



# ISHR

International Society for Heart Research

## The Research Achievement Award 2021

“Elucidating the role of the L-type calcium channel in excitability and energetics in the heart”



Livia Hool, PhD

2021 Honored Speaker  
ISHR-JPN Virtual Meeting

Dr Livia Hool is Professor and Head of the Cardiovascular Electrophysiology Laboratory at The University of Western Australia (UWA). She will commence appointment as the Wesfarmers, UWA, Victor Chang Cardiac Research Institute endowed Chair in Cardiovascular Research in 2022 at UWA. She is recognised internationally for her major contributions to understanding the role of calcium in sudden cardiac death and mitochondrial dysfunction in cardiomyopathies.

Her research career began with a fascination for a Nobel prize-winning technique that had been adopted mainly by neuroscientists in Australia at the time. A cardiologist, Helge Rasmussen had established a lab with a single patch-clamp set up in a small room in a disused orthopaedic ward at Royal North Shore Hospital in Sydney and was looking for PhD students. Keen to learn the technique, Dr Hool joined his laboratory and characterised the beneficial effects of angiotensin converting enzyme inhibition on  $\text{Na}^+$  transport in the heart using ion selective microelectrode technique in papillary muscle and patch-clamp electrophysiology in rabbit myocytes. Following her PhD (Macquarie University) she studied the regulation of the cardiac CFTR chloride channel and L-type  $\text{Ca}^{2+}$  channel by G proteins during adrenergic receptor stimulation as an American Heart Association Postdoctoral Fellow with Bob Harvey in the Physiology and Biophysics Department at Case Western Reserve University, Cleveland, Ohio. She returned to Australia and moved to The University of Western Australia where she established her own laboratory as a National Health and Medical Research Council of Australia (NHMRC) Peter Doherty Fellow. Her multi-disciplinary work has been recognised with continuous funding from competitive external awards and is directed to building basic knowledge, discovery and translation.

A major focus of her work is the role of the L-type  $\text{Ca}^{2+}$  channel in cardiovascular health and disease and Dr Hool has made several key discoveries that have challenged and advanced the field. Early in her career, she identified a role for the L-type  $\text{Ca}^{2+}$  channel in sudden cardiac death. Specifically, she identified that hypoxia increased the channel's sensitivity to beta-adrenergic stimulation. This work was published as two separate single author publications in *Circulation Research*.

Subsequently, Dr Hool characterised the effect of hypoxia on repolarising currents. With Yoram Rudy at Washington University, St Louis, she examined the relative contribution of depolarising and repolarising currents and identified a critical role for the channel in triggering arrhythmias in the presence of subthreshold concentrations of isoproterenol. She identified that this was associated with induction of arrhythmia following a parasympathetic pause. This work explained the development of early afterdepolarisations and ventricular arrhythmias in the clinical setting during coronary artery occlusion (hypoxia) and increased sympathetic stimulation.

Her work has provided an early understanding of the role of mitochondria in the generation of reactive oxygen species during acute changes in oxygen tension. She showed that the L-type  $\text{Ca}^{2+}$  channel can facilitate further oxidative stress (and pathology) via the mitochondria following a transient exposure to  $\text{H}_2\text{O}_2$ . She demonstrated that this occurs as a result of glutathionylation of the channel and identified that the channel is glutathionylated in ischemic human heart. She also showed that glutathionylation of the channel is associated with an increase in  $\text{Ca}^{2+}$  influx through the channel, sufficient to activate calcium calmodulin-dependent pathways and myocyte hypertrophy.

It has been proposed that the mitochondria can rapidly track changes in cytosolic  $\text{Ca}^{2+}$  from beat to beat. However, a rapid uptake mechanism capable of responding to changes in cytosolic  $\text{Ca}^{2+}$  had not been identified in the mitochondria and alternative mechanisms for regulating mitochondrial function have been sought. Dr Hool examined if activation of the L-type  $\text{Ca}^{2+}$  channel alone is sufficient to regulate mitochondrial function. She characterised the contribution of  $\text{Ca}^{2+}$  influx via the channel to mitochondrial reactive oxygen species production, NADH, flavoprotein oxidation and ATP production. She noted that mitochondrial membrane potential became hyperpolarised following activation of the channel under diastolic  $\text{Ca}^{2+}$  influx but since the driving force for calcium uptake into the mitochondria was not sufficient to alter mitochondrial membrane potential she searched for an alternative explanation. This led to the discovery that the L-type  $\text{Ca}^{2+}$  channel can regulate mitochondrial function on a beat-to-beat basis *via* movement of cytoskeletal proteins. She has shown that this involves the transduction of movement of the beta auxiliary subunit of the channel (following activation of the channel) eventually modulating the function of the voltage dependent anion channel in the outer mitochondrial membrane that regulates the shuttling of ADP and ATP into the mitochondria. Since the response is rapid and does not require calcium, this finding has provided a potential mechanism for the regulation of mitochondrial function on a beat-to-beat basis.

In pathology where cytoskeletal architecture is altered, this communication between the L-type  $\text{Ca}^{2+}$  channel and mitochondria is compromised, contributing to the altered oxygen consumption and energy supply by the mitochondria. She has used this response to “report” mitochondrial function in models of cardiomyopathy. She has demonstrated that treatment of *mdx* mice (a model of Duchenne Muscular Dystrophy) with morpholino oligomers that induce exon skipping of the dystrophin mutation (and synthesis of a shorter but functional dystrophin protein) improves mitochondrial function and prevents the development of cardiomyopathy. She has also used a peptide (delivered using nanoparticle technology) to target the L-type  $\text{Ca}^{2+}$  channel and alter mitochondrial function as a first therapy to prevent hypertrophy.

Dr Hool has also made important discoveries in the physiological regulation of the  $\text{Ca}^{2+}$  channel. She has determined the molecular mechanism for activation of the cardiac calcium channel responsible for the “Fight or Flight” response. It was unknown if direct modification of  $\text{Ca}_v1.2$  was responsible for altered function and as a result the sites for PKA-mediated phosphorylation of the channel have remained controversial. Characterising single channel currents in purified channel protein reconstituted in liposomes, she showed that phosphorylation of a single serine (Ser1458) is responsible for inducing a conformational change in the chan-

nel protein that is necessary and sufficient for increased calcium influx through the channel. Using the same approach, she identified the cysteine responsible for altered function during oxidative stress.

Dr Hool's research has been recognised by several awards including the Cardiac Society of Australia and New Zealand RT Hall Prize for recognition of sustained and outstanding research achievement, Australian Physiological Society Invited Lecturer Medal, and the Basic Science Lecturer of the Cardiac Society of Australia and New Zealand. Dr Hool has made distinguished contributions and shown great leadership at the level of professional involvement, supervision/mentoring and community engagement. She serves on several international committees including the American Heart Association BCVS Leadership Committee and BCVS Katz Award Committee, she is elected Treasurer of ISHR World Council (2022-25), past President ISHR Australasian section (2013-16; re-elected 2016-19), Statutory Member of ISHR World Council (2013-16) and Elected Member ISHR World Council (2016-19; 2019-22).

Dr Hool also advocates strongly for medical research funding in Australia as a Founding Director and Secretary of the Australian Cardiovascular Alliance (2014- 2019). She established and Chairs the Western Australian Cardiovascular Research Alliance (2019 –on). She serves on several editorial boards and has mentored and trained 24 PhD students and 20 postdoctoral researchers from New Zealand, Russia, Hungary, UK and Australia. She is a Fellow of the American Heart Association, a Fellow of the Cardiac Society of Australia and New Zealand and a Fellow of the International Society for Heart Research.

## The Research Achievement Award

This Award recognizes an internationally prominent scientist with a sustained and distinguished record of major scientific achievements in the field of cardiovascular research. Awardees will have already had, and are expected to continue to have, a major impact on our understanding and/or treatment of cardiovascular disease. While both the Outstanding Investigator Award (OIA) and the Research Achievement Award (RAA) recognize established investigators, the OIA is targeted at more junior individuals (at least Assistant/Associate Professor or the equivalent), while the RAA is targeted at more senior individuals (full Professors or the equivalent).

The Research Achievement Award is presented at the triennial ISHR World Congress or, in non-Congress years, at one of the ISHR Section meetings on a rotating basis. The Award consists of a plaque and a monetary prize of \$1,500. An announcement of this Award, along with a photograph and a biosketch, will be published in Heart News and Views, and posted in the ISHR website.