BIOGRAPHICAL SKETCH

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NAME: Tyner, Jeffrey Wallace

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

POSITION TITLE: Associate 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
Grinnell College	B.A.	05/1999	Biology/Music
Washington University in St. Louis	Ph.D.	05/2005	Molecular Cell Biology
Oregon Health & Science University (OHSU)	N.A.	2005-2010	Hematology/Oncology

A. Positions and Honors

Positions & Employment

1999-2005 Ph.D. Student at Washington University in St. Louis
2005-2010 Post-Doctoral Fellow, Oregon Health & Science University (OHSU)
2010-2012 Research Assistant Professor, Division of Hematology & Medical Oncology, OHSU
2012-2016 Assistant Professor, Department of Cell & Developmental Biology, OHSU
2016-present Associate Professor, Department of Cell & Developmental Biology, OHSU
2017-present Director, Cancer Biology Graduate Program, OHSU
2018-present Co-Director, Translational Oncology Program, Knight Cancer Institute

Honors

2009 OHSU Knight Cancer Institute Career Development Award
2010 NIH/NCI K99/R00 Career Development Award
2012 V Foundation for Cancer Research – V Scholar Award
2013 Gabrielle's Angel Foundation for Cancer Research – Medical Research Award
2014 AAAS Martin and Rose Wachtel Cancer Research Award
2014 OHSU Excellence in Teaching Award
2015 OHSU Business Partnership Award
2015 OHSU Top 10 Investigators for Sponsored Research Award

B. Contributions to Science

1. Establishment of a Platform for Functional Genomic Screening of Primary Cells Derived from Patients with Hematologic Malignancies

Central Findings – I developed a team that has screened specimens from over 2,000 patients diagnosed with a diversity of different hematologic malignancies. We have found that the vast majority of cases (70-90%) exhibit hypersensitivity to at least one targeted agent, even though most of these patients are not yet being treated with these targeted agents. As detailed below, we have also worked extensively to understand the mechanistic underpinnings of these sensitivity profiles, which has enabled discovery of novel diagnostic and therapeutic properties of a variety of hematologic malignancies and has also led to new implementation of therapies currently in trials.

Influence of the Findings on the Progress of Science – Since I began this functional profiling in 2006, a number of laboratories around the world have begun similar programs, and functional screening as a tool for both biological discovery as well as clinical care is expanding dramatically.

My Specific Role – Conception, Development, and Implementation

a. Tyner JW et al. Functional Genomic Landscape of Acute Myeloid Leukemia. *Nature*, in press (2018).

b. Tyner, JW, Deininger, MW, Loriaux, MM, Chang, BH, Gotlib, JR, Willis, SG, Erickson, H, Kovacsovics, T, O'Hare, T, Heinrich, MC & Druker, BJ. RNAi screen for rapid therapeutic target identification in leukemia patients. *Proc Natl Acad Sci U S A* 106, 8695-700 (2009). PMID: 19433805. PMCID: PMC2680429.
c. Tyner, JW, Yang, WF, Bankhead, A, 3rd, Fan, G, Fletcher, LB, Bryant, J, Glover, JM, Chang, BH, Spurgeon, SE, Fleming, WH, Kovacsovics, T, Gotlib, JR, Oh, ST, Deininger, MW, Zwaan, CM, Den Boer, ML, van den Heuvel-Eibrink, MM, O'Hare, T, Druker, BJ & Loriaux, MM. Kinase pathway dependence in primary human leukemias determined by rapid inhibitor screening. *Cancer Res* 73, 285-96 (2013). PMID: 23087056. PMCID: PMC3537897.

2. **ROR1 and the pre-B-cell receptor in t(1;19)-positive and related subsets of Acute Lymphoblastic Leukemia**

Central Findings – t(1;19)-ALL uniformly expresses high levels of the cell surface receptor, ROR1, as well as expression of the pre-B-cell receptor. Both of these pathways are required for maintenance of t(1;19)-ALL growth and viability, and cross-talk between these pathways results in synergistic killing of these cells with agents that target both pathways.

Influence of the Findings on the Progress of Science – Collectively, our and other studies indicate that antagonists of ROR1 and the pre-B-cell receptor may be beneficial for upwards of 15% of ALL patients who are not currently treated with targeted therapies. The concept of crosstalk between ROR1 and the B-cell receptor has also been validated in mature B-cell neoplasms, and clinical trials have been initiated in this setting that pair immunotherapies targeting ROR1 with small-molecules targeting B-cell receptor signaling.

My Specific Role – Collection of initial data leading to the discovery; mentorship of graduate students, Dr. Vincent Bicocca and Marilynn Chow, and collaboration with colleagues, Drs. Bill Chang and Markus Muschen, to further understanding of the specific role and regulation of these pathways in t(1;19)-ALL and other subsets of lymphoid malignancy.

a. Crosstalk between ROR1 and the Pre-B cell receptor promotes survival of t(1;19) acute lymphoblastic leukemia. *Cancer Cell* 22, 656-67 (2012). PMID: 23153538. PMCID: PMC3500515.
b. Glover, JM, Loriaux, M, Tyner, JW, Druker, BJ & Chang, BH. In vitro sensitivity to dasatinib in lymphoblasts from a patient with t(17;19)(q22;p13) gene rearrangement pre-B acute lymphoblastic leukemia. *Pediatr Blood Cancer* 59, 576-9 (2012). PMID: 22038978. PMCID: PMC3291800.

3. **Mutation of CSF3R as a Diagnostic and Therapeutic Marker for Philadelphia-Negative CML**

Central Findings – Nearly all (~80) of CNL cases and a lower percentage (~5-30%) of aCML cases exhibit activating mutations of CSF3R. The most common mutations alter threonine residues just extracellular of the transmembrane domain, and mutation of these residues leads to constitutive dimerization and hyperactive JAK-STAT signaling. Consequently, these membrane proximal mutations confer sensitivity to JAK kinase inhibitors. The minority of mutations result in truncation of varying portions of the CSF3R cytoplasmic domain. These mutations lead to defective internalization and degradation of the receptor, resulting in increased CSF3R surface expression and activation of SRC family kinases and TNK2.

Influence of the Findings on the Progress of Science – These findings have been widely validated, and have been incorporated into the World Health Organization diagnostic criteria for CNL. We have also begun an investigator-initiated clinical trial testing a JAK kinase inhibitor for CNL/aCML patients.

My Specific Role – Collection of initial data leading to the discovery, collaboration and mentorship of the post-doctoral fellow, Dr. Julia Maxson, who completed the work. Collaboration with Dr. Kim-Hien Dao who has developed the clinical trial.

a. Maxson, JE, Gotlib, J, Pollyea, DA, Fleischman, AG, Agarwal, A, Eide, CA, Bottomly, D, Wilmot, B, McWeeney, SK, Tognon, CE, Pond, JB, Collins, RH, Goueli, B, Oh, ST, Deininger, MW, Chang, BH, Loriaux, MM, Druker, BJ & Tyner, JW. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med* 368, 1781-90 (2013). PMID: 23656643. PMCID: PMC3730275.
b. Fleischman, AG, Maxson, JE, Luty, SB, Agarwal, A, Royer, LR, Abel, ML, Macmaniman, JD, Loriaux, MM, Druker, BJ & Tyner, JW. The CSF3R T618I mutation causes a lethal neutrophilic neoplasia in mice that is responsive to therapeutic JAK inhibition. *Blood* 122, 3628-31 (2013). PMID: 24081659. PMCID: PMC3837511.
c. Maxson, JE, Luty, SB, Macmaniman, J, Abel, ML, Druker, BJ & Tyner, JW. Ligand-independence of the colony stimulating factor 3 receptor (CSF3R) T618I mutation results from loss of O-linked glycosylation and increased receptor dimerization. *J Biol Chem*, (2014). PMID: 24403076. PMCID: PMC3937653.

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/sites/myncbi/jeffrey.tyner.1/bibliography/44061228/public/?sort=date&direction=descending