Sean D. Reiff
PhD Candidate

“Utilizing Reversible Bruton’s Tyrosine Kinase Inhibitors to Circumvent Acquired Resistance to Ibrutinib”

March 26th, 2018
DHLRI 165
1:00 p.m.
VITA

June 2, 1989...........................................Born – Cincinnati, Ohio

2007....................................................LaSalle High School

2011....................................................B.S. Biology, B.S. Chemistry,
Lee University,
summa cum laude

2011-Present........................................MD, PhD Candidate,
The Ohio State University

COMMITTEE MEMBERS

Jennifer Woyach MD, Advisor

John Byrd MD, Advisor

Robert Baiocchi MD, PhD

William Carson III MD
ABSTRACT

Chronic lymphocytic leukemia (CLL) is a cancer of monoclonal B cells caused by dysregulated proliferation within the bone marrow, which disrupts normal hematopoiesis leading to anemia, immune deficiencies, and increased rates of morbidity and mortality. With approximately 150,000 affected individuals and an annual incidence exceeding 20,000 the United States, CLL is the most prevalent leukemia in the western hemisphere. Recent appreciation for the extent to which B cell receptor (BCR) signaling contributes to the pathogenesis of CLL has spurred the development of small molecule inhibitors which block signaling initiated at the BCR. One such molecule designed to abrogate BCR signaling is ibrutinib, an irreversible inhibitor of Bruton’s tyrosine kinase (BTK).

Patients treated with ibrutinib benefit from durable remission and prolonged progression free survival. However, despite ibrutinib’s multiple Breakthrough Therapy Designations, it is not a panacea and resistance to therapy occurs in many patients. Resistance to ibrutinib is most commonly mediated by mutation of BTK’s Cys481 amino acid to serine (C481S), which prevents ibrutinib’s covalent binding, reducing its potency.

The kinase inhibitors GDC-0853 and ARQ 531 reversibly and potently inhibit BTK at low nanomolar concentrations. Like ibrutinib, these compounds are mildly cytotoxic, reduce chemotaxis, and abrogate NF-κB mediated gene transcription. Because GDC-0853 and ARQ 531 are reversible inhibitors which do not rely upon the Cys481 amino acid of BTK for activity, we hypothesized that these compounds would maintain efficacy in mutated C481S BTK. As expected, both GDC-0853 and ARQ 531 inhibit C481S BTK in biochemical assays, as well as cell lines and patient cells expressing C481S BTK.

While GDC-0853 possesses exquisite specificity for BTK, ARQ 531 is a relatively promiscuous kinase inhibitor that targets multiple SRC and TEC family kinases. Interestingly, their distinct inhibitory profiles bestow unique properties of potential clinical
benefit. For example, GDC-0853 lacks the ITK inhibition possessed by ibrutinib. Because ITK is necessary for antibody dependent NK cell mediated cytotoxicity, immunotherapies are much more effectively combined with GDC-0853 than with ibrutinib in vitro. Conversely, our results with ARQ 531 suggest that non-specific kinase inhibition may also provide clinical benefit. In vivo, ARQ 531 improved survival over ibrutinib the Eμ-TCL1 murine model of CLL and improved survival in the Eμ-MYC/TCL1 murine model of Richter’s syndrome (in which ibrutinib was ineffective). Additionally, ARQ 531 inhibits downstream signaling in models with ibrutinib resistance due to PLCγ2 mutations.

As the prevalence and duration of ibrutinib therapy continue to increase, so too will the incidence of ibrutinib resistance in patients. The observation that the majority of patients who develop resistance to ibrutinib do so by mutating components of the BCR pathway rather than by upregulating an accessory survival pathway indicates that BCR signaling is critical to CLL progression. Therefore, there is strong rationale to utilize reversible BTK inhibitors like GDC-0853 and ARQ 531 in order to maintain inhibitory pressure on BTK in the setting of ibrutinib resistance. Based upon the findings contained herein I propose that reversible BTK inhibition may be a viable therapeutic option for patients with acquired ibrutinib resistance.
RECENT ABSTRACTS & PRESENTATIONS

Abstracts:

Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. Ohio State Trainee Research Day; 2016; Columbus, OH

Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. American Society of Clinical Oncologists; 2016; Chicago, IL.


Presentations:

Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. Oral presentation at Ohio State Biomedical Science Program retreat; 2016; Columbus, OH
Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. Oral presentation at 30th Annual Edward F. Hayes Graduate Research Forum; 2016; Columbus, OH

Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. Oral presentation at Medical Scientist Training Program Winter Retreat; 2016; Columbus, OH

Reiff SD, Johnson AJ, Byrd JC, Woyach JA. GDC-0853 inhibits C481S mutated Bruton’s tyrosine kinase and is effective in combination with αCD20 antibodies. Oral presentation at 4th Annual Ohio State Department of Medicine Clinician Scientist Trainee Research Day; 2016; Columbus, OH

RECENT PUBLICATIONS


AWARDS AND HONORS

2013-2014 University Fellowship, OSU

2016 Hayes Graduate Research Forum, 3rd Place Oral Presentation

2016 MSTP Winter Retreat, 1st Place Oral Presentation

FUTURE PLANS

Following graduation I will return to medical school to complete my M.D. training. Afterwards, I intend to pursue a residency specializing in internal medicine and a fellowship in hematology/oncology with the ultimate goal of achieving an academic position as a physician scientist identifying novel therapeutics with clinical applications.