CD80 vIgD-Fc Proteins Combine Checkpoint Antagonism and Costimulatory Signaling for Potent Anti-Tumor Immunity

Ryan Swanson, Mark Maurer, Chris Navas, Chelsea Gudgeon, Joe Küppers, Martin Wolfson, Katherine Lewis, Stacey R. Dillon, Steven D. Levin, Michael Kornacker, Stanford Peng

ABSTRACT

• Introduction: PD-1 pathway antagonists have revolutionized the treatment of metastatic melanoma in combination with anti-CTLA-4. However, inconsistent clinical outcomes remain challenging for their optimal use. Inhibitory signaling through CD28 is critical to this process, but the CD28 ligands CD80 and CD86 are often poorly expressed in tumors. This presents a gap for new therapeutic strategies to enhance PD-1/PD-1 ligand interactions in multiple tumor types.

• Experiments: Prattender et al. have shown that CD80 vIgD-Fc can only agonize CD28 in the context of L1-dependent costimulation. This provides an opportunity for the development of new CD80 derivatives that could improve antitumor immunity.

• Data Summary: The tumor CD28 ligand engagement was found to be essential for high PD-1/P-L and 288 staining. A panel of CD80 variants was generated using yeast display affinity maturation and selections against all three CD80 counterstructures. CD80 vIgD and vIgD-Fc were plated with titrated CD80 Fc, and vIgD-Fc demonstrated a range of binding towards human PD-1 dependent costimulation.

• Conclusions: Engineered CD80 vIgD-Fc proteins that deliver a localized CD28 costimulatory signal to T cells while selectively antagonizing the inhibitory PD-1/PD-1 pathway may provide a novel therapeutic strategy for enhancing antitumor immunity. Preclinical development of these candidates is ongoing.

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SUMMARY AND CONCLUSIONS

• CD80 vIgD-Fc are dual PD-1/P-L/CTLA-4 antagonists with PD-1-dependent, CD80 costimulation

• CD80 vIgD-Fc demonstrate superior tumor clearance and increased CD8 costimulation in vivo compared to durvalumab, an FDA-approved PD-L1 inhibitor

• This potential novel mechanism of action may represent a new, best-in-class immunotherapy for cancer patients

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