# Discovery of a Novel, Dual CD73 & PD-1 Targeting Multispecific Drug Fc-Conjugate (DFC) for the Treatment of Cancer

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## Background

The approval of several PD-1/L1 axis inhibitors has revolutionized cancer therapy and established a role for $CD8^+$ T cells in tumor destruction. While anti-PD-1 therapy has demonstrated durable responses, only a subset of patients respond. To improve response rates, we developed a multispecific PD-1/CD73 targeting DFC. CD73 catalyzes the rate limiting step in production of immuno-suppressive adenosine, which inhibits immune cell activation through a mechanism distinct from PD-1. Herein, we describe a first-in-class dual targeting DFC, comprising a multivalent conjugate of a small molecule CD73 inhibitor to a proprietary human IgG1 Fc-fusion with a PD-1 inhibitor peptide. This dual-targeting DFC has potential for differentiation from approved PD-1/L1 inhibitors.

## Methods

Binding of the dual targeting DFC to biotinylated hPD-1 was determined using a commercial kit and to human $CD8^+$ T cells by flow cytometry. CD73 inhibition was determined in cell-free and cell-based assays. Efficacy was evaluated in transgenic mice expressing human PD-1/PD-L1 with MC-38 (hPD-L1) tumors (Genoway, France). Tumor volumes were recorded and statistical analysis was conducted by t-test (Mann-Whitney) or two-way ANOVA.

## Results

The dual targeting DFC demonstrated potent activity against both checkpoint targets: Binding to hPD-1 with an $IC_{50}$ of < 1 nM and functional inhibition of CD73 with an $EC_{50}$ of 9 nM. Efficacy was determined in a humanized mouse model against the colon cell line MC-38 (hPD-L1). The dual targeting DFC demonstrated a statistically significant reduction in tumor volume (~55%) at a dose of 3 mg/kg ($P<0.0001$). Pembrolizumab biosimilar at 10 mg/kg did not result in a significant reduction in tumor volume.

## Conclusions

This work describes a dual targeting DFC with potent activity against two validated immune checkpoint pathways. The in vitro activity translated to efficacy in a humanized mouse model at doses as low as 3 mg/kg. The relative contributions of each ligand to activity against different tumors is under investigation as Cidara's first multispecific DFC advances through preclinical development.