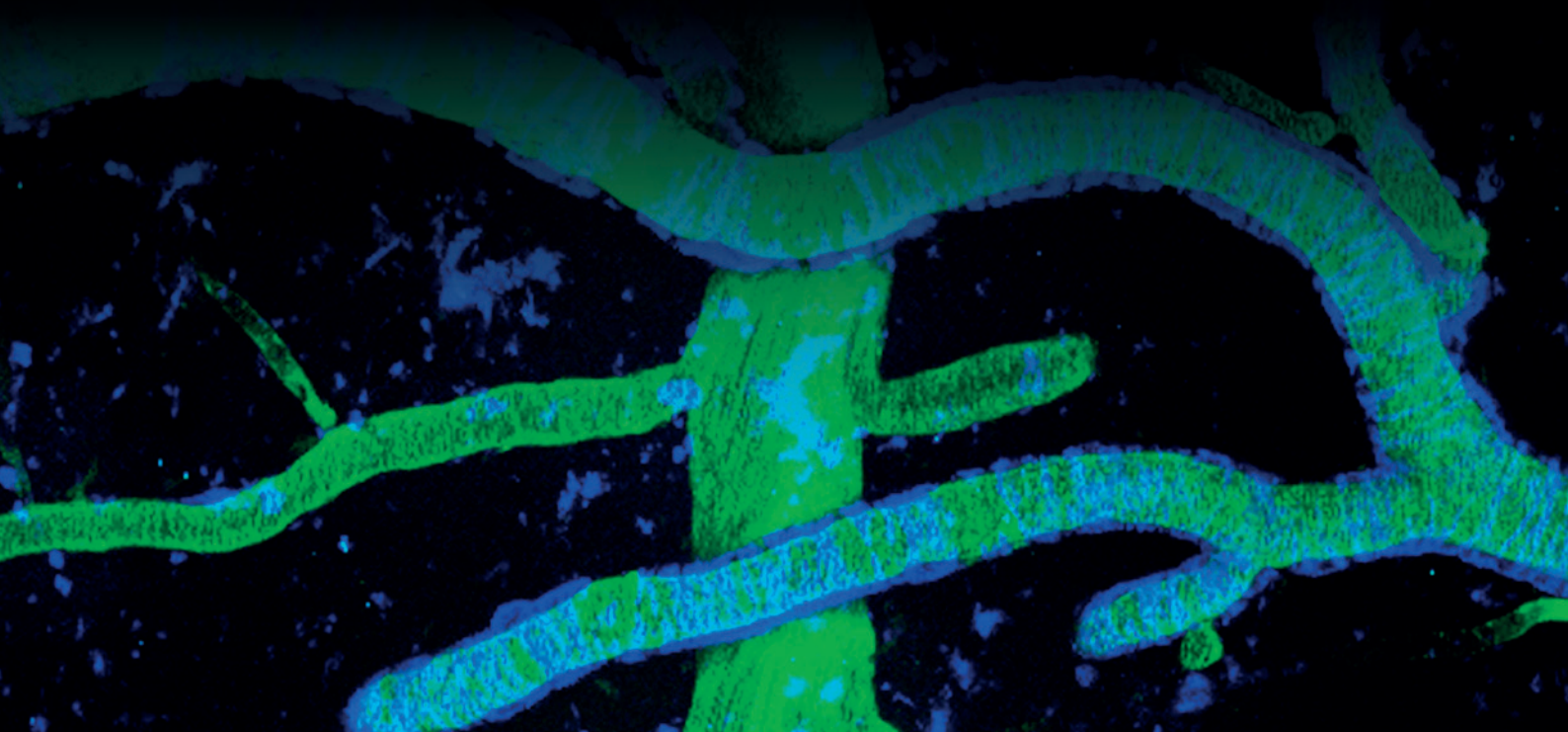
Translational Coordination



Cardiovascular imaging and population studies

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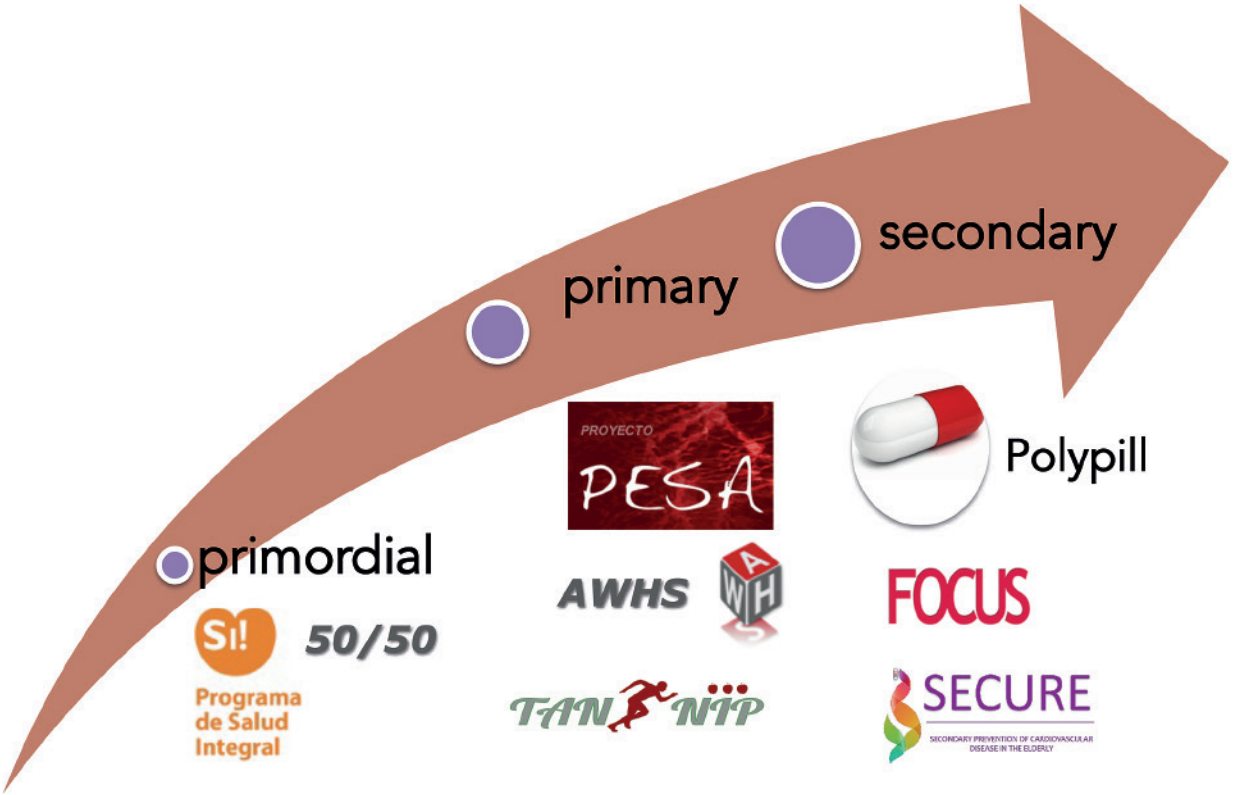
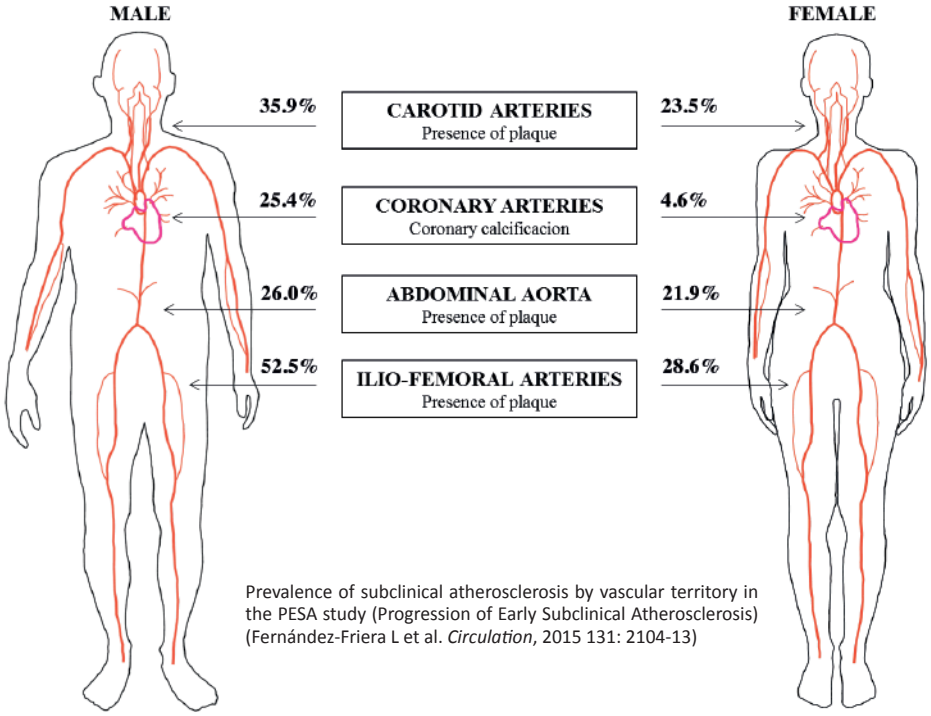
RESEARCH INTEREST

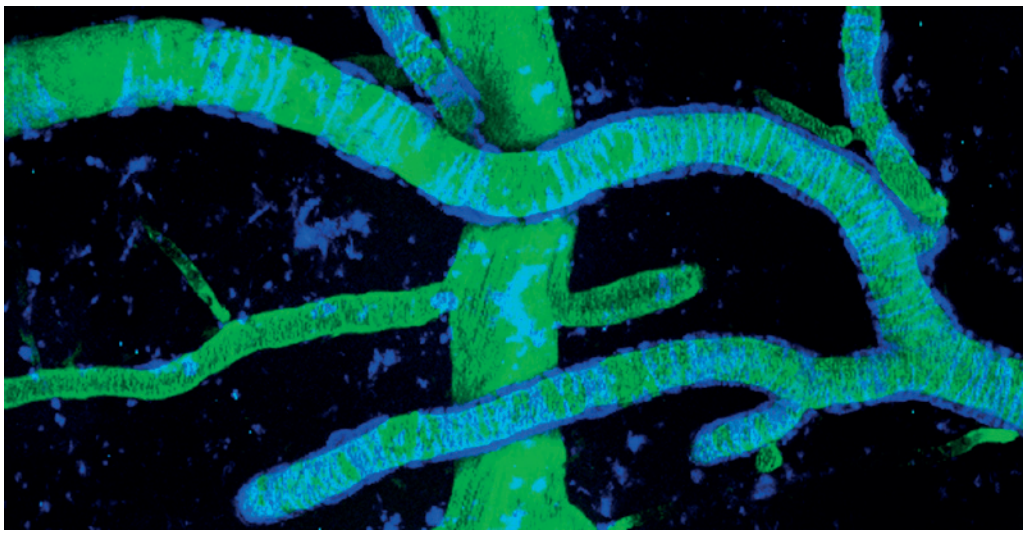
We are a highly multidisciplinary research group dedicated to conducting clinical studies for cardiovascular prevention using the latest advances in advanced imaging. Our research covers major CVD risk factors including diet, exercise, genetics and epigenetics, metabolic factors, the environment, and psychosocial factors. This work goes hand in hand with the development and research application of noninvasive, advanced imaging technologies for the early diagnostic and prognostic assessment of atherosclerosis. The group participates in the CNIC´s major population studies PESA (Progression of Early Subclinical Atherosclerosis), AWHS (Aragon Workers Health Study), 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). We are also involved in educational programs to promote healthy habits for cardiovascular prevention in children (Program SI!), and adults (50/50 Project, in collaboration with the *Observatorio de la Nutrición y de Estudio de la Obesidad*). Our most recent research line focuses on analyzing the vascular component present in Alzheimer disease (AD). The evidence indicates the presence of increased thrombosis, decreased fibrinolysis and a higher number of obstructed blood vessels in the AD brain. We use in vivo noninvasive imaging (PET, MRI) on small and large animal models to identify these phenomena in the AD brain. Chronic heart failure is recognized as a cause of cerebral hypoperfusion and dementia, establishing the fundamental importance of heart-brain integration in health and disease.



Research and educational programs for cardiovascular prevention from infancy to adulthood



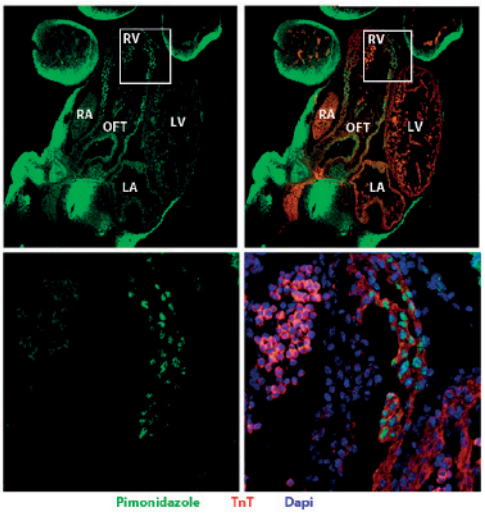
Prevalence of subclinical atherosclerosis by vascular territory in the PESA study (Progression of Early Subclinical Atherosclerosis) (Fernández-Friera L et al. *Circulation*, 2015 131: 2104-13)



Brain vasculature in Alzheimer disease (AD). Cranial windows were opened over the cortex of AD mice. Blood flow (green) and amyloid (blue) were visualized in vivo with a two-photon microscope. Blood vessels in the brain of AD mice are surrounded by cerebral amyloid angiopathy and by amyloid plaques in the brain parenchyma (Modified from Cortes-Canteli M et al. *Neuron* 2010 66: 695-709)

Another research line within the group is led by Dr Silvia Martín Puig. Hypoxia and HIF factors are proposed to play an important role in heart development and cardiovascular diseases, but the underlying molecular mechanisms and the cell populations involved in these processes remain largely unkown. Our main goal is to understand the role of the VHL-HIF pathway in cardiovascular homeostasis, with particular interest in heart development and homeostasis. We have generated several gain and loss of function mouse models of the hypoxia pathway, paying special attention to early cardiovascular populations that contribute to the various cell types of the mature heart. Using these genetic tools, we are interrogating whether changes in oxygen tension influence mammalian cardiogenesis. Our data indicate that hypoxia, through the VHL-HIF axis, is essential for the correct development of the ventricular chambers, myocardium maturation and the homeostasis of the coronary vasculature. We are currently unraveling the molecular mechanisms and functional adaptations underlying the phenotypes found in the different models generated, and we are analyzing the transcriptional responses mediated by HIF factors. We believe that our research has potential therapeutic applications and will help to elucidate the role of low oxygen tension and VHL-HIF signaling in congenital heart disease, opening up new perspectives in the arena of translational medicine.

Translational Coordination



Hypoxic regions at mid cardiogenesis. Representative E10.5 mouse heart sections showing low oxygen areas stained with the hypoxia probe pimonidazole (green) within the developing myocardium stained by immunofluorescence for troponin T (TnT, red). The pimonidazole signal is strong in the right ventricle (RV) and at the base of the outflow tract (OFT), with intermediate signal strength in the interventricular septum close to the left ventricle (LV). Both atria are negative for pimonidazole (LA, RA). Bottom panels show magnifications of the insets in the top panels.

MAJOR GRANTS

- *H2020-PHC-2014-two-stage (GA633765). PI: V Fuster*
- *NHLBI-BAA-10-08 Co-Project Director of Project #3: V Fuster*
- *NHLBI - 5U01HL114200-02 PI: V Fuster*
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- *Departamento de Salud y Consumo of the regional government of Aragon, General Motors Spain and CNIC (AWHS). PI: V Fuster*
- *FP7-PEOPLE-2013-IIF (GA 624811). PI: M Cortés*
- *EU FP7. Marie Curie European Reintegration Grant (276891). PI: S Martín Puig*
- *Ministerio de Ciencia e Innovación. FIS (CP09/00100). PI: S Martín Puig*
- *Comunidad de Madrid: (S2010/BMD-2542). PI: S Martín Puig*
- *COST – European Cooperation in Science and Technology. PI: S Martín Puig*
- *Instituto de Salud Carlos III (PI13/02339). PI: A García*
- *Instituto de Salud Carlos III (PI15/02019). PI: L Fernández-Friera*
- *Instituto de Salud Carlos III (CP08/112). PI: M Laclaustra*
- *Instituto de Salud Carlos III (FIS PI14/00009). PI: M Laclaustra*
- *Instituto de Salud Carlos III (PI11/00403). PI: JL Peñalvo*

SELECTED PUBLICATIONS

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

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Vedanthan R, Seligman B, Fuster V. **Global perspective on acute coronary syndrome: a burden on the young and poor.** *Circ Res* (2014) 114: 1959-75

Castellano JM, Sanz G, Peñalvo JL, Fernández-Ortiz A, Alvarez L, Guzmán L, Linares JC, García F, D'Aniello F, Arnáiz JA, Varea S, Martínez F, Lorenzatti A, Imaz I, Sánchez-Gómez LM, Roncaglioni MC, Baviera M, Smith S, Taubert K, Pocock S, Brotons C, Fuster V. **A polypill strategy to improve adherence: results from FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) Project**. *J Am Coll Cardiology* (2014) 64: 2071–82

Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. **A Polypill Strategy to Improve Global Secondary Cardiovascular Prevention: From Concept to Reality.** *J Am Coll Cardiol* (2014) 64: 613-621

Martin-Puig S, Tello D and Aragones J. **Novel perspectives on the PHD-HIF oxygen sensing pathway in cardioprotection mediated by IPC and RIPC.** *Front Physiol* (2015) 6: 137. doi: 10.3389/fphys.2015.00137