43. Engineered tolerogenic artificial APCs

(Johns Hopkins University)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Cell Therapy
Disease Area	Immunology
Indication	Autoimmune Disease
Current Stage	Lead Optimization
Target	Regulatory T cell
MoA	A biodegradable particle comprising a polyester or polyester blend , a first protein that binds to an immune cell , and a second protein that promotes proliferation and / or activation of immune cells , and a third soluble protein or small molecule encapsulated within the particle . The second protein is a fusion protein comprising at least a portion of an antibody and at least a portion of a Cytokine
Brief Description	• Tolerogenic antigen presenting cells (TolAPCs) consisting of a biodegradable particle surface-conjugated with a combination of IC and autoantigen-loaded MHC tetramers have been developed. • TolAPCs are synthesized by forming a polymer core and covalently attaching ICs and specific autoantigen complexes to the surface. To evaluate performance, TolAPCs were incubated in-vitro with CD4+ T cells and compared to free IL-2 cytokine and free IC complexes. • TolAPCs selectively stimulated Treg populations and achieved the same stimulation as free IC and greater stimulation than free IL-2. In an in-vivo mouse model, TolAPCs also increased the ratio of Treg cells compared to a no treatment condition. • Altogether, the inventors have demonstrated efficacy of TolAPCs as an antigen specific IC based regulatory T cell modulator.
Intellectual Property	US20220160891A1
Publication	Biomimetic tolerogenic artificial antigen presenting cells for regulatory T cell induction. Acta Biomater. (2020)
Inventors	Jordan J. Green, Stephany Yi Tzeng, Kelly Rhodes, Giorgio Raimondi, Marcos Iglesias, Jamie SPANGLER, Jakub Tomala, Derek VanDyke, Randall A. Meyer

Highlights

- PLGA/PBAE aAPCs interact more with naïve CD4+ T cells compared to PLGA aAPCs
- PLGA/PBAE aAPCs induce significantly more iTregs compared to PLGA aAPCs
- TGF-β is required for PLGA and PLGA/PBAE aAPC-mediated Treg induction
- Cell populations induced by PLGA/PBAE aAPCs more effectively suppress
- proliferation of naïve CD4+ T cells compared to those induced by PLGA aAPCs
- PLGA/PBAE TolAPCs more effectively induce Tregs *in vivo*.

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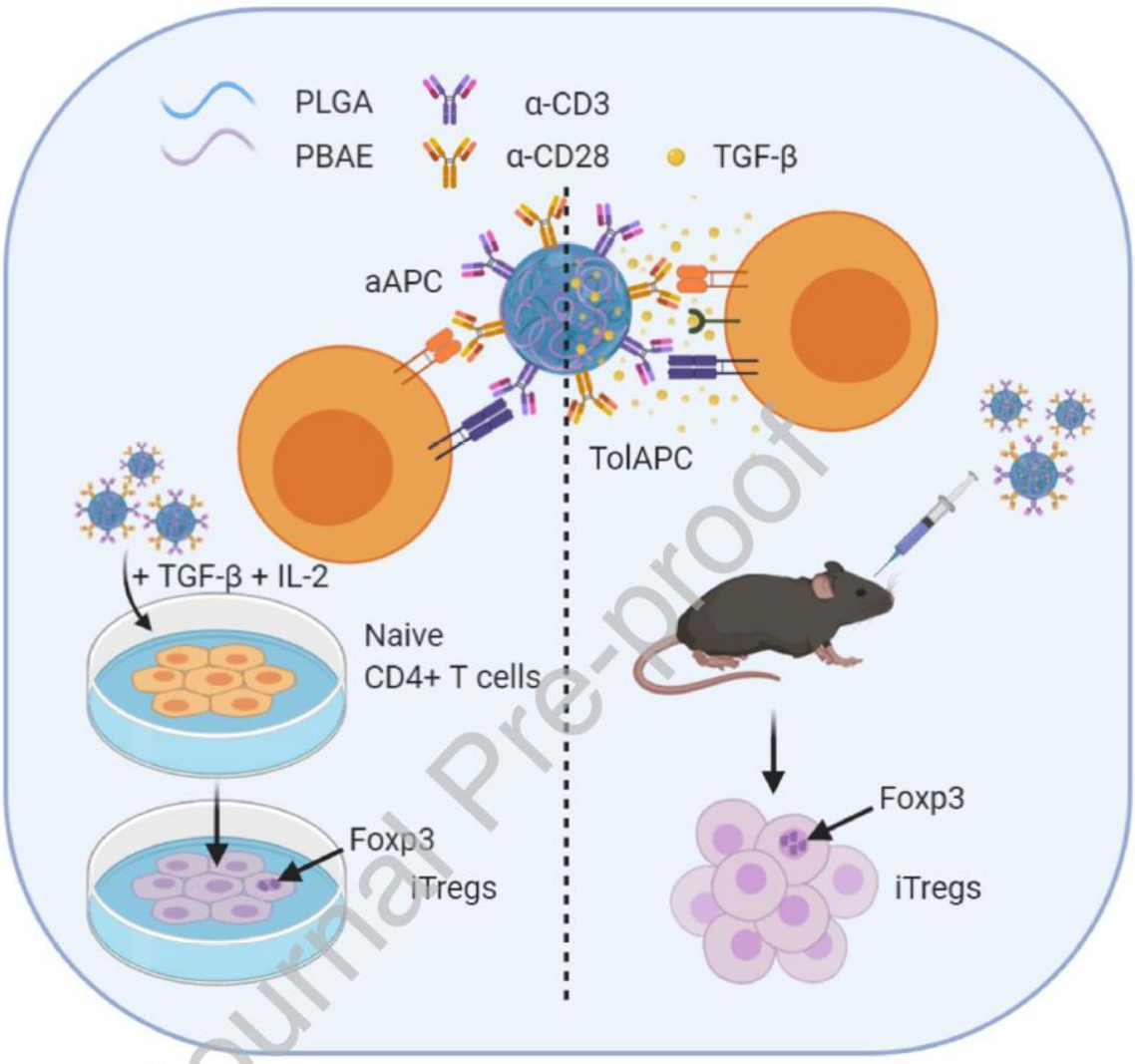
Key Data

The graphical abstract



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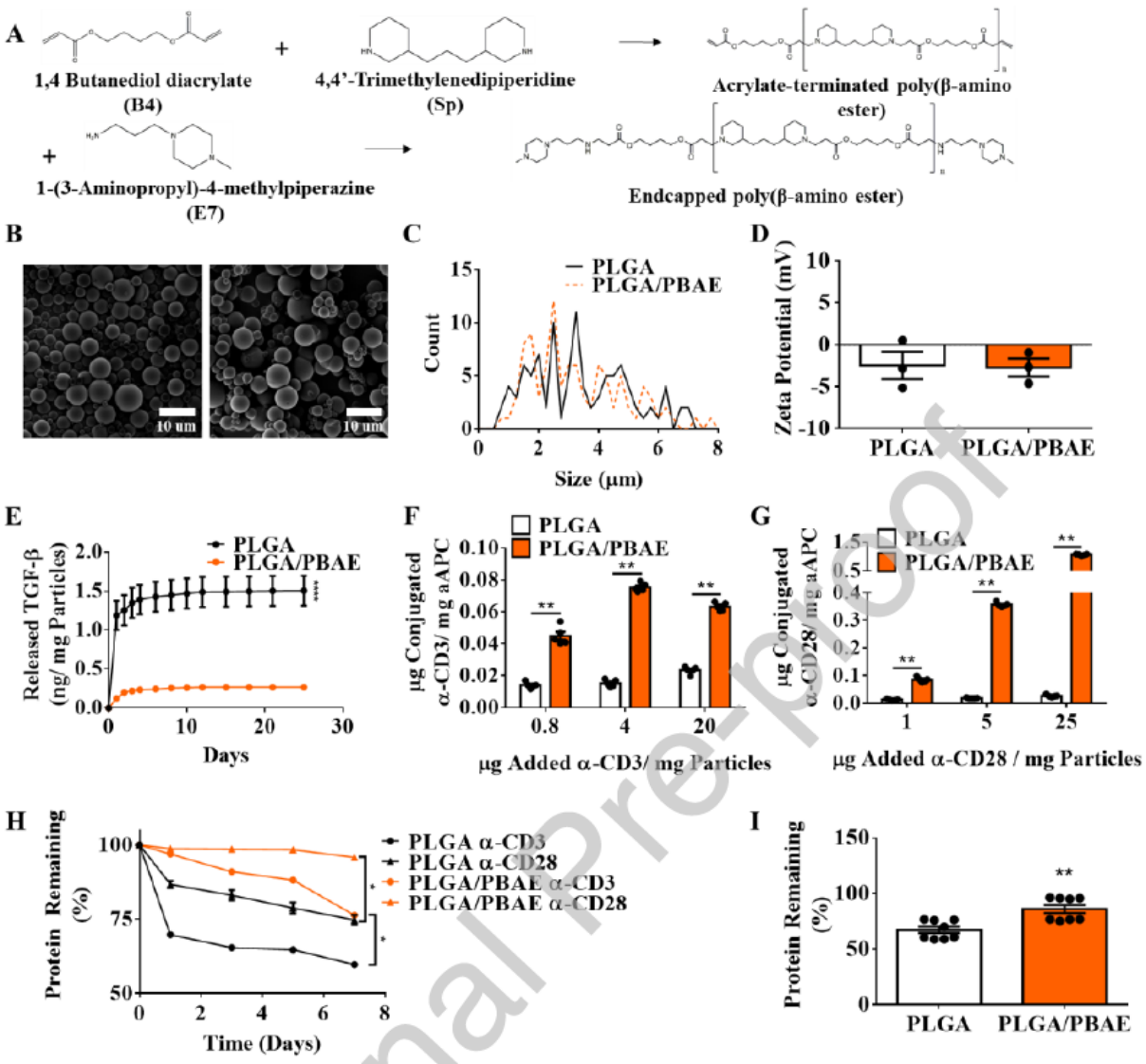
Key Data

aAPC synthesis and characterization



A) PBAE was synthesized through two sequential Michael Addition reactions. First, a diacrylate-terminated base monomer was reacted in excess with a hydrophobic diamine-terminated side chain monomer to generate a diacrylate terminated PBAE. The base PBAE polymer was then end capped with a small amine-terminated molecule. **B)** SEM images of PLGA (left) and PLGA/PBAE (right) microparticles reveal similar size and spherical morphology. **C)** PLGA and PLGA/PBAE microparticles have similar size distributions. **D)** PLGA and PLGA/PBAE microparticles have slightly negative zeta potentials. **E)** TGF- β release from PLGA and PLGA/PBAE particles. **F-G)** Protein conjugation to PLGA and PLGA/PBAE particles. PLGA/PBAE aAPCs conjugate significantly more **F)** α-CD3 and **G)** α-CD28 to their surface compared to PLGA aAPCs across a range of protein doses added during conjugation. **H)** Surface protein stability. PLGA/PBAE aAPCs retain significantly more surface bound α-CD3 and α-CD28 over a 7-day period compared to PLGA aAPCs. Error bars may be smaller than symbols. **I)** Average percent of surface protein remaining on aAPCs after 7 days. PLGA/PBAE retain 86 % stable protein presentation on their surface after 7 days at 37°C while PLGA aAPCs retain 67%. Error bars are the SEM of 3-8 technical replicates and may be smaller than symbols. (**=p<0.01, ****=p<0.0001).

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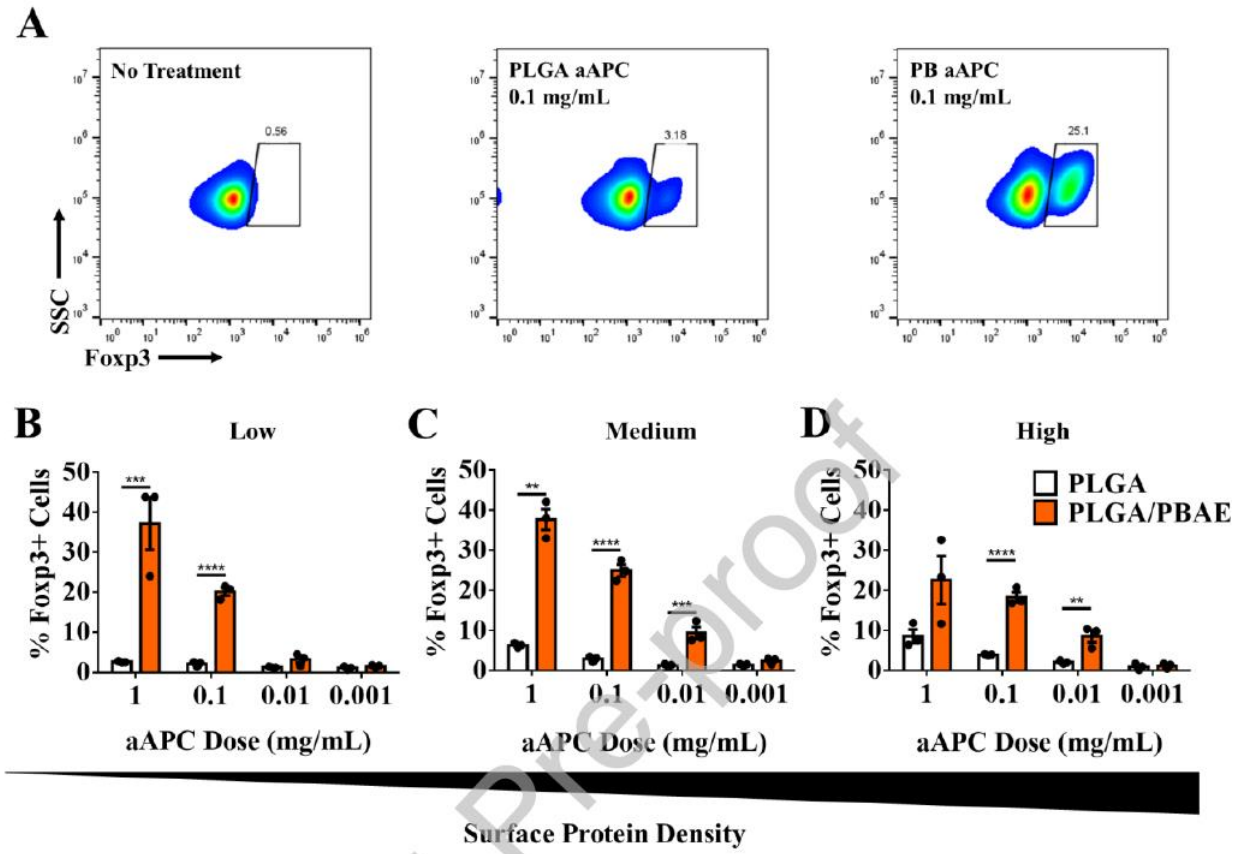
PLGA/PBAE aAPCs induce significantly more iTregs compared to PLGA aAPCs



A) Representative flow plots. PLGA and PLGA/PBAE aAPCs conjugated with **B)** 1/5x **C)** 1x and D) 5x signal protein densities were incubated with naïve CD4+ T cells in the presence of TGF-β and IL-2 for five days, and then stained for Foxp3 (FJK-16s) – APC. Enhanced induction efficacy of PLGA/PBAE aAPCs was seen over a range of aAPC doses. Error bars are the SEM of three technical replicates. (**=p < 0.01, ***=p < 0.001, ****=p < 0.0001).

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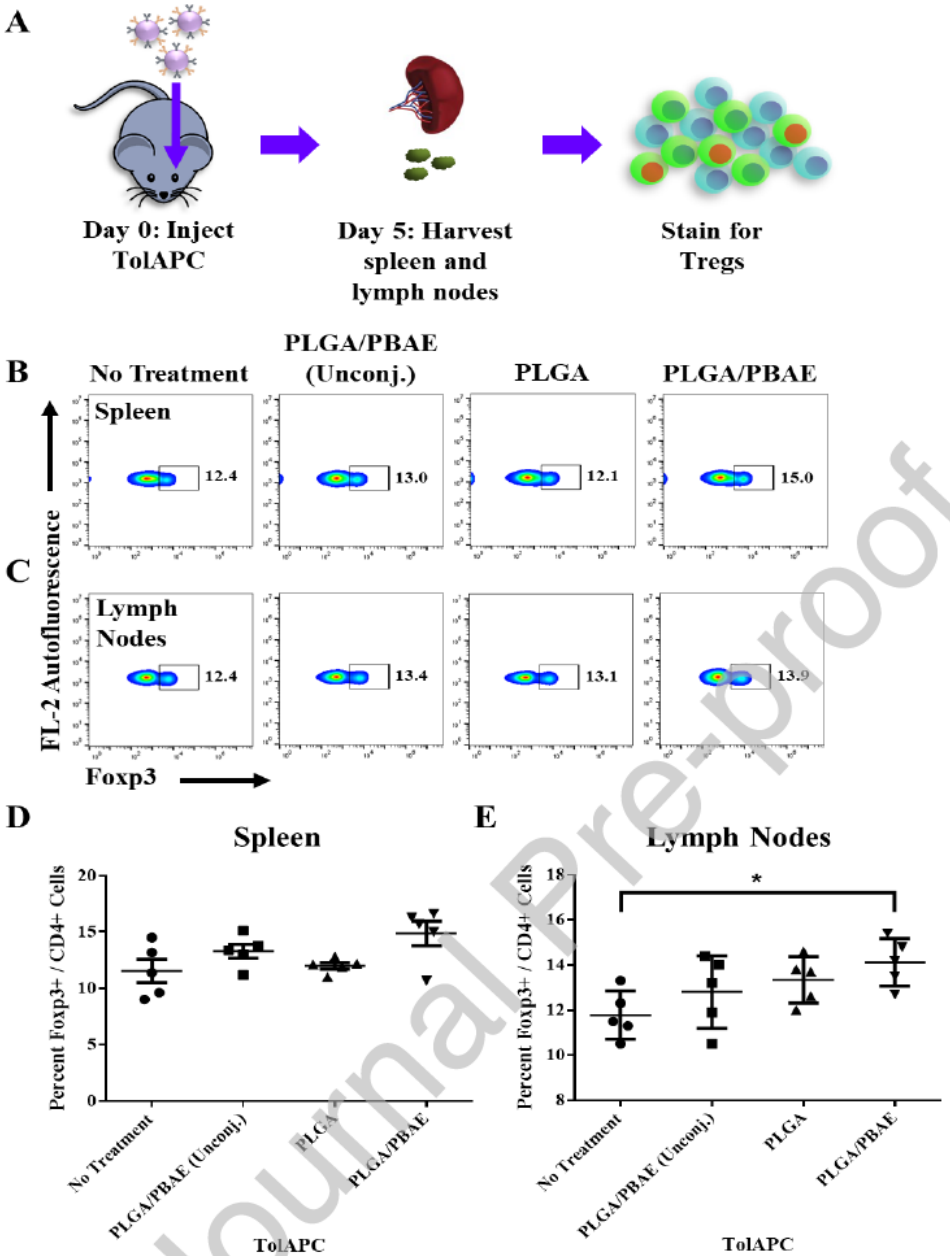
Key Data

PLGA/PBAE TolAPCs more effectively induce Tregs in vivo.



A) TolAPCs were injected retro-orbitally into C57BL/6J mice. After 5 days, the spleens and lymph nodes were harvested and stained for CD4 and Foxp3 expression. Representative flow plots showing CD4+ cells from **B)** spleens and **C)** lymph nodes of mice. **D)** Spleens and **E)** lymph nodes of C57BL/6J mice injected with PLGA/PBAE TolAPCs contained more Foxp3+ cells than those injected with PLGA TolAPCs, and significantly increase the percentage of Foxp3+ cells compared to untreated mice in the lymph nodes. Error bars represent the SEM with n = 5 animals per condition. **D)** is significant based on an ANOVA, $p < 0.5$. (*=$p < 0.05$, only conditions marked with (*) are significant and all other comparisons were performed and found to be not significant.)