RUTGERS
School of Graduate Studies

Office of Student Affairs and Admissions
SGS at New Jersey Medical School
Rutgers, The State University of New Jersey
185 South Orange Avenue, MSB C-696
Newark, NJ 07103

http://njms.rutgers.edu/gsbs/
p. 973-972-4511
f. 973-972-7148

YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"β-Adrenergic Stimulation Precipitates Cardiac Dysfunction in Mice Treated with Microtubule-Targeting Chemotherapy Drugs"

by

Kelli Gaul-Muller

M.D./Ph.D. Program

B.A. 2015, Rutgers, The State University of New Jersey,
New Brunswick, NJ

Thesis Advisor:
Jorge E. Contreras, Ph.D.
Professor, Department of Physiology and Membrane Biology, UC Davis

Andrew P. Thomas, Ph.D.
Professor and Chair, Department of Pharmacology, Physiology & Neuroscience

Monday, June 10, 2024
2:00 P.M.
MSB H-Level Conference Room (H-609), Zoom
Meeting ID: 920 3774 9399
Password: 546990
https://rutgers.zoom.us/j/92037749399?pwd=TFY0VmNDWFNTQjBCeEpRcGNUR0RRUT09

Abstract

Although long-term survival rates have increased for many types of cancer, cancer therapy-related cardiotoxicity (CTRC) has emerged as a dangerous complication of chemotherapy regimens. The clinical manifestations of CTRC can vary widely, including left ventricular dysfunction, heart failure, endomyocardial fibrosis, cardiac tamponade, ischemia, pericarditis, myocarditis, and arrhythmias. Despite recent advances in the field of cardio-oncology, the pathophysiology of specific chemotherapy agents is unknown. Additionally, CTRC is currently treated with conventional therapies for heart failure despite increased mortality compared to idiopathic cardiomyopathy. Therefore, further investigation into the mechanisms underlying disease development and progression for various therapies is imperative to advance the field and to improve outcomes for cancer patients affected by CTRC. Microtubule targeting agents (MTAs) are known to cause CTRC, however, little is known about their mechanism of injury. Two MTAs in particular, paclitaxel and vincristine, are widely used to treat various cancers and earmarked by the World Health Organization as essential medications. Current animal studies investigating the effect of MTAs use higher doses than would be used in humans, limiting their clinical translation. This thesis aims to characterize the acute effect of long-term chemotherapy treatment with clinically relevant doses of two MTAs, paclitaxel and vincristine, on the mouse heart *in vivo.* Electrocardiography and echocardiography revealed sex-dependent changes in the structure and function of the mouse heart immediately following 4 weeks of MTA therapy and β-adrenergic challenge. Chemotherapy-treated male mice had greater arrhythmogenesis and cardiac hypertrophy following the treatment cycle, while female mice did not. Western blot, RT-qPCR and immunofluorescence were used to elucidate potential mechanisms behind the observed functional and structural changes. Male mice showed alterations in cytokine levels and redistribution of connexin-43, consistent with pathological changes associated with cardiac dysfunction. This study provides critical insights regarding potential mechanisms of β-adrenergic stress-induced cardiac changes during chemotherapy treatment, which is the basis for identifying drug targets that can be used to prevent and treat CTRC.