



**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*

HAYLEY LAU

on Wednesday, September 8, 2021 at 9:30 a.m. (online)

Thesis Title: **Characterizing novel functions of the ShcD phosphotyrosine adaptor protein in receptor tyrosine kinase signaling**

Examination Committee:

Dr. Ray Lu, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. Nina Jones, Dept. of Molecular and Cellular Biology
Dr. Scott Ryan, Dept. of Molecular and Cellular Biology
Dr. Laura Favetta, Dept. of Biomedical Sciences
Dr. Josie Ursini-Siegel, Depts. of Oncology and Biochemistry, McGill University
(External Examiner)

Advisory Committee:

Dr. Nina Jones (Adv)
Dr. Scott Ryan
Dr. Bettina Kalisch

Abstract: Cell signaling involves a highly orchestrated cascade of molecular events that convert external stimuli into a biological response. Protein-protein interactions form the foundation for all intracellular signaling networks and are largely regulated by posttranslational modifications such as phosphorylation. Central to these pathways are surface receptor tyrosine kinases (RTKs), including the prototypical epidermal growth factor receptor (EGFR) and Trk neurotrophin receptors, which are phosphorylated and activated upon ligand binding. Once activated, RTKs recruit intracellular signaling molecules, including Shc (Src homology and collagen) adaptors, to the developing signaling complex. The Shc family (ShcA, B, C, D) of phosphotyrosine adaptor proteins consists of four structurally similar paralogs. ShcD is the fourth and most recently discovered member and shares the greatest homology with the well-characterized ShcA. Intriguingly, ShcD possesses several variations that have the potential to modify elicited signaling outcomes. ShcD contributes to melanoma and glioma metastasis and has been recently implicated in breast cancer signaling. ShcD also uniquely promotes ligand-independent EGFR hyperphosphorylation; however, the biological consequences of this phenomenon remain elusive, and warrant further investigation. Using a combination of biochemical approaches and cell-based assays, we show that the event of ShcD-induced EGFR hyperphosphorylation correlates with enhanced cell invasion and repressed PI3K/Akt signaling in metastatic breast cancer cells. Targeted disruption of EGFR-ShcD complexes reduces receptor phosphorylation and cell invasion, suggesting the interaction between EGFR and ShcD may contribute to breast cancer metastasis. We also demonstrate that ShcD negatively regulates Ras/MAPK pathways distal to neural specific Trk RTKs. In cultured cells, we show that ShcD binds TrkA and TrkB neurotrophic receptors and suppresses downstream Erk phosphorylation. We also observe

enhanced pErk levels in the brains of ShcD knockout mice, indicating that this mechanism may have physiological relevance. Lastly, we describe another ShcD-mediated event of EGFR hyperubiquitination. ShcD disrupts normal EGFR internalization and trafficking, and here we demonstrate that this may be attributed to novel associations between ShcD and the Cbl ubiquitin ligase which regulates receptor ubiquitination. Collectively, this work further demonstrates the ability of ShcD to uniquely regulate RTK dynamics and repress Ras/MAPK and PI3K/Akt signaling outcomes. Our findings also reveal a novel role for ShcD in breast cancer cell signaling which will help uncover deregulated signaling pathways in metastasis that may be targeted in the development of new therapeutics.

Curriculum Vitae: Hayley obtained her B.Sc. (Hons), Molecular Biology and Genetics at the University of Guelph. In the summer of 2016, she began her M.Sc. in Molecular and Cellular Biology under the supervision of Dr. Nina Jones and in the summer of 2017, transferred to the Ph.D. program.

Awards: Heather Funston Memorial Scholarship Award (2019), Alexander Graham Bell Canada Graduate Scholarship CGS-D (2018), Alexander Graham Bell Canada Graduate Scholarship CGS-M (2017), Ontario Graduate Scholarship (2017), Heather Funston Memorial Scholarship Award (2016), GIBCO/BRL Microbiology Research Excellence Prize (2016)

Publications: Robeson HR, Lau HR, New LA, Lalonde J, Armstrong JN, Jones N. 2019. Localization of the phosphotyrosine adaptor protein ShcD/SHC4 in the adult rat nervous system. *BMC Neuroscience*. 20:57.

Wills MK, Lau HR, Jones N. 2017. The ShcD phosphotyrosine adaptor subverts canonical EGF receptor trafficking. *Journal of Cell Science*. 130:2808-2820.

Wills MK, Lau HR, Keyvani Chahi A, Tilak M, Guild B, New L, Lu, P, Jacquet K, Meakin SO, Bisson N, Jones N. 2017. Signaling adaptor ShcD suppresses Erk phosphorylation distal to the TrkA, TrkB and Ret neurotrophic receptors. *Journal of Biological Chemistry*. 292:5748-5759.