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**PhD DEFENCE Wednesday, August 10th, 2016**

**Student:** Ada Leung

**Title:** IMPROVING PLATINUM-BASED TREATMENTS FOR ADVANCED NON-SMALL CELL LUNG CANCER

**Time and location:** 9:00am PDT, Room 200 of the Graduate Student Centre (6371 Crescent Road), UBC Vancouver Point Grey Campus

**Supervisor:** Marcel Bally

## **ABSTRACT**

Novel treatments are urgently needed for patients with non-small cell lung cancer (NSCLC). Currently, these patients are almost always first treated with cisplatin (CDDP)-containing drug combinations. In an effort to identify therapeutic targets that could enhance CDDP activity, a genome-wide siRNA screen looking for synthetic lethal partners with low-dose CDDP was completed. These data were combined with results from a microarray study assessing differentially expressed genes in NSCLC cells exposed to low-dose CDDP. The results indicated that 151 genes were differentially expressed in cells exposed to low-dose CDDP. Nine up-regulated genes ranked within the top 10% of the siRNA screen based on a scoring method that considered minimal loss of cell viability from gene knockdown alone and significant enhancement of CDDP activity. Five genes were further validated and two (*RRM2B* and *CABYR*) were found to significantly improve CDDP activity. Pathways involved in repairing double-stranded DNA breaks and INO80 chromatin remodeling were enriched in both datasets. Analysis of the kinome subset of the siRNA screen also identified PAPSS1 (3'-phosphoadenosine 5'-phosphosulfate synthase 1) as a protein that when silenced sensitized NSCLC cells to CDDP. PAPSS1 produces the biologically active form of sulfate for sulfonation reactions. PAPSS1-silencing combined with low-dose CDDP reduced the clonogenicity of NSCLC cells by 98.7%, increased DNA damage, and induced G1/S phase cell cycle arrest. PAPSS1 suppression also sensitized NSCLC cells to radiation and topoisomerase I inhibitors. Sensitization was cancer cell specific. The extent of CDDP potentiation increased substantially when NSCLC cells were stressed by starvation or hypoxia. In NSCLC cell spheroids and zebrafish xenografts, PAPSS1 silencing in combination with CDDP decreased tumor size, while the same dose of CDDP combined with non-silencing controls led to increases in tumor size. In a subcutaneous tumour model, expression of PAPSS1-targeting shRNA in combination with a non-curative dose of CDDP enhanced activity compared to controls. Future studies are needed to identify small molecule inhibitors and proteins that interact with PAPSS1. These tools will be useful to fully understand the mechanisms by which chemosensitization occurs and such tool compounds may prove useful as therapeutics that would benefit NSCLC patients when first treated.