PhD DEFENCE Monday, September 25th, 2017
Student: Jonathan Lim
Title: THE IMPACT OF ONCOGENIC KRAS ON REDOX BALANCE TO SUPPORT CELLULAR TRANSFORMATION AND TUMORIGENICITY
Time and location: **2:00pm** PDT; Room 203 of the Graduate Student Centre (6371 Crescent Road), UBC Vancouver Point Grey Campus
Supervisor: Dr. Poul Sorensen

ABSTRACT

Activating mutations in *KRAS* are found in ~90% of pancreatic cancers, ~40% of colorectal cancers, and ~30% of non-small cell lung cancers. To date no effective therapies exist for cancer patients of this genetic subset, driving an impetus to develop novel therapeutic agents that target KRAS or downstream effectors of KRAS. The impact of oncogenic KRAS on the intracellular redox balance and its contribution to tumorigenicity is still controversial. Many studies have reported that oncogenic RAS enhances intracellular reactive oxygen species (ROS) levels, while recent major work by several groups described that oncogenic RAS drives antioxidant programs, which are necessary to mediate tumorigenicity. It is therefore critical to further explore the role of oncogenic KRAS on redox balance and its impact on cellular transformation and tumorigenicity.
To this end, I utilized whole transcriptome profiling in normal and oncogenic KRAS-transformed cells to identify redox pathways regulated by oncogenic KRAS to support tumorigenicity. Whole transcriptome analysis revealed that the Cystine/Glutamate Transporter, *xCT* had the highest positive fold change in KRAS-transformed cells in response to exogenous oxidative stress. xCT is responsible for the cellular uptake of cystine, the rate-limiting precursor in the synthesis of glutathione (GSH), which is the major intracellular antioxidant. As such, I postulated that oncogenic KRAS signaling promotes transcriptional upregulation of xCT to support cellular transformation and tumorigenicity by preventing oxidative stress. Notably, inhibition of xCT in KRAS-transformed cells exacerbates oxidative stress causing cell death and also impaired cellular transformation and tumorigenicity, providing the first evidence that xCT is a downstream effector of oncogenic KRAS signaling. In addition, I found clinical evidence for the upregulation of xCT in subsets of cancer with activating mutations in KRAS and for the association of high xCT expression with poorer patient outcome. Finally, I delineated a novel mechanism of xCT activation involving the cooperative interaction between ETS1, which lies downstream of the RAS-MAPK signaling cascade, and ATF4, a known regulator of xCT. Overall, my findings demonstrate that oncogenic KRAS signaling modulates cellular redox balance by upregulating xCT expression to promote transformation and tumorigenicity.