sanger Institute, The Wellcome Trust Genome Campus, UK

Seminars, Events and Awards

May

04 **Deborah Yelon,**
New York University School of Medicine, USA

11 **Juan Cinca,**
Institut de Recerca de L'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

18 **Martha S. Cyert,**
Stanford University, Standford, USA

21 **Symposium on Developmental Biology from a Cell Biology and Biophysics Perspective**

Margaret Buckingham,
Pasteur Institut, Paris, France
Valeria Caiolfa,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
José Luis de la Pompa,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
José Antonio Enríquez,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Ignacio Flores,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Marcos González-Gaitán,
University of Geneva, Switzerland
Anna-Katerina Hadjantonakis,
Sloan-Kettering Institute, New York, USA
Carl-Philipp Heisenberg,
Max Planck Institute, Dresden, Germany
Pedro Herrera,
University of Geneva, Switzerland
Alfonso Martínez-Arias,
University of Cambridge, UK
Marco Milán,
Instituto de Investigación Biomédica, Barcelona, Spain
Eduardo Moreno,
Centro Nacional de Investigaciones Oncológicas, Madrid, Spain
James Sharpe,
Center for Genomic Regulation, Barcelona, Spain
Shankar Srinivas,
University of Oxford, UK
Miguel Torres,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Joachim Wittbrodt,
European Molecular Biology Laboratory, Heidelberg, Germany

25 **Richard T. Lee,**
Brigham and Women's Hospital. Harvard Medical School, Boston, USA

26 **Robb Krumlauf,**
Stowers Institute for Medical Research, Kansas City, USA

June

01 **Satyajit Mayor,**
National Centre for Biological Science, Karnataka, India

08 **Stefanie Dimmeler,**
Institute of Cardiovascular Regeneration, Centre for Molecular Medicine, Frankfurt, Germany

09 **Miguel Angel Herrero,**
Universidad Complutense de Madrid, Spain

16 **Robert G. Kelly,**
Developmental Biology Institute of Marseilles, Luminy IBDML, Marseille Cedex, France

22 **Roderic Guigó,**
Institut Municipal d'Investigació Mèdica - Universidad Pompeu Fabra, Barcelona, Spain

26 **Juan Carlos López,**
Editor in Chief, Nature Medicine

Seminars, Events and Awards

July

06 **Judith Campisi,**
Buck Institute for Aging Research / LNBL, Novato, USA

13 **Jesús Almendral,**
Hospital General Universitario Gregorio Marañón, Madrid, Spain

September

04 **Richard Harvey,**
Deputy Director, Victor Chang Cardiac Research Institute & Sir Peter Finley Professor of Cardiac Research, University of New South Wales

09 **Carola García de Vinuesa,**
John Curtin School of Medical Research, Australian National University, Canberra, Australia

14-15 **International Workshop.**
Principios de las técnicas de fluorescencia

Beniamino Barbieri,
ISS, Inc., Champaign, USA
David M. Jameson,
University of Hawaii at Manoa, Honolulu, USA
Susana Sánchez Donoso,
University of California, Irvine, USA
Martin vandeVen,
trans-National University Limburg (tUL), Biomedical Research Institute,Diepenbeek, Belgium
Enrico Gratton,
University of California, Irvine, USA
Don Lamb,
Ludwig-Maximilians-Universität München, Lehrstuhl für Physikalische Chemie I, München, Germany
Valeria Caiolfa,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Catherine Royer,
CNRS, Centre de Biochimie Structurale, Montpellier CEDEX, France
A. Ulises Acuña,
Consejo Superior de Investigaciones Científicas, Instituto de Química Física, Madrid, Spain

17 **Raphael Kopan,**
Washington University High Throughput Center, USA

October

06 **Jens Stein,**
Theodor Kocher Institute, University of Bern, Switzerland

19 **Richard Cooper,**
Loyola University Chicago Stritch School of Medicine, USA

22-23 **Programa del 3er Simposio de la Red Española de Adhesión y Migración Celular (RAMIC)**
Molecular Biology and function of cell polarity

Vivek Malhotra,
Center for Genomic Regulation, Barcelona, Spain
Miguel A Alonso,
Centro de Biología Molecular, Madrid, Spain
Carole Parent,
National Cancer Institute, Bethesda, USA
Jim Norman,
Beatson Institute, Glasgow, UK
Enrique Rodríguez-Boulán,
Weil Cornell Medical College, New York, USA
Kozo Kaibuchi,
University of Nagoya, Japan
Mirna Pérez-Moreno,
Centro Nacional de Investigaciones Oncológicas, Madrid, Spain
Juan M. Serrador,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Jacky Goetz,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Manuel López-Cabrera,
Centro de Biología Molecular, Madrid, Spain
Erik Sahai,
Cancer Research, London, UK
Federico Mayor,
Centro de Biología Molecular, Madrid, Spain
Richard Klemke,
University of California, San Diego, USA
Ian G. Macara,
University of Virginia, Charlottesville, USA
Xosé Bustelo,
Centro de Investigación del Cáncer, Salamanca, Spain
José Luis de la Pompa,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Marcos Malumbres,
Centro Nacional de Investigaciones Oncológicas, Madrid, Spain
Reinhard Fässler,
Max Planck, Martinsried, Germany

Seminars, Events and Awards

22 **Jornada Cicerone.**
Lo que necesitas saber sobre la Investigación Cardiovascular

Valentín Fuster,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Eliseo Guallar,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Javier Díez,
Facultad de Medicina, Universidad de Navarra - Centro para la Investigación Médica Aplicada - Clínica Universitaria de Navarra, Spain
Joan Rodés,
Instituto de Investigaciones Sanitarias IDIBAPS - Hospital Clínic, Barcelona, Spain
Robert Bonow,
Northwestern University Medical School Chicago, USA
Vicente Andrés,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
José Mª Ordovás,
Tufts University, Boston, USA
Zahi A. Fayad,
Mount Sinai School of Medicine, New York, USA
Ginés Sanz,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain

26 **Thomas Braun,**
Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany

27 **Dmitry Penkov,**
Russian Cardiology Research Center, Moscow, Russia

30 **Frederic Geissmann,**
King's College London. CMCBI - Centre for Molecular and Cellular Biology of Inflammation

November

17 **Pilar Alcaide,**
Centre for Excellence in Vascular Biology, Dept. of Pathology, Brigham and Women's Hospital, Harvard Medical School, USA

23 **Luca Scorrano,**
University of Genève Medical School, Switzerland

20-21 **Curso de Fisiopatología Cardiovascular**
Del síntoma a los genes

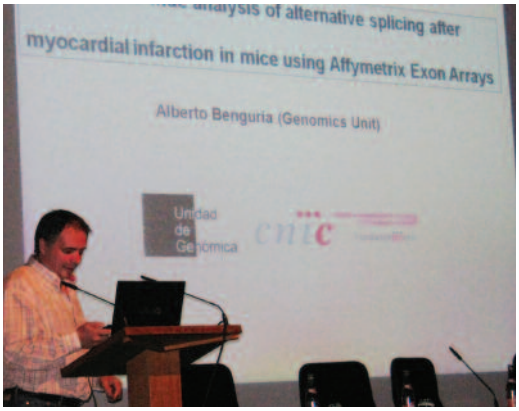
Ginés Sanz,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Carlos Macaya,
Sociedad Española de Cardiología, Madrid, Spain
Ana Dopazo,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
María Vinaixa,
Metabolomics Platform, Universitat Rovira i Virgili, Tarragona, Spain
Josep Brugada,
Hospital Clínic, Barcelona, Spain
Antonio Zaza,
Universitá di Milano-Bicocca, Milano, Italy
Antonio Berruezo,
Hospital Clínic, Barcelona, Spain
Javier Díez,
CIMA, Universidad de Navarra, Spain
Alberto San Román,
Hospital Clínico Universitario, Valladolid, Spain
Eduardo de Teresa,
Hospital Virgen de la Victoria, Málaga, Spain
Javier Escaned,
Hospital Clínico San Carlos, Madrid, Spain
Jesús Jiménez Borreguero,
Centro Nacional de Investigaciones Cardiovasculares & Hospital de la Princesa, Madrid, Spain
Nieves Gonzalo,
Hospital Clínico San Carlos, Madrid, Spain
Antonio Fernández Ortiz,
Hospital Clínico San Carlos, Madrid, Spain
Borja Ibáñez,
Centro Nacional de Investigaciones Cardiovasculares & Hospital Clínico San Carlos, Madrid, Spain
Inmaculada Roldán,
Hospital Universitario La Paz, Madrid, Spain
Francisco Marín,
Hospital Virgen de la Arrixaca, Murcia, Spain

27 **II Encuentro sobre Investigación Traslacional**

Eulalia Roig,
Hospital Clínic, Barcelona, Spain
Pilar Martín,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Manuel Pablo Anguita,
Hospital Reina Sofía, Córdoba, Spain

Seminars, Events and Awards

Jesús Jiménez-Borreguero,
Centro Nacional de Investigaciones Cardiovasculares & Hospital de La Princesa, Madrid, Spain
Ginés Sanz,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Nuria Gironés,
Centro de Biología Molecular, Madrid, Spain
Javier Segovia,
Hospital Puerta de Hierro, Madrid, Spain
José Ramón Gonzalez-Juanatey,
Hospital Clínico Universitario, Santiago de Compostela, Spain
Valentín Fuster,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Vicente Andrés,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Carlos Zaragoza,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
José Luis de la Pompa,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
José Mª Ordovás,
Centro Nacional de Investigaciones Cardiovasculares, Madrid & Tufts University, Boston, USA
Eliseo Guallar,
Centro Nacional de Investigaciones Cardiovasculares, Madrid & Johns Hopkins University Baltimore, USA
José Tuñón,
Fundación Jiménez-Díaz, Madrid, Spain
Emilio Ros,
Hospital Clínic, Barcelona, Spain



December

14

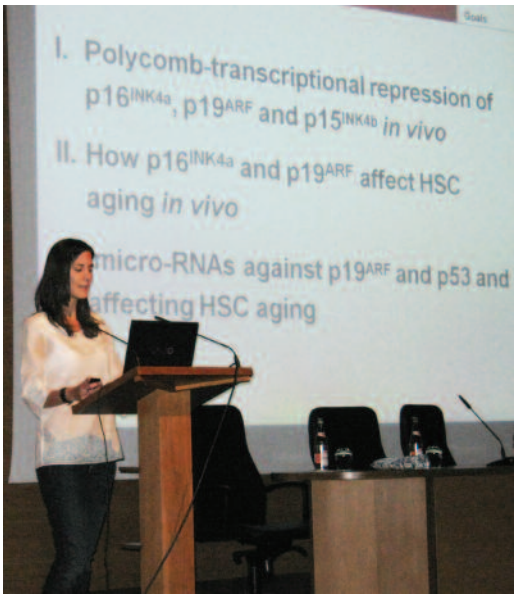
1er Curso teórico-práctico Virus Recombinantes Básica y clínica
Principios y actualización de su empleo como vectores génicos

Juan A. Bueren,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain
Adrian Thraser,
UCL Institute of Child Health, London, UK
Ramón Alemany,
Institut Català d'Oncologia, Barcelona, Spain
Gustavo Tiscornia,
Centro de Medicina Regenerativa de Barcelona, Spain
Mariano Esteban,
Centro Nacional de Biotecnología, Madrid, Spain
Juan Carlos Ramírez,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
África González-Murillo,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain
Paula Río,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain
Miguel Chillón,
Institució Catalana de Recerca i Estudis Avançats - Centro de Biotecnología Animal y Terapia Génica, Barcelona, Spain
Guillermo Güenechea,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain
José Carlos Segovia,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain
Elena Almarza,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain

Seminars, Events and Awards

Cristina Fillat,
Center for Genomic Regulation, Barcelona, Spain
Pilar Martín,
Fundación Araid - I+CS, Zaragoza, Spain
Gloria Gonzalez,
Centro de Investigación Médica Aplicada, Pamplona, Spain
Francisco Martín,
Instituto López Neyra - Consejo Superior de Investigaciones Científicas, Granada, Spain
Javier Díaz Nido,
Centro de Biología Molecular Severo Ochoa - Universidad Autónoma de Madrid, Spain
Esther Grueso,
Centro de Biología Molecular Severo Ochoa - Universidad Autónoma de Madrid, Spain
Antonio Diez,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Luís Miguel Criado,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain
Susana Navarro,
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas - Centro de Investigación Biomédica en Red de Enfermedades Raras, Madrid, Spain

22 **Victor Mulero,**
Department of Cell Biology and Histology Faculty of Biology, University of Murcia, Spain



Awards

Vascular Biology and Inflammation

Prize: Miguel Catalán Prize of the Comunidad Autónoma de Madrid
Prize winner: **Francisco Sánchez-Madrid**

Prize: Fundación Biogen Idec. IV Young Investigators Award, Cardiovascular Area
Prize winner: **Olga Barreiro**

Prize: Real Academia de Doctorado de España. Prize for the best docotoral thesis in the life sciences
Prize winner: **Olga Barreiro**

Prize: Universidad Autónoma de Madrid. Special Thesis Award
Prize winner: **Olga Barreiro**

Cardiovascular Epidemiology and Population Genetics

Prize: Gold Medal of the Sociedad Española de Cardiología (SEC)
Prize winner: **José Mª Ordovás**

Proteomics

Prize: Biannual Award of the Sociedad Española de Proteómica for the best proteomics publication in 2007-2008
Prize winner: **Enrique Calvo**

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 Institue) of the Ministerio de Ciencia e Innovación (Spanish Science and Innovation Ministry), 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 Goverment 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 recently 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, some of the largest companies in the country have made a long-term commitment to biomedical research which 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 is 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 since joined the ProCNIC Foundation, 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 not only provides 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.

Funding

Public funding

MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

Private funding

Fundaciónprocnic

acciona

BBVA

fundación abertis

endesa

FUNDACIÓN MM

Fundación Marcelino Botín

ARCES

gasNatural fenosa

INDITEX

"la Caixa"

PRISA

Fundación REPSOL

Telefónica

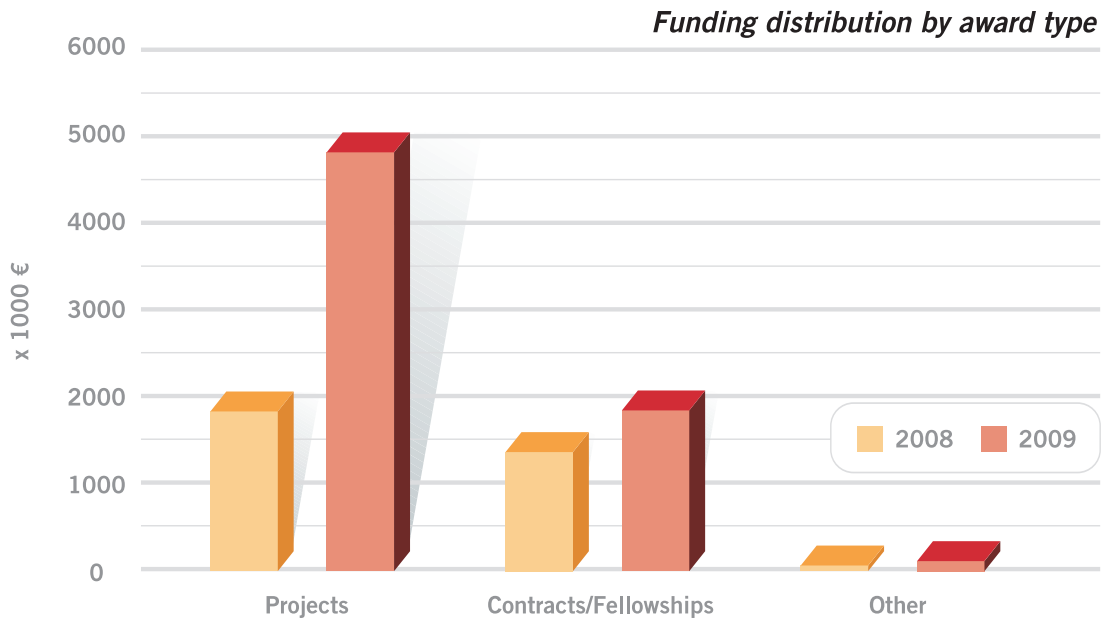
ProCNIC International Collaborator

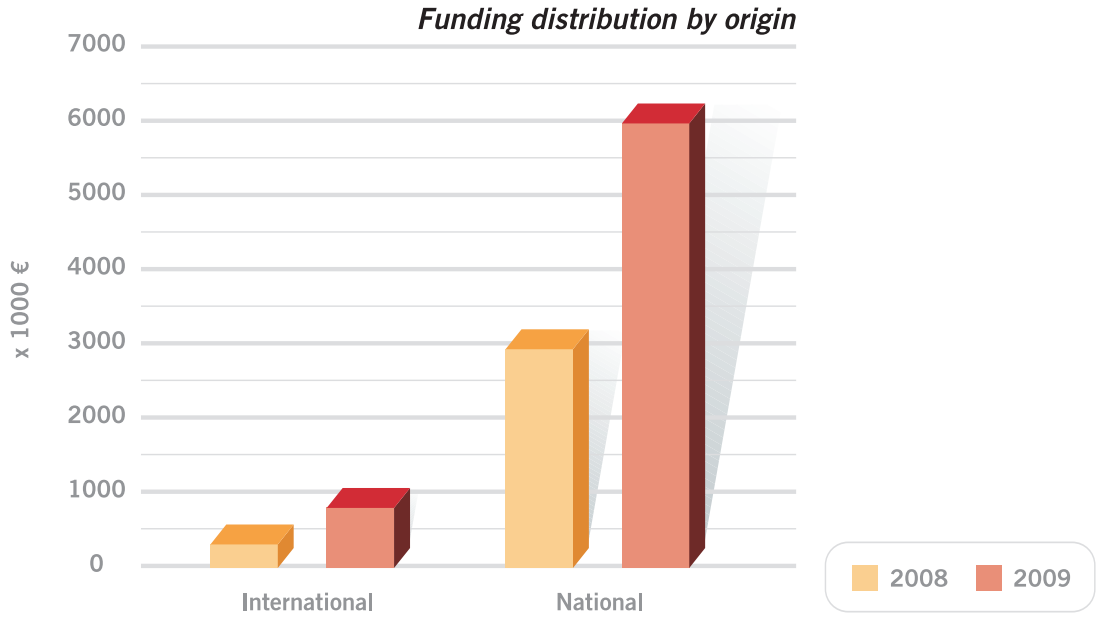
Mitsubishi Corporation

Competitive funding

A total of 47 applications for competitive funding were approved last year, providing a total of about €6.8 million external funding to the CNIC. Of this, ~€0.8 million came from international sources and ~€6 million from national sources. Most of the funding obtained was for research projects (€4.8 million), and most of the rest (€1.8 million) was funding for contracts and fellowships, with ~€60 .000 for other types of awards. Compared to 2008, this corresponded to a doubling of the amount of competitive funding obtained in 2009. Funding obtained for research projects increased by ~160%, whereas funding for contracts/fellowships increased by ~40% compared to 2008. Regarding the origin of funding, compared to 2008 the amounts of funding obtained from international sources increased by a factor of three, compared to a doubling of funds obtained from different national funding sources.

Funding





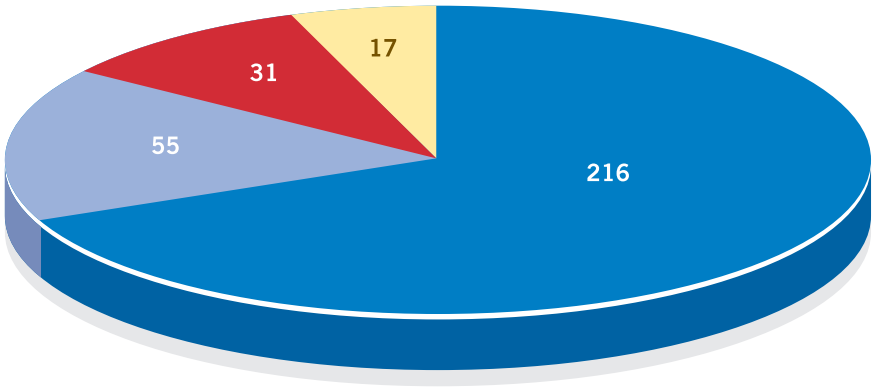
Technology Transfer

The CNIC pursues an active exploitation strategy, in line with the strong focus of the centre on translational and applied research. Considering the high potential for exploitation of several of the results protected, it is expected that CNIC will start obtaining important income from royalties during the next two years or so. Moreover, it is foreseen that during the next three years the first company will be spun off the CNIC.

Four new patent applications were presented during 2009, and four previously presented applications were extended to international patent applications. In total there were 12 patents with CNIC participation at various stages of the patent application process.

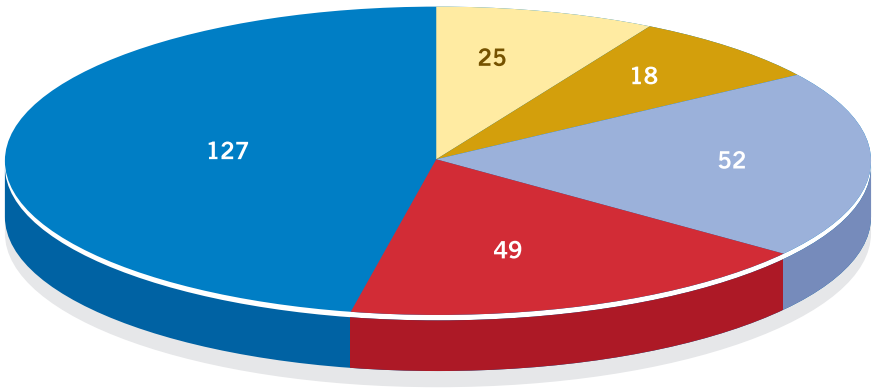
Staff Figures

CNIC staff 2009 (319)



Research		Support	
Departments	Technical Units	Administration	ScientificServices

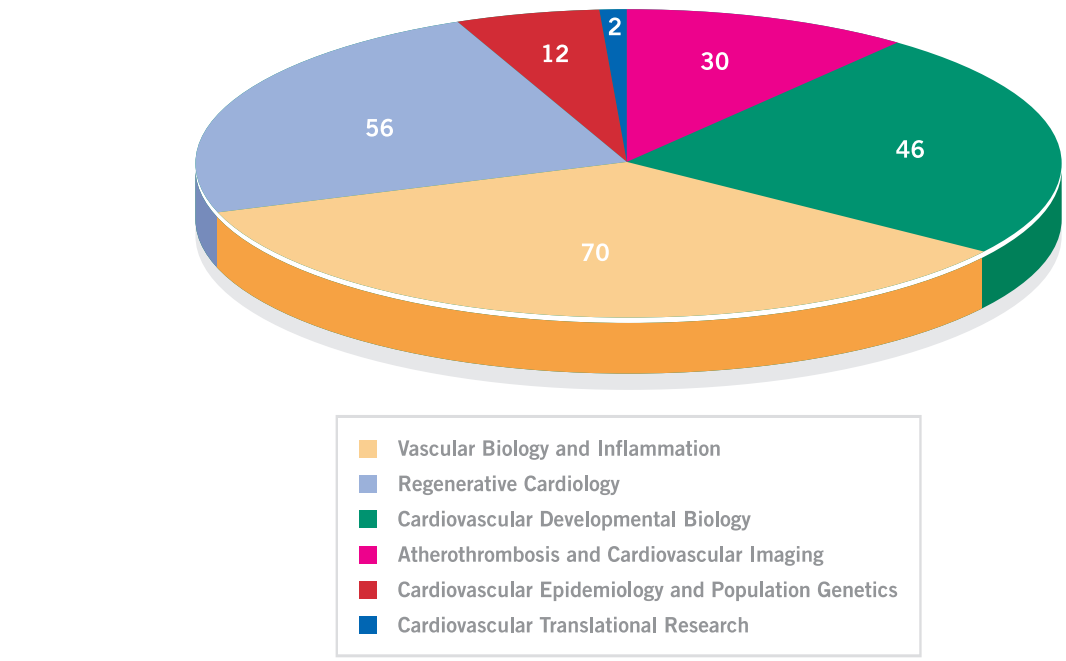
CNIC scientific staff 2009 (271)



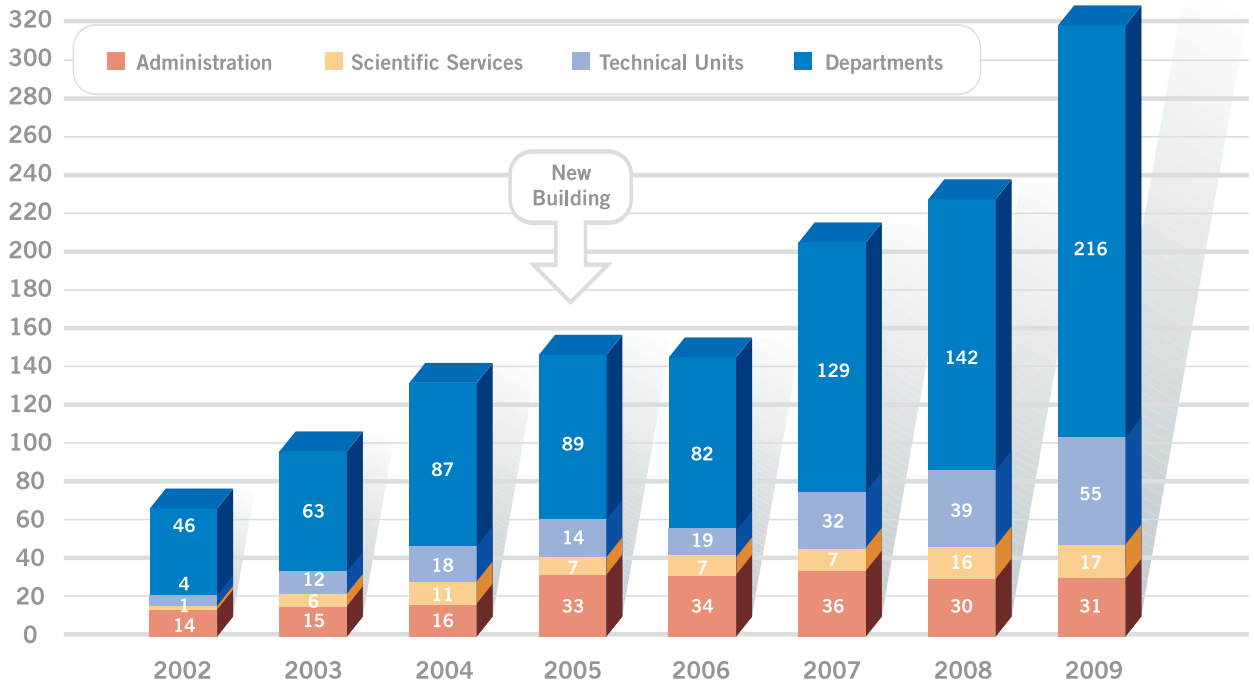
- Head of Laboratory
- Research Scientists
- Postdoctoral Researchers
- Predoctoral Researchers
- Technicians

Staff Figures

Staff by department 2009 (216)

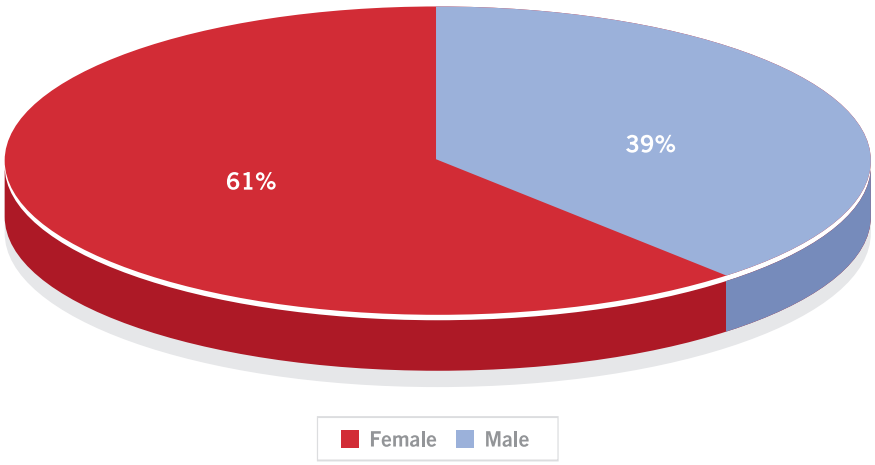


Growth and current status

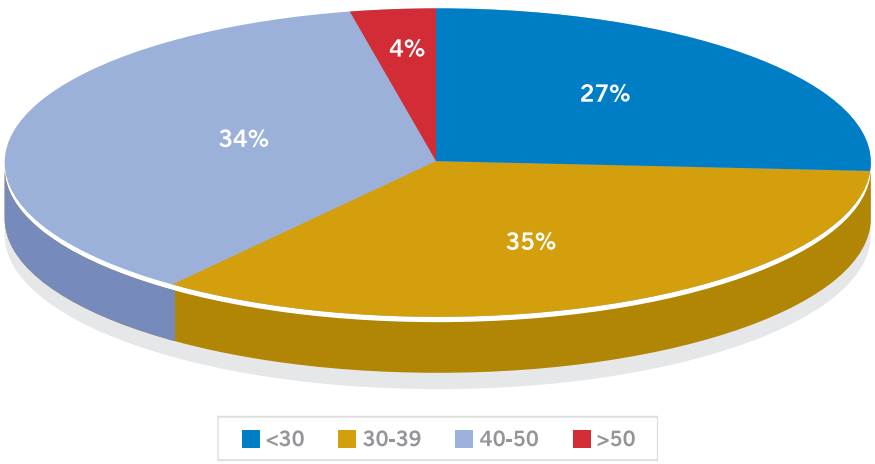


Staff Figures

Gender distribution 2009



Age distribution 2009



MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

Fundaciónprocnic

cnic

Melchor Fernández Almagro, 3 - 28029 Madrid. España T. (34) 91 453 12 00 - F. (34) 91 453 12 45 - www.cnic.es

Addenda to Appendix
CNIC Scientific Report 2009

Page 112

Physicians & Researchers

POSTDOCTORAL Program

The POSTDOCTORAL Program is designed to attract young researchers (both Spanish and citizens of other countries) to receive top level training in one of the areas of cardiovascular research being carried out in the laboratories at our center. Research projects can also be carried out in collaboration with international centers with which the CNIC has established training agreements. With this program the CNIC aims to make a significant contribution to the creation of a strong base of internationally-trained scientists specialized in areas of interest to cardiovascular research.

Fellowships in 2009

Candidate	Scientist (Supervisor)	Research line
Evangelista, Marta B.	José Luis de la Pompa	Notch signalling in aortic valve stenosis and atherosclerosis
Pellinen, Teijo	Miguel Ángel del Pozo	Mechanisms of prostate cancer extravasation
Rodríguez Cortés, José	Pilar Martín	Development of STAT6 Inhibiting Compounds: Therapeutic Application in Murine Model of Asthma
Sanz Rosa, David	Borja Ibañez	Role of beta-adrenergic system in acute myocardial infarction