



The University of Wisconsin - Madison

CMP

Cellular and Molecular Pathology

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.

Honors & Awards

- Graduate with high honors and distinction in the major: 2008
- Shapiro Award Recipient: 2009-2010
- National Science Foundation Graduate Research Fellowship: Honorable Mention: 2009
- National Science Foundation Graduate Research Fellowship: Honorable Mention: 2010
- Cellular and Molecular Pathology T32 Fellowship: 2010-2013
- MD Anderson 2011 Young Investigator Travel Fellowship Award: September 2011
- Michael N. Hart Pathology Research Day, Poster Award Winner: August 2012
- Mont Ste Odile 2012 Young Investigator Travel Grant Award, October 2012
- American Association for Cancer Research Late Breaking Abstract 2013
- Cellular and Molecular Pathology Travel Scholarship 2013
- 13th International Wolfsberg Meeting on Molecular Radiation Biology/Oncology, Invited speaker presentation 2013.
- American Association for Cancer Research Late Breaking Abstract 2014

In Loving Memory of Terry Brand (Dad)



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 through out 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.



**Cellular and
Molecular
Pathology Graduate
Program**
Joanne Thornton
3170-10K MFCB

The University of Wisconsin - Madison
CMP
Cellular and Molecular Pathology

Publications

1. **Brand TM**, Wheeler DL. Treating PIK3CA and EGFR overexpressing breast cancers with lithium citrate. *Cancer Biol Ther*. 2011 Feb 1;11(3):368-70
2. **Brand TM**, Iida M, Wheeler DL. Molecular mechanisms of resistance to the EGFR monoclonal antibody cetuximab. *Cancer Biol Ther*. 2011 May 1;11(9):777-92. PMID: 21293176,
3. **Brand TM**, Dunn EF, Iida M, Myers RA, Kostopoulos KT, Li C, Peet CR, Wheeler DL. Erlotinib is a viable treatment for tumors with acquired resistance to cetuximab. *Cancer Biology and Therapy*. 2011 Sep 1;12(5):436-46.
4. **Brand TM**, Iida M, Li C, Wheeler DL. The nuclear epidermal growth factor receptor signaling network and its role in cancer. *Discov Med*. 2011 Nov;12(66):419-32. PMID: 22127113,
5. **Brand TM***, Iida M*, Campbell DA, Li C, Wheeler DL. Yes and Lyn play a role in nuclear translocation of the epidermal growth factor receptor. *Oncogene*. 2012 Feb 7;32(6):759-67.
6. **Brand TM**, Wheeler DL. KRAS mutant colorectal tumors: past and present. *Small GTPases*. 2012 Mar;3(1):34-9.
7. Iida M, **Brand TM**, Campbell D, Starr M, Luthar N, Traynor AM, Wheeler, DL. Targeting AKT With The Allosteric AKT Inhibitor MK-2206 in Non-Small Cell Lung Cancer cells with Acquired Resistance to Cetuximab. *Cancer Biology and Therapy*. 2013 Jun;14(6):481-91.
8. Traynor AM, Weigel TL, Oettel KR, Yang DT, Zhang C, Kim K, Salgia R, Iida M, **Brand TM**, Hoang T, Campbell TC, Hernan HR, Wheeler DL. Nuclear EGFR protein expression predicts poor survival in early stage non-small cell lung cancer. *Lung Cancer*. 2013 Jul;81(1):138-41.
9. **Brand TM**, Iida M, Luthar N, Starr MM, Huppert EJ, Wheeler, DL. Nuclear EGFR as a therapeutic target in cancer. *Radiotherapy Oncology*. 2013 Jul 3. S0167-8140 (13)00286-7.
10. Kawada, I, Hasina, R, Lennon, FE, Bindokas V, Usatyuk, P, Tan, YH, Krishnaswamy, S, Q, Arif, Carey, G, Hseu, RD, Robinson, M, Tretiakova, M, **Brand, TM**, Iida, M, Ferguson, MK, Wheeler, DL, Husain, AN, Natarajan, V, Vokes, EE, Singleton, PA, Salgia, R. Paxillin mutations affect focal adhesions and lead to altered mitochondrial dynamics: relevance to lung cancer. *Cancer Biology and Therapy*. 2013 Jul;14(7):679-91.
11. **Brand TM***, Li C*, Iida M, Huang S, Armstrong EA, Van Der Kogel B, Wheeler, DL. Human epidermal growth factor receptor 3 (HER3) blockade with U3-1287/AMG888 enhances the efficacy of radiation therapy in lung and head and neck carcinoma. *Discovery Medicine*. 2013 Sep;16(87):79-92.
12. **Brand TM**, Iida M, Luthar N, Wleklinski MJ, Starr MM, Wheeler DL. Mapping C-terminal transactivation domains of the nuclear HER family receptor tyrosine kinase HER3. *PLoS One*. 2013; 8(8):e71518.
13. Iida I, **Brand TM**, Starr M, Li C, Uppert EJ, Luthar N, Pedersen M, Horak ID, Kragh M, Wheeler DL. Sym004, a novel EGFR antibody mixture, can overcome acquired resistance to cetuximab. *Neoplasia*. 2013; 15(10):1196-206.
14. Rolle, CE, Kanteti, R, Surati, M, Nandi, S, Dhanasingh I, Yala S, Tretiakova M, Arif Q, Hembrough T, **Brand TM**, Wheeler DL, Husain AN, Vokes EE, Bharti A, Salgia R. Combination MET inhibition and Topoisomerase I inhibition block cell growth of Small Cell Lung Cancer. *Molecular Cancer Therapeutics*. 2013.
15. **Brand, TM**, Iida, M, Dunn, E, Luthar, N, Kostopoulos, KT, Corrigan, KL, Wleklinski, MJ, Yang, D, Wisinski, KB, Salgia, R, Wheeler, DL. Nuclear EGFR is a functional molecular target in TNBC. *Molecular Cancer Therapeutics*. Feb 2014. (in press)
16. **Brand, TM**, Iida, M, Corrigan, KL, Luthar, N, Hornung, M, Toulany, M, Gill, P, Salgia, R, Wheeler, DL. The receptor tyrosine kinase Axl plays a role in acquired resistance to cetuximab. Submitted, March 2014, *Molecular Cancer Therapeutics*
17. **Brand, TM**, Iida, M, Corrigan, Braverman, C, Toulany, Wheeler, DL. Axl is a logical molecular target in head and neck squamous cell carcinoma. Submitted, March 2014, *Cancer Biology and Therapy*

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-AACR symposium on "Molecular Targets and Cancer Therapeutics" Berlin, Germany, November 2010
3. Li, C, Iida, M, **Brand, TM**, Peet, CR, and Wheeler, DL, Dasatinib blocks cetuximab- and radiation-induced nuclear translocation of the epidermal growth factor receptor in head and neck squamous cell carcinoma. 22nd EORTC-NCI-AACR symposium on "Molecular Targets and Cancer Therapeutics" Berlin, Germany, November 2010
4. **Brand, TM**, Dunn, EF, Iida, M, Myers, RA, Kostopoulos, KT, Li, C, Peet, CR, and Wheeler, DL, Erlotinib is a viable treatment for tumors with acquired resistance to cetuximab. Am. Assoc. Cancer Res. Orlando, FL, April 2011
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
6. **Brand, TM**, Iida, M, Myers, RA, Kostopoulos, KT, Li, C, Wheeler, DL, Nuclear EGFR and Resistance to Cetuximab: Identifying Novel Approaches for Targeting Nuclear EGFR to Improve Cetuximab therapy. MD Anderson Symposia on Cancer Research, Identifying New Roles for the EGFR Family in Cancer. MD Anderson Cancer Center, Houston, TX, September 2011. **Young Investigator Travel Award Winner**
7. **Brand, TM**, Iida, M, Wleklinski, M, Luthar, N, Li, C, Wheeler, DL, Full length nuclear HER3 regulates the cyclin D1 promoter via a bipartite C-terminal transactivation domain. 1st annual Michael N. Hart Pathology Research Day, Madison, WI, August 2012. **Michael N. Hart Poster Award Winner**
8. **Brand, TM**, Iida, M, Wleklinski, 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**
9. **Brand TM**, Iida, M, Wleklinski, M, Luthar, N, Starr, M, Wheeler, DL, Mapping C-terminal transactivation domains of nuclear HER family receptor tyrosine kinases. Am. Assoc. Cancer Res. Washington, DC, April 2013. **Cellular and Molecular Pathology Travel Scholarship Winner**
10. **Brand, TM**, Iida, M, Luthar, N, Wleklinski, M, Kostopoulos, KT, Wheeler, DL, Nuclear EGFR Serves as a Functional Molecular Target in Triple-negative Breast Cancer. Am. Assoc. Cancer Res. Washington, DC, April 2013. **Late Breaking Abstract**
- II. **Brand, TM**, Iida, M, Luthar, N, Li, C, Wheeler, DL, and Nuclear EGFR serves as functional molecular target in triple-negative breast cancer. Wolfsberg Meeting on Molecular Radiation Biology/Oncology, Switzerland, June 2013. **Ranked top 10% of all abstracts and invited speaker presentation**
12. **Brand, TM**, Iida, M, Corrigan, KL, Luthar, N, Hornung, M, Toulany, Gill, P, Salgia, R, Wheeler, DL, The receptor tyrosine kinase Axl plays a role in acquired resistance to cetuximab. Am. Assoc. Cancer Res. San Diego, CA, April 2014. **Late Breaking Abstract**