Graduate School of Arts & Sciences

Final Examination of

Alison Leigh Arter

For the Degree of

Doctor of Philosophy

Integrative Physiology and Pharmacology

May 2014

Winston-Salem, North Carolina

Committee in Charge

E. Ann Tallant, PhD, Co-Advisor

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Wake Forest School of Medicine
Medical Center Boulevard
Hanes Building, Room 1064
Friday, April 11th, 2014
1:00 p.m.
PROFESSORS IN CHARGE OF RESEARCH
E. Ann Tallant, PhD, Professor
Patricia E. Gallagher, PhD, Associate Professor
Hypertension and Vascular Research Center
Department of Surgical Sciences
Department of Physiology & Pharmacology
Wake Forest School of Medicine

FIELDS OF GRADUATE STUDY
Major Subject: Integrative Physiology and Pharmacology
Correlated Topics: Cancer Biology, Molecular Biology

SUMMARY OF DISSERTATION
MOLECULAR MECHANISMS FOR THE ANGIOTENSIN-(1-7)-MEDIATED INHIBITION OF METASTATIC TRIPLE NEGATIVE BREAST CANCER

Approximately 40,000 women in the U.S. die from breast cancer annually. An estimated 15% of all breast cancers are triple negative, characterized by a lack of estrogen receptor and progesterone receptor expression and unamplified human epidermal growth factor receptor 2 (HER2) levels, contributing to an absence of effective, targeted therapeutics. Furthermore, triple negative breast cancer (TNBC) is highly aggressive with greater patient mortality rates compared with other breast cancer subtypes, necessitating development of novel treatment options. Angiotensin-(1-7) [Ang-(1-7)] is an endogenous peptide hormone of the renin-angiotensin system with anti-proliferative, anti-fibrotic and anti-metastatic properties. Ang-(1-7) inhibited the growth of human MDA-MB-231 and murine 4T1 TNBC cells and orthotopic tumors. Phosphorylated Akt [p-Akt(Ser473) and p-Akt(Thr308)], a major driver of cell proliferation and survival, was concomitantly reduced suggesting that the heptapeptide decreases the activation of Akt to inhibit TNBC growth. The serine/threonine phosphatase responsible for Akt inactivation, protein phosphatase 2A (PP2A), is upregulated in TNBC cells and tumors treated with Ang-(1-7). This suggests that the heptapeptide hormone mediates inhibition of TNBC growth via increased PP2A to prevent Akt activity.

Metastasis remains a serious medical issue for which few therapies have been effective for treatment or prevention, thus contributing to a death rate of 90% in patients with solid tumors. Human TNBC has a high rate of metastasis to the lung, liver, bone and brain, a pattern mimicked by the 4T1-Balb/c syngeneic mouse model of TNBC. Ang-(1-7) reduced the growth of metastatic 4T1 tumors in the lungs of mice, demonstrated by decreased lung wet weight, tumor number and tumor area. Breast tumor fibrosis facilitates tumor growth and progression via cancer-associated fibroblast (CAF)-mediated extracellular matrix (ECM) protein production. Ang-(1-7) inhibited the growth of CAFs isolated from orthotopic 4T1 tumors as well as the fibrotic mediators transforming growth factor-beta (TGF-β), p-Smad2, connective tissue growth factor (CTGF) and tenascin C in 4T1 CAFs, metastatic 4T1 tumors, and primary orthotopic 4T1 tumors. These results are the first to show the anti-fibrotic effects of Ang-(1-7) in reducing metastatic TNBC growth, thus supporting the role for the heptapeptide hormone as a novel treatment for metastatic TNBC.
SCHOLASTIC VITAE

EDUCATION
2014 - PhD, Integrative Physiology and Pharmacology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

2009 - BS, Pharmacology & Toxicology
University at Buffalo
Buffalo, New York

PROFESSIONAL MEMBERSHIPS
2010 - Present American Association for Cancer Research
2011 - Present AACR Women in Cancer Research
2013 - Present Association for University Technology Managers

GRADUATE FELLOWSHIPS
2009 - 2014 Graduate Fellowship
Wake Forest University Graduate School of Arts and Sciences

AWARDS
2014 Finalist, Bespoke Therapeutics, LLC
International Breast Cancer Startup Challenge
Avon Foundation/NCI/Center for Advancing Innovation

2013 Silver Award, Poster Competition, Basic Science, Student
Wake Forest University Division of Surgical Sciences Research Day

2013 Wake Forest University Alumni Student Travel Award
Tumor Microenvironment and Cellular Stress Meeting, Corfu, Greece

2013 Wake Forest University Alumni Student Travel Award
AACR Tumor Invasion and Metastasis Meeting, San Diego, CA

2013 First Place, Poster Competition
Wake Forest University Graduate Student and Post-Doctoral Research Day

2012 First Place, Poster Competition
Charlotte Research Institute Life Sciences Conference

2012 Wake Forest University Alumni Student Travel Award
AACR Annual Meeting, Chicago, IL

2011 Scholar-in-Training Award Finalist
AACR Annual Meeting, Orlando, FL

2011 Wake Forest University Alumni Student Travel Award
AACR Annual Meeting, Orlando, FL

2010 Wake Forest University Alumni Student Travel Award
Experimental Biology Meeting, Anaheim, CA
PUBLICATIONS


Manuscripts:


SELECTED ABSTRACTS


