Fondation Leducq

2014 NEWSLETTER

Improving health through international cardiovascular research

Volume 6

Sylviane Leducq (1925-2013)

The Fondation Leducq mourns the passing of its founder and president, Sylviane Leducq, who along with her late husband Jean, inspired and supported so many in cardiovascular and neuro-vascular research.

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FONDATION LEDUCQ ANNOUNCES 2014 TRANSATLANTIC NETWORKS OF EXCELLENCE AWARDS

Four new Transatlantic Networks (TNE) were selected by the Scientific Advisory Committee (SAC) at its April 2014 meeting in Napa Valley. These programs were chosen from among **118 Letters of Intent** (LOI) that were received in September 2013, representing a **30% increase in the number of LOIs** received over the previous year. Submission now proceeds through a user-friendly online application service through the **Altum proposalCENTRAL** platform, which was introduced in the cycle 2013-2014.

The networks awarded funding in 2014 are :

1 Deciphering the Genomic Topology of Atrial Fibrillation

Patrick Ellinor, *MGH, Boston, US* ***and***
Vincent Christoffels, *Academic Medical Center, Amsterdam, The Netherlands*

Atrial fibrillation (AF) affects over 3 million individuals in the US and 4.5 million individuals in Europe. Currently, both medical and interventional therapies for AF are only partially effective, and are associated with substantial morbidity. Although recent genome-wide association studies (GWAS) have identified over a dozen genetic loci associated with AF, we have only a **limited understanding of mechanisms through which these genetic variants lead to AF**. By combining deep insights into GWAS-signals, knowledge of the 3D topology of the human genome, and expertise in the translation of genetic changes, the members of this network will address the major question in AF genetics: **how do the genetic mutations affect the electrical rhythm of the heart**? Filling the gap of our understanding of the molecular pathways underlying the arrhythmia should ultimately provide new diagnostic tools and therapeutic strategies to reduce the unacceptable burden of stroke, death, and hospitalizations associated with this common arrhythmia.

2 SphingoNet - Sphingosine 1-Phosphate in Neurovascular Biology and Disease

Timothy Hla, *Cornell University, New York, US* ***and***
Christer Betsholtz, *Uppsala University, Sweden*

Understanding the control and regulation of the BBB is of significant clinical importance because the BBB remains one of the major obstacles in the delivery of drugs to the central nervous system. The transatlantic network led by Christer Betsholtz and Timothy Hla brings together experts in blood vessels, immunology and nervous system function to focus on the **central role of sphingosine 1-phosphate (S1P) in the development and regulation of the neurovascular unit and blood brain barrier** (BBB) in health and disease. This is a novel approach to the investigation of the neurovascular unit prompted by the discovery of a drug that influences sphingosine signaling and has been found to be effective in multiple sclerosis. The network project will further characterize the **role of S1P in ischemia**. When dysregulated, S1P signaling causes neuroinflammation and neurovascular disease. As very little is known about S1P and its receptor systems that are expressed on multiple cell types and tissues in vessels and brain, the proposed experiments will concentrate on **genetic targeting of receptors and related pathways**. Building on a strong body of literature implicating S1P in vascular regulation and blood brain barrier permeability, network members propose specifically **to identify the cell types responsive to SIP-mediated BBB regulation** in large part by the use of a variety of genetically engineered mice. If successful this group could help to launch a entirely new platform for the treatment of neurovascular disease.

3 Molecular Genetics, Pathogenesis and Protein-Replacement Therapy in Arrhythmogenic Cardiomyopathy

Ali Marian, *The University of Texas, Houston, US* ***and***
William McKenna, *University College of London , UK*

This network is designed to delineate the molecular genetics, genomics, and pathogenesis of arrhythmogenic cardiomyopathy (AC). The classic right-dominant form of AC, known as arrhythmogenic right ventricular cardiomyopathy, is a leading cause of sudden cardiac death in young people. **The burden of AC is almost certainly underestimated**, however, owing to frequent missed diagnoses and under-recognition of the left-dominant and biventricular subtypes. Initially in this disease, the heart has a normal structure and function and as the disease progresses, there is ventricular dilation, dysfunction and aneurysm formation. Clinical heart failure is a late manifestation. **A switch in the fate and differentiation of a subset of cardiac resident cells to fibro-adipocyte is the pathological hallmark of AC**. The present challenge lies in elucidating the intervening steps - from mutation to pathologically overt disease - and identifying therapeutic targets therein. This network pooling resources and sharing expertise will have access to a **well phenotyped AC patient population**. They will continue searching for new genes and new mutations, but most important of all, they will investigate **protein replacement in transgenic mouse models to attempt to reverse the phenotype**. The synergistic interactions between clinicians and scientists in this network will ultimately improve the quality of life and survival of AC patients.

4 Programming the failing heart to a regenerative state

Richard Lee, *Brigham & Women Hospital, Cambridge, US* ***and***
Mauro Giacca, *ICGEB, Trieste, Italy*

Given the global burden of heart disease and its increasing prevalence in aging populations, one of the most important challenges of modern medecine is the development of strategies to regenerate the human heart. This network is focused on **promoting the regenerative potential of endogenous cells of the heart** a different strategy from that found in many stem cell programs where exogenous cells are added to produce a therapeutic effect. Building on the finding that mouse fibroblasts can be reprogrammed toward a cardiac cell fate in vitro and in vivo, improving cardiac function and reducing adverse ventricular remodeling, this network will use a combination of factors, including microRNAs, to reprogram adult human fibroblasts into cardiomyocyte-like cells. The members of this network will collaboratively develop a series of interrelated strategies to enhance cardiac regeneration and repair by the **reprogramming of non-cardiac cells, like macrophages, into cardiomyocytes** and by promoting **the homing of cardiac regenerating cells**. Through activation and stimulation of repair mechanisms, they will define and optimize methods for enhancing function of injured mammalian hearts, and will extend these studies to **a large animal model to bring this knowledge toward translation**, in mini-pigs, non-human primates and **human engineered myocardium**. This line of research should provide new therapeutic approaches to enhance the limited capacity of the heart to regenerate, having applications in diverse cardiac disorders, including both genetic and acquired forms of heart disease.

FONDATION LEDUCQ 2013 TRANSATLANTIC NETWORKS OF EXCELLENCE AWARDS

Four Transatlantic Networks (TNE) were selected by the Scientific Advisory Committee (SAC) at its April 2013 meeting in Nice. The networks awarded funding in 2013 are :

1 Cellular and Molecular Targets to Promote Therapeutic Cardiac Regeneration

Toren Finkel, *NIH, Bethesda, US* ***and***
David Sassoon, *University Pierre et Marie Curie-Sorbonne University, Paris, France*

The limited regenerative capacity of the mammalian heart was long thought to reflect the lack of a cellular reservoir to generate new cardiac tissue.
However, numerous lines of evidence now suggest that the heart may have a significant capacity for cardiac regeneration and repair. The first major discovery was the identification of cardiac progenitor cells, which showed the ability to differentiate into the specialized cell types that make up the heart. **Resident cardiac stem cells** (CSCs) that persist throughout life were discovered only within the last decade and have been shown to be an important mechanism of **cardiac adaptation and repair**. In addition, emerging data now suggest that **cardiomyocyte de-differentiation and proliferation** may be another major component of the cardiac adaptation/repair program.

Cardiomyocyte de-differentiation may either lead directly to new cardiac muscle formation or proceed through a transient CSC state. Furthermore, a resident population of adult **mesenchymal stem cells that originate in the epicardium has emerged as a major potential contributor to cardiac repair**. Collectively, these data suggest that the adult heart is likely to have significant intrinsic regenerative capacity, but the regulatory mechanisms that direct and limit this process remain to be delineated.
At present, no scientific consensus has emerged regarding the processes regulating cardiac regeneration. The rationale for this network lies in the need for defining the mechanisms regulating and ultimately limiting regenerative responses of the adult heart. A shared, robust platform of in vitro and in vivo models will facilitate characterization of resident cardiac stem and progenitor cells, and a thorough dissection of the process of direct cardiac de-differentiation. **Unraveling the complex and poorly understood processes mediating the age-dependent decline in cardiovascular stem cell efficacy and regenerative capacity is a core objective of this network**. These mechanistic studies will lead to the identification of targets that can be modulated to boost the endogenous regenerative potential of the adult mammalian heart, including the use of small molecules that stimulate the mobilization of endogenous CSCs or transiently activate de-differentiation. With a little help the heart may just be capable of repairing itself in the setting of injury or disease.

2 MicroRNA-based Therapeutic Strategies in Vascular Disease (MIRVAD)

William C. Sessa, *Yale University School of Medicine, New Haven, US* ***and***
Thomas Thum, *Hannover Medical School, Hannover, Germany*

MicroRNAs (miRNAs) are small non-coding RNAs that modulate gene expression. In the emerging field of vascular miRNA research, the members of this network have identified several **intracellular miRNAs regulating vascular biology** that play key roles in vascularization, atherosclerosis and vascular remodeling. Additionally, they have characterized **circulating miRNAs** in the blood, as novel biomarkers and potential signaling mediators of vascular disease, which may provide additional prognostic information over what can be gained from established risk factors and co-morbidities.
Surprisingly, the cellular source and functional significance of circulating miRNAs in vascular disease are still unknown. Determining the importance of miRNAs as novel cell/cell communicators may allow for the development of biomarker profiles based on circulating mi-RNAs. **The central aim of this project, however, is to target selected mi-RNAs as potential therapies for vascular diseases**. With the finding that newly-discovered non-coding RNAs are associated with vascularization, atherosclerosis and aneurysm formation, researchers now believe that vascular miRNAs are central targets for therapeutic manipulation. The network will focus on new and previously identified candidate miRNAs as potential therapies for these three vascular disease areas using genetically modified animal models and pharmacologic strategies.
Therapeutic approaches to silence pathologic miRNAs will be tested in clinically relevant, large animal models as a pathway to first-in-man clinical trials to treat human disease.

The diverse and synergistic talents of the investigative team will provide an unprecedented, comprehensive approach towards **understanding the biological role and therapeutic potential of miRNAs**. This networking and training strategy on vascular miRNAs will significantly contribute to future diagnostic and therapeutic benefits for patients with CVD.

MIRVAD-Transatlantic Network of Excellence in Yale University on March 2014

From left to right:

Constanza Emanueli, Nathan Lawson, Manuel Mayr, Stefanie Dimmeler, Carlos Fernandez-Hernando, Anna Zampetaki (Mayr lab), Jan Fiedler (Thum lab), in the front: Bill Sessa & Thomas Thum.

3 The function and regulation of PCSK9: a novel modulator of LDLR activity

Nabil G. Seidah, *Clinical Research Institute of Montreal, Canada* ***and***
Anders Hamsten, *Karolinska Institute, Stockholm, Sweden*

This team of 17 scientists and clinicians from 6 distinct research centers in Canada, France and Sweden is dedicated to the comprehensive understanding of **the biology of PCSK9 and its implication in hypercholesterolemia and cardiovascular disease** (CVD). Elevated cholesterol levels fuel the atherosclerotic disease process that leads to CVD and premature death. Familial hypercholesterolemia, which affects 1 in 500 subjects worldwide, is known to be caused by genetic mutation. One of the most exciting developments in cardiovascular research in the last decade is the discovery in 2003 of PCSK9, an enzyme encoded by a gene whose mutations are associated with hypercholesterolemia. This relationship was established in French families by members of this team, and revealed an unsuspected regulatory component of the LDL receptor (LDLR). **The role of PCSK9 in LDLR protein degradation in cells, animal models and humans signifies that its inhibition or suppression will be a powerful means of reducing LDL-cholesterol levels**, and thus the burden of atherosclerosis and the incidence of CVD. Pharmaceutical companies are racing to develop PCSK9 inhibitors that may in the future substitute or complement the use of statins, and would be especially beneficial in a setting of statin intolerance. Promising monoclonal PCSK9 antibody-based therapies that block PCSK9-LDLR interaction have now reached Phase-3 clinical trials, but there is still much to be learned about the biology of PCSK9, its regulation, its interacting proteins and genetics.

This research program will address many of the current knowledge gaps surrounding PCSK9 biology. What will be learned could be critical to **develop new therapeutic approaches to achieve optimal serum LDL-cholesterol levels**. Although highly valuable, this line of inquiry is not likely to be pursued by pharmaceutical companies, and can only be obtained by an international team of significant size, made up of multidisciplinary experts dedicated to **the study of PCSK9, and its role in lipid metabolism**. The knowledge gained will be put towards the development of therapeutics involving PCSK9 for people with high cholesterol levels and cardio-vascular disease.

PCSK9-TNE in Montreal on March 2014

4 Mechanical Triggers to Programmed Cell Death in Cardiomyocytes – and how to prevent their Action in Failing Hearts

Siegfried Labeit, *University of Heidelberg, Mannheim, Germany* ***and*** ***Hendrikus Granzier,*** *University of Arizona, Tucson, US*

A progressive loss of cardiac myocytes-heart muscle cells-by cell death (apoptosis) is a feature of all types of heart failure. It appears that the heart, exposed to lifelong cycles of stretch and release, loses its capacity to regenerate over time. This proposal focuses on **mechanisms linking mechanical stress to apoptosis in cardiomyocytes**, a phenomenon known as **mechanoptosis**. The members of this network argue that mechanoptosis is an important determinant of heart failure, and that by preventing this process, cardiomyocytes can be preserved and cardiac function maintained. They plan to address this problem by focusing on mechanical failure of the titin cytoskeleton as a trigger of apoptosis. Recent findings strongly indicate that cell loss is a leading primary pathological mechanism in HF driven by changes in the titin filament, a giant protein that contributes to the elasticity of the heart. Elasticity, in turn, helps to determine the conditions under which the heart fills with blood during diastole, the period in the cardiac cycle when the heart is not actively pumping blood. A loss of elasticity is associated with diastolic heart failure. A recently published genetic study identified a **mutation in titin as the cause of arrythmogenic cardiomyopathy**, a primary disease of the heart muscle caused by a breakdown of healthy myocardium.

This network is tightly focused on the **role of titin mediated stretch as a mechanical trigger of cardiomyocyte apoptosis**. The program brings together an interdisciplinary team of world-leading experts who will work to **identify the cellular mechanisms underlying progressive cytoskeletal pathologies in HF**. Transgenic mouse models with genetically altered titin compliances will be examined, and the network has the ability to transition from mouse to large mammal studies in the case of promising gene candidates. Furthermore, the network will support the development of innovative therapies for heart failure by identifying plausible targets for **regenerative/protective therapy to prevent cardiomyocyte death** in the setting of disease.

SCIENTIFIC ADVISORY COMMITTEE CHANGES

The **2014 Spring meeting of the Scientific Advisory Committee** (SAC) marked the conclusion of the terms of three members: Dr. Robert Roberts (University of Ottawa, Canada), Dr. Thomas Meinertz (University of Hamburg, Germany), and Dr. Stephen O'Rahilly (University of Cambridge, UK).

SAC Meeting, Ehlers Estate, St-Helena, Napa Valley, CA, USA- April 2014

From left to right:

Martin Landaluce, Hugh Watkins, Friedhelm Beyersdorf, Joseph Woo, Shaun Coughlin, Alain Tedgui, Dan Roden, Helen Hobbs, Robert Bonow, Bo Norrving, Thomas Meinertz, Robert Roberts, Margaret Buckingham, David Tancredi, Steve O'Rahilly, Michael Moskowitz.

At the April 2014 meeting in Napa Valley, the newly named to the SAC were

- **Dr. Christian Hamm**, Kerckhoff Heart Center, Bad Nauheim, Germany
- **Dr. Göran Hansson**, Karolinska Institute, Stockholm, Sweden
- **Dr. Daniel Drucker**, Lunenfeld Tanenbaum Research Institute, Toronto, Canada.

CALL FOR APPLICATION CYCLE 2014-2015

Fondation Leducq announces a **call for applications for the 2014-2015** Transatlantic Networks of Excellence Program. Under this program the Fondation Leducq awards grants of up to **U.S. $6,000,000** over five years for internationally collaborative research in cardiovascular and neuro-vascular disease. As of 2014, the foundation has supported **43 networks**, representing more than 390 investigators at 128 institutions in 18 countries.

For the 2014-2015 application cycle, Fondation Leducq will use a web-based application system hosted by **Altum proposalCENTRAL**. Information about the application process and details about important dates in the 2014-2015 application cycle can be found on our website at **flcq.org** under **Transatlantic Networks of Excellence**.

Due date for letters of intent is **Friday, September 5, 2014**, 11:59 pm Paris time.

NEXT TRANSATLANTIC NETWORK SYMPOSIUM

Fondation Leducq announces the **fifth Leducq Symposium**, to be held in **Paris on April 16th, 2015**. It will call together researchers from six different networks that were launched in 2009 and 2010. This symposium provides the fondation 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 TO BEGIN TO CONNECT NETWORKS

Later this year the Fondation Leducq will begin to put in place a mechanism to allow different Leducq networks to collaborate with each other. This initiative comes at the request of network investigators, who perceive the advantage of making connections with members of other networks who are working in related fields. The designers of the Fondation Leducq's new website are setting up a **listserv service** through which all members and coordinators from any Transatlantic Network of Excellence can pose questions to any member of another TNE on issues in cardiovascular and neurovascular research. Appropriate topics include **grant administration, program evaluation, and issues related to data access or to the sharing of resources** like animals, biological samples, and images. The audience for this email group is the universe of **investigators participating in any TNE**. It is hoped that by facilitating communication among networks, investigators can benefit from additional collaborative advantages through the Leducq program. The foundation will be examining other ways to leverage the expertise of the TNEs to promote internetwork collaboration.

A GREAT LADY!

Sylviane Leducq passed away in December 2013. She was 88. Until she was diagnosed with cancer in early 2013 she was very active in the management and oversight of the foundation that she had created with her husband Jean 17 years ago. She was tremendously dedicated to the foundation, and deeply recognizant of and grateful for the participation of the scientific community in foundation activities. Members of the SAC and investigators attending the 2013 fall and spring meetings will remember that she attended, and spoke at, the social events surrounding the meetings, despite her ongoing chemotherapy treatment.

After Jean Leducq passed away in 2002, Sylviane Leducq carried on the work of the foundation as President of the Board of Directors. She oversaw the implementation of the Transatlantic Networks Program, and the development of the venture philanthropy program Broadview Ventures, Inc. In 2009, she was awarded the French Legion of Honor in recognition of her generosity and leadership of the foundation. Her work helped to assure that the foundation will remain a family legacy in perpetuity, dedicated to its mission in cardiovascular and neurovascular research.

We would like to thank all the wonderful tributes to Sylviane that were sent to the Fondation Leducq following the announcement of her death. Costantino Iadecola, Cornell Medical College, New York, has agreed to let us publish his text in our Newsletter. It gives a good idea of the esteem and gratitude expressed by all the people who had the chance to know Sylviane personnally.

«The impact of the Fondation Leducq on the international scientific scene has been substantial and continues to grow from year to year. The Fondation has enabled hundreds of scientists to explore new ideas and to test groundbreaking hypotheses that could not otherwise be done within the boundaries of conventional funding agencies and foundations. In the prescient mind of Jean and Sylviane Leducq it was clear that new, game-changing discoveries in cardiovascular medicine, as in other disciplines, require efforts that go beyond individual laboratories, departments, universities, and even countries. Drawing from their transatlantic experience and with the help and guidance of dedicated scientists and administrators, they conceived and implemented the "Transatlantic Leducq Network" concept. Now the foundation provides vital support to the foremost centers of cardiovascular and neuro-vascular research throughout the world. The research portfolio is spectacular in depth and breadth, the discoveries breathtaking, and the number of publications in high impact journals is impressive. Leducq investigators are opening new avenues in cardiovascular research, which are now starting to bear fruit in the clinical arena, leading to new drugs, new medical devices and new surgical procedures to alleviate human suffering. This is exactly what Sylviane and Jean hoped to achieve. In truth, when I joined the Leducq Scientific Advisory Committee (SAC) in 2007, I was not aware of the Fondation. Now, I cannot attend a scientific meeting or visit a university without being asked about it. Being in a Leducq network has become a sign of distinction: investigators list their Leducq funding as a badge of honor on their curriculum vitae, and Medical School Deans seek it as a mark of distinction for their institutions. I often wondered how the Fondation became so successful in such a short time. As I got to know Sylviane a little I started to see a glimpse of a few driving principles: keep uncompromisingly high standards, foster a harmonious interaction among research teams, invest in the next generation, and provide unconditional support. It is not "throwing enough money at the problem", but creating the conditions in which culturally and scientifically diverse groups of out-standing individuals work together in harmony, keeping in mind that their ultimate goal is to improve the lives of our patients. As Sylviane rejoins Jean, she leaves us with a long lasting legacy that will continue to inspire the lives of a growing number of scientists on both side of the Atlantic, who work together under the Leducq aegis to alleviate human suffering. Sylviane we miss you.»

For more information about the Fondation Leducq, please visit our website at
www.flcq.org

or contact our Executive Director, Dr. David Tancredi at
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