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The Dobney Hypertension Centre

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Markus Schlaich, the current Treasurer, Chair of Corporate Liaison and Co-Chair of the North Asia, South-East Asia and Oceania Regional Advisory Group (RAG) of the ISH, is the inaugural Dobney Chair in Clinic Research which has been established in 2014 by a collaboration between the Royal Perth Hospital (RPH) Medical Research Foundation (MRF), The University of Western Australia (UWA) and the WA Department of Health. The appointment recognises the extraordinary contribution made to the MRF and medical research by the late Mr Ray Dobney. Well-known for its research and clinical teaching, the UWA Medical School is ranked 39th in the world by the 2018 *Academic Ranking of World Universities* in clinical medicine and just celebrated its 60th anniversary. To complement the ongoing work in cardio-metabolic and diabetic medicine, clinical nutrition, geriatrics and stroke medicine he was appointed due to his extensive experience as a Renal Physician and ESH certified Hypertension Specialist to direct the Hypertension Services at RPH and further strengthen the field both clinically and academically. The clinical service of the Dobney Hypertension Centre (DHC) was recognised as an ESH Hypertension Centre of Excellence in 2016, one of only a few outside of Europe. In conjunction with an extensive research program these efforts will continue the legacy set by some of the greats in the field including the former ISH president Professor Lawrie Beilin (2002-2004).

Prof Markus Schlaich and Prof Lawrie Beilin in front of the University Club

Clinical Services at the Royal Perth Hospital

As a state-wide service the Dobney Hypertension Centre acts as a tertiary referral centre for the largest state in Australia covering an area of 2.5 million square kilometres, around 10 times the size of the UK (242,495 km2) with ~ 2 million people in its direct catchment area. The sheer size of WA renders management of patients in remote areas a real challenge and telemedicine has been an integral part of clinical care for many years. The iconic R*oyal Flying Doctor Service of Australia* continues to set the standards in the field. The centre manages all aspects of clinical hypertension with a specific focus on difficult to control and resistant hypertension. All relevant disciplines required for thorough diagnostic work-up and management including nephrology, cardiology, endocrinology and radiology are key stakeholders in the Dobney Hypertension Centre and work collaboratively to achieve best outcomes for each patient.

Understanding the close and bi-directional links between hypertension and cardiovascular, metabolic and other risk factors, we work closely with dietitians, exercise physiologists, psychologists and other allied health disciplines. Obesity related hypertension is very common in Australia and collaborations with bariatric surgeons allows us to use these options if deemed appropriate. We also routinely screen for obstructive sleep apnea which is highly prevalent in the patient cohorts we see in our clinics, as well as assessing central BP and pulse wave velocity. A large ambulatory BP monitoring service complements our diagnostic work up and is used to ensure optimal management of patients.

Clinical research

Clinical research is a key component of the Centre's work and the close proximity between the Royal Perth Hospital and the MRF building where the dedicated clinical research laboratories are housed enables and facilitates translational research. The research arm of the DHC comprises two fully equipped cath-lab style clinical research rooms for semi-invasive tests and procedures, 2 clinical rooms for non-invasive testing and 5 clinical consulting rooms. Adjacent to these are 2 "wet-labs" for direct

processing of patient samples obtained from research studies and a large array of molecular biology techniques. This is complemented by an animal facility on the campus, primarily for small animal research.

A major aim of the DHC is to bring together scientists and clinicians from various backgrounds and with complementary expertise and skills to address the most relevant questions related to human health. We do this through scientific discussions, seminars, collaborative grant applications as well as provision of our own expertise to other groups who may be able to utilise our specific research techniques for their own research. The core DHC research team currently consists of members from 8 countries including 6 research fellows (3 clinicians, 3 scientists), 5 research officers, one administrative staff, and 9 MD/PhD/Masters students.

Scientifically, the DHC's interest focus on 3 major areas including hypertension, cardio-metabolic risk factors, and autonomic/sympathetic function as depicted in more detail below.

HYPERTENSION	CARDIO-METABOLIC RISK FACTORS	AUTONOMIC FUNCTION
• Resistant hypertension	• CKD / ESRD	• Stress (Takosubo) cardiomyopathy
• Interventional approaches	• Metabolic Syndrome / T2DM	• POTS Syndrome
• Obesity related hypertension	• OSA (Obstructive Sleep Apnea)	• Diabetic autonomic neuropathy
• Renal hypertension (CKD, RAS, FMD)	• Pre-eclampsia	• Orthostatic intolerance
• Pregnancy related HTN	• PCOS (Polycystic Ovary Syndrome)	• Sympathetic regulation of SGLT-2
• Hypertensive urgencies / emergencies	• Salt / Inflammation	• Sympathetic hyperinnervation

CKD: chronic kidney disease; RAS: renal artery stenosis; FMD: fibromuscular dysplasia; ESRD: end stage renal disease; T2DM: type 2 diabetes; POTS: postural orthostatic tachycardia syndrome; SGLT-2: sodium glucose transporter 2.

Some key members of the DHC team (from left): Ms Justine Chan, A/Prof Vance Matthews, Ms Anu Joyson, Ms Derrin Brockman, Dr Revathy Carnagarin, Prof Markus Schlaich, Mr Kearney Tan, Ms Alice Rothwell, Dr Jan Ho.

Research Highlights

Improving management of patients with resistant hypertension has been a key area of our research for the last decade. Given our interest in the role of the sympathetic nervous system, in particular the renal nerves, in the development of hypertension we have been deeply involved in the development and assessment of catheter-based ***renal denervation (RDN)*** as a novel interventional approach for this and other conditions. The hype triggered by our first-in human studies in 2009 (1) was dampened by results from the Symplicity HTN-3 study which reported no additional effect of RDN beyond that of a sham control, but has now been rectified by data from 3 appropriately designed sham-controlled studies clearly demonstrating a significant BP lowering effect, as recently summarized (2). While further and larger studies are currently being conducted it is likely that RDN will become an integral part of modern hypertension management.

We have also explored other avenues of targeting central sympathetic outflow in hypertension and beyond. The ***carotid body*** is a peripheral chemosensor strategically positioned between the internal and external carotid arteries and amongst others governs cerebral blood flow and senses oxygen levels. Once activated, the carotid body via afferent signalling from sensory nerve fibres stimulates central integrative nuclei which in turn increase central sympathetic outflow thereby contributing to rise in BP. Data from our first-in-man study targeting the carotid body and its sensory fibres via a transvenous ultrasound ablation approach are promising and demonstrate a significant 24h BP reduction.

Obesity and its metabolic and cardiovascular consequences represent a large burden on general health

worldwide. Aside from hypertension being frequently associated with obesity, we have been struck by the substantial cardio- and reno-protective effects conferred by ***SGLT-2 inhibitors*** with a 38% relative risk reduction in death from cardiovascular (CV) causes. Interestingly, sudden cardiac death and hospitalization for heart failure were the major drivers of CV risk reduction, raising the possibility that SGLT-2 induced antagonism of increased sympathetic nervous system (SNS) activation may be an important underlying mechanism. Indeed, our own A/Prof Vance Matthews was able to demonstrate in human proximal tubular cells and a mouse model of obesity that SNS activation through increased release of noradrenaline (NA) up-regulates SGLT-2 expression and promotes translocation to the cell membrane and that pharmacologic inhibition of SGLT-2 reduces sympathetic innervation both in the kidney and the heart (3). These findings are indeed indicative of a sympatho-inhibitory action of SGLT-2 inhibition. In a translational approach we now aim to further investigate the apparent crosstalk between the SNS and SGLT-2 regulation in relevant animal models and in patients with T2DM. Unravelling the mechanisms of SGLT-2 inhibitor induced cardio-renal protection will have wide ranging implications beyond diabetes.

Other currently ongoing studies address the role of the immune system and its inhibition for human hypertension, the role of the SNS in polycystic ovary syndrome and pre-eclampsia associated cardiovascular and metabolic disturbances, the effect of specific targeting of renal sympathetic nerves in loin-pain-haematuria syndrome, investigation of the central pathways involved in regulating sympathetic outflow using functional MRI imaging, and several others. We are also a site for several national and international randomized controlled clinical trials.

As always, it is the people who make a real difference and we would be pleased to hear from anyone with a passion for clinical research who would be interested in joining us in our efforts to combat the large burden that cardiovascular and metabolic disease puts on the global community.

References

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