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*

NATHANIEL PETERSEN

On Thursday, August 22, 2024 at 1:30 p.m. (SSC 2315)

Thesis Title: **Modulation of Receptor Tyrosine Kinases Using Ubiquitin Variant-Induced Proximity**

Examination Committee:

Dr. Jasmin Lalonde, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Nina Jones, Dept. of Molecular and Cellular Biology
Dr. Siavash Vahidi, Dept. of Molecular and Cellular Biology
Dr. Ray Lu, Dept. of Molecular and Cellular Biology

Advisory Committee:
Dr. Nina Jones (Advisor)
Dr. Siavash Vahidi

Abstract: Targeted protein degradation and stabilization are increasingly being shown as promising tools for disease treatment and protein research. Degradation occurs through small molecule-based proteolysis targeting chimeras, which recruit a ubiquitin ligase enzyme (E3) to a target protein to facilitate its ubiquitination (the process of adding ubiquitin moieties to a target leading to its degradation). By contrast, stabilization occurs through deubiquitinase targeting chimeras, which remove ubiquitin moieties and prevent degradation. Unfortunately, these molecules show limited ability to target diverse proteins, thus Ubiquitin Variant Induced Proximity molecules (UbVIPs) are being developed. UbVIPs use a protein-based structure consisting of a Ubiquitin Variant E3 binder, a linker, and a protein target binder. This structure may allow utilization of endogenous proteins as target binders, thereby increasing the pool of potential targets. SH2 domains are one category of endogenous protein domain that target phosphotyrosine-containing proteins. Here, modified SH2 domains known as superbinders have been integrated into UbVIPs to target the receptor tyrosine kinases EGFR and IGF1R, as a novel method to induce their degradation. Proof-of-concept stabilizing UbVIP molecules were then created by swapping the E3 ligase-binding UbV for a deubiquitinase-binding UbV. Degrading UbVIPs were successfully shown to reduce IGF1R levels, while stabilizing UbVIPs were shown to increase EGFR levels. The study highlights the potential for UbVIPs to utilize endogenous protein domains to function as a therapeutic tool to degrade proteins, while also demonstrating an alternate application for UbVIPs in the stabilization of excessively degraded proteins, which is known to occur with some tumor suppressors.

Curriculum Vitae: Nathaniel completed his BSc. (Honours) in Molecular Biology and Genetics with a minor degree in Economics at the University of Guelph in 2022. He began his MSc. program in Molecular and Cellular Biology in the Fall of 2022 under the supervision of Dr. Wei Zhang and later Dr. Nina Jones.

Publication: Aminu B., Fux J., Mallette E., **Petersen N**., Zhang W. (2022) Targeted Degradation of 53BP1 Using Ubiquitin Variant Induced Proximity. *Biomolecules* 12, 479.