In vivo programming of prostate tumor-specific T-cells using synthetic nanoparticles

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BACKGROUND: A major thrust of current prostate cancer research involves programming the immune system to attack tumors. For example, vaccines are capable of eliciting anti-tumor immunity in some cancer patients, but immune responses are usually insufficient to control advanced disease and can require months to mature; in this timeframe, prostate cancers can progress or be fatal. **METHODS**: We are developing a radically new treatment approach to induce effective active immunity against prostate cancer within days, based on an unconventional merger of concepts from materials science, immunology, and gene therapy. Specifically, we hypothesized that appropriately engineered synthetic nanoparticles can program prostate cancer recognition properties into T cells in just days, working within the patient's circulatory system. As the first step in testing this hypothesis, our cross-disciplinary team of bioengineers and immunologists has engineered a novel polymeric nanoparticle that, after adaptation with T cell targeting ligands, efficiently introduces genes encoding the prostate tumor antigen-specific receptor P28z (provided by M. Sadelain, Memorial Sloan Kettering Cancer Center) into lymphocytes cultured in vitro. P28z is a fusion receptor composed of a single-chain antibody (scFv) specific for the extracellular domain of PSMA (J591) combined with CD28 and CD3ζ cytoplasmic signaling domains. Expression of P28z enables T cells to both lyse PSMA-expressing tumor targets and to undergo repeated rounds of antigen-dependent stimulation and expansion. **RESULTS**: We found that 30 h after nanoparticle transfection ~23% of the T cells expressed the P28z receptor on their surface. Nanoparticle-transfected T cells were functional, selectively lysing PSMA-expressing C42 prostate tumor cells. When systemically injected into mice, nanoparticles exclusively transfected circulating host T-cells, with relatively low binding to off-target cells. Based on these data, we are currently testing whether repeated infusions of these nanoparticles lead to regression of metastatic prostate cancer in mice. **CONCLUSIONS:** Successful completion of these studies will provide the first demonstration that synthetic nanoparticles can be engineered to generate cancer-reactive T cells de novo. Nanoparticle T-cell gene therapy could be a game-changing approach for treating metastatic prostate cancer by providing clinicians with the ability to rapidly treat diagnosed patients using an off-the shelf reagent that can reprogram the immune system to selectively destroy cancer cells without damaging healthy non-prostate tissue. To further augment the anti-tumor potency of this technology, nanoparticles could readily be administered in combination with adjuvant and/or supplemental agents that enhance T-cell survival, increase T-cell expansion, and offset T-cell suppression in the tumor microenvironment, such as vaccine adjuvants, stimulatory cytokines, co-stimulatory antibodies, or anti-checkpoint blockade agents. Given the ease of manufacturing and distributing nanoparticles, this technology has the potential to be translated into clinically viable prostate cancer therapy over the next five to ten years.

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