Abstract for: 2014 AIChE Conference, Atlanta, GA, November 16 – 21, 2014

Tumor-Penetrating Nanoparticles Capable of Tandem Delivery of Agents for the Treatment of Lung Cancer

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The overall survival rate for patients with lung cancer is still low and many affected patients are ineligible for current first-line treatments (surgery, chemotherapy, and radiation) for non-small cell lung cancer (NSCLC) due to severe side effects. Paclitaxel (PTX) along with doxorubicin (DOX) are current first-line therapies for most types of NSCLC. In the descried research, these drugs have been encapsulated in tumor-penetrating polymeric nanoparticles (NPs) for application in the treatment of lung cancer. Due to the limitations in NP systems where particles are often unable to penetrate into the tumor parenchyma to deliver its dose of drug, little has been seen in terms of an increase in clinical outcome for cancer patients treated with such systems. Therefore, there is an imperative need for the development of system capable of tumor penetration. Our aim was to develop and optimize peptide-conjugated polymer nanoparticles to tandem anticancer agents capable of enhancing the targeting and treatment of NSCLC. Acetalated dextran (Ac-Dex) was used to encapsulate both PTX and DOX in NPs, which in turn were conjugated with the tumor-penetrating peptide iRGD.

Ac-Dex was synthesized using dextran (9,000 - 11,000 MW), pyridinium p-toluenesulfonate, anhydrous DMSO, 2-methyoxypropene, and triethylamine. H-NMR data showed the cyclic acetal coverage (CAC) to be 60%, which was similar to previously reported results. PTX and DOX Ac-DEX nanoparticles were synthesized by single and double emulsion methods, respectively. Dynamic light scattering (DLS) and SEM images showed that the nanoparticles ranged from 200 to 360 nm in diameter. The drug loading for 0.1% PTX and 2% DOX-loaded Ac-DEX nanoparticles were 50% and 30%, respectively. PTX was successfully released in a controlled manner after an initial burst release and DOX release studies are underway. *In vitro* analysis of the nanoparticles demonstrated their ability to effectively kill both 2D A549 lung cancer cells and 3D tumor spheroids. Nanoparticle penetration into the spheroids was confirmed by confocal microscopy.

This multifunctional particle not only releases PTX and DOX in tandem, but is capable of tumor penetration through a mechanism imparted by the peptide. The parameters of the emulsion-based NP system (size, shape, drug loading, peptide-conjugation, cytotoxicity, penetration into NSCLC tumor spheroids, etc.) have been optimized to ensure effective targeting and delivery.

Submitted to: Nanoscale Science and Engineering Forum(22)-Bionanotechnology(22B)