Contribution ID : **96** Type : **not specified**

Prodrug Amphiphile Nanoparticles of Gemcitabine and 5-Fluorouracil

Prodrug analogues of the chemotherapeutic drugs gemcitabine and 5-fluorouracil have been developed in order to overcome the severe systemic toxicity and limitations often associated with these types of drugs such as lack of selectivity, high toxicity, low bioavailability, poor pharmacokinetic profiles, and low stability. Prodrug modification was achieved through the covalent attachment of hydrophobic chains to the hydrophilic drugs which conferred amphiphilic properties onto the prodrugs. The amphiphilic nature of the prodrugs allows for the self-assembly into nanostructured partcicles when dispersed in water. This effectively fuses the concept of the prodrug and sustained targeted delivery systems into high payload prodrug nanoparticles.

A series of gemcitabine prodrug amphiphiles with varying hydrophobic chains were synthesized and characterized for their molecular structure and purity, using 1H – NMR, ESI – MS and HPLC. The thermal stability profiles of the prodrug amphiphiles were determined using TGA and DSC analysis. The gemcitabine prodrugs were incorporated within the membrane of a synthetic high density lipoprotein constructed from a combination of phospholipids and cholesterol due to its inability to self-assemble into stable lyotropic liquid crystalline nanostructures without the assistance of a matrix lipid. The physicochemical properties of the gemcitabine high density lipoproteins have been assessed using cryo-TEM, dynamic light scattering and synchrotron SAXS, indicating that these high density lipoproteins formed liposomal particles and of ~120 nm in size. The prodrug nanoparticles efficacy *in vitro* have been assessed through cell proliferation assays which have shown superior cytotoxicity compared to the naked drug alone. Preliminary *in vivo* experiments to evaluate localization of the nanoparticle and antitumour efficacy on a pancreatic cancer cell-derived animal model in NOD/SCID mice have also been conducted and have shown superior efficacy compared to gemcitabine.

In order to enhance the efficacy of the nanoparticle treatment and utilize the benefits of multidrug treatments, the gemcitabine prodrug amphiphile has also been combined with a 5-fluorouracil prodrug amphiphile, resulting in a dual drug nanoparticle. The physicochemical properties of this nanoparticle were also determined using the same techniques, as well as their efficacy assessed *in vitro* and *in vivo*. The results thus far indicate the potential of the gemcitabine and 5-fluorouracil prodrug amphiphiles as promising nanomedicinal chemotherapeutics.

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