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Bioreducible cross-linked polymer coated mesoporous silica nanoparticles for targeted delivery of siRNA and chemotherapeutics to HER2+ breast cancer

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Gene silencing via small interfering-RNA (siRNA) has potential for the treatment of diseases with high target specificity. Despite the great promise, siRNA based therapies have not been widely used clinically, mainly due to the lack of an enabling delivery platform. To overcome the barrier of systemic siRNA delivery, we have developed a nanoparticle platform that is a hybrid of inorganic and polymeric materials by taking full advantage of both materials to achieve good control of particle size, charge, and solubility, leading to excellent in vivo efficacy, batch-to-batch reproducibility, and scalability. Bioreducible crosslinkers were introduced to the cationic polymer, allowing for better buffering capacity while lowering its toxicity. Antibody was also conjugated on the nanoparticles for specifically targeting cancer cells. We first evaluated the therapeutic potential of siHER2 (siRNA against HER2) in HER2+ breast cancer cells. Human epidermal growth receptor type 2 (HER2) has been linked to cancer aggressiveness and drug resistance. siHER2 was optimized by systematic screening of 76 siRNA sequences. We have shown that siRNA delivered by our nanoparticles can silence HER2, leading to the death of HER2+ breast cancer cells resistant to Herceptin and Lapatinib. Nanoparticle delivery of siHER2 resulted in >80% HER2 silencing and >85% cell growth inhibition in HER2+ cells, while little impact was found on HER2- cells, indicating high specificity of the treatment. The in-vitro efficacy has translated well to efficacy in mice bearing human HER2+ breast tumors. Co-delivery of siRNA and chemotherapeutics on the same nanoparticle platform has been accomplished. Assessments of the material for their cytotoxicity, blood and immunological toxicity, and kidney and liver functions, also yielded a very favorable safety profile.

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