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

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ISIRV 2023 Conference
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

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

Vaccines
Limited VE

Monoclonal Abs
Type specific

Small molecules
Limited prophylaxis

Significant limitations with existing flu therapeutics
Drug Fc-Conjugates (DFCs) are a novel modality for prevention of Influenza

CD388

- 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
**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

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<tbody>
<tr>
<td>A/H1N1 (n=17)</td>
<td>1.29 (0.01 to 2.36)</td>
<td>0.26 (0.16 to 0.56)</td>
<td>0.74 (0.16 to 1.85)</td>
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<tr>
<td>A/H3N2 (n=18)</td>
<td>2.24 (0.31 to 3.88)</td>
<td>0.32 (0.25 to 2.75)</td>
<td>0.25 (0.07 to 0.54)</td>
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<tr>
<td>B (n=13)</td>
<td>2.37 (0.05 to 7.44)</td>
<td>1.93 (0.16 to 8.88)</td>
<td>27.05 (5.91 to 42.88)</td>
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<td>H275Y</td>
<td>0.98</td>
<td>0.16</td>
<td>426.80</td>
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<td></td>
<td>A/Alabama/03/2020 (H1N1)pdm09</td>
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<tr>
<td>H134N</td>
<td>4.66</td>
<td>310.80</td>
<td>171.80</td>
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<td>B/Laos/0080/2016</td>
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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*

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

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.

- 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
In vitro potency translates to efficacy in lethal challenge models

CD388 activity against influenza A (H1N1)

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

*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)
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
Acknowledgements – Preclinical development of CD388

Cidara Therapeutics
Les Tari (CSO) and the rest of the management team
Department of Chemistry
Department of Protein Chemistry
Department of Microbiology
Department of Immunology
Department of Preclinical Development

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

The team at Janssen Pharmaceuticals

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