

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circ Res. 2014;115:419-422

doi: 10.1161/CIRCRESAHA.115.304626

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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Fondation Leducq

David Tancredi, Eugene Braunwald

The Fondation Leducq was created in 1996 by French entrepreneur Jean Leducq and his wife Sylviane. Based in Paris, the foundation seeks to improve human health through international efforts to combat cardiovascular and neurovascular disease. By forging scientific alliances that transcend national borders, and promoting the education of young researchers who thrive in an international context, it hopes to promote innovative research, an efficient use of research resources, and the development of long-term collaborations that will help to meet the challenge of cardiovascular and neurovascular disease in the future. The foundation awarded its first research grants in 1999.

The foundation is constituted according to French law, having a 9-member Board of Directors and an observer appointed by the Minister of the Interior. Responsibility for evaluating the scientific merit of all funding requests made to the foundation lies with the Scientific Advisory Committee, which currently has 14 members serving on a rotating basis and is composed equally of North American and European members who are experts in cardiology, cardiac surgery, and neurovascular medicine (see below). The foundation's geographic reach reflects the internationalism of the founders, who were equally at home on both sides of the Atlantic.

After the death of Jean Leducq in 2002, Sylviane Leducq took over as President of the foundation's Board of Directors and remained in this role until she passed away in December 2013. Despite having had little previous experience in executive or management roles, she led the foundation with a mission-driven, common sense approach, overseeing the development and implementation of the Transatlantic Networks Program, and the creation of Broadview Ventures, Inc. Preferring to avoid publicity, she, initially with her husband, discreetly directed contributions of \geq \$350 millions to cardiovascular and neurovascular research. In 2009, the French government, in recognition of her leadership and generosity, awarded Sylviane Leducq the Legion of Honor. Now, after the death of both founders, the family bequest will ensure that the foundation will remain true to its mission in cardiovascular and neurovascular research and will have the resources to continue the work that Jean and Sylviane Leducq began 15 years ago.

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(*Circ Res.* 2014;115:419-422.)

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Circulation Research is available at <http://circres.ahajournals.org>
DOI: 10.1161/CIRCRESAHA.115.304626

Transatlantic Networks

In 2003, the Fondation Leducq introduced the Transatlantic Networks of Excellence, a program designed to promote collaborative research among investigators in North America and Europe in the areas of cardiovascular and neurovascular disease. Its aims are to develop international research networks that advance science; to apply the knowledge gained; to promote the development of technology and therapeutics to improve human health; to allow researchers to benefit from the added value of collaborative work at the international level; and to support early career investigators. Each network aims to advance knowledge on a defined theme, by pooling a critical mass of competence and skills, creating effectively a virtual center of excellence. Network activities, capitalizing on the network's human and institutional resources, are oriented toward long-term goals, not at producing predefined results.

Each network is led by 2 coordinators (one in Europe and one in North America), who are jointly responsible for the design of the research program, the composition of the network, the execution of the research plan, and the expenditure of funds. Each network includes other participating scientists (members) who are well-established investigators with a successful track record of independent research. The Fondation Leducq has recently opened the Transatlantic Network to investigators worldwide, with the condition that network coordinators will still be based in Europe and North America. Nonfoundation funded investigators may also participate in network activities.

Evaluation Criteria

Fondation Leducq evaluates applications to the Transatlantic Networks of Excellence Program in a 2-stage process. Interested applicants must first submit a letter of intent describing the composition of the proposed network and the general research plan. The Scientific Advisory Committee reviews the letters of intent and requests a full proposal from a selected number of network applicants. In previous years, the number of such requests has ranged between 8 and 12 of \approx 100 to 120 letters of intent. Full proposals are then evaluated by the Scientific Advisory Committee and \leq 4 per application cycle are recommended to the Board of Directors for funding; this number may be increased in future application cycles. Networks are funded for 5 years up to a total of \$6 million and are not renewable. However, it is hoped that scientific collaboration between investigators in the network will continue after the funding period.

Networks should strive to advance knowledge on a defined theme by pooling a critical mass of competence and skills. The theme of a network may cover a variety of inter-related topics or subjects. Network activities are oriented toward long-term goals not at producing predefined results. The total number of institutions involved in a network should generally not exceed 6. All network applicants must demonstrate, in the

application, how the composition of the network advances the scientific objectives of the research program.

The criteria used by the Scientific Advisory Committee in assessing Transatlantic Network applications include the quality of the scientific work to be pursued; the scientific excellence and experience of the coordinators and members; the extent and depth of the collaborative effort; the potential added value of the collaborative enterprise; the capacity of the network to implement the proposal; and the commitment to the training and promotion of early career investigators.

Networks are granted a high degree of flexibility and autonomy in the implementation of their joint program of activities, including

1. Discretion in network structure and governance
2. Capacity to modify the joint program of activities
3. Ability to reallocate financial resources

The application timetable for 2014 to 2015 is as follows:

Due date for letters of intent: Friday, September 5, 2014
 Notification of application status: Early November 2014
 Full application deadline: February 2015
 Scientific Advisory Committee review: April 2015
 Board review: June 2015
 Award announcements: June 2015
 Funding to commence: October 2015

Funding from the Fondation Leducq is not to be the sole source of support for the networks. Indeed, it is important that applicants demonstrate other competitive peer review funding sources for some of their research. It is expected that Fondation Leducq funding will be used in large part, although not exclusively, to create and support the network, its coordination, and the proposed collaboration.

As of early 2014, the foundation has supported 39 networks, representing ≥360 investigators at 123 institutions in 18 countries, covering themes across the spectrum of cardiovascular and neurovascular research (see below). Leducq researchers have played prominent roles in the identification and characterization of cardiac stem cells, the discovery of genomic markers identifying patients at risk for arrhythmias, the description of immune mechanisms in atherogenesis, and the demonstration of the clinical use of remote ischemic preconditioning in patients with acute myocardial infarction. Research from Leducq networks has contributed to the understanding of vascular malformations, highlighted the fundamental role of perturbations in myocardial calcium handling in atrial fibrillation, identified calcium calmodulin kinase II as a critical node in signaling pathways in atrial fibrillation and heart failure, assessed the pathophysiological role and therapeutic potential of microRNAs in heart disease, provided new models of mitral valve disease and implicated pericytes in the persistence of diminished blood flow after a stroke. There is clearly more to come, as the Transatlantic Network Program continues to attract outstanding applicants.

2014 to 2015 Members of the Fondation Leducq Scientific Advisory Committee

North American members:

1. Dr Robert Bonow, Northwestern University, Chicago, IL, USA

2. Dr Shaun Coughlin, University of California, San Francisco, CA, USA
3. Dr Daniel Drucker, Lunenfeld Tanenbaum Research Institute, Toronto, Canada
4. Dr Helen Haskell Hobbs, University of Texas Southwestern, Dallas, TX, USA
5. Dr Michael Moskowitz, Massachusetts General Hospital, Boston, MA, USA
6. Dr Dan Roden, Vanderbilt University School of Medicine, Nashville, TN, USA
7. Dr Joseph Woo, Stanford University, Palo Alto, CA, USA

European members:

1. Dr Friedhelm Beyersdorf, Heart Center Freiburg University, Germany
2. Dr Margaret Buckingham (President), CNRS/Pasteur Institute of Paris, France
3. Dr Christian Hamm, Kerckhoff Heart Center, Bad Nauheim, Germany
4. Dr Göran Hansson, Karolinska Institute, Stockholm, Sweden
5. Dr Bo Norrving, Lund University, Lund, Sweden
6. Dr Alain Tedgui, Paris-Cardiovascular Research Center, Paris, France
7. Dr Hugh Watkins, University of Oxford, Oxford, United Kingdom

Fondation Leducq Transatlantic Networks of Excellence: 2010 to 2014, per year of activation

2014

Deciphering the Genomic Topology of Atrial Fibrillation

1. European coordinator: Vincent Christoffels, Academic Medical Center (AMC), Amsterdam, Netherlands
2. North American coordinator: Patrick Ellinor, Massachusetts General Hospital, Boston, MA, USA

Sphingosine 1-Phosphate in Neurovascular Biology and Disease (SphingoNet)

1. European coordinator: Christer Betsholtz, Uppsala University, Uppsala, Sweden
2. North American coordinator: Timothy Hla, Weill Medical College of Cornell University, New York, NY, USA

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

1. European coordinator: William McKenna, University College of London, London, United Kingdom
2. North American coordinator: Ali J. Marian, University of Texas Health Sciences Center and Texas Heart Institute, Houston, TX, USA

Programming the Failing Heart to a Regenerative State

1. European coordinator: Mauro Giacca, International Center for Genetic Engineering and Biotechnology, Trieste, Italy

2. North American coordinator: Richard Lee, Brigham and Women's Hospital, Boston, MA, USA

2013

Cellular and Molecular Targets to Promote Therapeutic Cardiac Regeneration

1. European coordinator: David Sassoon, UPMC-Sorbonne Universités, Paris, France
2. North American coordinator: Toren Finkel, NIH, Bethesda, MD, USA

MicroRNA-Based Therapeutic Strategies in Vascular Disease

1. European coordinator: Thomas Thum, Hannover Medical School, Hannover, Germany
2. North American coordinator: William Sessa, Yale University, New Haven, CT, USA

The Function and Regulation of PCSK9: a Novel Modulator of LDLR Activity

1. European coordinator: Anders Hamsten, Karolinska Institute, Stockholm, Sweden
2. North American coordinator: Nabil G. Seidah, IRCM, Montreal, Canada

Mechanical Triggers to Programmed Cell Death in Cardiomyocytes—and How to Prevent Their Action in Failing Hearts

1. European coordinator: Siegfried Labeit, University of Heidelberg, Mannheim, Germany
2. North American coordinator: Hendrikus Granzier, University of Arizona, Tucson, AZ, USA

2012

Pathogenesis of Small-Vessel Disease of the Brain

1. European coordinator: Anne Joutel, INSERM, Université Paris 7-Denis Diderot, France
2. North American coordinator: Mark T. Nelson, University of Vermont, Burlington, VT, USA

Understanding Coronary Artery Disease Genes

1. European coordinator: Heribert Schunkert, University of Lübeck, Lübeck, Germany
2. North American Coordinator: A. Jake Lusis, University of California, Los Angeles, CA, USA

Mechanistic Interrogation of Bicuspid Aortic Valve associated Aortopathy

1. European coordinator: Bart Loeys, University of Antwerp, Antwerpen, Belgium
2. North American coordinator: Harry Dietz, Johns Hopkins University, Baltimore, MD, USA

TNT-Triglyceride Metabolism in Obesity and Cardiovascular Disease

1. European coordinator: Rudolf Zechner, University of Graz, Graz, Austria

2. North American coordinator: Stephen G. Young, UCLA, Los Angeles, CA

2011

Genomic, Epigenomic, and Systems Dissection of Mechanisms Underlying Dilated Cardiomyopathy

1. European coordinator: Stuart Cook, Imperial College, London, United Kingdom
2. North American coordinator: Christine Seidman, Harvard Medical School, Boston, MA, USA

Translating Human Pluripotent Stem Cells From Heart Disease Models to Cardiac Repair

1. European coordinator: Michel Puceat, Université Paris Descartes, INSERM U633, Evry, France
2. North American coordinator: Andre Terzic, Mayo Clinic, Rochester, MN, USA

Lymph Vessels in Obesity and Cardiovascular Disease

1. European coordinator: Kari Alitalo, University of Helsinki, Helsinki, Finland
2. North American coordinator: Mark Kahn, University of Pennsylvania, Philadelphia, PA, USA

Proteotoxicity: An Unappreciated Mechanism of Heart Disease and Its Potential for Novel Therapeutics

1. European coordinator: Mathias Gautel, King's College, London, United Kingdom
2. North American coordinator: Jeffrey Robbins, Cincinnati Children's Hospital, Cincinnati, OH, USA

2010

Transatlantic Network on Newborn Stroke: Inflammatory Modulation of Neurovascular Injury

1. European coordinator: Pierre Gressens, INSERM U676, Hôpital Robert Debré, Paris, France
2. North American coordinator: Donna Ferrero, University of California, San Francisco, CA, USA

Multidisciplinary Program to Elucidate the Role of Bone Morphogenetic Protein Signaling

1. European coordinator: Nicholas Morrell, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom
2. North American coordinator: North American Coordinator Kenneth Bloch, Harvard Medical School, Boston, MA, USA

Molecular Mechanisms of Novel Genes Associated With Plasma Lipids and Cardiovascular Disease

1. European coordinator: Christian Weber, Ludwig-Maximilians-Universität, München, Germany
2. North American coordinator: Daniel Rader, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

High-Density Lipoprotein Dysfunction in the Development of Cardiovascular Disease and as a Therapeutic Target

1. European coordinator: Thomas Luscher, University of Zurich, Zurich, Switzerland

2. North American coordinator: Alan Fogelman, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, USA.

Broadview Ventures

In 2008, the foundation's trust created a philanthropic venture fund, Broadview Ventures, Inc, a new program dedicated to accelerating innovation in the area of cardiovascular and neurovascular disease through a direct investment model, to make targeted investments in early stage companies to accelerate the development of technology for the diagnosis and treatment of cardiovascular and neurovascular diseases. Based in Boston, MA, Broadview Ventures was designed to help overcome the translational funding gap faced by early stage companies that are too far advanced for traditional academic funding but not sufficiently developed to attract conventional venture capital investment. Although nominally operating as a for-profit company, Broadview is mission, not profit, driven. The sole shareholder of Broadview is the Leducq Trust, which can accept both the risks and the long-term capital lockups associated with early stage investing. Any profits earned through Broadview investment are to be used for additional Broadview investment or to provide further funding for the Transatlantic Center of Excellence program.

The 21 investments made thus far by Broadview include technologies in microRNA therapy, stem cell therapy,

percutaneously inserted mitral valves, hypertension, and mechanical and pharmacological treatments for atrial fibrillation, diabetes, and obesity. Five of these investments are in companies related to previous grantees of the foundation. The Broadview investment team, led by Christopher Colecchi, consists of physicians, scientists, and business professionals who manage the due diligence and investment process. After investment, Broadview plays an active role in supporting its portfolio companies via board participation. Although success in this endeavor, defined by improving care for patients, can only be measured in the long term, early indicators are promising that Broadview is having an effect on technology development.

Further information about the Fondation Leducq and the Transatlantic Networks of Excellence Program can be found on the Website (www.flcq.org). Further information about Broadview Ventures can be found on the Website (www.broadviewventures.org).

Disclosures

D.T. is employed full time as Executive Director of the Fondation Leducq, 1, rue Laurent Pichat, 75116 Paris, France. E.B. was a founding member of the Fondation Leducq's SAC and currently serves on the SAB of Broadview Ventures, Inc.

KEY WORD: cardiovascular diseases