## BIOGRAPHICAL SKETCH

NAME: Jessica E. Thaxton

eRA COMMONS USER NAME (credential, e.g., agency login): JESSTHAXTON

POSITION TITLE: Assistant Professor, Departments of Orthopedic Surgery & Microbiology and Immunology

EDUCATION/TRAINING *(Begin with baccalaureate education, include postdoctoral training and residency training if applicable.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Amherst College, Amherst, MA | BS | 2001 | Psychology |
| Brown University, Providence, RI | PhD | 2009 | Pathobiology |
| Oregon Health & Sciences University, Portland, OR | Postdoctoral | 2012 | Viral Immunology |
| Medical University of South Carolina, Charleston, SC | Postdoctoral | 2015 | Tumor Immunology |
| Medical University of South Carolina, Charleston, SC | MsCR | 2014 | Clinical Research |

### A. Personal Statement

My research focuses on the role of the endoplasmic reticulum (ER) stress response in defining immune cell function and fate in cancer and autoimmune disease. During my postdoctoral work in the laboratory of Dr. Zihai Li, MD, PhD, I generated or contributed to multiple manuscripts that established the role of the ER as a force that shapes immunity in health and disease (1-3). My work was the first to demonstrate that modulation of the ER stress response alters T cell metabolism and is a tool to produce potent T cell anti-tumor immunity (1). I also demonstrated that the ER drives myeloid derived suppressor cell (MDSC) development in autoimmune disease (2). I contributed to work from our group that established the critical role of an ER chaperone to guide T regulatory cell suppressive function in cancer and autoimmunity (3). I was supported by a Department of Defense Breast Cancer Research Program Postdoctoral Fellowship that trained me in translational research for cancer patients.

I am an Assistant Professor at the NCI designated Hollings Cancer Center at Medical University of South Carolina and hold an NCI K Award in Clinical Oncology. I lead a research team comprised of basic researchers, surgical, and medical oncologists. Our work focuses on manipulation of the ER stress response to remodel T cell metabolism in tumors as a novel treatment strategy for cancer patients. We have found that the chronic PERK axis of the unfolded protein response (UPR) is a master regulator of CD8 T cell metabolism and death in tumors. We have found that terminal PERK UPR drives metabolic exhaustion and death of PD-1+ CD8 TILs in tumors (4). Our recent work has determined that terminal PERK UPR drives a cycle of protein synthesis that is the mechanism of metabolic exhaustion in PD-1+ T effector CD8 TILs.


1. **Thaxton, JE**, Wallace, C, Reisenberg, B, Zhang, Y, Beeson, CC, Paulos, CM, Liu, B, Li, Z. Modulation of endoplasmic reticulum stress controls CD4+ T cell activation and anti-tumor function. *Cancer Immunol Res*. 2017. doi: 10.1158/2326-6066.CIR-17-0081. PMID: 28642246.
2. **Thaxton, JE,** Liu, B, Zheng, P, Li, Z. Deletion of CD24 impairs development of heat shock protein gp96-driven autoimmune disease through expansion of myeloid-derived suppressor cells. *J Immunol.* 2014: 192(12) 5679-86. PMID: 2480359 PMCID: PMC267098.
3. Zhang, Y, Wu, BX, Metelli, A, **Thaxton, JE**, Ansa-Addo, E, Sun, S, Vasu, C, Yang, Y, Liu, B, Li, Z. Gp96 is a GARP chaperone and controls T regulatory cell functions. *J Clin Invest*. 2015: 125(2)859-69. PMID: 25607841 PMCID: PMC4319419.
4. Hurst, KE, Lawrence, KA, Essman, MT, Walton, ZJ, Leddy, LR, **Thaxton, JE**. Endoplasmic reticulum stress contributes to mitochondrial exhaustion of T cells. *Cancer Immunol Res.* In Press, Dec 2018.

## B. Positions and Honors

**Positions and Employment**

| | |
|---|---|
| 1999 | Research Intern, Harvard Center for Risk Analysis |
| 2001 | Research Technician, Amherst College Organic Chemistry Department |
| 2002-2003 | Research Assistant, Dept. of Surgical Transplantation, Harvard Medical School |
| 2003-2004 | Research Assistant, Dept. of Allergy & Inflammation, Garvan Institute of Medical Research |
| 2015-Present | Assistant Professor, Depts. Of Orthopedics, Microbiology & Immunology, MUSC |

**Other Experiences and Professional Memberships**

| | |
|---|---|
| 2005-2009 | Harriet W. Sheridan Center for Teaching and Learning, Brown University, Providence RI |
| 2015-Present | Member, Cancer Immunology Program, Medical University of South Carolina |
| 2016-Present | American Association of Cancer Research |
| 2017-Present | Society for Immunotherapy of Cancer |

**Honors**

| | |
|---|---|
| 2005 | GAAAN Training Award Brown University |
| 2006 | 1st Place Research Retreat Presentation Brown University |
| 2007 | ISRI Graduate Travel Award, Rio de Janeiro Brazil |
| 2007 | Environmental Toxicology Award Brown University |
| 2008 | ASRI Graduate Travel Award, Chicago, IL |
| 2008 | ASRI Outstanding New Investigator Award |
| 2009 | SRI Graduate Travel Award, Philadelphia, PA |
| 2010 | NIH Ruth Kirschstein NRSA Fellowship |
| 2011 | Early Clinical Investigator Award |
| 2012 | Department of Defense Breast Cancer Research Fellowship |
| 2013 | ESMO Postdoctoral Travel Award, Brussels, Belgium |
| 2015 | NCI Paul Calabresi Clinical Oncology Scholar, Hollings Cancer Center |
| 2017 | Selection to Immuno-oncology Young Investigators' Forum, Houston TX |
| 2017 | Dean's Nominee, AAMC Young Female Faculty Leadership Series |
| 2017 | Harper Drolet Award for Excellence in Sarcoma Research |
| 2017 | Society for Immunotherapy of Cancer Young Investigator Award, National Harbor MD |
| 2018 | Society for Immunotherapy of Cancer, Selection to Sparkathon Cohort, Chicago IL |
| 2018 | Society for Immunotherapy of Cancer, Sparkathon Winner, Team SITCure, Chicago IL |

## C. Contributions to Science

1. **ER stress in anti-tumor T cells**:

We were the first group to define a role for ER stress in T cell activation and development. We found that TCR engagement is a form of acute ER stress in the context of antigen-driven activation. Through conditional deletion of ER stress chaperone gp96 in CD4 T cells we reported that gp96 is essential for T cell activation and subsequent induction of glycolysis. We attributed a partial mechanism of ER stress control of T cells to mediation of ER-mitochondrial calcium crosstalk (1). The long-term implication of this work was demonstration that modulation of ER stress is able to produce T cells fit for superior anti-tumor responses (1, 2). This work laid the foundation for my lab to study the major ER stress sensor PERK as a target to shift T cell metabolic fate in tumors. Using a unique TCR transgenic conditional gene deletion mouse model of PERK, we reported that chronic activation of PERK induces mitochondrial exhaustion and death of tumor antigen-specific PD-1+ CD8 TILs in mouse and human sarcomas. The long-term implication of this work is that targeting the chronic ER stress axis holds the power to repair and revitalize PD-1+ CD8 TIL metabolism and survival in tumors. This work has important implications to augment anti-PD-1 therapy (3).


1. **Thaxton, JE**, Wallace, C, Reisenberg, B, Zhang, Y, Beeson, CC, Paulos, CM, Liu, B, Li, Z. Modulation of endoplasmic reticulum stress controls CD4+ T cell activation and anti-tumor function. *Cancer Immunol Res*. 2017. doi: 10.1158/2326-6066.CIR-17-0081. [Epub ahead of print]. PMID: 28642246.
2. **Thaxton, JE,** Li, Z. To affinity and beyond: Harnessing the T cell receptor for cancer immunotherapy. *Hum Vaccin Immunther*. 2014; 10(11):3313-21. PMID: 25483644 PMCID: PMC4514023.
3. Hurst, KE, Lawrence, KA, Essman, MT, Walton, ZJ, Leddy, LR, **Thaxton, JE**. Endoplasmic reticulum stress contributes to mitochondrial exhaustion of T cells. *Cancer Immunol Res.* In Press, Dec 2018.

2. **Regulatory cells in cancer and autoimmunity**

T regulatory (Tregs) and myeloid derived suppressor cells (MDSCs) inhibit effector T cell functions in tumors. The tumor microenvironment presents a tempest of ER stress activating conditions. Our work defined a role for ER stress in promoting the development of both Treg and MDSC populations. We discovered that ER stress protein gp96 is responsible for Treg cell suppressive function through its role as a chaperone to latent TFG-β receptor GARP. Gp96 deficient Tregs were unable to actively suppress development of effector T cell-mediated autoimmunity (1). Our group went on to demonstrate the critical importance of GARP in control of TGF-β-mediated suppressive function in cancer (Metelli et al, *Cancer Research* 2016) (2). Also in the context of autoimmunity, our group used a novel ER stress-mediated mouse model of lupus to demonstrate that ER stress promotes MDSC development to inhibit T effector cell functions. In the context of autoimmunity, MDSC development and recruitment was protective from T effector-mediated rheumatic disease (4). Together, these works show that ER stress is a positive mediator of suppressor cell development and functions in the context of disease.

1. Zhang, Y, Wu, BX, Metelli, A, **Thaxton, JE**, Ansa-Addo, E, Sun, S, Vasu, C, Yang, Y, Liu, B, Li, Z. Gp96 is a GARP chaperone and controls T regulatory cell functions. *J Clin Invest*. 2015: 125(2)859-69. PMID: 25607841 PMCID: PMC4319419.
2. Ansa-Addo EA, **Thaxton JE**, Hong F, Wu BX, Zhang Y, Fugle CW, Metelli A, Riesenberg B, Williams K, Gewirth DT, Chiosis G, Liu B, Li Z. Clients and oncogenic roles of molecular chaperone gp96/grp94. Curr Top Med Chem. 2016; 16(25):2765-78. PMID: 27072698 PMCID: PMC5041304.
3. **Thaxton, JE,** Liu, B, Zheng, P, Li, Z. Deletion of CD24 impairs development of heat shock protein gp96-driven autoimmune disease through expansion of myeloid-derived suppressor cells. *J Immunol.* 2014: 192(12) 5679-86. PMID: 2480359 PMCID: PMC267098.

3. **TLRs in immune tolerance:**

We discovered that IL-10 was a key immune-suppressive cytokine in the uterine microenvironment during the course of pregnancy. We found that IL-10 was necessary to induce tolerance to toll like receptor (TLR)-mediated pathogenic insults in the context of pregnancy (1). We found that in response to TLR9 ligation by CpG motifs, IL-10 induced tolerance to spontaneous abortion and preterm birth by protecting from pathogenic macrophages at the maternal-fetal interface (2). We also discovered that in response to TLR3-mediated activation by pathogens bearing poly(I:C) motifs, IL-10 protected the maternal-fetal interface from infiltration of effector T cells that promote fetal rejection (3). These data lend mechanistic insight to the cause of pathogen-induced adverse pregnancy outcomes and may be translated to immunotherapies that aid patient care.

1. **Thaxton JE**, Sharma S. Interleukin-10: a multifaceted agent of pregnancy. *Am J Reprod Immunol*. 2010; 63(6):482-91. PMID: 20163400 PMCID: PMC3628686.
2. **Thaxton JE**, Romero R, Sharma S. TLR9 activation coupled to IL-10 deficiency induces adverse pregnancy outcomes. *J Immunol*. 2009 Jul 15;183(2):1144-54. PMID:19561095 PMCID: PMC2785500.
3. **Thaxton JE**, Nevers T, Lippe EO, Blois SM, Saito S, Sharma S. NKG2D blockade inhibits poly(I:C)-triggered fetal loss in wild type but not IL-10-/- mice. *J Immunol*. 2013: 190(7):3639-47. PMID 23455498 PMCID: PMC3608719.

**Complete List of Published Work in My Bibliography:**
https://www.ncbi.nlm.nih.gov/sites/myncbi/16aFgzWLuokAp/bibliography/52674852/public/?sort=date&direction=ascending.

**D. Research Support**

**Ongoing**

K12 NIH/NCI — Lilly (PI) — 9/01/2015-12/31/2018
Project Title: Programming CD8 T cell metabolism for Cancer Immunotherapy
The goal of this project is to develop immunotherapeutic strategies and implement clinical trials that target the ER stress response in order to remodel CD8+ T cell metabolism in the tumor microenvironment
Role: Trainee

TEVA Pharmaceuticals — Thaxton (PI) — 10/01/2018-9/30/2019
Project Title: Omacetaxine for Cancer Immunotherapy

The goal of this project is to test the efficacy of protein synthesis inhibitor Omacetaxine in combination with α-PD-1 therapy in mouse models as a novel treatment option for metastatic cancer patients
Role: Principal Investigator

**Completed**

ACS IRG Thaxton (PI) 1/01/2017-12/31/2017
Project Title: Lone Survivor: Stress Role of the ER in CD8+ T cell metabolism
The purpose of this work is to determine the mechanisms of pharmacological inhibition of PERK T cell development and tumor control.
Role: Principal Investigator

ACS IRG Thaxton (PI) 1/01/2016-12/31/2016
Project Title: Lone Survivor: Stressful Role of the ER in CD8+ T cell metabolism
The objective of this work is to determine the contribution of IP3R-mediated Ca2+ release to T memory cell metabolism and to elucidate the molecular mechanisms of ER stress-mediated pro-survival autophagy in T memory cell formation.
Role: Principal Investigator

DOD BCMRP Postdoctoral Fellowship Thaxton (PI) 05/01/2012-04/30/2015
Project Title: Chemotherapy necessitates increased immune control of chronic HHVs: A cause of persistent inflammation enabling protracted cancer treatment related fatigue in breast cancer survivors
The goal of this work was to determine whether breast cancer survivors who experienced high levels of cancer treatment related fatigue showed higher burdens of HHVs.
Role: Principal Investigator