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.
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.

Valentin Fuster. General Director
Miguel Torres. Associate Director
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Basic Research Departments

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Molecular regulation of heart development and disease
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AWHS
PESA, CNIC2-Santander
Polypill/FOCUS

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Imaging the cardiovascular inflammation and the immune response
Andrés Hidalgo
Vascular wall remodelling and cardiovascular disease
Carlos Zaragoza
Molecular and genetic cardiovascular pathophysiology
Vicente Andrés
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Technical Units

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Genomics
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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 Ferreira

**Logistics:** Teresa Casaseca

**Administrative support:** Sandra Cillero
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 transcription 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 unknown. 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.
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)


Green and cyan fluorescent proteins report induced genetic mosaicism in the mouse epiblast.
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 myocardium 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 the contribution of altered Notch signaling to neonatal and adult cardiac disease.

**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.

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**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

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

**Predoctoral Researchers:** Gonzalo del Monte, Gaetano D’Amato, Álvaro González Rajal, Luis Luna-Zunta, Guillermo Luxán, Julianne Münch

**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.
SCIENTIFIC REPORT ’09

Cardiovascular Developmental Biology


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

- 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 calcification (arrows). (E, F) RBP KO/+ mice fed a hypercholesterolemic diet plus vitamin D show signs of severe calcification (arrows in F).
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.
Cardiovascular Developmental Biology

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


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.

RESEARCH INTEREST

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.

MAJOR GRANTS

- Ministerio de Ciencia e Innovación (SAF2009-10480)

SELECTED PUBLICATIONS


* Joint 1st authors
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; α-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


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

Basic Research Departments

Regenerative Cardiology
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
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.
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 (PLE 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


Our laboratory researches the mammalian mitochondrial electron transport chain (MiETC) 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).
The three functional processes of the mitochondrial OXPHOS system: electron transport (blue); proton pumping (red) and ATP synthesis.

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.

MAJOR GRANTS

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

SELECTED PUBLICATIONS


The INK4b-ARF-INK4a locus encodes three tumor suppressors, p15INK4b, ARF, and p16INK4a. Together, these factors constitute one of 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.
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.

MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS (P1080070)

SELECTED PUBLICATIONS


*D Corresponding author

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 pluripotent 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.

MAJOR GRANTS

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

SELECTED PUBLICATIONS

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


Transcriptional regulation of oxidative stress protection systems

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 in 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<sup>+</sup> and PGC-1α<sup>-/-</sup> 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)
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.

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

SELECTED PUBLICATIONS
Prieur X, Röszer T, Ricote M. Lipotoxicity in macrophages: evidence from diseases associated with the metabolic syndrome. Biochim Biophys Acta (accepted)
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 Hoechst (blue).
Human cardiac mesoangioblasts isolated from hypertrophic cardiomyopathies are greatly reduced in proliferation and differentiation potency.


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
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.
Vascular Biology and Inflammation

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. 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


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 aneurysm (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.
MAJOR GRANTS

- Ministerio de Ciencia e Innovación (SAF 2006-08348).
- Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA; RD06/0014/0005).
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- Fundació La Marató TV3 (081731).
- Fundación Genoma España. MEICA Project.

SELECTED PUBLICATIONS

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Integrin signaling

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**Postdoctoral Researchers:**
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- 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 caveola 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.
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


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 GM1 ganglioside (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.
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 isotope 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.
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


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.

P.E.S.A. CNIC-2
Progression of Early Atherosclerosis in Santander.

5000 employees: men (65%), women (35%) (40-54 years old)

• Classical risk factors:
  • Physical activity
  • Psychosocial

• Novel risk factors:
  • Genomic
  • Epigenomic
  • Metabolomic

Unrecognized / subclinical atherosclerosis

Unrecognized myocardial scar

Unrecognized / subclinical atherosclerosis

Progress
Associations with RFs
Women

Unrecognized myocardial infarction
Prevalence and incidence
Associations with RFs

Basic and advanced imaging
6-year follow-up
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).
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
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.

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.

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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:

MAJOR GRANTS

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

SELECTED PUBLICATIONS


Imaging cardiovascular inflammation and the immune response

**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) induce 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


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.
Atherothrombosis and Cardiovascular Imaging

**SELECTED PUBLICATIONS**


**MAJOR GRANTS**

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

**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.
Mechanisms of atherosclerosis

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**


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.

### 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.

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### SELECTED PUBLICATIONS


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.
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 Cardiovascular 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 Atherosclerosis) 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 Atherosclerosis (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.
SELECTED PUBLICATIONS


José Mª Ordovás – *Nutrigenomics*
Coordinator of the CNIC - Tufts University Research Agreement

J. M. Ordovás’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 Téllez-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

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

During 2009 we completed the galenic 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 pharmacodynamic 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. Multidisciplinary 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:

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

Organization of the FOCUS project

World Heart Federation
CNIC (Spain) coordination
Federación Argentina Cardiología

DAMIC Ruscallada FDN
Argentina
Mario Negri Institute
Italy
FCRB Trial Unit
Spain

Istituto Salud Carlos III
Spain

FERRER Internacional
Spain

MAJOR GRANTS

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

SELECTED PUBLICATIONS


7 Technical Units
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.
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


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.
Technical Units

**SELECTED PUBLICATIONS**

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
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.

SELECTED PUBLICATIONS


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.

RESEARCH INTEREST

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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.


Identification of 15d-PGJ2-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-PGJ2-treated (A, lower panel) microtubule samples digested with trypsin. Arrows 1–5 indicate differences in peptide mass composition between control and 15d-PGJ2-treated samples. Peak 6 corresponds to the 15d-PGJ2 dimer. (B) Targeted analysis by multiple reaction monitoring (MRM) of control and 15d-PGJ2-treated microtubule samples. The main panels shows MRM of trypsin digested 15d-PGJ2-modified peptides 1–4. The inset shows the results for the corresponding control microtubule sample.
Transgenesis

Head of Unit: Luis-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.

SELECTED PUBLICATIONS


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.

**RESEARCH INTEREST**

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**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.
A chemokine targets the nucleus: Cxcl12-gamma isoform localizes to the nucleolus in adult mouse heart.


Lentiviral-delivered cre mediates recombination in human cells containing a floxed hygromycin 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

Appendix

Publications 2009
Training Programs and Courses
Seminars, Events and Awards
Funding
Staff Figures
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 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

Cross-sectional, prospective study of MRI reproducibility in the assessment of plaque burden of the carotid arteries and aorta.
IF: 5.970

Andres V, Gonzalez JM.
Role of A-type lamins in signaling, transcription, and chromatin organization.
IF: 9.120

Badimon JJ, Ibanez B, Cimmino G.
Genesis and dynamics of atherosclerotic lesions: implications for early detection.
IF: 3.041

Farkouh ME, Fuster V.
Diabetes and aspirin: beware of underpowered negative trials.
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.
IF: 5.460

Fuster V.
Prime time for a polypill after myocardial infarction?
IF: 5.970

Fuster V, Bansilal S.
JUPITER strikes earth.
IF: 5.970

Fuster V, Sanz J.
[Visualizing arterial macrophage warfare with nuclear magnetic resonance, positron-emission tomography and computerized tomography].
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.
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.
IF: 5.947

Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury.
IF: 27.550

Hidalgo A, Frenette PS.
When integrins fail to integrate.
IF: 27.550

Quantification of serial changes in plaque burden using multi-detector computed tomography in experimental atherosclerosis.
IF: 4.601

Quantification of serial changes in plaque burden using multi-detector computed tomography in experimental atherosclerosis.
IF: 4.601
IF: n/a

IF: 5.105

IF: 5.105

IF: 11.438

IF: 5.690

IF: 5.970

IF: 11.438

IF: 4.601

IF: 11.438

IF: 6.858

IF: 4.586
CARDIOVASCULAR DEVELOPMENTAL BIOLOGY


Appendix SCIENTIFIC REPORT ’09

Publications 2009


Moore LV, Diez Roux AV, Nettleton JA, Jacobs DR, Franco M.


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


TNT-alpha is required for the attraction of mesenchymal precursors to white adipose tissue in Ob/ob mice. *PLoS One* (2009) 4: e4444
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

Oxidized LDL, lipoprotein (a) and other emergent risk factors in acute myocardial infarction (FORTIAM study).
IF: 2.880

**Clinical profile of Trypanosoma cruzi infection in a non-endemic setting: immigration and Chagas disease in Barcelona (Spain).**
IF: 1.707

**Sanz G, Fuster V.**
Fixed-dose combination therapy and secondary cardiovascular prevention: rationale, selection of drugs and target population.
IF: 5.970

VASCULAR BIOLOGY AND INFLAMMATION

Macrophage oxygen sensing modulates antigen presentation and phagocytic functions involving IFN-gamma production through the HIF-1 alpha transcription factor.
IF: 6.000

**Alfranca A.**
VEGF therapy: a timely retreat.
IF: 5.947

*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.
IF: n/a

Barreiro O, Sanchez-Madrid F.
Molecular basis of leukocyte-endothelium interactions during the inflammatory response.
IF: 2.880

Cerезo A, Guadamillas MC, Goetz JG, Sanchez-Perales S, Klein E, Assion RK, del Pozo MA.
The absence of caveolin-1 increases proliferation and anchorage-independent growth by a Rac-dependent, Erk-independent mechanism.
IF: 5.942

Appendix

Publications 2009
IF: n/a

IF: 6.291

IF: 8.830

IF: 25.110

IF: 12.900

IF: 16.432

IF: 4.500

IF: 4.879

IF: 8.947

IF: 16.432

IF: 4.500

IF: 25.110

IF: 12.900

Appendix
Publications 2009
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IF: 6.858

IF: 10.432

IF: 35.420

IF: 31.434

IF: n/a

IF: 9.380

IF: 13.385

IF: 2.138

IF: n/a

IF: 3.848

IF: 1.510

IF: 4.371
Publications 2009

- **Domínguez F, Garrido-Gomez T, Lopez JA, Camafeita E, Quinonero A, Pellicer A, Simon C.**
  IF: 3.773

- **Fernández-Gonzalez R, Hourcade JD, Lopez-Vidriero I, Benguria A, Rodríguez De Fonseca F, Gutiérrez-Adan A.**
  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.**
  IF: n/a

- **Gómez A, Lopez JA, Pintos B, Camafeita E, Bueno MA.**
  IF: 4.590

  IF: 9.989

  IF: 2.530

- **Konstantinidou O, Khymenets O, Fito M, De La Torre R, Anglada R, Dopazo A, Covas MI.**
  IF: 1.140

- **Lucas D, Escudero B, Ligos JM, Segovia JC, Estrada JC, Terrados G, Blanco L, Samper E, Benad A.**
  IF: 8.880

- **Marrero-Díaz R, Bravo-Cordero JJ, Megías D, Garcia MA, Bartolome RA, Teixido J, Montoya MC.**
  IF: 2.625

- **Megías D, Marrero R, Martinez Del Peso B, Garcia MA, Bravo-Cordero JJ, Garcia-Grande A, Santos A, Montoya MC.**
  IF: 1.883


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


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

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<th>Department</th>
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<th>TOTAL IF Publications (*)</th>
<th>CUMULATIVE IF</th>
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(*) 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 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

<table>
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<tr>
<th>Name</th>
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<th>Comunidad Autónoma</th>
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<td>Barbón Fernández, Omar</td>
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<td>González de la Postilla-Concha, Carmen María</td>
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<td>Martí Gómez-Adaravi, Carlos</td>
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<td>Vale Varela, Cristian</td>
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<td>Galicia</td>
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### 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.
Fellowships in 2009

<table>
<thead>
<tr>
<th>Name</th>
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<td>Villarroya Beltrí, Carolina</td>
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</table>

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.
Fellowships in 2009

<table>
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<td>Izquierdo Fernández, Helena María</td>
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<td>Biochemistry</td>
<td>Autónoma de Madrid</td>
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</table>

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
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

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<td>González Calero, Laura</td>
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<td>Lozano Vidal, Noelia</td>
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<td>Peralta López, Marina</td>
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</table>
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

<table>
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<tr>
<th>Name</th>
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<th>University</th>
<th>CNIC Department</th>
<th>Thesis Advisor(s)</th>
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<td>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</td>
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<td>Cardiovascular Developmental Biology</td>
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<td>Ibiza Martínez, Sales</td>
<td>Óxido nítrico y respuesta inmune adaptativa: papel del NO en la activación de los linfocitos T</td>
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## Training Programs and Courses

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

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### Training Programs and Courses

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<tr>
<td>Moreno Rodríguez, Vanessa</td>
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<tr>
<td>Olmos Buchelt, Yolanda</td>
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<td>Rayón Alonso, Teresa</td>
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<td>Cardiovascular Developmental Biology</td>
<td>Autónoma de Madrid</td>
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</tbody>
</table>
### Training Programs and Courses

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Field</th>
<th>Institution Location</th>
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<tbody>
<tr>
<td>Roselló Díez, Alberto</td>
<td>FPI (Spanish Ministry of Education and Science)</td>
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<td>Sánchez Ramos, Cristina</td>
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<td>Sala Valdes, Mónica</td>
<td>FIS (Spanish Ministry of Health)</td>
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<td>Autónoma de Madrid</td>
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<tr>
<td>Silvestre Roig, Carlos</td>
<td>Mariano Losantos del Campo Foundation</td>
<td>Atherothrombosis and Cardiovascular Imaging</td>
<td>Valencia</td>
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<td>Tarín Cerezo, Carlos A.</td>
<td>FPI (Spanish Ministry of Education and Science)</td>
<td>Atherothrombosis and Cardiovascular Imaging</td>
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<td>Tejera Puente, Emilio</td>
<td>FIS (Spanish Ministry of Health)</td>
<td>Vascular Biology and Inflammation</td>
<td>Autónoma de Madrid</td>
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<td>Tomé Pizarro, María</td>
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<td>Autónoma de Madrid</td>
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<td>Uribe, Verónica</td>
<td>La Marató, TV3 Foundation</td>
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<td>Autónoma de Madrid</td>
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</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Arias Guedón, Teresa</td>
<td>Centro de Investigación Aplicada - Navarra</td>
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<tr>
<td>González Mirelis, Jesús</td>
<td>Hospital Puerta de Hierro - Madrid</td>
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<tr>
<td>Herranz Sánchez, Beatriz</td>
<td>Universidad de Alcalá - Madrid</td>
</tr>
<tr>
<td>Mateo de Castro, Jesús</td>
<td>Centro Nacional de Investigaciones Cardiovasculares - Madrid</td>
</tr>
<tr>
<td>Torrente Regidor, María</td>
<td>Universidad Autónoma - Madrid</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital</th>
<th>CNIC Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Núñez Gil, Iván Javier</td>
<td>Hospital Clínico San Carlos</td>
<td>Regenerative Cardiology</td>
</tr>
<tr>
<td>Vivas Balcones, David</td>
<td>Hospital Clínico San Carlos</td>
<td>Atherothrombosis and Cardiovascular Imaging</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>García Ruiz, José Manuel</td>
<td>Hospital Universitario Central de Asturias</td>
</tr>
</tbody>
</table>
**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

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**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**

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

---

**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
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 Martinez-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 Médica - Universidadd 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,
Beaton Institute, Glasgow, UK

Enrique Rodríguez-Boulán,
Weill 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

José 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
Seminar, 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 Clinic, 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 Scorrono,
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 Clinic, Barcelona, Spain

Antonio Zaza,
Università di Milano-Bicocca, Milano, Italy

Antonio Berruezo,
Hospital Clinic, 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

José C. 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

II Encuentro sobre Investigación Traslacional

Eulalia Roig,
Hospital Clínico, Barcelona, Spain

Pilar Martín,
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain

Manuel Pablo Anguita,
Hospital Reina Sofía, Córdoba, Spain
December

14 1er Curso teórico-práctico Virus Recombinantes

Básica y clínica
Principios y actualización de su empleo como vectores gênicos

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

Jose 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

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 doctoral thesis in the life sciences
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

Victor Mulero,
Department of Cell Biology and Histology Faculty of Biology, University of Murcia, Spain
Public-Private Partnership

In spite of the enormous advances in diagnosis and treatment witnessed over the last 20 years, cardiovascular diseases continue to be the main cause of death in the developed world. The costs generated in economic, social and human terms are immense. In response to this reality, the Spanish Government, through the Instituto de Salud Carlos III (Carlos III Health Institute) 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 Government and a group of some of the most important Spanish businesses. Under the terms of this agreement these companies pledged their commitment to funding the CNIC up until 2012. This commitment has 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.
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.
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.
Appendix

Staff Figures

CNIC staff 2009 (319)

<table>
<thead>
<tr>
<th>Research</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Departments</td>
<td>Technical Units</td>
</tr>
<tr>
<td>Administration</td>
<td>Scientific Services</td>
</tr>
</tbody>
</table>

CNIC scientific staff 2009 (271)
Staff Figures

Staff by department 2009 (216)

- Vascular Biology and Inflammation: 56
- Regenerative Cardiology: 70
- Cardiovascular Developmental Biology: 46
- Atherothrombosis and Cardiovascular Imaging: 30
- Cardiovascular Epidemiology and Population Genetics: 12
- Cardiovascular Translational Research: 2

Growth and current status

- Administration: 46
- Scientific Services: 12
- Technical Units: 18
- Departments: 7

New Building

2002: 46
2003: 63
2004: 87
2005: 89
2006: 82
2007: 129
2008: 142
2009: 216

Administration: 17
Scientific Services: 10
Technical Units: 10
Departments: 7

Total: 46
Staff Figures

Gender distribution 2009

- Female: 61%
- Male: 39%

Age distribution 2009

- <30: 35%
- 30-39: 27%
- 40-50: 34%
- >50: 4%

female, male
Addenda to Appendix
CNIC Scientific Report 2009

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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

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