In Vivo Efficacy of CD388 Against Seasonal Influenza in Prophylaxis in Immune Competent Mice, and in a Severe Immunodeficient (SCID) Mouse Model

James Levin, PhD
IDWeek 2023
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

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

Source: CDC, WHO
Drug Fc-Conjugates (DFCs) are a novel modality for prevention of Influenza

- The DFC platform is tunable and modular
  - The inhibitor is a potent, broad spectrum small molecule NA inhibitor
  - 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
  - **Multivalent presentation of inhibitor allows for retention of activity against NAI-resistant isolates**
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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<thead>
<tr>
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<tbody>
<tr>
<td>A/H1N1 (n=16)</td>
<td>0.80 (0.01 to 11.25)</td>
<td>185.3 (29.39 to &gt;10,000)</td>
<td>128.5 (17.22 to 7482)</td>
<td>1.44 (0.11 to 26.55)</td>
</tr>
<tr>
<td>A/H3N2 (n=15)</td>
<td>1.27 (0.03 to 8.53)</td>
<td>1166 (2.58 to &gt;10,000)</td>
<td>2160 (3.06 to &gt;10,000)</td>
<td>1.62 (&lt;0.00001 to 8.92)</td>
</tr>
<tr>
<td>B (n=13)</td>
<td>1.72 (0.03 to 8.71)</td>
<td>1483 (151.9 to &gt;10,000)</td>
<td>401.1 (31.9 to 2991)</td>
<td>9.99 (0.12 to 40.82)</td>
</tr>
</tbody>
</table>

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

*MOI not optimized to determine a formal resistance profile
### 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

<table>
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<tbody>
<tr>
<td>H275Y A/Alabama/03/2020 (H1N1)pdm09</td>
<td>0.98</td>
<td>0.16</td>
<td>426.80</td>
</tr>
<tr>
<td>H134N B/Laos/0080/2016</td>
<td>4.66</td>
<td>310.80</td>
<td>171.80</td>
</tr>
</tbody>
</table>

- **CD388 retains activity against clinically relevant neuraminidase variants**

  (CDC NAI Susceptibility Reference Panel; version 2/3)
CD388 mouse efficacy screening models - prevention

**Administration (IM/SC)**
* (T-7d)

**Infection (3x LD\(_{95}\))**
* (T+0d)

**Health checks**
* Body weight (T+21d)

**Kaplan-Meier Survival curves**

**Additional in vivo studies:**

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

**Additional readouts:**

- Cytokine profile
- Lung burden
In vitro potency translates to efficacy in lethal challenge models

**Model:** T-7d prophylaxis against H1N1 (single dose)

**CD388 activity against influenza A (H1N1)**

(A/Puerto Rico/8/1934)

- % Survival
- Day post infection

- **Vehicle (PBS)**
- **hIgG1 Fc (1 mg/kg)**
- **CD388 (1 mg/kg)**
- **CD388 (0.3 mg/kg)**
- **CD388 (0.1 mg/kg)**
- **CD388 (0.03 mg/kg)**
Minimal body weight reduction with low doses of CD388

Model: T-7d prophylaxis against H1N1 (single dose)
CD388 is a potent antiviral in both prevention and treatment models

### Prevention (T-7d)

<table>
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<th>Subtype</th>
<th>Number of isolates tested</th>
<th>Fully protective dose required for complete subtype coverage (mg/kg)</th>
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<tbody>
<tr>
<td>A (H1N1)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>B (Victoria)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>B (Yamagata)</td>
<td>1</td>
<td>0.3</td>
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### Treatment (T+2h)

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<td>0.3</td>
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<tr>
<td>B (Yamagata)</td>
<td>1</td>
<td>0.3</td>
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- 1 mg/kg fully protective @ T+72h in a delayed treatment model

- A single dose of CD388 at 1 mg/kg is fully protective against lethal challenge by seasonal isolates
- This includes H275Y and H134N isolates resistant to oseltamivir and zanamivir, respectively
CD388 is more active than approved drugs in an immune-compromised model

Model: Severe Combined Immunodeficient (SCID) - Mice lacking B and T lymphocytes

CD388 activity in a SCID model (A/PR/8/34) (H1N1)

Dosing (n=5/group):
Oseltamivir (5 mg/kg, bid x5d)
Baloxavir (15 mg/kg, bid x1d)
CD388 (1, 3, & 10 mg/kg, single)

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<td>Baloxavir</td>
<td>16</td>
</tr>
<tr>
<td>CD388</td>
<td>&gt;21</td>
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CD388 achieves prolonged protection in a murine SCID model

Model: Severe Combined Immunodeficient (SCID) - Mice lacking B and T lymphocytes

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<td>16</td>
</tr>
<tr>
<td>CD388 (1 mg/kg)</td>
<td>26</td>
</tr>
<tr>
<td>CD388 (3 mg/kg)</td>
<td>30</td>
</tr>
<tr>
<td>CD388 (10 mg/kg)</td>
<td>35</td>
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CD388 activity in a SCID model (A/PR/8/34) (H1N1)

% Survival

Day Post Infection

CIDARA THERAPEUTICS
CD388 has a low resistance potential and is active at low [plasma]

- No significant change in CD388 susceptibility over time in this model
- Re-emergence of infection when plasma levels drop below ~0.2 µg/mL (0.091 – 0.171)
CD388 is a potent antiviral superior to existing therapeutic options

CD388 demonstrates:

- Exceptional activity against seasonal influenza in prevention and treatment models
- Activity against naturally occurring neuraminidase variants
- Superior protection in an immune-deficient model of influenza
- A low resistance potential and activity at low plasma concentrations
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

The team at Janssen Pharmaceuticals

External Collaborators
Stacey Schultz-Cherry, PhD (St. Jude’s)
Sumit Chanda, PhD (TSRI)
Laura Martin-Sancho, PhD (Imperial College)
Paul DeJesus (TSRI)

Efficacy of CD388, a Novel Drug Fc-Conjugate (DFC), is Driven by the Small Molecule Neuraminidase Inhibitor (NAI)
Simon Döhrmann, PhD
Session Title: Antimicrobial Novel Agents
Session Date: Saturday October 14, 2023
Session Time: 12:15 PM - 1:30 PM
Session Location: BCEC Poster Hall

Single Ascending Dose Safety, Tolerability, and Pharmacokinetics of Subcutaneous and Intramuscular CD388, a Novel Long-acting Drug-Fc Conjugate for Universal Prevention of Seasonal and Pandemic Influenza
Shawn Flanagan, PhD
Session Title: New Antimicrobial Drug Development
Session Date: Saturday, October 14, 2023
Session Time: 12:15 PM – 1:30 PM
Session Location: Hall B + C