Subject: Dissertation defense - Emna El Gazzah, PHD Biosciences
Date: Tuesday, March 26, 2024 at 12:35:07 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: Emna El Gazzah

Program: PhD Biosciences

Date: Wednesday, April 10, 2024

Time: 3:00 PM

Location:
In person - conference room 1004, IABR, Science & Tech campus
Via Zoom
https://gmu.zoom.us/j/93064760799?pwd=dFpzenlQVDJ6WUd0d3FaTmZwZ3g5UT09&from=addon

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+13017158592,,93064760799#,,,,*374404# US (Washington DC)
+12678310333,,93064760799#,,,,*374404# US (Philadelphia)

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+1 301 715 8592 US (Washington DC)
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Join by SIP
93064760799@zoomcrc.com

Committee chair: Dr. Mariaelena Pierobon
Committee members: Dr. Isela Gallagher, Dr. Emanuel Petricoin, Dr. Raymond Wadlow

Title: “Targeting Mechanisms of Resistance to Endocrine Therapy in Combination with CDK 4/6 inhibitors in ER+/ HER2- Metastatic Breast Cancer”

Abstract:
Despite the great success of the selective CDK4/6 inhibitors in treating Estrogen receptor positive (ER)+/ HER2- metastatic breast cancer (MBC), acquired and intrinsic resistance remain inevitable. To date, there are no known reliable biomarkers for predicting treatment response or to redirect therapy and overcome resistance to CDK4/6 inhibitors in the clinic. Preliminary

findings collected by the Side Out 3 (SO3) trial (ClinicalTrials.gov ID: NCT03195192), a clinical study aiming at identifying predictive markers of response to endocrine therapy (ET) in combination with CDK4/6 inhibitors, showed that increased expression of the epigenetic regulator EZH2 was associated with lack of response to treatment. Using a combination of observational and mechanistic approaches, this study aimed at understanding the role of EZH2 in the development of resistance to CDK 4/6 inhibitors in ER+/HER2- metastatic breast cancer and exploring its potential as a therapeutic target to redirect treatment. To investigate EZH2 role, isogenic ER+/HER2- breast cancer model systems with stable acquired resistance to CDK4/6 inhibitors palbociclib and abemaciclib were developed. To determine if EZH2 expression alone is sufficient to modulate response to CDK 4/6 inhibition, EZH2 overexpression was induced in non-resistant cells through lentivirus transduction. To assess EZH2 therapeutic potential, EZH2 was knocked down in CDK4/6 resistant cell lines with shRNA transfection and response to treatment with two EZH2 inhibitors, Tazemetostat and MS1943, was compared across parental and resistant cell lines in 2D and 3D culture. Taken together, our data suggest that EZH2 may represent a new therapeutic target in ER+/HER2- MBCs that are resistant to CDK 4/6 inhibition in combination with ET. Our data also indicate that resistance to treatment may be driven through EZH2 non-canonical activities opening new opportunities for developing new precision targeted approach for MBC patients.

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