Mohammed Aldughaim et al., J Pharm Drug Deliv Res 2017, 6:3 (Suppl)
http://dx.doi.org/10.4172/2325-9604.C1.018

Targeting liposomal Doxorubicin to tumor tissues using a novel peptide

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Background & Aim: We have identified a novel peptide, derived from a cell matrix protein, which inhibits multiple receptors known to be up regulated in tissues from a wide variety of cancers. While the peptide inhibits tumor growth *in vivo*, it is not cytotoxic and eventually the tumors regrow. In order to increase the therapeutic efficacy of the peptide, we aimed to exploit this receptor specificity to target PEGylated liposomes containing the cytotoxic drug, Doxorubicin (Doxil®) to tumor tissue.

Method: Azide functionalized, FITC-labeled-peptide with a polyethylene glycol (PEG12) spacer was conjugated to dibenzocyclooctyl (DBCO) functionalized Doxil® by click chemistry and coupling determined by flow cytometry. Binding of the product (Doxil-peptide) to primary human dermal micro vascular endothelial cells (HDMEC), and human (MCF-7) and mouse breast tumor (4T1) cell lines, was determined by flow cytometry and internalization of both peptide and Doxorubicin determined by confocal microscopy. The effect of increasing concentrations of peptide alone, Doxil or Doxil-peptide on the viability of MCF-7, HDMEC and 4T1 cells was assessed by cytotoxicity (MTS) assay.

Result: The peptide was efficiently coupled to Doxil®. Doxil-peptide retained its receptor binding profile. In contrast to Doxil alone, it was rapidly internalized by mouse (4T1) and human (MCF7) breast cancer cells with Doxil-peptide showing an approximately 100-fold increase in uptake relative to Doxil alone. Internalization by normal human dermal micro vascular endothelial cells was much lower than cancer cells. Furthermore, this enhanced uptake increased the sensitivity of breast cancer cells to Doxil.

Conclusion: Conjugating this novel peptide to Doxil® greatly increases internalization of the cytotoxic drug, potentially resulting in increased tumor specificity which should, in turn, decrease off target effects.

Biography

Mohammed Aldughaim has completed his Biomedical Science degree in Manchester with second-class honours (1st division) before he completed his MSc degree in Molecular Medicine at the University of Sheffield. Mohammed is currently in the final year of his Phd degree in the same university where he is researching into the use of a novel peptide to specifically target therapeutic drugs to tumours. In his project, he employ different approaches to test the efficacy of this peptide to deliver a cytotoxic drug into both human and mouse endothelial cells, potentially resulting in increased tumour specificity. His interest in Molecular Medicine granted him the understanding of the importance of molecular genetics in human disease and more specifically in cancer as well as studying disease pathways for targeted treatment such as those employed in biomarker targeting for cancer treatments.

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