Nanoparticle Platform for siRNA Delivery for Treating Pancreatic Cancer

W. Ngamcherdtrakul, S. Goodyear, J. Morry, S. Gu, D. Castro, T. Sangvanich, M. Reda, B. Beckman, S. Mihelic, X. Li, Z. Hu, J. Gray, and W. Yantasee

Biomedical Engineering, Oregon Health and Science University, Portland, OR

Gene silencing via small interfering-RNA (siRNA) has great potential for cancer therapies due to high target gene 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 advantages 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. We evaluated the efficacy of the nanoparticle platform for delivery of siRNA against HER2 to HER2+ breast cancer as the therapeutic model; we achieved >80% of HER2 knock-down in vitro, resulting in apoptotic cell death that was specific to HER2+ cancer and not HER2- cancer or normal cells. Using a human xenograft mouse model, i.v. administered siRNA-nanoparticles could inhibit tumor growth compared to saline and scrambled siRNA control and yield 60% knock-down of HER2 protein levels in the tumors. To extend the nanoparticle platform to treat pancreatic cancer, we exploited dual targeting siRNA against Akt1 and Bcl2 and achieved greater than 95% cell death in the AsPC1 and Capan-2 pancreatic cancer cell lines following a low dose of 30 nM of siRNA. In addition to delivery of siRNA, the nanoparticle platform could also effectively deliver therapeutic antibodies (e.g., trastuzumab) and chemotherapeutics (e.g., docetaxel and paclitaxel). In this regard, we have investigated the synergy of siRNA against survivin given in combination with gemcitabine and found enhanced cell death of Capan-1 compared to siRNA or drug alone.