Circumventing Traditional Bottlenecks in Glioma Genetic Therapy: Ultra-pH Sensitive Nanodelivery Vehicles

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RNAi-based modalities offer sequence-specific knockdown of tumor survival and growth, presenting a novel alternative to ineffective conventional treatments. This study investigated a pH sensitive siRNA nanoparticle which circumvents traditional barriers in genetic therapy by promoting intracellular delivery, reducing cytotoxic off-target transfections, and facilitating endosomal escape of siRNA. Additionally, Acyl-CoA synthetase 5 (ACSL5) was explored as a potential molecular target for knockdown of glioma viability. Poly(2-(diisopropylamino) ethyl methacrylate) (PDPA) nanoparticles were synthesized with cationic C18 grafts via nanoprecipitation, measured for cell uptake with Leica fluorescence microscopy, and assessed for pH-sensitivity using Picogreen assay. ACSL5 silencing and growth inhibition was measured with qPCR and Ki67 staining, respectively. Designed PDPA NPs exhibited a high affinity for glioma cells and lacked cytotoxicity, thereby confirming the ability of the nanoplatforms to facilitate nontoxic siRNA transfection. pH-responsive PDPA NPs selectively initiated siRNA release at 6.0 pH (90% release) as opposed to 7.4 pH (<30% release), preventing premature siRNA release in neutral pH bloodstream and promoting specific low pH intratumoral delivery. Moreover, NP-siACSL5 constructs exhibited 80% silencing of ACSL5 expression and five-fold inhibition of glioma growth (<22%). This study potentiates the clinical feasibility of genetic therapy by establishing an optimal proof-of-concept nanoparticle for circumvention of delivery bottlenecks. Furthermore, the study exhibited novel knockdown of glioma survival and proliferation via fatty acid oxidation disruption. Future studies include the application of transferrin to promote intratumoral influx of siRNA complexes.

Awards Won:
Second Award of $2,000