Efficacy of CD377, a Novel Antiviral Fc-Conjugate, Against Seasonal Influenza in Lethal Mouse Infection Models

James Levin, PhD
Cidara Therapeutics
San Diego, CA
IDWeek 2020
Abstract 159
All authors are employees and stockholders of Cidara Therapeutics, Inc.
Cidara’s Cloudbreak AVCs: a new class of long-acting antiviral

Long acting antiviral activity and potential immune engagement

AVC = Anti Viral Conjugate

Designed for rapid onset, potent activity coupled with 3-6 months of protection
Not vaccines, monoclonal antibodies, or traditional small-molecule therapeutics

A stable conjugate of a potent neuraminidase inhibitor with a human antibody Fc

<table>
<thead>
<tr>
<th>TARGETING MOIETY (TM)</th>
<th>Fc MOIETY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Direct anti-viral activity</td>
<td>• To engage immune system</td>
</tr>
<tr>
<td>• Inhibits essential surface target</td>
<td>• To extend PK: 3 – 6 months</td>
</tr>
</tbody>
</table>

Potent antivirals ➔ Fc antibody fragment
The challenges of seasonal influenza

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**

**Dominant influenza type varies by season and even within a season**

**Need for preventatives with broad, universal activity**

Source: CDC, WHO
The challenges of seasonal influenza – incomplete vaccine coverage

**Vaccine Effectiveness (2018-19)**

- **Age Group**: 18-49, 50-64, 65+
- **% VE**:
  - 18-49: 30%
  - 50-64: 20%
  - 65+: 10%

**Vaccine Effectiveness (%)**

- 2014-15: 20%
- 2015-16: 40%
- 2016-17: 50%
- 2017-18: 50%
- 2018-19: 20%
### FLU AVC profile summary

**Now in IND-enabling studies**

<table>
<thead>
<tr>
<th>Target Attribute</th>
<th>AVCs in Preclinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Universal prevention and treatment</td>
</tr>
<tr>
<td><strong>Spectrum</strong></td>
<td>A &amp; B + drug resistant strains, low resistance potential</td>
</tr>
<tr>
<td><strong>Safety/Tolerability</strong></td>
<td>High safety margin for long term prevention</td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>1 to 2x per flu season</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>SubQ, IM and IV dosing</td>
</tr>
<tr>
<td><strong>Target Populations</strong></td>
<td>Higher risk populations where vaccines are not effective</td>
</tr>
</tbody>
</table>

Data available at: [https://ir.cidara.com/presentations](https://ir.cidara.com/presentations)
CD377 mouse efficacy screening models

BALB/c, SCID, Tg32 mice
(ketamine or isoflurane anesthesia)

Virus (3x LD$_{95}$)
T+0h

T-28d  T-7d  T+2h  T+72h

Dose route (IV, SC, IM)
Single dose (0.03 to 3 mg/kg)

14 – 28 days post viral challenge

Survival
Body weight (BW)
Lung burden
Histopathology
Cytokines
Potency of CD377 against an H1N1 pandemic isolate

Lethal infection in BALB/c mice. Single IM dosing at T+2h

CD377 activity against pandemic H1N1 (A/CA/12/2012)

CD377 has been tested against 10 H1N1 isolates with fully protective doses between 0.03 and 0.3 mg/kg
Potency of CD377 against an H3N2 isolate

Lethal infection in BALB/c mice. Single IM dosing at T+2h

CD377 dose response evident in daily body weight measurements

Slightly greater potency against H3N2
Potency of CD377 against influenza B isolates

Lethal infection in BALB/c mice. Single IM dosing at T+2h
Summary of CD377 activity against influenza A/B

CD377 efficacy screening against influenza A/B (to date)

<table>
<thead>
<tr>
<th>Influenza</th>
<th>Subtype</th>
<th>n</th>
<th>Fully protective dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H1N1</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>A</td>
<td>H3N2</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>A</td>
<td>H5N1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>A</td>
<td>H1N1 (H275Y)</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>B</td>
<td>Victoria</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>B</td>
<td>Yamagata</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- A single 0.3 mg/kg dose of CD377 is fully protective against seasonal influenza
- Against highly pathogenic influenza (H5N1), 1.0 mg/kg was protective
- **CD377 demonstrated exceptional potency against 16 seasonal isolates**
Activity of CD377 in long-term prevention models

Lethal infection in BALB/c mice. Single, IM dosing at T-28 days

- Single 1 mg/kg (or less) doses protective against H1N1, H3N2, B (Yamagata/Victoria)
- Data strongly supportive of CD377 use as a long-term preventative
Investigating body weight trends in our LRT screening model

Increasing the translatability of data to the clinic

Virus: 3x LD$_{95}$
Ketamine anesthesia

Question: Is the initial BW loss a technical artifact of a severe screening model?
When virus was introduced in the URT, the model was still lethal, with CD377 fully protective at 0.1 mg/kg.

When virus was seeded into the URT, the previously observed BW loss was absent for all dose groups (0.1, 0.3, 1 mg/kg).

 Isoflurane anesthesia

*When virus was introduced in the URT, the model was still lethal, with CD377 fully protective at 0.1 mg/kg.*
Oseltamivir was not protective when dosed 72h post-challenge at 20 mg/kg (bid x 5)

A single dose of CD377 at 1 mg/kg was protective

CD377 has significant potential as both a preventative and a therapeutic treatment against seasonal influenza
Highly active against seasonal influenza with single doses of 0.3 mg/kg or less

Active against seasonal influenza in 28-Day prevention models @ 1 mg/kg or less

Active against H275Y harboring H1N1 isolates

Effective in immune compromised (SCID) models (see poster 1276)

Superior activity to oseltamivir in therapeutic models

Equivalent potency by IV, SC, or IM dosing routes

Significant reduction in lung burden in mouse and ferret models (see talk 162)
Acknowledgments

✓ a supportive management team

✓ an innovative and dedicated R&D team

- Chemistry department
- Protein Chemistry department
- Microbiology department
- Immunology department
- In vivo team

Special thanks to Dr. Amy Krafft (NIH/NIAID) and their Preclinical Services Program for the H5N1 study run at Utah State.