2017 Lucian Award

John McMurray

Susan Ince

The 2017 Louis and Artur Lucian award for research in circulatory disease, established by a bequest to McGill University in 1965, has been awarded to John J.J.V. McMurray, MD, of the University of Glasgow. McMurray has dedicated much of his career to heart failure, with more than 900 publications ranging from basic research and epidemiology to the design and completion of numerous clinical trials that have altered our understanding of the condition and its treatment and prognosis.

> *"He's done a tremendous amount that is clinically relevant and has resulted in new medications for heart failure. He was head and shoulders above the other applicants this year, with an incredible track record and extensive publications," says James Martin, MD, chair of the McGill University department of medicine and chair of the Lucian Committee.*

As McMurray was completing medical school, American and European investigators were beginning to understand the disease mechanisms of heart failure and to identify targets for treatment other than digoxin and diuretics. At that time, there was no way to directly influence the weakness in cardiac contraction underlying heart failure, but inappropriate and sustained activation of the renin–angiotensin–aldosterone system (RAAS) helped explain why the function of blood vessels, kidneys, and heart muscle deteriorated over time. Shortly after the introduction of the angiotensin-converting enzyme (ACE) inhibitor captopril, McMurray witnessed the Lazarus-like recovery and discharge from the hospital of an extremely ill woman with heart failure after she was given the new drug—spurring a career-long interest in heart failure.

After 2 years of residency training, McMurray obtained a cardiovascular research fellowship in Dundee, Scotland, where physician scientist Allan Struthers was studying cardiac natriuretic peptides, newly described hormones produced by the heart, which helped that organ protect itself and the whole body from volume and pressure overload by, among other things, suppressing the RAAS and stimulating the kidneys to excrete sodium and water.

> *"That discovery and my enjoyable early experience of clinical research really shaped my career. It was*

John J.J.V. McMurray, MD, received both his BSc in physiology and his MD from the University of Manchester.

After residency training in Edinburgh and gaining membership in the Royal College of Physicians, McMurray completed a cardiovascular research fellowship in the department of clinical pharmacology at Ninewells Hospital in Dundee, Scotland, studying atrial natriuretic proteins. He completed his cardiology training at Western Infirmary in Glasgow, where he is currently professor of medical cardiology and deputy director (clinical) of the Institute of Cardiovascular and Medical Sciences at the University of Glasgow. McMurray maintains a part-time clinical practice in cardiology, seeing outpatients as well as hospitalized patients in the coronary care and cardiology units.

"My passion is finding answers to clinical problems, but unless you keep in contact with clinical practice you can't do that as well," McMurray says.

Born and raised in Ireland, McMurray is an active supporter of the Celtic Football Club and enjoys spending time with his family.

Among his many awards, in 2010 McMurray became the inaugural Eugene Braunwald Scholar in the Advancement of Cardiovascular Discovery & Care at the Brigham and Women's Hospital in Boston. In 2015, McMurray was named as a fellow of the Academy of Medical Sciences in the United Kingdom and, along with Salim Yusuf from McMaster University, was awarded the 9th Arrigo Recordati International Prize for Scientific Research. Earlier this year, he received the MacKenzie medal of the British Cardiovascular Society for his outstanding service to British cardiology.

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amazing that peptides secreted by the heart could have such remote effects, including on the kidneys. Many of us realized that these endogenous hormones could do potentially good things for patients with heart failure, but there was no way to deliver them orally, as they would be digested," says McMurray.

During the fellowship, McMurray and Struthers probed the interaction between the atrial natriuretic proteins and the RAAS system as they influenced kidney function. After the fellowship, he moved to Glasgow for further cardiology training, a position he sought because of the opportunity to work with Henry Dargie, MD, on an exciting new oral compound that might overcome the delivery problem by inhibiting neprolysin, the enzyme that breaks down the natriuretic peptides.

The effects of that initial agent, candoxatrilat, were not sustained, but McMurray was lucky enough to get two more chances to revisit this therapeutic approach, ultimately successfully demonstrating its value with sacubitril/valsartan (see below). He has also been fortunate during his career to help run a number of successful clinical trials with other drugs for heart failure, improving the standard of treatment over time and demonstrating the associated decline in mortality rate.[1]

Taking Cinderella to the Ball

As a cardiology trainee, McMurray was impressed by the first clinical trial demonstrating that a new ACE inhibitor, enalapril, reduced the risk of death in patients with severe heart failure and was later shown to improve survival in those with less severe symptoms.

"I said that's exactly the kind of work I want to do," said McMurray, who became friends and collaborators with the leaders of those studies, Karl Swedberg, Bertram Pitt, and Salim Yusuf.

In the early days, McMurray had to spur the interest of cardiologists and funders in heart failure, repeating the mantra that this "Cinderella" condition was common, costly, debilitating, and deadly—and bolstering his argument by conducting epidemiological studies to demonstrate that the condition was prevalent and expensive.

"We showed that heart failure was more malignant than cancer, with worse survival than most common cancers, with the exception of lung cancer.[2] We also showed that patients with heart failure have a worse quality of life than other chronic health conditions, and that heart failure costs 1–2%[3] of the total health expenditures in the United Kingdom's National Health Service, which is quite shocking when you're talking about one condition," says McMurray.

Better Drugs

Over the years, the trials that McMurray was involved in have provided overwhelming evidence of the benefits and limitations of manipulating the RAAS.[4] McMurray was fortunate in being able to test the findings of an early mechanistic study in a subsequent large randomized trial. He and colleagues had discovered that angiotensin II could be produced in human tissues by non-ACE pathways, opening the door to an alternative or additional target for treatment—using an angiotensin receptor blocker (ARB). In clinical trials, they showed that ARBs provided an additional benefit in reducing death and hospitalization when added to an ACE inhibitor[5] or as a replacement in patients unable to tolerate ACE inhibitors.[6]

Despite treatment with ACE inhibitors, ARBs, and β-blockers, patients with even mild heart failure often have persistently elevated plasma aldosterone and cortisol, so McMurray was also able to join Bertram Pitt, Faiez Zannad, and others in testing a mineralocorticoid receptor antagonist to block this other arm of the RAAS. Adding the mineralocorticoid receptor antagonist eplerenone to an ACE inhibitor and β-blocker reduced cardiovascular mortality and heart failure hospitalizations by 37% more than standard treatment—improving the clinical course more than adding an ARB.[7] He is now delighted to be helping one of the pioneers of modern clinical trials in cardiovascular medicine, a brilliant mentor and good friend, Marc Pfeffer, with a new trial investigating the potential value of sacubitril/valsartan in heart failure complicating acute myocardial infarction.

When nominating McMurray for the Lucian award, Jean-Lucien Rouleau, MD, clinical professor of medicine at the University of Montreal and director of the myocardial research axis at the Montreal Heart Institute, cited the development of the angiotensin receptor and neprilysin inhibitor drug sacubitril/valsartan as the most striking example of McMurray's multidisciplinary skills. First, McMurray published experimental studies on the pharmacology of neprilysin and helped identify the potential advantages and disadvantages of this class of drugs (Figure). Then, he co-led, with Milton Packer, the development of an angiotensin receptor and neprilysin inhibitor through phase 2 of clinical trials, eventually leading to the large phase III PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure). That trial showed that sacubitril/valsartan had an overwhelming benefit over enalapril in reducing

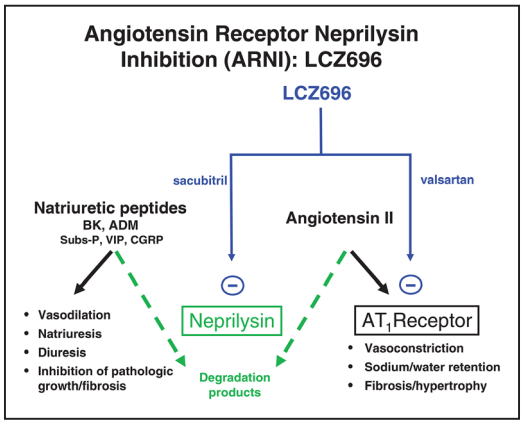

Figure. Mechanism of action of LCZ696 (sacubitril valsartan). ADM, adrenomedullin; AT_1, angiotensin II type 1; BK, bradykinin; CGRP, calcitonin gene-related peptide; Subs-P, substance P; VIP, vasoactive intestinal (poly)peptide. For possible sacubitril substrates, larger font size indicates greater evidence for such an effect in humans. Reprinted from McMurray[11] with permission. Copyright © 2015, John Wiley and Sons.

death, hospitalization, symptoms, and physical limitations in people with heart failure and reduced ejection fraction.[8] The trial was stopped early because of the drug's clear benefit.

"McMurray's multidisciplinary expertise and his now vast experience as a leader of clinical trials, helps explain why many consider his leadership of a clinical trial as a guarantee that an optimal test of the hypothesis will be conducted," says Rouleau.

Although PARADIGM-HF was a major success, there have been set-backs and disappointing trial results along the way—3 drugs that looked promising but showed no benefit in clinical trials (bosentan, tezosentan, and nolomirole), 1 trial stopped early for futility (etanercept), and 1 stopped early because of increased mortality in those on the study drug (dronedarone).

"What John does so well is he is able to learn from the trials that are negative as much as the trials that are positive," says Scott D. Solomon, MD, the Edward D. Frolich distinguished chair of medicine at Harvard Medical School and the Brigham & Women's Hospital in Boston.

"John McMurray is one of the great clinical trialists because he pays enormous attention to detail and to truth, and that is something that he has imparted to all of the people fortunate enough to work and train with him", adds Solomon.

The Heart of the Matter

Thirty years after the anniversary of the first report of a drug improving survival in patients with heart failure, McMurray is excited to be one of the people steering the first Phase III trial of omecamtiv, designed to determine whether the cardiac myosin activator helps patients with heart failure improve their quality of life, stay out of the hospital, and lower their risk of cardiovascular death.

"If we could get, at long last, a treatment that went to the root of the problem, that would be tremendously exciting and complementary to everything else we've done to treat heart failure," says McMurray. "This massive trial [~8000 patients, 900 sites in 35 countries] will tell us one way or the other whether it works."

McMurray is also leading a global team of friends and colleagues conducting a trial to test whether dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, might provide another completely different approach to improving outcomes in patients with heart failure and reduced ejection fraction, possibly by improving renal function and myocardial metabolism.

Although an understanding of the pathophysiology has led to the development of multiple drugs and dramatically changed treatment for patients who have heart failure with a reduced ejection fraction, the same can't be said for those with preserved ejection fraction. That disease, with an entirely different mechanism (problems with relaxation rather than contraction of heart muscle, and filling rather than emptying of the heart) and distinct clinical course (described by McMurray as a chronic disease with repeated hospitalizations and the death often from noncardiovascular causes) possibly requires different therapeutic approaches and maybe even different end points in trials.

The ongoing PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) will test whether adding sacubitril to valsartan will help keep patients alive and out of the hospital.[9]

"The biggest part of this disease is being admitted to the hospital and feeling like you're drowning over and over again. This is the first trial that attempts to look at effectiveness beyond a first event and consider CVD deaths plus total HF hospitalizations, which better reflects the burden of the disease but is statistically difficult because events are likely to be related. In addition to this Phase III trial, there are other drugs at earlier stages of development. These patients need help, and we haven't given up on them," says McMurray.

Clinical Trials of Healthcare Delivery

Although best known for his leadership in clinical trials of potential drugs for heart failure, McMurray has long believed that healthcare services and delivery systems can and should be properly evaluated in clinical trials.

"I come from a public health perspective, where every penny is precious and should be spent as wisely as possible," McMurray says.

In 2001, for example, McMurray et al[10] showed in a randomized controlled trial that patients were less likely to die or be readmitted to the hospital if they received visits from a nurse specialist after an acute hospitalization for heart failure. After further trials in various countries and a meta-analysis of the data, current clinical guidelines endorse disease management programs for heart failure.

McMurray's skill as a clinician and health systems researcher has been acknowledged by his assignment to leading roles in the development of clinical guidelines for heart failure and other cardiovascular conditions.

"Cardiology is a tremendously exciting specialty to be in. I can't think of another that has transformed the lives of patients more in my lifetime. Cardiology created the culture of clinical trials, which has now spread to most of medicine. We can do things that matter and tell patients, 'if I do this for you there is evidence that it will make your life better'," says McMurray.

The next deadline for a dean or department chair to nominate a scientist for the Lucian award is March 23, 2018. Further information is available at www.mcgill.ca.lucianaward/.

Disclosures

None.

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