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 ***Doctor of Philosophy*** *of*

ADAM GOLDING

on Wednesday, October 6, 2021 at 9:00 a.m. (online)

Thesis Title: **Investigation of the Nck1 and Nck2 in mammary gland development and breast cancer**

Examination Committee:

Dr. Ray Lu, 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. Andrew Bendall, Dept. of Molecular and Cellular Biology
Dr. Carrie Shemanko, Dept. of Biological Sciences, University of Calgary (External Examiner)

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

Abstract: The adaptor proteins Nck1 and Nck2 are well-established signalling nodes which mediate diverse biological processes including cell proliferation and actin remodelling. Although they were first identified as oncogenes over 25 years ago and determined to have critical roles in development of many tissues, there has been limited investigation into Nck function in breast cancer and breast development. In this thesis, we have used a series of loss-of-function mouse models to advance the understanding of Nck1 and Nck2 function in normal mammary gland morphogenesis and HER2+ breast cancer progression. In the first study, we confirmed broad localization of Nck1 and Nck2 in the mammary gland. Using single knockout mice, we found that loss of Nck1 or Nck2 led to distinct defects in mammary gland branching throughout puberty, along with disruptions in the formation and persistence of terminal end buds, which drive mammary outgrowth. Mechanistically, we identified changes in cell proliferation but not apoptosis in these mice. In a parallel study, we found that Nck1 and Nck2 are both upregulated in aggressive human breast cancers, including HER2+ and triple-negative subtypes. Using a transgenic mouse model of HER2+ breast cancer coupled with conditional Nck deletion in the mammary gland, we showed that compound loss of both Nck1 and Nck2 significantly delayed tumour onset and reduced lung metastasis, and that these effects were not seen with deletion of a single paralog. Tumours isolated from these mice displayed changes in key regulators of actin and adhesion-based signalling. Altogether these findings provide new physiological insights verifying the requirement of Nck proteins in mammary gland development and in promoting HER2+ breast cancer, and they reveal their potential as targets to inhibit breast cancer initiation.

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Curriculum Vitae: Adam obtained his B.Sc. in Biochemistry, Molecular and Cellular Biology from the University of New Hampshire with Magna Cum Laude in 2014. In 2016, he began an M.Sc. in Molecular and Cellular Biology under the supervision of Dr. Nina Jones, transferring to the Ph.D. program in the spring of 2017.

Awards: International Graduate Tuition Scholarship (2016)