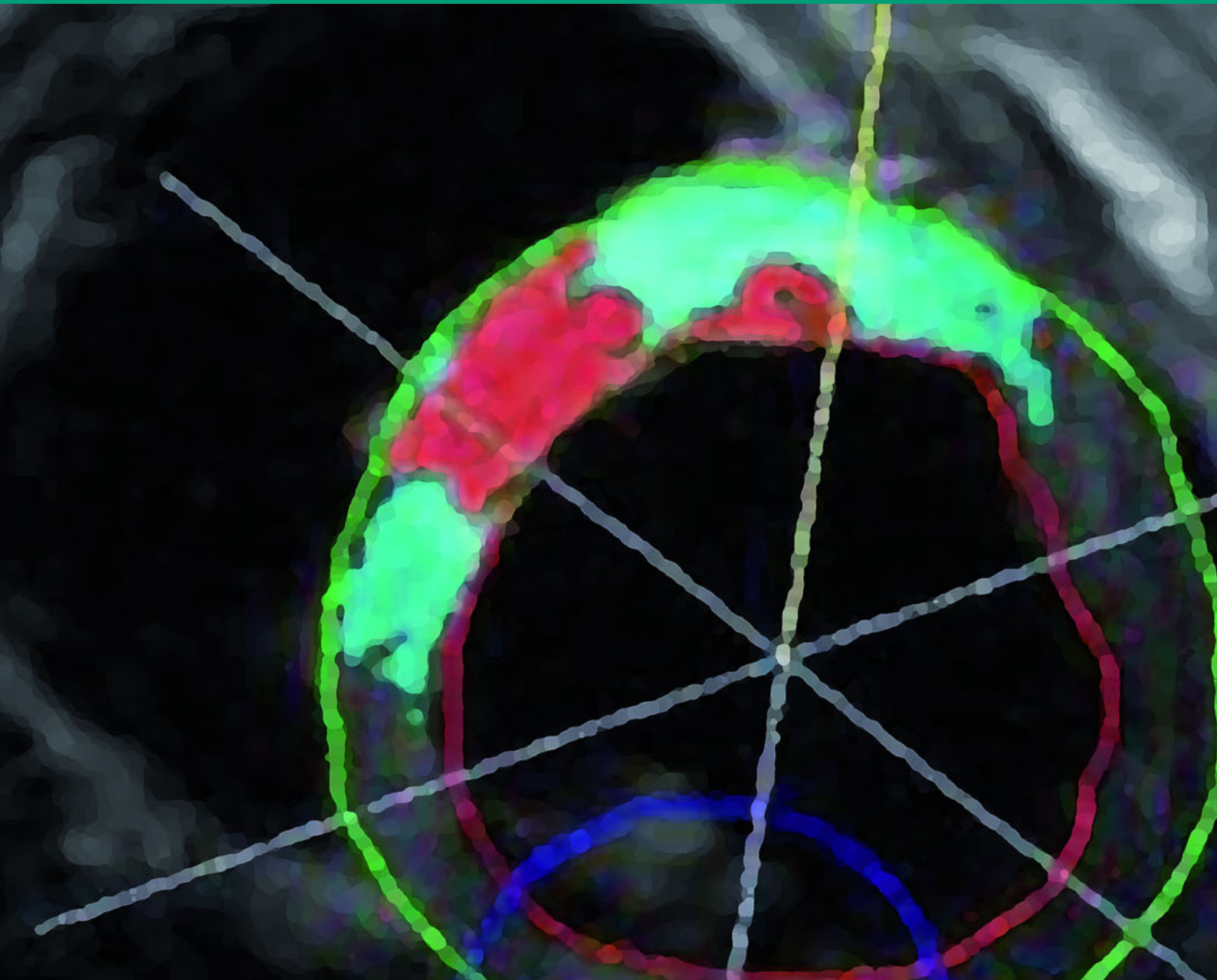
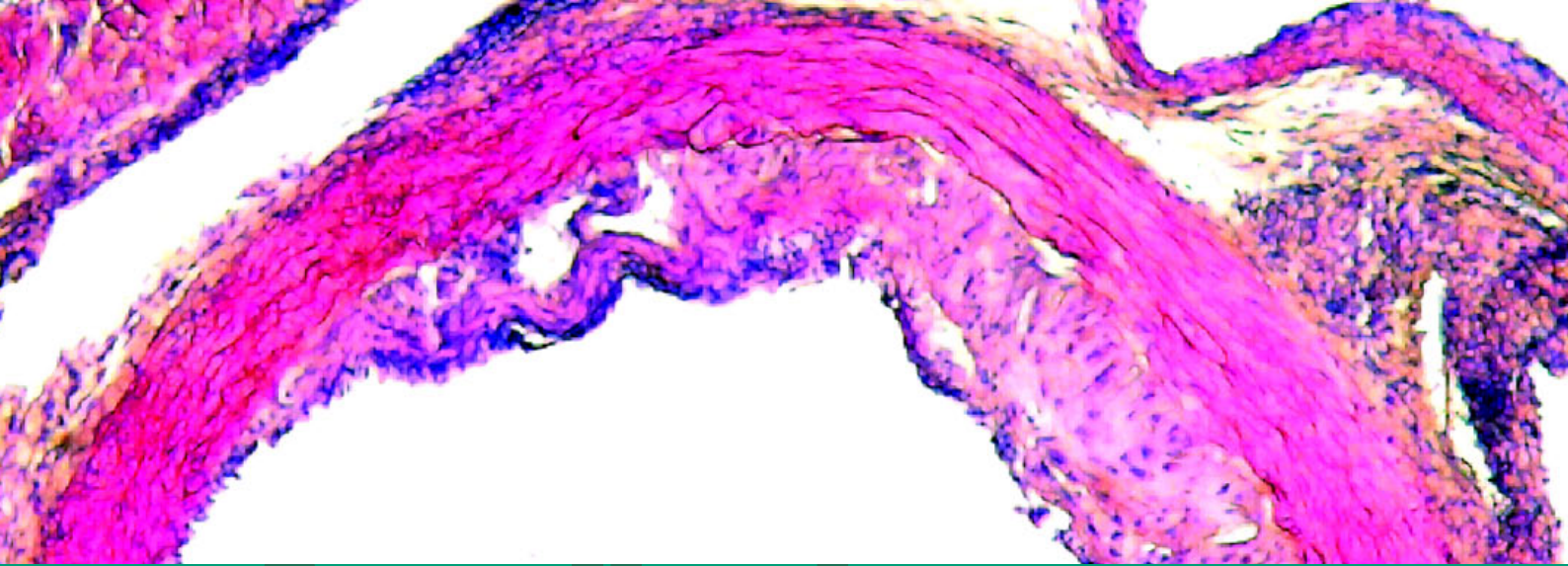


# Applied Research Departments

# 4

Epidemiology, Atherothrombosis and Imaging





# Applied Research Departments

## 4 Epidemiology, Atherothrombosis and Imaging

The EAI Department pools the expertise of molecular and cell biologists, cardiologists, epidemiologists, nutritionists, statisticians and physicists to develop and apply sophisticated non-invasive procedures for the investigation, diagnosis and treatment of cardiovascular diseases. Several groups work on the development of molecular-resolution imaging technologies and use them to investigate the molecular mechanisms underlying cardiovascular disorders. These imaging technologies can identify and characterize various types of atherosclerotic plaques, providing invaluable information on the underlying molecular mechanisms of disease and leading to tools for accurate diagnosis and targeted drug delivery. Our experimental strategy involves a multifaceted approach that combines *in vitro*, cellular, animal and human studies and a variety of technologies, including genetic engineering, proteomics, transcriptomics, and the most advanced imaging techniques. The epidemiology and genetics area integrates population studies with the results of basic and clinical research to identify environmental and genetic risk factors underlying the incidence, development and prognosis of cardiovascular disease.

**DEPARTMENT DIRECTOR:** *Valentín Fuster*

**DEPARTMENT MANAGER:** *Ana Isabel Castillo*

**ADMINISTRATIVE SUPPORT:** *Ana Gutiérrez*  
*Eeva Inari Soininen*

**TECHNICIANS:** *Javier Mateos*  
*Inés Ortega*

## Cardiovascular imaging

**Head of Laboratory:**

*Valentín Fuster (CNIC, Mt. Sinai Medical Center, New York)*

**Research Scientists:**

*Luis Jesús Jiménez Borreguero (CNIC - Hospital de la Princesa Research Agreement)  
Oliver Weber (CNIC, Philips)  
Zahi Fayad (Mt. Sinai Medical Center)  
Juan José Badimón (Mt. Sinai Medical Center)  
Jesús Mateo (CNIC)*

**Project Managers:**

*Laura García Leal  
Luz Alvarez Vilela*

**CardioImage Fellow:**

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

**Predocctoral Researchers:**

*Patricia García (CNIC)*

**Technicians:**

*Carolina Rojas Murcia  
Natalia Serrano Juzgado  
Isabel Pérez García  
Aurora del Barrio Mantecas  
Alberto Ávila Morales  
Ricardo Ponce Sánchez  
Sergio Cárdenas Melero*



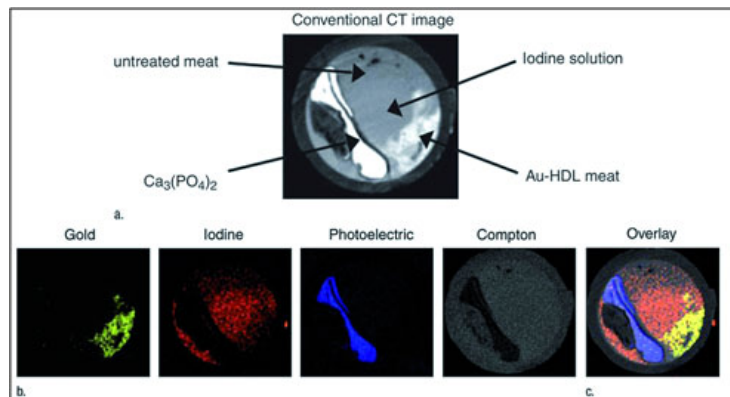
### RESEARCH INTEREST

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

Our work covers all of these aspects. Our preclinical work involves the use of positron emission tomography-computed tomography (PET/CT), molecular magnetic resonance imaging and other technologies to characterize plaque composition and development. We also lead the European Commission financed HYPERImage project, devoted to the development and validation of an integrated PET/MR system to substitute PET/CT technology. Last year the new Imaging Facility was established. This major installation, established through the CNIC's strategic alliance with Philips, is equipped with state-of-the-art imaging technology for animal studies at the main CNIC site, and further equipment for studies with patients at the nearby Carlos III Hospital. Aside from capabilities in echocardiography, computed tomography and magnetic resonance imaging, the facility will also be equipped with technology for magnetic particle imaging, a tomographic imaging technique developed by Philips that achieves resolutions finer than one millimeter.

We also participate in the CNIC's clinical studies of imaging technologies, working closely with the Epidemiology group and the Department of Translational Research. Our work in this area involves the use of novel imaging algorithms that can provide significant information for sensitive risk stratification in asymptomatic subjects. Highlights last year included the launch of the PESA-CNIC/Santander trial and the continuation of the AWHS study. These sibling studies examine the association of bioimaging parameters with the presence of genetic, epigenetic, metabolomic, proteomic and environmental factors in two populations with different characteristics. Examinations include include coronary calcium scoring by multidetector computed tomography scan (MDCT) and carotid and abdominal aorta 3D ultrasound. Participants in PESA showing evidence of atherosclerotic disease are studied in greater depth by MRI and PET/CT. Advanced non-invasive imaging analyses are also the main endpoints of the IMJOVEN and METOCARD-CNIC trials, into the the excess risk in young women with acute myocardial infarction and the cardioprotective effect of pre-reperfusion administration with the  $\beta$ -blocker metoprolol within the first two hours in patients with acute myocardial infarction.

# 4 Epidemiology, Atherothrombosis and Imaging



*Amira 3D reconstruction compiled from a confocal Z-stack of a random mosaic E9.5 heart. The image shows a ventral view of the heart tube, encompassing the outflow tract and the right and left ventricles. The cell distribution in the mosaic reveals the regional tissue deformation occurring during heart morphogenesis*



## MAJOR GRANTS

- European Commission FP7 (201651 HyperImage)
- European Commission FP7 (241559 FOCUS)
- Ministerio de Sanidad y Política Social. (EC10-042 Metocard, CNIC Translational Projects)
- Departamento de Salud y Consumo of the regional government of Aragon, General Motors Spain and CNIC (AWHS)
- NIH Grant (U01 HL-071988-01A1)
- NIH Grant (R01 HL-092989)
- NIH Grant (NHLBI-BAA-10-08)



## SELECTED PUBLICATIONS

[Fuster V.](#) Fine-tuning therapy for acute coronary syndromes. *N Engl J Med* (2010) 363: 976-7

[Fuster V.](#), Farkouh ME. General Cardiology Perspective: Decision making regarding revascularization of patients with type 2 diabetes mellitus and cardiovascular disease in the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial. *Circulation* (2010) 121: 2450-2

[Fuster V.](#), Bansilal S. Promoting Cardiovascular and Cerebrovascular Health. *Stroke* (2010) 41: 1079-83

Muntendam P, McCall C, Sanz J, Falk E, [Fuster V.](#); High-Risk Plaque Initiative. The Biolmage Study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease--study design and objectives. *Am Heart J* (2010) 160: 49-57

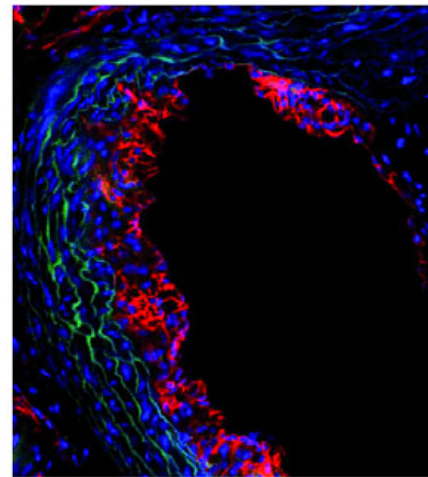
Sanz J, Moreno PR, [Fuster V.](#) The year in atherothrombosis. *J Am Coll Cardiol* (2010) 55: 1487-98.

*Molecular and genetic  
cardiovascular pathophysiology***Head of Laboratory:** *Vicente Andrés García***Postdoctoral Researchers:**  
*Raphaël Chèvre*  
*José Javier Fuster Ortuño*  
*José María González Granado*  
*Oscar Muñiz Pello*  
*Yafa Naim Abu Nabah Soriano*  
*José Rivera Torres*  
*Laia Trigueros Motos***Predocctoral Researchers:**  
*Pedro Molina Sánchez*  
*Ana Navarro Puche*  
*Carlos Silvestre Roig***Technicians:**  
*María Jesús Andrés Manzano*  
*Cristina González Gómez***RESEARCH INTEREST**

Accumulation of blood-borne leukocytes and their proliferation within the atherosclerotic plaque is a hallmark of atherosclerosis. During disease progression, inflammatory mediators produced by activated neointimal macrophages and lymphocytes induce the proliferation of vascular smooth muscle cells (VSMCs) and their migration towards the growing lesion. Moreover, accumulation of non-cellular material such as modified lipids and extracellular matrix components contributes 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. We use 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.

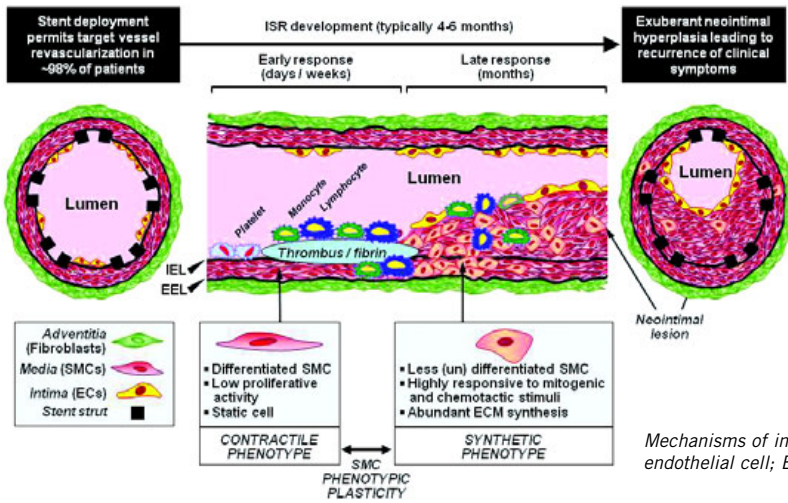
Specific projects in the lab include: 1) Characterization of the molecular and cellular mechanisms that control the development of vascular obstructive lesions in the setting of native atherosclerosis and *in-stent* restenosis; 2) Studies of the consequences of single nucleotide polymorphisms in cell-cycle regulatory genes for human susceptibility to *in-stent* restenosis and the underlying molecular mechanisms; and 3) Research into the role of nuclear lamins in the regulation of gene expression, age-associated cardiovascular disease and the immune response.



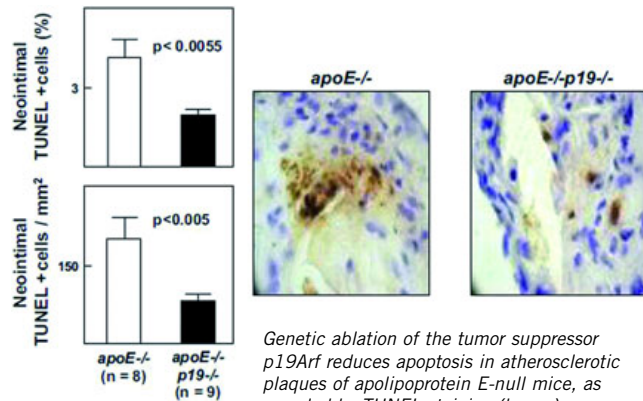
Adventitia Media Atheroma

*RhoA* activity in macrophages within an atherosclerotic plaque of an apolipoprotein E-null mouse, as revealed by phospho-ERM immunostaining (red).

# 4 Epidemiology, Atherothrombosis and Imaging



Mechanisms of in-stent restenosis (ISR). SMC, smooth muscle cell; EC, endothelial cell; ECM, extracellular matrix.



Genetic ablation of the tumor suppressor p19Arf reduces apoptosis in atherosclerotic plaques of apolipoprotein E-null mice, as revealed by TUNEL staining (brown).



## MAJOR GRANTS

- Ministerio de Ciencia e Innovación. FIS RETICS (RECAVA: RD06/0014/0021)
- Fundación Ramón Areces. Funds held at the CSIC
- Ministerio de Ciencia e Innovación (SAF2007-62110). Funds held at the CSIC



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Fuster JJ, Fernández P, González-Navarro H, Silvestre C, Naim Abu Nabah Y, Andrés V. Control of cell proliferation in atherosclerosis: Insights from animal models and human studies. *Cardiovasc Res* (2010) 86: 254-64

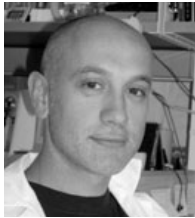
González-Navarro H, Naim Abu Nabah Y, Vinué A, Andrés-Manzano MJ, Collado M, Serrano M, Andrés V. p19<sup>Arf</sup> deficiency reduces macrophage and vascular smooth muscle cell apoptosis and aggravates atherosclerosis. *J Am Coll Cardiol* (2010) 55: 2258-68

Fuster JJ, González JM, Edo MD, Viana R, Boya P, Cervera J, Verges M, Rivera J, Andrés V. The tumor suppressor p27<sup>Kip1</sup> undergoes endo-lysosomal proteolysis through its interaction with sorting nexin 6. *FASEB J* (2010) 24: 2998-3009

Rodríguez J, Calvo F, González JM, Casar B, Andrés V, Crespo P. ERK1/2 MAP kinases promote cell cycle entry by rapid, kinase-independent disruption of retinoblastoma-lamin A complexes. *J Cell Biol* (2010) 191: 967-79

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

## Imaging cardiovascular inflammation and the immune response



**Head of Laboratory:** *Andrés Hidalgo Alonso*

**Postdoctoral Researchers:** *María Nacher Espuig*

**Predoctoral Researchers:** *María Casanova Acebes*

**Technician:** *Christophe Pitaval*

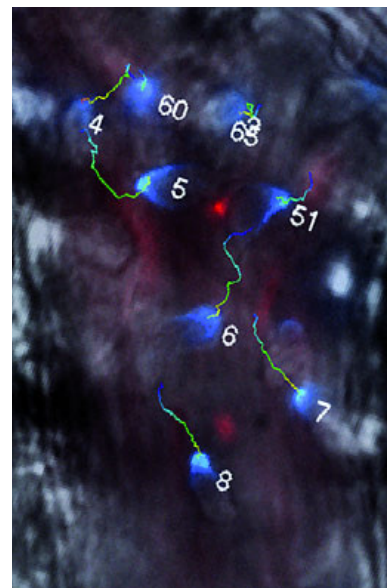


### RESEARCH INTEREST

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

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

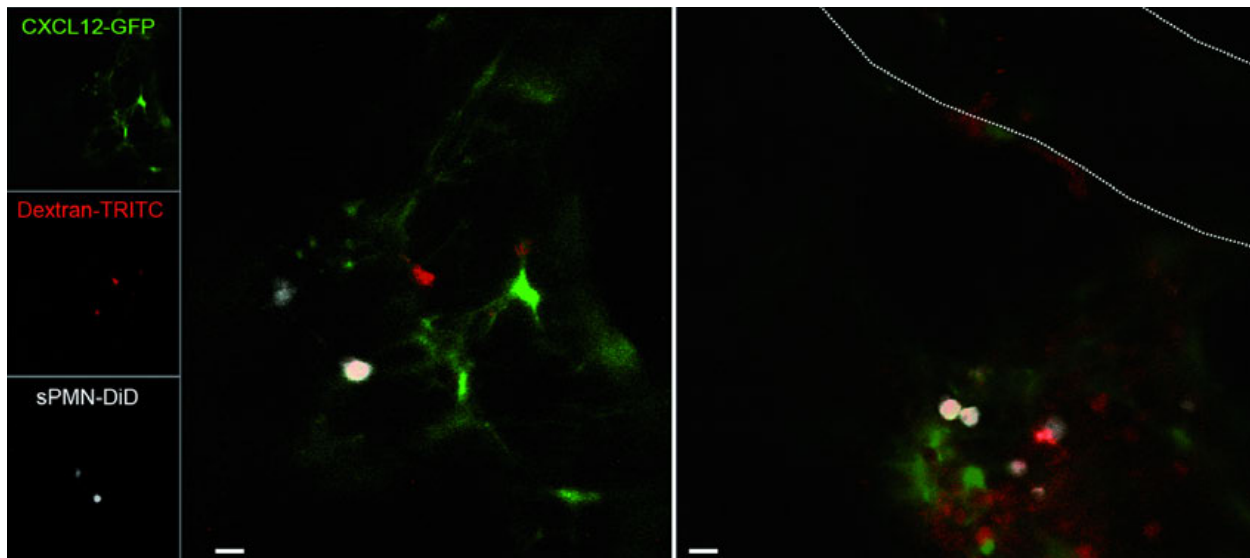
**Control of leukocyte production and release:** We are also interested in dissecting the links between inflammation and alterations in the bone marrow niches, the home of hematopoietic stem cells and their differentiated progeny. We are addressing this through the use of gene-targeted mouse models with alterations in the immune and hematopoietic compartments. 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 leukocyte behavior during inflammation.**

Neutrophils adhered to inflamed vessels move or "crawl" on the endothelium, a process mediated by activated  $\beta 2$ -integrins. Tracking the paths of these cells during one minute (colored lines) in the venules of mice provides an index of leukocyte activation status under different experimental or genetic conditions. Bar = 10  $\mu$ m.

## 4 Epidemiology, Atherothrombosis and Imaging



### **Interactions of phagocytes with the hematopoietic niche.**

*In vivo* imaging of the bone marrow of mice treated with senescent neutrophils (white). Macrophages are labeled with TRITC-Dextran (red) and niche cells—characterized by the production of high levels of CXCL12—are genetically tagged with GFP (green). We are interested in the interplay among these cells and its consequences during inflammatory injury and repair.



### MAJOR GRANTS

- MINISTERIO DE CIENCIA E INNOVACION (SAF2009-11037)
- MINISTERIO DE CIENCIA E INNOVACION (RYC-2007-00697)
- European Commission FP7 (246655 LEMPIT)
- NATIONAL INSTITUTES OF HEALTH (1RC1HL099545-01). co-PI, A. Hidalgo. Funds held at the Albert Einstein Institute, New York



### SELECTED PUBLICATIONS

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

[Hidalgo A and Frenette PS. When integrins fail to integrate. \*Nature Med\* \(2009\) 15: 249-50](#)

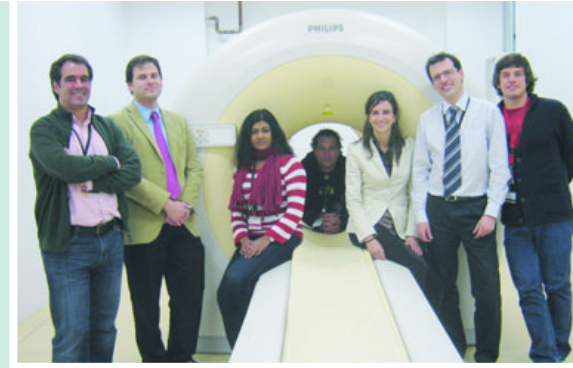
*Imaging in experimental cardiology*

**Head of Laboratory:** *Borja Ibáñez Cabeza*

**Postdoctoral Researchers:**  
*David Sanz-Rosa*  
*David Vivas Balcones*  
 (CNIC - Hospital Clínico San Carlos, Madrid)  
*Leticia Fernández Frieria*  
 (CNIC - Mt. Sinai Medical Center, New York, Hospital Marques de Valdecilla-IFIMAV, Santander)  
*Gonzalo Pizarro Sánchez*  
 (CNIC - Hospital Quirón Madrid)

**Predocctoral Researcher:** *Jaime García-Prieto*

**Technician:** *José Luis Martín Rivillo*

**RESEARCH INTEREST**

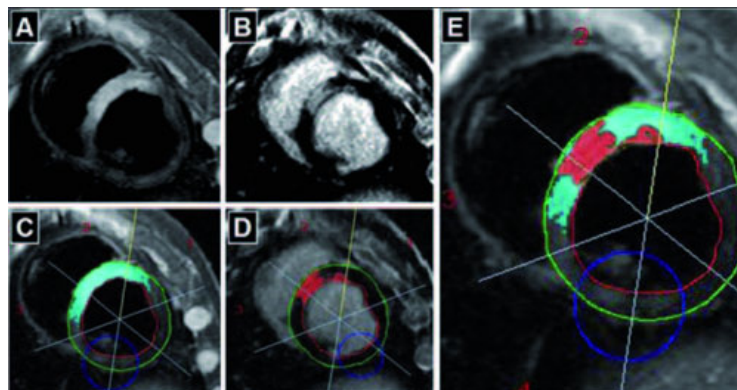
Our laboratory focuses on the development of experimental models of cardiovascular diseases in order to obtain knowledge on the mechanisms underlying the origin and progression of these diseases and to test the efficacy of novel interventions. Our studies span the molecular origins of disease and their manifestations at the macro anatomical and physiological levels, and our group comprises experts in molecular biology, clinical cardiology and cardiovascular imaging. Our evaluation of experimental animal models makes use of advanced imaging techniques that can also be applied to humans, strengthening the translational potential of our research. To exploit this potential, we work on multi-disciplinary programs in close collaboration with hospitals and clinical researchers.

One of our main interests is cardioprotection during myocardial infarction (MI). We have established different models of MI in rodents and large animals, and we are using

these to study the mechanisms underlying of the beneficial effects of various cardioprotective strategies (mainly those related to modulation of the adrenergic system).

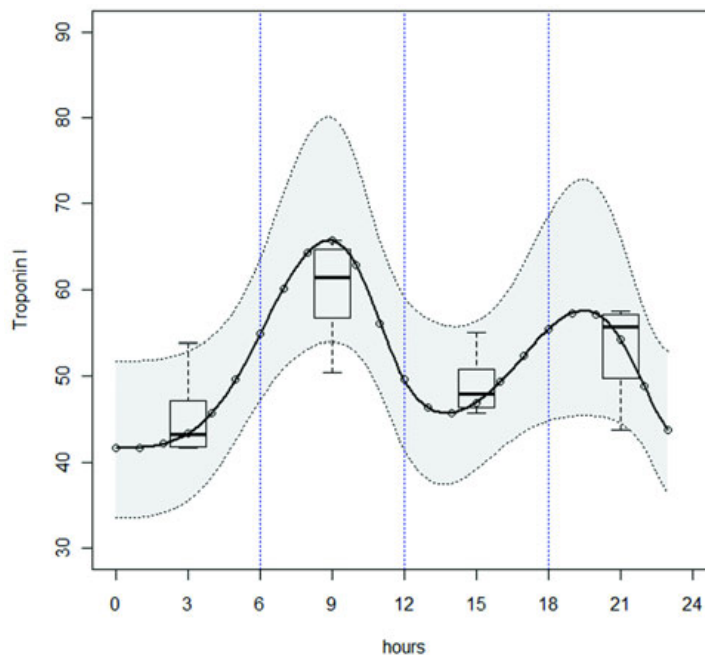
We also investigate the relationship between circadian oscillations and spontaneous cardioprotection. Our aim here is to exploit natural changes in the levels of salvage kinases, which have been shown to significantly affect infarct size.

Working closely with the Department of Translational Research, we are leading a clinical trial (METOCARD-CNIC), which uses magnetic resonance imaging to evaluate the effectiveness of a cardioprotective strategy based on beta adrenergic modulation in patients with a previous myocardial infarction. We also participate in European Commission funded HYPERImage project for the development of new imaging technologies.



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

## 4 Epidemiology, Atherothrombosis and Imaging



**Time-of-the-day of the onset of acute MI influences infarct size.** The spline regression curve shows clear circadian oscillations in infarct size that were independent of clinical variables. Patients suffering an MI during the dark-to-light transition have larger infarct sizes than those in whom ischemia begins at other times of day.



### MAJOR GRANTS

- Ministerio de Sanidad y Política Social FIC1 (EC10-042)
- Ministerio de Ciencia e innovación. FIS (PI10/02268)



### SELECTED PUBLICATIONS

Cimmino G, Ibáñez B, Giannarelli C, Prat-González S, Hutter R, García M, Sanz J, Fuster V, Badimon JJ. **Carvedilol administration in acute myocardial infarction results in stronger inhibition of early markers of left ventricular remodeling than metoprolol.** *Int J Cardiol* (accepted)

Ibáñez B, Fuster V. **Ischaemic conditioning for myocardial salvage after AMI.** *Lancet* (2010) 375: 1691; author reply 1692

Speidl WS, Cimmino G, Ibáñez B, Elmariah S, Hutter R, García MJ, Fuster V, Goldman ME, Badimon JJ. **Recombinant apolipoprotein A-I Milano rapidly reverses aortic valve stenosis and decreases leaflet inflammation in an experimental rabbit model.** *Eur Heart J* (2010) 31: 2049-57

Badimón JJ, Ibáñez B. **Increasing High-Density Lipoprotein as a Therapeutic Target in Atherothrombotic Disease.** *Rev Esp Cardiol* (2010) 63: 323-33

Ibáñez B, Cimmino G, Prat-González S, Vilahur G, Hutter R, García MJ, Fuster V, Sanz J, Badimon L and Badimon JJ. **The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion.** *Int J Cardiol* (accepted)

## Vascular wall remodeling and cardiovascular disease



**Head of Laboratory:** Carlos Zaragoza Sánchez

**Postdoctoral Researcher:** Beatriz Herranz Sánchez

**Predoctoral Researchers:** Begoña Lavin Plaza  
Carlos Tarín

**Technician:** Mónica Gómez Parrizas



### RESEARCH INTEREST

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

The following projects are currently running in our laboratory.

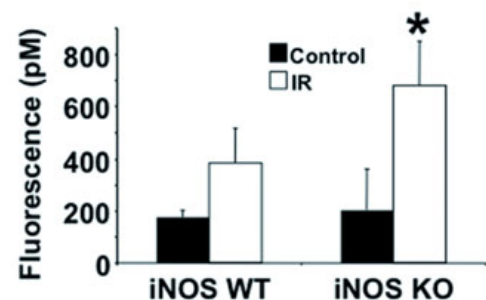
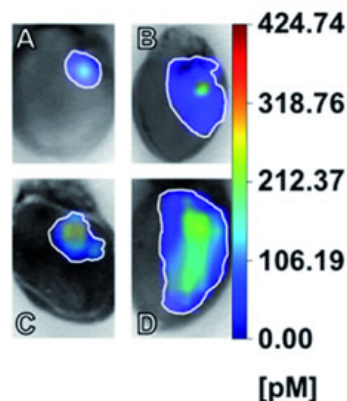
1) Identification of molecular determinants involved in the development, progression, and rupture of abdominal aortic aneurysms (AAA) and the development of new molecular imaging tools for noninvasive detection.

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.

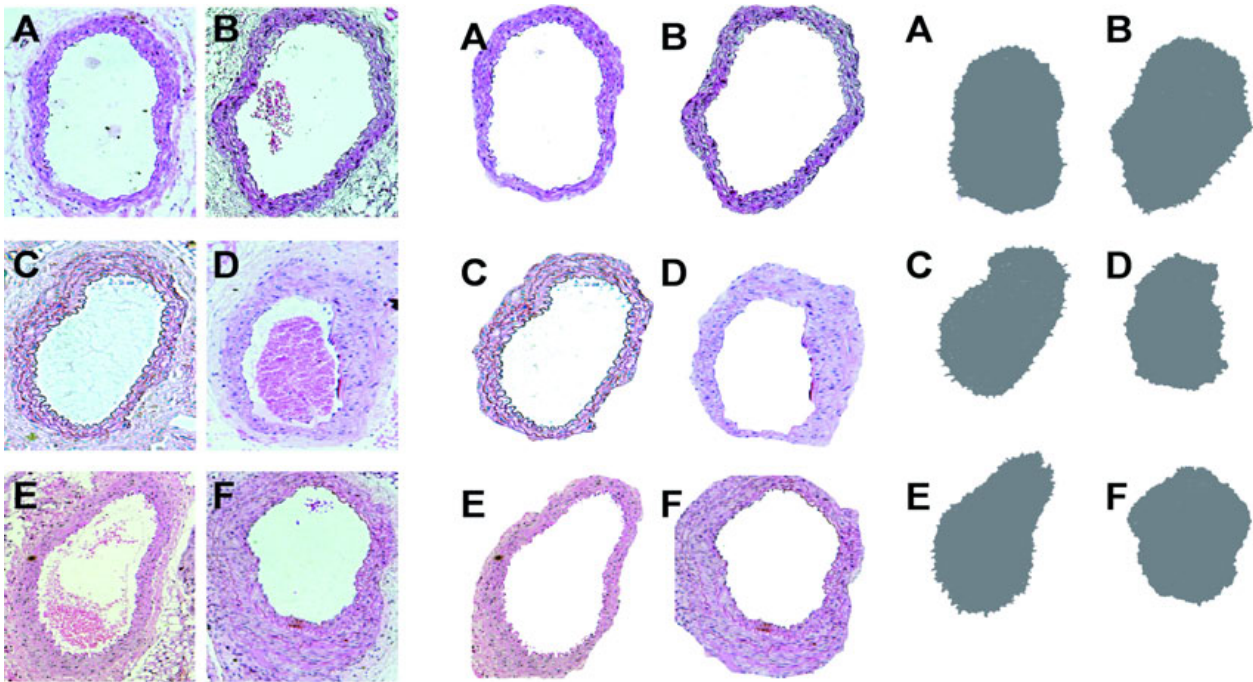
3) Identification of molecular determinants responsible for cardioprotection during late ischemic preconditioning, with the aim of devising noninvasive strategies for in vivo molecular imaging detection of myocardial infarction biomarkers by nanoparticle technology coupled with magnetic resonance.

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

**Noninvasive molecular imaging detection of collagen by magnetic resonance in abdominal aortic aneurysms.** **A**, Sagittal image acquired by magnetic resonance at time 0 in a mouse injected with nanoparticles conjugated to peptide EP-3553. **B**, Image acquired at 24 h. Insets show magnified views of the abdominal aorta. **C and D**, Similar images from mice injected with nanoparticles conjugated to a scramble peptide.

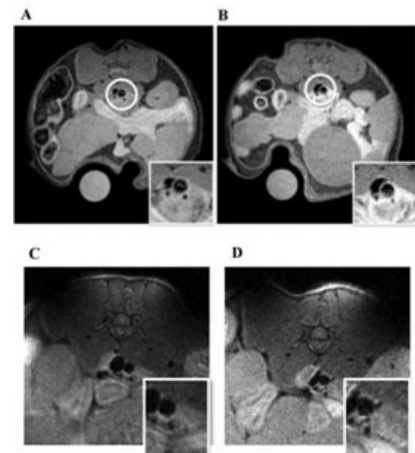


## 4 Epidemiology, Atherothrombosis and Imaging



**Lack of iNOS increases myocardial damage during ischemia/reperfusion.** iNOS wild type (A, B) and iNOS knockout (KO) mice were injected with the cathepsin-B probe Prosense-680 and either mock operated (A,C; control) or subjected to left coronary artery ischemia/reperfusion (B,D; IR). The images show representative fluorescence molecular tomography detection of cathepsin-B in hearts isolated postmortem. The chart shows results from  $x$  mice (\*  $p < 0.05$  iNOS WT IR vs iNOS KO IR).

**eNOS-deficient mice show significantly greater neointimal thickening than wild type mice in response to in vivo aortic endothelial denudation.** Left panels show serial sections of aortas extracted with increasing time after wire-mediated endothelial denudation. The middle panels show the smooth muscle cells in isolation. The right panels show the lumen area.



### MAJOR GRANTS

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



### SELECTED PUBLICATIONS

Zaragoza C, Ibañez B, Jiménez-Borreguero LJ, Schulz V, Fayad Z, Fuster V. Future perspectives in cardiovascular imaging: Simultaneous PET/MRI technology in biomedical research. *Nat Rev Cardiol* (CNIC Edition) (2010) 7: 7-10

Saura M, Tarin C, Zaragoza C. Recent Insights into the implication of nitric oxide in bone development. *Sci World J* (2010) 10: 624-32

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

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

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

## CNIC-JHU COLLABORATIVE PROGRAM: *Epidemiology and population genetics*



<b>Program Director:</b>	<i>Eliseo Guallar</i>
<b>Senior Researcher:</b>	<i>José M<sup>a</sup> Ordovás (CNIC - Tufts University Research Agreement)</i>
<b>Research Scientists:</b>	<i>Manuel Franco José Luis Peñalvo Martín Laclaustra</i>
<b>Post-residency Researcher:</b>	<i>María Téllez</i>
<b>Biostatistician:</b>	<i>Pedro López</i>
<b>Support Scientist:</b>	<i>Marta Ledesma Laura García</i>
<b>Technicians:</b>	<i>Alicia Usón Belén Moreno Raquel Langarita Esther Rovira Damaris Tamayo</i>

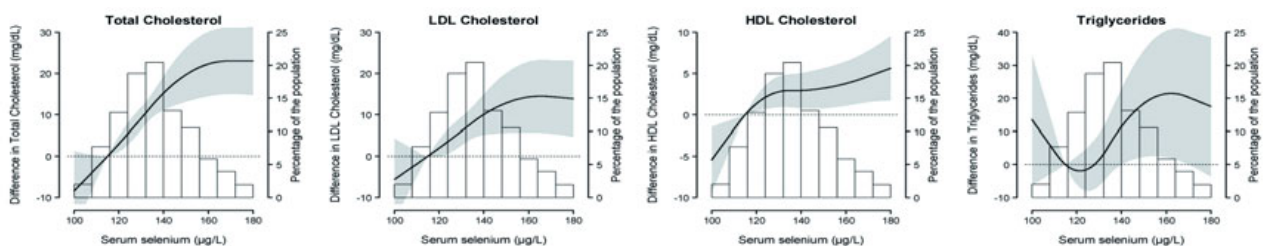


### RESEARCH INTEREST

The group conducts high-quality and high-impact population research studies into the environmental, individual and genetic risk factors that are causally related to cardiovascular disease. The group works closely with Department of Translational Cardiovascular Research in the design of clinical studies and the analysis of population data from advanced imaging methodologies. We are deeply involved in the Aragon Workers Health Study (AWHS). Enrollment was completed in 2010, with 5589 workers recruited, a response rate of 95%. Follow-up is continuing as scheduled, and in 2011 we will commence measurement of subclinical atherosclerosis in the cohort. The group also plays a major role in the planning of the PESA (Progression of Subclinical Atherosclerosis) study, that started in 2010 and has already recruited over 500 participants, and in the IMJOVEN study, which has recruited over 300 young women who have suffered a myocardial infarction. The members of the group also continue to make significant contributions to leading international studies such as the Framingham Heart Study,

the Atherosclerosis Risk in Communities (ARIC) Study, the Multiethnic Study of Atherosclerosis (MESA), the Strong Heart Study, the US National Health and Nutrition Examination Survey, and the UK National Diet and Nutrition Survey.

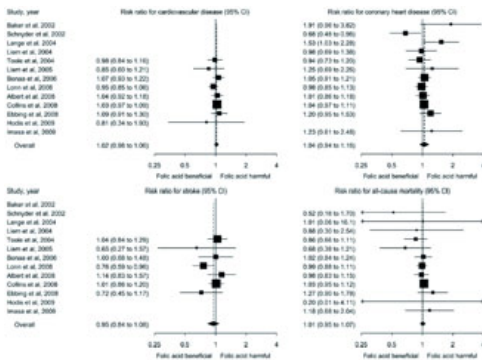
Members of the group pursue highly innovative research lines that cover the major risk factors for cardiovascular disease, including diet (Ordovás, Guallar, Franco, Laclaustra, Peñalvo), genetics and epigenetics (Ordovás, Téllez), metabolic factors (Ordovás, Laclaustra, Peñalvo), the environment (Guallar,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



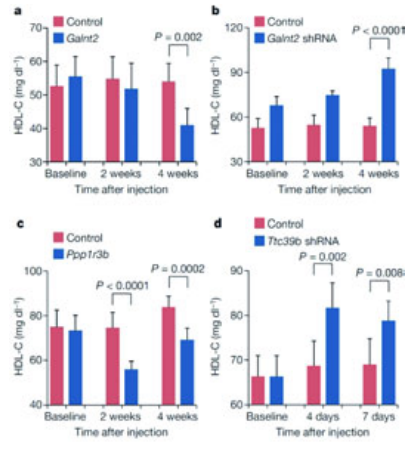
#### **Adjusted differences (95% CI) in serum lipids by serum selenum concentrations in the US population (NHANES 2003-2004)**

Models were adjusted for sex, age, race, education, body mass index, smoking, cotinine, postmenopausal status, cholesterol, total fat, saturated fatty acids, selenum intake, and use of vitamin and mineral supplements. Lipid concentrations at the 10th percentile (115 microg/L) of the serum selenum distribution were used as reference. The histograms show the distribution of selenum concentrations in the study population.

# 4 Epidemiology, Atherothrombosis and Imaging



**Risk ratios and pooled estimates for cardiovascular disease, coronary heart disease, stroke, and all-cause mortality in randomized controlled trials of folic acid supplementation**  
 The area of each square is proportional to the study weight in the analysis. Pooled estimates (diamonds) and 95% CIs (horizontal lines) were obtained from inverse-variance weighted random-effects models.



**Effects of altered Galnt2, Ppp1r3b or Ttc39b expression in mouse liver on plasma lipid levels**  
 Charts show plasma HDL-C levels at baseline and at the indicated times after injection with viral vectors. a, Overexpression, and b, knockdown of Galnt2; n = 56 mice per group. c, Overexpression of Ppp1r3b; n = 57 mice per group. d, Knockdown of Ttc39b. n = 56 mice per group. Error bars show standard deviations. Since independent experiments were performed at different times or sites, baseline HDL-C levels varied.

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