BIOGRAPHICAL SKETCH
Training Partner.

NAME: Lisa M. Arendt

eRA COMMONS USER NAME: LMARENDT

POSITION TITLE: Assistant 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
University of Wisconsin, Madison	B.S.	1996	Genetics
University of Wisconsin, Madison	D.V.M.	2002	Veterinary Medicine
University of Wisconsin, Madison	Ph.D.	2007	Cell and Molecular Biology
Tufts University, Boston		2014	Postdoctoral Training

A. **Personal Statement**

After obtaining my DVM, I developed a strong interest in oncology. I focused on basic science research, and I completed my doctoral degree in cellular and molecular biology. From these experiences, I have developed interests in developing mouse models to examine how systemic changes in endocrine processes alter tumor formation and progression.

The focus of my laboratory is understanding how obesity alters normal function of the breast, including lactation, as well as pathological changes such as breast cancer. We examine how obesity alters adipose tissue in the breast, leading to inflammation, adipose tissue fibrosis, and changes in the breast epithelium. My thesis work focused on hormonal interactions between estrogen and prolactin that promote breast cancer. These studies expanded my knowledge of transgenic mouse models and breast biology. As a post-doctoral fellow with Charlotte Kuperwasser (Tufts University), I developed a novel human in mouse (HIM) technique to model the microenvironment of the obese breast utilizing human tissues transplanted within the mammary glands of mice. To study obesity in my laboratory, we utilize a high fat diet model in mice, patient derived xenograft models of tumorigenesis, and breast tissue from reduction mammoplasty surgeries for comparative biology. Obesity impacts multiple disease processes, and we have collaborated with other researchers in areas of childhood development, hormonal biology and sleep apnea. I have successfully published in the area of obesity-associated breast cancer, as well as multiple other peer-reviewed articles in the field of breast cancer research.

B. Positions and Honors

Positions and Employment

2002-2008 Research Assistant, UW-Madison, School of Veterinary Medicine
2004 Laboratory Instructor, Veterinary Histology, UW-Madison, School of Veterinary Medicine
2008-2014 Senior Research Associate, Department of Anatomy, Tufts University
2013-2015 Editor, Boston Professional Group (BPG) Editing
2014-2015 Research Assistant Professor, Developmental, Molecular, and Chemical Biology Department, Tufts University
2015-present Assistant Professor, Department of Comparative Biosciences, UW-Madison, School of Veterinary Medicine

Other Experience and Professional Memberships

2002-	Member, American Veterinary Medical Association
2013-	Member, The Endocrine Society
2013-	Member, American Association for Cancer Research
2014	Chair, Gordon Research Symposium for Mammary Gland Biology, Barga, Italy
2015-	Trainer, Endocrinology/Reproductive Physiology (ERP) Program, University of Wisconsin-Madison
2015-	Member, University of Wisconsin Carbone Cancer Center, University of Wisconsin-Madison

Honors

2002-2005	NIH T32 Postdoctoral Fellowship
2006-2011	NIH K08 (PI) "Interactions of PRL, Estrogen, and TGFα in Mammary Cancer"
2009	Cover Art, Journal of Endocrinology (J Endocrinol 2009, 203(1))
2013	Tufts Medical Center Poster Award Recipient
2013	Cover Art Competition Winner, Journal of Endocrinology (J Endocrinology 2013, 219(3))
2015	Finalist, Burroughs Wellcome Career Award for Medical Scientists
2016	Jon Shevell Travel Scholarship
2017	Finalist, Shaw Scientist Award

C. Contribution to Science

1. Elucidation of the hormonal regulation of the normal breast epithelial hierarchy: Unlike the mouse mammary gland, the human breast is composed of lobules demarcated from each other by fibroblasts and collagen. These lobules are defined at birth, begin alveolar differentiation at puberty, and continue to develop until terminal differentiation during lactation. By examining breast tissue isolated from reduction mammoplasty surgeries, I showed that immature lobular structures within the breast were enriched for different types of luminal and basal progenitor cells. Utilizing assays that identify stem cell activity, I demonstrated that luminal and basal progenitor cells contribute to distinct functional growth regulated by ovarian steroids, with progesterone favoring the expansion of basal ductal progenitors and estrogen favoring the expansion of luminal alveolar progenitors. In combination, progesterone and estrogen maximized ductal/alveolar expansion. I found that progesterone-mediated expansion of the basal ductal progenitor occurred through TBX3, while luminal alveolar progenitor expansion was stimulated by WNT signaling. These findings provide insight into the function and regulation of human breast progenitor cells that could serve as focal points during the development of pathological conditions.

a. Arendt LM, St. Laurent J, Wronski A, Cabellero S, Lyle SR, Naber SP, Kuperwasser C. (20014) Human breast progenitor cells numbers are regulated by WNT and TBX3. *PlosOne* 9:3111442. PMCID: PMC4211891.
b. Arendt LM, Keller PJ, Skibinski A, Goncalves K, Naber SP, Buchsbaum RJ, Gilmore H, Come SE, and Kuperwasser C. (2014) Anatomic localization of progenitor cells in human breast tissue reveals enrichment of uncommitted cells within immature lobules. *Breast Cancer Res* 16:453. PMCID: PMC4303132.
c. Arendt LM, Kuperwasser C. (2015) Form and function: how estrogen and progesterone regulate the mammary epithelial hierarchy. J Mammary Gland Biol Neoplasia. 20:9-25. PMCID: PMC4596764.
d. Sokol ES, Miller DH, Arendt LM, Gupta PB. (2016) Growth of human breast tissue from patient cells in 3D hydrogel scaffolds. *Breast Cancer Res* 18:19.

2. Mechanisms of endocrine resistance in breast cancer: Utilizing transgenic mice that overexpressed prolactin under control of a hormonally-insensitive promoter, I established that prolactin enhances the formation of ERα positive and negative breast tumors. The formation of these tumors is enhanced in the presence of estrogen; however, estrogen is not necessary for the early development or progression of the breast tumors. I determined that once the tumors were established, ERα positive prolactin-induced tumors were not responsive to therapeutic ERα antagonists. These results suggested that prolactin activity may play a role in the pathogenesis of breast cancer in patients that develop resistance to anti-estrogenic therapies. In addition, transgenic expression of TGFα further enhanced the estrogen insensitive phenotype induced by prolactin. Together, PRL and TGFα uncoupled ERα and progesterone receptor expression in normal mammary epithelium, and generated tumors that were strikingly progesterone receptor negative. Both *in vitro* and *in vivo*, prolactin and TGFα cooperatively enhanced AKT phosphorylation, which is associated with endocrine resistance in human disease.

a. Arendt LM, Schuler LA. (2007) Prolactin drives estrogen receptor-alpha-dependent ductal expansion and synergizes with transforming growth factor-alpha to induce mammary tumors in males. *Am J Pathol* 172:194-202. PMCID: PMC2189634.
b. Arendt LM, Evans LC, Rugowski DE, Garcia-Barchino MJ, Rui H, Schuler LA. (2009) Ovarian hormones are not required for PRL-induced mammary tumorigenesis, but estrogen enhances neoplastic processes. *J Endocrinol* 203:99-110. PMCID: PMC2841967.
c. Arendt LM, Grafwallner-Huseth TL, Schuler LA. (2009) Prolactin-growth factor crosstalk reduces mammary estrogen responsiveness despite elevated ERalpha expression. *Am J Pathol* 174:1065-74. PMCID: PMC2665765.
d. Arendt LM, Rugowski DE, Grafwallner-Huseth TA, Garcia-Barchino MJ, Rui H, Schuler LA. (2011) Prolactin-induced mouse mammary carcinomas model estrogen resistant luminal breast cancer. *Breast Cancer Res* 13:R11. PMCID: PMC3109579.

3. Immune cells in obesity and tumorigenesis: Under conditions of obesity, we have shown that activated macrophages are recruited into mammary adipose tissue and secrete cytokines which promote angiogenesis within the adipose tissue. I developed an innovative HIM model to study obesity-associated breast cancer development and progression *in vivo*. Utilizing breast reduction mammoplasty tissues, I created an obesity-like microenvironment that recapitulated inflammatory changes from the obese mammary gland. With this model, I demonstrated that increased numbers of macrophages enhance angiogenesis within ductal carcinoma *in situ* (DCIS) lesions, promoting the formation of larger, more aggressive tumors. In collaboration, we have also demonstrated that myeloid lineage cells promote the growth of estrogen receptor (ER)-negative tumors. Our work has also demonstrated that macrophages interact with cancer associated fibroblasts to promote tumor growth through enhanced angiogenesis and inflammatory signaling. In particular, these inflammatory cells promotes the expansion of aggressive cancer stem-like cells though expression of IL-6. In addition, we established that physiologic changes may increase inflammatory signaling in normal breast stromal cells, which may contribute to early tumor development. Hormonal changes associated with lactation diminished the ability of adipose stromal cells to accumulate lipid and increased IL-6 signaling, resulting in accelerated growth of carcinoma cells. These findings suggest that stromal cells may promote the growth of aggressive tumors through increased cytokine secretion.

a. Rudnick JA, Arendt LM, Klebba I, Hinds JW, Iyer V, Gupta PB, Naber SP, Kuperwasser C. (2011) Functional heterogeneity of breast fibroblasts is defined by a prostaglandin secretory phenotype that promotes expansion of cancer-stem like cells. *PLosOne* 6:e24605. PMCID: PMC3177828.
b. Iyer V, Klebba I, McCready J, Arendt LM, Betancur-Boissel M, Wu MF, Zhang X, Lewis MT, Kuperwasser C. (2012) Estrogen promotes ER-negative tumor growth and angiogenesis through mobilization of bone marrow-derived monocytes. *Cancer Res* 72:2705-13.
c. Arendt LM, McCready J, Keller PJ, Baker DD, Naber SP, Seewaldt V, Kuperwasser C. (2013) Obesity promotes breast cancer by CCL2-mediated macrophage recruitment and angiogenesis. *Cancer Res* 73:6080-93. PMCID: PMC3824388.
d. McCready J, Arendt LM, Glover E, Iyer V, Briendel JL, Lyle SR, Naber SP, Jay DG, Kuperwasser C. (2014) Pregnancy-associated breast cancers are driven by differences in adipose stromal cells present during lactation. *Breast Cancer Res*. 16:R2. PMCID: PMC3978436.

4. Defining cell populations that lead to tumors of different histotypes: My collaborators and I investigated the cell of origin of the diverse range of human breast tumors, and its association with the normal mammary hierarchy. Human breast cancers are broadly classified based on their gene-expression profiles into luminal- and basal-type tumors. To determine which cells in the human breast give rise to the various forms of breast cancer, we isolated luminal (EpCAM+) and basal/myoepithelial (CD10+) epithelial cells from breast reduction mammoplasty surgeries, transformed the cells, and transplanted the cells into humanized fat pads of NOD/SCID mice. We showed that EpCAM+ epithelial cells formed tumors similar to the common forms of human breast cancer, including ER-positive and negative tumors, whereas transformation of CD10+ cells resulted in the development of rare metaplastic tumors. These studies identified normal cellular precursors to human breast cancers and revealed the existence of a population of cells with the capacity to form metaplastic breast tumors. In addition, we showed that cancer cell lines were enriched for rare basal and mesenchymal phenotypes, which were normally present in small numbers within human tissues. These findings suggest that collections of cell lines representing multiple cell types, rather than single cell lines, can be used to model the cellular heterogeneity of tissues.

a. Keller PJ, Lin AF, Arendt LM, Klebba I, Jones AD, Rudnick JA, DiMeo TA, Gilmore H, Jefferson DM, Graham RA, Naber SP, Schnitt S, Kuperwasser C. (2010) Mapping the cellular and molecular heterogeneity of normal and malignant breast tissues and cultured cell lines *Breast Cancer Res* 12:R87. PMCID: PMC3096980.
b. Keller PJ, Arendt LM, Skibinski A, Logvinenko T, Klebba I, Dong S, Smith AE, Prat A, Perou CM, Gilmore H, Schnitt S, Naber SP, Garlick JA, Kuperwasser C. (2012) Defining the cellular precursors to human breast cancer. *Proc Natl Acad Sci U S A* 109:2772-7. PMCID: PMC3286919.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1dWBeGdq735/bibliography/48844495/public/?sort=date&direction=ascending.

D. Research Support

Current Research Support

Komen Foundation Arendt (PI) 10/15/15-10/14/18
Obesity-Activated Macrophages Promote Tumorigenesis
Career Catalyst Award: The goal of this study is to investigate how macrophages, activated in the obese microenvironment, promote the expansion of estrogen receptor alpha positive (ERα+) epithelial cells prior to tumorigenesis, enhance the growth of ERα+ aggressive tumors, and through interactions with adipose stromal cells, promote the formation of a microenvironment that supports the rapid growth of ERα+ tumors.

Department of Comparative Biosciences, University of Wisconsin-Madison
Laboratory Start-up Funds: Flexible funding for the purchase of laboratory equipment, supplies, and personnel to initiate research project.

Completed Research Support

Expedition Inspiration Arendt (PI) 10/1/13-1/31/15
Obesity-Activated Macrophages Promote Tumorigenesis
Brenda Williams Young Investigator Award: The goal of this study was to determine how macrophages polarized by obese mammary tissue contribute to the tumor microenvironment and elucidate how obesity-associated macrophages promote aggressive breast tumors.