PhD DEFENCE – Tuesday, March 31st, 2015
Student: Melissa McConechy
Title: ***PPP2R1A* MUTATIONS IN GYNAECOLOGIC CANCERS: FUNCTIONAL CHARACTERIZATION AND USE IN THE GENOMIC CLASSIFICATION OF TUMOURS**
Time and Location: ***9:00am, Room 9299, Gordon and Leslie Diamond Health Care Centre, 2775 Laurel Street.***
Supervisor: Dr. David Huntsman

ABSTRACT
Endometrial carcinoma is the most common gynaecological cancer in developed countries, and ovarian cancer is the most lethal. The current pathologic classification system lacks reproducibility, which has hampered the development of new treatment approaches for this cancer.

Objectives: To determine the role of somatic *PPP2R1A* mutations in subtype specific classification of gynaecological tumours. In addition, mutational profiles from multiple genes will be used to improve subtype classification of endometrial carcinomas. Lastly, the functional effect of a *PPP2R1A* mutation on PP2A subunit interactions will be determined, in the context of endometrial cancer cell lines.

Methods: Next-generation sequencing and Sanger sequencing was used to determine the presence of mutations in endometrial and ovarian carcinomas. PPP2R1A isogenic endometrial specific cell lines were generated using somatic cell gene knockout by homologous recombination. Co-immunoprecipitation coupled to mass spectrometry was used to determine the effects of the PPP2R1A W257L mutation on the ability to interact with PP2A subunits.

Results: Subtype-specific somatic *PPP2R1A* mutations were identified in endometrial serous carcinomas. Low-grade endometrial endometrioid carcinomas were defined by mutations in the genes: *ARID1A, PTEN, PIK3CA, CTNNB1*, and *KRAS*, whereas high-grade endometrioid also harbor *TP53* mutations. Endometrial serous carcinomas harbor mutations in *PPP2R1A, FBXW7, PIK3CA* and *TP53*. Consequently, the molecular profiles proved useful in assisting classification of seven tumours with overlapping morphological features that cause irreproducibility in diagnoses. Proteomic analysis of the isogenic cell lines determined that the PPP2R1A W257L mutation disrupts the interaction with PPP2R5C and PPP2R5D B subunits. In addition, PPP2R1A mutated protein caused an increased interaction with the endogenous PP2A inhibitor SET/I2PP2A.

Conclusions: The integration of mutational profiles and other genomic features will be used to improve clinical and pathological classification in endometrial tumours that are difficult to diagnose. *PPP2R1A* mutations are likely playing an important role in the transformation of gynaecological carcinoma, by disrupting PP2A subunit interactions with tumour suppressor functions. Increased interaction of mutant PPP2R1A with SET/I2PP2A adds another layer of complexity to the tumour suppressive role of PP2A. In the future, targeting the PP2A complex with novel therapeutics could provide an alternative method for treating these gyneacological cancers with poor outcomes.