COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

The Pharmaceutical Sciences Department
is pleased to announce the
Ph.D. Dissertation Defense Seminar of

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Pharmaceutical Sciences, Ph.D. Candidate
(Mentor: Dr. Duxin Sun)

Monday, June 11, 2018
1:00 pm
NCRC Building 10 in the South Atrium

"Meox1 Regulates Proliferation and Metastasis of Drug Resistant P53 and PTEN Deficient Triple Negative Breast Cancer Offering a Specific Therapeutic Target"

Abstract: Relative to other breast cancer subtypes, triple negative breast cancer (TNBC) exhibits more aggressive clinical behavior and poorer patient outcome. Lacking specified targets to improve long-term patient outcome of overall survival, chemotherapy is the mainstay of treatment for patients with TNBC. Unfortunately, only 30% of TNBC patients achieve pathological complete response (pCR) following neoadjuvant chemotherapy, the remaining majority exhibit drug resistant residual disease. Given the aggressive characteristics of TNBC, drug resistant patients inevitably experience disease recurrence, distant metastasis, and mortality within 5 years following diagnosis. Genetic aberrations in tumor suppressor genes of p53 and PTEN are frequent critical 'driver mutations' for tumorigenesis and drug resistance in TNBC. While the significance of p53 and PTEN are well recognized, the molecular biology of their combined loss of function is not well known in TNBC; moreover, no actionable specified targets exist for TNBC patients displaying genetic aberrations in both tumor suppressor genes. To offer insight, the functional and mechanistic role of mesenchyme homeobox 1 (Meox1) is examined in the context of p53 and PTEN deficient TNBC, offering a specific therapeutic option.

RNA expression analysis shows Meox1 is upregulated in TNBC. Additionally, Meox1 expression is negatively regulated by p53 and PTEN; *in vitro* experiments show combined siRNA knockdown of both tumor suppressor genes increases Meox1 expression. Furthermore, *in vitro* cell proliferation assays show siRNA knockdown of Meox1 significantly decreases cell growth of p53 and PTEN deficient TNBCs of both claudin-low and basal-like intrinsic subtypes. Interestingly, this decrease in cell growth is attributed to apoptosis in claudin-low but cell cycle arrest in basal-like cells. *In vivo* tumor xenograft mouse models corroborate *in vitro* data, where knocking down Meox1 using doxycycline inducible shRNA significantly decreases tumor growth in an adjuvant and neoadjuvant setting. Meox1 knockdown in both intrinsic subtypes also significantly decreases migration and invasion, ascribing to its functional role in regulating metastasis. RNA-sequencing and integrative pathway analyses show knocking down Meox1 in claudin-low and basal-like p53 and PTEN deficient TNBCs inactivates important canonical pathways involved in growth and survival as well as migration and invasion. One such important canonical pathway inactivated is Stat3 signaling in the Jak/Stat pathway. Western blot examination of Jak/Stat signaling shows Meox1 knockdown decreases Tyk2, Stat5, Stat6, and P-Stat3 (Tyr705) protein levels in claudin-low, but only decreases Tyk2 and Stat6 protein levels in basal-like cells. These results demonstrate Meox1 functional regulation of proliferation and metastasis can be elicited via the Jak/Stat mechanistic pathway. However, it is evident that Meox1 regulates Jak/Stat signaling differently between the two different intrinsic subtypes. Furthermore, Meox1 knockdown also affects distinct mechanistic pathways of apoptosis in claudin-low and cell cycle arrest in basal-like p53 and PTEN deficient TNBC. As such, data indicates Meox1 may have different transcriptional regulation in different TNBC subtypes.

While functional and mechanistic analysis of Meox1 offers insight into the complex molecular biology of p53 and PTEN deficient TNBC, results indicate that targeting Meox1 will have a critical role in ameliorating the aggressive proliferative and metastatic potential of these drug resistant tumors. Utilizing peptide inhibitors or breakthrough therapies such as siRNA delivery against Meox1 may translate to effective treatments in the clinic for chemo-resistant p53 and PTEN deficient TNBC patients with poor prognoses.

Defenses are open to the public.