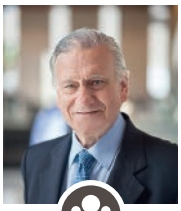


RESEARCH AREAS

TRANSLATIONAL COORDINATION

1. Myocardial Pathophysiology
2. Vascular Pathophysiology
3. Cell and Developmental Biology



Cardiovascular imaging and population studies



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RESEARCH INTEREST

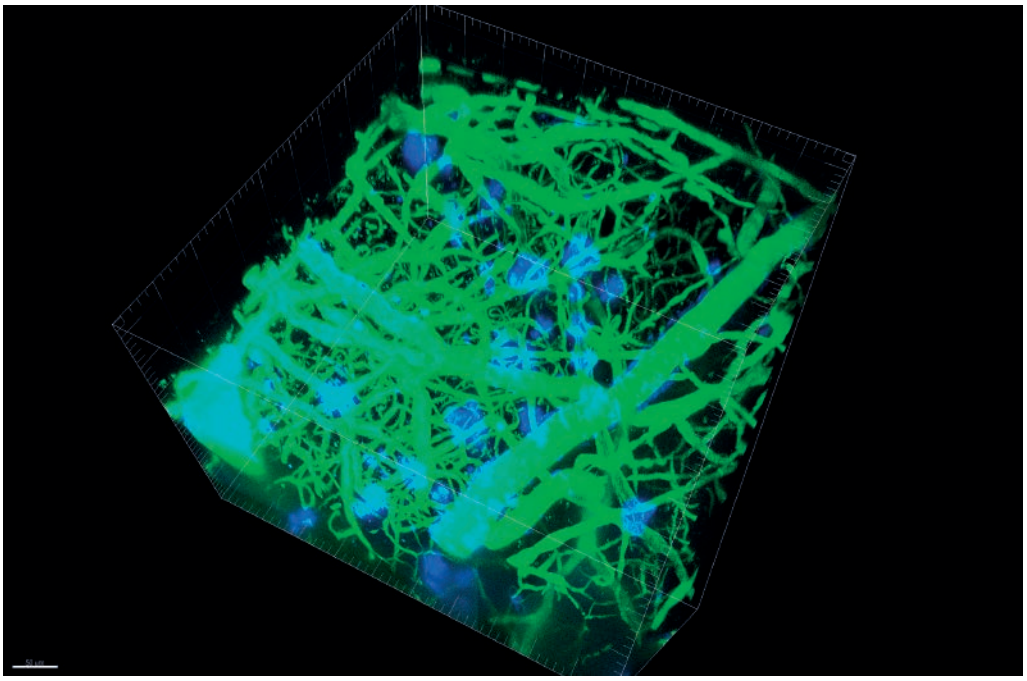
Our multidisciplinary research group brings together investigators from basic to clinical research, promoting collaboration between experts from different disciplines. This unique mix of professionals from different fields creates a fertile environment that maximizes the translational potential of our research, which centers on clinical studies for cardiovascular prevention by using the latest advanced imaging methodologies. We believe that early prevention is the key to winning the battle against cardiovascular diseases (CVD), and this conviction underpins our leadership of several educational programs promoting healthy habits in children (Program SI!) and adults (50/50 Project, in collaboration with the *Observatorio de la Nutrición y de Estudio de la Obesidad*).

Our research covers major CVD risk factors including diet, exercise, genetics and epigenetics, metabolic factors, the environment, and psychosocial factors. These themes are combined in the development and research application of advanced noninvasive imaging technologies for the early diagnostic and prognostic assessment of atherosclerosis. We are central participants in the CNIC's major population studies: PESA (Progression of Early Subclinical Atherosclerosis), TANSNIP (Trans-Atlantic Network to Study Stepwise Noninvasive Imaging as a Tool for Cardiovascular Prognosis and Prevention), SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly Population, an EU Horizon2020-funded continuation of research into the successful Fuster-CNIC-Ferrer polypill concept), and SPHERE (testing the efficacy of a novel therapy discovered at the CNIC for the treatment of pulmonary hypertension).

In our newest research line, we are using advanced imaging techniques to analyze the damaged cerebral vasculature in the Alzheimer's disease (AD). The delivery of oxygenated blood, glucose, and nutrients to the brain is essential for correct cerebral function, and therefore any disruption to the cerebral vasculature plays a fundamental role in the progression of neurological disorders. We are using PET and MRI to develop new imaging tools to noninvasively identify the composition and origin of vessel obstructions in the AD brain, which are partly responsible for the brain hypoperfusion found in this disease. We perform these studies in different animal models of AD, including transgenic mouse models and also large animals, providing the study with important translational applicability.



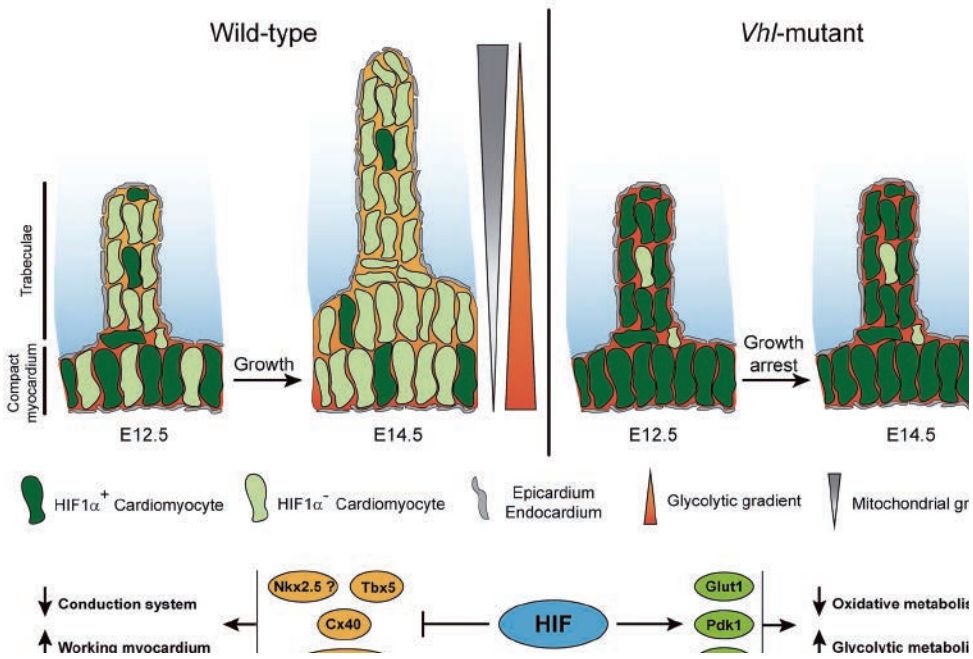
Recruitment map for the SECURE trial.



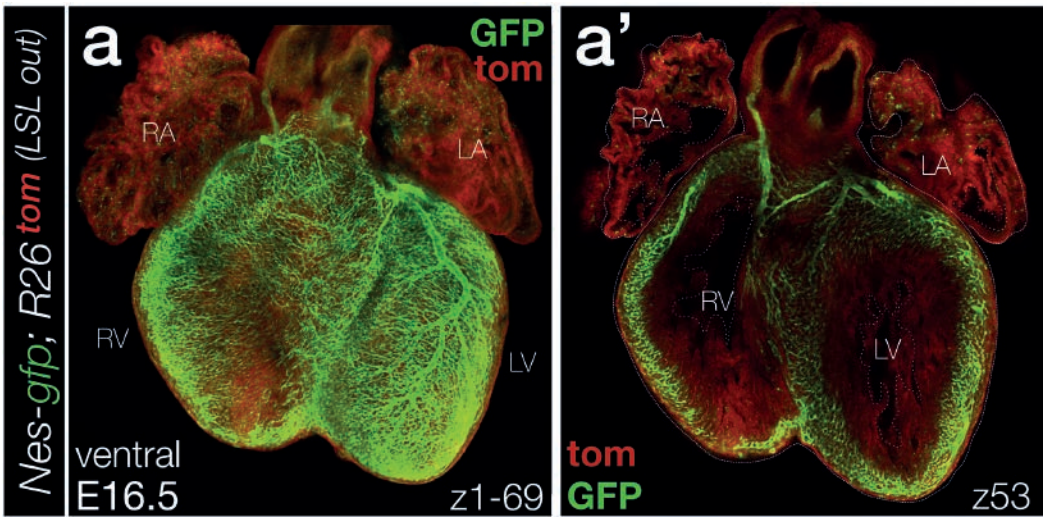
Brain vasculature in Alzheimer's disease (AD). Cranial windows were opened over the cortex of AD mice. Blood flow (green) and amyloid deposits (blue) were visualized *in vivo* with a two-photon microscope. 3D reconstruction of a Z-stack acquisition shows the first 400 µm of the mouse cerebral cortex. Blood vessels in the brain of AD mice are surrounded by cerebral amyloid angiopathy and by amyloid plaques in the brain parenchyma.

Another independent research line in the group, led by Dr. Silvia Martín Puig, examines the role of oxygen homeostasis in the cardiovascular system. Our goal is to understand the function of hypoxia inducible transcription factors (HIFs) in heart development and disease. Using novel genetic tools, we have determined the critical roles played by HIF1 and VHL in delineating discrete metabolic territories during cardiac development; these metabolic territories are essential for proper ventricular chamber formation and maturation and the correct establishment of cardiac conduction system. Our results link the hypoxia pathway to cardiac function and metabolism, and may have therapeutic implications in the setting of ischemic heart disease and cardiomyopathies when HIF1 is reactivated upon oxygen deprivation. We are currently characterizing the phenotype of additional mouse models to evaluate the role of VHL/HIFs in the formation and stability of the coronary vascular network, and are examining possible connections between the observed defects and human congenital heart disease.

Another independent research line in the group, led by Dr. Joan Isern, is mainly interested in tissue organogenesis, focusing on the mammalian cardio- & hemato-vascular systems. Our team is currently investigating how the coronary vasculature is assembled during cardiac development, using both in vitro and in vivo genetic murine models and high-resolution imaging approaches.



Myocardial VHL-HIF signaling controls an embryonic metabolic switch essential for cardiac maturation. Model illustrating how spatiotemporal activation of VHL/HIF signaling within the developing myocardium delineates metabolic compartments with an enhanced glycolytic signature in the compact myocardium, compared with increased mitochondrial activity in midgestation trabeculae. Sustained HIF1 activation results in ventricular chamber defects, cardiac dysfunction, and altered expression of conduction system genes (Menendez-Montes et al. Dev Cell 2016).



High-resolution imaging of intact tissue-clarified hearts. (a) Whole-mount view of E16.5 mouse heart. The image (ventral side) is resulting from a max-intensity projection over a 0.5-mm-thick volume dataset (composed by 69 individual optical sections); GFP marks the developing coronary vessels. (a') Selected single optical plane from the z-stack at the indicated depth. Inner cardiac cavities and intramyocardial coronary endothelium can be appreciated.

MAJOR GRANTS

- H2020-PHC-2014-two-stage (GA633765). PI: V. Fuster
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- NIH/NIHLBI RO1. Collaborator: V. Fuster
- PESA CNIC-Santander. PI: Fuster V.
- Ayudas proyectos investigación La Marató. (Subproject 20151731) PI: V. Fuster
- FP7-PEOPLE-2013-IIF (GA 624811). PI: M. Cortés
- Instituto de Salud Carlos III (PI13/02339). PI: A. García
- Instituto de Salud Carlos III (PI15/02019). PI: L. Fernández-Friera
- Ministerio de Ciencia e Innovación. FIS (CP09/00100). PI: S. Martín Puig
- Ayudas proyectos investigación La Marató. (Subproject 20150731). PI: S. Martín Puig
- Ministerio de Economía y Competividad (BFU2012-35892). PI: J. Isern
- Ministerio de Economía y Competividad (RYC-2011-09209). PI: J. Isern

SELECTED PUBLICATIONS

Fuster V, Ibanez B, Andres V. The CNIC: a successful vision in cardiovascular research. *Circ Res* (2016) 119: 785-9

Arbab-Zadeh A, Fuster V. **The risk continuum of atherosclerosis and its implications for defining CHD by coronary angiography**. *J Am Coll Cardiol* (2016) 68: 2467-78

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Fernandez-Friera L, Penalvo JL, Fernandez-Ortiz A, Ibanez B, Lopez-Melgar B, Laclaustra M, Oliva B, Mocoroa A, Mendiguren J, Martinez de Vega V, Garcia L, Molina J, Sanchez-Gonzalez J, Guzman G, Alonso-Farto JC, Guallar E, Civeira F, Sillesen H, Pocock S, Ordovas JM, Sanz G, Jimenez-Borreguero LJ, Fuster V. **Prevalence, vascular distribution and multi-territorial extent of subclinical atherosclerosis in a middle-aged cohort: The PESA (Progression of Early Subclinical Atherosclerosis) study**. *Circulation* (2015) 131: 2104-13

Álvarez S, Diaz M, Flach J, Rodriguez.Acebes J, Lopez-Contreras A, Martinez D, Canamero M, Fernandez-capetillo O, Isern J, Passegué E and Méndez J. **Replication stress caused by low MCM expression limits fetal erythropoiesis and hematopoietic stem cell functionality** *Nature Communications* (2015) 6:8548.