PUBLICATION REVIEW

Biopolymers codelivering engineered T cells and STING agonists can eliminate heterogenous tumors

Reprogramming T cells to recognize specific tumor associated antigens using chimeric antigen receptors (CARs) has revolutionized the field of cancer immunotherapy. Despite remarkable success in treating hematological malignancies, CAR-T cell approaches have failed to achieve meaningful efficacy in solid tumors. The limited efficacy of CAR-T therapy in solid tumors is attributed in part to the inability of CAR-T cells to traffic to and persist in the immunosuppressive solid tumor microenvironment. Moreover, solid tumor cells have inherent phenotypic diversity, thus CAR-T cell targeting of a single tumor associated antigen commonly leads to tumor antigen escape and relapse.

To overcome these limitations of CAR-T cell therapy for solid tumors, an implantable biopolymer device coated in immune-stimulatory antibodies (anti CD3/CD28/CD137) was generated to deliver CAR-T cells directly to the solid tumor surface. In orthotopic murine models of pancreatic cancer, biopolymer-mediated CAR-T cell delivery alone was insufficient to control tumor burden. Supplementation with a stimulator of IFN genes (STING) agonist, cdGMP, was able to stimulate the endogenous immune system to trigger robust tumor-specific host lymphocyte responses. This combination therapy generated sufficient antitumor immunity to circumvent antigen escape and clear both primary solid tumors and metastases.

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Publication highlights:

Non-invasive imaging using Revvity IVIS® Spectrum optical system successfully quantified tumor-specific T cells responses in NFAT-luciferase transgenic mice. IVIS imaging of bioluminescent tumor cell burden following treatment clearly demonstrated the synergistic antitumor effect of codelivery of CAR-T cells and STING-agonists via biopolymer scaffolds.

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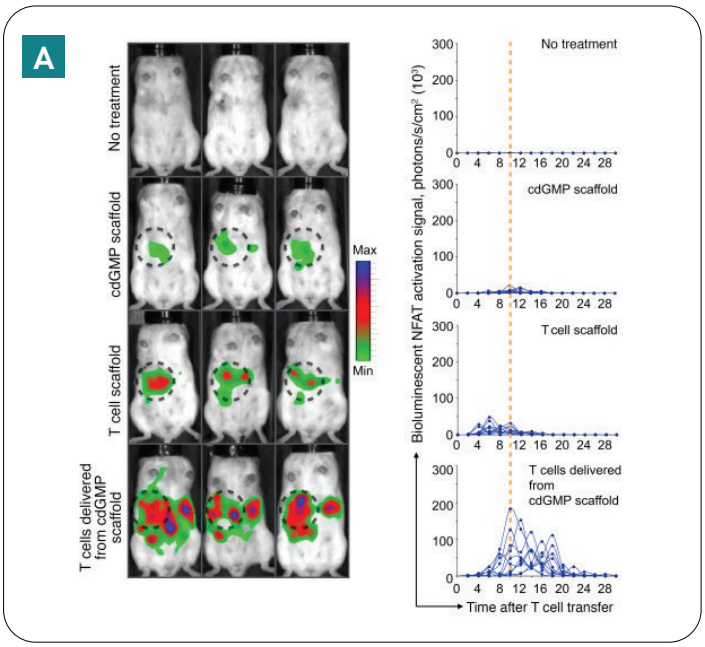

Figure A) NFAT-Luciferase-expressing transgenic mice with established orthotopic KPC pancreatic tumors were treated with biopolymers carrying cdGMP, tumor-specific CAR-T cells, or a combination of both. NFAT-luc signal was measured on the IVIS® Spectrum Imaging System to non-invasively quantify activated host T-cells over time. Codelivery of CAR-T cells and cdGMP robustly enhanced host T cells activation, as demonstrated by NFAT-luciferase signal extending beyond the pancreatic tumor into the spleen and mesenteric lymph nodes.

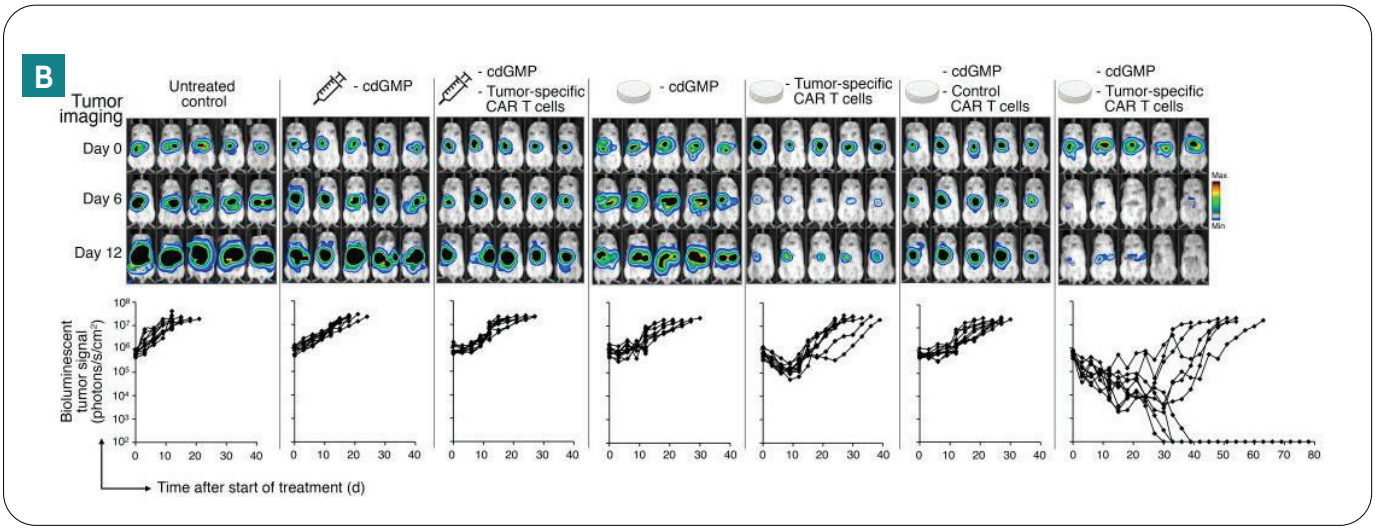

Figure B) KPC-luciferase tumor cells (1 x 105) were implanted orthotopically in the head of the pancreas in Albino B6 mice and established for one week prior to treatment (at day 0) with biopolymers carrying cdGMP, tumor-specific CAR-T cells, or the combination of both. IVIS was used to measure bioluminescent tumor signal to track tumor burden following treatment. Sustained antitumor efficacy was observed in 4/10 mice treated with the combination therapy. (Top panel shows 5/10 representative mice).

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