Use of a nano carrier for effective siRNA delivery to liver sinusoid endothelial cells

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Small interfering RNA (siRNA) is a repressive molecule that can cause gene inhibition leading to mRNA degradation[1]. It is presently under investigation for use as a therapeutic intervention[2], however RNA cannot freely diffuse across the cell membrane and requires an efficient delivery system to facilitate uptake that also overcomes any potential for nonspecific off-target effects or immune stimulation[3]. Previously, we utilised silver sulfide quantum dots (QDs) for targeted delivery of medications and peptides to liver sinusoid endothelial cells (LSECs) with no immune recognition[4]. Here we will demonstrate the effectiveness of the QDs for delivery of bioactive siRNA for their potential use in mRNA targeting therapy.

In this study, the delivery of siRNAs using a nano carrier of siRNA conjugated to an organic quantum dot and coated in various polymers that guide endocytosis, lysosomal determination and cytosolic release has demonstrated a reduction in GAPDH gene expression following oral administration. In vitro studies found a reduction in both LSEC and hepatocyte expression of GAPDH following 4, 24 and 48hr siRNA treatment compared to healthy controls, with no toxicity indicated by cell death and cell proliferation assays. In vivo studies demonstrated a dramatic reduction in LSEC GAPDH expression following orally delivered nano siRNA comparable to healthy controls. Gene knockdown of the nano carrier was comparable to galNAc tail vein injection treated mice. Hepatocytes demonstrated minimal GAPDH downregulation, indicating LSEC specific targeting and delivery. This preliminary work suggests that our nano carrier is a viable delivery agent for gene therapeutics and warrants further investigations.

References:

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