Utilization of Nanotechnology and Chemotherapeutics to Increase Radiosensitivity of Cancer Cells

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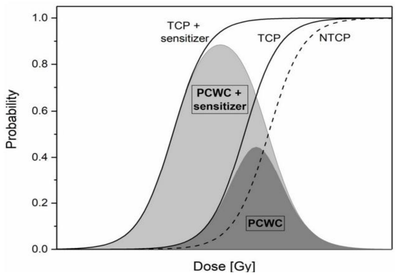
Introduction & Hypothesis

Limitations of Radiotherapy



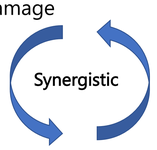
- Probability of Cure Without Complication (PCWC)
- Tumour Control Probability (TCP, Solid Line)
- Normal Tissue Complication Probability (NTCP, Dashed Line)

The efficacy of radiotherapy is currently limited due to the normal tissue toxicity induced during treatment, thus increasing the radiation response in tumours is essential to improve curative results for radiotherapy.

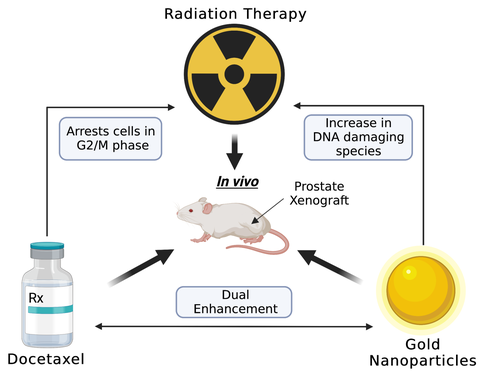
Proposed Strategy

We propose introducing docetaxel (DTX), a chemotherapeutic drug, to complement gold nanoparticle (GNP) enhanced radiotherapy (RT) to generate a better therapeutic outcome.

Incident radiation interacts with GNPs resulting in a shower of secondary electrons that inflict DNA damage



Docetaxel arrests cells in the G2/M phase of the cell cycle, the phase most sensitive to radiation damage

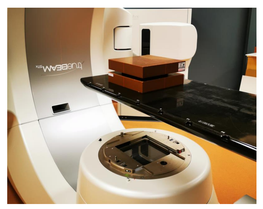


Hypothesis

The addition of docetaxel and gold nanoparticles will make cancer cells more susceptible to radiation damage. This will result in an increase in the radiotherapeutic effect exhibited in cells post irradiation.

Materials & Methods

- Animal Model: Human prostate cancer PC-3 cell line xenograft mice model was used.
- Mice were dosed with GNPs at a concentration of 2 mg/kg 24 h prior to downstream applications
- Mice were dosed with docetaxel at a concentration of 6 mg/kg 24 h prior to radiation treatment
- A dose of 5 Gy was delivered to mice using a clinical 6 MV linear accelerator for radiation assays



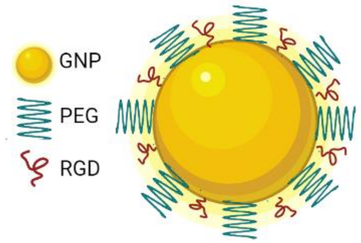
BC Cancer Linear Accelerator

Acknowledgements

UTHealth Houston, BC Cancer, University of Victoria, NSERC CRSNG, NMIN, Mitacs

Results

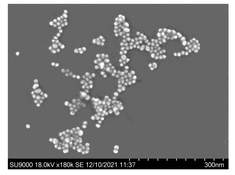
Gold Nanoparticle Functionalization & Characterization



- GNPs were functionalized with polyethylene glycol (PEG) and a RGD peptide
- PEG increases the circulation time for GNPs and also provides stability for conjugation with RGD
- RGD facilitates greater uptake in cancer cells since many overexpress integrins

Complex	Peak Wavelength (nm)	Hydrodynamic Diameter (nm)	Zeta Potential (mV)
GNP	518.6	15.53 ± 0.02	-39.2 ± 2.8
GNP + PEG	519.4	22.08 ± 0.12	-7.1 ± 1.5
GNP + PEG/RGD	521.0	24.34 ± 0.07	-1.1 ± 0.5

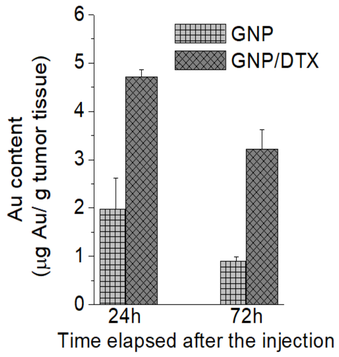
GNP Characterization Table

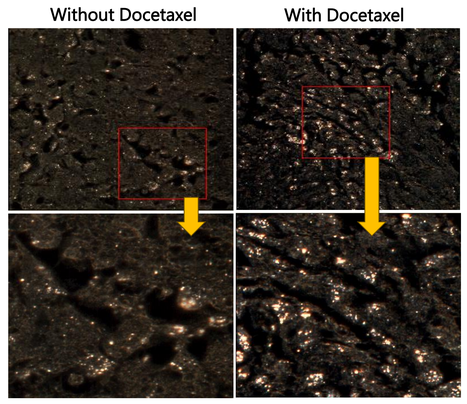


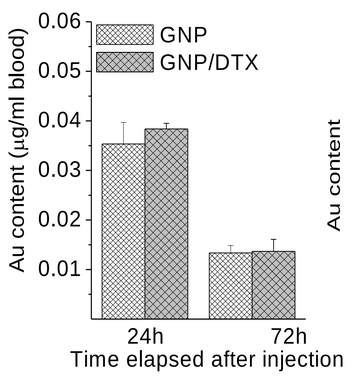
GNP TEM Image

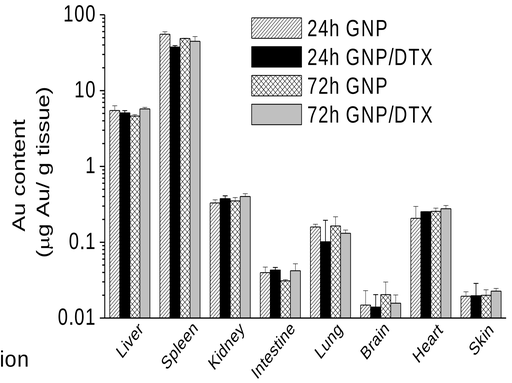
Characterization measurements were made at each step of the functionalization process. The shift in the values indicates successful conjugation of the GNPs with the ligands. Transmission electron microscopy (TEM) images were taken to verify size of GNPs.

Gold Nanoparticle Uptake



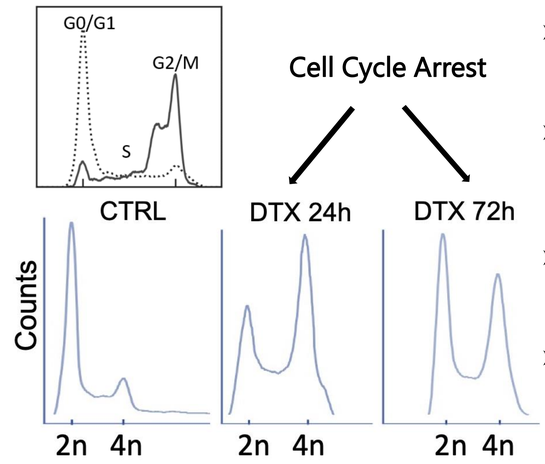






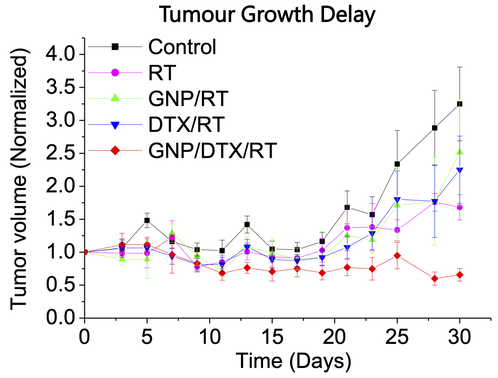
Results cont.

Cell Cycle Analysis



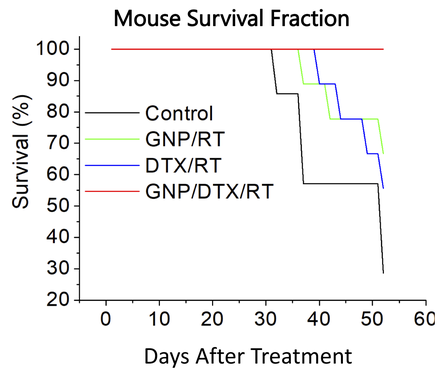
- Cell cycle analysis of mouse tumour tissue cell population
- 2n represents G0/G1 phase, 4n represent G2/M phase
- DTX caused an increase in the population of cells in the G2/M phase
- Maximum arrest was observed 24 hours after treatment with DTX

Radiation Efficacy Results



- 24 hours after mice received injections of GNPs and DTX, mice were irradiated at a dose of 5 Gy
- Significant reduction in tumour growth was observed for the GNP/DTX/RT treatment arm vs RT ($p = 0.02$)

- Mice were euthanized at 20% body weight loss, excessive clinical observations, or the experimental endpoint of the tumour volume reaching 1000 mm^3.
- Radiation results suggest that the combination of DTX, GNPs, and RT could result in better tumour control for patients



Conclusions

- Our results show that the synergistic combination of using DTX and GNPs can increase the radiotherapeutic effect experienced by cancer cells
- Our future goal is to deliver our treatment strategy using lipid nanoparticles as a delivery mechanism