Fondation Leducq

2015

NEWSLETTER

Improving health through international cardiovascular research

Volume 7

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NEW TRANSATLANTIC NETWORKS

The Fondation Leducq is pleased to announce the **four Networks** selected for funding in 2015. These programs were chosen from among **111 Letters of Intent** (LOI) that were received in September 2014. Submission now proceeds through **Altum proposalCENTRAL** platform, an online application service, which was introduced in the cycle 2013-2014.

1 22q11.2 deletion syndrome: Novel approaches to understand cardiopharyngeal pathogenesis.

Antonio Baldini-Institute of Genetics and Biophysics, Naples, Italy
Bernice Morrow-Albert Einstein College of Medicine, Bronx, USA

DiGeorge Syndrome, or the 22q11.2 deletion syndrome, is the most frequent human congenital heart syndrome. Investigators in this Leducq network hope to understand the origins of the problem. DiGeorge Syndrome, and other congenital heart syndromes, often involve craniofacial abnormalities. New findings have linked some of the most common human congenital heart defects to a **progenitor cell population named the cardiopharyngeal mesoderm (CPM)**, which as the name implies, forms not only the heart, but part of the face and neck. This Leducq network's multidisciplinary team will investigate the **role of the Tbx1 gene**, **which is essential for development of the CPM cell population** and the formation of the heart, relying upon models in the mouse and the sea squirt Ciona; mice recapitulate faithfully the human patient phenotype and Ciona has recently emerged as an excellent model for CPM biology. Investigators hope to gain novel insights concerning 22q11.2DS pathogenesis, and the mechanisms controlling cardiopharyngeal development. The results should add considerably to our knowledge of genetic heart defects, and could have implications for the diagnosis and prognosis of human patients.

2 Evoked neuronal activity: a new neuroprotectant for acute ischemic stroke?

Jean-Claude Baron-University of Paris, France
Ron Frostig-University of California, Irvine, USA

One of the great challenges in the treatment of acute stroke is the narrow time window, on the order of several hours, in which medications and interventions are effective. In addition, many patients may be ineligible for thrombolysis, an intravenous treatment that dissolves the blood clot that is blocking the artery and causing the symptoms. There is a great need to develop other treatment options. An exciting new possibility being developed by this network is **contralateral somatosensory stimulation (SSS)**. In this non-pharmacological approach, caregivers provide touch stimulation to the body on the side opposite the one where the artery is blocked in the brain. This rather simple treatment has been shown to markedly **reduce infarct volume** following temporary middle cerebral artery occlusion in rats. It is believed that **SSS's effects derive from enhanced blood flow to the damaged brain through collateral blood vessels**. Interestingly, Frostig, one of the network coordinators, has recently found that although SSS may be effective in the early stages of stroke, it appears to be detrimental after three hours from stoke onset. This international consortium, with expertise in the basic science of neurophysiology and in clinical experimental stroke, hopes to take what they learn from various rodents and apply the knowledge to translational human pilot studies.

3 Eliciting Heart Regeneration through Cardiomyocyte Division

Kenneth Poss-Duke University, Durham, USA
Elly Tanaka-Center for Regenerative Therapies, Dresden, Germany

The human heart shows limited natural muscle regeneration in response to myocardial infarction. Instead of re-growing functional heart tissue, the human heart, in response to a heart attack, produces a non-function scar. There is currently no therapy that successfully regenerates heart tissue, and this despite more than a decade of stem cell research that initially appeared to be very promising in this regard. One new promising line of research focuses on **expanding the heart's limited ability to produce new muscle cells**. This network enlists an interdisciplinary team of biologists, clinicians and engineers with the following objectives: 1) Discover factors that **stimulate cardiomyocyte (cardiac muscle cell) division** using in vivo models of embryonic and postnatal heart development, natural heart regeneration in zebrafish and mice, engineered human cardiac muscle constructs, and the classical models of tissue regeneration in salamanders; 2) Elucidate the mechanism to discover how we might be able to **influence mammalian cardiac repair**; 3) Develop pre-clinical mammalian models of regenerative therapy through the **delivery of cardiomyocyte mitogens** and the **engineering of cardiac tissue patches from stem cell-derived cardiomyocytes**. These approaches will define regulatory mechanisms for heart regeneration and derive new regenerative approaches to cardiovascular disease.

4 Modulating autophagy to treat cardiovascular disease

Junichi Sadoshima-Rutgers New Jersey medical School, Newark, USA
Luca Scorrano, University of Padova, Italy

Autophagy is a process in which cellular proteins, lipids, and organelles are transported to specialized processing centers called lysosomes for degradation. It is becoming clear that autophagy is critical to a number of functions within the cell, including protein and organelle quality control, defense against cellular stresses, and metabolic regulation. Autophagy can also be damaging to cells. It is believed to play a role in ischemia reperfusion injury, a phenomenon where the tissue supplied by an artery that becomes blocked, such as during a heart attack or stroke, is at risk of cell death when the artery becomes unblocked and blood flow is re-established. Network investigators begin from the premise that the heart and blood vessels, continually under metabolic and mechanical stress, are relatively more dependent on autophagy to maintain normal function than other tissues. The Leducq network will study **how autophagy functions as a protective or damaging process in the pathogenesis of cardiovascular disease**. Potential therapeutics to modulate autophagy, already developed by the team, will be tested in relevant animal models with respect to their abilities to preserve cardiac and vascular function.

CALL FOR APPLICATION CYCLE 2015-2016

Fondation Leducq announces a call for applications for the **2015-2016 Transatlantic Networks of Excellence Program**. Under the Transatlantic Networks of Excellence in Cardiovascular Research Program, the Fondation Leducq awards grants of up to **U.S. $6,000,000** over five years for internationally collaborative research in cardiovascular and neurovascular disease. As of 2015, the foundation has supported **47 networks**, representing more than 400 investigators at 130 institutions in 19 countries. Fondation Leducq applications are submitted via an online application service hosted by **Altum proposalCENTRAL**. Information about the application process and details about important dates in the 2015-2016 application cycle can be found on our website at **flcq.org** under **Transatlantic Networks of Excellence**.

Due date for letters of intent is **Sunday, September 6, 2015,** 11:59 pm US Eastern time.

NEWS FROM THE 5TH LEDUCQ SYMPOSIUM

Fondation Leducq held the **fifth Leducq Symposium** in **Paris on April 16th, 2015**.
It called together researchers from six different networks that were launched in **2009 and 2010.** This symposium provides the foundation with an opportunity to take stock of the work performed with its support and helps researchers to make contact among other Fondation Leducq network coordinators.


Fondation Leducq, SAC Meeting – Paris, April 2015

From Left to Right:
Back:
Christian Hamm, Daniel Drucker, Friedhelm Beyersdorf, Joseph Woo, Robert Bonow, Göran Hansson, Dan Roden, Shaun Coughlin, Hugh Watkins, Bo Norrving

Front:
Michael Moskowitz, Margaret Buckingham, Martin Landaluce, David Tancredi, Helen Hobbs, Alain Tedgui.

SCIENTIFIC ADVISORY COMMITTEE CHANGES

On April 17th, 2015, the **Spring meeting of the Scientific Advisory Committee** (SAC) marked also the conclusion of the terms of two members of the SAC: **Robert Bonow** and **Bo Norrving.**

NETWORK FOCUS

Leducq investigators led by Nicholas Morrell and Donald B. Bloch demonstrate the promise of direct enhancement of endothelial BMP signaling as a new therapeutic strategy for PAH. From the abstract of the Nature Medicine article: Genetic evidence implicates the loss of bone morphogenetic protein type II receptor (BMPR-II) signaling in the endothelium as an initiating factor in pulmonary arterial hypertension (PAH). However, selective targeting of this signaling pathway using BMP ligands has not yet been explored as a therapeutic strategy. Here, we identify BMP9 as the preferred ligand for preventing apoptosis and enhancing monolayer integrity in both pulmonary arterial endothelial cells and blood outgrowth endothelial cells from subjects with PAH who bear mutations in the gene encoding BMPR-II, BMPR2. Mice bearing a heterozygous knock-in allele of a human BMPR2 mutation, R899X, which we generated as an animal model of PAH caused by BMPR-II deficiency, spontaneously developed PAH. Administration of BMP9 reversed established PAH in these mice, as well as in two other experimental PAH models, in which PAH develops in response to either monocrotaline or VEGF receptor inhibition combined with chronic hypoxia.

Long L, Ormiston ML, Yang X et al.
Nature Medicine 21, 777–785 (2015).