Shaneice Mitchell  
PhD Candidate  

“Nicotinamide phosphoribosyltransferase as a therapeutic target in AML”  

December 6th, 2018  
DHLRI 165  
1:00 p.m.
VITA

1991. ........................................... . . . Born
Ahoskie, NC

2013 ........................................... Biochemistry, B.S.
North Carolina State University, Raleigh, NC

2013-present. ............................... Biomedical Sciences, PhD
The Ohio State University, Columbus, OH

COMMITTEE MEMBERS

John Byrd, MD -Advisor

Rosa Lapalombella, PhD -Advisor

Vinay Puduvalli, MD

Sameek Roychowdhury, MD, PhD
ABSTRACT

Acute Myeloid Leukemia (AML) is the most common acute leukemia in adults affecting almost 12,000 people each year in the US. This disease is collectively characterized by an accumulation of rapidly proliferating neoplastic cells of the myeloid lineage with differentiation defects. In spite of the vast amount of information known about AML and the identification of favorable prognosis factors, a large percentage of patients relapse and succumb to this disease. In addition, the inter- and intra-tumor heterogeneity of AML makes the identification of therapeutic targets for this disease particularly challenging. Future studies are warranted to identify multi-targeted agents that could influence AML as a composite disease. A target that shows promise in targeting the bulk AML leukemic cell population is nicotinamide phosphoribosyltransferase (NAMPT).

NAMPT is a protein involved in the generation of NAD+ in tumor cells, an important mediator of enzymatic reactions involved in various functions of leukemic disease progression. Leukemic blasts show a higher NAD+ turnover rate than normal cells, suggesting that NAD+ biosynthesis could be critically required in hematologic malignancies and therefore targeting the regeneration of NAD+ offers an attractive alternative strategy in AML. Inhibitors of NAMPT that have been described by others have shown potent anti-tumor activity and selectivity of several tumor models, including AML, while preserving the viability and functionality of normal tissues.

While two agents targeting NAMPT have been tested in Phase I clinical trials, dose-limiting toxicities including thrombocytopenia and gastrointestinal toxicities led to their clinical discontinuation. Novel compounds with improved tolerability are needed. Considering this, we sought to determine the mechanism of anti-tumor activity and AML leukemic cell population selectivity after NAMPT inhibition using a novel compound KPT-9274. We will also highlight several strategies used to antagonize AML disease progression via NAMPT.
inhibition that are cancer cell intrinsic and extrinsic, while minimizing toxicity in normal cells.

To this end, I begin my studies by characterizing KPT-9274 as a selective target of AML leukemic cells. KPT-9274 was able to induce potent cytotoxicity of AML patient cells and significantly increase overall survival in murine models of disseminated AML. In addition, the selectivity of KPT-9274 allow for the overall preservation of the viability and function of normal hematopoietic cells. Further studies demonstrate that NAMPT inhibition is able to selectively target resistant-derived leukemic stem cell population \textit{in vitro} and \textit{in vivo} using AML patient derived xenograft models (PDX), a more sophisticated way to observed therapeutic efficacy \textit{in vivo} in AML models. Finally, I was able to demonstrate that on-target unwanted toxic effects of KPT-9274 is mitigated by the selective activation of an alternative pathway of NAD$^+$ production via NAPRT1 and niacin supplementation. Overall, KPT-9274 demonstrates broad preclinical activity across a variety of AML subtypes and warrants further investigation as a potential therapeutic agent for AML. The knowledge gained from this work will facilitate the clinical development of a promising therapeutic in AML, a disease in dire need new therapeutic options.
RECENT ABSTRACTS AND PRESENTATION

Oral Presentations


Poster Presentations


RECENT PUBLICATIONS


AWARDS AND HONORS

♦ Minority Abstract Achievement Award | American Society of Hematology | San Diego, CA (2018)

♦ Michael L. Hess Prize for Cancer Research Excellence | The Ohio State University Comprehensive Cancer Center Annual Meeting | Columbus, OH (2018)

♦ 1st Place in Translational/Clinical Science | The Ohio State University Comprehensive Cancer Center Annual Meeting | Columbus, OH (2018)

♦ Conference Travel Award | FASEB Hematological Malignancies Conference | Saxton Rivers, VT (2017)

♦ Research Supplement to Promote Diversity in Health Related Research | National Cancer Institute | National Institute of Health | Bethesda, MD (2016-2018)

♦ Minority Abstract Achievement Award | American Society of Hematology | Orlando, FL (2015)

FUTURE PLANS

Following graduation, Ms. Mitchell will pursue a post-doctoral training in the field of hematology. Ultimately, Ms. Mitchell’s career goal is to become an independent investigator focusing on translational research in hematological malignancies.
Biomedical Sciences Graduate Program
1170 Graves Hall
333 W. 10th Avenue
Columbus, Ohio 43210