Doctoral Dissertation Defense Announcement

Luke Christiansen

“The Role of JMJD1C in MLL-rearranged Acute Myeloid Leukemia”

Candidate for Doctor of Philosophy in Cell Biology, Neurobiology, and Anatomy
Graduate School of Biomedical Sciences
Medical College of Wisconsin

Committee in Charge:
Nan Zhu, PhD (Advisor and Chair)
Demin Wang, PhD
Lisa Cirillo, PhD
Sridhar Rao, MD, PhD
Qizhen Shi, MD, PhD

Friday, February 25th, 2021, 9:30 AM (CST)

Live Public Viewing: https://mcw-edu.zoom.us/j/92057708962?pwd=aWxYejZpbEk3NmM4bDNpSjFQNEhTz09
Meeting ID: 920 5770 8962
Passcode: 1En7B1iA
Graduate Studies:
Biochemistry of the Cell
Techniques in Molecular & Cell Biology
Molecular and Cellular Biology
Mechanism of Cellular Signaling
Classical and Molecular Genetics
Ethics & Integrity in Science
Advanced Cell Biology
Research Ethics Discussion Series
Current Concepts of Cancer Biology
Journal Club
Reading and Research
Doctoral Dissertation
Doctoral Dissertation Continuation
Abstract

JMJD1C, a member of the lysine demethylase 3 family, is aberrantly expressed in mixed lineage leukemia (MLL) gene rearranged (MLLr) leukemias. Previously, we have shown JMJD1C is required for self-renewal of acute myeloid leukemia (AML) leukemia stem cells (LSCs) but not normal hematopoietic stem cells. However, the regions within JMJD1C that promote LSC self-renewal are unknown. Here, we used clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein-9 nuclease (Cas9) negative-selection screening and identified a requirement for the catalytic Jumonji (JmjC) domain and zinc finger domain (ZFD) for leukemia cell survival in vitro and in vivo. Moreover, we performed single cell transcriptome analysis of mouse leukemia cells harboring a single guide RNA (sgRNA) against the JmjC domain and identified increased activation of RAS/MAPK and the JAK-STAT pathway in cells harboring the JmjC sgRNA. We discovered that upregulation of interleukin 3 (IL-3) receptor genes facilitates increased activation of IL-3 signaling upon JMJD1C loss or mutation. Accordingly, we observed resistance to JMJD1C loss in MLLr AML bearing activating RAS mutations, suggesting that RAS pathway activation confers resistance to JMJD1C loss. These data demonstrated the functional importance of the JMJD1C JmjC domain in AML leukemogenesis and a novel interplay between JMJD1C and the IL-3 signaling pathway as a potential resistance mechanism to targeting JMJD1C catalytic activity.

We further studied the role of JMJD1C in human MLL-AF9 leukemia in human CD34+ umbilical cord blood MLL-AF9 model as well as MLLr patient-derived xenograft model. First, we performed a sgRNA screen with a lentiviral sgRNA library against JMJD1C in clonal Cas9 CD34+ cord blood derived MLL-AF9 cells (CD34-MLL-AF9) and demonstrated that JMJD1C is required for CD34-MLL-AF9 cell survival. Then using a CRISPR/Cas9 approach to target the JmjC and ZFD in CD34-MLL-AF9 leukemia, we found JMJD1C to be required in vivo by suppressing cell differentiation and apoptosis. Additionally, we used the same approach in MLL-AF9 patient-derived xenograft (PDX) and observed that JMJD1C plays a role in MLL-AF9 PDX leukemia by suppressing cell differentiation and cell death. To understand the mechanism of JMJD1C function in human AML, we performed bulk RNA-seq analysis on human CD34-MLL-AF9 harboring a sgRNA against the JmjC domain and ZFD of JMJD1C. We identified hematopoietic stem cell (HSC), AML, and cell apoptosis gene pathways as being regulated by JMJD1C, consistent with the observed phenotype in JMJD1C mutated cells. These data showed JMJD1C plays a role in human MLL-AF9 leukemia by regulating cell differentiation and apoptosis.
Curriculum Vitae

Luke Christiansen, BS
PhD Graduate Student, Medical College of Wisconsin

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EDUCATION

08/2016-Present
PhD Graduate Student, Interdisciplinary Biomedical Sciences Program (IDP), Department of Cell Biology, Neurology, and Anatomy, Medical College of Wisconsin, WI (Mentor: Nan Zhu, PhD. Expected graduation March 2022).

09/2010-12/2015
BS in Biology, University of Wisconsin – Parkside, Kenosha, WI

RESEARCH

05/2017-Present
Doctoral Dissertation Research
Versiti Blood Research Institute & Medical College of Wisconsin, Milwaukee, WI
Role of JMJD1C in mouse and human MLL-AF9 leukemia
Mentor: Nan Zhu, PhD, Associate Investigator
My research involved determining the role of JMJD1C in MLL-rearranged leukemia using in MLL-AF9 mouse overexpression and xenograft models.

03/2017-05/2017
Graduate Doctoral Rotation Student
Medical College of Wisconsin, Milwaukee, WI
Antibiotic-resistant bacteria
Mentor: Christopher J. Kristich, PhD, Professor
This research involved cloning DNA in bacteria to identify functionally important regions of an enzyme for antibiotic-resistance.
10/2016-12/2016 Graduate Doctoral Rotation Student
Medical College of Wisconsin, Milwaukee, WI
Homeostasis and proteostasis in neurodegenerative diseases
*Mentor: Kenneth Matt Scaglione, PhD, Assistant Professor*
Performed a drug screen to identify small molecule regulators of a protein involved with protein folding and degradation, in which mutations are implicated in a rare neurodegenerative disorder.

08/2016-10/2016 Graduate Doctoral Rotation Student
Medical College of Wisconsin, Milwaukee, WI
Cytokine and steroid hormone signaling in prostate cancer
*Mentor: Marja T. Nevalainen, MD, PhD, Professor*
Investigated the effect of PARP inhibitors in prostate cancer cell lines.

08/2016-Present PhD Graduate Student, Medical College of Wisconsin, Milwaukee, WI

06/2015-08/2015 Undergraduate Student Research
University of Wisconsin – Parkside, Kenosha, WI
Circadian rhythms and dietary fibers in cancer
*Mentor: Fabian Preuss, PhD, Associate Professor*
Examined the effect of fibers on circadian rhythms and the microbiota in mouse models.

OTHER WORK

09/2015-12/2015 Biochemistry Tutor, University of Wisconsin – Parkside, Kenosha, WI
Assisted students with challenging concepts in the Biochemical Metabolism course offered at UW-Parkside.

POSTERS

MCW welcome poster session. 2020.


* indicates both authors contributed equally

**MANUSCRIPTS IN PROGRESS**