



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

DMYTRO BROZDNYCHENKO

On Monday, December 12, 2022 at 1:30 p.m. (SSC 2315)

Thesis Title: Investigating the interaction mechanism of ClpP protease with small-molecule antimicrobials using H/D exchange mass spectrometry

Examination Committee:

Dr. Matthew Kimber, Dept. of Molecular and Cellular Biology (Exam Chair)

Dr. Siavash Vahidi, Dept. of Molecular and Cellular Biology

Dr. Steffen Graether, Dept. of Molecular and Cellular Biology

Dr. Rui Huang, Dept. of Chemistry

Advisory Committee:

Dr. Siavash Vahidi (Advisor)

Dr. Steffen Graether

Abstract: The caseinolytic protease P (ClpP) is a cylindrical serine protease that works together with energy-dependent unfoldases to degrade target proteins. In prokaryotes, the ClpP degradation machinery plays an essential role in maintaining proteostasis and is essential for many human pathogens. As such, ClpP is a prime target for the development of novel antimicrobials. Emerging antibiotics such as acyldepsipeptides (ADEPs), activators of compartmentalizing proteases (ACPs), diocatin, and boron-based active site inhibitors bind ClpP and dysregulate its activity. Despite the availability of high-resolution structures of ClpP bound to these small molecules, their mechanism of action remains poorly characterized. Here I use hydrogen-deuterium exchange mass spectrometry (HDX-MS) to probe the interactions of a diverse set of small-molecule antimicrobials with *N. meningitidis* ClpP (NmClpP). These measurements provide a dynamic molecular framework for the mechanism by which antimicrobials dysregulate ClpP function and highlight the complementarity of HDX-MS to X-ray crystallography and electron cryomicroscopy.

Curriculum Vitae: Dmytro completed his Bachelor of Science (Hons.) specializing in Biology at the University of Western Ontario in 2018. In Fall 2020, he began his Master of Science program in the lab of Dr. Siavash Vahidi.

Awards: Poster selected to be presented at the Annual American Society for Mass Spectrometry Conference (2022)

Publications: Barghash, M.; Mabanglo, M.; Brozdnychenko, D.; Hoff, S.; Bonomi, M.; Vahidi, S.; Houry, W. A., **Mechanism of the allosteric activation of *N. meningitidis* ClpP protease by substrates and active-site inhibitors**, (In preparation)