University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Master of Science

of

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BSc (University of Victoria, 2017)

"Modulation of Nanoparticle Uptake, Intracellular Distribution, and Retention with Docetaxel to Enhance Radiotherapy"

Department of Physics and Astronomy

Friday, November 1, 2019
10:00 A.M.
Elliott Building
Room 503

Supervisory Committee:
Dr. Devika Chithrani, Department of Physics and Astronomy, University of Victoria (Supervisor)
Dr. Isabelle Gagne, Department of Physics and Astronomy, UVic (Member)
Dr. Cornelia Hoehr, Department of Physics and Astronomy, UVic (Member)

External Examiner:
Dr. Mohsen Akbari, Department of Mechanical Engineering, UVic

Chair of Oral Examination:
Dr. Marty Wall, Department of Educational Psychology and Leadership Studies, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

OBJECTIVE: One of the major issues in current radiotherapy (RT) is the normal tissue toxicity. A smart combination of agents within the tumor would allow lowering the RT dose required while minimizing the damage to healthy tissue surrounding the tumor. We chose gold nanoparticles (GNPs) and docetaxel (DTX) as our choice of two radiosensitizing agents. They have a different mechanism of action which could lead to synergistic effect. Our first goal was to assess the variation in GNP uptake, distribution, and retention in the presence of DTX. Our second goal was to assess the therapeutic results of the triple combination, RT/GNPs/DTX.

METHODS: We used HeLa and MDA-MB-231 cells for our study. Cells were incubated with GNPs (0.2nM) in the absence and presence of DTX (50nM) for 24 hrs for determination of uptake, distribution, and retention of NPs. For RT experiment, treated cells were given a 2 Gy dose of 6 MV photons using a linear accelerator.

RESULTS: Concurrent treatment of DTX and GNPs resulted in over 85% retention of GNPs in tumor cells. DTX treatment also forced GNPs to be closer to the most important target, the nucleus, resulting in a significant decrease in cell survival with the triple combination of RT, GNPs, and DTX vs. RT plus DTX alone. Our experimental therapeutics results are supported by Monte Carlo simulations.

CONCLUSION: The ability to not only trap GNPs at clinically feasible doses but also to retain them within the cells could lead to meaningful fractionated treatments in future combined cancer therapy. Furthermore, the suggested triple combination of RT/GNPs/DTX may allow lowering the RT dose to spare surrounding healthy tissue.

ADVANCES IN KNOWLEDGE: This is the first study to show intracellular GNP transport disruption by DTX, and its advantage in radiosensitization.

KEYWORDS: Gold nanoparticles, Docetaxel, endocytosis, exocytosis, microtubules, tumor cells, cell cycle