



Abstract 8820

Fc-mediated Fc γ receptor engagement of CD377, a novel antiviral Fc-conjugate, translates into potent antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity activity

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Background: Cidara's AVCs (antiviral Fc-conjugates) are novel, immunotherapeutic conjugates of potent, antiviral agents with the Fc domain of human IgG1. CD377 is an AVC development candidate for the prevention and treatment of seasonal and pandemic influenza that has demonstrated potent, broad-spectrum activity and efficacy in multiple influenza challenge mouse models. Herein, we characterize Fc-mediated interaction of CD377 with Fc γ receptors and the function of CD377 in antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) against influenza.

Materials/methods: CD377 interaction with multiple Fc γ receptors (human and murine) was determined by ELISA. For ADCC and ADCP experiments, MDCK cells were infected with varying multiplicity of infection (MOI) for 18-24 h and treated with CD377 ranging from 0.1 – 1000 nM. ADCC and ADCP was determined according to manufacturer's instructions.

Results: CD377 binding affinity to human Fc γ receptors (I, IIa, IIIa) was comparable to unconjugated Fc (hIgG1 Fc), demonstrating that the conjugation chemistry did not interfere with Fc-mediated effector functions of the antiviral Fc-conjugate, CD377. Additionally, the Fc γ receptor binding profiles of CD377 are comparable to those observed for a full-length human IgG1 antibody.

Immune cells, such as NK cells and macrophages, are crucial mediators of host defense against influenza infection. A hallmark of macrophage function in immunity is phagocytosis of antibody-opsonized infected cells. CD377 mediated MOI- and dose-dependent ADCP via Fc γ RIIa engagement (Figure). NK cells have been demonstrated to be important in immune defense against influenza infection by inducing apoptosis of infected cells through the release of perforin/granzymes. CD377 induced robust ADCC via Fc γ RIIIa engagement with MOI- and dose-dependency against multiple seasonal and pandemic influenza A/H1N1, influenza A/H3N2, and influenza B strains.

Conclusions: CD377 triggers potent, broad-spectrum induction of ADCP and ADCC, thereby contributing to immune defense against multiple seasonal and pandemic influenza A and B strains. This potent induction of Fc-mediated effector function of CD377 in combination with potent efficacy in lethal mouse models of influenza infection support further development of CD377 for the prevention and treatment of influenza infection.

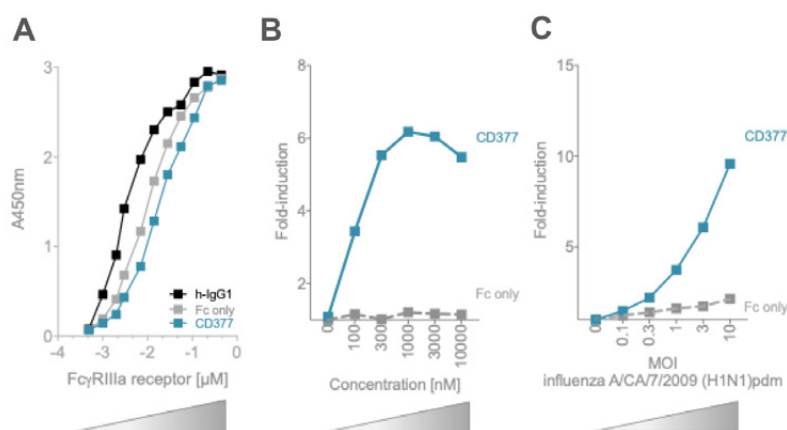


Figure: CD377 engages immune cells. CD377 (A) binds to human Fc γ RIIIA receptor and triggers ADCC in (B) dose- and (C) MOI dependency.

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