



RACP Foundation Research Awards

FINAL REPORT

Project / Program Title	Early detection of chemotherapy-induced cardiomyopathy
Name	A/Prof Aaron Sverdlov
Award Received	2016 The Servier Staff "Barry Young" Research Establishment Fellowship
Report Date	24 June 2018
Chief Investigator / Supervisor	A/Prof Aaron Sverdlov
Administering Institution	The University of Adelaide
Funding Period	Start Date: 1 January 2016
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PROJECT SUMMARY

Cancer and heart disease are two commonest disease conditions in the developed world and the two leading causes of death in our society. Cancer therapy is more effective than ever before at treating cancer, but has a price.

Chemotherapy (anticancer medications) for many cancers do not come without risk and can result in treatment-related toxicities that produce serious side effects. Chemotherapy-induced cardiotoxicity (CIC) is defined as a poisonous or detrimental effect upon the heart that can delay cancer treatment, decrease survival, and increase morbidity.

CIC can affect anywhere between 5 and 25% of patients receiving chemotherapy, depending on the specific agent and the total dose. Currently, the diagnosis of CIC is made either when patient presents with symptoms of heart disease or during monitoring with ultrasound or MRI scans of the heart, both of which are costly. By that stage there are usually significant changes in heart structure and function that require urgent intensive long-term treatment and complete recovery rate is low.

Early treatment with conventional heart failure medications significantly improves recovery from CIC and leads to much better long term prognosis and survival. At present there are no reliable ways to predict which patients are more likely to develop CIC before initiation of chemotherapy.

Thus, the aim of this project is to test if a simple blood test, for a novel biomarker of heart disease, prior to initiation of chemotherapy can identify those patients who would develop CIC. In that were the case, these patients could be more intensively monitored and receive heart-specific treatment early to avoid detrimental effect on their heart health, quality of life and survival.

PROJECT AIMS / OBJECTIVES

The aim of this project is to test if a simple blood test, for a novel biomarker of heart disease, prior to initiation of chemotherapy can identify those patients who would develop chemotherapy-induced cardiotoxicity.

During this project (which has only commenced mid-2017 – detailed explanation was provided and accepted by the RACP Foundation in November 2017) we are prospectively following-up a cohort of patients starting chemotherapy associated with risk of cardiotoxicity. We are obtaining blood samples to assess the levels of novel biomarkers, Galectin and Follistatin, prior to starting chemotherapy. The patients are also undergo comprehensive heart ultrasound (echo) and medical assessments prior to and at regular intervals after starting chemotherapy. We are following these patients for a year and assessing if the level of the biomarkers before starting cancer treatment can identify those who will develop chemotherapy-induced cardiotoxicity as identified with echo or clinically.

This research addresses a huge area of unmet need. As many as 1 in 4 people alive today will develop cancer and most of those will receive chemotherapy treatment. Up to 40% of those people could develop heart complications. Early identification and treatment of those individuals at risk would substantially reduce adverse health outcomes, morbidity and mortality as well as reduce health care costs.

SIGNIFICANCE AND OUTCOMES

Cardiotoxicity is a rising issue connected to use of chemotherapy and radiotherapy in the treatment of cancer. The early diagnosis and adequate evaluation of the cardiotoxic effects of chemotherapeutic drugs are of paramount importance for clinicians to set the best therapeutic management, and careful surveillance is recommended. Evaluation of left ventricular ejection fraction by echocardiography and nuclear medicine techniques is widely used in clinical practice; however, their sensitivity in detecting early cardiac damage is low.

The risk of cardiotoxicity is related to cumulative dose and limits the duration and intensity of therapy, limiting its effectiveness and placing patients at increased risk of treatment failure or relapse. The main reason for long-term morbidity, mortality and healthcare costs is engendered by the fact that the early detection of the cardiomyopathy is delayed due to imperfect techniques that are currently available.

We expect that the change in the novel biomarkers, Galectin-3 and Follistatin-like 3 will antecede that in previously established monitoring modalities leading to earlier detection of cardiotoxicity. As early detection is the cornerstone of early treatment and improved outcomes, this could in future lead to change in clinical practice/guidelines and translate in earlier discontinuation/change in chemotherapeutic regimen and earlier initiation of heart failure therapy. This may lead to substantial improvement in quality of life, morbidity, mortality and hospitalizations in long-term cancer survivors.

If results are robust, the implementation of these biomarkers into routine clinical practice would be relatively straightforward from logistics point of view. The biomarkers are measured from routine blood test, are stable in plasma and measured using commercially-available ELISA kits and the cost is less than \$50 per patient. The potential health care and health outcomes benefit of such simple testing could not be overestimated.

PUBLICATIONS / PRESENTATIONS

Full-text journal publications:

1. Murtha LA, Morten M, Schuliga MJ, Mabotuwana NS, Hardy SA, Waters DW, Burgess JK, Ngo D, Sverdlov AL, Knight DA, Boyle AJ. The role of pathological aging in cardiac and pulmonary fibrosis. *Aging Dis* 2018; in press.
2. Ezad S, Al-Omary MS, Davies AJ, Sverdlov AL, Boyle AJ. Heart Failure Admissions Following ST Segment Elevation Myocardial Infarction. *Aust J Rural Health* 2018; in press.
3. Al-Omary MS, Khan AA, Davies AJ, Fletcher PJ, Mclvor D, Bastian B, Oldmeadow C, Sverdlov AL, Attia JR, Boyle AJ. Outcomes Following Heart Failure Hospitalization in a Regional Australian Setting Between 2005-2014. *ESC Heart Fail* 2018; 5(2):271-278.
4. Sverdlov AL, Ngo DT. Response to the letter to editor: Galectin-3 and atrial fibrillation. *Int J Cardiol* 2017; 229:2. doi: 10.1016/j.ijcard.2016.12.006.
5. Chen D, Procter N, Goh V, Liu S, Chua SJ, Assadi-Khansari B, Horowitz JD, Sverdlov AL, Ngo DT. New onset atrial fibrillation is associated with elevated Galectin-3 levels. *Int J Cardiol* 2016; 223:48-49.

We also lodged a patent for the use of these novel biomarkers in chemotherapy-induced heart disease (as well as other conditions) to identify patients at risk:

Methods and products for identifying conditions associated with cardiac fibrotic remodelling. Inventors: Ngo DT and Sverdlov AL. Australian Provisional Patent Application No. 2016902369. Lodged 17/06/2016

This patent has now progressed to the Patent Cooperation Treaty Stage, which in itself has limited our ability to publish in this field (we have at least 3 additional full-text manuscripts ready to submit as soon as the patent office gives us a green light).

I had 8 invited presentations on this and related topics nationally and internationally:

1. Sverdlov AL. Diagnosis of Heart Failure. Webinar for the NSW Agency for Clinical Innovation (ACI) as part of the ACI Quality Improvement Collaboration, May 2018, Sydney, Australia.
2. Sverdlov AL. The Burden and Aetiology of HFpEF. 27th Annual Scientific Meeting of the Indonesian Heart Association, April 2018, Jakarta, Indonesia.
3. Sverdlov AL. Heart Failure in Australia - Disease Burden and Public Health Approaches to Prevention and Treatment. American College of Cardiology (ACC) Annual Scientific Session, March 2018, Orlando, USA.
4. Sverdlov AL. Chemotherapy-induced cardiotoxicity: Focus on early prevention. Medical Oncology Grand Round. Calvary Mater Hospital, October 2017, Newcastle, NSW, Australia.
5. Sverdlov AL. Contemporary management of Heart Failure. Presented at the 50th Academic Sessions of the Ceylon College of Physicians, September 2017, Colombo, Sri Lanka.
6. Sverdlov AL. Novel concepts in Heart Failure. Presented at the 50th Academic Sessions of the Ceylon College of Physicians, September 2017, Colombo, Sri Lanka.
7. Sverdlov AL. Heart Failure: New Biomarkers and directions. Cardiology grand round presentation at the John Hunter Hospital, August 2016, Newcastle, NSW, Australia.
8. Sverdlov AL. Chemotherapy-induced cardiotoxicity. Invited plenary presentation at the Australian Cardiovascular Health and Rehabilitation Association (ACRA) 26th Annual Scientific Meeting, August 2016, Adelaide, Australia.

Furthermore, our group had abstracts accepted at major national and international meetings related to these biomarkers (see section below):

Furthermore, our group had abstracts accepted at major national and international meetings related to these biomarkers (see section below):

1. Chen D, Liu S, Horowitz JD, Sverdlov AL, Ngo DT. Effects of doxorubicin-induced cardiotoxicity on follistatin-like 3. Accepted for presentation at CSANZ Scientific Sessions 2018, Brisbane, Australia.

2. Morten MM, Senanayake T, Butel-Simões L, Mabotuwana N, Boyle AJ, Ngo DT, Sverdlov AL. Expression of follistatin-like 3 is not altered in the right atrial appendage in patients with myocardial infarction. Accepted for presentation at CSANZ Scientific Sessions 2018, Brisbane, Australia.

3. Chu M, Chua SJ, Assadi-Khansari B, Amarasekera A, Horowitz JD, Sverdlov AL, Ngo DT. Circulating secreted frizzled-related protein 5 (Sfrp5) is decreased in patients with diabetes and is associated with diabetic control. Oral presentation at CSANZ Scientific Sessions 2017, Perth, Australia. Winner of ISHR Student Prize for Best Free Communication.

Heart Lung Circ 2017; 26: S115

4. Chua SJ, Goh V, Assadi-Khansari B, Chen D, Hii JTY, Horowitz JD, Sverdlov AL, Ngo DT. Follistatin-like 3 is elevated in patients with atrial fibrillation but is unchanged following ablative therapy. Oral presentation at CSANZ Scientific Sessions 2017, Perth, Australia.

Heart Lung Circ 2017; 26: S165

5. Liu S, Assadi-Khansari B, Ajaero C, Chua SJ, Horowitz JD, Ngo DT, Sverdlov AL. Follistatin-like 3 Is Elevated in Acute Heart Failure Patients. Oral presentation at the American Heart Association Scientific Sessions 2016, New Orleans, USA.

Circulation 2016;134:A19797

6. Chen D, Procter N, Chua SJ, Goh V, Liu S, Assadi-Khansari B, Horowitz JD, Ngo DT, Sverdlov AL. New Onset Atrial Fibrillation Is Associated with Elevated Galectin-3 And Follistatin-like 3 Levels. Presented at the American Heart Association Scientific Sessions 2016, New Orleans, USA.

Circulation 2016;134:A19666

7. Chua SJ, Ajaero C, Assadi-Khansari B, McGavigan A, Horowitz JD, Sverdlov AL, Ngo DT. Galectin 3 is markedly elevated in severe heart failure and predicts improvement in LV volumes post cardiac resynchronisation therapy. Presented at the ESC Congress 2016, Rome, Italy.

Eur Heart J 2016; 37 (Suppl 1):23.

8. Assadi-Khansari B, Chua SJ, Chapman M, Ali OA, Nguyen H, Horowitz JD, Sverdlov AL, Ngo DT. Follistatin-like 3 predicts aortic root enlargement in patients with bicuspid aortic valve. Presented at the ESC Congress 2016, Rome, Italy.

Eur Heart J 2016; 37 (Suppl 1):747.

9. Chua SJ, Assadi-Khansari B, Horowitz JD, Sverdlov AL, Ngo DT. Galectin-3 Levels Is not a Predictor of Increased Left Ventricular Mass in a Healthy Ageing Population. Winner of ISHR Best poster presentation at the CSANZ/ISHR Scientific Sessions 2016.

Heart Lung Circ 2016; 25: S78.

10. Chen D, Procter N, Goh V, Liu S, Chua SJ, Assadi-Khansari B, Horowitz JD, Sverdlov AL, Ngo DT. New onset atrial fibrillation is associated with elevated galectin-3 and follistatin-like 3 levels. Presented at the CSANZ Scientific Sessions 2016, Adelaide, Australia.

Heart Lung Circ 2016; 25: S81

11. Chua SJ, Ajaero C, Assadi-Khansari B, McGavigan A, Horowitz JD, Sverdlov AL, Ngo DT. Galectin 3 predicts functional capacity in patients with severe congestive heart failure (CHF). Oral presentation at the CSANZ Scientific Sessions 2016, Adelaide, Australia.

Heart Lung Circ 2016; 25: S110-111

12. Chua SJ, Ajaero C, Assadi-Khansari B, McGavigan A, Horowitz JD, Sverdlov AL, Ngo DT. Galectin 3 is markedly elevated in severe heart failure and predicts improvement in LV volumes post cardiac resynchronisation therapy. Oral presentation at the CSANZ Scientific Sessions 2016, Adelaide, Australia.

Heart Lung Circ 2016; 25: S110

13. Assadi-Khansari B, Chua SJ, Chapman M, Ali OA, Nguyen H, Horowitz JD, Sverdlov AL, Ngo DT. Follistatin-like 3 predicts aortic root enlargement in patients with bicuspid aortic valve. Winner of CSANZ Best poster presentation at the CSANZ/ISHR Scientific Sessions 2016. Heart Lung Circ 2016; 25: S77-78

14. Assadi-Khansari B, Chua SJ, Horowitz JD, Sverdlov AL, Ngo DT. Follistatin-like 3 is associated with increased left ventricular mass in an ageing population. Presented at the CSANZ Scientific Sessions 2016, Adelaide, Australia.

Heart Lung Circ 2016; 25: S77

15. Assadi-Khansari B, Liu S, Ajero C, Chua SJ, Horowitz JD, Sverdlov AL, Ngo DT. Follistatin-like 3 is elevated in acute heart failure patients. Presented at the CSANZ Scientific Sessions 2016, Adelaide, Australia.

Heart Lung Circ 2016; 25: S109-110

16. Chua SJ, Ajaero C, Assadi-Khansari B, McGavigan A, Horowitz JD, Ngo DT, Sverdlov AL. Galectin 3 predicts improvement in LV volumes after Cardiac Resynchronisation Therapy. Presented at the Heart Failure 2016 Congress of the ESC, May 2016, Florence, Italy. Eur J Heart Fail 2016; 18 Suppl 1:232