Cardio-Oncology: A Tale of Two Cities

The art of preventing broken hearts in women with breast cancer

Davinder S. Jassal MD, FACC, FRCPC

Section of Cardiology, Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences,
University of Manitoba, Winnipeg, Manitoba, Canada

Dr. Davinder S. Jassal was born in Thompson, MB, obtained an International Baccalaureate Degree at Sisler High School in Winnipeg, and graduated from the University of Manitoba with an MD in 1998. He completed a residency in Internal Medicine at the University of Manitoba from 1998-2001 and then a residency in Adult Cardiology at Dalhousie University in Halifax, NS, between 2001-2004. Subsequently, he completed a clinical and research fellowship in multimodality cardiac imaging between 2004-2006, specializing in echocardiography, computed tomography and MRI at Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Dr. Jassal joined the University of Manitoba in 2006 as an Academic Clinician Scientist, where half of his time is devoted to patient care in the Coronary Care Unit and cardiac imaging and the other half devoted to translational research. As a distinguished contributor to the field of non-invasive cardiovascular imaging, he holds numerous academic and administrative positions at the University of Manitoba. Dr. Jassal is Professor of Medicine, Radiology, and Physiology and Pathophysiology; Section Head of Cardiology, Department of Internal Medicine, University of Manitoba; and Principal Investigator of the Cardiovascular Imaging Laboratory in the Institute of Cardiovascular Sciences at the St. Boniface Hospital Albrechtsen Research Centre.

Dr. Jassal has received a number of prestigious academic awards, including the Heart and Stroke Foundation of Canada New Investigator Award, the Royal College of Physicians and Surgeons of Canada Mentor of the Year Award, Canadian Cardiovascular Society Young Investigator Award, the Liam Murphy Young Investigator Award from the Department of Internal Medicine, the University of Manitoba Rh Award for Outstanding Contributions to Scholarship and Research in the Health Sciences Category, and Doctors Manitoba Scholastic Award. Dr. Jassal has secured grant support from a total of over 50 local, provincial, and national agencies amounting to \$6.0M in funding since joining the University of Manitoba. He has over 375 peer-reviewed publications, consisting of original research, editorials, chapters and abstracts, many published in high impact journals including the New England Journal of Medicine, Circulation, Journal American College of Cardiology and the European Heart Journal.

Correspondence to:
Dr. Davinder S. Jassal
Email: djassal@sbgh.mb.ca

Clin Invest Med 2019; 42 (1): E13-18.

Clinician Scientists: Yesterday, today and tomorrow

Is the Clinician Scientist one of those perennially deficient in numbers, diversity, and effectiveness in Canada who will become an endangered species in the near future? A Clinician Scientist is defined as an individual who holds a MD or MD/PhD splitting her/his time between research, educational, administrative and clinical responsibilities. Clinician Scientists contribute to effective development, translation and dissemination of research into clinical practice and traditionally focus on one of the CIHR pillars including basic science, clinical research, health services and systems research and/or population and public health research. In academic medicine, although teaching hospitals promote delivery of excellent patient care, the expectation is that Clinician Scientists will continue to contribute significantly to their research mission. With the pressures of both the academic and clinical worlds, Clinician Scientists must secure external national funding, supervise and mentor junior trainees, produce peer-reviewed publications in high impact journals, manage administrative responsibilities and, above all else, provide excellent patient care. In this fine balancing act, are there any potential solutions to help prevent Clinician Scientists in Canada from becoming endangered?

To understand the current status and future paradigm of Clinician Scientists, we must first explore the common training pathways available in Canada. Young scientists are often first infected with the “research bug” at an early stage of their careers in the high school setting through participation in annual science fairs. In undergraduate training programs, a number of universities offer summer studentships and research forums that continue to foster research excellence in our young scientists. For individuals interested in research as a major component of their future academic career, several options currently exist for training our Clinician Scientists of the future. At the University of Manitoba, the Bachelor of Science Medicine (BSc Med) program was established to provide medical students an opportunity to engage in basic science, clinical and/or community health research under the supervision of a faculty member. During the first two summers of the BSc Med program, medical students develop skills in research design, hypothesis testing, synthesis of data and knowledge translation of research findings. Formal training in either a MD/MSc or MD/PhD program provides trainees with the skillset to acquire expertise in a particular discipline, critical

thinking and experimental design skills, grant writing and effective communication of research findings to both the lay public and the academic community. Finally, the Royal College of Physician and Surgeon’s Clinician Investigator Program (CIP) offers the unique opportunity to train medical and surgical residents with skills required to truly succeed as a Clinician Scientist in academic medicine. Whether formal research training is pursued in the early medical school years (BSc Med, MD/MSc, or MD/PhD) and/or in the postdoctoral years (CIP), the complete training period may encompass nearly 20 years. Although this may seem like a formidable task, formal research training, mentorship and networking are truly required for Clinician Scientists to succeed in the current competitive market of national and international grant competitions.

As a new faculty member at a Canadian university in the role of a Clinician Scientist, there are a number of key considerations that should be entertained in the early stages of negotiations. First and foremost, new Clinician Scientists should secure protected research time at a minimum of 50% but ideally closer to 75%, to focus on their research endeavours; “working on the evenings and weekends” serves as a nidus for early failure. In the competing interest of clinical activities, which are never ending, protected time is necessary to establish an effective research program that will allow for the following: i) successful mentorship of junior trainees; ii) ability to secure national and international grant funding; and iii) dissemination of scientific findings in high impact peer reviewed journals. Second, human resources, infrastructure and start-up funding should be discussed at the time of recruitment. With respect to personnel, start-up funds will be required for hiring of laboratory technicians and graduate students in the basic science realm as compared to study coordinators, “big data” managers and statisticians in population health research. In terms of infrastructure, Clinician Scientists may require laboratory space, special equipment and access to health care registries to initiate their research career. Both salary support for protected research time and operating costs for research personnel and infrastructure should be clearly delineated. Finally, senior mentorship is an invaluable asset for the new faculty member to successfully navigate the research abyss. As national and international funding continues to become increasingly competitive on an annual basis, one must break the barriers of MD and PhD scientists competing with one another. In 2019, a team approach of Clinician Scientists and Basic

Scientists working collaboratively together will translate into a high success rate in securing peer reviewed grant finding.

How did I become a Clinician Scientist at the University of Manitoba and did I follow any of the aforementioned advice? Born and raised in Thompson, Manitoba, I obtained an International Baccalaureate degree at Sisler High School in Winnipeg. I was mentored by Mr. Charles Carrington and Ms. Chris Ottawa while participating in annual science fairs in the field of biological sciences. During my medical school training at the University of Manitoba, I completed a BSc Med degree, under the tutelage of Dr. Ian Dixon who focused my research interests in the field of heart failure. During my residency in General Internal Medicine at the University of Manitoba and a residency in Adult Cardiology at Dalhousie University in Halifax, Nova Scotia, I was mentored by multiple exceptional Clinician Scientists including Dr. James Tam, Dr. John Embil and Dr. Susan Howlett. They provided me with an important skill set: i) how to formulate a research question; ii) how to design and implement a study from inception to completion; and iii) how to translate the knowledge of the research findings to the clinical setting. Finally, during my clinical research fellowship in multimodality cardiac imaging at Massachusetts General Hospital, Harvard Medical School, Boston, MA, I was fortunate to collaborate with mentors who have shaped my current research focus in the field of Cardio-Oncology. Since joining the Section of Cardiology, Department of Internal Medicine at the University of Manitoba as a Clinician Scientist in 2006, my core research training allowed me to successfully establish the Cardiovascular Imaging Laboratory at the St. Boniface Albrechtsen Research Centre. More than a decade later, I continue to collaborate with senior PhD mentors at the Research Centre, including Dr. Pawan Singal and Dr. Grant Pierce in the field of Cardio-Oncology. Together, our multidisciplinary translational laboratories focus on the detection, early diagnosis and prevention of cardiovascular disease in the cancer population.

Cardio-Oncology: Cancer treatment and heart failure

Cardio-Oncology is an evolving discipline that focuses on the prevention, diagnosis and management of cancer patients who are at risk of developing cardiovascular complications as a result of their cancer treatment. The treatment for each patient is individualized, involving a combination of surgery, radiation, chemotherapy and

targeted biological therapies. Despite the beneficial effects of this multidisciplinary approach in improving overall survival in cancer patients, cardiotoxicity remains a serious complication of many anti-cancer therapies [1-3]. Although doxorubicin (DOX) and trastuzumab (TRZ) improve overall survival in breast cancer patients in both the adjuvant and metastatic settings [4-7], these two anti-cancer drugs may lead to cardiac dysfunction in as many as 8000 Canadian women annually, demonstrating the clinical significance of this disease [8-10].

Over the past decade, our multidisciplinary team has pioneered a number of basic science and clinical studies in the field of Cardio-Oncology evaluating: i) the prevalence of chemotherapy-mediated cardiotoxicity in Manitoba; ii) the role of cardiac imaging for the characterization of chemotherapy-mediated cardiotoxicity; and iii) the prevention of cardiotoxicity due to common anti-cancer drugs [11-21]. Serial monitoring of left ventricular ejection fraction (LVEF) using non-invasive cardiac imaging is the single most important diagnostic tool in the detection of cardiac dysfunction among cancer patients. When heart failure develops in the setting of a reduced LVEF, irreversible cardiac injury may occur. In the emerging field of Cardio-Oncology, echocardiographic indices to detect early left ventricular (LV) systolic dysfunction could be useful for addressing the cardiac safety profile of anti-cancer drugs to potentially avoid the detrimental effects of end stage heart failure. In 2007, we performed a retrospective clinical study evaluating 152 women with HER-2 positive breast cancer who received treatment with DOX+TRZ in the adjuvant setting at CancerCare Manitoba [18]. Approximately 25% of women with breast cancer in Manitoba discontinued their treatment with DOX+TRZ due to development of cardiac dysfunction and symptomatic heart failure [18]. Risk factors for the development of DOX+TRZ-mediated cardiotoxicity included a history of hypertension, smoking and family history of premature coronary artery disease [18]. In a separate prospective clinical study, from 2007 to 2010, we evaluated the accuracy of a multi-gated acquisition scan, two dimensional transthoracic echocardiography and real time three dimensional transthoracic echocardiography for determining LVEF in comparison with cardiac magnetic resonance imaging in a breast cancer population receiving adjuvant DOX+TRZ therapy [20]. Although two dimensional transthoracic echocardiography demonstrated a weak correlation with cardiac magnetic resonance imaging for LVEF assessment,

both real time three dimensional transthoracic echocardiography and multi-gated acquisition scans demonstrated a strong correlation for LVEF assessment when compared with cardiac magnetic resonance imaging [20].

As leading experts in the field of Cardio-Oncology in Canada, we were the first to demonstrate the utility of tissue velocity imaging (TVI) as a novel echocardiographic technique for the early detection of DOX+TRZ-mediated cardiotoxicity in both the basic science and clinical settings [8,15,22]. Tissue velocity imaging obtained using echocardiography is a modification of conventional blood flow Doppler that allows for the visualization of tissue-derived, high amplitude and low velocity Doppler signals [22]. As such, TVI and strain imaging are sensitive, non-invasive echocardiographic techniques that detect early LV systolic dysfunction prior to a decrease in conventional LVEF parameters [8,15,22]. We evaluated the cardiotoxic side effects of DOX, TRZ and the combination of both agents in an acute *in vivo* murine model of chemotherapy induced cardiomyopathy [15]. In the same basic science study, we also studied whether TVI would be useful for addressing early detection of chemotherapy induced cardiotoxicity [15]. Co-administration of DOX+TRZ was associated with severe LV systolic dysfunction, increased cardiomyocyte apoptosis and increased mortality as compared with either agent alone. We demonstrated that TVI values were abnormal in mice, receiving either DOX or DOX+TRZ, as early as 24 hours after treatment and were predictive of ensuing LV systolic dysfunction and increased mortality [15]. Translating these basic science findings into the clinical arena, we evaluated the role of TVI and strain imaging in the early detection of DOX+TRZ-mediated cardiac dysfunction in women with breast cancer [8]. Of 42 women prospectively followed between 2007 and 2010 at CancerCare Manitoba, 10 (25%) women developed DOX+TRZ-mediated cardiomyopathy with symptomatic heart failure. We demonstrated that both TVI and strain imaging detected changes in LV systolic function three months earlier than conventional LVEF parameters in this patient population [8]. Based on our translational findings, a number of Cardio-Oncology practice guidelines recommend incorporating strain parameters as routine surveillance for monitoring cardiac function in the breast cancer population [21].

With an increasing number of breast cancer survivors experiencing significant cardiovascular complications as a

result of anti-cancer drugs, an important opportunity also exists to develop research studies focused on the prevention of cardiotoxicity in this unique patient population. Over the past five years, we have focused much of our research efforts on the role of various pharmacological and nutraceuticals therapies including anti-oxidants (probucol and N-acetylcysteine amide), renin-angiotensin system (RAS) antagonists, and flaxseed in the partial prevention of DOX+TRZ-mediated cardiotoxicity in murine models [11,12,23]. Recently, we translated our basic science findings into the clinical arena by completing the Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE) study. Through collaborative efforts with our colleagues at the University of Alberta, this study confirmed that the prophylactic administration of either RAS inhibitors or beta blockade may prevent cardiotoxicity in women with breast cancer patients treated with DOX+TRZ [23]. As we embark on a new clinical trial evaluating the role of dietary flaxseed in preventing broken hearts in women with breast cancer, our journey in the evolving field of Cardio-Oncology has only begun.

Rather than asking the question, “How do we prevent Clinician Scientists in Canada from becoming endangered?”, we should rephrase the query as, “How do we continue to foster the successful Clinician Scientists of the future?” If I were to advise a young physician on the prerequisites, merits and challenges of becoming a Clinician-Scientist, my recommendations would include the following: i) one must have an innate desire and enthusiasm to pursue research; ii) one must establish a strong scientific mentorship in order to develop the necessary skillset to perform research; iii) one must have protected research time to allow the self-disciplined individual to truly focus on their academic mission; and finally iv) one must continue to collaborate as a member of a multidisciplinary team. The future success of our next generation of Clinician Scientists will rest on these key principles.

References

1. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol*. 2009 Apr;10(4):391-9.
2. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res*. 2008 Jan 1;14(1):14-24.

3. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med*. 1998 Sep 24;339(13):900-5.
4. Gewirtz DA. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. *Biochem Pharmacol*. 1999 Apr 1;57(7):727-41.
5. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN, Singletary SE. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. 1999 Feb;17(2):460-9.
6. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56(2):185-229.
7. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, Wood WC. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol*. 2003 Feb 15;21(4):588-92.
8. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick ID, Singal PK, Krahn M, Grenier D, Jassal DS. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol*. 2011 May 31;57(22):2263-70.
9. Guglin M, Hartlage G, Reynolds C, Chen R, Patel V. Trastuzumab-induced cardiomyopathy: not as benign as it looks? A retrospective study. *J Card Fail*. 2009 Oct;15(8):651-7.
10. McArthur HL, Chia S. Cardiotoxicity of trastuzumab in clinical practice. *N Engl J Med*. 2007 Jul 5;357(1):94-5.
11. Walker JR, Sharma A, Lytwyn M, Bohonis S, Thliveris J, Singal PK, Jassal DS. The cardioprotective role of probucol against anthracycline and trastuzumab-mediated cardiotoxicity. *J Am Soc Echocardiogr*. 2011 Jun;24(6):699-705.
12. Akolkar G, Bhullar N, Bews H, Shaikh B, Premecz S, Bordun KA, Cheung DY, Goyal V, Sharma AK, Garber P, Singal PK, Jassal DS. The role of renin angiotensin system antagonists in the prevention of doxorubicin and trastuzumab induced cardiotoxicity. *Cardiovasc Ultrasound*. 2015 Apr 3;13:18.
13. Zeglinski M, Premecz S, Lerner J, Wtorek P, Dasilva M, Hasanally D, Chaudhary R, Sharma A, Thliveris J, Ravandi A, Singal PK, Jassal DS. Congenital absence of nitric oxide synthase 3 potentiates cardiac dysfunction and reduces survival in doxorubicin- and trastuzumab-mediated cardiomyopathy. *Can J Cardiol*. 2014 Mar;30(3):359-67.
14. Walker JR, Singal PK, Jassal DS. The art of healing broken hearts in breast cancer patients: Trastuzumab and heart failure. *Exp Clin Cardiol*. 2009 Fall;14(3):e62-7.
15. Jassal DS, Han SY, Hans C, Sharma A, Fang T, Ahmadi R, Lytwyn M, Walker JR, Bhalla RS, Czarnecki A, Moussa T, Singal PK. Utility of tissue Doppler and strain rate imaging in the early detection of trastuzumab and anthracycline mediated cardiomyopathy. *J Am Soc Echocardiogr*. 2009 Apr;22(4):418-24.
16. Bordun KA, Premecz S, daSilva M, Mandal S, Goyal V, Glavinovic T, Cheung M, Cheung D, White CW, Chaudhary R, Freed DH, Villarraga HR, Herrmann J, Kohli M, Ravandi A, Thliveris J, Pitz M, Singal PK, Mulvagh S, Jassal DS. The utility of cardiac biomarkers and echocardiography for the early detection of bevacizumab- and sunitinib-mediated cardiotoxicity. *Am J Physiol Heart Circ Physiol*. 2015 Aug 15;309(4):H692-701.
17. Goyal V, Bews H, Cheung D, Premecz S, Mandal S, Shaikh B, Best R, Bhindi R, Chaudhary R, Ravandi A, Thliveris J, Singal PK, Niraula S, Jassal DS. The Cardioprotective Role of N-Acetyl Cysteine Amide in the Prevention of Doxorubicin and Trastuzumab-Mediated Cardiac Dysfunction. *Can J Cardiol*. 2016 Dec;32(12):1513-1519.
18. Wadhwa D, Fallah-Rad N, Grenier D, Krahn M, Tang F, Ahmadi R, Walker JR, Lister D, Arora RC, Barac I, Morris A, Jassal DS. Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast Cancer Res Treat*. 2009 Sep;117(2):357-63.
19. Fallah-Rad N, Lytwyn M, Tang F, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson* 2008 Jan;10:5.
20. Walker J, Bhullar N, Fallah-Rad N, Lytwyn M, Golian M, Fang T, Summers AR, Singal PK, Barac I, Kirkpatrick ID, Jassal DS. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multi-gated acquisition scans, and cardiac magnetic resonance imaging. *J Clin Oncol*. 2010 Jul;28(21):3429-36.
21. Virani SA, Dent S, Brezden-Masley C, Clarke B, Davis MK, Jassal DS, Johnson C, Lemieux K, Paterson I, Sebag I, Simmons C, Sulpher J, Thain K, Thavendiranathan P, Wentzell JR, Wurtele N, Cote MA, Fine NM, Haddad H, Hayley BD, Hopkins S, Joy AA, Rayson D, Stadnick E, Straatman L.

- Canadian Cardiovascular Society guidelines for evaluation and management of cardiovascular complications of cancer therapy. *Can J Cardiol.* 2016 Jul;32(7):831-41.
22. Ducas RA, Tsang W, Chong AA, Jassal DS, Lang RM, Leong-Poi H, Chan KL. Echocardiography and vascular ultrasound: new developments and future directions. *Can J Cardiol.* 2013 Mar;29(3):304-16.
23. Pituskin E, Mackey JR, Koshman S, Jassal DS, Pitz M, Haykowsky MJ, Pagano JJ, Chow K, Thompson RB, Vos LJ, Ghosh S, Oudit GY, Ezekowitz JA, Paterson DI. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. *J Clin Oncol.* 2017 Mar 10;35(8):870-877.