ABSTRACT

Imprime PGG\* (Imprime), is a soluble 8-1,3/1,6 immunomodulatory glucan, being developed in combination with monoclonal antibody therapy for multiple oncologic indications. To date, limited studies exist on the recognition and immunomodulatory activities of soluble glucans on the human immune system. Although yeast β-glucans have been shown to be capable of binding human cells through lecto-cyte complement receptor 3 (CR3), Mac-1, and CD11a integrin, the key components for this event were not elucidated. Here, we demonstrate that Imprime, a soluble carbohydrate pathogen associated molecular pattern (PAMP), is recognized by only certain human cells expressing CR3 (i.e., band to CR3-expressing myeloid cells, but not to CR3 expressing NK cells) and requires association by complement components. Inactivation of serum complement components restored a bias of binding and function. Surprisingly, not all healthy donor myeloid cells were capable of binding Imprime despite the presence of complement components. Looking into potential reasons for differential binding led to a strong correlation between being a high-immune binder and having a high-natural anti-β-glucan titer. Both in vitro and in vivo feasibility studies in humans demonstrate the potential for converting a lower-immune binder to a high-binder with anti-β-glucan antibodies. Given the preclinical requirement for Imprime binding to myeloid cells for antifungal effects, we propose that assessing imprinted binding to blood immune cells could be a predictive biomarker, and screening for high-binder patients or converting low-binders to high-binders by heating with high-titer plasma or IVIG, would enhance therapeutic efficiency.

OBJECTIVES

- Determine the characteristics of Imprime PGG binding to immune subsets in human whole blood (WB).
- Correlate Imprime PGG binding to function.
- Identify a predictive biomarker to screen for those patients with the highest potential to respond to Imprime PGG therapy in the clinic.

IMPRIME PGG\*

Imprime PGG binding to innate immune cells was significantly higher than that of β-glucan and mannose-terminated mannosides (MaA) (as tested by flow cytometry and intracellular staining). Taken together, this suggests Imprime is capable of binding to innate immune cells in a unique manner.

Oligochitosan (OCH) induced a dose-dependent increase in IL-8 release in WB, while the addition of β-glucan MAb induced a much smaller increase in IL-8 release compared to OCH. These data suggest that Imprime PGG binding to innate immune cells is not directly linked to the induction of IL-8 release.

Requirements for Imprime PGG Binding to Human Myeloid Cells in Whole Blood

Figure 4. Correlation of Imprime PGG Binding to Function in Healthy Human Whole Blood

- Ability of Serum/Plasma to Modify Imprime PGG Binding: Ability to alter a subject's ability to bind and activate a functional response to Imprime PGG

Figure 5. Requirements for Imprime PGG Binding to Human Myeloid Cells, Plasma, Mannose-terminated Mannosides (MaA), and Complement Components (CR3, Mac-1, and C5a).

- Potential to Modify Imprime PGG Binding in Healthy Human Whole Blood

Figure 6. Potential to Modify Imprime PGG Binding by Anti-β-glucan Antibodies

- Preclinical MOA & Lessons from Translation

Figure 11. Differential Imprime PGG Binding in Healthy Humans: Potential Predictive Biomarker

- Impact of serum/plasma on Imprime PGG Function: Ability to alter a subject's ability to bind and activate a functional response to Imprime PGG

Figure 12. Correlation of Imprime PGG Binding to Function: Ability to alter a subject's ability to bind and activate a functional response to Imprime PGG

- Potential to Modify Imprime PGG Mediated Cytokine Release in Vitro by Intravenous Immunoglobulin (IVIG)

Figure 13. Potential to Modify Imprime PGG Mediated Cytokine Release by Intravenous Immunoglobulin (IVIG)

- Potential to Modify Imprime PGG Binding by Intravenous Immunoglobulin (IVIG)

Figure 14. Potential to Modify Imprime PGG Binding by Intravenous Immunoglobulin (IVIG)

- Potential to Modify Imprime PGG Binding in Healthy Donors can be Modified with Intravenous Immunoglobulin (IVIG)

Figure 15. Potential to Modify Imprime PGG Binding in Healthy Donors can be Modified with Intravenous Immunoglobulin (IVIG)

- Preclinical MOA & Lessons from Translation

Figure 16. Potential to Modify Imprime PGG Binding by Intravenous Immunoglobulin (IVIG)

- Impact of serum/plasma on Imprime PGG Function: Ability to alter a subject's ability to bind and activate a functional response to Imprime PGG

Figure 17. Potential to Modify Imprime PGG Mediated Cytokine Release in Vitro by Intravenous Immunoglobulin (IVIG)