FONDATION LEDUCQ NEWSLETTER

Improving health through international cardiovascular research

2013

The FONDATION LEDUCQ NEWSLETTER is published once a year.
Publication Director: David TANCREDI
Editor: Sylvie LORAND-HULOT
1, rue Laurent Pichat
75116 Paris FRANCE
Tel: +33 (0)1 45 00 59 65
Fax: +33 (0)1 45 00 07 88
http://fondationleducq.org
ISSN 2103-7094

New Transatlantic Networks

Four new Transatlantic Networks were selected for funding by the Scientific Advisory Committee (SAC) at its April 2012 meeting in Philadelphia. These four, chosen from among the 96 expressions of interest received by the Fondation Leducq the previous autumn, hold great promise for improving our understanding and treatment of cardiovascular diseases. The networks awarded funding in 2012 are:

1) Pathogenesis of Small Vessel Disease of the Brain

Anne Joutel, INSERM Paris7-Diderot and Mark Nelson, University of Vermont, Burlington

Small vessel disease (SVD) involving the structure and function of small penetrating vessels within the brain accounts for 25% to 30% of ischemic strokes and is a leading cause of cognitive decline and disability worldwide. Very little is known about the underlying causes of SVD. There are currently no specific treatments, and therapeutic options for secondary prevention are particularly limited compared to other common causes of stroke. The identification of genes involved in two genetic forms of non-hypertensive adult-onset SVD marks an important advance in the understanding of SVD.

CADASIL (Cerebral Autosomal

New Transatlantic Networks

Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an archetypal SVD that emerges as the most common heritable cause of stroke and vascular dementia worldwide. CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), predominantly reported in Japanese families, is a rare SVD with a more complex phenotype. This Transatlantic Network of Excellence aims to use unique mouse models of CADASIL and CARASIL as a basis to explore common forms of SVD, and ultimately to identify potential therapeutic targets. In addition, there is considerable emphasis placed on training the next generation of investigators in this nascent field.

2) CADgenomics: Understanding Coronary Artery Disease Genes

Jake Lusis, UCLA and Heribert Schunkert, Lübeck University, Germany

In the last several years, Genome-wide Association (GWA) studies carried out by some of the members of this Transatlantic Network have identified genetic loci linked to an increased susceptibility to coronary artery disease (CAD). In many cases, despite a clear association of a particular gene with cardiovascular disease, its exact role in pathogenesis remains elusive. The main objective of the CADgenomics network is to use the GWAS results as a starting point, together with evidence at the molecular, cellular, and tissue level, to examine the underlying functional biology of the cardiovascular disease pathways in which they are involved. Members of this multidisciplinary network will focus on genes likely to act at the level of the arterial wall and/or affecting local inflammation. State of the art bioinformatics approaches coupled with manipulations of gene expression and function will be used to reach this goal. By yielding major advances in understanding the genetic pathogenesis of CAD this program may, it is hoped, identify novel therapeutic targets to tackle this important human disease. Junior scientists will work alongside experienced investigators in each participating institution, promoting further research in this exciting and fast-moving field.

3) MIBAVA-Mechanistic Interrogation of Bicuspid Aortic Valve associated Aortopathy

Bart Loeys, University of Antwerp, Belgium and Harry Dietz, Johns Hopkins University, Baltimore

Bicuspid aortic valve (BAV), a condition in which there are two valve leaflets instead of the normal three, is the most common congenital cardiac malformation, affecting from 1% to 2% of the population. It appears to be highly heritable, is more common in males than females, and is frequently associated with other aortic pathology, such as ascending aortic aneurysm. The goal of the MIBAVA network is to identify factors that affect the clinical outcome of patients with BAV, with particular attention to the progression of aortic aneurysm. The scope of the research program will span natural history and epidemiologic studies, exploration and application of advanced imaging techniques, use of advanced genetic methods to identify disease-related genes and pathways, basic science investigations to identify predisposing mechanisms at the biochemical, cellular and tissue

New Transatlantic Networks

level, and the complementary use of various model systems. With progress in understanding the etiology of aneurysm formation, the network will turn to the search for novel therapeutic strategies and the development of individualized treatment protocols.

4) TNT-Triglyceride Metabolism in Obesity and Cardiovascular Disease

Rudolf Zechner, University of Graz, Austria and Stephen Young, UCLA

Although triglycerides have long been implicated in the pathogenesis of cardiovascular disease, comparatively little is known about their metabolism or role in disease. The Transatlantic Network on Triglycerides (TNT) aims to fill in our gaps in knowledge, concentrating on triglyceride metabolism as it relates to obesity and heart disease. Triglycerides, three molecules of fatty acid bonded to a molecule of the alcohol glycerol, are synthesized during the process of digestion, and are stored in the body's adipose (fat) tissues. High levels of triglycerides in the blood are associated with insulin resistance.
In cells, defects in the proteins governing the breakdown of triglycerides lead to massive accumulation in the heart. The resulting injury, as occurs in patients with diabetes mellitus, can lead to congestive heart failure. In the liver, an excess of triglycerides can lead to cirrhosis. The mechanism of injury is unknown. Each TNT investigator has made novel and highly significant discovery in the understanding of triglyceride metabolism. Because no single group has the perspective or tools to investigate the cross-regulation of intracellular and intravascular triglyceride metabolism, the network approach can provide a significant boost to research efforts in the field. Network members plan to concentrate on the use of novel mouse models to understand triglyceride storage and overload, in order to develop therapeutics for triglyceride related obesity and cardiovascular disease.

New CDAs 2011-2012

1) Determining novel causal risk factors for CVD: An original genome-wide approach

Genome wide association studies have revealed a number of genes that appear to be implicated in cardiovascular disease. Yet these GWAS are only able to account for a small part of what is believed to the role genes play in causing complex phenomena like cardiovascular disease. **Mary-Jo Brion**, currently at the University of Bristol, proposes to find this "missing heritability" by marrying GWAS with an approach called Mendelian Randomization in order to assess the importance of the environmental risk factors. Working with Joel Hirschhorn at the Broad Institute in Cambridge, Massachusetts, Brion will develop a new platform to

New CDAs 2011-2012

identify novel causal risk factors that would allow doctors and patients to put measures in place to prevent or delay the onset of cardiovascular disease. Following her work at the Broad Institute, Brion plans to return to the United Kingdom to continue her internationally collaborative research in genetics and epidemiology.

2) The role of copeptin, midregional natriuretic peptide and procalcitonin as markers of ischemic stroke risk in the Northern Manhattan study

Supported by a grant from the Swiss National Foundation, neurologist **Mira Katan**, came to Columbia University in 2010 to do clinical research with Mitchell Elkind in the area of biomarkers and stroke. Her one-year Leducq Career Development Award will allow her to extend her research at Columbia through a project designed to assess a test, independent of those that currently exist, which would allow physicians to know that a patient was at risk for stroke. Looking at patients enrolled in the Northern Manhattan Study (NOMAS), Katan will focus on three promising biomarkers that there is reason to believe might be predictive of future stroke: copeptin, midregional natriuretic peptide, and procalcitonin. After completing this biomarker study Katan will return to Switzerland to take a position as a clinician researcher in neurology.

3) Flow through the Right Heart after Repair of Tetralogy of Fallot: an Image-Based Modeling Approach

An Assistant Professor of Biomedicial Engineering and Medicine at the University of California Irvine, **Arash Kheradvar**, focused his research on understanding the mechanics of flow across the mitral valve. For his CDA project Kheradvar will take his insights from his study of fluid mechanics to the problem of the tetralogy of Fallot, a common form of cyanotic congenital heart disease. Four anatomical features characterize the tetralogy of Fallot: a narrowing of the pulmonic valve, a shift in the position of the aorta, a ventricular septal defect (known in common terms as a "hole in the heart") and a hypertrophy or thickening of the right ventricle. Early on children with tetralogy of Fallot undergo early a surgical repair, leading to temporary improvement. Over time, however, patients experience more heart related problems because of changes to the right ventricle. Working with Philip Kilner, a specialist in cardiac magnetic resonance imaging, Kheradvar aims to understand how changes in blood flow in the heart contribute to the progressive failure of the heart over time. Using physical and computer modeling, he hopes to be able to provide assistance to surgeons and cardiologists who are confronted with the problem of managing patients with persistent problems after their first operation.

New CDAs 2011-2012

Kheradvar intends to return to his academic research at the University of California Irvine after his two-year research project winds down.

4) Oxidized CaMKII in Atrial Fibrillation – Impact on Atrial Remodeling

CaMKII has recently been implicated in atrial fibrillation, the most common cardiac arrhythmia, which appears on the EKG as rapid and disorganized electrical impulses in the atria, the smaller chambers of the heart. Atrial fibrillation is clinically important for its association with a greatly increased risk of stroke. It appears that atrial fibrillation brings about structural changes in the atria, called remodeling, that are responsible for transforming the arrhythmia from something intermittent into something more permanent. **Adam Rokita**, having studied with Lars Maier at the University of Göttingen in Germany, will work with Mark Anderson at the University of Iowa. Both senior investigators participate in a Fondation Leducq Transatlantic Network focused on CaMKII. Rokita intends to investigate the role of CaMKII in the molecular pathways and mechanisms responsible for structural atrial remodeling. An understanding of how the heart changes in the setting of atrial fibrillation could allow researchers to develop new treatments for atrial fibrillation. Following the conclusion of his research program in Iowa City, Rokita plans to return to Germany to continue his work in cardiovascular research.

5) Characterizing the cellular functions of novel cardiovascular disease genes and genomic variants

Heiko Runz, a physician and specialist in genetics and inborn errors of metabolism in Heidelberg, is interested in identifying genes responsible for coronary artery disease and myocardial infarction, and in understanding the mechanisms by which these genes produce their effects. With his mentor Rainer Peppercock he participates in the Fondation Leducq Transatlantic Network entitled *Molecular mechanisms of novel genes associated with plasma lipids*. Currently he is investigating the use of cellular tests to show, on a large scale, how genes might function to provoke or worsen cardiovascular disease. In his CDA project, Runz will follow up on genes identified in large genetic studies-- notably through the work of Sekar Kathiresan at the Broad Institute--as being associated with cardiovascular disease,. The strategy pursued by Runz and his two senior collaborators is first to identify promising genes from patients who have either extremely low or extremely high lipid levels. They will then introduce RNA molecules into cells to inhibit selectively these genes (RNAi) to ascertain whether this change is associated with differences in the way the cell handles lipids. Runz plans to return to Heidelberg to continue his academic research at the conclusion of the research project.

New CDAs 2012-2013

1) Immunological acceptance of embryonic stem cell-derived cardiomyocytes: Learning from Nature

Using embryonic stem cells as a treatment for heart failure is attractive because these cells can differentiate into all of the cell types needed to repair the heart. The problem is that these cells provoke an immune reaction similar, to rejection arising in organ transplantation, which could lead to failure of the therapy, or the need for long-term immunosuppression. In her CDA project, **Sonja Schrepfer** will examine a case that nature provides in immune tolerance: the fetus, although immunologically distinct from the mother, is not rejected by the maternal immune system. The goal is to investigate whether mechanisms at work here might someday be put to the service of therapeutic embryonic stem cell therapy to avoid unwanted immune reactions.

2) Cardiac tissue engineering by using Cardiac stem cells, heart derived extracellular matrix and Tissue Printing technology for cardiac regeneration

During the last few years, implanted Cardiac Progenitor Cells have shown encouraging results on cardiac function for the diseased heart. However, direct injections of cells into the ischemic heart has shown limitations, as both the cardiomyocytes and the extracellular matrix are destroyed or modified. **Roberto Gaetani**, 31, has recently been working in Utrecht where he has been developing tissue engineering approaches and comparing different methods of cardiac progenitor cell isolation.

With the support of the Leducq CDA award, he will spend time at UCLA where there is an active program in the study of synthetic extracellular matrices. In regenerative medicine, 3D printers, called bioprinters, are now used to print functional human tissue for medical research. His objective is to use this Tissue Printing Technology to deliver, in a defined and organized manner, scaffolding materials and cardiac progenitor cells, in order to obtain a construct with cardiogenic potential for in vitro or in vivo application.

New Scientific Advisory Committee Members and President

Fondation Leducq, SAC Meeting
Philadelphia, PA – April 2012

Back Row: M. Landaluce, S. Lorand-Hulot, Bo Norrving, Hugh Watkins, David Ginsburg, Ludwig von Segesser, Robert Bonow, David Tancredi, Thomas Meinertz,
Front Row: Richard Weisel, Joseph Loscalzo, Robert Roberts, Costantino Iadecola, Sylviane Leducq, Garret FitzGerald, Steve O'Rahilly, Margaret Buckingham, Michel Lazdunski.

Margaret Buckingham was chosen as the new President of the Fondation Leducq Scientific Advisory Committee (SAC). She succeeds Costantino Iadecola who arrived at the end of his term.

Three other members rotated off of the SAC at the April 2012 meeting: Dr. Garret FitzGerald (University of Pennsylvania), Dr. David Ginsburg (University of Michigan), and Dr. Ludwig von Segesser (University of Lausanne). Newly named to the SAC are Dr. Shaun Coughlin (University of California San Francisco), Dr. Michael Moskowitz (Mass General Hospital) and Dr. Friedhelm Beyersdorf, (Freiburg University).

Agenda 2013

The next SAC meeting will hold at **The Palais de la Méditerranée in Nice, France on April 5th, 2013.**

The day before, on April 4th, 2013, the fourth symposium of the Fondation Leducq will call together researchers from several networks including the first networks selected with a theme in neurovascular diseases. Also giving presentations will be a number of the Career Development Award recipients, who will discuss the work they have done with the support of the foundation.

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. The Board of

Changes to Fondation Leducq programs

Directors of the Fondation Leducq recently approved important changes to the research grant programs of the foundation, following the recommendations of the Scientific Advisory Committee. These changes will take effect starting with the 2013-2014 application cycle, and will be announced at the time of the next call for application in June.

About Fondation Leducq

The Fondation Leducq was created by Jean and Sylviane Leducq in 1996. Having had significant business interests and personal connections in Europe and the United States, the Leducqs oriented the foundation towards collaborative medical research, believing that the battle against cardiovascular and neurovascular disease should be waged at the international level.

By forging scientific alliances that transcend national borders, and promoting the education of young researchers who thrive in an international context, Fondation Leducq hopes to encourage innovative research, an efficient use of resources, and the development of long-term collaborations that will continue to meet the challenges of cardiovascular and neurovascular disease.

Fondation Leducq awarded its first research grants in 1999 and the Transatlantic Networks of Excellence program was initiated in 2003. To date, the Network program has awarded 35 grants totaling more than $210 million to 331 investigators in 17 countries (Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Sweden, Switzerland, the United Kingdom, and the United States). Since the first funding in 1999, the Fondation Leducq has committed a total amount of $250 million.

For more information about the Fondation Leducq, please visit our website at http://fondationleducq.org/ or contact our Scientific Director, Dr. David Tancredi, at mailto:contact@flcq.org.