Subject: Thesis Defense - Scott Parker, MS Biology
Date: Tuesday, April 1, 2025 at 3:22:10 PM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
To: SSB-FACULTY-LIST-L@LISTSERV.GMU.EDU

Thesis Defense Announcement
To: The George Mason University Community

Candidate: Scott Parker

Program: M.S. in Biology

Date: Wednesday April 16, 2025

Time: 10:00 AM Eastern Time (US and Canada)

Join Zoom Meeting
https://gmu.zoom.us/j/93323109900?pwd=kjb7VXacpCO8QKhCjguFN8ut67ISXB.1
Meeting ID: 933 2310 9900
Passcode: 985906

Committee chair: Dr. Mariaelena Pierobon

Committee members: Dr. Ancha Baranova, Dr. Farhang Alem

Title: Evaluation of EZH2 as a Therapeutic Target in Murine Models of HR+/HER2- Breast Cancer

Abstract:
Breast cancer remains a significant challenge to global public health. The HR+/HER2- breast cancer subtype, named for the presence and absence of estrogen/progesterone and human epidermal growth factor receptor 2 on its cells, respectively, is the most common. Metastatic HR+/HER2- breast cancers make up 20-30% of this group and affected patients have a 5-year relative survival rate of only 35.4%, making it a compelling target for new therapies. Patients affected by this disease are routinely treated with endocrine therapy in combination with an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6). Despite significantly improving survival, most patients eventually develop resistance to these targeted agents; understanding the mechanisms of resistance to these compounds remains a priority in oncology. Our group has found that the Enhancer of Zeste Homolog 2 (EZH2), an epigenetic regulator involved in histone methylation, modulates the development of resistance to CDK4/6 inhibition through non-canonical activities. Previously completed in vitro studies demonstrated that targeting EZH2 in CDK 4/6 inhibitor-resistant breast cancers resulted in the significant reduction of tumor growth. However, to fully understand the role of EZH2 as an actionable target in cancer requires in vivo models. This work describes the establishment and optimization of cell-derived xenograft (CDX) models to assess EZH2 actionability in a complex model system. CDX were generated with isogenic parental and abemaciclib-resistant cells generated from the commercially available

ER+/HER2- T47D line. Similar to our in vitro work, CDX models generated with the resistant line retain high levels of EZH2 expression compared to those established from the parental cells. EZH2 degradation with MS1943 successfully degrades EZH2 in T47D-AbR tumors in vivo, resulting in significant reductions in tumor growth, while sparing parental cells. Future investigations should determine the extent to which EZH2 degradation may be integrated in the clinic to treat patients with metastatic HR+/HER2- breast cancer.

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