BSc , MSc, Ph.D.

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Radiosensitizing Prostate Cancer Through the Simultaneous Administration of Gold Nanoparticles and Chemotherapeutics

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Abstract

Purpose: Radiotherapy with a 6 MV linear accelerator is extensively employed in cancer treatment, particularly for targeting deep-seated tumors. In our work, we have focused on maximizing the dose that can be safely delivered to patients. Our primary goal is to optimize the radiation dose by combining it with radiosensitizing agents that have complementary effects. This approach aims to enhance the effectiveness of radiotherapy, allowing for increased doses to the tumor while minimizing the risk of additional side effects

Methods: A battery of assays were performed on human PC3 and LNCaP prostate cancer cell lines in vitro. GNP uptake and retention of was measured using inductively coupled plasma mass spectrometry. Cell cycles were then analyzed using Flow Cytometry. DNA double strand break (DSB) assays quantified DNA damage enhancement. All assays included testing control, GNP-only, chemotherapy-only, and combined GNP + chemotherapy.

Results: Adding a chemotherapy drug increased GNP uptake by 34% and retention by 148%. Live-cell confocal images of drug-treated cells showed microtubule stabilization and multinucleation, markers for cellular arrest in the radiosensitive G2/M phase of the cell-cycle. This result was confirmed by Flow Cytometry, which found a larger cell population in the G2/M phase at the 24 h timepoint for cells that had been treated with chemotherapy. Finally, a 50% increase in the number of DNA DSBs was observed for combined GNP + chemotherapy treatments.

Conclusions: The combined administration of chemotherapy and GNPs enhances the radiosensitivity of cancer cells by promoting increased uptake and retention, inducing cell cycle arrest in the radiosensitive, G2/M phase, and leading to cell death. The synergistic effect of GNPs and chemotherapeutic agents holds significant promise for significantly improving the effectiveness of radiation therapy. Future research will focus on identifying the most effective combination treatment strategies to optimize therapeutic outcomes.

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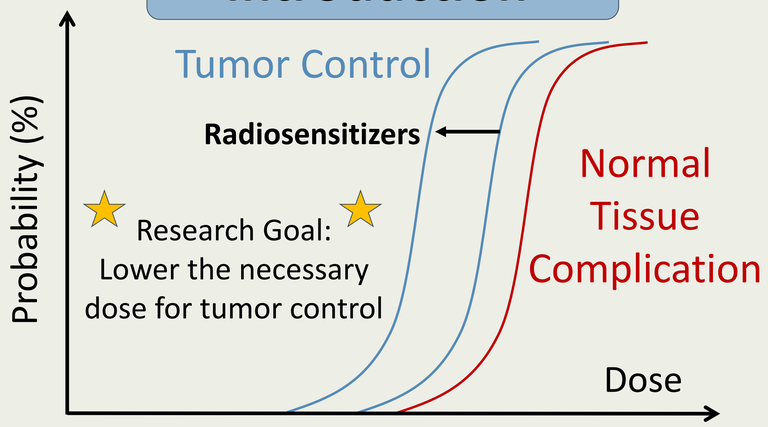
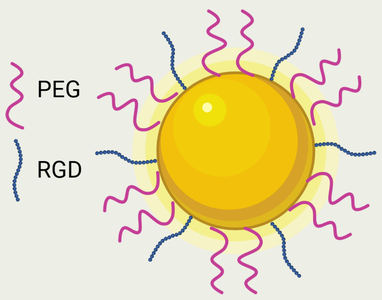
Introduction



The efficacy of radiation therapy (RT) is fundamentally limited by normal tissue toxicity surrounding the tumor.



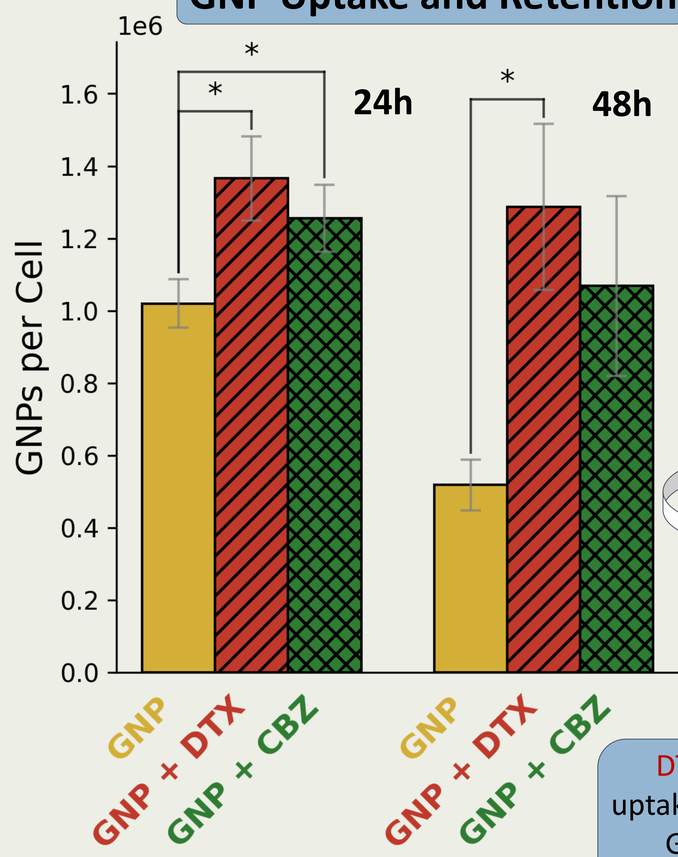
- Gold nanoparticles (GNPs) provide a physical dose enhancement to RT.
- Gold's **high atomic number** (Z=79) interacts strongly via the photoelectric effect, generating a cascade of short-range secondary electrons that deposit their dose locally[1].

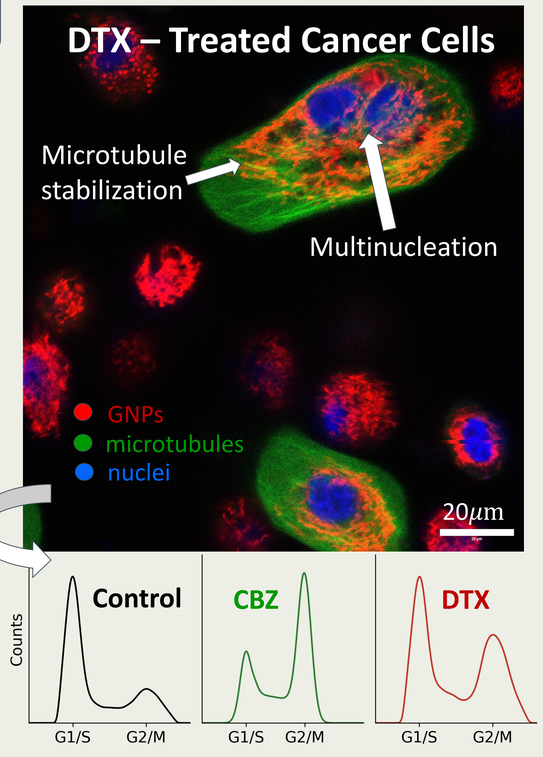
Docetaxel (DTX)
Cabazitaxel (CBZ)

- DTX and CBZ are taxane chemotherapeutics already used to treat prostate cancer.
- By binding to microtubule subunits, they promote polymerization and prevent disassembly, arresting cells in the **radiosensitive G2/M phase**[2].

A **synergy** between GNPs and DTX/CBZ exists whereby cells treated with drug **retain** GNPs for much longer than untreated cells. Through this mechanism we may achieve maximal radiosensitization.

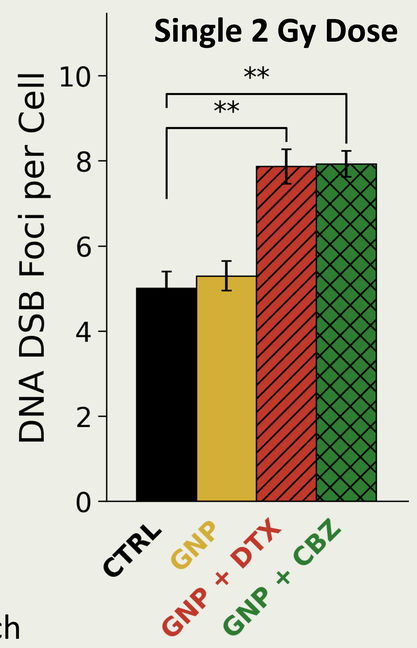
GNP Uptake and Retention

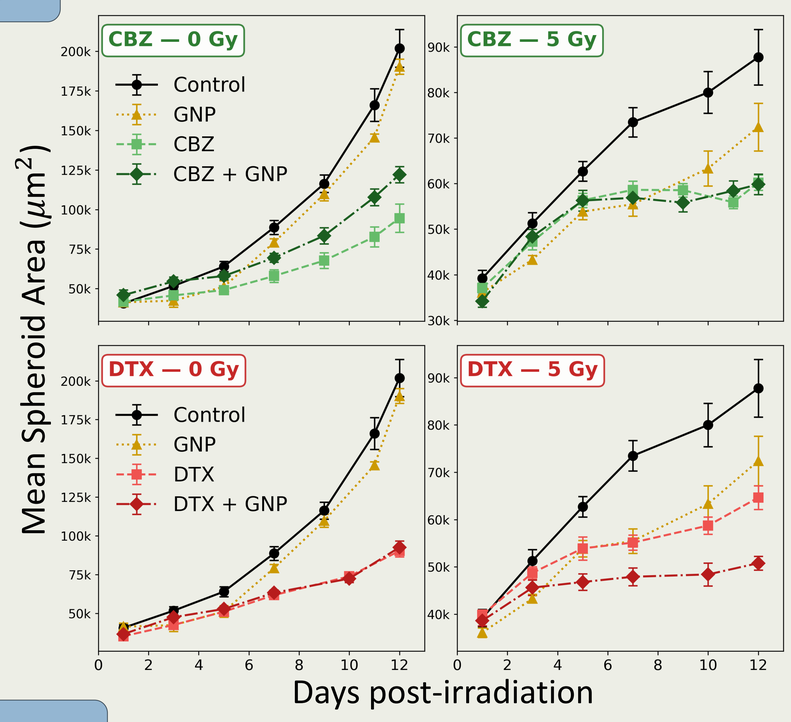




DTX, CBZ significantly enhance the 24h uptake and 48h retention of GNPs and induce G2/M phase cell cycle arrest. This is a **practical benefit for fractionated** treatments.

Radiation Assays





Conclusions

- DTX is a promising radiosensitizing agent when administered in conjunction with GNPs.
- CBZ performed similarly to DTX in monolayer across all assays.
- In spheroids, differences between the RT/GNP/CBZ and RT/GNP/DTX treatment arms may be caused by differential in drug lipophilicity[3] (penetration kinetics).

- DTX, CBZ both further enhanced radiosensitization compared to GNP monotherapy.
- In spheroid models, combined GNP + DTX treatment outperformed GNP + CBZ, indicating **DTX benefits more from the addition of GNPs** in the context of RT.

Methods

1. **Cell monolayer assays**: Confocal live-cell imaging, darkfield imaging, inductively coupled plasma mass spectrometry (ICPMS), DNA double strand break assay (radiation; 2Gy), clonogenic assay (radiation; 0,2,4,6,8 Gy) in PC-3, LNCaP prostate cancer cell lines.

2. **Tumor Spheroid Growth Assay** (PC-3 cells)

References

1. Chithrani et al., 2010 — *Radiat Res* 173(6):719-728
2. Paoletti et al., 1997 — *J Cell Sci* 110(19):2403-2415
3. Kyle et al., 2007 — *Clin Cancer Res* 13(9):2804-2810