Background and Objective: Although checkpoint inhibitors (CPI) have shown tremendous efficacy in cancer treatment, a significant fraction of patients eventually develop resistance to CPI. Therefore, there is a growing need to identify resistance mechanisms as well as rational combination strategies to combat this resistance. Imprime PGG [Imprime], a yeast-derived β-glucan pathogen-associated molecular pattern (PAMP), is being developed as a combination agent with CPI in patient populations who have failed single-agent CPI therapy. In pre-clinical mechanistic studies, Imprime has been shown to reprogram the immunosuppressive myeloid cells in the microenvironment and enhance the effector functions of tumor infiltrating T cells. The objective of this study was to focus on IDO, one of the critical resistance mechanisms in the immunosuppressive microenvironment that hinders T cell antitumor immunity.

Methods: The anti-tumor efficacy of Imprime in combination with anti-PD-1 was evaluated in the murine colon cancer model MC38. Transcriptional changes in the tumor were assessed by Quantigene Multiplex platform. IDO gene expression in IFN-g-stimulated human whole blood post Imprime treatment was assessed by qRT-PCR. Trypsinophan and kynurenine levels were measured in the serum by LC/MS.

Results: In the MC38 model, Imprime in combination with anti-PD-1 resulted in significantly reduced tumor growth as compared to anti-PD-1 monotherapy. Consistent with our previous results, transcriptional analyses of tumor tissues showed that Imprime alone induced a M1 skewing gene expression profile by modulating several genes including IDO, TNF, CCL10, Ang, and CCL7. Anti-PD-1 treatment alone upregulated several genes affecting T cell functionality, such as IFNg, PD-L1 and GzmB. Interestingly, anti-PD-1 treatment also resulted in increased expression of several immunosuppressive genes, such as IL10, Arg1, and most notably, IDO1. Furthermore, IDO1 expression was inversely correlated with tumor volume, suggesting IDO1 upregulation is a counter-regulatory mechanism induced in the tumor and/or myeloid cells in response to enhanced IFN-g production by anti-PD-1 treated tumor-infiltrating T-cells. Interestingly, this anti-PD-1 mediated IDO1 induction was dampened significantly by the addition of Imprime to anti-PD-1. Flow cytometry showed that Imprime treatment affected IDO expression in the Ly6C+ monocytes/macrophages, but not in tumor cells. In human whole blood and isolated monocytes, IFNg treatment increased the transcriptional level of IDO1 and the ratio of tryptophan to kynurenine, but Imprime treatment significantly inhibited this IFN-g-induced IDO1 increase.

Conclusion: These results collectively demonstrate that Imprime treatment can enhance efficacy of anti-PD-1 treatment and may do so by restricting compensatory immunosuppressive mechanisms mediated by myeloid cells.

Imprime synergizes with anti-PD-1 antibody therapy in the murine MC38 tumor model

- Imprime PGG, a yeast-derived pharmacological-grade soluble 1,3/1,6 β-glucan is being developed for the treatment of cancer in conjunction with tumor targeting and immunomodulatory antibodies (Abs).
- Imprime has shown promising results in multiple Phase 2 clinical trials in non-small cell lung cancer (NSCLC) and chronic lymphocytic leukemia (CLL).
- Galactic markers were found in the cell wall of unicellular and multicellular pathogens. They are considered pathogen-associated molecular patterns (PAMPs) recognized by the pattern recognition receptors including Dectin-1 and Complement Receptor 3 (CR3).
- Imprime forms a unique complex with endogenous serum immunoglobulin IgG or IgM anti-beta-glucan antibodies (ABA) before being recognized by CR3 and FcgRIIA on innate immune cells.

Imprime has shown promising results in multiple Phase 2 clinical trials. 

Imprime/anti-PD-1 combination therapy reduces anti-PD-1 Ab-mediated IDO1 mRNA enhancement in mouse tumor and enriched TAM, and Imprime reduces IDO1 levels in tumor suspension cells. 

Imprime-treated human monocytes have reduced IDO expression and display M1-like characteristics.

Conclusion: Immunotherapy can up-regulate immunosuppressive pathways, such as IDO as contributor to compensatory mechanisms to thwart T-cell anti-tumor immunity. Imprime, by programming monocytes to an M1 orientation can not only subvert the existing immunosuppressive forces restraining T-cell immunity, but also ameliorate some of the immunotherapy treatment-related emerging rebound immunosuppressive pathways. Imprime’s unique mechanistic feature of remodeling the suppressive tumor microenvironment could potentially sensitize, as well as sustain the efficacy of other immunotherapeutic modalities.