Cancer nanomedicine: combination of gold nanoparticles with DNA repair inhibitor drugs to improve radiotherapy

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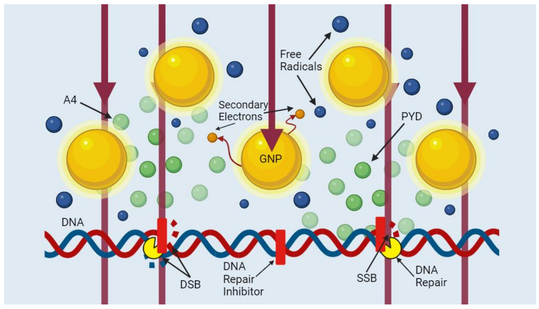
Introduction & Hypothesis

Purpose

Radiation therapy (RT) is one of the major modalities used to treat more than 50% of cancer patients. One of the current challenges of RT is normal tissue toxicity.



Introducing radiosensitizing agents, such as gold nanoparticles (GNPs), will increase the local dose to the tumour, in turn decreasing the overall dose to the surrounding normal tissue.

Hypothesis

Incorporating DNA repair inhibitor drugs, pyronaridine and A4, with GNPs will inhibit the mechanism of DNA repair from the GNP-induced damage post-irradiation. This will lead to an increase in DNA damage to cancerous cells.

Materials & Methods

- GNPs were synthesized and functionalized with PEG and RGD.
- Cervical cancer cell line (HeLa) and human colorectal carcinoma cell line (HCT-116) were cultured.
- Cells were dosed with 7.5 µg/mL of GNPs and 500 nM of DNA repair inhibitor drugs, pyronaridine and A4.
- Cells were irradiated using a clinical linear accelerator at 6 MV with a dose of 2 Gy.
- Intracellular uptake, cellular proliferation, and DNA double-strand break (DNA DSB) damage were quantified.

Acknowledgements

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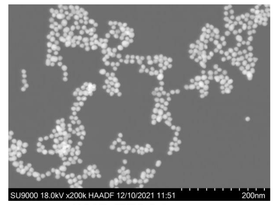
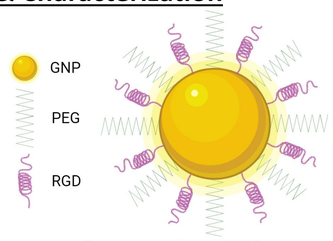
Results

GNP Functionalization & Characterization

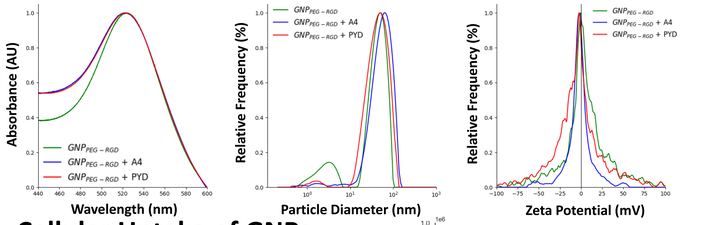


GNP TEM Image



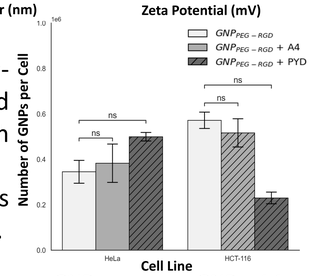
Functionalized GNP

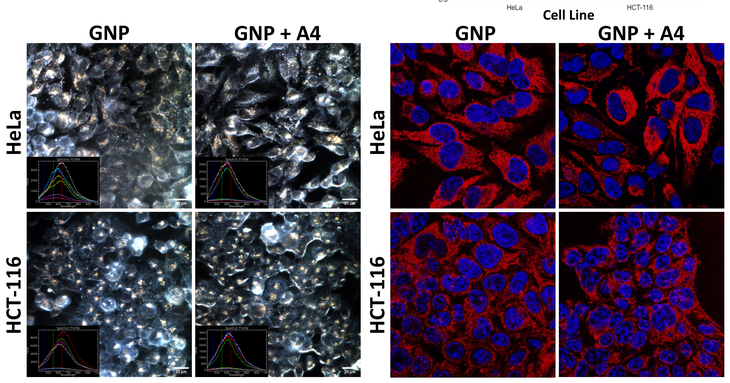
Polyethylene glycol (PEG) and an integrin-binding domain RGD were used to increase circulation time and enhance cellular uptake into cancerous cells, respectively. The characterization measurements estimated the size and concentration, and the hydrodynamic diameter and the surface charge of the GNPs.



Cellular Uptake of GNPs

- Inductively coupled plasma-mass spectrometry quantified the uptake of GNPs with pyronaridine and A4 in cells.
- No significant difference was measured between conditions.

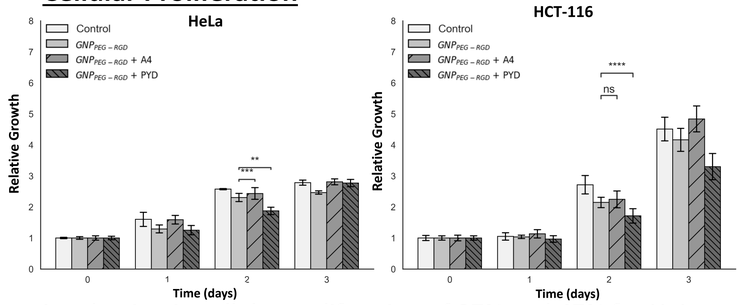




- Hyperspectral and live cell images visualized the intracellular uptake of GNPs in cancerous cells. The scale for all images is 20 µm.
- In the live cell images, the blue and red stains represent the nuclei and GNP clusters, respectively.

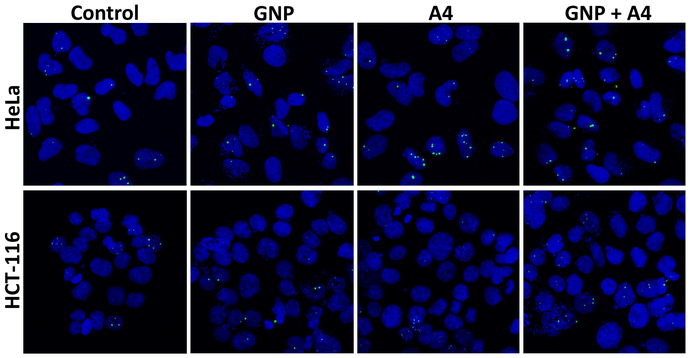
Results

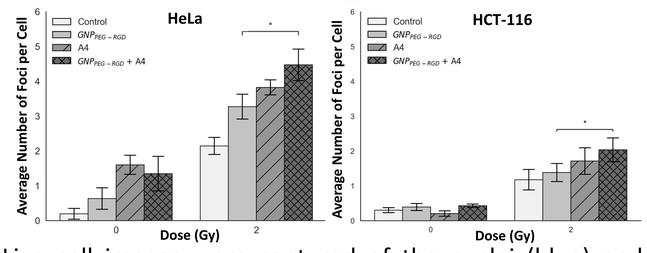
Cellular Proliferation



A reduction in cellular proliferation of 37% and 47% for HeLa and HCT-116 irradiated cells, respectively, with the combined treatment of RT, GNP, and DNA repair inhibitor drugs was demonstrated.

DNA Double-strand Break (DNA DSB) Damage





Live cell images were captured of the nuclei (blue) and a DNA repair protein, 53BP1, marked in green. Quantification of the live cell images showed an enhancement in DNA DSBs of 40% and 46% in HeLa and HCT-116 cells, respectively.

Conclusions

Our results show that the combined treatment with GNPs and DNA repair inhibitor drugs, pyronaridine and A4, demonstrates strong potential in further enhancing the effects of gold-mediated therapy. This will lead to reducing the overall dose delivered to normal tissue.