Influenza pre-immune ferrets vaccinated with computationally optimized recombinant HA proteins generate sero-protective antibody responses against H1N1 and H3N2 viruses from the last decade

Dr. James Allen
Cleveland Clinic
Florida Research and Innovation Center
Port Saint Lucie, FL, USA
September 19, 2023
ESWI 2023: Future Vaccination Strategies Session
COBRA Approach for Designing Broadly Reactive Vaccines

• In-silico layered consensus building approach
  • Utilizes HA sequence data from flu surveillance databases (GISAID, GenBank)
    • Natural viral evolution dictates antigen design

• Capable of eliciting potent, broadly reactive HA-specific antibody responses
  o Effective against seasonal and pandemic influenza virus strains
    o H1, H3, & H5 subtypes
    o Mice, ferrets, non-human primates
      • Y2 H1 COBRA (2014-2016)
      • NG2 H3 COBRA (2016-2018)
Overview of different COBRA vaccine delivery platforms

- HA and NA recombinant proteins
- mRNA LNP
- DNA vaccination
- Nano, Micro, & Virus-like particles (VLP)
- Recombinant ChAd3
- Self-amplifying mRNA
- Inactivated/Split vaccine
- Live or Attenuated Viruses
- AAV - Vectored
Infectimune® Adjuvant

- **Infectimune® (R-enantiomer of DOTAP)**
- **Cationic lipid nanoparticle adjuvant**
  - Quaternary ammonium head with two 18 carbon length unsaturated fatty acid (acyl) chains
  - Binds to surface of DCs and is endocytosed via a clathrin-mediated mechanism
  - Efficient at transporting protein or peptides into cells
  - Safe and effective at eliciting cellular and humoral immune responses in human clinical trials

Gandhapudi et al. *J Immunology*. 2019
Pre-immune Ferret Model

- Mimic human response to vaccination by first infecting ferrets with influenza viruses
  - H1N1 (A/Singapore/6/1986)
  - H3N2 (A/Panama/2007/1999)
H1N1 HAI Response

- H1/H3 Pre-immune ferrets vaccinated 2x with Y2/NG2 rHA (15ug) + Infectimune® or wild-type rHA + Infectimune®
H3N2 HAI Response

- H1/H3 Pre-immune ferrets vaccinated 2x with Y2/NG2 rHA (15ug) + Infectimune® or wild-type rHA + Infectimune®
H1N1 Infection Results

A/Victoria/2570/2019 H1N1
1e6 PFU/mL

% Original Body Weight

Days Post Infection

D0  D1  D2  D3  D4  D5  D6  D7  D8  D9  D10  D11  D12  D13  D14

80  90  100  110  120

Vaccine Group

Y2 + NG2
Mich/15 + Sing/16
Mock

D3 Nasal Wash Viral Titers

PFU/mL

10^0 10^1 10^2 10^3 10^4 10^5

Mock
Y2 + NG2
Mich/15 + Sing/16

LOD

Days Post Infection

80  90  100  110  120

% Original Body Weight

Vaccine Group

D0  D14  D60  D74  D88  D102

Virus Prime (Preimmunity)  Bleed  Vaccinate  Bleed  Boost  Bleed

D116  D119  D130

H1N1 Virus Challenge  Nasal Wash  Terminate Study

PDS Biotechnology
Conclusions

• COBRA rHA vaccines adjuvanted with Infectimune® capable of eliciting protective HAI antibody responses in pre-immune ferrets across panels of viruses from the last decade
  - Also elicit HAI reactive antibodies against future drifted viral isolates from 2019-2020
  - Prevent weight loss and H1N1 viral replication in the lungs of vaccinated animals

• In a population that has a more extensive pre-immune background to influenza, like humans, we expect these vaccines to generate a more broadly reactive antibody profile due to the recall of a more diverse population of memory B cells
Acknowledgements

Cleveland Clinic
- Dr. Ted Ross
- Jessica Medina
- Matthew Thomas
- Julia Aguirre
- Zachary McGuire
- Spencer Pierce
- Michael Carlock

PDS Biotechnology

University of Kentucky
- Dr. Jerry Woodward
- Dr. Siva Gandhapudi

CIVICs

This project has been funded by the National Institute of Allergy and Infectious Diseases, a component of the NIH, Department of Health and Human Services, under contract 75N93019C00052.

Hua Shi
- Dr. Xiaojian Zhang