## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Salisbury, Travis

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

POSITION TITLE: Associate Professor

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 |
|---|---|---|---|
| Kent State University, Kent, OH | B.S | 05/97 | Zoology |
| Kent State University, Kent, OH | PhD | 05/03 | Physiology |
| Case Western Reserve, School of Medicine, Cleveland, OH | Post doctoral Research | 10/03 | Molecular Endocrinology |
| Washington State University, Pullman, WA | Post doctorate Research | 09/09 | Molecular Endocrinology |

### A. Personal Statement

My research focus is breast cancer. One project investigates targeting nutrient transport to suppress breast cancer in obesity. The premise for this project stems from clinical work showing that obesity significant increases breast cancer mortality, worsens breast cancer outcomes, renders tumors less responsive to cancer therapy and increases the rate of metastatic breast cancer. The mechanisms of breast cancer progression in obesity is a knowledge gap. We hypothesize that paracrine and endocrine factors released by adipose tissue during obesity induce signaling in breast cancer cells that increases leucine absorption by cancer cells. In addition to being an essential amino acid that is required for protein synthesis, leucine can also induce and sustain oncogenic mTOR signaling in cancer. Thus, suppressing leucine uptake by cancer cells will not only starve tumor cells, but it will also reduce mTOR pathways that promote the growth and metastatic potential of cancer. Others and we have published that L-Type Amino Acid Transporter 1 (LAT1) is a critically important leucine transporter that is expressed by breast cancer. Others and we have published that suppressing LAT1 inhibits the growth of breast cancer cells. We have new data showing that adipose tissue secretes factors that induce LAT1 expression and activity in breast cancer cells. We therefore hypothesize that obesity promotes breast cancer by inducing LAT1 expression and activity in breast tumors. We are currently investigating the unique regulation of LAT1 in breast cancer during obesity.

Our second project involves targeting the aryl hydrocarbon receptor (AHR) to suppress breast cancer. The AHR is a ligand activated transcription factor. Others and we have shown that certain AHR ligands inhibit the growth and metastatic potential of breast cancer cells. We recently published that the putative endogenous AHR ligand, ITE, reduces the JAG1-NOTCH1 pathway in triple negative breast cancer (TNBC) cells. The JAG1-NOTCH1 pathway is an embryonic pathway that upon being overactive induces and promotes breast cancer. There are drugs in clinical trials to suppress the JAG1-NOTCH1 pathway for breast cancer therapy. However, our report is the first to show that AHR signaling suppresses JAG1-NOTCH1 signaling in cancer. This new finding provides mechanistic evidence for a new way to target JAG1-NOTCH1 signaling in breast cancer by treating with AHR ligands. We are currently investigating

mechanisms by which ITE inhibits breast cancer growth by inhibiting cell cycle and the JAG1-NOTCH1 pathway.

### B. Positions and Honors

**Positions and Employment**

| | |
|---|---|
| 2003 – 2004 | Postdoctoral Fellow, Case Western School of Medicine |
| 2004 - 2009 | Postdoctoral Fellow, Washington State University |
| 2009-2015 | Assistant Professor, Marshall University, School of Medicine |
| 2015- | Associate Professor with tenure, Marshall University, School of Medicine |

### C. Contribution to Science

1. My postdoctoral publications directly investigated the mechanism by which the transcriptional coactivator β catenin was required for maximal expression of the LHβ gene, which encodes the β subunit of luteinizing hormone (LH) in response to GnRH signaling. This publication identified that β-catenin increases transcription of the LHβ gene by binding to the transcription factor steroidogenic factor 1 (SF1). We then published that GnRH signaling induces a functional interaction between β-catenin and the TCF/LEF family of transcription factors, and that this was required for the induction of JUN expression and JUN target genes. Collectively, these publications demonstrated that GnRH can signal through β-catenin to regulate the expression of genes that define a functional gonadotrope and are essential for reproduction. Publications by other laboratories have now demonstrated that the regulation of SF-1 or TCF/LEF gene targets by hormones that signaling through G protein coupled receptors (GPCRs) occurs at many gene promoters and in different tissues such as the ovary or testis.

    a. **Salisbury TB**, Binder AK, Grammer JC, Nilson JH. GnRH-regulated expression of Jun and JUN target genes in gonadotropes requires a functional interaction between TCF/LEF family members and beta-catenin. Mol Endocrinol. 2009 Mar;23(3):402-11. PubMed PMID: 19131506; PubMed Central PMCID: PMC2654513.
    b. **Salisbury TB**, Binder AK, Nilson JH. Welcoming beta-catenin to the gonadotropin-releasing hormone transcriptional network in gonadotropes. Mol Endocrinol. 2008 Jun;22(6):1295-303. PubMed PMID: 18218726.
    c. **Salisbury TB**, Binder AK, Grammer JC, Nilson JH. Maximal activity of the luteinizing hormone beta-subunit gene requires beta-catenin. Mol Endocrinol. 2007 Apr;21(4):963-71. PubMed PMID: 17244763.

2. My current studies are investigating signal-induced regulation of gene expression in human breast cancer cells. We have focused on adipokines (which refers to paracrine and endocrine factors released by adipocytes), aryl hydrocarbon receptor (AHR) ligands, tumor necrosis factor (TNF) and insulin like growth 2 (IGF2). In this proposal, we show a role for interleukin 6 (IL-6) in mediating the effects of peritumor breast adipose tissue on LAT1 regulation and cell migration and invasiveness in breast cancer cells. We have discovered that the regulation of gene expression and cancer processes (such as proliferation or viability) by each of these diverse signals (adipokines, TCDD, IGF2 and TNF) in breast cancer cells. Our continued work on RNA-seq projects has led to a manuscripts published in Biochemical Pharmacology that show mechanisms of gene regulation in breast cancer. These publications and our proposed experiments are providing evidence to target LAT1 and associated leucine signaling for breast cancer therapy in obesity.

    a. The putative endogenous AHR ligand ITE reduces JAG1 and associated NOTCH1 signaling in triple negative breast cancer cells. Piwarski SA, Thompson C, Chaudhry AR, Denvir J, Primerano DA, Fan J, **Salisbury TB**. Biochem Pharmacol. 2020 Apr;174. PubMed PMID: 32032581

b. Aryl hydrocarbon receptor (AHR) regulation of L-Type Amino Acid Transporter 1 (LAT-1) expression in MCF-7 and MDA-MB-231 breast cancer cells. Tomblin JK, Arthur S, Primerano DA, Chaudhry AR, Fan J, Denvir J, **Salisbury TB**. Biochem Pharmacol. 2016 Apr 15;106:94-103. PubMed PMID: 26944194 PubMed Central PMCID: PMC4813787
c. **Salisbury TB**, Tomblin JK. Insulin/Insulin-like growth factors in cancer: new roles for the aryl hydrocarbon receptor, tumor resistance mechanisms, and new blocking strategies. Front Endocrinol (Lausanne). 2015;6:12. PubMed PMID: 25699021; PubMed Central PMCID: PMC4313785.
d. **Salisbury TB**, Tomblin JK, Primerano DA, Boskovic G, Fan J, Mehmi I, Fletcher J, Santanam N, Hurn E, Morris GZ, Denvir J. Endogenous aryl hydrocarbon receptor promotes basal and inducible expression of tumor necrosis factor target genes in MCF-7 cancer cells. Biochem Pharmacol. 2014 Oct 1;91(3):390-9. PubMed PMID: 24971714; PubMed Central PMCID: PMC4157967.
e. Tomblin JK, **Salisbury TB**. Insulin like growth factor 2 regulation of aryl hydrocarbon receptor in MCF-7 breast cancer cells. Biochem Biophys Res Commun. 2014 Jan 17;443(3):1092-6. PubMed PMID: 24380854; PubMed Central PMCID: PMC3932621.
f. **Salisbury TB**, Morris GZ, Tomblin JK, Chaudhry AR, Cook CR, Santanam N. Aryl hydrocarbon receptor ligands inhibit igf-2 and adipokine stimulated breast cancer cell proliferation. ISRN Endocrinol. 2013;2013:104850. PubMed PMID: 24171117; PubMed Central PMCID: PMC3793317.
g. **Salisbury TB,** Arthur S. The Regulation and Function of the L-Type Amino Acid Transporter 1 (LAT1) in Cancer. Int J Mol Sci. 2018 Aug 12;19(8). PMID: 30103560 PMCID: PMC6121554

**Complete list of Published Work in MyBibliography:**
https://www.ncbi.nlm.nih.gov/pubmed/?term=salisbury+tb

**D. Additional Information: Research Support and/or Scholastic Performance**

**Ongoing Research Support:**

1P20GM121299-01A1 Center of Biomedical Research Excellence (COBRE)
Appalachian Center for Cellular transport in Obesity Related Disorders (ACCORD)
Sundaram (PI) Feb. 2018- Feb.2021
Title: Inhibition of Leucine- Stimulated Induction of mTOR1
to Suppress Breast Cancer in Obesity.
Role: Junior Investigator (PI of project 1 - 50% effort)

**Completed Research Support**
WV-INBRE Next Generation Sequencing pilot grant, Marshall University 2016-2017
The goal of this projected is to define adipocyte regulated genes in human breast cancer cells that are also aryl hydrocarbon receptor gene targets.
Salisbury (PI)

Marshall University School of Medicine Pilot Award, Marshall University 2014-2015
The goal of this pilot award was to investigate whether adipocyte-secreted factors promote breast cancer by increasing the regulation and function of amino acid transporters Salisbury (PI)

Research Starter Grant from the Pharmaceutical Manufacturers Association of America 2012-2013
The goal of this project was to investigate the role of the aryl hydrocarbon receptor in breast cancer cells stimulated by the adipocyte-derived secretome.

Salisbury (PI)

WV-INBRE next generation sequencing challenge grant, Marshall University 2012-2013
The goal of this project was to establish signal-induced aryl hydrocarbon receptor gene targets in human breast cancer cells.
Salisbury (PI)

WV-INBRE next generation sequencing challenge grant, Marshall University 2011
The objectives of this proposal was to identify genome-wide AHR binding sites in breast cancer cells
Salisbury (PI)

Cell Differentiation and Development Center (CDDC) grant, Marshall University 2011-2012
The objectives of this proposal was to investigate gene expression effects of endocrine disrupting chemicals in ovarian cells.
Salisbury (PI)