Thesis Title: Nanomedicine and Gene Therapy to Treat Glioblastoma

PhD Thesis Abstract:

Glioblastoma (GBM) is an extremely malignant and aggressive forms of central nervous system (CNS) tumours, with mortality rate of fewer than 5% of patients surviving beyond five years post diagnosis. Despite decades of research to understand the underlying pathophysiological causes, it has witnessed very slow progress in terms of clinical translation of therapies. This is partially due to the lack of effective delivery strategies for overcoming major obstacles, predominantly the blood-brain barrier (BBB), tumour microenvironment (TME), and blood-tumour barrier (BTB). Out of the pool of the oncogenic microRNAs, miR-21 and miR-210 are known to regulate several hallmarks of GBM tumorigenesis. Targeting these dysregulated microRNAs using antisense oligonucleotides has a huge therapeutic potential for GBM therapy. However, such microRNAs cannot be delivered without an effective delivery system, which is one of the biggest hurdles in developing RNA-based therapeutics for GBM. Herein, we have developed ultra-small mesoporous silica nanoparticles (USMP) of ~40 nm size and modified with Polyethyleneimine (PEI) in a w/w ratio ranging from 1:1 to 1:0.01 (USMP-PEI). We have successfully demonstrated that by optimizing the PEI ratio with close to neutral surface charge, we were able to reduce PEI-induced cytotoxicity without compromising the transfection efficiency. Using the optimized USMP-PEI (1:0.025) w/w ratio and using it to further complex with different (w/w) ratios with antisense oligonucleotides (miR-21 and miR-210), we report a slow and sustained release of antisense oligonucleotides at pH 7.4. With the current strategy, we report significant cellular uptake of microRNAs in the 2D cellular model (LN229 cells) 1hr post-transfection as well as significant penetration of oligonucleotides deep within the hypoxic core of 3D GBM spheroids. The modified USMP complexed with antisense oligonucleotides possesses the inherent ability to transiently penetrate the BBB validated by transwell assay. Simultaneously, they were also able to significantly reduce the tumor spheroid size generated by LN229 GBM cells by around 30% and colony count by around 40% when anti-miRs were delivered in combination for effective GBM therapy. Taken together, these promising data will pave the way for further pre-clinical assessment of this newly developed nanomedicine for the delivery of microRNAs across the brain.