**Subject:** Dissertation Defense - Abduljalil Mohammed Alsubaie, PhD Biosciences
**Date:** Wednesday, July 3, 2024 at 1:50:06 PM Eastern Daylight Time
**From:** SSB Faculty List on behalf of Diane St. Germain
**To:** SSB-FACULTY-LIST-L@LISTSERV.GMU.EDU

Dissertation Defense Announcement
To: The George Mason University Community

## Candidate: Abduljalil Mohammed Alsubaie

## Program: PhD Biosciences

## Date: Wednesday July 24, 2024

## Time: 10:30 AM Eastern Time (US and Canada)

## Location: In person, IABR conference room #1004
## And via zoom

Join Zoom Meeting:
https://gmu.zoom.us/j/94828708206?pwd=UFLrYSLI9Y3IOxk2zTXj6VfUDTy2za.1

**Meeting ID: 948 2870 8206**
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**Committee chair:** Dr. Mariaelena Pierobon

**Committee members:** Dr. Alessandra Luchini, Dr. Emanuel Petricoin, Dr. Barney Bishop

**Title:** “Dissecting the Role of Enhancer of Zeste Homolog 2 (EZH2) in Neuroendocrine Transdifferentiation in Non-Small Cell Lung Cancer (NSCLC) of Epithelial Origin”

**Abstract:**

Lung cancer is a highly prevalent and lethal disease that is responsible for a significant number of cancer related deaths worldwide. The introduction of targeted treatments in lung cancer, like EGFR inhibitors and immunotherapies, has profoundly affected survival of NSCLC patients. Even so, the therapeutic effects of these compounds are often temporary, and resistance is regularly acquired by tumor cells to adapt to unfavorable and harmful. Lineage plasticity, or the ability of cancer cells to change their physical characteristics and functions, and histological shift is emerging as important defense mechanism tumors utilize to survive treatment. For example, in response to treatment, Non-Small Cell Lung Cancers (NSCLCs) can acquire neuroendocrine (NE) characteristics and transform into Small Cell Lung Cancers (SCLCs). Conventional chemotherapy can achieve short-term response in these transformed tumors, but this mechanism of resistance remains largely untreatable and results in high levels of mortality. That is why identifying molecular drivers of NE transdifferentiation (TD) is of primary importance for devising effective therapeutic interventions and reducing lung cancer associated mortality. Overexpression of the epigenetic regulator histone-lysine N-methyltransferase Enhancer of Zeste Homolog (EZH2) has been associated with the development of SCLCs and NE-TD in prostate cancer, however, EZH2 functions has not been explored in NE transdifferentiated NSCLCs. In this study, we demonstrated that overexpression of EZH2 is associated with the acquisition of NE traits in NSCLCs and other cancers of epithelial origine. We have also demonstrated that inhibition of EZH2 in NE-TD NSCLCs reverses cancer cells to a non-NE state. Lastly, we showed that EZH2 inhibition in RB proficient tumors expressing NE markers reinstates Rb function and sensitivity to CDK4/6 inhibition. Our data provide novel understanding on the role of EZH2 in NE-TD of NSCLCs. If validated in more complex model systems, these data may provide a foundation for future clinical investigations specifically targeting for patients affected by tumors for which effective therapeutic options are limited.

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