Imprime PGG, a β-glucan PAMP (pathogen-associated molecular pattern) activates the direct killing functions of innate immune cells in concert with tumor targeting antibodies

Steven Leonard, Ross Fulton, Kat Fraser, Ben Harrison, Takashi Kangas, Adria Jonas, Anissa Chan, Nadine Ottoson, Yumi Yokoyama, Nandita Bose, Keith Gordon, Jeremy Graff
Biothera, Inc. Eagan, MN. s.leonardo@biothera.com

Abstract

Imprime PGG (Imprime) is a soluble yeast 1,3/1,6-β-glucan. We have previously shown that Imprime can bind to and activate innate immune cells. Imprime has been administered to >400 humans and has consistently shown promising increases in both objective tumor cell maturation and antigen presentation, driving T cell expansion and activation. In this study, we sought to better characterize the effect of Imprime in concert with tumor targeting antibodies. We show that Imprime enhances the effector functions of multiple innate immune cell lineages. We first evaluated the generation of Reactive Oxygen Species (ROS) in neutrophils isolated from healthy volunteer whole blood. These neutrophils, but not those from vehicle treated whole blood, specifically recognized B cell lymphomas (Raji) only after opsonization with anti-CD20 Mabs (rituximab, ofatumumab, obinatuzumab), generating a substantial ROS burst that coincided with enhanced tumor cell cytolysis. Similarly, increased antibody dependent cellular phagocytosis (ADCP) mediated by monoclonal antibody dependent macrophages was evident against antibody-opsonized lymphomas (T238 B cell lymphomas with obinutuzumab) and solid tumor cells (SKBR3 breast cancer cells) when cocultured with Imprime treated monocyte-derived macrophages. These results demonstrate that Imprime enhances the direct killing functions of innate immune cells in concert with tumor targeting antibodies.

Background

- As a PAMP, Imprime is recognized by and binds to cells of the innate immune system to orchestrate a coordinated anti-cancer immune attack
- Imprime has been administered to >400 humans intravenously and is well tolerated
- Clinically Imprime has been used in randomized phase 2 studies in NSCLC, consistently showing promising increases in both objective tumor response and patient survival
- We have previously shown that Imprime can bind to and activate cells of the innate immune system via association with CR3, FcRs, and Dectin-1
- We here investigate multiple immune effectors in vitro and in vivo for the ability of Imprime to synergize with monoclonal antibody therapy

Figure 1. A general structure of yeast-derived Imprime PGG

Figure 2. Imprime enhances Neutrophil ROS production against tumor lines bound by monoclonal antibodies

Figure 3. Imprime enhances ADCP by monoclonal-derived macrophages of tumor cell lines bound by monoclonal antibodies

Figure 4. Imprime treatment enhances ADCP against antibody coated tumor targets

Figure 5. Imprime enhances the anti-tumor efficacy of trastuzumab in a patient derived xenograft model of breast cancer

Figure 6. Imprime PGG synergizes with tumor-targeting monoclonal antibody TAA9 to reduce B16 lung metastases

Summary

1. Imprime can act to prime multiple cell types of the innate immune system to better respond to and kill monocular antibody coated tumor cells.
2. These in vitro effects of Imprime on innate immune cells translate to efficacy in our in vivo mouse studies.
3. Imprime’s ability to prime immune cells allows for combination with multiple different tumor targeting antibodies in multiple different tumor types, setting the stage for multiple different clinical combinations