UNIVERSITY of GUELPH

COLLEGE of BIOLOGICAL SCIENCE

DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY

Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of ***Master of Science*** *of*

CHEN LIANG

On Tuesday, January 3, 2023 at 1:30 p.m. (online)

Thesis Title: **Development of synthetic modulators for the BRCA1-BARD1 heterodimer**

Examination Committee:

Dr. John Vessey, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Wei Zhang, Dept. of Molecular and Cellular Biology
Dr. George van der Merwe, Dept. of Molecular and Cellular Biology
Dr. Jim Uniacke, Dept. of Molecular and Cellular Biology

Advisory Committee:

Dr. Wei Zhang (Advisor)
Dr. George van der Merwe

Abstract: Cancer is the leading cause of death worldwide, with breast cancer being one of the most common types. To date, more than 1700 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's stability and E3 ubiquitin ligase activity. The BRCA1-BARD1 heterodimer has been shown to promote double stranded break (DSB) repair in the DNA damage response (DDR) signaling pathway. Although its E3 ligase function has been confirmed, the significance with respect to DSB repair remains unclear and highly debated. To better clarify its involvement in DDR, I have utilized the ubiquitin variant (UbV) technology to develop modulators targeting the BRCA1-BARD1 heterodimer. Here, 22 UbVs were identified in phage display sections using different versions of the BRCA1-BARD1 complex, 21/22 were protein purified, 17/21 biochemically characterized in substrate ubiquitination assays and 4/17 assessed in cellular assays. One of the UbV binders was shown to influence specific DSB repair pathway by modulating BRCA1-BARD1 activity. In the future, more work is needed to fully characterize this UbV and its cellular effects. I conclude that this UbV provides a foundation that will allow us to further explore BRCA1-BARD's involvement in DDR.

Curriculum Vitae: Chen completed his Bachelor of Science (Hons.) in Microbiology at the University of Guelph in August 2019. In September 2020, he began his Master of Science program in Molecular and Cellular Biology under the supervision of Dr. Wei Zhang.

Publications: Liang, C.T., Roscow, O.M.A., and Zhang, W. (2021). Recent developments in engineering protein-protein interactions using phage display. Protein Eng. Des. Sel. *34*, 1–13.

Liang, C.T., Roscow, O.M.A., and Zhang, W. (2022) Generation and characterization of engineered ubiquitin variants to modulate the ubiquitin signaling cascade. Cold Spring Harbor Protocols (submitted).