Nicholas Alexander Zorko
PhD Candidate

“The role of the mixed lineage leukemia partial tandem duplication in acute myeloid leukemogenesis”

May 10th, 2013
233 Meiling Hall
9:00 AM
VITA

December 29th, 1983. . . . . . . . . . . . . . . . . . . Born – Akron, Ohio

June 2006 . . . . . . . . . . . . . . . . . . . . . . . . Bachelor of Science
The Ohio State University

COMMITTEE MEMBERS

Michael A. Caligiuri, M.D.
John Byrd, M.D.
Guido Marcucci, M.D.
Danilo Perrotti, M.D., Ph.D.

AWARDS AND HONORS

Outstanding Research Mentor Award Nominee, Undergraduate Research Office, The Ohio State University-March 2013

Poster Session Finalist, The Ohio State University Comprehensive Cancer Center Annual Scientific Meeting, April 2012

Pelotonia Graduate Fellowship-July 2011-Present

Poster Presentation Award, OSUMC Research Day, April 2010

Travel Award Winner, American Society of Hematology Annual Meeting, Orlando, FL-December 2009


FUTURE PLANS

After completing his graduate work in Dr. Caligiuri’s lab, Nicholas will return to The Ohio State University College of Medicine to complete 3rd and 4th year clinical clerkship requirements. He will graduate with his Doctor of Medicine degree in the Spring of 2015 and will then complete his residency training.
RECENT PUBLICATIONS


ABSTRACT

The MLL-PTD and FLT3-ITD are co-present in a subset of adult patients with cytogenetically normal acute myeloid leukemia (CN-AML) and poor clinical outcomes. While the single mutant knock-in mice (MLL-PTD or Flt3-ITD) exhibit enhanced myeloid progenitor self-renewal or reduced apoptosis, respectively, neither model develops acute leukemia. We hypothesized that with mutant expression driven via the endogenous promoters, the two mutations may cooperate in vivo to induce an acute leukemia that mimics the human counterpart. MllPTD/WT:Flt3ITD/WT and MllPTD/WT:Flt3ITD/ITD mice developed transplantable, CN-AML leukemia exhibiting expansion of monocyctic/myelomonocytic Gr1±/Mac1+ and/or immature CD3-/CD19-/CD117+/Mac1-/B220lo cell populations, splenomegaly, leukocytosis, and anemia. MllPTD/WT:Flt3ITD/WT mice had significantly reduced lifespans compared to single-mutant controls. Increased ITD gene dosage (MllPTD/WT:Flt3ITD/ITD) was associated with an even shorter lifespan, consistent with previous findings in human patients. As in human MLL-PTD AML, the Mll-WT allele was downregulated in the murine model. To dissect the role of Mll-PTD in leukemogenesis, we obtained Mll-WT conditional knock-out (cKO) mice and generated functionally hemizygous MllPTD/ mice after conditional deletion of Mll-WT in adult mice. These mice survived and did not demonstrate signs of early BM failure seen in Mll/- mice. Notably, MllPTD/- mice began to develop myeloproliferative disease at approximately 80 weeks of age, indicating that the Mll-WT allele may be functioning as a tumor suppressor. HoxA9 and its cofactor Meis1 were upregulated 15- and 5-fold, respectively, in MllPTD/WT:Flt3ITD/WT mice with leukemia versus WT BM, while single MllPTD/WT exhibited increased HoxA9 (~6-fold) but not Meis1. We therefore overexpressed GFP-tagged Meis1 in MllPTD/WT BM to test whether this would be sufficient to generate leukemia. Meis1-GFP transduced MllPTD/WT cells maintained Meis1 expression, but have yet to develop leukemia 16 months post-engraftment.
ABSTRACT (CONTINUED)

Conditional deletion of *Meis1* in mice transplanted with leukemic *Mll<sup>PTD/WT</sup>:Flt3<sup>ITD/ITD</sup> bone marrow did not result in a significant survival advantage. These results indicate that *Meis1* may not be critical for *Mll*-PTD-mediated initiation nor maintenance of AML. In summary, we have developed a novel murine model of AML that phenotypically, molecularly, and epigenetically mimics the human AML counterpart, and are currently undertaking mechanistic studies to further evaluate the role of *Mll*-PTD and *Meis1* in AML development.

RECENT ABSTRACTS AND PRESENTATION


The *Mll*-PTD and *Flt3-ITD* Double Knock-in Mouse Develops Acute Myeloid Leukemia and Recapitulates Phenotypic, Molecular and Epigenetic Characteristics of the Counterpart Human Acute Myeloid Leukemia. American Society of Hematology Annual Meeting. Orlando, FL, December 5, 2010.