Thrombin Receptor Activation Work Wins 2011 Lucian Award

Alice McCarthy

For more than 30 years, the Lucian Award for Research in Circulatory Disease has recognized the contribution of an investigator or team whose work has had a significant impact on our understanding of cardiovascular disease. Designed to promote innovative research and a collaborative spirit, the 35th Lucian Award was awarded last summer at McGill University in Montreal, Quebec.

The Lucian Award
Created in 1965 by a $2 million bequest of Olga Leibovici in honor of her two brothers, Louis and Artur Lucian, the Lucian Award is a $60,000 CDN prize that was first awarded in 1978. The terms of the bequest state that McGill University or its representative will use part of the income from the original $2 million endowment to create the Louis and Artur Lucian Award. “Very specifically, it should be given to the best work recently published related to diseases of the cardiovascular system,” explains Jacques Genest MD, FRCP(C), Professor, Faculty of Medicine at McGill University, and Scientific Director, Center for Innovative Medicine at the Research Institute at the McGill University Health Center, and current Chair of the Lucian Selection committee. “As such, this award has had a huge influence over the course of the last nearly 40 years.”

Each year the Lucian Award jury, which is composed of a mix of past Lucien Award recipients and former graduates or current faculty of McGill University, meets to review the approximately 20 to 30 applications received each year. “It was a very tough choice this year. We had truly outstanding applicants,” says Dr Genest.

This year’s winner is Shaun Coughlin, MD, PhD, of the University of California, San Francisco Cardiovascular Research Institute, whose laboratory studies signaling mechanisms involved in cardiovascular biology and disease. Dr Coughlin was awarded the prize for his work on how proteases regulate cellular behaviors and the importance of such regulation in vivo.

A cell and molecular biologist by research training and a cardiologist by clinical training, Dr Coughlin has long been interested in the receptors and signaling mechanisms that control biological processes. “They are not only central to understanding cell and tissue biology and physiology but they often suggest targets for therapeutics,” he explains.

Shaun R. Coughlin, MD, PhD

Dr Shaun R. Coughlin, MD, PhD, received his undergraduate and graduate training from Massachusetts Institute of Technology and his MD from Harvard Medical School. After internship and residency in internal medicine at Massachusetts General Hospital, he moved to the University of California San Francisco, for cardiology and postdoctoral research fellowships. He joined the University of California San Francisco, faculty in 1986 and is currently a Distinguished Professor of Cardiovascular Biology and Medicine and Director of the University of California San Francisco Cardiovascular Research Institute. In 1991, Coughlin’s laboratory’s discovery of a thrombin receptor, now known as PAR-1, revealed the molecular mechanism by which thrombin, a protease, can regulate the behavior of platelets and other cells like hormones do. The laboratory’s characterization of PAR-1 and other members of the PAR family led to a greater understanding of how cells sense and respond to tissue injury to orchestrate hemostasis, thrombosis, and inflammation, and pointed to PAR-1 antagonism as a possible strategy for antithrombotic therapy. A PAR1 antagonist is in phase 3 trials for secondary prevention of myocardial infarction. The laboratory currently explores the roles of PAR and other G-protein-coupled receptors in cardiovascular biology and disease and in embryonic development. Dr Coughlin is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences.

Thrombin Receptor Activation

Dr Coughlin was recognized by the Lucian committee for his work on the thrombin receptor and related receptors and the mechanism by which they are activated by proteases. Known as protease-activated receptors (PARs), these molecules play important roles in hemostasis and thrombosis. PARs are activated when a protease cleaves part of their extracellular domain.

“The coagulation protease thrombin is arguably the most potent activator of platelets,” explains Dr Coughlin. It also triggers a variety of responses in endothelial cells, smooth muscle cells, fibroblasts, and other cell types. “Because thrombin and platelets help form the clots that cause

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Correspondence to Alice McCarty. E-mail alice@alicemccarthy.com


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myocardial infarction and a subset of strokes, uncovering the mechanism by which thrombin activates platelets held out the possibility of revealing targets for novel antithrombotic drugs.”

This framed a fundamental basic question, how does a protease—like a hormone—regulate the behavior of a cell? Dr Coughlin utilized an expression-cloning approach to identify a G-protein-coupled receptor for thrombin now known as PAR-1. He discovered that limited proteolysis of this receptor by thrombin unmasks a peptide agonist hidden within the receptor’s N-terminal exodomain. Once unmasked, this “tethered ligand” binds to the receptor’s heptahelical bundle to trigger transmembrane domain movement and G-protein activation (Figure). “Thus, PARs explained how a protease can act like a hormone, and they also provided tools for understanding the roles of protease signaling,” says Dr Coughlin. “The general model that emerged is that, together,
the coagulation cascade and PARs link tissue injury to cellular responses that help orchestrate hemostasis, inflammation, cytoprotection, and repair.” A PAR-1 antagonist is now in phase 3 clinical trials as an antithrombotic therapy for secondary prevention of myocardial infarction.

What convinced the Lucian jury to award the prize to Dr Coughlin is that this discovery has extremely important ramifications in the cardiovascular field and other areas of biology and translates into a potentially useful treatment in humans. Explains Dr Genest, “We felt the contribution to the cardiovascular field, but also to the broad overall knowledge was impressive enough that it warranted the prize this year. When you think of normal receptor function, we all were taught to look for ligand–receptor interaction that triggers action. But the concept that a receptor could be activated by a protease such as thrombin opened the field enormously.”

Although Dr Coughlin does not maintain a clinical practice, he found that the time he spent with patients drove home for him the toll taken by atherothrombosis and instilled in him an enduring interest in improving prevention and treatment. “This shaped my laboratory’s choice to tackle the thrombin receptor problem and [it] continues to influence some of the questions we ask today,” he said.

Advancing Cardiovascular Research

Dr Coughlin believes that fostering application of chemical, physical, engineering, and computational tools to biological problems remain strong areas of opportunity to advance basic and translational cardiovascular research. “More generally, my bias is that the entry of new investigators who bring novel ideas and approaches and the focused, sustained efforts of individual labs to crack important problems will continue to be the main sources of breakthroughs,” he says. As such, he wants to see that the National Institutes of Health R01 funding mechanism is protected during these tough times.

In the translational/clinical research arena, Dr Coughlin sees a great need to develop better biomarkers, imaging techniques, and other tools for studying pathophysiology in humans to enable informative small-scale mechanistic studies. This includes better disease phenotyping and patient stratification. “Advances in these areas will be key, not only for improving basic understanding of disease but also for reducing the risk and cost of therapeutic development,” he adds. “This highlights a need for individuals who can bridge basic and clinical research.”

Dr Genest is concerned that maintaining the pace and breadth of basic cardiovascular research represents a huge challenge. “As the molecular biology revolution came forth, the training is now much more lengthy and the gap between clinicians who must be technically skilled and be a good diagnostician and a scientist who must strive to reach excellence is ever-widening,” he says. “My personal feeling is the program like the MD/PhD clinician–scientist award and prolonged training in an institution of excellence is absolutely essential.” He admits though that the difference in remuneration favoring a clinical practice and the ever-present challenge in securing research funding can be a drawback for those interested in a purely research-based career. Citing the salaried practice plan for scientists and clinicians alike at institutions such as the Mayo Clinic and Cleveland Clinic, Dr Genest believes this model is appealing for those who wish to devote their work to advancing basic cardiovascular research. “Plus, academic research is so incredibly fun, exciting, highly competitive, and it certainly drives many of us,” he adds. “It is that kind of enthusiasm that we must continue to share with our younger colleagues. For example, it is one of the greatest joys of my career to phone the Lucian recipient each year. It is fantastic how a philanthropic gift given 50 years ago still allows recognition of international cardiovascular research excellence.”

The next deadline for submitting nominations for the Lucian Award is March 16, 2012, and further information can be found on their Web site at http://www.mcgill.ca/lucianaward/.
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