Imprime PGG modulates the myeloid component of the tumor microenvironment to coordinate an anti-tumor immune response

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Abstract

Imprime PGG (Imprime) is a soluble, yeast-derived 1-3,1-6 β-glucan that acts as a pathogen associated molecular pattern (PAMP), binding to and activating cells in innate immune systems to drive a coordinated anti-cancer immune response. In a randomized phase 2 clinical study, stage IV NSCLC patients treated with Imprime plus the anti-VEGF antibody bevacizumab (bev), carboplatin and paclitaxel showed a median overall survival of 16.1 months versus 11.6 months in patients not receiving Imprime. We sought to explore a mechanistic understanding for this promising clinical nature of myeloid cells both in vitro as well as in an in vivo xenograft model of NSCLC.

Results

1. Imprime PGG interacts with multiple human myeloid subsets in vitro including macrophages, MDSCs, and neutrophils, resulting in a more immunostimulatory phenotype.

2. Imprime PGG treatment in vivo can activate myeloid cells within both the tumor and spleen to orchestrate a profound shift in the immune microenvironment which promotes tumor recognition and suppression.

Background

- Imprime is a soluble yeast-derived 1-3,1-6 glucan immunomodulator (Figure 1) being developed for cancer treatment in combination with anti-tumor antibodies and chemotherapy.

- In a randomized phase 2 clinical study, stage IV NSCLC patients treated with Imprime plus the anti-VEGF antibody bevacizumab (bev), carboplatin and paclitaxel showed a median overall survival of 16.1 months versus 11.6 months in patients not receiving Imprime.

- Imprime, a pathogen associated molecular pattern (PAMP), forms an immune complex with endogenous anti-β-glucan antibodies, then binds and primes innate and adaptive immune cells including macrophages, monocytes, neutrophils, B cells and DCs. Activation of the above innate cells is central to confounding adaptive immune cell responses. Generating functional and long-lived anti-tumor innate and adaptive immune responses is key to providing durable tumor control.

- OBJECTIVE: To evaluate the ability of Imprime to alter the immunosuppressive nature of myeloid cells both in vitro as well as in an in vivo xenograft model of NSCLC.

Figure 1: The general structure of yeast-derived Imprime PGG

Figure 2: Imprime treated human monocyte-derived M2 macrophages display M1-like characteristics.

Figure 3: Generation of MDSCs from human cord blood

Figure 4: Imprime treatment reduces the ability of MDSCs to inhibit T cell proliferation.

Figure 5: Imprime treatment enhances human in vitro neutrophil activity.

Figure 6: Imprime treatment affects the balance of lymphocytes.

Figure 7: Splenic macrophages isolated from Imprime+Bev treated mice display an M1-like phenotype.

Figure 8: Imprime+Bev splenic MDSC display an increase in iNOS and decrease in Arginase 1.

Figure 9: Imprime+Bev tumor associated myeloid cells show a more activated phenotype and an increase in PD-L1.

Figure 10: Imprime+Bev treated animals had reduced concentration of TGFβ within the tumor.

Summary

- Tumors from Imprime+Bev treated animals made less TGFβ. Cells were harvested from the tumor using type I collagenase and incubated overnight in 10%Ko/10% media. Supernatants were then analyzed for TGFβ concentration by ELISA. %TGI was calculated by %TGI = (1 - (Imprime+Bev + Bev)/Imprime+Bev control) x 100.

- Imprime PGG treatment in vivo can activate myeloid cells within both the tumor and spleen to orchestrate a profound shift in the immune microenvironment which promotes tumor recognition and suppression.