BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

NAME Oesterreich, Steffi	POSITION TITLE Professor of Pharmacology and Chemical Biology
eRA COMMONS USER NAME steffio	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
Humboldt University, Berlin, Germany	B.S.	1989	Biochemistry
Humboldt University/Max-Delbrück-Center for Mol. Medicine, Berlin-Buch, Germany	Ph.D.	1992	Molecular Biology
UT Health Science Center at San Antonio	Postdoc	1996	Breast Cancer

A. Personal Statement

My area of interest is endocrine resistance in breast cancer, with a focus on invasive lobular breast cancer (ILC). By using diverse cell and molecular biology approaches, mouse models, and clinical specimens, we aim to identify the genetic and epigenetic changes that cause resistance to anti-estrogen therapies and that can be targeted to prevent, overcome or reverse resistance. My primary research has focused on estrogen receptor signaling in breast cancer for more than two decades. Specifically, I am interested in endocrine resistant breast cancer, and my group is using diverse cell and molecular biology approaches, mouse models, and clinical specimens to identify genetic and epigenetic changes that cause resistance to antiestrogen therapies, and that can potentially be targeted to prevent, overcome or reverse resistance. In my position as Director of Education in the Women's Cancer Research Center, I am also organizing and overseeing a series of training and mentoring opportunities for the next generation of scientists interested in women's cancer.

I have previously participated and led research teams, for example as PI of a Program Project at my prior institution Baylor College of Medicine. Other leadership roles include my role as Director of Training in the Womens Cancer Research Center and Vice-Chair of the Department of Pharmacology, a completion of service as Chair of Tumor Cell Biology Study Section, and serving as Chair of the next Gordon Research Conference on "Hormones and Cancer". Furthermore, I was recently elected as Susan G Komen fellow, joining a selective group of leading national and international breast cancer experts.

I am passionate about understanding ILC biology, and identifying novel ways to target the disease. In the fall of 2016, I organized and chaired the first ever International ILC Symposium in Pittsburgh with 130 national and international attendees (https://upci.upmc.edu/wcrc/ilcsymposium-info.cfm). This meeting was a success, as it resulted in increased awareness of the disease, a number of new collaborations, and the formation of a national ILC survivor advocacy group (LBCA), headed by Leigh Pate and Lori Pettite.

B. Positions and Honors

Positions and Employment

05/96-12/97	Instructor, Dept. of Medicine, Med Oncology, UT Health Science Center San Antonio, TX
01/98-05/99	Asst. Professor, Dept. of Medicine, Med Oncology, UTHSC San Antonio, TX
06/99-10/04	Asst. Professor, Dept. of Medicine and MCB, Baylor College of Medicine, Houston, TX.
10/04-07/10	Associate Professor, Dept. of Medicine and MCB, BCM, Houston, TX
07/07-07/10	Director of Qualifying Exam Committee for Translational Biology and Molecular Medicine (TBMM) Graduate Program, BCM, Houston, TX
07/07-07/10	Associate Director, TBMM Graduate Program, BCM
07/07-07/10	Co-Director Nuclear Receptor Program, DL Duncan Cancer Center, BCM, Houston, TX
08/10-present	Professor, University of Pittsburgh, UPCI, Department of Pharmacology and Chemical Biology, Pittsburgh, PA
08/10-present	Director of Education, Women's Cancer Research Center (WCRC), Magee Womens Research Institute, University of Pittsburgh, UPCI, Pittsburgh, PA
05/14-present	Faculty member, McGowan Institute for Regenerative Medicine, University of Pittsburgh
11/15-present	Director, UPCI Academy (Summer Program for High school students)
07/16	Vice-Chair, Precision and Translational Pharmacology, University of Pittsburgh

Awards

1993	Postdoctoral Fellowship Grant from Susan G. Komen Breast Cancer Foundation
1995	SPORE Career Development Grant
1996	Howard Hughes Institutional Grant
1998	Howard Temin Award (K01), Career Development Grant (NIH)
2000	Chao Award/ Baylor College of Medicine
2002	ACS Research Scholar Grant (ranked #1 of 47 - declined due to overlap with R01)
2002	Women's Health Research Award (Women in Endocrinology) – Only 1 award/ yr.
2006	Alexander von Humboldt Fellow (08/06-07/07) at the EMBL Heidelberg, Germany
2008	Faculty of 1000 article ("Novel egg white-based 3D cell culture system"; *Biotechniques*)
2016	Susan G Komen Scholar

Honors and Study Section/Committees

1997-2000	Massachusetts Department of Public Health Breast Cancer Review
2001-2005	Department of Defense Breast Cancer Review Boards
2007	Ad Hoc member DOD Breast Cancer Research Program (BCRP) Integration Panel (IP)
2002-2005	California Breast Cancer Research Program Review Board
2002-2009	Member of Organizing Committee, San Antonio Breast Cancer Symposium
2002-present	Member, San Antonio Breast Cancer Symposium Abstract review
2006-212	Ad hoc NIH ZRG1, TPM, TCB and ICER Study Section
2011	NIH P01 Study Section (Cellular and Tissue Oncology)
2012-2016	NIH TCB Study Section permanent member
2013, 2015	Department of Defense IP Panel member
2007-2012	Editorial Board, *Endocrinology*
2008-2013	Associate Editor, *BMC Cancer*
2009-2014	Editorial Board, *Endocrine-related Cancer*
2014-present	Editorial Board, *Hormones and Cancer*
2014-2016	NIH Tumor Cell Biology (TCB) Study Section, Chair
2015-present	Associate Editor, *Breast Cancer Research*
2016-present	Editorial Board, *Cancer Research*
2017	Ad hoc NIH CAMP Study Section

C. Contributions to Science

C.1) Estrogen Receptor (ER) co-repressors*: I cloned and characterized SAFB as an estrogen receptor (ER) coregulator, that binds to ER, and represses its transcriptional activity. These studies were pioneering at the time in that they contributed to the new and growing field of nuclear receptor co-regulators. While co-activators had previously been described, there was limited knowledge about mechanism of action and biological relevance of co-repressors.*

1. **Oesterreich** S, Zhang Q, Hopp T, Fuqua SAW, Michaelis M, Zhao HH, Davie JR, Osborne CK, Lee AV. Tamoxifen-bound estrogen receptor strongly interacts with the nuclear matrix protein HET/SAF-B, a novel inhibitor of estrogen receptor-mediated transactivation. *Mol Endo,* 14:369-382, 2000. PMID: 10707955
2. Townson S, Zhang Q-P, Clark GM, Osborne CK, Lee AV, **Oesterreich** S. HET/SAF-B overexpression causes growth arrest and multinuclearity and is associated with aneuploidy in human breast cancer. *Clin Cancer Res,* 6:3788-3796, 2000. PMID: 10999774
3. Townson S, Dobrzycka KM, Lee AV, Air M, Deng W, Kang K, Jiang S, Michaelis K, **Oesterreich** S. SAFB2 – A new SAFB homolog and ER corepressor. *J Biol Chem,* 278:20059-68, 2003. PMID: 12660241
4. Ivanova M, Dobrzycka KM, Jiang S, Michaelis K, Meyer R, Kang K, Adkins B, Barski OA, Divisova J, Lee AV, **Oesterreich** S. Scaffold Attachment Factor B1 functions in development, growth, and reproduction. *Mol Cell Biol,* 25:2995-3006, 2005. PMID: 15798188; PMCID: PMC1069606

C.2) Estrogen-mediated repression of genes: *Our continued study of co-repressor action lead us to the findings a) that co-repressors are involved in estrogen-mediated repression of target genes, and b) that many estrogen-repressed genes are critical in (breast) tumorigenesis. We have also shown that there can be a tight*

link between estrogen-mediated repression of genes, and epigenetic silencing of the same genes when ER signaling is perturbed, for example in the presence of antiestrogen therapy.

1. **Oesterreich** S, Deng W, Jiang S, Cui X, Ivanova M, Schiff R, Kang K, Hadsell D, Behrens J, Lee AV. Estrogen-mediated downregulation of E-cadherin in breast cancer cells. *Cancer Res*, 63:5203-8, 2003. PMID: 14500345
2. Jiang S, Meyer R, Kang K, Osborne CK, Wong J, **Oesterreich** S. SAFB1 suppresses ER-mediated transcription in part via interaction with N-CoR. *Mol Endo,* 20:311-20, 2006. PMID: 16195251
3. Malik S, Jiang J, Garee J, Verdin E, Lee AV, O'Malley BW, Zhang W, Belaguli NS, **Oesterreich** S. Histone deacetylase 7 and FoxA1 in estrogen-mediated repression of RPRM. *Mol Cell Biol*., 30:399-412, 2010. PMID 19917725. PMCID: PMC2798473
4. Hammerich-Hille S, Kaipparettu BA, Tsimelzon A, Creighton CJ, Jiang S, Polo JM, Melnick A, Meyer R, **Oesterreich S**. SAFB1 mediates repression of immune regulators and apoptotic genes in breast cancer cells. J Biol Chem. 2010 Feb 5;285(6):3608-16. doi: 10.1074/jbc.M109.066431. PMID: 19901029. PMC2823501

C.3) Genetic changes in ER pathway: *As a postdoctoral fellow, I was involved in first studies describing mutations in ER (ESR1) in endocrine resistant disease. Subsequent studies weren't able to find ESR1 mutations, and as we know now, this was the result of studying primary as compared to metastatic disease. Given the potential clinical relevance of these mutations, I have focused my efforts on these studies. Our paper on the identification of ESR1 mutations in metastatic disease, and in cfDNA has recently been published in Cancer Research. More recently, we were able to show mutation and context dependency of the mutations, which is in part the foundation for this CDMRP proposal.*

1. Zhang Q-X, Borg A, Wolf DM, **Oesterreich S**, Fuqua SAW. An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer. *Cancer Res,* 57:1244-1249, 1997. PMID: 9102207
2. **Oesterreich S**, Davidson NE. The search for ESR1 mutations in breast cancer. *Nat Genet*. 45(12):1415-6. 2013. PMID: 24270445. NIHMSID: 775489
3. Wang P, Bahreini A, Gyanchandani R, Lucas PC, Hartmaier RJ, Watters RJ, Jonnalagadda AM, HTrejo Bittar HE, Berg A, Hamilton RL, Kurland BF, Weiss KR, Mathew A, Leone JP, Davidson NE, Nikiforova MN, Brufsky AM, Ambros TF, Stern AM, Puhalla SL, Lee AV, **Oesterreich S**. Sensitive detection of mono- and polyclonal ESR1 mutations in primary tumors, metastatic lesions and cell free DNA of breast cancer patients. *Clinical Cancer Research*. 2016 Mar 1;22(5):1130-7. PMCID: PMC4775406
4. Bahreini A, Li Z, Wang P, Levine KM, Tasdemir N, Cao L, Weir HM, Puhalla SL, Davidson NE, Stern AM, Chu D, Park BH, Lee AV, **Oesterreich S**. Mutation site and context dependent effects of ESR1 mutation in genome-edited breast cancer cell models. Breast Cancer Res. 2017 May 23;19(1):60. doi: 10.1186/s13058-017-0851-4. PMID: 28535794

C.4) Metastatic breast cancer. *Over the last few years, we have formed a cross-disciplinary group to study pathways that drive metastases. I am collaborating with other breast cancer investigators (e.g. Drs Adrian Lee and Nancy Davidson), and clinicians (e.g. Drs Shannon Puhalla and Adam Brufsky) with the goal to identify pathways that can be targeted to prevent and/or treat metastatic disease. We have characterized epigenetic regulation of genes in metastatic progression, and more recently have begun to characterize genome-wide expression in large numbers of brain, ovarian, and bone metastases. Most of these studies are still ongoing, but I expect to publish 2-3 impactful papers in 2017.*

1. Pathiraja TN, Nayak SR, Xi Y, Jiang S, Garee JP, Edwards DP, Lee AV, Chen J, Shea MJ, Santen RJ, Gannon F, Kangaspeska S, Jelinek J, Issa JP, Richer JK, Elias A, McIlroy M, Young L, Davidson NE, Schiff R, Li W, and **Oesterreich S**. Epigenetic reprogramming of HOXC10 in endocrine-resistant breast cancer. *Science Transl Med*.6(229):229ra41. 2014. PMID: 24670685. PMCID: PMC4277862
2. Priedigkeit N, Hartmaier RJ, Chen Y, Vareslija D, Basudan A, Watters RJ, Thomas R, Leone JP, Lucas PC, Bhargava R, Hamilton RL, Chmielecki J, Puhalla SL, Davidson NE, **Oesterreich S**, Brufsky AM, Young L, Lee AV. Intrinsic Subtype Switching and Acquired ERBB2/HER2 Amplifications and Mutations in Breast Cancer Brain Metastases. *JAMA Oncol*. 2016 Dec 7. doi: 10.1001/jamaoncol.2016.5630. [Epub ahead of print] PMID: 27926948
3. Jankowitz R, **Oesterreich S**, Lee AV, Davidson NE. New Strategies in Metastatic Hormone Receptor-Positive Breast Cancer: Searching for Biomarkers to Tailor Endocrine and other Targeted Therapies. *Clin Cancer Res*. In press. DOI: 10.1158/1078-0432.CCR-16-0591

4. Priedigkeit N, Watters RJ, Lucas PC, Hartmaier RJ, Basudan A, Bhargava R, Horne W, Kolls JK, Fang A, Rosenzweig MQ, Brufsky AM, Weiss KR, **Oesterreich S**, Lee AV. RNA-sequencing of decade-old breast tumors and paired decalcified bone metastases identifies recurrently dysregulated transcriptional programs and clinically actionable targets. JCI Insight. In press.
(also in: BioRxiv. http://biorxiv.org/content/early/2017/03/26/1207092017)

C.5) Invasive lobular carcinoma (ILC). *ILC is understudied, and despite obvious histological and outcome differences between IDC and ILC, both are treated exactly the same at this moment. We were the first to show that there are fundamental differences in ER signaling comparing IDC and ILC. We have more recently expanded this research area, and have started to collaborate with a number of local, national, and international experts. We expect that our studies will have major impact on treatment of patients with ILC in the future.*

1. 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*. Nov 21. S0039-128X(12)00302, 2012. PMID: 23178159. PMCID N/A
2. Sikora MJ, Cooper KL, Bahreini A, Luthra S, Wang G, Chandran UR, Davidson NE, Dabbs DJ, Welm AL, **Oesterreich S.** Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. *Cancer Res*. 74(5):1463-74, 2014. PMID: 24425047. PMCID: PMC3955299
3. Ciriella G, Gatza ML, Beck AH,…**Oesterreich S**,…TCGA Research Network, Perou CM. Molecular Portraits of Invasive Lobular Cancer. *Cell* 163, 506-519. 2015. PMCID: PMC4603750
4. Sikora MJ, Jacobsen BM, Levine K, Chen J, Davidson NE, Lee AV, Alexander CM, **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. doi: 10.1186/s13058-016-0748-7. PMID: 27650553 PMCID: PMC5028957

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1jOultDrfuEkl/bibliography/41452697/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

BCRF Research Award Oesterreich (PI) 10/01/2011 – 09/30/2018
"Endocrine Resistance in Invasive Lobular Cancer"
This project is designed to study endocrine response and resistance in the subtype of breast cancers classified as invasive lobular carcinoma, an understudied breast cancer subtype, focusing on HDAC7, and also performing an unbiased screen.

Susan G Komen Leadership Grant Oesterreich (PI) 07/01/2016 – 06/30/2019
"Identification of unique drivers of ILC progression"
This project is aimed at analyzing models and clinical specimens from ILC to identify genes/pathways unique to therapy resistance in ILC, with the ultimate goal to personalize medicine for this breast cancer subtype.

Susan G Komen CCR14300865 Jankowitz (PI) 09/24/2014 - 09/23/2017
"A Trial of Endocrine Response in Patients with Invasive Lobular Carcinoma"
We have therefore designed a trial to study response to tamoxifen, anastrozole (an AI), and fulvestrant in the tumor tissue of women with newly-diagnosed ILC.
Role: Mentor

NIH R01 CA174305-02 Li (PI) 12/02/2013-11/30/2018
"Targeted Combination Therapy for Breast Cancer"
This application is focused on improving the delivery system through systematic study on structure-activity relationship (SAR). Their efficiency in synergistic action with PTX is then examined both in vitro and in vivo.
Role: Co-Investigator

Pending:

PABCC Award (PI Oesterreich)
Generation and characterization of ESR1 mutant models

R01 (PI Oesterreich)
FGFR4 – A new druggable target in endocrine resistant breast

R01 (PI Oesterreich)
Mechanism-based target of ER-mutant breast cancer

Past Funding:

NIH R01 CA97213 Oesterreich (PI) 08/01/2002-07/31/2014
"ER Co-Repressor Function of SAFB in Breast Cancer"
The major goal is to define the mechanism of repression and the biological significance of the estrogen receptor corepressor SAFB.

NIH R01-GM-099143 Rae (PI) 06/15/2011 - 03/31/2016
"Genetic Predictors of Anti-Estrogen Clinical Activity in Breast Cancer Patients"
The main goal is to identify polymorphisms associated with resistance to tamoxifen and aromatase inhibitor resistance, and with altered side effects.
Role: Co-Investigator

NIH 1R03EB018575-01 Sant (PI) 04/01/2014-03/31/2016
"Engineered microenvironments to model effect of size in tumor progression"
The objective of this study is to create a microfabricated platform that will allow generation of uniform, size-controlled microtumors in a high throughput manner.
Role: Co-Investigator

CDMRP OC120275/W81XWH-13-1-0205 Oesterreich (PI) 09/01/2013 – 08/31/2016
"Understudied Orphan Receptors – Novel treatment targets in ovarian cancer?"
In this study, we will test the feasibility of targeting NR4A in a series of serous OvCa cell lines, and in unique mouse models of serous OvCa.