University of South Carolina
Department of Biological Sciences

In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy,

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Will defend his dissertation:

*Tumor suppressor miR-489 regulates proliferation, autophagy and overcomes drug-resistance in Breast Cancer*

**Abstract:** Breast cancer is a highly heterogeneous disease with 21 distinct histological subtypes and four major molecular subtypes which are biologically variable in presentation, response to treatment and outcomes. This variability is due to significant transcriptional and genomic discrepancies, even in patients with the same molecular subtype. Similar to protein coding genes, significant discrepancies in microRNA expressions have also been shown to play an essential role in breast cancer progression, metastasis and drug resistance. We investigated role of one such microRNA, miR-489, in breast cancer progression and therapy resistance. Our studies reveal that miR-489 expression is lost in breast cancer and in endocrine resistant and chemoresistant tumors. Functional assays demonstrated that miR-489 inhibits proliferation, induces apoptosis and sensitizes breast cancer cells to doxorubicin *in vitro and in vivo* through autophagy inhibition and doxorubicin redistribution into the nucleus. Nanoparticle delivered miR-489 decreased the tumor growth and sensitized tumors to doxorubicin in xenograft mouse model. Our clinical analysis found that miR-489 expression levels may predict overall survival in patients with 8q22 amplification which possess *de novo* anthracycline resistance. Our gene set enrichment analysis showed significant enrichment of pathways involved in tamoxifen resistance. Through molecular studies, for the first time, we report that miR-489 acts as a negative feedback loop to confine uncontrolled estrogen signaling and cell proliferation in breast cancer. Mechanistically, miR-489 modulates estrogen signaling by hindering receptor phosphorylation and its nuclear localization. Our data demonstrates positive feedback loop between E2-ER axis and p38 MAPK and indicate potential use of p38 MAPK as prognostic marker and therapeutic target specifically in pre-menopausal ER+ breast cancer. We then demonstrated that restoration of miR-489 significantly inhibits proliferation and overcomes both *de novo* and acquired tamoxifen resistance. Clinical analysis also suggest that high miR-489 expression predicts better overall survival in hormone treated ER+ breast cancer patients, further supporting our *in vitro* data. In summary, these results demonstrate that miR-489 expression is inversely correlated with aggressiveness of breast cancer and drug resistance and suggests miR-489 as a promising prognostic biomarker or therapeutic agent in breast cancer.

**Monday, November 5th, 2018, PSC-409 at 1 pm**
Committee: Dr. Hexin Chen (Advisor), Dr. Marj Pena (Chair), Dr. Alan Waldman, Dr. Jason Stewart, and Dr. Daping Fan