**Abstract:**

The unfolded protein response (UPR) contributes to human cancer (Miao and Randal 2014). Inositol requiring enzyme 1a (IRE1a) is an important UPR signaling molecule. The IRE1a RNase domain splices X-box binding protein 1 (XBP1), important in ER stress adaptation gene, mRNA to the active form. (Gardner et al. 2013). Increased XBP1s expression occur in human multiple myeloma (Croft et al. 2014) and solid tumors such as breast cancer (Davies et al., 2008; Fujimoto et al., 2007). IRE1a also promotes degradation of select mRNAs through regulated IRE1a dependent decay (RIDD) process under chronic ER stress associated with cell death (Lee et al. 2011).

Preliminary studies in our lab revealed that IRE1a mediated XBP1 cleavage inhibits Ras-induced senescence, while IRE1 mediated RIDD promotes senescence to oncogenic Ras activation. The function of RIDD in tumorigenesis is poorly understood, but a number of IRE1a mutations have been identified in human cancer (Carrasco et al. 2007). **We hypothesize that mutant IRE1a contributes to cancer through defective RIDD function.** We will express human cancer specific IRE1a mutants in primary epithelial cell carcinogenesis model to determine these mutants' function. These data will provide new information of IRE1a function and determine how IRE1a mutations impact the cancer phenotype.