CD377, a novel antiviral Fc-conjugate, demonstrates superior reduction of viral burden and cytokine levels compared to oseltamivir in a lethal mouse model of influenza A(H1N1) infection

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Background: AVCs (antiviral Fc-conjugates) are novel, long-acting immunotherapeutic conjugates of potent antivirals and the Fc domain of human IgG1. CD377, an AVC development candidate for the prevention and treatment of influenza A and B, comprises a novel neuraminidase inhibitor conjugated to IgG1 Fc. CD377 has demonstrated potent, broad-spectrum activity against influenza at levels greater than current influenza antivirals and efficacy in multiple influenza challenge models. Herein we characterize the activity of CD377 on viral lung burden and host immune responses in a lethal mouse model of influenza infection.

Materials/methods: BALB/c mice were challenged intranasally with 3 x 10^2 PFU (3 x LD95) of mouse-adapted influenza A/Puerto Rico/8/1934 (H1N1). Treatment was started 2 h post-challenge with either CD377 as a single subcutaneous dose (0.1 – 3 mg/kg) or oral oseltamivir (5 or 50 mg/kg BID x 4 days). At day 4 post-infection, lungs were harvested; cytokine levels were determined via ELISA and viral burden was determined by plaque assay.

Results: CD377 demonstrated a dose-dependent reduction in viral lung burden resulting in 1.06 log at 0.1 mg/kg, 2.12 log at 0.3 mg/kg, 3.17 log at 1 mg/kg, and 3.63 log at 3 mg/kg compared with PBS control titers of 5.1 x 10^7 PFU/g (Figure). Oseltamivir demonstrated minimal effects on reduction of viral lung burden with 0.8 and 0.78 log reductions at the humanized dose (5 mg/kg) and 50 mg/kg, respectively. Minimal difference in lung burden was observed between negative controls, PBS and hIgG1 Fc of 0.47 log. The dose-dependent reduction of viral burden by CD377 correlated with a dose-dependent reduction of multiple cytokines TNF-α, IL-6, MCP-1, MIP-1α, and KC, which at the 3 mg/kg dose approached levels observed in uninfected control mice (Figure). Oseltamivir showed a lesser effect on cytokine reduction compared to CD377.

Conclusions: CD377 demonstrated a superior profile compared to oseltamivir in controlling infection and inflammation in a lethal H1N1 influenza model. CD377 mediated protection via multi-log reduction in viral lung burden correlating with reduction in pro-inflammatory cytokines. These results underscore the novel mechanism of action of AVCs and support further development of CD377 for prevention and treatment of influenza infection.

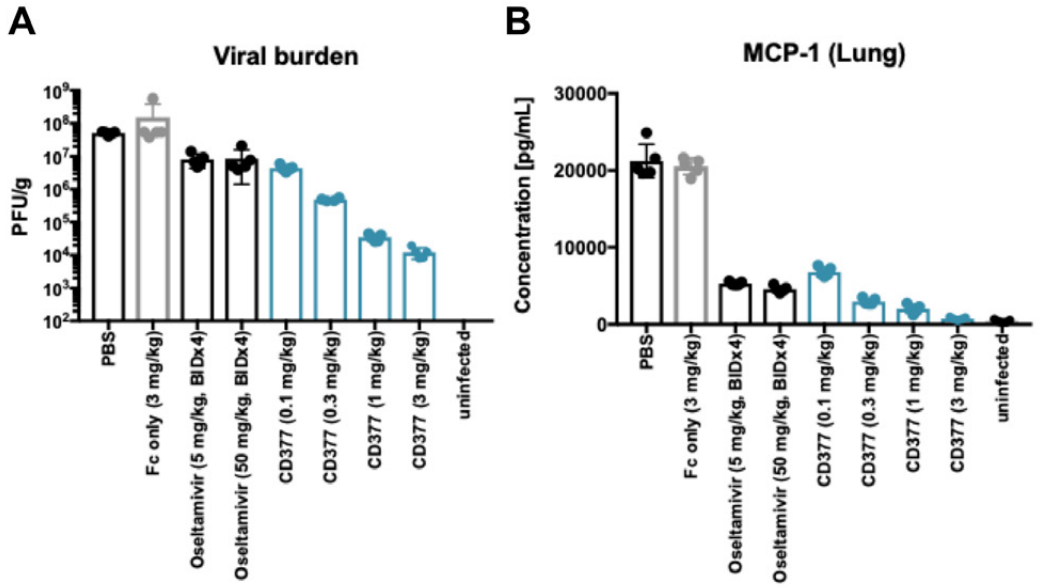

Figure: CD377 reduces viral burden and cytokine MCP-1 with dose-dependency. CD377 efficacy in a lethal mouse model of influenza A/PR/8/1934 (H1N1) reduces (A) viral burden and (B) MCP-1 levels in the lung in dose-dependency on day 4 post-infection.

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