Biographical Sketch

Provide the following information for each individual included in the Research & Related Senior/Key Person Profile (Expanded) Form.

NAME	POSITION TITLE
IRIDA KASTRATI	ASSISTANT PROFESSOR IN CANCER BIOLOGY

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
University of Illinois at Chicago, Chicago, IL	BA	2000 -2003	Chemistry
University of Illinois at Chicago, College of Pharmacy, Chicago, IL	PhD	2004-2009	Medicinal Chemistry
Northwestern University, Chicago, IL	Postdoc	2009-2010	Cancer Biology
University of Illinois at Chicago, College of Medicine, Chicago, IL	Komen Postdoc Fellow/Research Assistant Professor	2011-2019	Cancer Biology

A. Personal Statement

My research has focused on various aspects of breast cancer and women's health in general. My commitment to breast cancer research is not only a scientific challenge, but is also a cause dear to my heart because I have lost two family members to this disease. I received my PhD training in Medicinal Chemistry at UIC - College of Pharmacy where I studied chemical carcinogenesis and toxicology with Dr. Judy Bolton, and also rational drug design, drug development and mechanisms of drug action with Dr. Gregory Thatcher. For my postdoctoral training in Cancer Biology, I joined Dr. Jonna Frasor's lab at UIC – College of Medicine to work on hormone action, gene regulation, and inflammatory pathways in breast cancer. During this time I was awarded the prestigious Susan G. Komen postdoctoral fellowship to study how estrogen receptor (ER) and the pro-inflammatory NFκB pathway work together to increase breast cancer stem cells. Most recently, I joined Loyola University Chicago, Cardinal Bernardin Cancer Center as an Assistant Professor in Cancer Biology. My longstanding interest is to apply my multi-disciplinary training to identify fundamental drivers in aggressive, deadly breast cancer disease, and how to best therapeutically intervene to improve patient outcome.

B. Positions and Honors

2004-2009 **Graduate Research Assistant**, Medicinal Chemistry, College of Pharmacy, University of Illinois at Chicago (UIC), Chicago, IL. Mentor: Gregory R. J. Thatcher, PhD.

2009-2010 **Postdoctoral Fellow**, Division of Endocrinology, Feinberg School of Medicine, Northwestern University, Chicago, IL. Mentor: Vincent L. Cryns, MD.

2010-2011 **Postdoctoral Fellow**, Medicinal Chemistry, College of Pharmacy, UIC, Chicago, IL. Mentor: Judy L. Bolton, PhD.

2012-2016 **Susan G. Komen Postdoctoral Fellow**, Physiology and Biophysics, College of Medicine, UIC, Chicago, IL. Mentor: Jonna Frasor, PhD.

2016-2019 **Research Assistant Professor**, Physiology and Biophysics, UIC, Chicago, IL.

2019-Present **Assistant Professor**, Cancer Biology, Loyola University Chicago, Chicago, IL.

Other Experience and Professional Memberships

2005-present **Teaching Assistant**, **Research Supervisor, and Instructor** at Colleges of Pharmacy and Medicine, University of Illinois at Chicago.

2007-present **Peer Reviewer** for the following journals: Chemical Research in Toxicology, Hormones and Cancer, Journal of Steroid Biochemistry and Molecular Biology, Molecular and Cellular Endocrinology, Molecular Cancer Therapeutics, Oncogene, PloS One, and Scientific Reports.

2007-present American Association for Cancer Research.
2011-present UIC Association for Women in Cancer Research.
2012-present Endocrine Society, Women in Endocrinology.
2014-present American Society for Biochemistry and Molecular Biology.

Honors

2002 Norman Nachtrieb Award for Scientific Promise, University of Illinois at Chicago.
2003 Benjamin B. Freud Award for Scientific Excellence, University of Illinois at Chicago.
2004 University Graduate Fellowship, University of Illinois at Chicago.
2005 Ludwig Bauer Scholarship in Medicinal Chemistry, University of Illinois at Chicago.
2006 Travel Award, Women in Science and Engineering (WISE), University of Illinois at Chicago.
2007 Deiss Endowment in Biomedical Research, Graduate College, University of Illinois at Chicago.
Van Doren Scholar Award, University of Illinois at Chicago.
2008 Travel Award, Society of Toxicology 47th Annual Meeting.
Travel Award, Graduate Student Council, University of Illinois at Chicago.
Travel Award, Graduate College, University of Illinois at Chicago.
2012 Susan G. Komen for the Cure Postdoctoral Training Fellowship.
Outstanding Abstract, 5th Great Lakes Nuclear Receptor Conference, Chicago, IL.
2013 Gold Medal Abstract, College of Medicine Research Forum, University of Illinois at Chicago.
Travel Award and Outstanding Abstract, Endocrine Society 95th Meeting, San Francisco, CA.
2014 Outstanding Abstract, Endocrine Society 96th Annual Meeting, Chicago, IL.
First Place Abstract, College of Pharmacy Research Day, University of Illinois at Chicago.

C. Contributions to Science

1. Determine the mechanisms of estrogen's chemical carcinogenesis in human breast epithelial cells. My PhD training in toxicology was with Dr. Judy Bolton, a leader in the field of chemical toxicology in postmenopausal women's health. In breast cancer etiology, chemical carcinogenesis by catechol metabolites derived from oxidative metabolism of estrogens is thought to play an important role, yet exact mechanisms are unclear. My PhD work explored these mechanisms and impact on human breast epithelial cells. I established a correlation and provided the mechanistic link between malignant cellular transformation and a specific, quantifiable type of DNA damage arising from estrogen's oxidative metabolism. In addition, I showed that certain drugs, such as Selective Estrogen Receptor Modulators (SERMs), attenuate this type of DNA damage. The most significant aspects of this work were: (i) to establish a potential fluid biomarker for breast cancer risk, and (ii) establish the assay to screen for chemopreventive agents in breast cancer. Furthermore, I evaluated the safety and malignant transformation potential of human versus equine estrogen components of hormone replacement therapy

and their catechol metabolites. My work provided the basis for three graduate student projects in the lab, and was crucial in providing preliminary data of an R01 application that scored in the 6th percentile. In a separate project that I spearheaded despite being outside of the lab's expertise, I identified a novel estrogen extracellular signaling and its dependence on nitric oxide for survival in normal human breast epithelial cells.

a. Chang, M., Peng, K. W., **Kastrati, I.**, Overk, C. R., Qin, Z. H., Yao, P., Bolton, J. L. and Thatcher, G. R. (2007) Activation of estrogen receptor-mediated gene transcription by the equine estrogen metabolite, 4-methoxyequilenin, in human breast cancer cells. **Endocrinology**, 148, 4793-4802. PMID: 17584965
b. Chang M., Overk C. R., **Kastrati I.**, Peng K. W., Yao P., Qin Z. H., Petukhov P. A., Bolton J. L., Thatcher G. R. (2008) Estrogenic activity of the equine estrogen metabolite, 4-methoxyequilenin. **Adv Exp Med Biol**, 617, 601-607. PMID: 18497087
c. **Kastrati, I.**, Edisisinghe, P. D., Wijewickrama, G. T., Thatcher, G. R. (2010) Estrogen induced apoptosis of breast epithelial cells is blocked by NO/cGMP and mediated by extranuclear estrogen receptors. **Endocrinology**, 151(12), 5602–5216. PMID: 20943808 PMCID: PMC2999489
d. **Kastrati, I.**, Edirisinghe, P. D., Hemachandra, M. P., Chandrasena, E. R., Choi, J., Wang, Y., Bolton, J. L., Thatcher, G. R. (2011) Raloxifene and desmethylarzoxifene block estrogen-induced malignant transformation of human breast epithelial cells. **PloS One**, 6(11): e27876. PMID: 22140478 PMCID: PMC3226622

2. Optimize SERMs for breast cancer therapy and chemoprevention. My PhD training in drug discovery and development was with the renowned medicinal chemist and currently director of the UIC-Drug Discovery Center, Dr. Gregory Thatcher. As a trainee, I was an integral part of the team working on designing, synthesizing, and profiling the biological activities, both in vitro and in vivo, of novel Selective Estrogen Receptor Modulators (SERMs) for breast cancer therapy and chemoprevention. During this time, I conducted research in SERM lead optimization, determined the structure-activity relationship (SAR) of a family of benzothiophene SERMs in vitro and in vivo, evaluated SERM's metabolism in liver and intestinal microsomes, used in silico screening to profile SERM's receptor isoform selectivity, and applied theoretical calculations to determine the susceptibility of SERMs to oxidative metabolism. Besides the technical and intellectual skills, this project helped me develop collaborative and teamwork skills that are critical to advance research. I have effectively utilized this knowledge and fostered collaborations for novel drug design and testing later in my career as indicated below.

a. Overk, C. R., Peng, K. W., Asghodom, R. T., **Kastrati, I.**, Lantvit, D. D., Qin, Z., Frasor, J., Bolton, J. L. and Thatcher, G. R. (2007) Structure-activity relationships for a family of benzothiophene selective estrogen receptor modulators including raloxifene and arzoxifene. **ChemMedChem**, 2, 2418-2428. PMID: 17654759
b. Qin, Z., **Kastrati, I.**, Chandrasena, R. E., Liu, H., Yao, P., Petukhov, P. A., Bolton, J. L. and Thatcher, G. R. (2007) Benzothiophene selective estrogen receptor modulators with modulated oxidative activity and receptor affinity. **J Med Chem**, 50, 2682-2692. PMID: 17489582.
c. Yu, B., Dietz, B. M., Dunlap, T., **Kastrati, I.**, Lantvit, D. D., Overk, C. R., Yao, P., Qin, Z., Bolton, J. L. and Thatcher, G. R. (2007) Structural modulation of reactivity/activity in design of improved benzothiophene selective estrogen receptor modulators: induction of chemopreventive mechanisms. **Mol Cancer Ther**, 6, 2418-2428. PMID: 17876041
d. Qin, Z., **Kastrati, I.**, Ashgodom, R. T., Lantvit, D. D., Overk, C. R., Choi, Y., van Breemen, R.

B., Bolton, J. L., Thatcher, G. R. (2009) Structural modulation of oxidative metabolism in design of improved benzothiophene selective estrogen receptor modulators (SERMs). **Drug Metab Dispos**, 37(1), 161-169. PMID: 18936111 PMCID: PMC2683656

3. Crosstalk between ER and NFκB expands breast cancer stem cells to promote aggressive phenotypes. For my postdoctoral training in cancer biology, I joined Dr. Jonna Frasor's lab, an expert in nuclear receptor actions in breast cancer, to work on hormone action, gene regulation, and inflammatory pathways in breast cancer. Within the context of Frasor lab research on crosstalk between estrogen receptor (ER) and inflammation/NFκB pathway in breast cancer, I myself developed an alternative hypothesis at explaining poor patient outcome based on the cancer stem cell (CSC) hypothesis. Breast CSCs are a small population of highly tumorigenic cells with stem-like features that sit at the apex of the hierarchy to drive tumor initiation, growth and progression. Breast CSCs evade standard therapies - they persist, and are thought to seed recurrent tumors and distant metastasis. Thereby, understanding the underlying biology of breast CSC is critical to effectively target and eradicate them. Among some of the most significant findings of my work are: (i) determining the regulatory mechanisms of ER and NFκB at controlling CSCs, and (ii) identifying a novel gene, PHLDA1, as the key mediator of the feed-forward loop between ER-NFκB-miRNA181 at promoting CSC properties. These findings together and implications to endocrine resistance provided the key evidence for a successful R01 application for the lab. More recently, I used new technologies, Fluidigm's single-cell transcriptomic profiling together with single-cell proteomics (CyTOF), to derive a comprehensive understanding of the relationship between ER and NFκB in breast CSCs at a single-cell resolution. One final first author paper concluding this work is currently in preparation.

a. **Kastrati, I.**, Canestrari, E., and Frasor, J. (2015) PHLDA1 expression is controlled by an estrogen receptor (ER)-NFκB-miR-181 regulatory loop and is essential for formation of ER+ mammospheres. **Oncogene**, 34(18): 2309-2316. PMID: 24954507 PMCID: PMC4275416
b. Stender J.D., Nwachukwu J.C., **Kastrati I.**, Kim Y., Strid T., Yakir M., Srinivasan S., Nowak J., Izard T., Rangarajan E.S., Carlson K.E., Katzenellenbogen J.A., Yao X.Q., Grant B.J., Leong H.S., Lin C.Y., Frasor J., Nettles K.W., and Glass C.K., (2017) Structural and Molecular Mechanisms of Cytokine-Mediated Endocrine Resistance in Human Breast Cancer Cells. **Mol Cell**, Mar 16; 65(6):1122-1135.e5. PMID: 28306507
c. El-Shennawy, L.K., Dubrovskyi, O., **Kastrati, I.**, Danes, J., Zhang, Y., Whiteley H.E., Creighton C.J., and Frasor, J. (2018) Coactivation of estrogen receptor and IKK-β induces a dormant metastatic phenotype in ER-positive breast cancer. **Cancer Res**, Feb 15;78(4):974-984.

4. Therapeutic targeting of the NFκB pathway in breast cancer cells and DMF's mechanism of action. Given the important role breast cancer stem cells (CSCs) play in therapy resistance, recurrence and metastasis**,** targeting them will sensitize resistant, aggressive tumors to therapy, and prevent future recurrence and metastasis. Despite this, an anti-CSCs drug has yet to be approved for use in the clinic. I proposed to tackle it with dual-targeting hybrid agents obtained through a collaboration I set up with Dr. Gregory Thatcher. Elucidating the underlying biology of breast CSCs (see #3) together with a novel targeting strategy provided the basis of my postdoctoral fellowship application, which was funded by the Susan G. Komen foundation in 2012. I have shown that novel fumarate hybrid drugs, such as aspirin-fumarate or SERM-fumarates, exhibit enhanced anti-inflammatory, anti-CSC, anti-resistance, and other anti-breast cancer activities. These findings suggest that fumarates are a class of drugs with tremendous potential, and that the fumarate itself is a versatile chemical moiety in rational drug design capable of bestowing pleiotropic anti-cancer properties. This drug-targeting strategy may prove valuable

to other pathologies, where multiple inflammatory pathways are activated and contribute to the pathogenesis.
In this past three years, as a Research Assistant Professor, I demonstrated that dimethyl fumarate (DMF, Tecfidera), a drug approved in the US for multiple sclerosis, is an anti-NFκB and an anti-CSC agent in breast cancer cells with significant anti-resistance and anti-tumor activities. By using a chemical biology approach, I established that DMF's mechanism of action is via direct covalent modification of p65. By analogy, I hypothesize that DMF can prevent recurrence by succination of key factors, which in turn are important determinants of recurrence. Thereby, identifying these targets/factors can be exploited to uncover druggable vulnerabilities in tumor recurrence. These findings together with DMF's favorable safety profile set the stage for advancing DMF in clinical testing to prevent tumor recurrence.

a. **Kastrati, I.**, Litosh, V.A, Zhao, S., Alvarez, M., Thatcher, G. R. J., and Frasor, J. (2015) A novel aspirin prodrug inhibits NFκB activity and breast cancer stem properties. **BMC Cancer**, 15: 485-497. PMID: 26530254 PMCID: PMC4632459
b. ***Kastrati, I.**, Siklos, M.I., Calderon-Gierszal, E. L., El-Shennawy, L., Georgieva, G., Thayer, E. N., Thatcher, G. R. J., and Frasor, J. (2016) Dimethyl fumarate inhibits the nuclear factor κB pathway in breast cancer cells by covalent modification of p65 protein. **J Biol Chem**, 291(7): 3639-3647. PMID: 26683377 PMCID: PMC4751401
c. ***Kastrati, I.**, Delgado-Rivera, Loruhama, Georgieva, G., Thatcher, G. R. J., and Frasor, J. (2017) Synthesis and characterization of an aspirin-fumarate prodrug that inhibits NFκB activity and breast cancer stem cells. **J Vis Exp**, Jan 18;(119). doi: 10.3791/54798. PMID: 28190074
d. ***#Kastrati I.**, Siklos M.I., Brovkovych S.D., Thatcher G.R., and Frasor J. (2017) A novel strategy to co-target estrogen receptor and nuclear factor κB pathways with hybrid drugs for breast cancer therapy. **Horm Cancer**, Apr 10. doi: 10.1007/s12672-017-0294-5. PMID: 28396978

****Corresponding author.***
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Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Irida+Kastrati

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

Ongoing Research Support

W81XWH19-1-0108, Department of Defense, Breast Cancer Research Program Breakthrough Award Level 2, 2019-2022.
Title: Exploit dimethyl fumarate to uncover druggable vulnerabilities and prevent recurrence of ER+ breast cancers. Role: PI. Level of funding: $1,038,133.

Completed Research Support

PDF12229484, Susan G. Komen Postdoctoral Fellowship, 2012-2015.
Title: ER and NFκB work together to increase breast cancer stem cell properties.
Role: PI. Level of funding: $180,000.

Deiss Endowment in Biomedical Research, University of Illinois at Chicago, 2007.
Title: Mechanism of estrogen carcinogenesis: depurinating DNA adducts from electrophilic oxidative estrogen metabolites correlate with cellular transformation, and can be used as biomarker of breast tissue malignancy risk. Role: PI. Level of funding: $4,000.