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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Better understanding of mechanisms underlying heart failure due to obesity
Name		A/Prof Aaron Sverdlov
Award Received		2019 RACP/Foundation for High Blood Pressure Research Establishment Fellowship
Report Date		June 2020
Chief Investigator / Supervisor		A/Prof Aaron Sverdlov
Administering Institution		
Funding Period	Start Date:	January 2019
	Finish Date:	December 2019

PROJECT SUMMARY

Heart failure (HF) is the commonest and most disabling form of chronic cardiovascular disease. HF is typically progressive, leading to frequent hospitalization and substantial health economic burden. The pathophysiology of HF is complex, and symptoms represent the integrated effects of wide-ranging abnormalities. Currently, there is an upward trend in heart failure-induced mortality and morbidity. One of the key reasons for that is the emergency of new type of heart failure – heart failure with preserved ejection fraction (HFpEF). This form of heart failure is mainly associated with advancing age, higher rates of diabetes and obesity that plague our society. It is estimated that the prevalence of HFpEF could be up to 5.5% worldwide, accounting for 40-70% of all heart failure cases, and is predicted to become the predominant type of heart failure within the next decade. The exact mechanisms for the development of HFpEF due to remain incompletely understood. Therefore, while treatments for some other forms of heart failure are established, there is no proven therapeutic strategy for the management of HFpEF, despite equivalent detrimental effects on patient's quality of life and its associated morbidity and mortality.

Thus, this project was designed to help understand the mechanisms underlying HFpEF due to obesity using experimental models. It relied on my previous discoveries of potential mechanisms and aims to take it to the next level. The overall aim was to identify most plausible biological mechanisms and targets and confirm them in a disease model. This may allow us to develop targeted and personalized treatments for patients with obesity-induced heart failure in the future.

PROJECT AIMS / OBJECTIVES

Objectives: To better understand the mechanisms underlying obesity-induced heart failure, energetic impairments that is associated with it, and biomarkers that can be used in humans for

detection and risk stratification in early stages of HFpEF.

Aim 1: Confirm that mitochondrial abnormalities that I have described in mouse models previously occur in humans. Specifically, I have previously described that mitochondrial ROS play a key part in mitochondrial dysfunction in obesity-induced heart disease in mice and identified complex II of mitochondrial transport chain as a likely source and also target of such ROS

We have now confirmed this in human adipose tissue. Our data have been published in prestigious American Journal of Physiology:

Ngo DTM*, **Sverdlov AL***, Karki S, Macartney-Coxson D, Stubbs RS, Farb MG, Carmine B, Hess DT, Colucci WS, Gokce N. Oxidative Modifications of Mitochondrial Complex II are associated with insulin resistance of visceral fat in obesity. Am J Physiol Endocrinol Metab 2019; 316(2):E168-E177. * denotes joint first authors

Aim 2: Demonstrate the key importance of ROS and specifically of ROS from mitochondrial complex II in development of impaired cardiac energetics in obesity-induced heart disease.

We have confirmed that and just published this data in top Redox Journal – Antioxidant and Redox Signaling:

Luptak I, Qin F, **Sverdlov** AL, Pimentel DR, Panagia M, Croteau D, Siwik DA, Bachschmid MM, He H, Balschi JA, Colucci WS. Energetic dysfunction is mediated by mitochondrial ROS and precedes structural remodeling in metabolic heart disease. Antioxid Redox Signal 2019;

31(7):539-549.

Aim 3: Investigate the role of novel biomarkers in humans as a method of detecting HFpEF, risk stratifying patients with subclinical cardiac remodelling abnormalities and detecting complications and comorbidities arising from HFpEF. We have published data on utility of novel biomarker, Galectin-3 in predicting early HFpEF and pulmonary hypertension in young people with obesity:

Gopal DM, Ayalon N, Wang YC, Siwik D, **Sverdlov** A, Donohue C, Perez A, Downing J, Apovian C, Silva V, Panagia M, Kolachalama V, Ho JE, Liang CS, Gokce N, Colucci WS. Galectin-3 is Associated with Stage B Metabolic Heart Disease and Pulmonary Hypertension in Young Obese Patients. J Am Heart Assoc 2019; 8(7):e011100.

SIGNIFICANCE AND OUTCOMES

Significance:

Heart failure due to obesity has an enormous societal impact related to lost productivity and health care costs. Yet, the cellular mechanisms responsible for its development are not known and specific therapeutic options do not exist. This research helps understand mechanisms responsible for the development of heart failure due to obesity. In particular, we further delineated the role of redox-dependent mechanisms and those involved in mitochondrial function.

Better understanding of these mechanisms can help drive therapeutic discoveries for this form of heart failure which at present has no proven medical or surgical treatments. The potential benefit of this research is improved outcomes and reduced health care costs in a very large group of Australians with obesity-induced heart disease.

Biomarkers are important tools to assist a clinician with the diagnosis, prognosis and/or screening for a variety of conditions, and also to assist with the clinical management of a patient. We identified a novel biomarker, Galectin-3 which has further cardiovascular utility. Galectin-3 may be useful in screening for preclinical MHD and identifying individuals with increased risk of progression to obesity-related heart failure with preserved ejection fraction.

Future directions:

Our ability to dissect these mechanisms will lead to further drug discovery and therapeutic studies in

future: we have used preliminary data from this project already to apply for further funding to expand this research.

We are also planning to expand the biomarker research to include a large diverse patient population to validate our initial discovery.

PUBLICATIONS / PRESENTATIONS

1. Ngo DTM*, Sverdlov AL*, Karki S, Macartney-Coxson D, Stubbs RS, Farb MG, Carmine B, Hess DT, Colucci WS, Gokce N. Oxidative Modifications of Mitochondrial Complex II are associated with insulin resistance of visceral fat in obesity. Am J Physiol Endocrinol Metab 2019; 316(2):E168-E177.

2. Gopal DM, Ayalon N, Wang YC, Siwik D, Sverdlov A, Donohue C, Perez A, Downing J, Apovian C, Silva V, Panagia M, Kolachalama V, Ho JE, Liang CS, Gokce N, Colucci WS. Galectin-3 is Associated with Stage B Metabolic Heart Disease and Pulmonary Hypertension in Young Obese Patients. J Am Heart Assoc 2019; 8(7):e011100.

3. Luptak I, Qin F, Sverdlov AL, Pimentel DR, Panagia M, Croteau D, Siwik DA, Bachschmid MM, He H, Balschi JA, Colucci WS. Energetic dysfunction is mediated by mitochondrial ROS and precedes structural remodeling in metabolic heart disease. Antioxid Redox Signal 2019; 31(7):539-549.

4. Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL#, Collins NJ#. Pulmonary Hypertension due to Left Heart Disease: Diagnosis, Pathophysiology and Therapy. Hypertension 2020; 75:1397–1408.

* denotes joint first authors; # denotes co-senior authors

Abstracts:

1. Croft A, Senanayake T, Butel-Simões L, Mabotuwana N, Boyle AJ, Sverdlov AL, Ngo DT. Anti-angiogenic vascular endothelial growth factor-A isoform: VEGF-A165b is present in human right atrial appendage, but is not altered in diabetes. Presented at CSANZ Scientific Sessions 2019, Adelaide, Australia.

2. Nesbitt A, Kelly C, Croft A, Chen D, Sverdlov AL, Ngo DTM. Neutralization of the anti-angiogenic isoform of vascular endothelial growth factor-A: VEGF-A165b is associated with weight gain independent of high fat/high sucrose feeding. Winner of ISHR Best poster Prize at the CSANZ/ISHR Scientific Sessions 2019, Adelaide, Australia.

3. Kelly C, Nesbitt A, Croft A, Senanayake T, Butel-Simões L, Mabotuwana N, Boyle AJ, Sverdlov AL, Ngo DT. Low expression of secreted frizzled receptor protein 5 (Sfrp5) in human right atrial appendage is associated with diastolic dysfunction. Presented at CSANZ Scientific Sessions 2019, Adelaide, Australia.

4. Chen D, Liu S, Horowitz J, Sverdlov A, Ngo D. FSTL3 release occurs synchronously with onset of doxorubicin-induced cardiotoxicity in an isolated myocardial cell model. Presented at the XXIII ISHR World Congress, June 2019, Beijing, China.

ACKNOWLEDGEMENTS

I would like to once again express my gratitude to the RACP Foundation and Foundation for High Blood Pressure Research for this award.

In addition to the academic outputs listed above, I have also generated preliminary data that contributed to the successful NSW Health Cardiovascular Capacity Building Grant and was used to apply for the 1 NHMRC Ideas grant (outcome pending).