abstract

Cancer diseases are among the leading cause of death in the United States. Advanced cancer diseases are characterized by genetic defects resulting in uncontrollable cell growth. Currently, chemotherapeutics are one of the mainstream treatments administered to cancer patients but are less effective if administered in the later stages of metastasis, and can result in unwanted side effects and broad toxicities. Therefore, current efforts have explored gene therapy as an alternative strategy to correct the genetic defects associated with cancer diseases, by administering genes which encode for proteins that result in cell death. While the use of viral vectors shows high level expression of the delivered transgene, the potential for insertion mutagenesis and activation of immune responses raise concern in clinical applications. Non-viral vectors, including cationic lipids and polymers, have been explored as potentially safer alternatives to viral delivery systems. These systems are advantageous for transgene delivery due to ease of synthesis, scale up, versatility, and in some cases due to their biodegradability and biocompatibility. However, low efficacies for transgene expression and high cytotoxicities limit the practical use of these polymers.

In this work, a small library of twenty-one cationic polymers was synthesized following a ring opening polymerization of diglycidyl ethers (epoxides) by polyamines. The polymers were screened in parallel and transfection efficacies of individual polymers were compared to those of polyethylenimine (PEI), a current standard for polymer-mediated transgene delivery. Seven lead polymers that demonstrated higher transgene expression efficacies than PEI in pancreatic and prostate cancer cells lines were identified from the screening. A second related effort involved the generation of polymer-antibody conjugates in order to facilitate targeting of delivered plasmid DNA selectively to cancer cells. Future work with the novel lead polymers and polymer-antibody conjugates developed in this research will involve an investigation into the delivery of transgenes encoding for apoptosis-inducing proteins both in vitro and in vivo.