Development of a polyamine-based gemcitabine nanocarrier for the treatment of pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains a major contributor to cancer-related mortality, ranking as the fourth leading cause of cancer-related deaths in 2020. Gemcitabine is the gold standard for the treatment of advanced-stage PDAC; however, its clinical efficacy is hindered by chemoresistance resulting from the rapid enzymatic deamination of the drug to the inactive metabolite, 2',2'difluorodeoxyuridine, (dFdU). Higher doses of gemcitabine (1000 mg/m^2) are administered to overcome this, often resulting in several severe side effects.

In this study, we present a novel approach to enhance the efficacy of gemcitabine and reduce side effects for PDAC therapy by chemically modifying the drug through amide conjugation with spermine. This new compound (GemSper) offers the potential to overcome chemoresistance barriers.

GemSper is noncovalently conjugated to hybrid gold-iron oxide nanoparticles (HNP) for targeted delivery, exploiting the electrostatic attraction between the negatively charged gold surfaces and cationic spermine.

Methods: Iron oxide-gold nanoparticles were synthesised in a two-step process: precipitation of iron salts at 90°C and capping of magnetic iron oxide nanoparticles with poly(ethyleneimine) (PEI) and subsequent reduction of gold(III) chloride. The physicochemical properties of the nanoparticles were determined using photon correlation spectroscopy (PCS), zeta potential measurements, and inductively coupled plasma-optical emission spectroscopy (ICP-OES). Conjugation of gemcitabine to spermine was via an amide linker at the N4 position of gemcitabine. The structure of the synthesised compound was confirmed using proton nuclear magnetic resonance spectroscopy (1H NMR), Fourier Transform Infrared Spectroscopy (FTIR) and liquid chromatography-mass spectrometry (LCMS). Cytotoxicity of the drug nanoparticle formulation on BxPC-3 pancreatic cancer cell lines was evaluated using MTT.

Results: Hybrid iron oxide-gold nanoparticles (zeta potential = +31.8 mV; size = 100 - 150 nm; Polydispersity Index, PdI = 0.36) were successfully synthesised. The synthesised GemSper molecules could attach to the surfaces of the nanoparticles via electrostatic interactions between the positive amines on the spermine backbone and the negative gold seeds on the HNPs. These interactions were more pronounced in slightly acidic pH due to the activation of the amine groups on protonation. The drug loading capacity of the nanoparticles for GemSper was 71.67% at pH 6.4, 64% at pH 7.0, and 66% at pH 7.4. Loading capacity for native gemcitabine was less than 4% at all pH. IC_{50} values of HNP@Gem and HNP@GemSper after 24 h incubation with BxPC-3 cell lines are 0.286 and 1.527 µg/ml. respectively.

Conclusion: Nanoformulations comprising hybrid iron oxide-gold nanoparticles were noncovalently conjugated to gemcitabine-spermine moieties. This formulation demonstrates the potential for improved tumour targeting and anticancer activities towards pancreatic cancer cells.