The 35th Louis and Artur Lucian Award for research in circulatory disease has been presented to physician scientist David Ginsburg, MD, of the University of Michigan, for his groundbreaking work on blood coagulation and cellular protein processing in cardiovascular diseases.

Since its beginnings with a $2 million bequest to McGill University in 1965, the Lucian Award has recognized the contributions of active investigators or teams whose work has already had a significant impact on the understanding of cardiovascular disease (Table). In her will, Olga Leibovici established the award to honor her brothers, both engineers, who had died prematurely. The $600000 CAN prize, the largest given in any biomedical field in Canada, was first awarded in 1978. The Lucian Award places no restrictions on the nationality of the recipients. The McGill University community and awardees benefit from collaborations that are established or furthered during the time winners spend at McGill.

Recipients are selected by a committee of scientists, approximately half of whom are former awardees, and each year approximately 15 top-notch applications make it to the last round.

“It is remarkable how much Ginsburg has transcended, seemingly effortlessly, traditional division and departmental lines in dealing with medicine, vascular biology, and basic molecular biology. His ability to work within a variety of disciplines is what made him the awardee this year,” 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.

Using Genetics to Unravel Bleeding Disorders

While a postdoctoral fellow in the laboratory of Stuart H. Orkin, MD, at Children’s Hospital, Boston, Massachusetts, Ginsburg was inspired by how thoroughly the identification of hemoglobin genes had transformed understanding of the thalassemias. Ginsburg decided to search for the gene for von Willebrand factor (VWF) to better comprehend von Willebrand disease (VWD), a bleeding disorder that turned up regularly in the clinic but varied so widely that it was often confusing and difficult to diagnose.

Independently and simultaneously, Orkin’s laboratory and 3 others cloned and characterized the gene in 1985, laying the groundwork for future work to dissect the molecular genetic basis of VWD.

After starting his own laboratory at the University of Michigan, Ginsburg identified various mutations in the gene that defined VWD subtypes and helped explain differences in disease severity. In addition, Ginsburg’s laboratory identified modifier genes that can result in many-fold differences in plasma VWF. While his laboratory has consistently explored VWF, the findings have also led Ginsburg into surprising and fruitful new directions, leading to better understanding...
of a catastrophic clotting disorder, the basic mechanisms of protein transfer within cells, and the means by which certain streptococcal infections become invasive.

From Patients to Systems and Back Again

As a physician board-certified in hematology, oncology, and genetics, Ginsburg cares for patients with rare and often mysterious diseases. He became intrigued by thrombotic thrombocytopenic purpura (TTP), an important hemolytic disease that can be either genetic or acquired. Suddenly, patients with TTP (often young and previously healthy) experience development of clots in blood vessels throughout the body. Before treatment with plasma exchange was developed, mortality could be 80% within 2 days. Ginsburg cloned the gene involved in a rare inherited form of TTP and found that it had an important relationship to VWF. It turned out the gene coded for a protease, a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 13 (ADAMTS13), which normally trims the large VWF molecule to the appropriate size so it can stick to platelets and the vessel injury site. When ADAMTS13 is lacking, the VWF protein remains overly large and sticky, sometimes resulting in spontaneous clots. Plasma exchange works by replacing the missing protease.

“Besides determining the genetics underlying the inherited forms of TTP, he has helped explain the interaction between the genetic predisposition and triggers and toxins that will result in an attack,” says Genest.

The work on TTP also led to an explanation for type 2a VWD. Instead of lacking ADAMTS13, these patients are overly sensitive to the protease, so their VWF gets cut into abnormally small pieces and bleeding can occur.

“The human diseases really taught us how this whole system worked and how von Willebrand’s function is controlled and the way it interacts with blood platelets. And of course we learned a lot about the diseases, including how to measure ADAMTS13 and how to make the diagnosis of TTP. Recombinant proteins are now being developed and hopefully will someday be used as treatment for VWD and TTP,” says Ginsburg.

Protein Trafficking Within Cells

When chasing a human disease, Ginsburg has found that the biology often leads a scientist in unanticipated directions. While investigating the cause of a mysterious inherited bleeding disorder, combined factor V and factor VIII deficiency, Ginsburg’s laboratory found the problem not in the genes for the factors themselves but in basic cellular transport. For the first time in mammalian cells, they identified a cargo receptor that sits in the endoplasmic reticulum and helps escort proteins from the endoplasmic reticulum to the Golgi apparatus. Factors V and VIII turned out to be supremely sensitive to mutations in 1 of 2 genes needed to form the cargo receptor. If the carrier complex was missing, then levels of the blood-clotting proteins were reduced $\approx 90\%$, creating the bleeding disorder.2

That finding furthered Ginsburg’s interest in intracellular protein transfer, a process well-studied in yeast but not in...
mammals. In recent years, Ginsburg has collaborated with Randy W. Schekman, PhD, of the University of California Berkeley, recipient of the 2013 Nobel Prize in Physiology or Medicine. They were curious about SEC24, a protein present in 1 copy in yeast but in 4 in humans. SEC24 forms part of the coating of coatomer II coated vesicles involved in endoplasmic reticulum-to-Golgi apparatus transportation.

To their surprise, when they created mice lacking 1 of the 4 types, SEC24A, the animals developed normally but had a 45% reduction in plasma cholesterol levels because they were unable to transport the secretory protein PCSK9 (proprotein convertase subtilisin/kexin type 9), a critical regulator of the cell surface low-density lipoprotein receptor. Without PCSK9, levels of the low-density lipoprotein receptor increase and blood cholesterol levels decrease3 (Figure 1).

Although clinical questions led Ginsburg into basic research, the findings may have pointed the way toward new cardiovascular disease therapy. An understanding of the cell transport defects in combined factor V/VIII deficiency presents a possible target for new anticoagulant drugs. Many companies are already pursuing various ways to interfere with PCSK9 to lower cholesterol, and SEC24A might present an alternative target.

“The implications of this basic research on protein transport are huge,” says Genest.

### Lucian Award Selection Committee

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McGill University, Canada  
Samuel O. Freedman, MD  
McGill University, Canada  

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Table. Previous Recipients of the Lucian Award

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<td>Nicolae and Maya Simionescu</td>
<td>Bucharest and Yale University</td>
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<td>James Bassingthwaighte</td>
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<td>1980</td>
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<td>Johns Hopkins University</td>
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<td>Aubrey Taylor</td>
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<td>1989</td>
<td>Francis Chirn</td>
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<td>1990</td>
<td>Ian Phillips</td>
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<td>1991</td>
<td>Barbara Meyrick</td>
<td>Vanderbilt University</td>
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<td>1992</td>
<td>José Jalife</td>
<td>State University of New York, Syracuse</td>
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<td>1993</td>
<td>Judah Folkman</td>
<td>The Children's Hospital, Boston</td>
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<td>1994</td>
<td>Arthur Brown</td>
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<td>1995</td>
<td>John B. Barlow</td>
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<td>1996</td>
<td>Andrew and Avril Somlyo</td>
<td>University of Virginia, Charlottesville</td>
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| 1997 | Robert Furchgott | State University of New York  
Salvador Moncada | University College, London |
| 1998 | Russell Ross | University of Washington |
| 1999 | Eduardo Marban | Johns Hopkins University |
| 2000 | Victor J. Dzau | Harvard Medical School |
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| 2002 | Mark C. Fishman | Harvard Medical School |
| 2003 | Salim Yusuf | McMaster University |
| 2004 | Eric N. Olson | University of Texas  
Southern Medical Center |
| 2005 | Robert Bolli | University of Louisville |
| 2006 | Michael A. Gimbrone, Jr | Harvard Medical School |
| 2007 | Peter Carmeliet | University of Leuven |
| 2008 | Not Awarded |  
Piero Anversa | Harvard Medical School |
| 2009 | Peter Libby | Harvard Medical School |
| 2010 | Marlene Rabinovitch | Stanford University School of Medicine |
| 2011 | Shaun R. Coughlin | University of California, San Francisco |
| 2012 | Garret A. Fitzgerald | University of Pennsylvania |
| 2013 | David Ginsburg | University of Michigan |
Blocking Bacterial Infection

“The ‘blessing and curse’ of genetics is you never know exactly where you’ll end up,” says Ginsburg. Some of his recent work has led from clot formation into the field of infectious diseases.

When confronted by bacterial infection, the formation and maintenance of a fibrin clot are key host defenses to block the entrance of bacteria into the bloodstream. All pathogenic group A streptococci produce species-specific streptokinase, a plasminogen activator that dissolves blood clots. Ginsburg’s laboratory showed that streptokinase is critical for allowing the microbes to invade surrounding tissues and cause lethal infections in mice

“If we find chemicals that can make the bacteria stop producing streptokinase, then the bacteria can be there but not cause so much harm. And if a compound doesn’t work by killing the bacteria it may not select for resistance as much,” explains Ginsburg.

After screening more than 300,000 chemicals, Ginsburg and colleagues identified a small set that specifically turned off streptokinase in the bacteria, several of which proved effective in protecting group A streptococci–sensitive mice from fatal infection.

“It’s difficult to know where this will lead but, from my point of view, anything that can be learned about the triggering of the coagulation cascade and how it is modified is critically important,” says Genest.

Future of Cardiovascular Disease Genetics

During his career, Ginsburg has witnessed—and deployed—the rapidly changing tools available for genetic research.

“In my very first research paper, in 1975, we worked for 1.5 years to sequence 4 nucleotides of ribosomal RNA in E. coli. Now, in the lab you routinely sequence a few hundred million base pairs in an afternoon,” recalls Ginsburg.

Ginsburg notes that there is still an important role for some old-fashioned genetic tools. To identify additional genetic determinants of VWF levels in the population, his laboratory applied genome-wide association analysis, finding a previously recognized association with the ABO blood groups locus but nothing really surprising. However, linkage analysis based on sibling relationships within the cohort revealed an area on chromosome 2 that explained almost 20% of the variance in VWF levels but was undetected in the genome-wide analysis.

“We think it’s likely there is a gene in that area with many different variations. Individually the variations are very rare, and that’s why not found by genome-wide association analysis, but in aggregate they account for a lot of people and that’s why we could find by linkage,” says Ginsburg. The group is now sequencing the region in many people and has found some potential candidate genes.

For the future, Ginsburg is particularly excited about 2 new techniques, next-generation sequencing and gene editing.

“The ability to precisely make just one change in the genome has gotten suddenly, spectacularly easier. You can use it in all kinds of model systems and, I suspect, one day in treating disease in humans. It’s still a ways off, but you can see it’s possible. I tell my students I’m a little jealous that they’re starting their careers now,” Ginsburg says.

The next deadline to nominate a scientist for the Lucian Award is March 21, 2014. Further information is available on their website at http://www.mcgill.ca/lucianaward/.

References

2013 Lucian Award: David Ginsburg
Susan Ince

Circ Res. 2013;113:1286-1289
doi: 10.1161/CIRCRESAHA.113.302984

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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