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

Disclosures

All authors are employees and stockholders of Cidara Therapeutics, Inc.

Cidara's Cloudbreak AVCs: a new class of long-acting antiviral

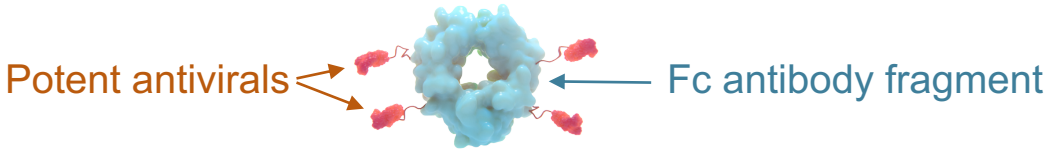
Long acting antiviral activity and potential immune engagement

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



TARGETING MOIETY (TM)	Fc MOIETY
• *Direct anti-viral activity* • *Inhibits essential surface target*	• *To engage immune system* • *To extend PK: 3 – 6 months*

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

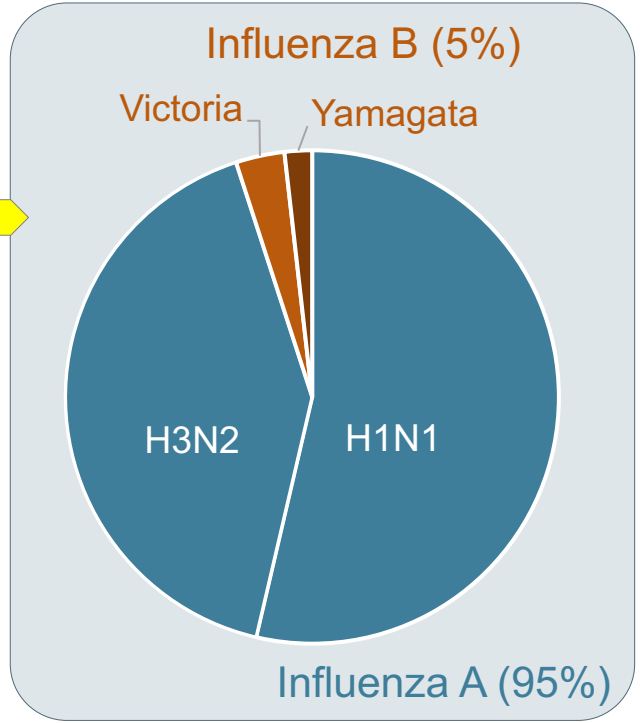
34,200
Deaths

Source: CDC, WHO

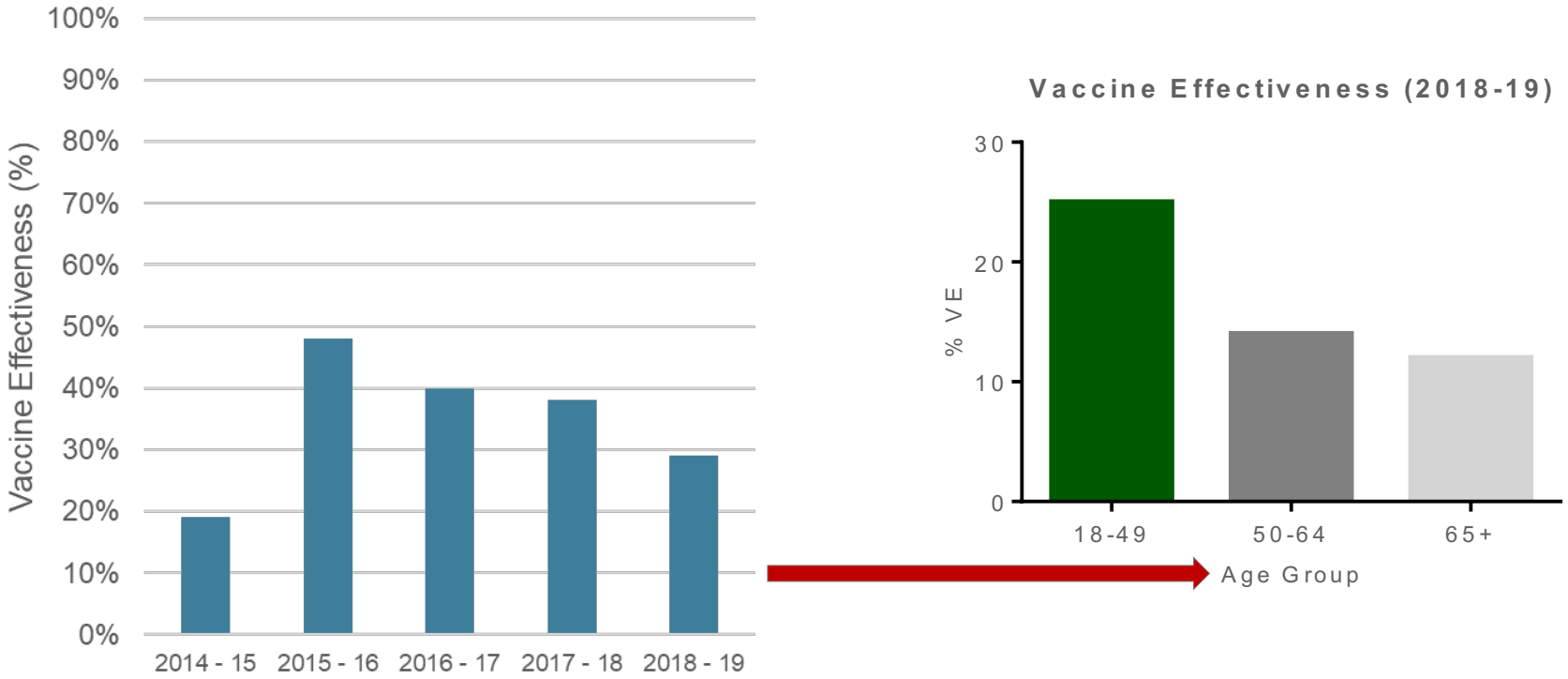
Significant healthcare burden and mortality

Dominant influenza type varies by season and even within a season

Need for preventatives with broad, universal activity



The challenges of seasonal influenza – incomplete vaccine coverage



FLU AVC profile summary

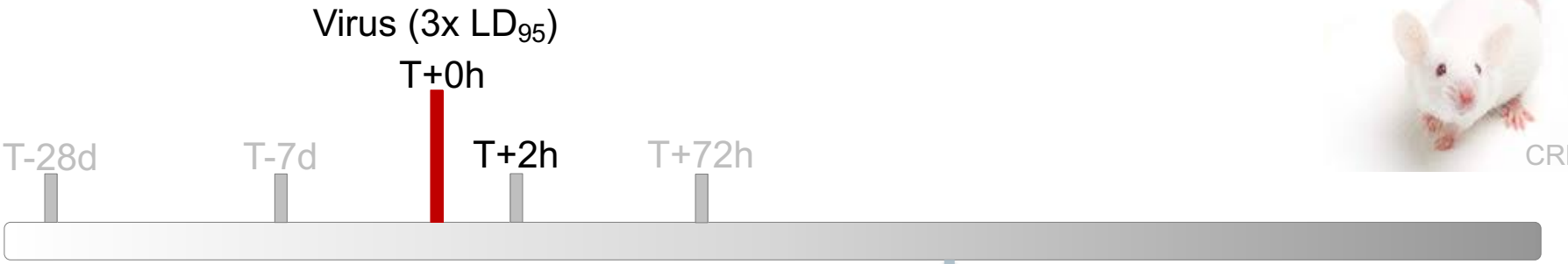
Now in IND-enabling studies

	Target Attribute	AVCs in Preclinical Development
Indication	Universal prevention and treatment	Data are supportive
Spectrum	A & B + drug resistant strains, low resistance potential	Potent *in-vivo* activity against all seasonal and pandemic strains
Safety/Tolerability	High safety margin for long term prevention	> 50x exposure margin in 14-day primate toxicity studies
Dosing Frequency	1 to 2x per flu season	Estimated 3 to 6-month coverage with single SC or IM dose
Route of Administration	SubQ, IM and IV dosing	Equivalent exposures and efficacy
Target Populations	Higher risk populations where vaccines are not effective	Equally effective in immune compromised & immune competent models at similar doses

Data available at: https://ir.cidara.com/presentations

CD377 mouse efficacy screening models

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



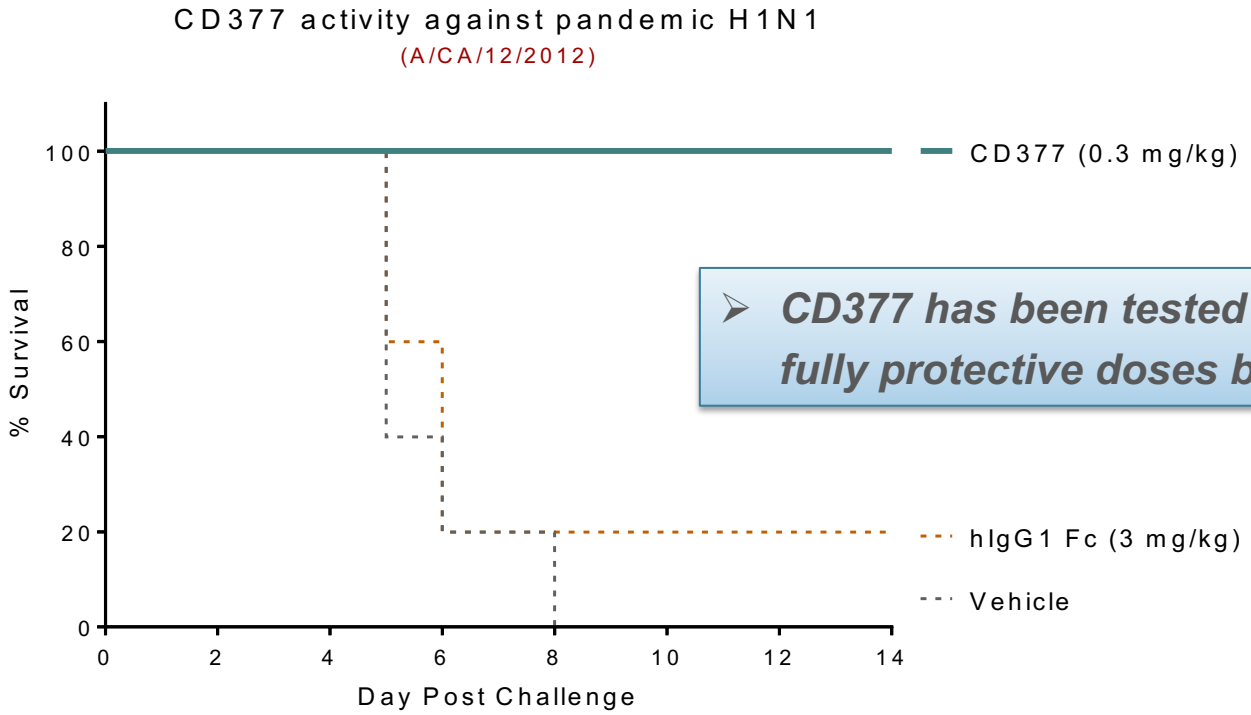
14 – 28 days post viral challenge

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

Survival
Body weight (BW)
Lung burden
Histopathology
Cytokines

Potency of CD377 against an H1N1 pandemic isolate

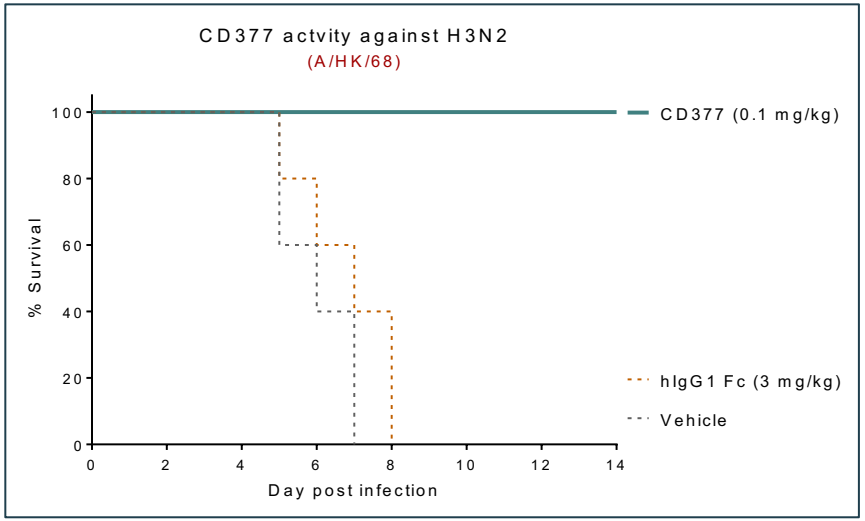
Lethal infection in BALB/c mice. Single IM dosing at T+2h



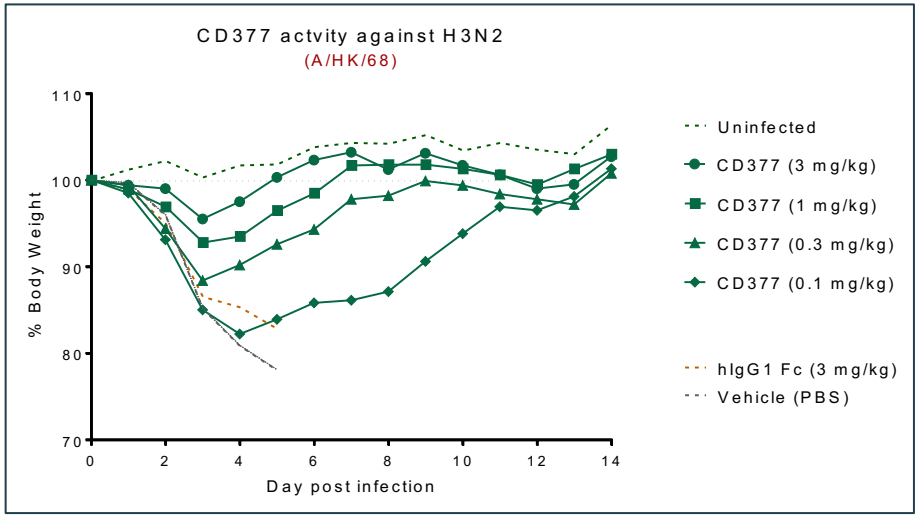
- ***CD377 has been tested against 10 H1N1 isolates with fully protective doses between 0.03 and 0.3 mg/kg***

Potency of CD377 against an H3N2 isolate

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



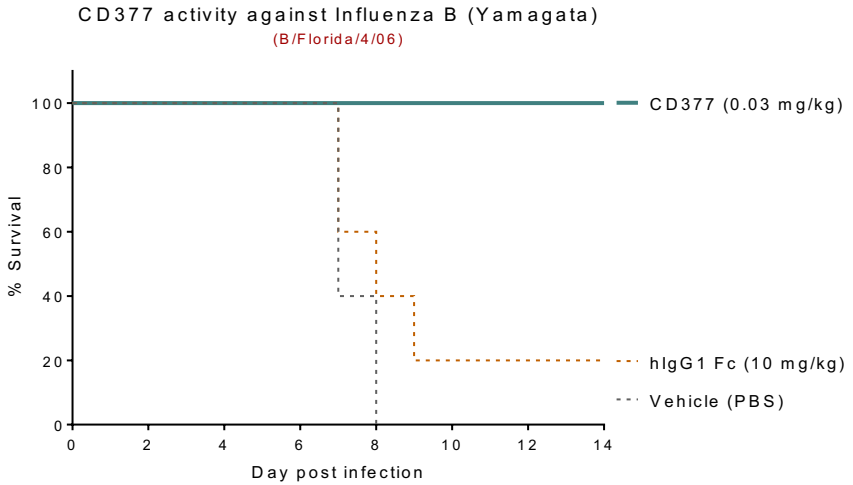
Slightly greater potency against H3N2

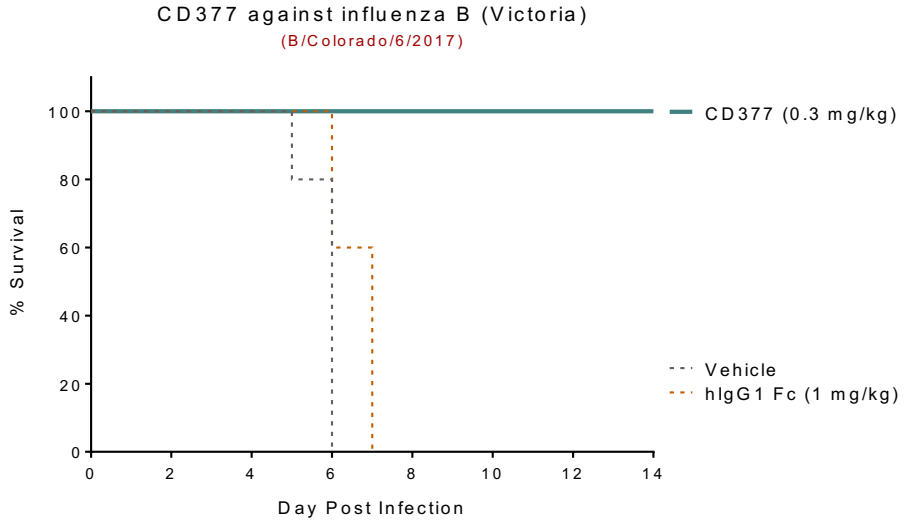


CD377 dose response evident in daily body weight measurements

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)

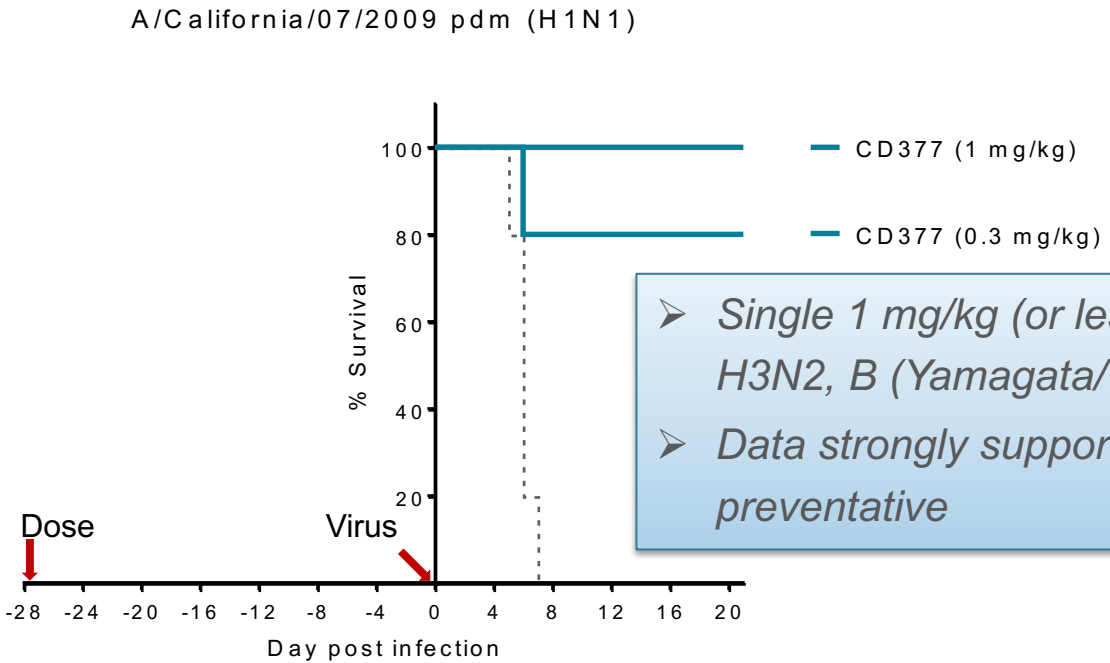
Influenza	Subtype	n	Fully protective dose (mg/kg)
A	H1N1	10	0.3
	H3N2	1	0.1
	H5N1	1	1.0
	H1N1 (H275Y)	2	0.3
B	Victoria	2	0.3
	Yamagata	1	0.1

- 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

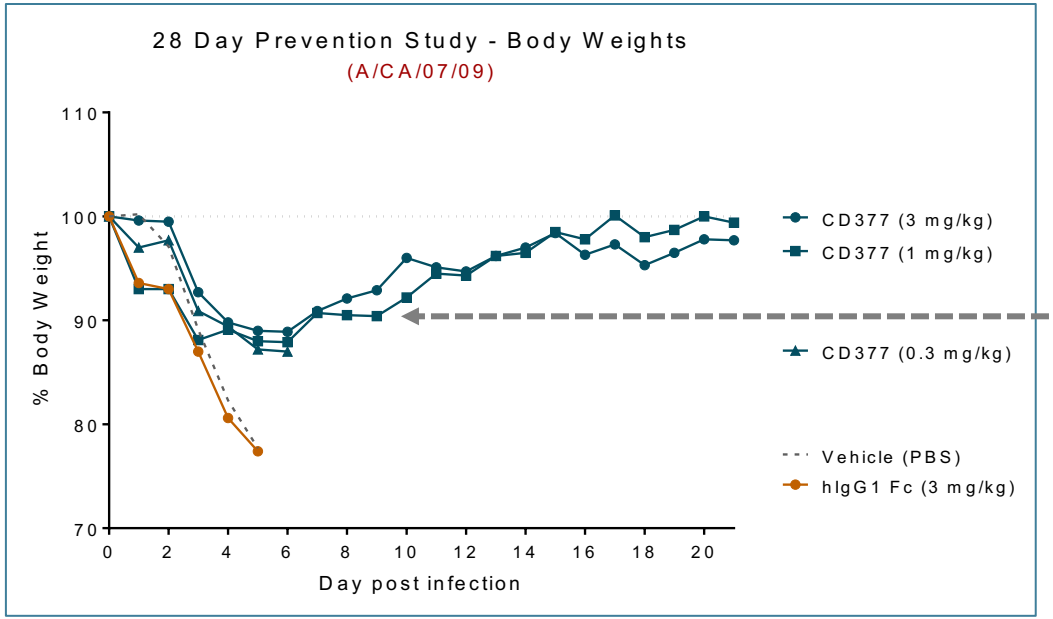
Lethal infection in BALB/c mice. Single, IM dosing at T-28 days



- *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

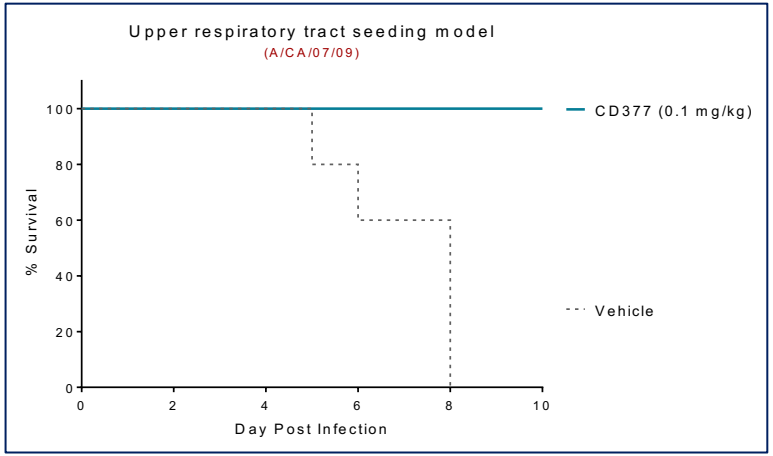


Virus: 3x LD_{95}
Ketamine anesthesia

Question: Is the initial BW loss a technical artifact of a severe screening model?

Improved translational model (upper respiratory tract seeding)

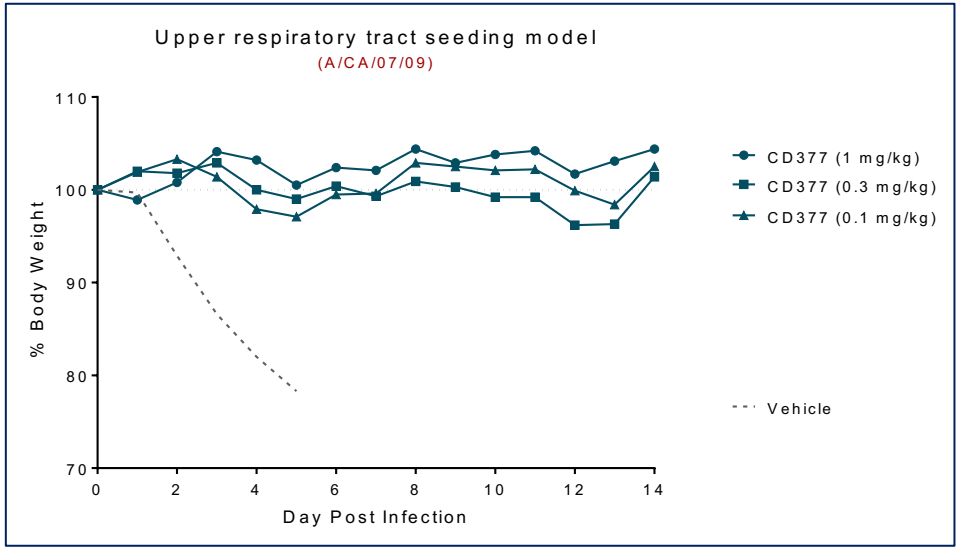
Lethal infection in BALB/c mice. Single IM dosing at T-3d



Isoflurane anesthesia

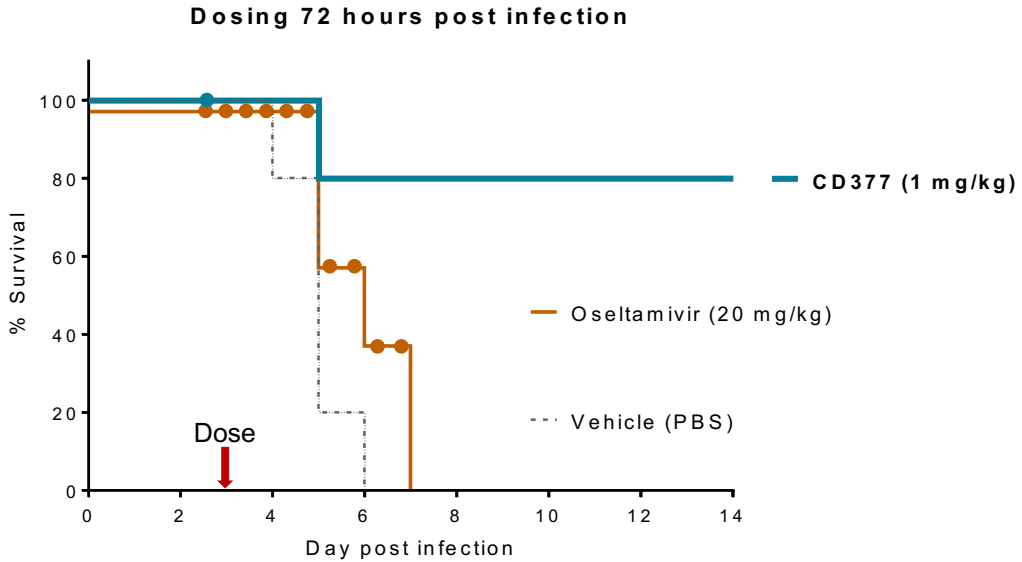
When virus was introduced in the URT, the model was still lethal, with CD377 fully protective at 0.1 mg/kg

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)



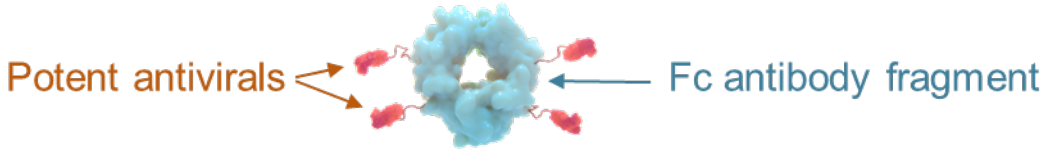
Extended treatment window with CD377

Lethal influenza model (H1N1: TX/36/91 in mice)



- *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*

Summary of key CD377 AVC data



- **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.