Site-Specific Delivery of Immune Agonists for Antitumoral Response of the Tumor Microenvironment

Ravichandran, Shruthi (School: Hathaway Brown School)

Tumor-mediated immunosuppression allows tumors to hide from the immune system and avoid recognition. One way of reversing this suppressive microenvironment is to activate antigen-presenting cells (APCs) within the tumor that recruit other immune cells to the area. Cyclic diguanylate monophosphate (c-di-GMP), a drug that works within the cytosol of APCs like macrophages, is used to release inflammatory cytokines like IFN-beta to recruit immune cells and initiate an anti-tumor response. However, therapy using freely injected c-di-GMP is limited because c-di-GMP cannot easily cross cell membranes and is quickly cleared from the body. It is hypothesized that c-di-GMP loaded into a nanoparticle will more effectively deliver drug into the cytosol of APCs, which are widespread within the tumor. 30μg of c-di-GMP was loaded into mesoporous silica nanoparticles, a versatile nanoparticle platform that is biocompatible and easily modified. In vitro studies showed c-di-GMP-loaded silica nanoparticles boosted the secretion of cytokine IFN-beta from murine macrophages by 6-fold compared to free c-di-GMP. Meanwhile, unloaded silica nanoparticles induced low levels of IFN-beta secretion comparable to untreated macrophages, verifying the particle has low immunogenicity. This preliminary work demonstrates a potential new treatment that safely increases the efficacy of c-di-GMP. Ongoing and future work includes in vivo studies optimizing the delivery of nanoparticles to tumor-associated macrophages and evaluating the therapeutic effects on tumor burden and overall survival.