1225 TRI-SIGNAL POLYMERIC ARTIFICIAL ANTIGEN PRESENTING CELLS FOR CANCER IMMUNOTHERAPY

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Background Decades of encouraging yet incomplete responses from cytotoxic ($CD8^+$) T cell-based cancer immunotherapies have invigorated recent efforts to develop highly tunable, robust, and more cost-effective artificial antigen presenting cells (aAPCs). These acellular platforms are modeled after natural antigen presenting cells that deliver signals to activate T cells; primary signal 1 (S1) proteins interact with the T cell receptor, co-stimulatory signal 2 (S2) proteins are essential for T cell activation, and secreted signal 3 (S3) are cytokines and chemokines that further aid in differentiation and localization of T cells. The objective of this study is to synthesize a novel aAPC platform with improved protein incorporation and stimulatory function, with hopes of generating more accessible and cost-effective cancer immunotherapies.

Methods Using emulsion-based synthesis,[1] we formulated a lipophilic biodegradable blend of poly(lactic-co-glycolic acid) (PLGA) and cationic poly(beta-amino-ester) (PBAE) polymers to modulate T cell responses in the context of melanoma antigen, Gp100. Transmission electron microscopy (TEM) analyzed the size and shape of microparticles. S1 (anti-CD3 or DbGp100) and S2 (anti-CD28) were conjugated to the surface of the particles via EDC/NHS chemistry, with S3 (murine IL-2) encapsulated into the core during emulsion. Conjugation was measured by fluorescence intensities of secondary antibodies specific to S1 and S2. ELISA assay measured S3 release. PLGA/PBAE aAPCs ('Formulation 5') were cultured with transgenic PMEL $CD8^+$ T cells *in vitro* for 7 days at a range of aAPC doses with IL-2.

Results Formulation 5 microparticles show an average size of 1.3 microns (figure 1A). Significantly more S1 and S2 conjugated to the surface of Formulation 5, compared to PLGA-only particles (figure 1B). Total IL-2 release from Formulation 5 shows 1000 pg IL-2/mg particles released over 60 hours (figure 1C). PMEL $CD8^+$ T cells showed over 50-fold proliferation at the highest doses after 7 days of culture with Formulation 5 (figure 1D).

Conclusions We have modified our biodegradable PLGA/PBAE aAPC platform to incorporate T cell activating proteins more efficiently and enhance immune cell mimicry. In ongoing studies, we are fully characterizing aAPC properties, including protein corona formation and particle stability. We are conducting phenotypic and functional characteristics of murine $CD8^+$ T cells post aAPC stimulation *in vitro* and characterizing aAPC-induced proliferation *in vivo*. Ultimately, our novel biomimetic and biodegradable aAPC technology has the potential to not only bear translational anti-cancer relevance but can also shed light on aspects of basic T cell biology that are not otherwise easily studied.

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REFERENCES

1. Rhodes KR, Meyer RA, Wang J, Tzeng SY, Green JJ. Biomimetic tolerogenic artificial antigen presenting cells for regulatory T cell induction. *Acta Biomater* 2020;**112**:136–148.

Ethics Approval All animal experiments were conducted following the guidelines of the Johns Hopkins University Animal Care and Use Committee (ACUC).

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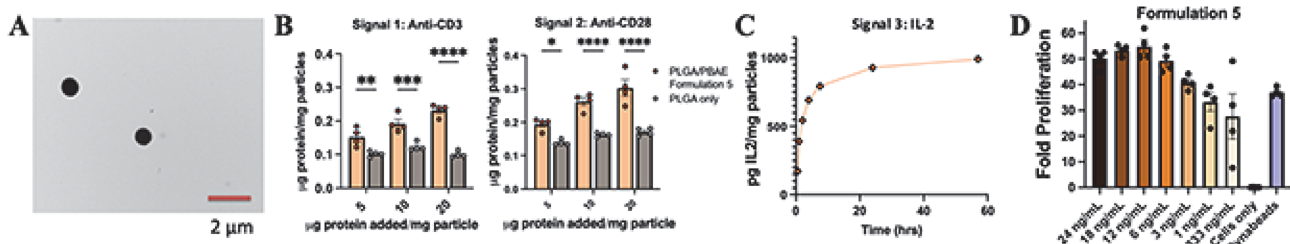

Abstract 1225 Figure 1 (A) TEM image showing spherical PLGA/PBAE Formulation 5 microparticles. Scale bar is 2 µm. (B) Surface conjugation readout of immunological signals 1 and 2 via EDC/NHS chemistry. Encapsulation efficiency of signal 3 during emulsion synthesis via ELISA. (D) Day 7/ Day 1- fold proliferation of $CD8^+$ PMEL T cells after incubation with varying doses of aAPC-bound signal 1.

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