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CD388, a novel Drug Fc-conjugate (DFC), demonstrates potent, universal activity against influenza A and B

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Disclosures

Employee and shareholder of Cidara Therapeutics

A universal influenza prophylactic agent does not yet exist

From the 2018-2019 flu season (USA)

35.5 million
Sick

16.5 million
Seek HCP care

490,600
Hospitalizations

34,200
Deaths

Source: CDC, WHO

Significant healthcare burden and mortality

Significant limitations with existing flu therapeutics

Vaccines
Limited VE

Monoclonal Abs
Type specific

Small molecules
Limited prophylaxis

Need for long-acting flu prevention with potent, universal activity

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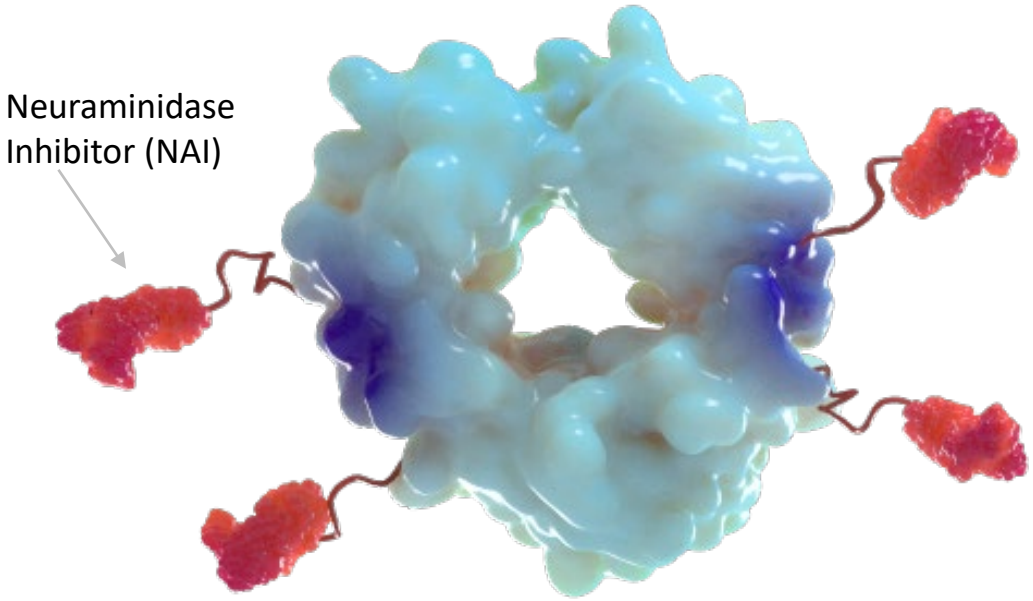
Drug Fc-Conjugates (DFCs) are a novel modality for prevention of Influenza

CD388



hIgG1 Fc fragment

- **The DFC platform is tunable and modular**
  - The inhibitor is a potent, broad spectrum small molecule NA inhibitor
  - Multivalent inhibitor presentation allows for retention of activity against NAI resistant isolates
  - The NAI is connected to the Fc fragment by a stable, non-cleavable linker
  - NAI to Fc ratio is tunable for efficacy and physical properties
  - Modified Fc to extend half-life

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CD388 is a potent antiviral that covers NAI resistant strains

Assay: in vitro cleavage of a neuraminidase substrate by virus in the presence of test articles

Influenza subtype	**CD388** Median IC_{50} [nM] (IC_{50} [nM] range)	**Zanamivir** Median IC_{50} [nM] (IC_{50} [nM] range)	**Oseltamivir** Median IC_{50} [nM] (IC_{50} [nM] range)
A/H1N1 (n=17)	**1.29** (0.01 to 2.36)	**0.26** (0.16 to 0.56)	**0.74** (0.16 to 1.85)
A/H3N2 (n=18)	**2.24** (0.31 to 3.88)	**0.32** (0.25 to 2.75)	**0.25** (0.07 to 0.54)
B (n=13)	**2.37** (0.05 to 7.44)	**1.93** (0.16 to 8.88)	**27.05** (5.91 to 42.88)
H275Y A/Alabama/03/2020 (H1N1)pdm09	**0.98**	**0.16**	**426.80**
H134N B/Laos/0080/2016	**4.66**	**310.80**	**171.80**

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CD388 outperforms approved small molecule antivirals in CPE assays

Assay: In vitro cell-based assay measuring test article ability to inhibit virus induced CPE*

Influenza subtype	CD388 Median EC_{50} [nM] (EC_{50} [nM] range)	Oseltamivir Median EC_{50} [nM] (EC_{50} [nM] range)	Zanamivir Median EC_{50} [nM] (EC_{50} [nM] range)	Baloxavir Median EC_{50} [nM] (EC_{50} [nM] range)
A/H1N1 (n=16)	**0.80** (0.01 to 11.25)	**185.3** (29.39 to >10,000)	**128.5** (17.22 to 7482)	**1.44** (0.11 to 26.55)
A/H3N2 (n=15)	**1.27** (0.03 to 8.53)	**1166** (2.58 to >10,000)	**2160** (3.06 to >10,000)	**1.62** (<0.00001 to 8.92)
B (n=13)	**1.72** (0.03 to 8.71)	**1483** (151.9 to >10,000)	**401.1** (31.9 to 2991)	**9.99** (0.12 to 40.82)

❖ *CD388 demonstrates superiority to oseltamivir and zanamivir; on par with baloxavir*

(Increased activity in CPE vs NAI assays likely due to avidity, or aggregation effects)

*MOI not optimized to determine a formal resistance profile

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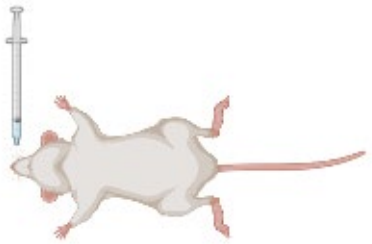
CD388 mouse efficacy screening models



Infection
(3x LD_{95})

Treatment (IM)
(T+2h)

Lung burden
(T+4d)

Health checks
Body weight
(T+14-21d)

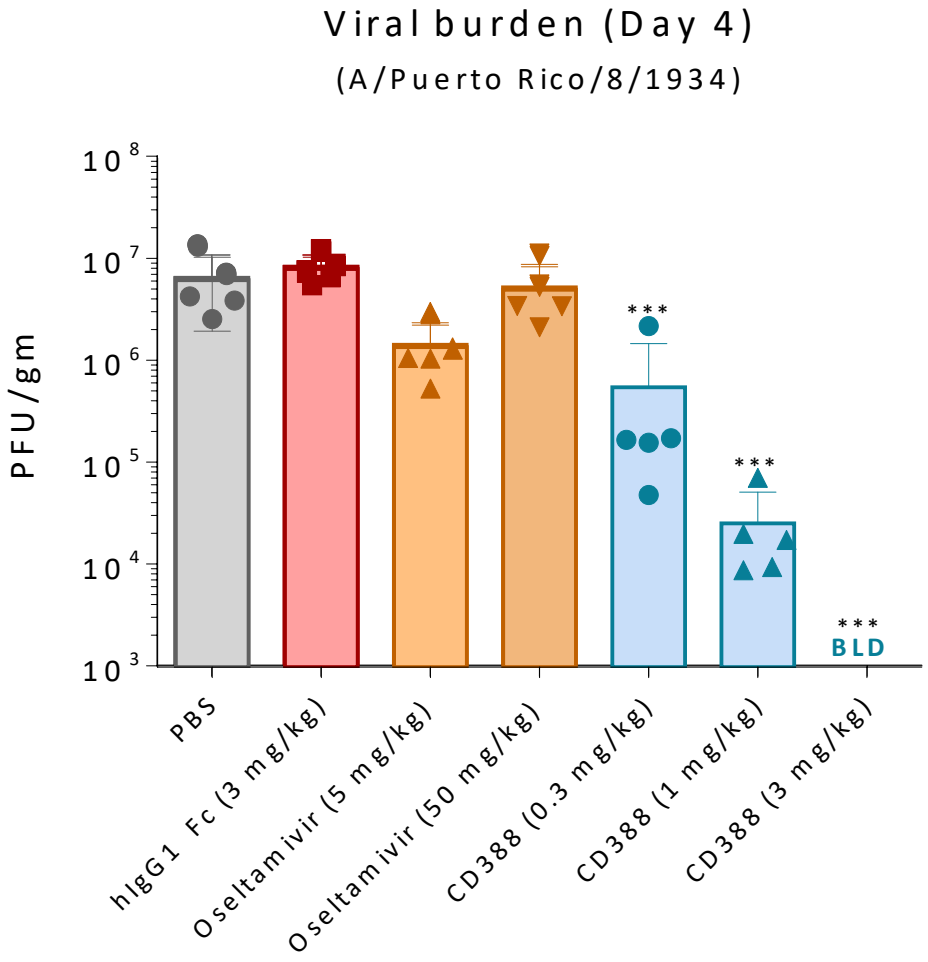
Additional in vivo studies:

BALB/c, SCID, Tg32, and Fcer1g-/- mice
Dose schedules (T-7d to T+72h)

Additional readouts:

Cytokine profile
Histopathology

Superior activity of CD388 in a lung burden model (A/PR/8/1934)



Oseltamivir dosed (PO) twice daily for 4 days
CD388 administered as a single IM dose

- No activity from Fc alone, as expected
- Very modest signal with oseltamivir at the human equivalent AND 10x human equivalent doses
- **A single 0.3 mg/kg dose of CD388 demonstrates similar efficacy to a 40 mg/kg total oseltamivir dose**

Statistical analysis was performed by one-way ANOVA using Dunnett's multiple comparisons test (***P<0.001) in GraphPad Prism. BLD = <10 pfu

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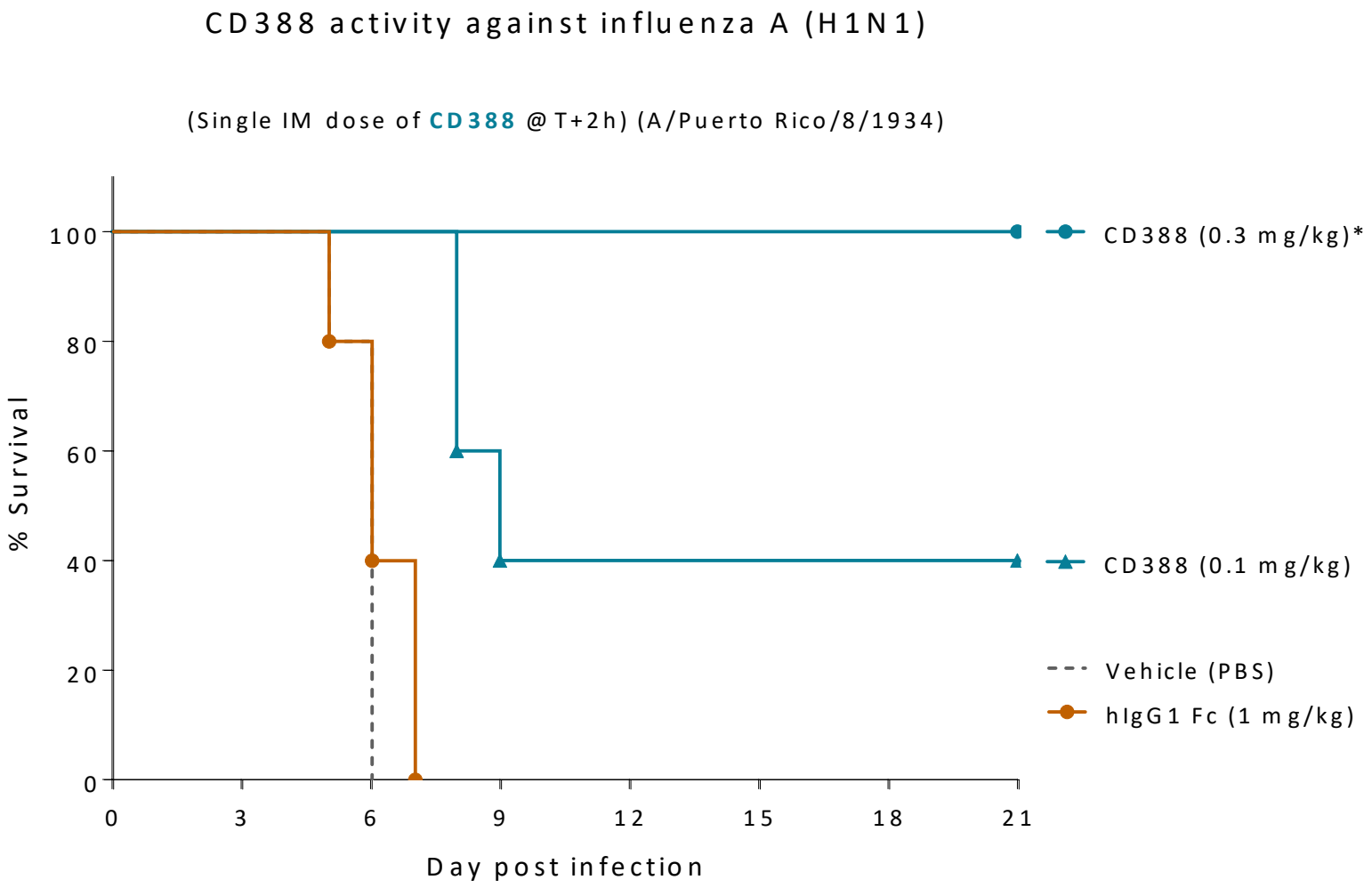
In vitro potency translates to efficacy in lethal challenge models

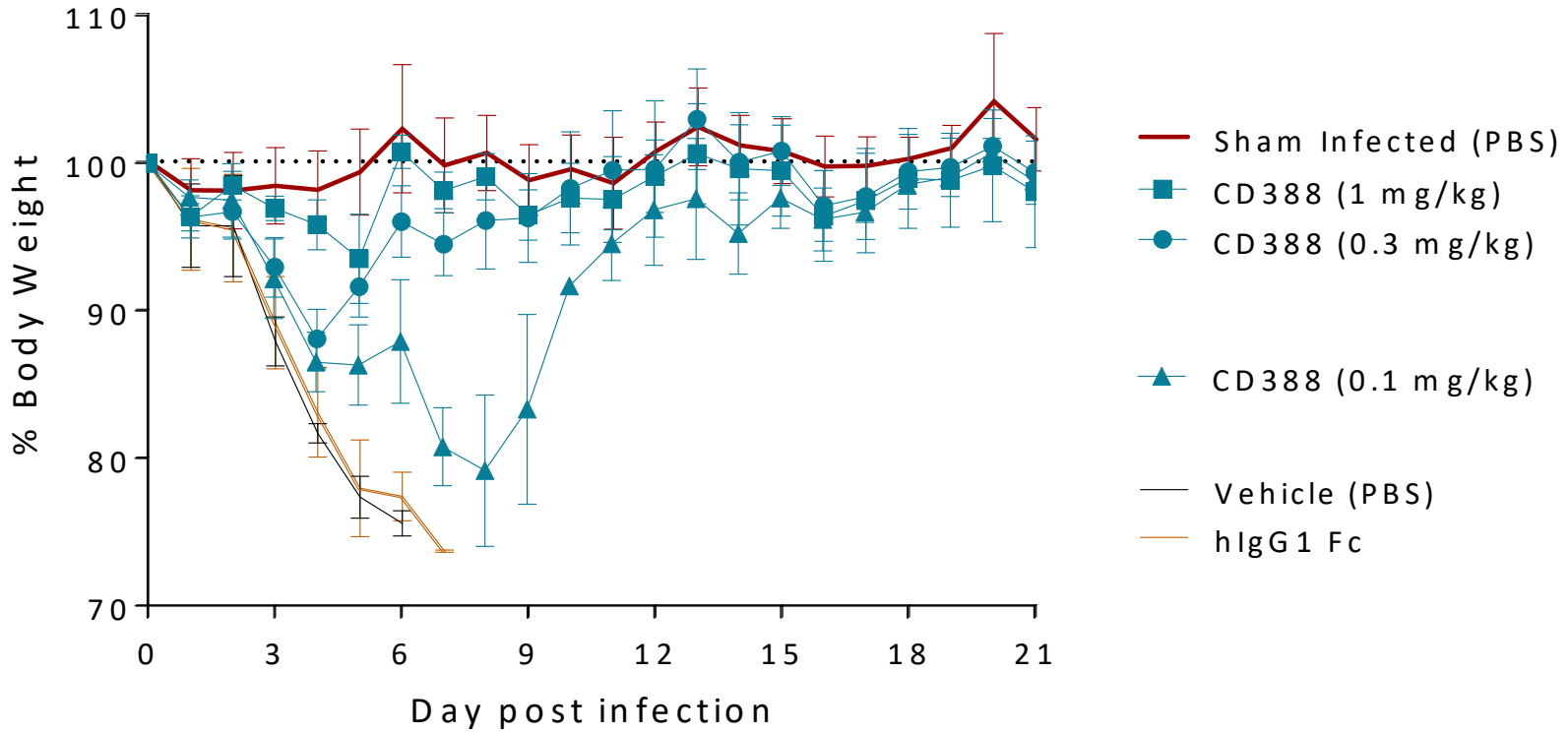


*P=0.0035 (Mantel-Cox)

Minimal body weight reduction with low doses of CD388

CD388 activity against influenza A (H1N1)

(Single IM dose of **CD388** @ T+2h) (A/Puerto Rico/8/1934)



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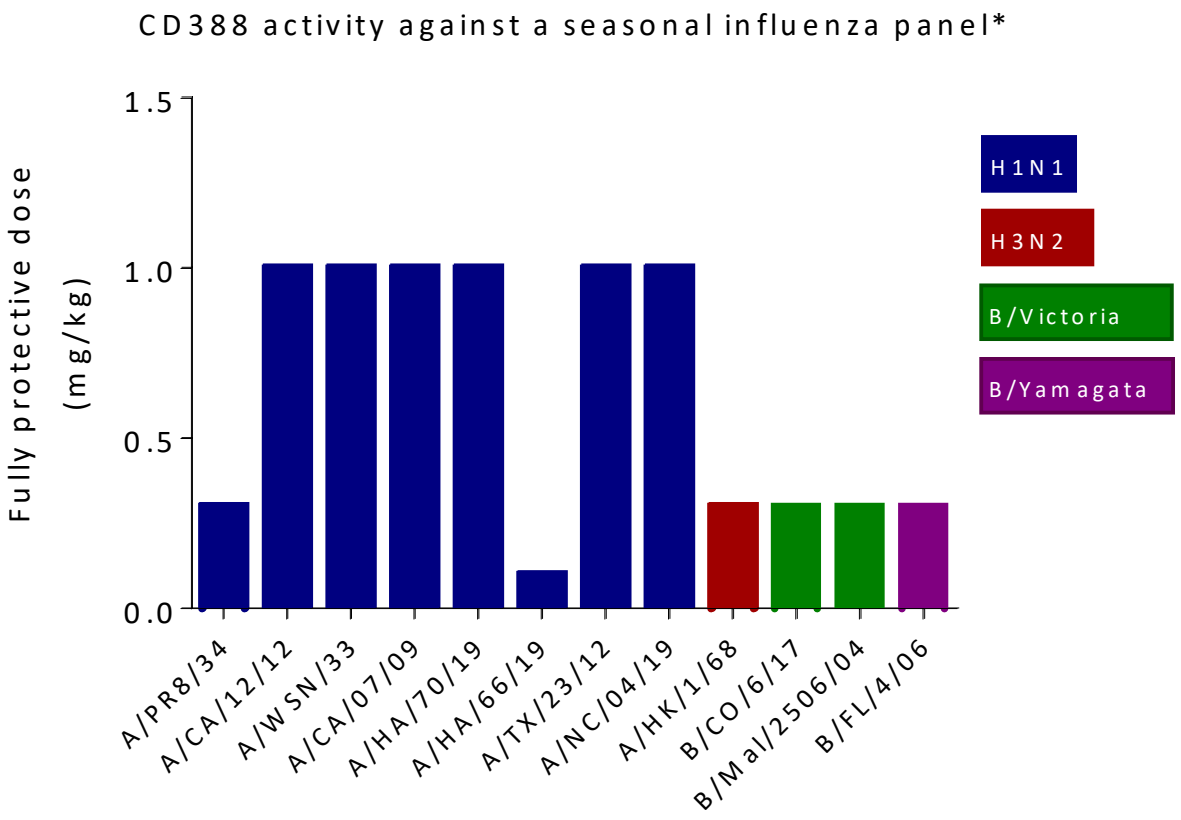
Potent and universal activity of CD388 against seasonal influenza*



- Single 1 mg/kg (or lower doses) fully protective against all four seasonal flu types
- Panel includes pandemic and neuraminidase-resistant (H275Y) isolates
- **Based on these and other preclinical data we believe CD388 has the potential to offer universal coverage against influenza A and B**

**Lethal influenza model in BALB/c mice with animals receiving 3x the LD_{95} of virus followed by a single dose of CD388, 2h post challenge*

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Acknowledgements – *Preclinical development of CD388*

Cidara Therapeutics
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Department of Microbiology
Department of Immunology
Department of Preclinical Development

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Sumit Chanda, PhD (TSRI)
Laura Martin-Sancho, PhD (Imperial College)
Paul DeJesus (TSRI)

CD388, a novel drug Fc-conjugate (DFC), demonstrates a high barrier to resistance and retains potent activity against neuraminidase inhibitor-resistant influenza A and B

Simon Döhrmann, PhD
Session: Antivirals, Monoclonal Antibodies and Combinations
Date: Thursday, May 4, 2023

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