DIELS-ALDER MEDIATED RELEASE OF COMBINATION THERAPIES FROM HYBRID NANOPARTICLES

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Background: Pancreatic cancer or pancreatic ductal adenocarcinoma (PDAC) is the deadliest type of cancerous malignancy with a 5-year survival rate of only 7%. The historic first line treatment is a drug called gemcitabine, which displays effectiveness in only 22% of patients over 12 months.[1] Combination therapies such as GemCap, has been shown to improve patient outcomes, by operating under different mechanisms reducing the likelihood drug resistance. Hybrid nanoparticles (HNPs) comprised of an iron oxide core and outer gold coat have shown great potential for heat triggered drug release.[2] This work seeks to utilize this knowledge to develop a combination therapy using both gemcitabine and capecitabine.

Methods: Following on from preliminary studies, the cycloadduct is being attached to capecitabine at various potential points such as; the pyrimidine amine group, the 3-OH, and/or the 5-OH ribose hydroxyl groups. All four capecitabine-linkers (Figure 1 (3-6)) will be evaluated for their release rates at elevated temperatures to determine the optimal linker anchor points. The initial use of protecting groups such as tert-butyloxycarbonyl (Boc) may be used to facilitate linker attachment desired locations. The capecitabine-linkers will be attached to HNP's via a gold-thiol bond.[2]

Results: Historically Gem-Mal's cytotoxicity was determined by MTT and trypan blue assay to be 4.6 times lower than gemcitabine. The 11-fold enhanced uptake aided by the HNP's, coupled with rDA mediated release at 44 ˚C, led to an 26% increase in cytotoxicity compared to gemcitabine, confirming its temperature driven activity.[2] Successful capecitabine-linkers synthesis and drug loading onto HNP's will be confirmed by NMR and HPLC. The dual drug loaded HNP's cytotoxicity will be determined by trypan blue exclusion and MTT assay.

Conclusions: The gemcitabine-linker-HNP formulation has already been shown to have improved cytotoxicity compared to gemcitabine alone.[2] This work will focus on determining whether dual attachment of gemcitabine and capecitabine to HNP's as drug delivery vehicles for controlled release improves cytotoxicity in vitro with the MTT assay and trypan blue exclusion. Beyond this, the attachment of deoxy-5-fluorocytidine and 5-fluorouracil, which are metabolites of capecitabine is also planned for future work. Optimal combined drug-HNP formulations determined by *in vitro* analysis will be evaluated *in vivo*.