Noncovalent Conjugation of Gemcitabine to Multifunctional Hybrid Nanoparticles for Pancreatic Cancer Therapy

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Background: Pancreatic cancer remains a major contributor to cancer-related mortality, ranking as the fourth leading cause of cancer-related deaths in 20201. Gemcitabine is the gold standard for the treatment of advanced-stage PDAC; however, its clinical efficacy is hampered by chemoresistance, primarily attributable to rapid enzymatic deamination leading to the formation of the inactive metabolite, 2',2'difluorodeoxyuridine, which is subsequently eliminated via urine. Higher doses of gemcitabine (1000 mg/m2) are administered to overcome this, which results in several severe side effects.

In this study, we present a novel approach to enhance the efficacy of gemcitabine 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 immobilised on hybrid gold-iron oxide nanoparticles to enable targeted delivery, exploiting the noncovalent, electrostatic attraction between the negatively charged gold surface of the nanohybrids and the cationic spermine.

Methods: The synthesis of these nanohybrids involves a multi-step process: the precipitation of iron salts at 90°C, capping of magnetic iron oxide nanoparticles with poly(ethyleneimine) (PEI), and subsequent reduction of gold(III) chloride. were characterised using photon correlation spectroscopy, zeta potential measurements, inductively coupled plasma-optical emission spectroscopy (ICP-OES), and transmission electron microscopy. Cytotoxicity of the drug nanoparticle formulation on BxPC-3 pancreatic cancer cell lines was evaluated using MTT and trypan blue assays.

Results: Hybrid iron oxide-gold nanoparticles (zeta potential = +31.8 mV; size = 100 - 150 nm; Polydispersity Index, PdI = 0.36) were successfully synthesised. The drug loading capacity of the nanoparticles is 71.67% in slightly at pH 6.4, 64% at pH 7.0 and 66% at pH 7.4. Gemcitabine showed slightly higher cytotoxicity compared to our novel prodrug. However, the cytotoxicity of native gemcitabine and GemSper was improved by conjugation with the hybrid nanoparticles.

Conclusions: A novel gemcitabine prodrug was successfully synthesized and immobilized on iron oxide-gold nanohybrids. The formulation showed comparable cytotoxicity as native gemcitabine.