Department of Molecular and Cellular Biology

Graduate Seminar MCB*6500

Friday, March 12, 2021 @12:45 p.m.

presented by:

Chen Ting Liang

(Advisor: Dr. Wei Zhang)

"Development of synthetic inhibitors for the BRCA1-BARD1 heterodimer"

Cancers are the leading cause of death worldwide, with breast cancer being one of the most common. To date, more than 800 distinct mutations have been identified in the Breast Cancer type-1 susceptibility (*BRCA1*) gene. One of the protein partners of BRCA1 is the BRCA1-Associated RING Domain protein 1 (BARD1). The association between these two proteins form the BRCA1-BARD1 heterodimer which is essential for the complex stability and its ubiquitin E3 ligase function. The BRCA1-BARD1 heterodimer has been identified to promote double stranded break (DBS) repair in homologous recombination (HR). Interestingly, although the E3 ligase function is defined, its significance to DSB repair through HR remains unclear and highly debated due to contradicting results surrounding mutations that disrupt the activity. Additionally, the substrate histone H2A has been identified as an E3 ligase target which is known to accumulate at DSB repair. We hypothesize by developing inhibitors to the BRCA1-BARD1 heterodimer, we can better clarify the significance of the E3 ligase function. This research proposal will focus on the development of an inhibitor for the BRCA1-BARD1 heterodimer using ubiquitin variant (UbV) technology. UbVs will be screened using phage display and charactered *in vitro* through ubiquitination assays. Finally, inhibitors will be extended to investigate the efficacy in cells. This study will be a major step forward in delineating the mechanisms of BRCA1-BARD's E3 ligase function to decipher its role in DSB repair.