Bladder cancer is one of the most aggressive malignancies and chemotherapy is an effective strategy for its treatment. Cisplatin is widely used to treat bladder cancer; however, the usage of cisplatin as an effective cancer treatment has been limited due to toxicity and developed drug resistance in cancer cells. To overcome the problem of resistance to Cisplatin, other drugs that induce chemosensitization in cancer cells are utilized. ATM, which is a key factor in genome integrity by activating cell cycle checkpoints is beneficial to normal cells because of its role in the DNA damage response, so its inhibitor KU55933 can inhibit cancer cell proliferation and prevent them from surviving metastasis. Due to its dual nature of being a cancer promoter and suppressor, AMPK activation can confer on cancer cells the plasticity to survive under metabolic stress such as hypoxia. However, AMPK inhibitor Compound C can work against the acquired resistance from tissue biopsies of patients with bladder cancer. These cells are cultured in vitro. Four 12-well plates were used to house all of the T24 and UMUC3 cells, 2 plates for T24 and 2 for UMUC3. Each well is seeded at 0.15 million cells.

Cell viability analysis: In the T24 experiment, two 12-well plates were used with 0.15 million cells per microliter - 3 wells were untreated and this will be used as the control group. 3 wells were treated with 10μM of Cisplatin, 3 wells were treated with 5μM of KU55933, 3 wells had 5μM of Compound C, 3 wells had a combination of 5μM of KU55933 and 10μM of Cisplatin, and the final 3 wells are treated with the combination of 5μM of Compound C and 10μM of Cisplatin.

The results indicated that untreated cancer cells continue to proliferate and more than doubled in count from the initial cell count of 15 million/mL. Cisplatin, when used alone, almost halved the amount of cells compared to the untreated cancer cells, however the cancer cells continue to proliferate. This could be an indication that cells likely developed resistance to Cisplatin. Similarly, the inhibitors, KU55933 and Compound C, when used alone caused minimal impact on stopping the cell proliferation. On the other hand, Cisplatin used in combination with either of the inhibitors significantly reduced the viability of T24 and UMUC3 cells. No significant differences were observed when using the ATM inhibitor, KU-55933, the AMPK inhibitor Compound C, along with Cisplatin. In addition, both cell lines, T24 and UMUC3, respond similarly to Cisplatin, KU55933, and Compound C treatments.

ATM, or Ataxia-Telangiectasia Mutated Kinase, is responsible for the genome stability as it initiates and coordinates the DNA-damage response. It phosphorylates many protein kinases that play a part in DNA damage response (DDR) or that arrest the cell cycle when the cells don’t divide with damaged DNA. ATM has the ability to modulate oxidative stress responses and maintain mitochondria homeostasis. ATM mutation or loss of ATM function in cancer stem cells survive by promoting the autophagic flux and ATM kinase activity is enhanced in some tumors. ATM inhibitor KU-55933 inhibits cancer cell proliferation by inducing apoptosis by triggering G1 cell cycle arrest. KU55933, also causes cellular radio and chemosensitization, making it an excellent combination to be used with other chemotherapeutic drugs.

Finally, kinase inhibitors like KU55933 and Compound C promote chemosensitization, a process in which a drug is used to enhance the activity of another selectively in the tumor cells, while limiting antitumor toxicity or side effects. This research aims to test the ability of each of these pharmacological compounds to stop the proliferation of T24 and UMUC3 urinary bladder cancer cells by themselves, and then test the effectiveness of Cisplatin when used in combination with ATM-inhibitor KU55933 and AMPK-inhibitor Compound C.