BIOGRAPHICAL SKETCH

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NAME: Thaxton, Jessica E.

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

POSITION TITLE: Associate Professor of Cell Biology & Physiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Amherst College, Amherst, MA	BA	2001	Psychology
Brown University, Providence, RI	PhD	2010	Immunology
Oregon Health & Science University, Portland, OR	Postdoc	2013	Tumor Immunology
Medical Univ. of South Carolina, Charleston, SC	Postdoc	2016	Tumor Immunology
Medical Univ. of South Carolina, Charleston, SC	MsCR	2015	Clinical Trials

A. Personal Statement

I am a tumor immunologist leading a translational research program composed of basic scientists and clinicians focused on modulation of cell stress and metabolism in tumor immunity to improve cancer immunotherapies. I am an Associate Professor at the University of North Carolina at Chapel Hill (UNC-CH) and I am a Co-leader of the Cancer Cell Biology Program at the Lineberger Comprehensive Cancer Center (LCCC, UNC-CH). My group was among the first to identify that T cells in solid cancers experience chronic endoplasmic reticulum (ER) stress. We found that the ER stress sensor PERK can be targeted to rewire T cell metabolism, efficacy, and response to PD1 inhibitor therapy in solid cancers (1). Due to PERK's role in regulation of metabolic homeostasis of the cell, I have developed an expertise in immunometabolism that has resulted in senior author and collaborative projects published in Cell Metabolism (2), Nature (3), and Immunity (4) as well as grant awards highlighted below. Recently, we uncovered that ER structure is altered by the tumor microenvironment, leading to proteosasis collapse and loss of cytotoxic function in T cells. The deficit could be repaired by modifying ER structure to reinvigorate T cell function in cancer (under review, Immunity). My group continues to focus on aspects of ER-directed signaling, metabolism, and organelle structure that define immune outcomes in cancer.

Individual and collaborative projects that I would like to highlight include:

5-P30-CA016086-43
NIH/NCI
Earp (PI) (Ferris)
Thaxton (Program Co-Leader)
06/01/1997 - 11/30/2027
Cancer Center Core Support Grant

R01CA288976-01A1
NIH/NCI
Thaxton (PI)
09/01/2024 - 08/31/2029
Manipulating Lipid Metabolism to Reverse Immune Dysfunction in Solid Cancers

V Foundation
Adult Translational Award
Thaxton (PI)
07/15/2025 - 07/314/2029
The Cellular Response to Stress as A Mechanism of ICI Resistance

R37CA269499-01
NIH/NCI
Guerriero (PI), Thaxton (Co-I)
04/01/2022 – 03/31/2029
Immunometabolic pathways enabled by PARP inhibition in breast cancer

R01CA310022-01, 4th Percentile, Pending
NIH/NCI
Thaxton (PI)
12/01/2025 – 11/30/2030
Regulation of Immunometabolism by the Integrated Stress Response in Cancer

1R01CA244361-01A1
NIH/NCI
Thaxton (PI)
07/01/2020 - 06/30/2025
Targeting Chronic ER Stress in T Cells to Improve Cancer Immunotherapy

1R01CA248359-01, NCI/NIH Cancer Moonshot Initiative
NIH/NCI
Thaxton (PI)
04/01/2020 - 03/31/2025
Exploitation of ER Stress Induced Immune Dysfunction to Improve Cancer Immunotherapy

Citations:

1. Hurst KE, Lawrence KA, Essman MT, Walton ZJ, Leddy LR, **Thaxton JE.** Endoplasmic Reticulum Stress Contributes to Mitochondrial Exhaustion of CD8 T cells. PMCID:PMC6397687 (2019) *Cancer Immunol Res*.
2. Hunt EG, Hurst EK, Riesenberg BP, Kennedy AS, Gandy EJ, Andrews AM, Alicea Pauneto CDM, Ball LE, Wallace ED, Gao P, Meier J, Serody JJ, Coleman MF, **Thaxton JE**. Acetyl-CoA Carboxylase Obstructs $CD8^+$ T-Cell Lipid Utilization in the Tumor Microenvironment. PMID: 38490211 (2024) *Cell Metabolism*.
3. Chung HK, Liu C, Jambor AN, Riesenberg BP, Sun M, Casillas E, Chick B, Wang A, Wang J, Ma S, Mcdonald B, He P, Yang Q, Chen T, Varanasi SK, LaPorte M, Mann TH, Chen D, Hoffmann F, Tripple V, Ho J, Modliszewski J, Williams A, Cho UH, Liu L, Wang Y, Hargreaves DC, **Thaxton JE**, Kaech SM, Wang W. Multi-Omics Atlas-Assisted Discovery of Transcription Factors for Selective T Cell State Programming. PMID: 36711632; PMCID: PMC9881845. (2025) *Nature.*
4. Alicea Pauneto CDM, Riesenberg BP, Gandy EJ, Kennedy AS, Clutton G, Hem JW, Hurst KE, Green JM, Hunt EG, Esther RJ, Guerriero JL, Soto-Pantoja D, Modliszewski J, Ferris RL, Chung HK, Milner JJ, Coleman M, Moschos SJ, Wiseman RL, **Thaxton JE**. Intra-tumoral hypoxia promotes $CD8^+$ T cell dysfunction via chronic activation of the integrated stress response transcription factor ATF4 (2025) *Immunity.*

B. Positions, Scientific Appointments, and Honors
Positions and Scientific Appointments

2025-Present Faculty Director, Metabolomics & Proteomics Core, UNC-Chapel Hill
2024-Present Co-Chair, National Awards Review Committee, SITC
2024-Present Co-Chair, Translational Immune Oncology, NIH/NCI
2024-Present Standing Member, Translational Immune Oncology, NIH/NCI

2023-Present Co-Leader, Cancer Cell Biology Program, LCCC, UNC-Chapel Hill
2022-Present Associate Professor, Cell Biology & Physiology, UNC-Chapel Hill
2022-2023 Member, Immunology Program, LCCC, UNC-Chapel Hill
2017-Present Member, SITC
2016-Present Member, AACR
2017-2021 Assistant Professor, Microbiology and Immunology, MUSC
2016-2018 Paul Calabresi NCI K12 Clinical Oncology Fellow
2012-2015 DOD Breast Cancer Research Program Postdoctoral Fellow
2006-2009 Member, Harriet W. Sheridan Center for Teaching and Learning, Brown University
2003-2005 Research Assistant, Allergy & Inflammation, Garvan Institute, Sydney, Australia
2002-2003 Research Assistant, Department of Surgical Transplantation, Harvard Medical School

Honors

2025 Paper of the Year Award, UNC-Chapel Hill
2025 Forebeck Faculty, Immunometabolism in Cancer Therapy
2025 V Foundation Adult Translational Award
2023 Developmental Funds Award, UNC-Chapel Hill
2022 Paper of the Year Award, UNC-Chapel Hill
2020 Foundation for Research Development Award, Medical University of South Carolina
2018 Sparkathon Winner, Society for Immunotherapy of Cancer
2018 Selected to Sparkathon, Society for Immunotherapy of Cancer
2017 Selected to Immuno-oncology Young Investigators' Forum
2017 Dean's Nominee, AAMC Young Female Faculty Leadership Series
2017 Harper Drolet Award for Excellence in Sarcoma Research
2017 Young Investigator Award, Society for Immunotherapy of Cancer
2016 NIH/NCI Paul Calabresi Clinical Oncology Fellowship
2013 ESMO Postdoctoral Travel Award
2012 Department of Defense Breast Cancer Research Fellowship Award
2011 Early Clinical Investigator Award
2010 NIH Ruth Kirschstein NRSA Fellowship
2010 Summa Cum Laude, Brown University Graduate School
2009 SRI Graduate Travel Award
2008 ASRI Graduate Travel Award
2008 ASRI Outstanding New Investigator Award
2007 ISRI Graduate Travel Award
2007 Environmental Toxicology Award, Brown University
2006 1st Place Research Retreat Presentation, Brown University

C. Contribution to Science

1. Stress Response Programming in Tumor Immunity

I have played a pioneering role in defining the contribution of cell stress signaling to mediate T cell responses in solid tumors. (A) I was among the first to describe a role for the endoplasmic reticulum (ER) stress response to undermine the capacity of T cell antitumor immunity. Using a T cell conditional gene deletion mouse model, I discovered that the glucose regulatory chaperone protein (gp/grp)96 impedes tumor control and undermines antitumor metabolism. (B) Two years later my independent research group was the first to publish that the major ER stress sensor PERK integrates stress signals from the tumor microenvironment to limit T cell antitumor immunity. This work found that PERK contributes to metabolic exhaustion of T cells in solid tumors. (C) On the heels of this discovery, we next published that T cells impaired in the ability to phosphorylate PERK-regulated stress element eIF2-α, a critical factor regulating protein translation, exhibit superior antitumor immunity in melanomas. (D) These works led us to identify that ATF4, the central node of the integrated stress response downstream of both PERK and p-eIF2-α, is the critical stress element controlling T cell function in the hypoxic stress of solid cancers. These works have laid the framework for ongoing R01-funded research in my lab that studies the role of cell stress signaling, metabolic, and protein homeostasis in T cells in solid tumors.

A. **Thaxton JE**, Wallace C, Riesenberg B, Zhang Y, Paulos CM, Beeson CC, Liu B, Li Z. Modulation of Endoplasmic Reticulum Stress Controls $CD4^+$ T-cell Activation and Antitumor Function. PMCID:PMC5585019 (2017) *Cancer Immunol Res*.
B. Hurst K, Lawrence KA, Essman MT, Walton ZJ, Leddy LR, **Thaxton JE**. Endoplasmic Reticulum Stress Contributes to Mitochondrial Exhaustion of CD8 T cells. PMCID:PMC6397687 (2019) *Cancer Immunol Res*.
C. Riesenberg BR, Hurst KE, Hunt EH, Andrews AM, Tennant MD, Leddy LR, Neskey DM, Hill EG, Rangel Rivera GO, Paulos CM, Gao P, **Thaxton JE.** Stress-Mediated Attenuation of Translation Undermines T Cell Tumor Control. PMCID: PMC9722626 (2022) *Cancer Res*.
D. Alicea Pauneto CDM, Riesenberg BP, Gandy EJ, Kennedy AS, Clutton G, Hem JW, Hurst KE, Green JM, Hunt EG, Esther RJ, Guerriero JL, Soto-Pantoja D, Modliszewski J, Ferris RL, Chung HK, Milner JJ, Coleman M, Moschos SJ, Wiseman RL, **Thaxton JE**. Intra-tumoral hypoxia promotes $CD8^+$ T cell dysfunction via chronic activation of the integrated stress response transcription factor ATF4 (2025) *Immunity*.

2. Immunometabolism of Tumor Immunotherapy

Findings from my work in cell stress signaling as a controller of tumor immunity led me to develop a unique expertise in cell stress and metabolism. Early work in Section 1 above suggested that stress signaling in immune cells responding to tumor microenvironment stressors (ie, glucose imbalance, amino acid imbalance, hypoxic stress) reprogrammed metabolism of tumor immunity. As detailed in Section 1, our discovery that Stress-Mediated Attenuation of Translation Undermines T Cell Tumor Control, Riesenberg et al. provided an understanding of how protein degradation regulated by the proteasome regulates $CD8^+$ T cell biology. (A) We leveraged this knowledge to collaborate on ground-breaking work that reveals a central defining feature of terminally exhausted $CD8^+$ TILs (TEX_{term}) is high proteasome activity. (B) Further, we found that hypoxic stress in the tumor microenvironment enforces lipid storage in TEX_{term}.. We demonstrated that lipid storage is a key metabolic event that limits lipid utilization for bioenergetic fuel in $CD8^+$ TILs. We are currently studying how the cellular response to stress integrates hypoxic signals from the TME to program $CD8^+$ TIL metabolism. Expertise in lipid metabolism and cell stress has enabled us to study abnormal immunometabolism in multiple immune subsets. (C) In a collaborate effort with the Guerriero lab, we identified that PARP inhibitors generate abnormal lipid metabolism in tumor associated macrophages that enhances suppressive capacity. Inhibition of fatty acid synthesis in breast tumor-bearing mice resulted in long-lived tumor control when combined with immune checkpoint inhibition. (D) In a collaborative effort with the Dotti lab, we identified that Cathepsin-G specific CAR-T cells undergo electron transport chain reprogramming that results in increased mitochondrial mass to enhance antitumor efficacy. My expertise in immunometabolism has generated high impact publications from my lab group and R01 awards.

A. Chung HK, Liu C, Jambor AN, Riesenberg BP, Sun M, Casillas E, Chick B, Wang A, Wang J, Ma S, Mcdonald B, He P, Yang Q, Chen T, Varanasi SK, LaPorte M, Mann TH, Chen D, Hoffmann F, Tripple V, Ho J, Modliszewski J, Williams A, Cho UH, Liu L, Wang Y, Hargreaves DC, **Thaxton JE**, Kaech SM, Wang W. Multi-Omics Atlas-Assisted Discovery of Transcription Factors for Selective T Cell State Programming. PMID: 36711632; PMCID: PMC9881845 (2025) *Nature.*
B. Hunt EG, Hurst EK, Riesenberg BP, Kennedy AS, Gandy EJ, Andrews AM, Alicea Pauneto CDM, Ball LE, Wallace ED, Gao P, Meier J, Serody JJ, Coleman MF, **Thaxton JE**. Acetyl-CoA Carboxylase Obstructs $CD8^+$ T-Cell Lipid Utilization in the Tumor Microenvironment (2024) *Cell Metabolism.*
C. Mehta AK, Cheney EM, Hartl CA, Pantelidou C, Oliwa M, Castrillon JA, Lin JR, Hurst KE, de Oliveira Taveira M, Johnson NT, Oldham WM, Kalocsay M, Berberich MJ, Boswell SA, Kothari A, Johnson S, Dillon DA, Lipschitz M, Rodig S, Santagata S, Garber JE, Tung N, Yélamos J, **Thaxton JE**, Mittendorf EA, Sorger PK, Shapiro GI, Guerriero JL. Targeting Immunosuppressive macrophages overcomes PARP inhibitor resistance in BRCA1-associated triple-negative breast cancer. PMCID: PMC7963404 (2021) *Nature Cancer*.
D. Walhart T, Song F, Biondi M, Stucchi S, Li G, Peishun P, Suzuki K, Hunt EG, Kennedy AS, **Thaxton JE**, Withers T, Hunsucker S, Tsahouridis R, Serafini M, Flick L, Lichtman EI, Woodcock M, Su L, Yang Z, Xiong G, Cui S, Wang P, Liu C, Savoldo B, Armistead P, Dotti G. High-avidity Cathepsin-G specific CAR-T cells for the treatment of Acute Myeloid Leukemia. (In Press) *Blood*.

3. Immune Cell State and Programming in Cancers:

Our independent and collaborative work has served to demonstrate that cell stress and metabolism defines immune cell states in tumor immunity. (A) We found that reprogramming lipid metabolism directly enhances formation of T cell memory. This contributes to the field of metabolic reprogramming in tumor immunotherapy. (B) Our discovery that cell stress programs loss of T cell function in tumors, led to the discovery that chronic cell stress signaling shapes the terminal exhaustion cell state in $CD8^+$ T cells in tumors. (C) Through collaborative work with the Milner lab, we found that $CD8^+$ T cell states are a product of tissue microenvironment. These data suggest that gradients of environmental stress may shape $CD8^+$ T cell state. (D) Through collaborative work with the Guerriero lab, we found that metabolic programming of tumor associated macrophages defines macrophage cell state in breast tumors.

A. Hunt EG, Hurst EK, Riesenberg BP, Kennedy AS, Gandy EJ, Andrews AM, Alicea Pauneto CDM, Ball LE, Wallace ED, Gao P, Meier J, Serody JJ, Coleman MF, **Thaxton JE**. Acetyl-CoA Carboxylase Obstructs $CD8^+$ T-Cell Lipid Utilization in the Tumor Microenvironment. PMID: 38490211 (2024) *Cell Metabolism*.
B. Alicea Pauneto CDM, Riesenberg BP, Gandy EJ, Kennedy AS, Clutton G, Hem JW, Hurst KE, Green JM, Hunt EG, Esther RJ, Guerriero JL, Soto-Pantoja D, Modliszewski J, Ferris RL, Chung HK, Milner JJ, Coleman M, Moschos SJ, Wiseman RL, **Thaxton JE**. Intra-tumoral hypoxia promotes $CD8^+$ T cell dysfunction via chronic activation of the integrated stress response transcription factor ATF4. (2025) *Immunity.*
C. Green WD, Gomez A, Plotkin AL, Pratt BA, Merritt EF, Mullins GN, Kren NP, Modliszewski JL, Zhabotynsky V, Woodcock MG, Green JM, Cannon G, Pipkin ME, Dotti G, **Thaxton JE**, Pylayeva-Gupta Y, Baldwin AS, Morris IV JP, Stanley N, Milner JJ. Enhancer-driven regulatory networks reveal transcription factors governing $CD8^+$ T cell differentiation and adaptation in the tumor microenvironment (2025) *Immunity*.
D. Mehta AK, Cheney EM, Hartl CA, Pantelidou C, Oliwa M, Castrillon JA, Lin JR, Hurst KE, de Oliveira Taveira M, Johnson NT, Oldham WM, Kalocsay M, Berberich MJ, Boswell SA, Kothari A, Johnson S, Dillon DA, Lipschitz M, Rodig S, Santagata S, Garber JE, Tung N, Yélamos J, **Thaxton JE**, Mittendorf EA, Sorger PK, Shapiro GI, Guerriero JL. (2021) Targeting Immunosuppressive macrophages overcomes PARP inhibitor resistance in BRCA1-associated triple-negative breast cancer. PMCID: PMC7963404 (2021) *Nature Cancer.*

https://www.ncbi.nlm.nih.gov/myncbi/jessica.thaxton.1/bibliography/public/