Toni M. Brand

Program of the Thesis Defense Seminar for the
Degree of Doctor of Philosophy
in Cellular and Molecular Pathology

“Investigations of Nuclear HER family receptors in cancer and resistance to cetuximab therapy”

Friday, March 21, 12:30pm
K6/120 Clinical Sciences Center

Research conducted in the lab of
Deric L. Wheeler, PhD
Department of Human Oncology
Toni Brand’s Thesis Abstract

Investigations of Nuclear HER family receptors in cancer and resistance to cetuximab therapy

Toni M. Brand
Under the supervision of
Professor Deric L. Wheeler, PhD
at the University of Wisconsin-Madison

As an undergraduate at the University of California, Santa Barbara I actively sought out learning opportunities to help me identify my passions. I was immersed in my campus community and obtained internships at both the UCSB Women’s Center, and the American Red Cross. My intense interest in biological research led to my obtaining an undergraduate research position in Dr. Peggy Cotter’s lab to study *Bordetella pertussis* pathogenesis and the role of secreted virulence factors in enhancing infection. After college, I furthered my interest in scientific research by working with Dr. Paul Mischel and Dr. Deliang Guo at the University of California, Los Angeles to study the role of PI3K/AKT signaling in the regulation of glioblastoma cellular metabolism.
My research with my mentor Dr. Deric L. Wheeler focuses on understanding the role of nuclear receptor tyrosine kinases (RTKs) in cancer progression and survival, and their ability to augment response to various cancer chemotherapeutic agents. My main research project focuses on understanding the role of nuclear EGFR in resistance to cetuximab therapy in Triple-Negative Breast Cancer (TNBC). This work is of high clinical importance because there have been very few molecular targets identified in TNBC patients. While a high percentage of TNBC patients express the EGFR, only minor clinical benefit has been observed upon treatment with EGFR inhibitors. Our research indicates that cetuximab resistance in TNBC is mediated by nuclear EGFR. We found that the abrogation of nuclear EGFR translocation with Src Family Kinase inhibition results in the accumulation of EGFR on the plasma membrane and sensitization to cetuximab therapy. Additionally, I have mapped specific regions on the C-termini of the HER family receptors EGFR, HER2, and HER3 that enable each receptor to function as a co-transcription factor in the nucleus. Future directions of this work will examine how the co-transcriptional functions of nuclear HER receptors impact cancer formation, progression, and resistance to anti-HER family therapies.

My current thesis research has made me very passionate about translational scientific research. Through my involvement in this field I have had the opportunity to build partnerships with not only PhD professors but also MD physicians who can work with me to mediate the flow of my basic scientific discoveries to the clinic. My direct contact with Dr. Wheeler throughout my graduate career has formulated into the success of many published manuscripts, numerous awards, and fruitful collaborations. Dr. Wheeler has pushed my projects forward from every angle, and I look forward to continuing work with him in the future. The team that we have built in the laboratory will be unforgettable, and for his guidance and support I am truly grateful. My long-term goals involve heading my very own translational medicine research laboratory, in addition to leading cancer awareness PR programs, influencing inner-city high school students to appreciate and study science, and designing my own cancer oriented college courses. I know that I have the passion and drive to obtain these goals, and I am looking forward to leading my own laboratory in the future.
Publications


Presentations

1. Brand, TM, Iida, M, Li, C, Peet, CR, and Wheeler, DL. Understanding molecular mechanisms of HER2 translocation to the nucleus. Cellular and Molecular Pathology graduate student symposium, Madison, WI, September 2010

2. Iida, M, Li, C, Brand, TM, Peet, CR, and Wheeler, DL. Identification of EGFR regulated genes in cetuximab resistant tumor cell models. 22nd EORTC-NCI-ACCR symposium on “Molecular Targets and Cancer Therapeutics” Berlin, Germany, November 2010

3. Li, C, Iida, M, Brand, TM, Peet, CR, and Wheeler, DL. Dastatinib blocks cetuximab- and radiation-induced nuclear translocation of the epidermal growth factor receptor in head and neck squamous cell carcinoma. 22nd EORTC-NCI-ACCR symposium on “Molecular Targets and Cancer Therapeutics” Berlin, Germany, November 2010


5. Brand, TM, Iida, M, Campbell, D, Li, C, Wheeler, DL. Yes And Lyn Are Necessary For EGFR Nuclear Translocation In Cells With Acquired Resistance To Cetuximab. Cellular and Molecular Pathology graduate student symposium, Madison, WI, August 2011


8. Brand, TM, Iida, M, Wleklnski, M, Luthar, N, Starr, M, Wheeler, DL. Full length nuclear HER3 regulates the cyclin D1 promoter via a bipartite C-terminal transactivation domain. 37th Symposium on Hormones and Cell Regulation: Receptor Tyrosine Kinases (RTKs); from Structural Biology to Systems Biology, Mont Ste Odile, Ascale, France, October 2012, October 11-14, 2012. Young Investigator Travel Award Winner


