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*

SARAH WISMER

on Friday, December 18, 2020 at 9:30 a.m. (online)

Thesis Title: **Investigation of the role of Nck in breast cancer cell invasion and invadopodia formation and its interaction with ADAM19**

Examination Committee:

Dr. Jasmin Lalonde, Dept. of Molecular and Cellular Biology (exam chair)
Dr. Nina Jones, Dept. of Molecular and Cellular Biology
Dr. Roger Moorehead, Dept. of Biomedical Sciences
Dr. Wei Zhang, Dept. of Molecular and Cellular Biology

Advisory Committee:
Dr. Nina Jones (Advisor)
Dr. Marc Coppolino
Dr. Roger Moorehead

Abstract: Despite advances in breast cancer treatment, metastatic breast cancer remains incurable, and the molecular signals that promote invasion of cancer cells from primary tumours to secondary sites are incompletely understood. During invasion, cells remodel their attachments to the surrounding extracellular matrix and form invadopodia that degrade this matrix to allow cell movement through it. Both processes require rearrangement of the actin cytoskeleton. Nck is an adaptor protein that links transmembrane proteins to the actin cytoskeleton and has been implicated in cancer cell invasion and invadopodia formation. We have recently identified elevated expression of Nck in several breast cancer subtypes, and the goal of this project was to study the effects of Nck signaling in the context of triple-negative breast cancer. Here we show that overexpression of Nck in MDA-MB-231 breast cancer cells increases 3D cell invasion, invadopodia formation and gelatin degradation, and decreases focal adhesion kinase phosphorylation. We also find that Nck interacts with ADAM19, another protein linked to invadopodia and invasion in several cancers. The ADAM19/Nck interaction can be disrupted by mutation of the first or possibly third SH3 domain of Nck. An inhibitor, AX- 024, that binds to the unique DY pocket found in the first SH3 domain of Nck can reduce the invasion of breast cancer cells, possibly by disrupting the ADAM19/Nck interaction. Altogether, these results show that Nck signaling can promote breast cancer cell invasion and that the ADAM19/Nck interaction and more specifically the DY pocket is an intriguing target for the reduction of cancer cell metastasis.

Curriculum Vitae: Sarah completed her Bachelor of Science (Hons.) at the University of Guelph in the spring of 2018, and then began her MSc in the lab of Dr. Nina Jones in the fall of the same year.

Awards: 2018-2020 Graduate Tuition Scholarship