**Human anti-PD-L1/PD-1 Antibodies Exhibit Potent Immune Cell Activation**

**ABSTRACT**

Abstract: Immunomodulatory antibodies have shown great promise in recent clinical studies. Via inhibition of immunosuppressive signals on cancer cells or direct agonistic stimulation of T cells, a strong sustained antitumor immune response could be induced. Disruption of the interaction between PD-L1 and PD-1 has been one target for such antibody therapy. Using its proprietary G-MAB® antibody library, Sorrento has identified a number of human anti-PD-L1 and anti-PD-1 monoclonal antibodies (mAbs) and is currently preclinically developing the lead compounds. These mAbs exert strong immunomodulatory activity in vitro via immune cell activation and induction of cytokine production as well as antitumor activity in vivo.

**Methods:** The human mAbs were identified from Sorrento's G-MAB® antibody library and candidate mAbs were produced as fully human IgG1 antibodies. Characterization of the mAbs included functional in vitro studies using mixed lymphocyte reactions (MLR) to measure T-cell activation and cytokine production in vitro, as well as anti-tumor release in a syngeneic mouse cancer model.

**Results:** Sorrento has selected two lead human anti-PD-L1 mAbs as well as one PD-1 antibody, all of which possess excellent affinity for their respective cellular target. Functional analyses demonstrated potent T-cell activation and increased release of interferon-γ (IFN-γ) in MLR assays as well as in vivo anti-tumor activity.

**Conclusions:** The human anti-PD-L1 and anti-PD-1 antibodies identified from Sorrento's G-MAB® antibody library have demonstrated excellent functional characteristics in vitro as well as in vivo, and thus, might hold potential as future anti-cancer therapeutics.

**INTRODUCTION**

Anti-PD-L1 and Anti-PD-1 Antibodies

The Programmed Death 1 (PD-1) inhibitory receptor is expressed by T cells during long-term antigen exposure. Upon ligation with its ligand PD-L1 and PD-L2, whose expression can be elevated within inflamed tissues and the tumor microenvironment, it results in negative regulation of T-cell activity. This PD-1/PD-L1 interaction happens during the effector phase of a T-cell response in peripheral tissues. The blockade of this molecular engagement with specific antibodies to PD-1 or PD-L1 has been shown to result in the preferential activation of T cells with specificity for the cancer.

**In vitro Immunomodulation by Anti-PD-L1 mAbs**

To measure the ability of the anti-PD-L1 antibody to modulate T-cell responses, purified CD4+ cells were cultured with allogeneic dendritic cells, prepared by culturing monocytes in GM-CSF and IL-4 for seven days. Parallel plates were set up to allow collection of supernatants at day 2 or 3 and day 5 to measure IL-2 and IFN-γ, respectively, using a commercial ELISA kit. The remaining cells of the day 5 culture were assayed for CD25 expression as a measure of cell activation. The competitor mAbs were produced in-house, and used as positive controls. IgG1 and an unrelated STI human mAb was utilized as negative control antibody.

**In vivo Tumor Growth Inhibition by Anti-PD-L1 mAbs in a Syngeneic Tumor**

Similar to the studies described for our PD-L1 mAbs, to measure the ability of anti-PD-L1 antibody to modulate T-cell responses, purified CD4+ cells were cultured with allogeneic dendritic cells, prepared by culturing monocytes in GM-CSF and IL-4 for seven days. Parallel plates were set up to allow collection of supernatants at day 2 or 3 and day 5 to measure IL-2 and IFN-γ, respectively, using a commercial ELISA kit. The remaining cells of the day 5 culture were assayed for CD25 expression as a measure of cell activation. The competitor mAbs were produced in-house and used as positive controls. An unrelated STI human mAb was utilized as a negative control antibody.

**REFERENCES**


**CONCLUSIONS**

The human anti-PD-L1 and anti-PD-1 antibodies generated by Sorrento have demonstrated substantial in vitro functional characteristics as potent immunomodulatory molecules, as well as antitumor activity in vivo. These observations confirm our hypothesis that these antibodies might possess potential as future anti-cancer therapeutic agents.