Abstract: Human epidermal growth factor receptor 2 (HER2 or ErBb2) is a receptor tyrosine kinase overexpressed in 20-30% of breast cancers and associated with poor prognosis and outcome. Dysregulation of several micro RNAs (miRs) plays a key role in breast cancer progression and metastasis. In this study, we screened and identified miRs dysregulated in HER2-positive breast cancer cells. Molecular study demonstrated that miR-489 was specifically downregulated by the HER2-downstream signaling, especially the MAPK pathway. Restoration or overexpression of miR-489 in HER2-positive breast cancer cells significantly inhibited cell growth in vitro and decreased the tumorigenicity and tumor growth in xenograft mice. Mechanistically, we found that overexpression of miR-489 led to the decreased levels of HER2 and thus attenuated HER2-downstream signaling. To dissect the role of miR-489 in mammary gland development and HER2 induced tumorigenesis, we generated and characterize MMTV-miR-489 mice that overexpressed miR-489 in mammary epithelial cells were developed and these mice exhibited an inhibition of mammary gland development in early ages with a specific impact on highly proliferative cells. Double transgenic MMTV-Her2-miR489 mice were then generated to observe how miR-489 overexpression affects Her2 induced tumorigenesis. miR-489 overexpression delayed Her2 induced tumor initiation significantly. Moreover, miR-489 overexpression inhibited tumor growth and lung metastasis. miR-489 overexpression reduced mammary progenitor cell population significantly in preneoplastic mammary glands of MMTV-Her2 mice which showed a putative transformed population in Her2 induced tumorigenesis. The miR-489 overexpression reduced CD49f^hi^CD61^hi^ populations in tumors that have stem-like properties, and miR-489 overexpression altered the Her2 signaling pathway in mammary tumors. Also, our in vitro data suggest miR-489 restoration can also induce significant cytotoxicity in basal breast cancer cells. We also have found low amount of miR-489 expression in basal cancer cell lines and basal breast cancer patients compare to other subtypes. Our GO pathway analysis from gene expression pattern from T47D cells transfected with scr and mimic-miR-489 suggest genes involved in cell cycle pathway significantly dysregulated upon miR-489 restoration. We found miR-489 restoration can inhibit CDK1 and FOXM1 in breast cancer cells. Overall, our data indicates that miR-489 acts as a tumor suppressor miRNA at least partially by targeting HER2 signaling pathway by targeting HER2 and SHP2, induce dramatic cell death of basal type of breast cancer cell lines by arresting cell cycle in G2/M phase by targeting CDK1 and FOXM1 and regulates Her2 targeted progenitor population. Thus, miR-489 represents a new prognostic biomarker and potential therapeutic agent in breast cancer.

**Monday, April 2nd, 2018 – GSRC 101 at 1 pm**

Committee: Dr. Hexin Chen (Advisor), Dr. Rekha Patel (Chair), Dr. Alan Waldman, Dr. David Reisman, and Dr. Michael Shtutman