Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of Doctor of Philosophy of

MANALI TILAK

on Thursday, December 12, 2019 at 9:30 a.m. in SSC 3317

Thesis Title: A comprehensive proteomic and transcriptomic approach to understand novel features of adaptor protein ShcD

Examination Committee:
Dr. R. Lu, Dept. of Molecular and Cellular Biology (Exam Chair)
Dr. B. Coomber, Dept. of Biomedical Science
Dr. T. Van Raay, Dept. of Molecular and Cellular Biology
Dr. A. Bendall, Dept. of Molecular and Cellular Biology
Dr. C. Antonescu, Dept. of Chemistry & Biology, Ryerson University

Advisory Committee:
Dr. N. Jones (Adv)
Dr. T. Van Raay
Dr. B. Coomber

Abstract: Most cellular processes are modulated by protein-protein interactions, which serve as the basis for intracellular signaling cascades. Perturbations in these cascades can lead to abnormal signaling events ultimately resulting in diseases like cancer. Specialized phosphotyrosine circuitry translates extracellular signals into cellular responses through altered phosphorylation states of tyrosine residues using receptor tyrosine kinases, phosphatases, and modular interaction domains. The Shc (Src homology 2 domain containing) family consists of four evolutionarily related proteins sharing structural homology, but distinct functional roles. The more recently identified and least characterized member, ShcD, is of clinical relevance on account of its overexpression in malignant gliomas. However, the mechanisms by which ShcD exerts this effect remain speculative and therefore warrant further inquiry. The purpose of this project accordingly is to identify and better understand the mechanisms through which ShcD precipitates and promotes interactions with other signaling molecules that supposedly result in malignant gliomas. Using a comprehensive, dual-pronged proteomic and transcriptomic approach, I have shown that ShcD associates with receptor Tie2 leading to synergistically promoted invasion of glioma cells. I have also shown that ShcD signaling network is not limited to RTKs but that it also associates with the phosphatase Shp2 and suppresses Erk signaling downstream of neurotrophic receptor TrkB. Lastly, this project describes the regulatory landscape of ShcD by identifying its upstream and alternative intronic promoters which show tissuespecific adaptation as well as dynamic usage through the course of development. Contribution of ShcD to signaling pathways in glioma progression as reported here can also be used to delineate
neurogenesis as well as for understanding other instances of disease occurrence and progression, including cancer and neurodegenerative disorders. The data presented in this thesis can therefore serve as a foundation to identify ShcD as a potential diagnostic marker and/or a therapeutic target.

**Curriculum Vitae:** Manali completed her B.Sc. in Cell and Molecular Biology at Concordia University in 2005, her M.Sc. in Biotech at the University of Pune in 2008, and Masters of Bioinformatics at the University of Guelph in 2013. She commenced her Ph.D. studies in the lab of Dr. Nina Jones in September 2014.

**Awards:** College of Biological Science (CBS) PhD Award (2014-2018); CIHR-ICR Travel Award (2018)

**Publications:**

