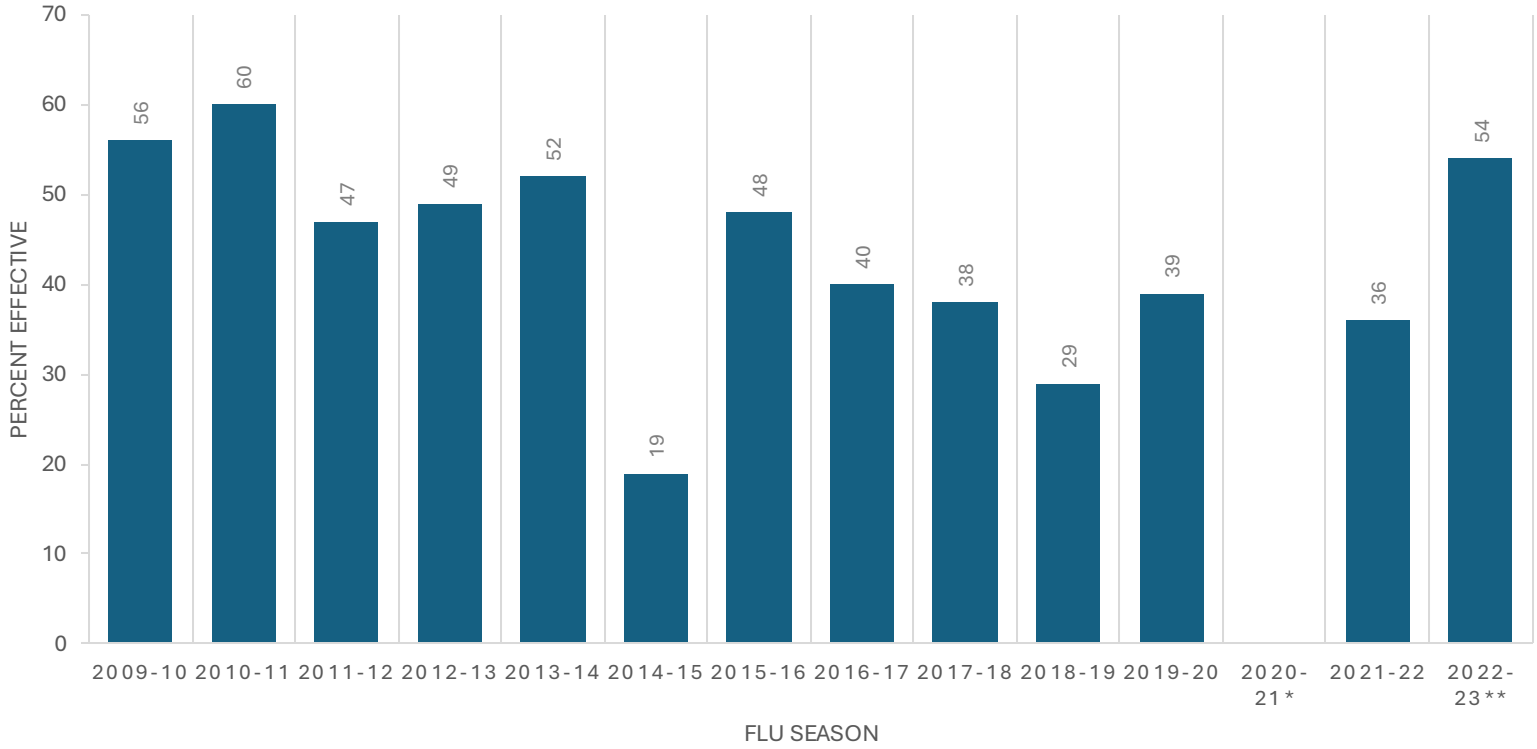
A UNIVERSAL INFLUENZA VIRUS VACCINE BASED ON CHIMERIC HEMAGGLUTININS

Peter Palese
Icahn School of Medicine at Mount Sinai
New York

GVN Tampa
March 5, 2025

SEASONAL FLU VACCINE EFFECTIVENESS



***2020-2021 flu vaccine effectiveness was not estimated due to low flu virus circulation during the 2020-2021 flu season.**

****In a Wisconsin study among patients aged 6 months to 64 years, VE was 54% against medically attended outpatient acute respiratory illness (ARI) associated with laboratory-confirmed influenza A.**

CDC – 8/24/23

LICENSED INFLUENZA VIRUS VACCINES IN THE US

- **Inactivated Vaccine, Split Vaccine, Egg-Based (Seqirus, GlaxoSmithKline, Sanofi Pasteur)**
- **Inactivated Vaccine, Surface Antigen Adjuvanted, Egg-Based (Seqirus)**
- **Recombinant Vaccine (Sanofi Pasteur)**
- **Inactivated Subunit Vaccine, Cell Culture-Based (Seqirus)**
- **Live Attenuated Vaccine (AstraZeneca)**

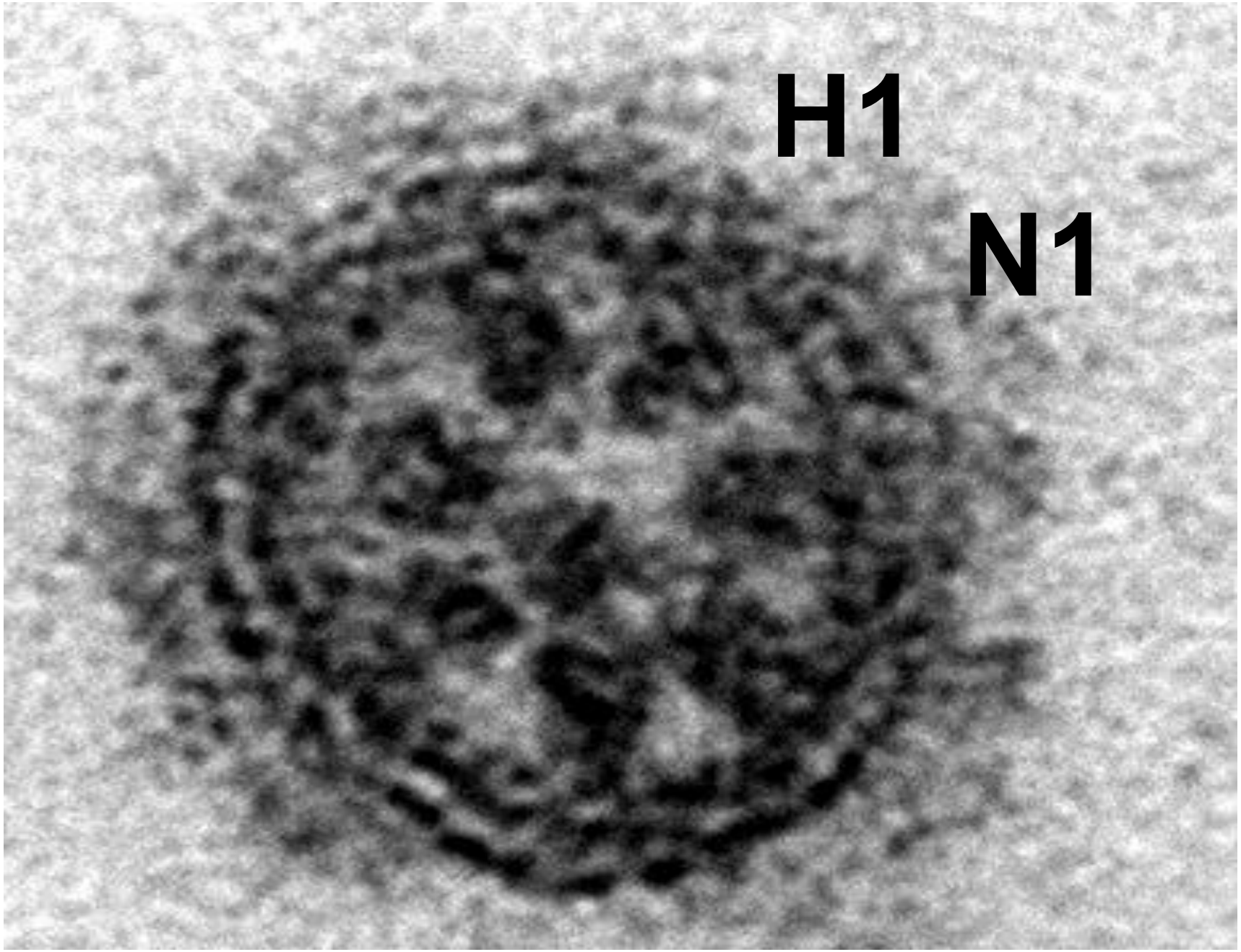
Adopted from NUWARD et al.
doi: 10.3390/vaccines9091032

INFLUENZA VIRUS VACCINE STRAINS 2025-2026

A/Victoria/4897/2022(H1N1)pdm09-like virus

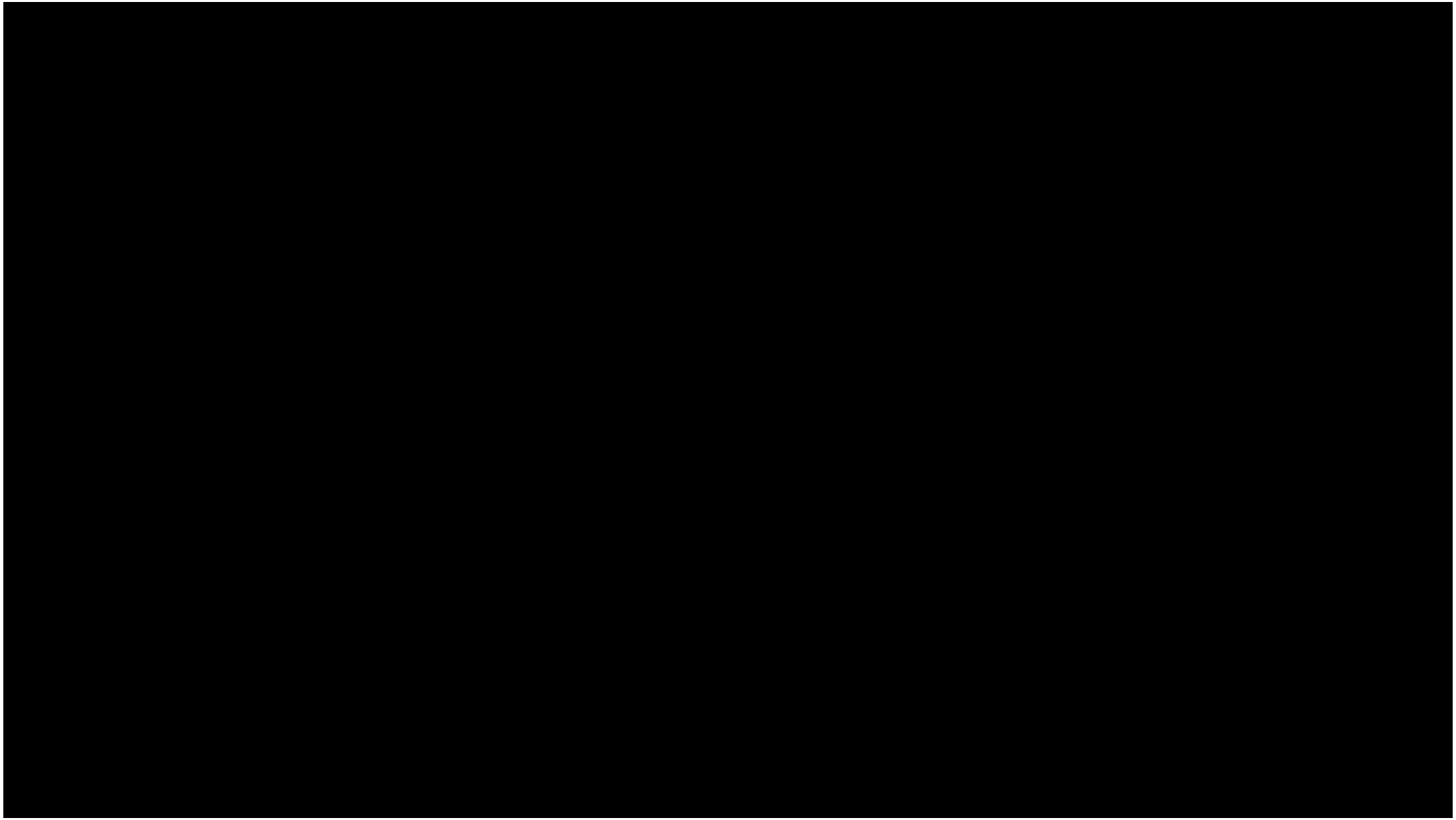
A/Croatia/10136RV/2023 (H3N2)-like virus

B/Austria/1359417/2021 (B/Victoria lineage)-like virus

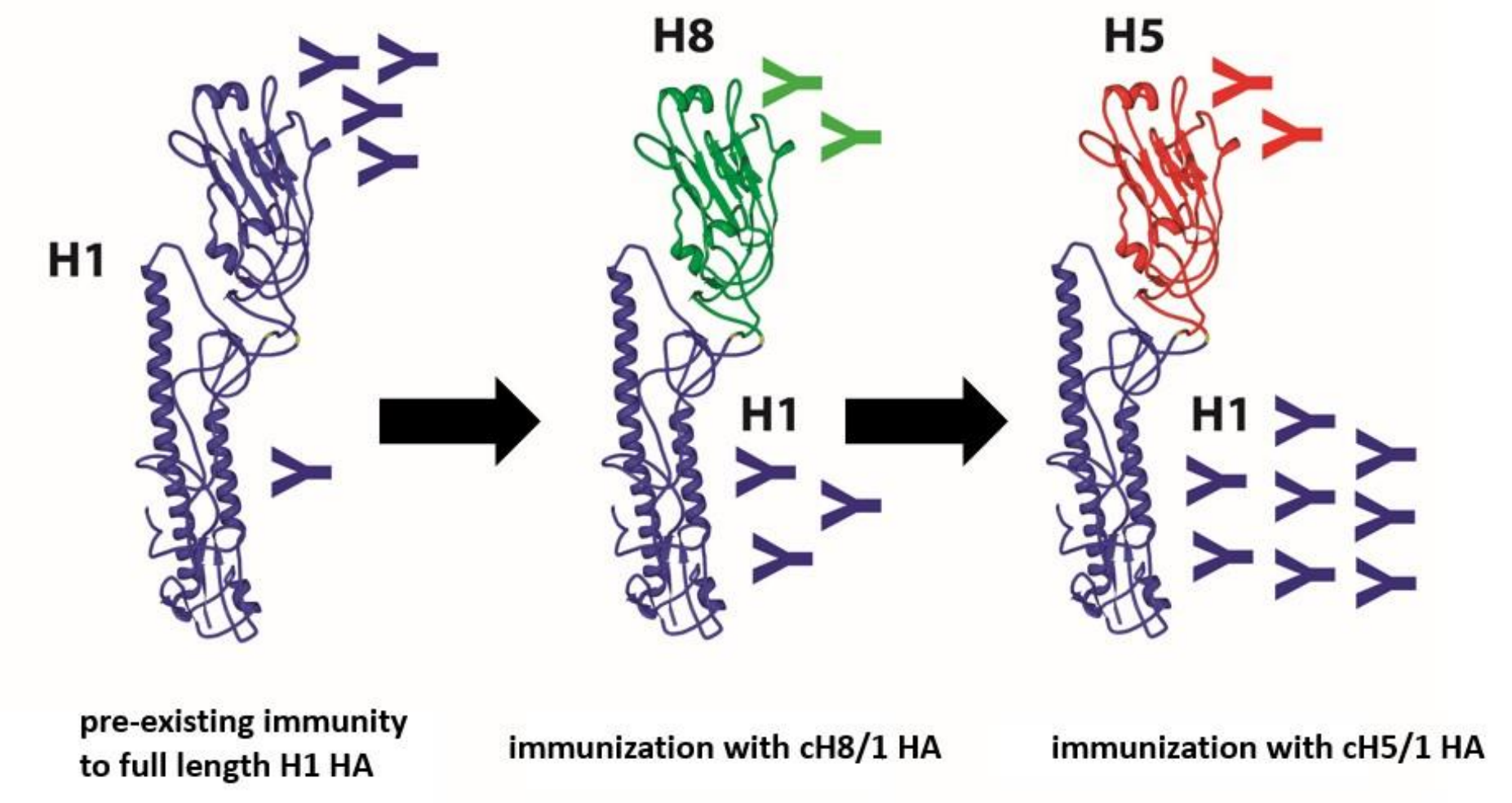


Yi-ying Chou

CONCEPT FOR A HUMAN UNIVERSAL INFLUENZA VIRUS VACCINE



CONCEPT FOR A HUMAN CHIMERIC HA (cHA) BASED UNIVERSAL INFLUENZA VIRUS VACCINE



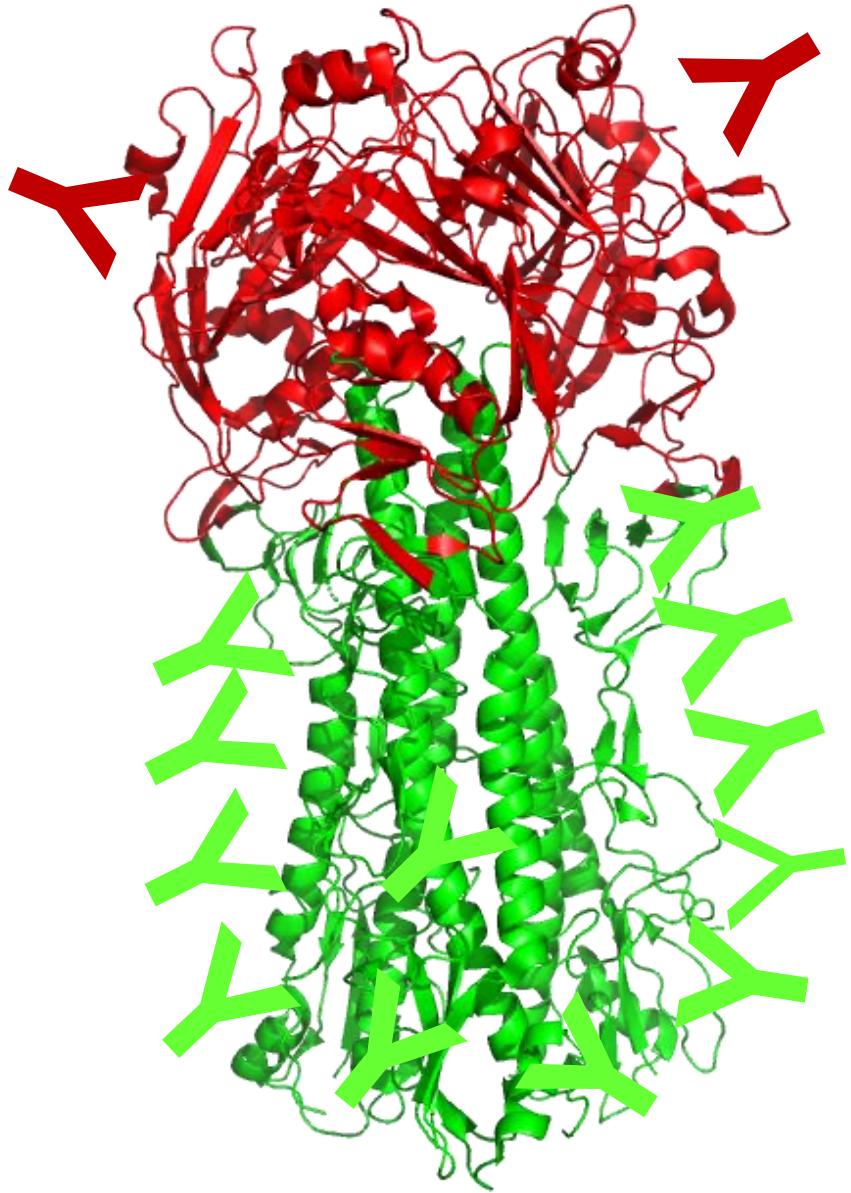
Krammer and Palese, Nat. Immunol., 2013

Trivalent vaccine with group 1, group 2 and influenza B stalk component

OVERVIEW OF UNIVERSAL INFLUENZA VIRUS VACCINE CANDIDATES IN CLINICAL AND PRECLINICAL DEVELOPMENT

- **Vaccine platform:** inactivated split virion vaccines
- **Epitope targeted**: immuno-subdominant, conserved, broadly protective stalk epitopes
- **Route of administration:** intramuscular administration
- **Adjuvant:** AS03/CpG+alum
- **Immunization regimens for a population with pre-existing immunity to influenza viruses:** a two-dose sequential vaccination regimen
- **Phase I and Phase II trials (Group 1)**

REDIRECTING THE IMMUNE SYSTEM FROM IMMUNODOMINANT VARIABLE SITES TO CONSERVED DOMAINS



CVIA 057 TRIAL DESIGN OVERVIEW

(clinicaltrials.gov ID NCT03300050)

- **Prospective, randomized, placebo-controlled, observer-blind, phase I trial**
- **Healthy male and female adults 18 through 39 years of age**
- **65 subjects (39 Duke, 26 CCHMC) randomized to one of five groups**
- **Median age 29 years; 40 female, 25 male**
- **Study start: December 2017**

Study Groups	Number of Subjects	Dose 1		Dose 2	
		Treatment	Route	Treatment	Route
1	20	cH8/1N1 LAIV	Intranasal	cH5/1N1 IIV + $AS03_A$	Intramuscular
2	15	cH8/1N1 LAIV	Intranasal	cH5/1N1 IIV	Intramuscular
3	5	Normal Saline	Intranasal	PBS	Intramuscular
4	15	cH8/1N1 IIV + $AS03_A$	Intramuscular	cH5/1N1 IIV + $AS03_A$	Intramuscular
5	10	PBS	Intramuscular	PBS	Intramuscular

LAIV: Live-attenuated influenza virus vaccine (Leningrad backbone)

IIV: Inactivated influenza virus vaccine → split vaccine

THE LANCET
Infectious Diseases

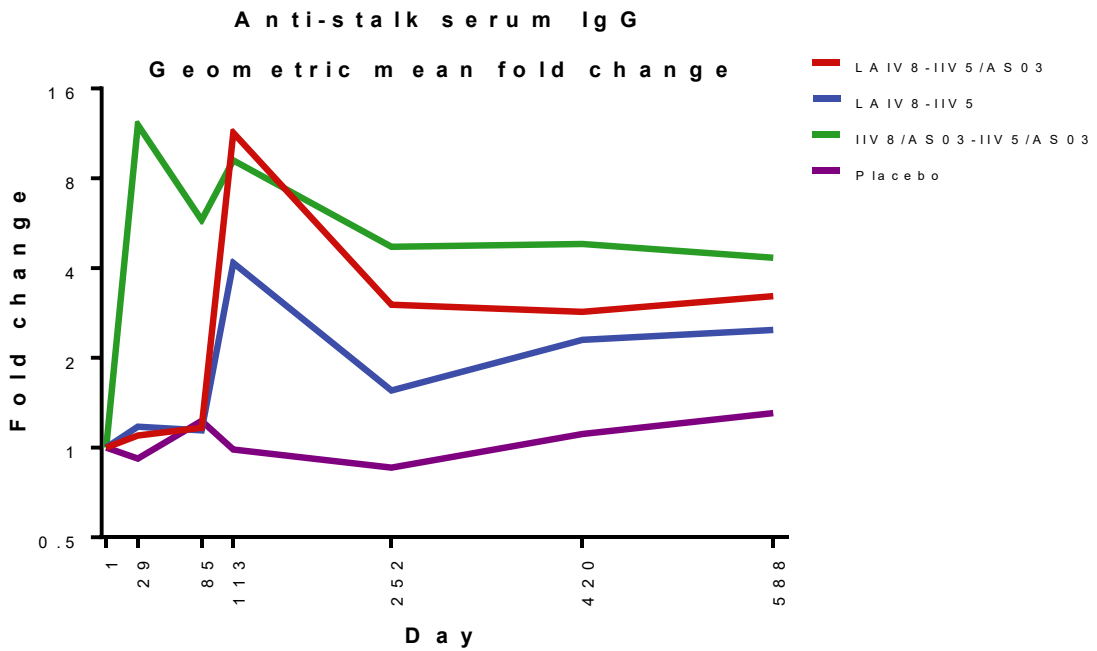
Volume 22, Issue 7, July 2022, Pages 1062-1075

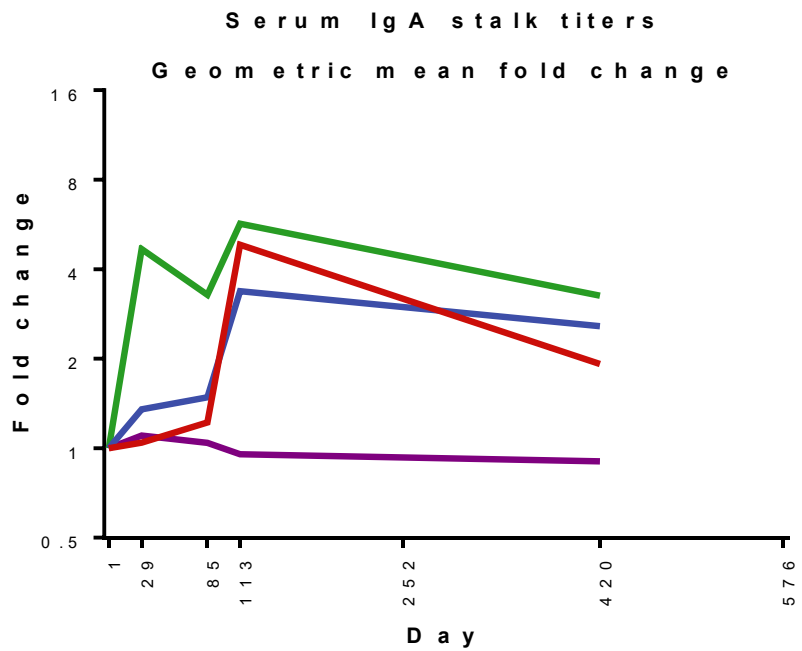
Articles

Reactogenicity, safety, and immunogenicity of chimeric haemagglutinin influenza split-virion vaccines, adjuvanted with AS01 or AS03 or non-adjuvanted: a phase 1–2 randomised controlled trial

Nicolas Folschweiller PhD [a b], Carline Vanden Abeele MSc [a], Laurence Chu MD [e], Prof Pierre Van Damme PhD [f], Prof Adolfo García-Sastre PhD [g h i j k], Prof Florian Krammer PhD [g j], Raffael Nachbagauer MD [g l], Prof Peter Palese PhD [g k], Alicia Solórzano PhD [g m], Dan Bi MD [a], Marie-Pierre David MSc [a], Damien Friel PhD [a], Bruce L Innis MD [n o], Juliane Koch PhD [a c], Corey P Mallett PhD [p], Ronan Nicolas Rouxel PhD [q r], Bruno Salaun PhD [q], Valerie Vantomme MSc [a], Céline Verheust PhD [a], Frank Struyf MD [a d]

Serum IgG and IgA stalk responses – fold induction



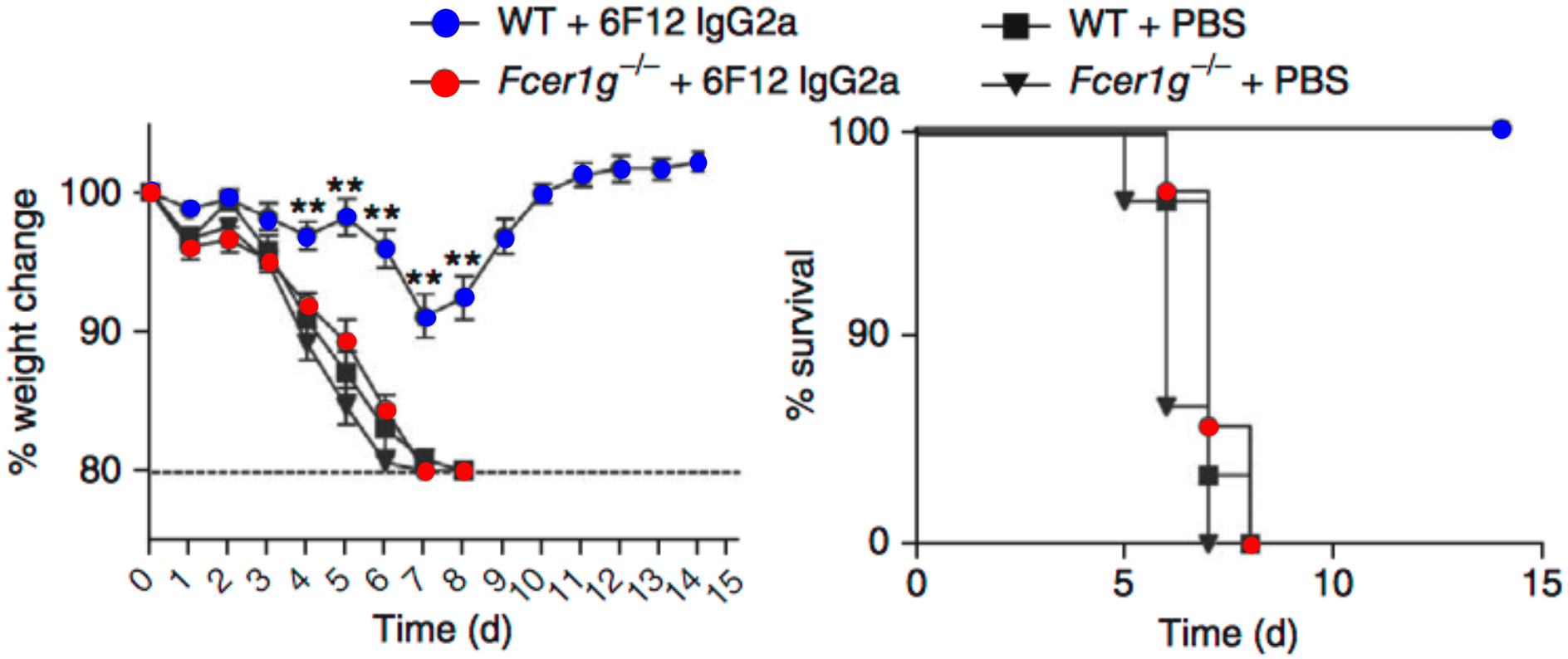


Nachbagauer *et al.*, Nat. Med., 2021

WHAT IS THE MECHANISM BY WHICH THESE BROADLY PROTECTIVE STALK-SPECIFIC ANTIBODIES MEDIATE THEIR ANTIVIRAL ACTIVITY?

nature medicine

Broadly cross-reactive hemagglutinin stalk-specific antibodies require FcγR interactions for protection against influenza virus *in vivo*



DiLillo *et al. Nature Medicine*

Towards a universal influenza virus vaccine: Reducing the immunodominance of the hemagglutinin head by the sequential administration of chimeric hemaglutinins (cHA) increases the immunogenicity of the hemagglutinin stalk

Protection is antibody mediated and involves activation of Fc-FcR effector functions

ANTI-H1 STALK TITERS ARE AN INDEPENDENT CORRELATE OF PROTECTION AGAINST H1N1 INFECTION IN HUMANS

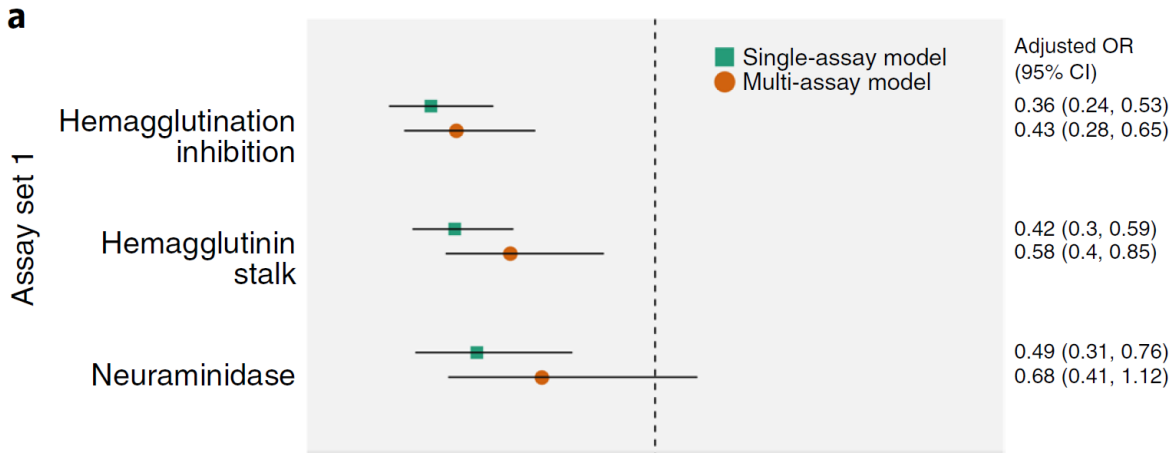
LETTERS
https://doi.org/10.1038/s41591-019-0463-x
nature medicine

Novel correlates of protection against pandemic H1N1 influenza A virus infection

Sophia Ng[1,2,3,9], Raffael Nachbagauer[3,4,5,9], Angel Balmaseda[6,7], Daniel Stadlbauer[3,4,5], Sergio Ojeda[7], Mayuri Patel[1,2,3], Arvind Rajabhathor[3,4,5], Roger Lopez[6,7], Andrea F. Guglia[4], Nery Sanchez[7], Fatima Amanat[3,4,5], Lionel Gresh[7], Guillermina Kuan[7,8], Florian Krammer[3,4,5,10*] and Aubree Gordon[1,2,3,10*]

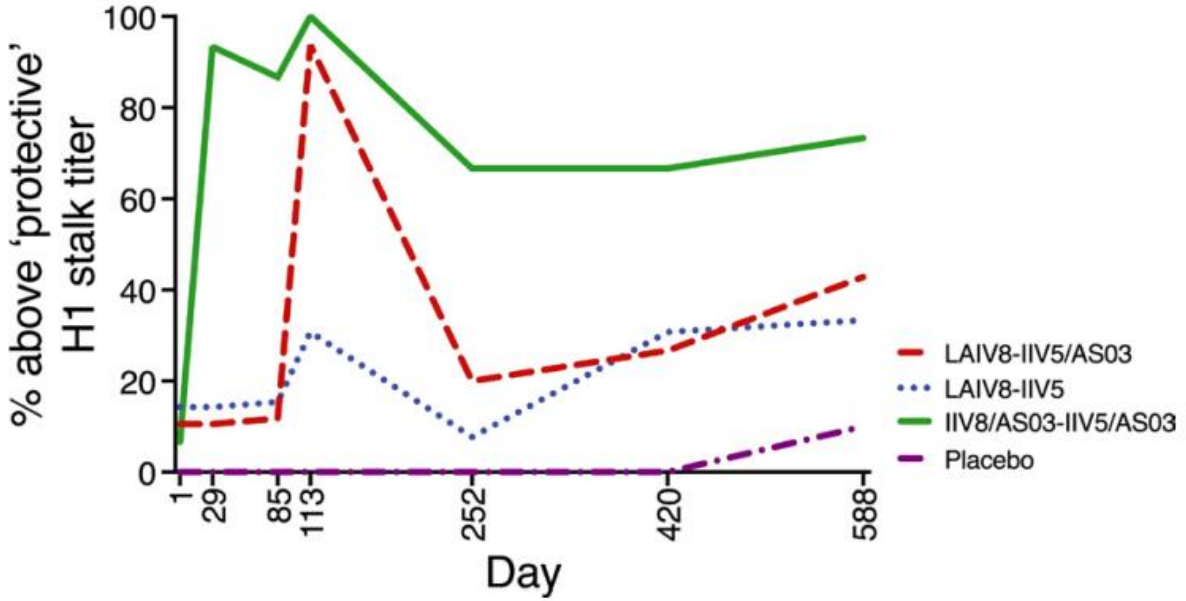
NATURE MEDICINE | VOL 25 | JUNE 2019

Odds ratio for PCR confirmed infection



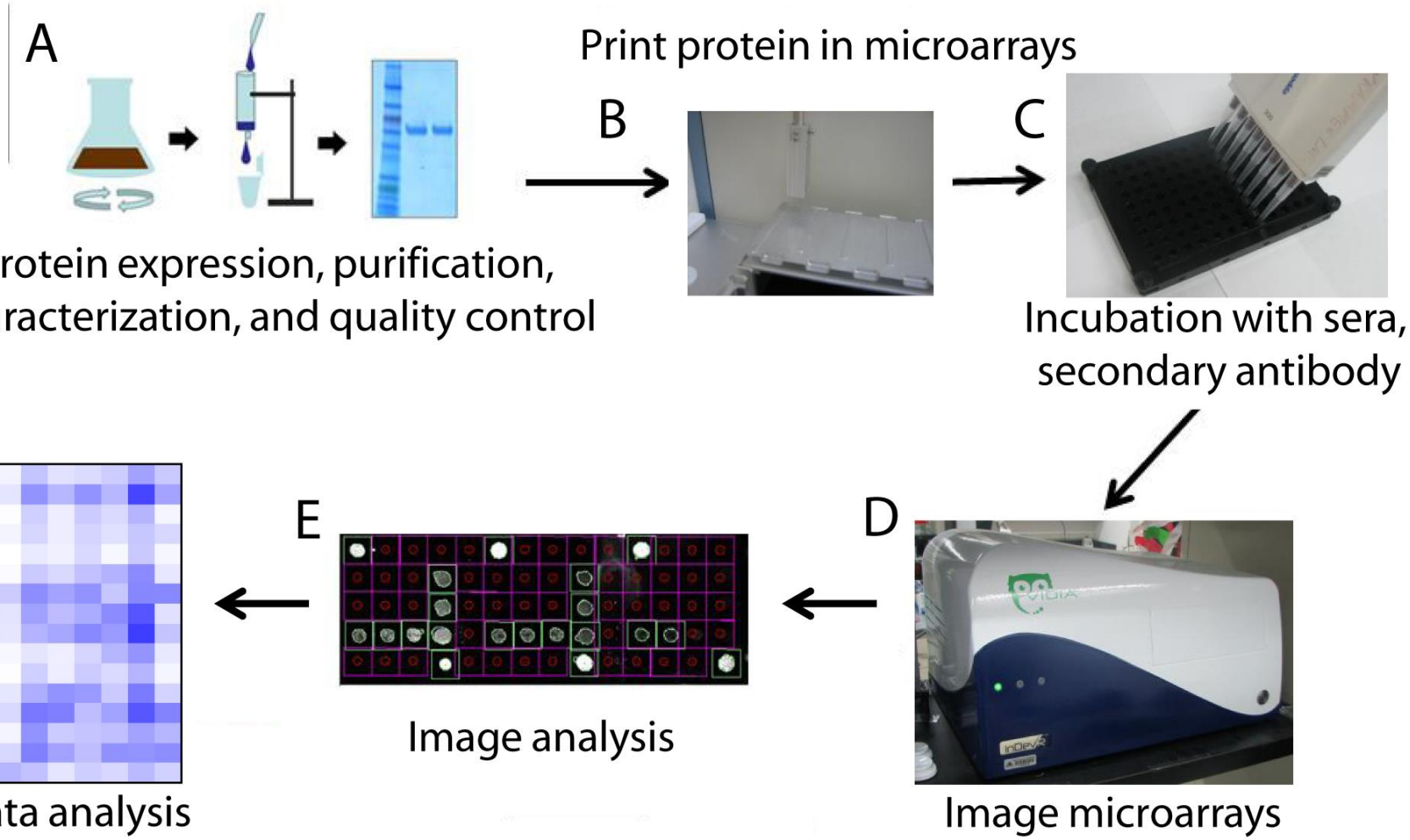
Ng *et al.*, Nat. Med., 2019

% individuals above "protective" stalk titers in human clinical trial

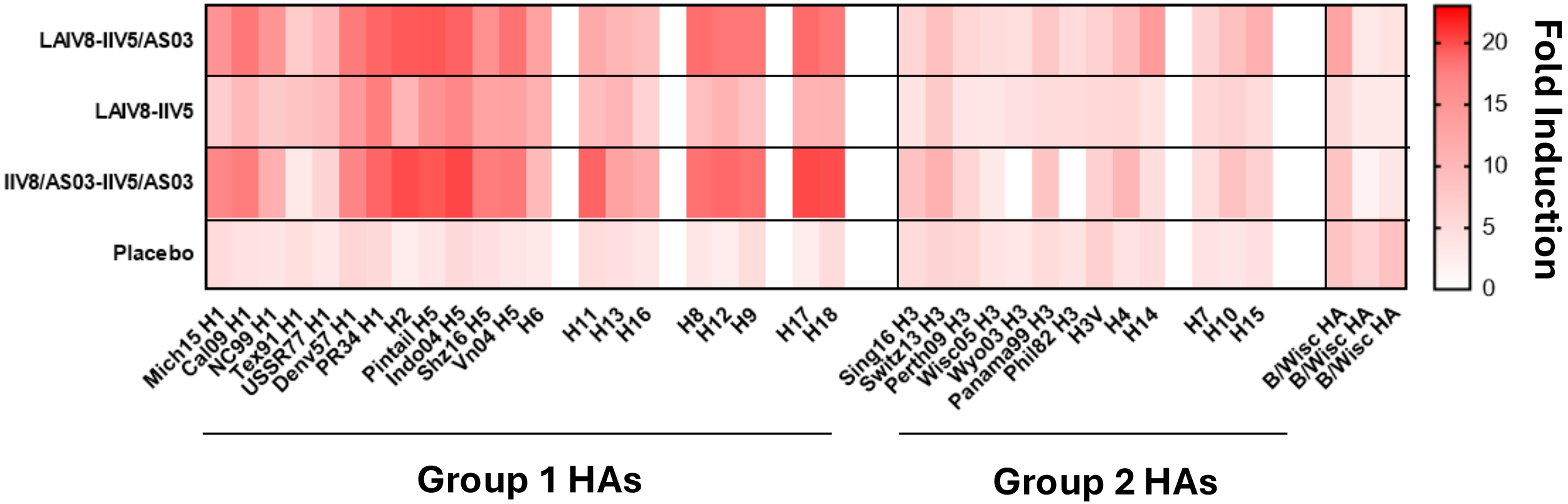


Nachbagauer *et al.*, Nat. Med., 2021

INFLUENZA VIRUS PROTEIN MICROARRAY (IVPM) TO MEASURE ANTIBODY BREADTH



HUMAN SERUM IgG RESPONSES – FOLD INDUCTION: DAY 1 – DAY 113



Meade *et al.*, JVI, 2023

CONCLUSIONS FOR GROUP 1 cHA PHASE I/II CLINICAL TRIALS

- **Proof of principle that anti-stalk antibodies can be induced in humans by a rationally designed vaccine**
- **The vaccines are safe (comparable to licensed quadrivalent, live attenuated influenza virus vaccine, H5N1/AS03)**
- **Adjuvants are important**
- **Adjuvanted cHA inactivated influenza virus vaccine (IIV) induces high stalk-reactive antibody titers even after one vaccination**
  - **Potential tool for pandemic preparedness**
- **The induced antibody response is very broad and durable**
- **The induced antibodies are multifunctional (NI, ADCC, ADCP, neutralization, trimer-interface antibodies, anchor epitope antibodies etc.)**

Icahn School of Medicine at Mount Sinai

- **Peter Palese, Ph.D – (212) 241-4635**
  peter.palese@mssm.edu
  http://labs.icahn.mssm.edu/paleselab/

- **Florian Krammer, Ph.D – (212) 241-8166**
  florian.krammer@mssm.edu
  https://labs.icahn.mssm.edu/krammerlab/

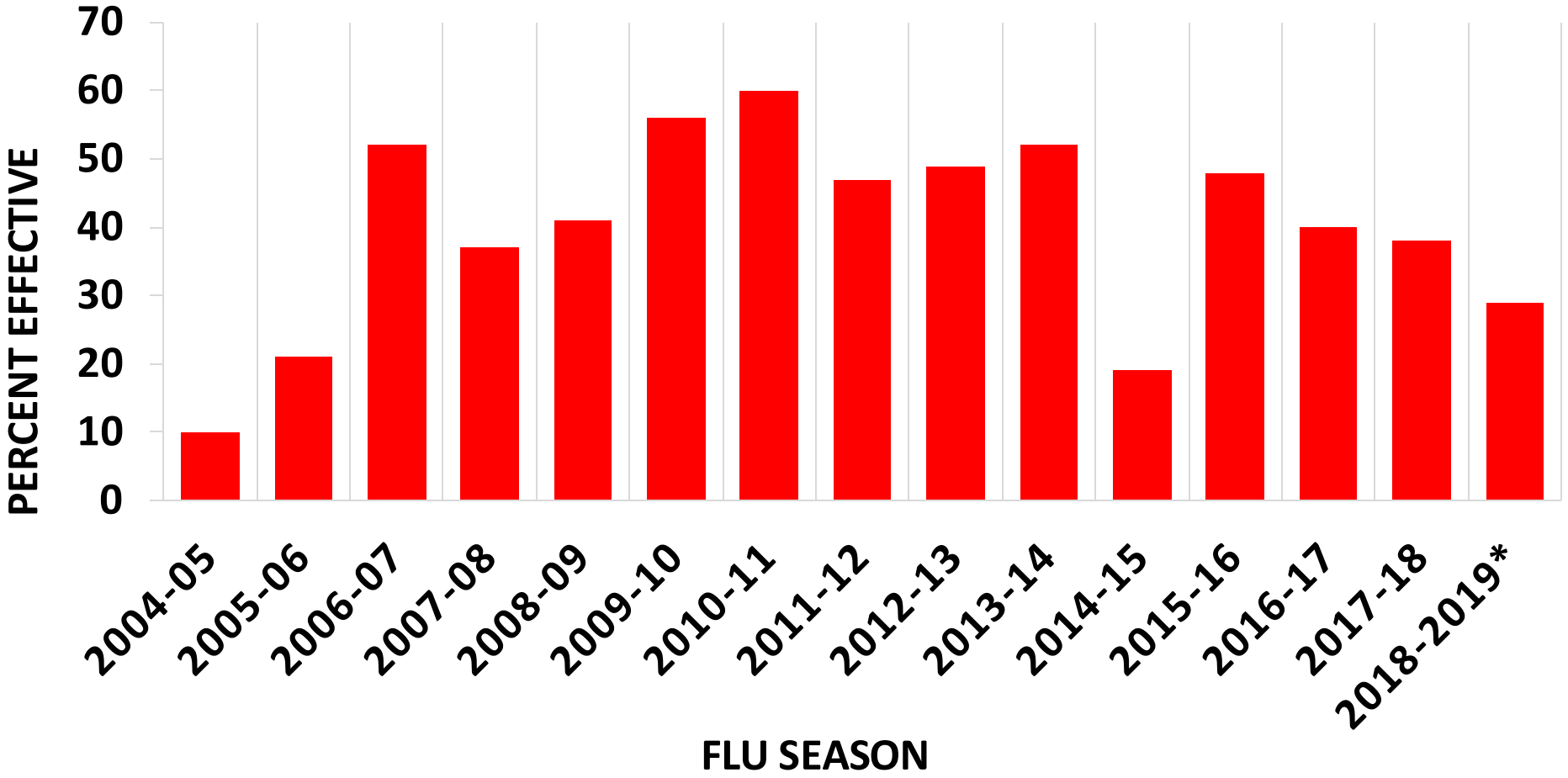
- **Adolfo García-Sastre, Ph.D – (212) 241-7769**
  adolfo.garcia-sastre@mssm.edu
  http://icahn.mssm.edu/research/labs/garcia-sastre-laboratory

- **Weina Sun, Ph.D – (212) 241-9959**
  weina.sun@mssm.edu
  https://labs.icahn.mssm.edu/weinasunlab/

CastleVax, Inc.

- **Michael Egan, Ph.D – (520) 904-3686**
  michael.egan@castlevax.com

SEASONAL FLU VACCINE EFFECTIVENESS



*Vaccine effectiveness estimates for 2018-2019 were presented to ACIP on June 27, 2019

Source: CDC Seasonal Flu Vaccine Effectiveness Studies
https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

Influenza A and B viruses circulating in the human population

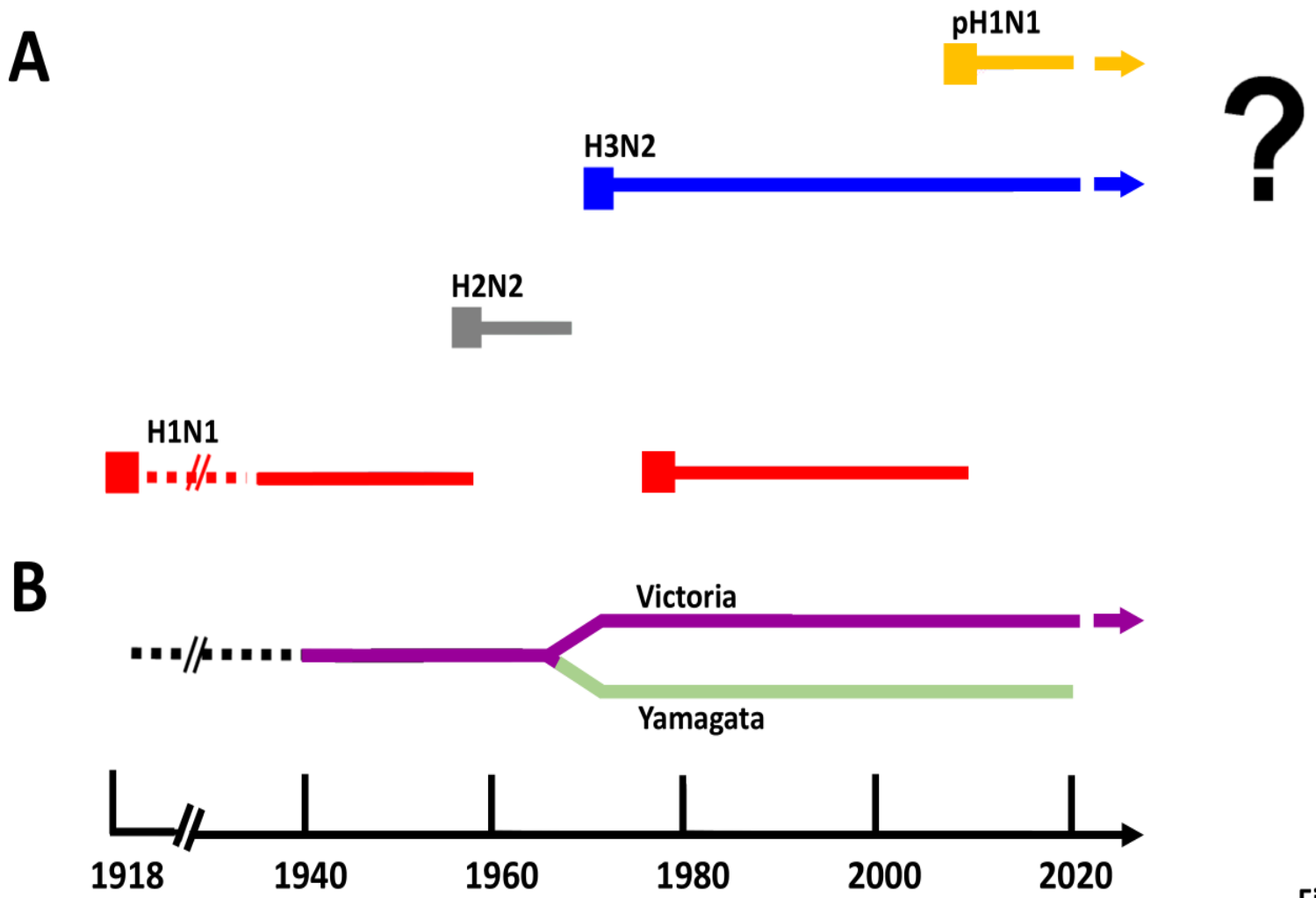
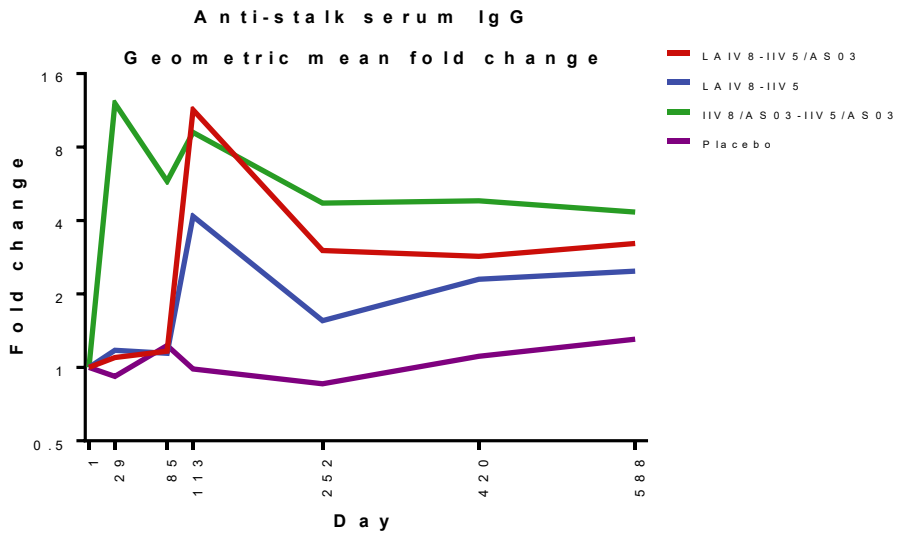
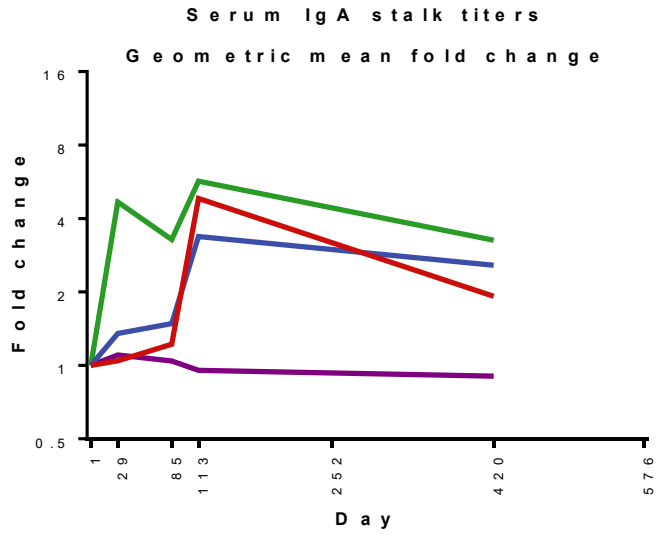


Fig. 1

Serum IgG and IgA stalk responses – fold induction





Nachbagauer *et al.*, Nat. Med., 2021