Lipid Nanoparticle Mediated Delivery of Docetaxel Prodrug for Exploiting Full Potential of Gold Radiosensitizers in the Treatment of Pancreatic Cancer

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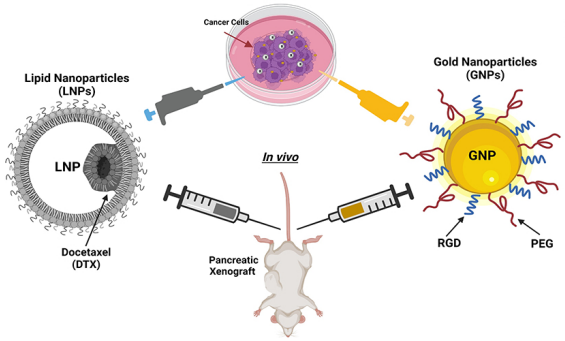
PURPOSE / HYPOTHESIS

- **Purpose:** Pancreatic cancer is one of the leading causes of cancer deaths worldwide. Current chemoradiation therapy suffers from normal tissue toxicity. We are proposing incorporating nanoparticles as radiosensitizers and as drug delivery vehicles to improve current chemoradiation treatments. Gold nanoparticles (GNPs) and Docetaxel (DTX) have shown very promising synergetic radiosensitization effects despite DTX toxicity to normal tissues. In this experiment, we explored the effect of the less toxic DTX prodrug encapsulated in lipid nanoparticles (LNP$_{DTX-P}$) on GNP uptake in pancreatic cancer models *in vitro* and *in vivo*.
- **Hypothesis:** LNP$_{DTX-P}$ will result in a significant increase in uptake and retention of GNPs in tumour tissue compared to control samples. This would allow the use LNP$_{DTX-P}$ as a substitute to the more toxic free DTX.

MATERIAL & METHODS

- **Set-up**: For *in vitro*: MIA PaCa-2 culture, for *in vivo:* MIA PaCa-2 implanted subcutaneously in NRG mice.
- **Radiosensitizers:** Gold nanoparticles (GNPs) of ~ 11 nm in diameter functionalized with PEG and RGD peptide.
- **Drug:** Free DTX vs 2 formulas of LNPs delivering prodrug DTX.
- **Dosing**: For *in vitro:* 7.5 µg/mL of GNPs and IC-50 dose of free DTX or equivalent dose of LNP$_{DTX-P}$. For *in vivo:* 2 mg/kg of GNPs and 6 mg/kg for DTX or equivalent dose of LNP$_{DTX-P}$.



RESULTS

- LNP$_{DTX-P}$ treated tumour samples have over %191 the amount of GNP uptake in both *in vitro* and *in vivo* models compared to control samples.
- LNP$_{DTX-P}$ treated tumour samples have retained over %188 GNP uptake *in vitro* and over %160 *in vivo* models compared to control samples.
- No significant difference was found in GNP uptake or retention between free DTX and LNP$_{DTX-P}$ in tumour treated samples *in vivo*.

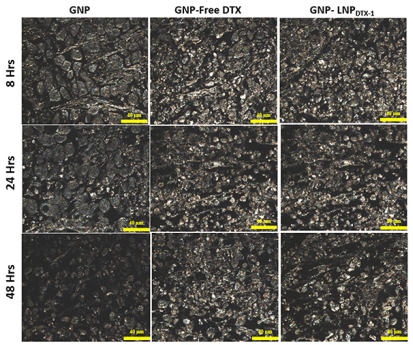


Figure 1. Effects of free DTX vs LNP$_{DTX-P}$ on *in vivo* tumour tissues. Darkfield images of 4 µm sections of untreated tumour tissues, tissues treated with free DTX, and tissues treated with LNP$_{DTX-1}$. The increase in GNP uptake and retention is visually evident in treated samples and have been verified quantitively using ICP-MS. Scale bar: 40 µm.

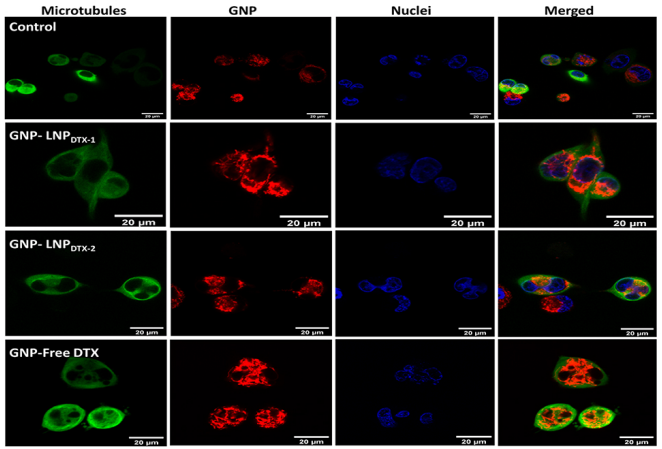


Figure 2. Visualization of intracellular GNP distribution in MIA PaCa-2 cells using confocal imaging. Control untreated cells (1st row), cells treated with LNP$_{DTX-1}$ (2nd row), cells treated with LNP$_{DTX-2}$ (3rd row), and cells treated with free DTX (4th row). Microtubules in green (1st column), GNPs in red (2nd column), nuclei in blue (3rd column), and all three merged (4th column). Scale bar: 20 µm.

CONCLUSIONS

- The uptake and retention of GNPs *in vitro* and *in vivo* was measured, using MIA PaCa-2 cells, following treatment with free DTX vs LNP$_{DTX-P}$.
- The addition LNP$_{DTX-P}$ displayed significant increase in GNPs uptake relative to control samples in both *in vitro* and *in vivo,* with LNP$_{DTX-P}$ displaying similar cancer toxicity when compared to free DTX.
- Because of their tumor targeting properties and minimal toxicity to normal tissues, both GNPs and LNP$_{DTX-P}$ can be ideal radiosensitization candidates in radiotherapy and would produce promising synergistic therapeutic outcome.

ACKNOWLEDGEMENT & FUNDING

The authors would like to acknowledge the support from University of British Columbia, BC Cancer (Vancouver & Victoria) & Integrated Nanotherapeutics Inc.

Funding: Kuwait Foundation for the Advancement of Sciences (KFAS) under project code CB21-63SP-01, Nanomedicines Innovation Network Strategic Initiative fund (NMIN-SI) from government of Canada, the John R. Evans Leaders Fund (JELF) from the Canada Foundation for Innovation (CFI) and British Columbia Knowledge Development Fund (BCKDF), the NSERC Discovery grant from the Natural Sciences and Engineering Research Council of Canada (NSERC), grants code R01CA257241, R01DE028105, R21CA252156 and R01CA274415 from the National Institutes of Health (NIH) of United States of America, and a collaborative health grant from the University of Victoria.