IN VIVO PROGRAMMING OF MYELOID CELLS BY MRNA MEDIATED DELIVERY OF NOVEL FCA FUSION RECEPTOR ACTIVATES ANTI-TUMOR IMMUNITY

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Background: Immunotherapy has revolutionized cancer treatment. However, for the majority of patients with advanced solid tumors, sustained clinical benefit has yet to be achieved. Myeloid cells such as monocytes and macrophages readily accumulate in tumors, in some cases contributing up to 75% of the tumor mass. Reprogramming circulating and tumor associated myeloid cells to activate their ability to elicit anti-tumor adaptive immunity by phagocytosis, cytokine secretion and antigen presentation is an attractive approach to harness and orchestrate systemic anti-tumor immunity. It remains challenging to specifically target and activate myeloid cells in vivo.

Methods: To overcome this hurdle, we have developed a novel in vivo myeloid cell engineering platform: Fca Receptor Fusion Constructs. Unlike other chimeric antigen receptors (CARs) the construct was engineered by fusing a tumor recognition scFv with the alpha chain of human Fc receptors. The stable expression and function of these receptors requires endogenously expressed Fc receptor gamma chain, a protein with limited expression to immune cells, mostly myeloid cells. Here, we present that intravenous infusion of lipid-nanoparticle (LNP) encapsulating the Fca Receptor Fusion Construct mRNA results in the uptake and expression of the construct by myeloid cells. In immunodeficient xenograft models of hepatocellular carcinoma and triple negative breast cancer, delivery of LNP mRNA encoding for GPC3 or TROP2 targeted Fca Receptor Fusion Constructs resulted in tumor killing, confirming the ability of this approach to program myeloid cells. Furthermore, in the B16 syngeneic melanomas melanoma model, treatment with the melanoma antigen GP75 targeted Fca Receptor Fusion Constructs was also associated with the initiation of broad systemic immune responses, characterized by tumoral accumulation of activated CD8+ T cells, reduced tumor associated Tregs and activation of antigen presenting cells in spleen. Together these studies highlight the potential of Fca Receptor Fusion Construct delivered directly in vivo to program myeloid cells to recognize and kill cancer.