BIOGRAPHICAL SKETCH

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NAME: Sikora, Matthew J.

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

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 Michigan, Ann Arbor, MI	BS	05/2006	Genetics and Molecular Biology
University of Michigan, Ann Arbor, MI	PhD	05/2011	Pharmacology
University of Pittsburgh, Pittsburgh, PA	Postdoctoral Fellow	03/2015	Breast Cancer

A. Personal Statement

My training provided extensive experience in breast cancer research, focused on the molecular biology of response and resistance to endocrine therapies, steroid hormone and endocrine therapy pharmacology, and estrogen receptor (ER)-driven gene regulation. Coupled with my strong background in translational cancer research and multidisciplinary translational research teams, this has led to my ultimate goal to **improve breast cancer patient outcomes through advanced understanding of hormone receptor biology and signaling.**

Toward this goal, my laboratory is focused on understanding the unique biology of invasive lobular carcinoma (ILC), as ILC represents a unique context for ER functions and anti-estrogen resistance. My post-doctoral work with Dr. Steffi Oesterreich, and ongoing independent work, pioneered the study of ER function specifically in ILC (see Contribution #1). Our research built the molecular basis of the hypothesis that endocrine signaling is distinct in ILC cells. These studies may explain a clinical paradox regarding anti-estrogen resistance in ILC, and form a new subfield of breast cancer research. My contributions to understanding breast cancer endocrinology and ER biology in ILC were recognized by the Endocrine Society Early Investigator Award in 2018. My ILC research has been supported by the Dept. of Defense, the American Cancer Society, Cancer League of Colorado, and the National Cancer Institute.

In August 2016, I joined the University of Colorado Anschutz Medical Campus as an Assistant Professor in the Department of Pathology. The outstanding resources and support available at CU Anschutz have allowed me to rapidly develop my independent research program. I am well positioned and supported to build a strong program to advance new therapeutic strategies and improve outcomes for patients with ILC and other hormone-driven breast cancers.

B. Positions and Honors

Positions and Employment

2016 -	Assistant Professor, University of Colorado Denver | Anschutz Medical Campus, Department of Pathology, Aurora, CO
2016 - 2018	Adjunct Assistant Professor, University of Pittsburgh, Department of Pharmacology & Chemical Biology, Pittsburgh, PA
2015 - 2016	Research Instructor, University of Pittsburgh, Pharmacology & Chemical Biology, Pittsburgh, PA

Other Experience and Professional Memberships

2017 -	Member, SWOG Breast Committee and Breast Translational Medicine Working Group
2016	Panel Member, Patient and advocate sessions "Q&A – Research Advocates, Clinicians, and Researchers" and "Hot Topics Breakfast", 1st Int'l Invasive Lobular Carcinoma Symposium
2016	Member, Organizing subgroup, Patient Advocacy sessions for 1st Int'l Invasive Lobular Carcinoma Symposium
2014 - 2015	Chair, Gordon Research Seminar - Hormone-Dependent Cancers
2012 -	Member, Endocrine Society
2005 -	Member, American Association for Cancer Research

Honors

2018	Endocrine Society Early Investigator Award
2016	AACR-Susan G. Komen Scholar-in-Training Award, American Association for Cancer Research Annual Meeting
2015	National Cancer Institute K99/R00 'Pathway to Independence' Award
2014	San Antonio Breast Cancer Symposium Clinical Scholar Award, American Association for Cancer Research
2014	AACR-Susan G. Komen Scholar-in-Training Award, American Association for Cancer Research Annual Meeting
2012	Dept. of Defense Breast Cancer Research Program Postdoctoral Fellowship Award
2005-2006	Thomas J. Bardos Science Education Award, American Association for Cancer Research

C. Contributions to Science

Full Bibliography (also at http://sikoralab.com/publications)**:**
https://www.ncbi.nlm.nih.gov/sites/myncbi/matthew.sikora.1/bibliography/40917407/public/?sort=date&direction=descending

1. Understanding endocrine response and resistance in invasive lobular carcinoma

Invasive lobular carcinoma (ILC) is the 2nd most common histological subtype of breast cancer, accounting for ~40,000 new breast cancers annually in the US. Despite this incidence, no ILC-specific treatment options exist. Most ILC tumors are estrogen receptor (ER)-positive (~95%); this and other biomarkers suggest that ILC patients are ideal candidates for endocrine therapies targeting ER. However, retrospective analyses suggest that a subset of ILC patients may not benefit from endocrine therapy. Understanding unique mechanisms of endocrine response and resistance in ILC is critical to improving ILC patient outcomes.

Our report in Cancer Research (Sikora, 2014) was the first to characterize ER in ILC systems. We identified distinct ER-regulated transcription in ILC, and identified *de novo* endocrine resistance in ILC models mimicking clinical observations. This work identified unique drivers of endocrine response in ILC, currently being studied. One such driver is WNT4, which we characterized in estrogen response and anti-estrogen resistance in ILC models (Contribution #2). We established the most comprehensive series of long-term estrogen-deprived (LTED) endocrine resistant ILC models currently available (Sikora, 2016; Martin, 2017; also contribution #4).

a. **Sikora MJ**, Jacobsen BM, Levine K, Chen J, Davidson NE, …Oesterreich S. WNT4 mediates estrogen receptor signaling and endocrine resistance in invasive lobular carcinoma cell lines. Breast Cancer Res. 2016 Sep 20;18(1):92. PMID: 27650553; PMCID: PMC5028957.
b. **Sikora MJ**, Cooper KL, Bahreini A, Luthra S, Wang G…Oesterreich S. Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. Cancer Res. 2014 Mar 1;74(5):1463-74. PMID: 24425047; PMCID: PMC3955299.
c. Martin, L-A, Ribas, R, Simigdala, N, Schuster, E, Pancholi, …**Sikora, MJ**, Turner, N, Zwart, W, Oesterreich, S, Carroll, J, Ali, S, Dowsett, M. Discovery of naturally occurring ESR1 mutations in breast cancer cell lines modelling endocrine resistance. Nature Communications. 2017 Nov 30;8(1):1865. doi:10.1038/s41467-017-01864-y. PMID: 29192207; PMCID: PMC5709387.
d. **Sikora MJ**, Jankowitz RC, Dabbs DJ, Oesterreich S. Invasive lobular carcinoma of the breast: patient response to systemic endocrine therapy and hormone response in model systems. Steroids. 2013 Jun;78(6):568-75. PMID: 23178159.

2. WNT4 as an atypical, non-canonical Wnt ligand driving lobular carcinoma biology

WNT4 is a critical signaling molecule in progesterone-driven mammary gland growth and development, but we identified that WNT4 regulation is co-opted specifically in ILC to be under estrogen control. WNT4 subsequently mediates estrogen-driven growth and is required for anti-estrogen resistance in ILC, but WNT4 functions as a non-canonical Wnt ligand in ILC. Recently, we reported that across diverse cell types, WNT4 engages its signaling pathway via an atypical pathway independent of canonical secretory pathways. Delineating WNT4 signaling is critical to developing targeted therapies to block ILC growth and survival.

a. Rao DM, Ferguson RL, **Sikora MJ**. WNT4 and WNT3A activate cell autonomous Wnt signaling independent of secretion. bioRxiv. 2018 May 30;333906 [Pre-print]. doi: https://doi.org/10.1101/333906.
b. **Sikora MJ**, Jacobsen BM, Levine K, Chen J, Davidson NE, …Oesterreich S. WNT4 mediates estrogen receptor signaling and endocrine resistance in invasive lobular carcinoma cell lines. Breast Cancer Res. 2016 Sep 20;18(1):92. PMID: 27650553; PMCID: PMC5028957.
c. **Sikora MJ**, Cooper KL, Bahreini A, Luthra S, Wang G…Oesterreich S. Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. Cancer Res. 2014 Mar 1;74(5):1463-74. PMID: 24425047; PMCID: PMC3955299.\

3. Steroidal and pharmacological partial estrogen receptor agonists in endocrine response and resistance in breast cancer

A potential mechanism of resistance to endocrine therapy is via activation of estrogen receptor or other steroid hormone receptors by non-classical estrogenic steroids or anti-estrogen therapies themselves. My work identified the androgen metabolite 3betaAdiol as an ER partial agonist and driver of aromatase inhibitor resistance. We demonstrated that physiological concentrations of 3betaAdiol could maintain breast cancer cell growth and viability, but could also permit development of endocrine resistance. Additionally, we identified contexts in which anti-estrogen therapies activate estrogen receptor and mediate resistance in model systems.

a. **Sikora MJ**, Johnson MD, Lee AV, Oesterreich S. Endocrine Response Phenotypes Are Altered by Charcoal-Stripped Serum Variability. Endocrinology. 2016 Oct;157(10):3760-3766. PMID: 27459541; PMCID: PMC5045515.
b. **Sikora MJ**, Cooper KL, Bahreini A, Luthra S, Wang G…Oesterreich S. Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. Cancer Res. 2014 Mar 1;74(5):1463-74. PMID: 24425047; PMCID: PMC3955299.
c. **Sikora MJ**, Strumba V, Lippman ME, Johnson MD, Rae JM. Mechanisms of estrogen-independent breast cancer growth driven by low estrogen concentrations are unique versus complete estrogen deprivation. Breast Cancer Res Treat. 2012 Aug;134(3):1027-39. PMID: 22456984; PMCID: PMC3951731.
d. **Sikora MJ**, Cordero KE, Larios JM, Johnson MD, Lippman ME, Rae JM. The androgen metabolite 5alpha-androstane-3beta,17beta-diol (3betaAdiol) induces breast cancer growth via estrogen receptor: implications for aromatase inhibitor resistance. Breast Cancer Res Treat. 2009 May;115(2):289-96. PMID: 18521740; PMCID: PMC2728015.

4. Establishing model systems for endocrine response and resistance in lobular carcinoma

ER-positive models of ILC are rare, but our work includes the most comprehensive characterization of endocrine response in ILC models to date. We have also established and characterized the largest series of models of acquired anti-estrogen resistance to date, including cell lines and patient-derived xenografts.

a. **Sikora MJ**, Jacobsen BM, Levine K, Chen J, Davidson NE, …Oesterreich S. WNT4 mediates estrogen receptor signaling and endocrine resistance in invasive lobular carcinoma cell lines. Breast Cancer Res. 2016 Sep 20;18(1):92. PMID: 27650553; PMCID: PMC5028957.
b. Du T, **Sikora MJ**, Levine KM, Tasdemir N, Riggins RB, Wendell SG… Oesterreich S. Key regulators of lipid metabolism drive endocrine resistance in invasive lobular breast cancer. Breast Cancer Res. 2018 Sep 4;20(1):106. doi: 10.1186/s13058-018-1041-8. PubMed PMID: 30180878; PMCID: PMC6124012.
c. Tasdemir N, Bossart EA, Li Z, Zhu L, **Sikora MJ**… Oesterreich S. Comprehensive phenotypic characterization of human invasive lobular carcinoma cell lines in 2D and 3D cultures. Cancer Res. 2018 Sep 18. pii: canres.1416.2018. doi: 10.1158/0008-5472.CAN-18-1416. [Epub ahead of print] PMID: 30228172.

d. Martin, L-A, Ribas, R, Simigdala, N, Schuster, E, Pancholi, …**Sikora, MJ**, Turner, N, Zwart, W, Oesterreich, S, Carroll, J, Ali, S, Dowsett, M. Discovery of naturally occurring ESR1 mutations in breast cancer cell lines modelling endocrine resistance. Nature Communications. 2017 Nov 30;8(1):1865. doi:10.1038/s41467-017-01864-y. PMID: 29192207; PMCID: PMC5709387.

5. The pharmacogenomics of cytochrome P450 2D6 and role in response to tamoxifen therapy

My graduate work in part focused on the development of methodology to assess single nucleotide polymorphisms in cytochrome P450 enzymes, with a focus on CYP2D6, from archival material. These novel methods allowed for studies on tamoxifen-related side effects and the role of changes in tamoxifen metabolism on the prevalence and intensity of side effects. These methods were also key in the development of two pivotal, large retrospective studies on tamoxifen efficacy and CYP2D6 polymorphisms.

a. **Sikora MJ**, Thibert JN, Salter J, Dowsett M, Johnson MD, Rae JM. High-efficiency genotype analysis from formalin-fixed, paraffin-embedded tumor tissues. Pharmacogenomics J. 2011 Oct;11(5):348-58. PMID: 20548328; PMCID: PMC2996486.
b. Henry NL, Rae JM, Li L, Azzouz F, Skaar TC, Desta Z, **Sikora MJ**, Philips S, …Stearns V. Association between CYP2D6 genotype and tamoxifen-induced hot flashes in a prospective cohort. Breast Cancer Res Treat. 2009 Oct;117(3):571-5. PMID: 19153830; PMCID: PMC2746261.
c. Rae JM, **Sikora MJ**, Henry NL, Li L, Kim S, …Stearns V. Cytochrome P450 2D6 activity predicts discontinuation of tamoxifen therapy in breast cancer patients. Pharmacogenomics J. 2009 Aug;9(4):258-64. PMID: 19421167; PMCID: PMC2991048.
d. Snider NT, **Sikora MJ**, Sridar C, Feuerstein TJ, Rae JM, Hollenberg PF. The endocannabinoid anandamide is a substrate for the human polymorphic cytochrome P450 2D6. J Pharmacol Exp Ther. 2008 Nov;327(2):538-45. PMID: 18698000; PMCID: PMC2704579.

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

Ongoing Research Support

R00 CA193734-03 (NCI) 12/09/16-12/08/19
Sikora, Matthew J (Role: PI)
WNT4 in endocrine response and resistance in invasive lobular carcinoma
Goals: Characterize the signaling pathways associated with WNT4 that mediate cell growth in invasive lobular carcinoma (ILC) cells, and identify putative biomarkers and therapeutic targets for ILC patients. Dr. Sikora developed the project, performs the described studies, and coordinates the laboratory's efforts on this project.

Completed Research Support

ACS-IRG 25M5073 01/01/17-12/31/17
(American Cancer Society Institutional Research Grant #16-184-56)
Sikora, Matthew J (Role: PI)
Identifying factors driving estrogen receptor function in invasive lobular carcinoma
Identifying factors driving estrogen receptor function in invasive lobular carcinoma
Goals: Identify co-factors and transcription factors associated with the estrogen receptor in ILC cells that a) mediate regulation of ILC-specific ER target genes and b) recognition of tamoxifen and other anti-estrogens as partial agonists. Dr. Sikora developed the project and performed the proposed studies.

Cancer League of Colorado #173664-MS 07/01/17-06/30/18
Sikora, Matthew J (Role: PI)
Exploiting apoptotic vulnerability in anti-estrogen response and resistance in lobular carcinoma
Goals: Characterize a putative ER signaling pathway via Akt/mTOR that may regulate cell survival via BCL-2 family proteins, and assess whether shifts in cell survival mechanisms can be advantageously targeted with anti-BCL2 small molecule inhibitors.

K99 CA193734-01 (NCI) 04/01/15-07/31/16

Sikora, Matthew J (Role: PI)

Elucidating the function of WNT4 in endocrine response and resistance in invasive lobular carcinoma

Goals: Identify the receptor complex and downstream signaling pathways driven by WNT4 in invasive lobular carcinoma (ILC) cells, and whether WNT4 may mediate endocrine resistance in these cells. Dr. Sikora developed the project and performed the described studies.

R13 CA195982-01 (NCI) 05/01/15-09/30/15

Sikora, Matthew J (Role: PI)

2015 Hormone-Dependent Cancers Gordon Research Conference and Gordon Research Seminar

Goals: Support the attendance of early career researchers (graduate students and postdocs) at the 2015 GRC and GRS “Hormone-Dependent Cancers”. Dr. Sikora served as Chair of the 2015 GRS.

Experiment.com Crowdfunding Project, DOI: 10.18258/3828 07/31/15-09/01/15

Sikora, Matthew J (Role: PI)

Train the next generation of cancer scientists

Goals: Support the travel of graduate students and postdocs submitting meritorious abstracts for the 2015 GRC and GRS “Hormone-Dependent Cancers”. Dr. Sikora served as Chair of the 2015 GRS.

W81XWH1210063, Congressionally Directed Medical Research Programs 03/01/12-03/31/15

Breast Cancer Research Program Post-doctoral Fellowship

Sikora, Matthew J (Role: PI)

HDAC7 in Tumor Aggressiveness and Resistance to Endocrine Therapy

Goals: Determine a role for the histone deacetylase HDAC7 in mediating estrogen signaling and anti-estrogen resistance in breast cancer, with a focus on invasive lobular carcinoma of the breast. Dr. Sikora developed the project and performed the described studies.