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GRADUATE SCHOOL

Doctoral Dissertation Defense Announcement

"Epigenetic Regulation in Normal and Malignant Hematopoiesis"

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Date: Wednesday, March 13th, 2024

Time: 10:00 AM (CST)

Defense Location: VBRI Seminar Room

Zoom: contact oarnold@mcw.edu for zoom link

Graduate Studies:

Foundations in Biomedical Science I-IV

Techniques and Molecular and Cell Biology

Professional Development I-II

Writing a Scientific Paper

Writing an Individual Fellowship

Reading and Research

Advanced Cell Biology

Statistics for Basic Sciences

Developmental and Stem Cell Biology

Basic Immunology

Ethics & Integrity in Science

Research Ethics Discussion Series

Doctoral Dissertation

Dissertation

"Epigenetic Regulation in Normal and Malignant Hematopoiesis"

Hematopoietic stem cells (HSCs) govern hematopoiesis through the processes of self-renewal and differentiation. The balance between these processes must be highly regulated to avoid hematopoietic dysfunction or malignant transformation. Epigenetic regulation is essential for regulating and maintaining proper hematopoiesis, and mutations of epigenetic regulators in hematopoietic stem and progenitor cells (HSPCs) are frequent drivers of hematological malignancies. Understanding the mechanisms behind the roles of epigenetic regulators in hematopoiesis can give insights into the pathophysiology of hematological diseases.

The Switch/Sucrose Non-Fermenting (SWI/SNF) nucleosome remodeling complexes are implicated in all stages of hematopoiesis and mutations of complex subunits have been observed over 25% of all cancers. One of the dominant forms of mammalian SWI/SNF is the BRG1/BRM Associated Factor (BAF) complex. BAF is distinguished from other SWI/SNF complexes by its incorporation of ARID1 proteins, Arid1a or Arid1b. Arid1a plays a crucial role in blood development. However, the role of Arid1b in this context is not well understood.

We utilized hematopoietic specific Cre mouse models to understand the role of Arid1b in normal hematopoiesis. We discovered Arid1b is dispensable for steady state and non-competitive hematopoiesis as the frequencies of all blood cell types were unaltered after its loss. Interestingly, we found Arid1b loss impairs the regenerative potential of HSPCs as we observed decreased chimerism of donor myeloid and HSPCs in competitive transplantations. Reconstitution of B cells was also impaired in constitutive knockout models only. These defects seemed to occur with incomplete penetrance as they were only observed in some transplantations dependent upon the donor mouse. We conclude Arid1b is largely dispensable for normal hematopoiesis but is required for HSC function under competitive conditions.

Acute Myeloid Leukemia (AML) is the most common leukemia in adults resulting from buildup of immature myeloid blast cells in the bone marrow and other tissues, eventually leading to hematopoietic failure if left untreated. Standard care for AML patients includes chemotherapy, however, 30-40% of patients will relapse, highlighting a need for more effective therapeutics.

A subset of patients with AML presents with chromosomal rearrangements of the mixed lineage leukemia (MLL1) gene, which result in the development of onco-fusion proteins that drive disease. The most common rearrangement of MLL1 (MLLr) in AML is MLL-AF9. JMJD1C, a member of the lysine demethylase 3 (KDM3) protein family, is a downstream target of MLL-AF9 and is aberrantly expressed in MLLr leukemias. Loss of JMJD1C causes differentiation and cell death of murine MLL-AF9 cells *in vitro* and impairment of leukemogenesis *in vivo*. Importantly, JMJD1C is dispensable for normal hematopoiesis, highlighting its potential as a therapeutic target. The role and function of of JMJD1C in human MLL-AF9 leukemia, however, is not well understood.

We utilized a CRISPR/Cas9 ribonucleoprotein (RNP) system to knockout JMJD1C in a human CD34+ umbilical cord blood derived model of MLL-AF9 leukemia (CD34-MLL-AF9). Loss of JMJD1C led to increased myeloid differentiation and apoptosis *in vitro* and impaired MLL-AF9 leukemogenesis *in vivo.* Further, we uncovered a novel interaction between JMJD1C and the nuclear co-repressor complex (NCoR) in human MLL-AF9, AML1-ETO, and PML-RARα cells. RNAseq analysis suggested this interaction may function to promote oncogenic fatty acid (FA) metabolism, as we observed significant downregulation of key players upon knockout of either JMJD1C or NCoR1. Further, we observed enrichment of FA metabolism pathways in the commonly downregulated genes. Together, this data proves a requirement of JMJD1C in human MLL-AF9 leukemia and shows JMJD1C interacts with NCoR to mediate oncogenic metabolism promoting leukemogenesis.

By studying the roles of Arid1b and JMJD1C respectively in normal hematopoiesis and AML, our work contributes to the understanding of epigenetic regulation in normal development and disease and identifies potential a therapeutic target for AML.

Olivia Arnold

Curriculum Vitae

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Education

- Medical College of Wisconsin – 2024 (expected)
  - PhD in Cell & Developmental Biology
- Marquette University- 2018
  - Bachelor of Science in Biology
  - Minor: Psychology

Professional Experience

- Graduate Student Research Assistant- Cell and Developmental Biology (2019-2024)
  - Medical College of Wisconsin and Versiti Blood Research Institute, Milwaukee, WI
- Undergraduate Intern- Molecular Immunology and Immunotherapy (2017)
  - Blood Center of Wisconsin, Milwaukee, WI

Other Experience and Professional Memberships

- Event Leadership Team- Relay for Life of Greater Milwaukee (2020-Present)
- Grassroots Member- American Cancer Society Cancer Action Network (2020-Present)
- Sub-Committee Co-Chair- Driving Equity and Inclusion for Students in Science (2023-2024)
- Co-Chair- Enhancing Scholarly Culture Committee (2023-2024)
- American Society of Hematology Leadership Institute (2023)
- Student Coach- Interdisciplinary Program in Biomedical Sciences (2020-2023)
- Chair- Young Professionals of the American Cancer Society (2020-2023)
- Intern- The White House, Washington DC, (2016-2017)

Honors and Awards

- Education Committee Award- Versiti Blood Research Institute (2023)
- Graduate Student Travel Award- Medical College of Wisconsin (2022)
- Graduate Student Travel Award- Cell and Developmental Biology (2022)

Publications

- Abstracts
  - **Arnold O**, Bluemn T, Stelloh C, Zheng Y, Wang D, Rao S, Zhu N. Arid1b Loss Impairs Hematopoietic Stem Cell Function in Normal Hematopoiesis. *Blood 2023*; 142 (Supplement 1): 5588. Published abstract, December 2023.
  - **Arnold, O,** Christiansen L, Izaguirre-Carbonell J, Bluemn T, M. Wunderlich MS, C. Stelloh, Y. Zheng PhD[1], H. Zhang PhD, J. Mulloy PhD, J. Pulikkan PhD, S. Rao MD,PhD, D. Wang PhD, J. Zhu PhD, N. Zhu PhD. JMJD1C Interacts with the NCoR Complex and Is Required for MLL-AF9 Leukemogenesis. Poster Presentation, Versiti Blood Research Institute, October 2023.
  - **Arnold O**, Christiansen L, Izaguirre-Carbonell J, Bluemn T, Wunderlich M, Zhu N. JMJD1C Interacts with the Ncor Corepressor Complex and Is Required for Human MLL-AF9 Leukemogenesis. *Blood* 2022; 140

(Supplement 1): 8700–8701. Poster Presentation, American Society of Hematology, December 2022
    - **Arnold O**, Izaguirre-Carbonelle J, Zhu N. The Role of Activating RAS mutations in Resistance to Epigenetic Modulation in Acute Myeloid Leukemia. Poster Presentation, Medical College of Wisconsin Graduate Student and Post-Doc Symposium, November 2021.
- Publications
    - **Arnold, O**., Barbosa, K., Deshpande, A. J., & Zhu, N. (2022). The Role of DOT1L in Normal and Malignant Hematopoiesis. Frontiers in Cell and Developmental Biology. 2022, May: 10:917125. doi: 10.3389/fcell.2022.917125
    - Bluemn T, Schmitz J, Zheng Y, Burns R, Zheng S, DeJong J, Christiansen L, **Arnold O**, Izaguirre-Carbonell J, Wang D, Deshpande AJ, Zhu N. Differential roles of BAF and PBAF subunits, Arid1b and Arid2, in MLL-AF9 leukemogenesis. Leukemia. 2022 Apr;36(4):946-955. doi: 10.1038/s41375-021-01505-w. Epub 2022 Jan 12. PMID: 35022500.
- Submitted Manuscripts
    - **Arnold, O.**, Christiansen L., Izaguirre-Carbonell J., Bluemn T., Wunderlich, M., Stelloh, C., Zheng, Y., Zhang, H., Mulloy, J., Pulikkan, J., Rao, S., Wang, D., Zhu, J., Zhu, N. JMJD1C and NCoR co-regulate fatty acid metabolism in human MLL-AF9 leukemia.