**1. Cardiovascular Development and Repair**

**B. Stem Cell Biology Program**

**Figure 2.** Neuropathy of the hematopoietic stem-cell niche is essential for myeloproliferative neoplasms. Model illustrating HSC niche alterations and rescue in myeloproliferative neoplasms (MPN). HSC, hematopoietic stem cell; SNS, sympathetic nervous system; MSC, mesenchymal stem cell; NA, noradrenaline; AR, adrenergic receptor; C, control (disease-free mice). (Arranz L et al. Nature 2014)

**Graphical Abstract**

**Figure 3.** Estrogen signaling selectively induces apoptosis of hematopoietic progenitors and myeloid neoplasms without harming steady-state hematopoiesis. Treatment of leukemic mice with the selective estrogen receptor modulator tamoxifen can block the development of myeloproliferative neoplasms and sensitize acute myeloid leukemia to conventional chemotherapy (Sánchez-Aguilera A et al. Cell Stem Cell 2014)

**Selected Publications**


**Major Grants**

- Comunidad de Madrid. Convocatoria de Programas de I+D en Biomedicina. (S2011/BMD-2542)
- Ministerio de Economía y Competitividad (RYC-2011-09209) PI: Joan Isern
- Ministerio de Ciencia e Innovación (RYC-2009-04703)
- Ministerio de Economía y Competitividad (RYC-2011-09726) PI: Abel Sánchez-Aguilera
- Ministerio de Economía y Competitividad (SAF-2011-30308)
- European Commission FP7. Marie Curie Career Integration Grant (294262)
- European Commission FP7. Marie Curie Career Integration Grant (294096) PI: Abel Sánchez-Aguilera
- Ministerio de Economía y Competitividad (BFU2012-35892) PI: Joan Isern
Cell-based therapy is a promising approach for many diseases, including ischemic heart disease. Our work focuses on cardiac mesoangioblasts, committed vessel-associated progenitors that can restore heart structure and function to a significant, albeit partial, extent in a mouse model of myocardial infarction. Low-intensity pulsed ultrasound (LIPUS) is a non-invasive form of mechanical energy that can be delivered into biological tissues as acoustic pressure waves, and is widely used for clinical applications including bone fracture healing. We hypothesized that the positive effects of LIPUS on bone and soft tissue, which include increased cell differentiation and cytoskeleton reorganization, could be applied to increase the therapeutic potential of mesoangioblasts for heart repair. During this year, we showed that LIPUS stimulation of cardiac mesoangioblasts isolated from mouse and human heart results in significant cellular modifications that provide beneficial effects to cells, including increased malleability and improved motility and invasiveness. Additionally, LIPUS stimulation increased the number of binucleated mesoangioblasts and induced cardiac differentiation to an extent comparable with 5-azacytidine treatment. Administration of LIPUS-stimulated mesoangioblasts in vivo resulted in greater retention and incorporation into cardiotoxin-damaged hearts. Taken together, these results provide functional evidence for the potential of LIPUS as a useful tool in heart cell therapy.

**MAJOR GRANTS**
- Ministerio de Economía y Competitividad (SAF2010-15239)

**Selected Publications**
ReSEARCH DEPARTMENTS
1. Cardiovascular Development and Repair
B. Stem Cell Biology Program

Functional genomics of embryonic pluripotency and heart development

RESEARCH INTEREST

We are interested in the gene regulatory networks that control the early stages of mammalian development and underlie cardiovascular disease. Our research focuses on understanding how cis-regulatory elements located in the non-coding portion of the genome influence the spatial and temporal expression of nearby genes, as well as how their activity is modulated by chromatin structure. We are also exploring how these elements are the target of variation that results in increased risk of human disease. Uncovering the regulatory basis of cardiovascular diseases is one of our major goals.

We are exploring how initial decisions and lineage choices occur in the mammalian embryo, before it implants in the maternal uterus and when pluripotent cell fate is established. We have shown how different signaling pathways act together to activate gene expression in the outer layer at the blastocyst stage, thus distinguishing the embryonic from the extraembryonic lineage. A critical event in this process is the regulation of the expression of CDX2 by the Notch and Hippo pathways through a specific enhancer.

By exploring the findings of genome-wide association studies, we have found that regulatory elements distal to the PITX2 gene lie in a genomic region associated with an increased risk of atrial fibrillation. We are exploring the genomic architecture of this and other atrial fibrillation associated loci, finding unsuspected interactions with other genes in these regions. Using mouse genetic models, we are conducting a genome-wide study of how chromatin structure crucially regulates proper gene expression in the heart, and how this could underlie certain cases of human cardiovascular disease.

Collection of mouse blastocysts showing expression of a fluorescent reporter driven by a Cdx2 enhancer (red), endogenous CDX2 expression (green), and nuclei (blue).
Diagram showing how different states of the Notch and Hippo pathways result in differential expression of the Cdx2 gene between the outer blastocyst cells, which will form the trophectoderm (TE, the precursor of the placenta), and the cells of the inner cell mass (ICM), which will give rise to the embryo proper and later to all adult lineages.

Differential expression of the Pitx2 and Hcn4 genes in arrhythmogenic regions of the developing 14.5 dpc mouse heart. While Pitx2, which encodes a transcription factor that has been linked to atrial fibrillation, is expressed in the pulmonary veins (PV) and the left atrium (LA), the ion-channel-encoding gene Hcn4 is expressed in the right and left superior vena cava (RSVC, LSVC), the atrioventricular node and His bundle (AVN-His), and the sinoatrial node (SAN). Mis-expression of both of these genes has been linked to the occurrence of atrial fibrillation.
Epigenetic regulation in cardiac aging and disease

**RESEARCH INTEREST**

Adult stem cells participate in the natural homeostasis of adult tissues through their ability to both self-renew and differentiate into multiple lineages to regenerate tissue in response to injury signals. During aging, the proliferation and differentiation capacity of tissue-specific stem cells decreases, and they lose their potential to regenerate tissues after damage. PcG-mediated alteration of the epigenetic status of hematopoietic stem cells (HSCs) is proposed as one of the driving forces behind many age-related HSC changes and is often found to be misregulated in human malignancies. Protection of the transcriptional “stemness” network is thus essential for maintenance of a healthy HSC compartment throughout life. A key unanswered question in the field is whether the functional decline in adult stem cells is related to reversible chromatin modifications. We propose that changes to the chromatin state can restore the regenerative capacity of stem cells. To investigate this hypothesis, we are exploring the role of the epigenetic Polycomb-mediated silencing mechanism in stemness maintenance, with particular emphasis on the self-renewal capacity and the microenvironment of HSCs, a key adult stem cell population with diverse regenerative capacities. Understanding molecular mechanisms by which Polycomb members control stem cell fate will provide new insights into hematopoietic stem cell biology and will also increase understanding of neoplastic transformation.

We are also interested in the emerging role of different classes of chromatin regulators and how their dysregulation in the adult heart alters specific gene programs, with subsequent development of major cardiomyopathies. Dilated cardiomyopathy (DCM) represents the third most common cause of heart failure but has been poorly modeled in nonhuman species. We propose that epigenetic remodeling could provide an important means of modulating the transcriptional reprogramming of cardiac gene expression in this condition. Understanding the action of Polycomb factors will allow the development of strategies to control physiological and pathological gene expression.

**MAJOR GRANTS**

- Ministerio de Ciencia e Innovación (SAF2010-15386)

**Selected Publications**
