News & Views

2015 Lucian Award
Jeffery Molkentin
Susan Ince

The 38th Louis and Artur Lucian Award for Research in Circulatory Diseases has been presented to Jeffery Molkentin, PhD, of Cincinnati Children’s Hospital Medical Center. Molkentin is being honored for several paradigm-changing discoveries about the molecular mechanisms of cardiac disease.

Fifty years ago, Dame Olga Leibovici established the Lucian award honoring her brothers—both engineers who died prematurely—when she bequeathed $2 million to McGill University. The $60,000 CAN prize recognizes the contributions of active investigators or teams whose work has had a significant impact on the understanding of cardiovascular disease (Table). The Lucian Award places no restrictions on the sex or nationality of recipients, who are selected by a committee of scientists that includes several former awardees. The Montreal community benefits from the award through collaborations that are nurtured during the awardee’s official visit to McGill.

At age 48, Molkentin is the youngest scientist to ever receive the Lucian award.

“Molkentin has made four fundamental discoveries in cardiology and basic cellular biology in a fairly short time span, and his trajectory is like a rocket that is still going up,” says Jacques Genest, MD, FRCP(C), Professor, Faculty of Medicine at McGill University, current Chair of the Lucian Selection Committee, and Novartis Chair in Medicine, McGill University.

New Thinking About Hypertrophy

During his postdoctoral training in Eric Olson’s laboratory at the University of Texas Southwestern Medical Center in Dallas, Molkentin discovered that a variety of pathological stimuli could induce cardiac hypertrophy via a calcium–calcineurin–nuclear factor of activated T cells (NFAT) signaling pathway and that transgenic mice expressing activated forms of calcineurin or NFAT3 in the heart develop hypertrophy and heart failure that mimic the disease in humans. Administration of the immunosuppressant agents, cyclosporine A and FK506, inhibited calcineurin’s ability to activate NFAT transcription factors and prevented hypertrophy in calcineurin transgenic mice. Shortly thereafter, Molkentin and Sussman et al showed that calcineurin signaling was necessary and sufficient for the heart to hypertrophy. The calcineurin inhibitors, cyclosporine A and FK506, prevented disease in mice that were genetically predisposed to develop hypertrophic cardiomyopathy, suggesting that the drugs might represent potential therapies for certain forms of human heart disease.
“This was initially a very surprising and controversial finding that was subsequently validated in hundreds of publications. Jeff’s work during that period opened a new avenue of investigation centering on the involvement of abnormal calcium signaling as a basis for heart disease. His work combines elegant molecular biology with the creation of animal models for human disease, and his productivity since establishing his own laboratory has been staggering. I especially admire Jeff’s boundless energy and scientific rigor and enthusiasm,” says Olson, who nominated Molkentin for the Lucian award.

Fine-Tuning Contractile Responsivity

In 2004, Molkentin identified a mechanism whereby protein kinase C-α (PKCα) directly regulates contractility in the cardiac myocyte by phosphorylating selected nodal calcium handling proteins at the level of the sarcoplasmic reticulum.4 Transgenic mice that overexpress PKCα have reduced cardiac function and an increased propensity toward heart failure. In contrast, PKCα null mice show enhanced cardiac calcium handling and contractility and are protected against the development of heart failure following multiple adverse stimuli. Pharmacological inhibition of PKCα showed similar protection, and Molkentin’s laboratory followed up with a series of papers strongly suggesting that PKCα inhibition might prove therapeutic in human heart failure.

“When you antagonize PKCα, it benefits the heart in a number of important ways. In collaboration with a few clinicians at Cincinnati Children’s Hospital and Christ Hospital, we are currently in the process of trying to bring this work into the clinic by investigating the use of known antagonists to PKCα in heart failure patients,” Molkentin says.

Programming Cellular Necrosis

While investigating the effects of blocking calcineurin with cyclosporine in mice with cardiac hypertrophy, Molkentin obtained perplexing results that sent his laboratory in an entirely new direction in cellular biology. In addition to blocking calcineurin’s action in the cell nuclei, cyclosporine changed the mitochondrial reaction to stress, boosting survival. Working with a series of transgenic mouse tissue cultures with key proteins knocked out, he identified cyclophilin D as the mitochondrial protein deactivated by cyclosporine. In 2005, he offered the first definitive proof that cellular necrosis can be a programmed event initiated at the level of the mitochondria, with cyclophilin D the initial player in the sequence of destruction.5

“Well, we’ve put a big push on this work in recent years and we’re trying to put together a molecular blueprint of all the genes that might regulate necrosis in vivo,” says Molkentin.

The work opens significant new possibilities for treating human disease. For example, Molkentin found that brain and heart cells lacking cyclophilin D are markedly protected from ischemic injury, suggesting that cyclophilin D inhibitors might be therapeutic in treating heart disease and other diseases involving progressive cell death.

“The paper on cellular necrosis was quite controversial at the time, but the fact that mitochondrial permeability may relate to cellular necrosis was a key finding and is now quite generally accepted,” Genest says.

Tracing Cardiac Stem Cells

In the quest to generate new myocytes in the heart after injury, multiple papers over a decade claimed that ckit progenitor...
cells could dramatically repair the heart after infarction by forming new myocytes. However, an equal number of reputable laboratories did not find that ckit+ cells generated new myocardium after injury.

In the face of these discordant results, Molkentin decided to apply a rigorous genetic analysis of ckit+ progenitor cells introduced into mice. Using genetic lineage tracing, they put fluorescent proteins into genetic tags so the cells would stay the same color no matter what type of cell they differentiated into (Figure). The researchers found that ckit+ cells make myocytes at an exceedingly low rate, on the order of 1 in 4000, whether during development, with aging, or following various types of injury.

“At least in the mouse heart, our data suggest that adult ckit+ cells are not primarily dedicated to making new myocytes. We haven’t ruled out that there are true adult stem cells that can make new myocytes, but it looks less likely now. One way these results can be interpreted is that ckit+ cells might not be the best choice to treat patients. However, our results don’t actually say that. ckit+ cells might be clinically useful because they secrete and generate a paracrine milieu and that might itself be reparative,” Molkentin says.

For example, this paracrine milieu might stimulate existing myocytes that retain some finite capability for proliferation, to aid in repair, Molkentin suggested in a recent review. Most adult stem/progenitor cells are now thought to exert their beneficial effects in the heart through paracrine mechanisms.

“This elegant and rigorous work to trace the fate of the ckit+ cells shows how much work needs to be done in this field before there can be true cardiac regeneration therapy,” says Genest.

In addition to his work on cardiac regeneration, Molkentin is currently using lineage tracing to better understand the source of cardiac fibroblasts (at least 5 different sources have been suggested in the literature) and how that may relate to long-term remodeling of the heart, for both good and bad.

“Clinically, this is important because within the first few days after a myocardial infarction, myocytes in the infarct area necrose and need to be replaced very quickly with a stable scar to prevent rupture of the ventricular wall. For the most part, that is mediated by fibroblasts, which sense the dying myocytes and the tension in the wall and become activated, secreting extracellular matrix collagen, attaching to that collagen, and contracting—thus putting stability in the scar. In the beginning, you need this to happen correctly, but over the long-term, when the wall remains under increased tension, those fibroblasts continue to stay active and can spread fibrosis throughout the remaining myocardial wall and create stiffening, giving you a restrictive cardiomyopathy,” Molkentin says.

The goal in understanding these cells and how to control them is to discover drugs that can shut down the cells acting long term without affecting the ones needed right away for healing.

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**Figure.** Myocytes (red) stained with α-actinin antibody and ckit+ lineage-derived cells (green) stained with GFP antibody in cells dissociated from the heart of a 4-week-old mouse containing the Rosa26-loxP-dependent eGFP reporter crossed with the Kit-MerCreMer allele. Tamoxifen was given at birth through 4 weeks of age to induce recombination in ckit+ lineage-derived cells. DAPI indicates 4',6-diamidino-2-phenylindole; and eGFP, enhanced-green fluorescent protein.

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In addition to pursuing multiple lines of research on heart disease, for the last 10 years Molkentin’s laboratory has examined the molecular mechanisms involved in muscular dystrophy, including the role of calcium influx in myofiber death. Some of his basic research findings have suggested a new way to protect muscle tissue, and Molkentin is currently working with a drug company to advance the potential treatment toward clinical trials.

“I think Molkentin’s work has the potential not only to generate fundamental new knowledge, but it is directly relevant to the treatment of patients with heart failure and muscular dystrophy who have a huge unmet clinical need,” says Steven Houser, PhD, director of the Cardiovascular Research Center at Temple University School of Medicine in Philadelphia.

The next deadline for a dean or department chair to nominate a scientist for the Lucian Award is March 18, 2016. Further information is available at http://www.mcgill.ca/lucianaward/.

Disclosures

None.

References

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