

**PhD DEFENCE Friday, July 27<sup>th</sup>, 2018**

**Student: Tina Yang**

**Title: PROTEOMIC INVESTIGATION OF PROTEIN FUNCTION AND REGULATORY PATHWAYS IN CANCER**

**Time and location:** 9:15 am PST; Room 202, Anthropology and Sociology Building, 6303 NW Marine Drive, UBC Point Grey Campus

**Supervisor:** Dr. Poul Sorensen

## **ABSTRACT**

Proteins are essential components of the cell and the organism, fulfilling diverse functions that are often dysregulated in cancer. As many proteins act as a component of multisubunit complexes and intricate pathways, understanding how these complexes and pathways function and become dysregulated is important to the understanding of tumour initiation, progression, and resistance to treatment. The rapidly-advancing field of proteomics has made important contributions to basic cancer research, due to its applicability to the study of various aspects of protein biology in a systemic way. The aim of this thesis was to apply state-of-the-art proteomics techniques to different aspects of basic cancer research; namely, to identify potential mechanisms of mTOR inhibitor resistance, and to uncover novel functions of the tumour suppressor HACE1.

Firstly, SILAC (stable isotope labelling by amino acids in cell culture) and Click-pulse-SILAC were used to comprehensively characterize cellular responses to the mTORC1/2 inhibitor Torin1.

Large-scale data with extensive coverage of the proteome was generated, from which data analysis identified RTK (receptor tyrosine kinase) upregulation as an important phenomenon in response to Torin1 that was at least in part affected by the transcriptional coactivator p300. p300 silencing by siRNA attenuated RTK upregulation as well as MAPK/PI3K signalling, and co-treatment of cells with Torin1 and the p300 inhibitor C646 enhanced the ability of Torin1 to inhibit cell proliferation. Secondly, the proximity labelling proteomics approach, APEX-MS, was used to capture potential interactors and substrates of the E3 ubiquitin ligase HACE1 (HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1), which has tumour suppressor activity in a number of contexts. Various data analysis and extraction approaches identified several novel pathways in which HACE1 may be involved, and characterized the novel interactor and substrate of HACE1, HGS (hepatocyte growth factor-regulated tyrosine kinase substrate). Collectively, these studies demonstrate the versatility of proteomics-based approaches in studying aspects of cancer biology and the diverse kinds of data that can be extracted from proteomic analyses.